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MIMS HANDBOOK OF ONCOLOGY

Treatment Approaches • Drug-Class Overview

VOLUME 2

MIMS HANDBOOK OF ONCOLOGY

VOLUME 2

Treatment Approaches
Drug-Class Overview

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About Vitalab

Vitalab is a Johannesburg based fertility clinic that has been committed to help building families since 1984. Vitalab offers a highly specialized program for preserving fertility to patients diagnosed with cancer. Our mission is to increase awareness and optimize accessibility to fertility-preserving options for cancer patients, prior to the initiation of cancer therapy. Vitalab became the first fertility clinic in Africa to become a member of the international Oncofertility Consortium in 2017.

Side Effects from Cancer Treatment

Females - can include damage or destruction of oocytes, premature menopause and a compromised ability to carry a pregnancy to term.

Males - can have a transitory as well as a permanent impact on male fertility.

Oncofertility Program

At Vitalab, cancer patients seeking our fertility preservation services are attended to immediately. Cancer patients will consult with one of our specialists within the week of making initial contact. The entire process may take between 10 to 14 days, in order to freeze specimens prior to commencing cancer treatment. Evidence has shown that the vitrification of oocytes, sperm and embryos does not negatively impact their viability.

Treatment Options	What Is It?	For Who Is It?
Oocyte Freezing	Includes immediate non-cycle related ovarian stimulation with harvesting and vitrification of eggs without fertilizing them over a time period of 10 to 14 days.	Women diagnosed with cancer, who do not have a male partner or do not wish to use donor sperm.
Sperm Freezing	The preservation of a number of ejaculated sperm samples within the time period of 2 to 3 days.	Post pubertal men diagnosed with cancer.
Embryo Freezing (IVF)	Embryo vitrification includes non-cycle related immediate ovarian stimulation, harvesting and fertilisation of oocytes, and freezing of embryos on day 5 or 6. The harvesting is done over a period of 10 to 14 days.	For women who have a male partner or are prepared to use donor sperm.
Ovarian Transposition Surgery	Surgery to reposition the ovaries to minimize the amount of exposure to the radiation.	Women diagnosed with cancer who require abdominal or pelvic radiation.
Ovarian Tissue Freezing	Involves the removal and freezing of ovarian tissue prior to oncotherapy via laparoscopy.	Prepubertal females or women who cannot delay chemotherapy for ovarian stimulation.

Success Rates

97% Embryos, oocytes or sperm surviving the thawing process.

Pregnancy rates **40% - 60%**

depending on method of treatment utilising the frozen gametes.

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Information for Prescribers

MIMS Handbook of Oncology – Volume 2 comprises two main editorial sections – Treatment Approaches and Drug-Class Overview.

Section 1: Treatment Approaches
These up-to-date, research-based therapeutic articles are geared to the medical practitioner who is participating in a multidisciplinary team and required to assist patients and their families across the continuum of care with the latest treatment approaches. The information, provided by leading academics and oncologists in South Africa, will enable the doctor to guide the patient appropriately when approached for information, understand the side effects of treatment modalities and assist with supportive care throughout the cancer journey. The *Handbook* is also accredited for Continuing Professional Development. Please see guidelines for CPD participation in the accompanying CPD booklet.

Section 2: Drug-Class Overview
This section features a comprehensive overview of a selection of drug classes relevant to oncology. In each case, this takes the form of an editorial review discussing the important aspects of the entire drug class. These summaries contain facts on disease and therapeutic entities, as well as general drug information, such as indications, common adverse reactions, drug interactions and more. Expert pharmacology consultants compiled this section and it is essentially based on the latest available international medical information.

Please note that some agents mentioned in the Drug-Class Overview may not be available in South Africa. Also, no reference is made to any "off-label" use of drugs. Readers are referred to current manufacturers' product literature for registered indications and dosages.

Important information of which to take cognisance when prescribing:
When prescribing any product mentioned in *MIMS Handbook of Oncology – Volume 2*, doctors should be mindful of the important points listed below:

- Hypersensitivity to the ingredient(s)/components of any medicine contraindicates its use.
- Medicines should not be prescribed to pregnant or lactating women unless the anticipated benefit clearly outweighs any potential risk to the foetus.
- The possibility of drug accumulation should be considered in the presence of significant renal or hepatic impairment.
- Tolerance to medicines is likely to be less with extremes of age.
- Drug interferences with laboratory tests and physical incompatibilities common with parenteral solutions have not been included.
- Monoamine oxidase inhibitors (MAOIs) have a prolonged action, so patients should not take any of the foods or medicines known to cause reactions for at least 14 days after stopping treatment.
- Certain medicines (i.e. those that cause CNS depression) may lead to drowsiness and impaired concentration, which may be aggravated by the simultaneous intake of alcohol or depression agents.

Introduction

Cancer Incidence and Response to the Crisis in Africa

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The global burden of disease research has shifted in recent years to focus on the non-communicable diseases, with an emphasis on the incidence of cancer prevalence and mortality. The projected number of cases worldwide will rise from 12 million in 2008 to 22.2 million by 2030, essentially a doubling of the burden of disease.[1] The availability of good quality data remains a challenge on the continent due to limited government input or lack of infrastructure for data collection in many countries. Data is limited specifically to pathology registries, and small centres or cities in most instances.

This introduction will review some basic global and South African incidence data, and provide examples of challenges and successes in service delivery and prevention on the continent.

INCIDENCE IN AFRICA

The frequently quoted Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) data provide estimates on the global and country-specific incidence of malignancies.[2] In Africa in 2012 there were more than 850 000 new cases of cancer, with the common causes including breast, cervix, prostate, liver and colorectal cancer.[2,3] In comparison to the GLOBOCAN data of 2008, the new cases were estimated at approximately 720 000. The risk of developing cancer by the age of 75 years is 12%.

The reality of cancer on the continent is the poor outcomes, with 590 000 patients succumbing to cancer in 2012; this is again relatively unchanged from 2008 with 540 000 deaths.[4] What is important to note is that only two countries in Africa provide national statistics on cancer deaths, namely Egypt and South Africa,[5] which makes mortality data highly unreliable on the continent. What is very likely is that the GLOBOCAN data underestimate both incidence and mortality rates. High mortality rates are due in part to a lack of basic health care, poor access to treatment centres or lack of available specialist services.

Average life expectancy is generally low due to non-communicable diseases, including heart disease and rampant infectious diseases, with many millions affected by malaria, diarrhoeal disorders, HIV infection and tuberculosis. As a result, certain areas of the continent are at the lowest population risk for malignancy in the world, i.e., Central and West Africa for men and Central and North Africa for women.[2]

Conversely, certain malignancies have a specifically high incidence in selected populations in Africa: cervical cancer in East African women and oesophageal cancer in South African men. These specific diseases and disease patterns are clearly linked to environmental factors and viral agents.[2]

In South Africa specifically, data show that despite the relative economic stability in comparison to many other African countries, the incidence of cancer deaths is only 9.5% in comparison to 19.5% from infectious diseases and 17.8% from heart disease.[5]

International Agency for Research in Cancer (IARC) data confirm that South Africa had nearly 80 000 cases of new malignancies diagnosed in 2012, with the majority being prostate (13%), breast (13%), and cervical and lung (9.4%) carcinoma.[2]

MEASURES IN PLACE TO RESPOND TO NEED

Estimations point to a significant increase of malignancies and disproportionately

high rates of death by 2030 due the projected increase in the African population.[1] Clearly, basic oncological services will have to be increased to meet this future need. This includes diagnostic and radiology services, as well as interventions with surgery, chemotherapy and radiotherapy.[6]

Pathology services are available in many countries, but delay, lost samples and poor infrastructure remain a challenge. The African Organization for Research and Training (AORTIC) and the African Strategies for Advancing Pathology (ASAP) are increasing educational activities and providing connections on the continent to support development of services. Telepathology is a vital key to improving services in countries with very limited resources and many such collaborations have been established, one such example being the Malawian-UK pathology collaboration to assist in the diagnosis of paediatric and haematological malignancies.[6] Pathology services are readily available across South Africa,[7] although limitations do exist in the state system because of limited qualified staff in some regions.

Access to radiology services is highly differential across the continent, with the well-resourced countries of Egypt and South Africa offering easy access and others suffering owing to lack of equipment or frequent equipment breakdowns. A review of public-sector radiology services in Tanzania showed a limited number of general x-ray units at 5.7 units per million population, in comparison to South Africa at 19.6 units per million (fewer than the WHO recommendation of 20 units per million).[8] There was also a distinct lack of access to CT-scanning which in many cases is essential for adequate staging information in oncology. Many clinicians will stage using a simple chest x-ray and USS due to lack of access or funding for more advanced radiological imaging modalities. Qualified staff and adequate training programmes in the resource-limited countries remain a challenge, but many larger centres are training specialists on a supernumerary basis in order to strengthen staff numbers in parent countries.

A Lancet commission was established to address challenges in delivering adequate and safe surgical care on a global scale.[9] A large prospective cohort study – The African Surgical Outcomes Study – was undertaken in 25 African countries in 2016 to assess peri-operative mortality results in order to inform the commission.[10] The study found many alarming outcomes. Staffing is wholly inadequate, with a ratio of 0.7:100 000 surgeons per population, and almost all surgical procedures were undertaken as emergencies or urgent cases. This clearly spells concern for oncology patients and access to what in most cases would be essential curative procedures in solid tumours. In addition, a significant lack of oncology-specialist surgeons further limits appropriate care. In South Africa, there is good access to subspecialists and to multidisciplinary teams working in established oncology departments or in private units across the country. Despite this, there remain challenges of extended waiting lists and bed shortages, which are common to almost all countries globally. Many health care systems prioritise cancer cases, but the large number of emergency cases will still lead to delays.

Radiotherapy resources are costly, technically challenging and skill-dependent. All these factors are a known barrier to the installation and functioning of radiotherapy centres in Africa. More than 90% of all radiotherapy equipment is found in South and Northern Africa.[11] More than 50% of the continent has no access to radiation services. Interruption of radiotherapy treatments are a frequent occurrence not only because of machine breakdowns, but because many patients cannot afford the daily costs of travelling for therapy.[12] Free or state-funded access is limited and user fees provide yet another barrier to accessing treatment and remaining compliant with ongoing daily schedules. Expanding radiation facilities is a major step towards improving outcomes through partnerships with the International Atomic Energy Agency (IAEA) and other public-private collaborations. Many countries are establishing new centres or upgrading

existing ones with modern radiotherapy equipment. Staff training in oncology and medical physics is being undertaken by a number of host countries, including Zimbabwe, Tanzania, South Africa and Egypt. Access to radiotherapy in South Africa is widely available in the private sector, but is challenging in some areas of the public sector, with many lacking functional equipment or qualified staff.

In addition to the challenges in delivering adequate radiotherapy services, similar difficulties are seen in delivering chemotherapy services. Although specialist training is not necessarily a prerequisite for chemotherapy prescription, access and affordability are persistent barriers. Complex issues are at play in the registration of drugs in many countries, including high taxes, untested generics and stock shortages.[13] The WHO Essential Medicines List drugs are not available in many countries due to these barriers.[14] Many of the so-called second-generation drugs which can treat a number of malignancies as well as tamoxifen for breast-cancer patients, are essentially very cheap, but supply issues, even in more developed centres such as Tanzania and South Africa, lead to product shortages. The major barriers to delivery of chemotherapy when stock is available is cost to the patient through user fees, or inadequate access to diagnostic services. Treatment algorithms abound and there is no lack of advice and support for the oncologist or physician prescribing chemotherapy; protocols adapted to resource-limited settings make these guidelines user-friendly and valuable.

Faced with the many challenges of diagnosis and access to treatment, many patients will be diagnosed in the later stages of cancer. Thus, palliative-care access is one of the most immediate and essential services that need to be upgraded on the continent. The majority of formal services are limited to Kenya, Uganda and South Africa. Many countries have no palliative care beyond that which is delivered by family physicians. It is thus vital that palliative-care education is a priority in all regions. Formal education is very limited, with only four countries offering any palliative-care training.[15] The World Health Assembly resolution WHA67.19, has specifically called for improved access to palliative care as a core service, with an emphasis on primary health care and community/home-based care.[16] The resolution has pushed palliative care to the top of the agenda for many government agencies and this will hopefully translate to an increase in access to services.

PRACTICAL IMPLEMENTATION OF PREVENTION

Many public health initiatives are driving the access to primary- and secondary-prevention measures in cancer. The challenge in Africa is multifaceted and complex. Most measures rely on functionally accessible primary health-care services to provide support for vaccination programmes and diagnostic screening. It is beyond the scope of this article to cover all activities in preventative medicine, but some examples are given below.

One of the many successes in Africa is the widespread awareness of the need for immunisation in West and North Africa against hepatitis B. This endeavour reduces the development of hepatocellular carcinoma which in most instances is an untreatable, fatal disease. In addition, The Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) project looks to improve point-of-care diagnostic tests to identify chronic hepatitis B-carriers and proactively provide antiviral therapy to reduce the incidence of the disease.[17]

The large positive clinical trials in the HPV-vaccination of girls and young women now present the opportunity of primarily preventing cervical cancer, but also of potentially preventing vulval carcinoma, anal carcinoma and oropharyngeal carcinoma, to mention a few.[18] Numerous successful roll-out programmes have started in many countries, with the assistance of funding from the Vaccine Alliance (GAVI). The challenges of vaccination uptake are many, particularly with regard to parents of young girls. Community

educational drives have greatly assisted with acceptance. The practical difficulties of the absence of integrated school vaccination programmes, the obtaining of parental consent and lack of immediate benefit have hampered roll-out programmes across the continent in both low- and middle-income countries.

The reduction of tobacco consumption is without a doubt the most urgent public health intervention needed on the continent. A study in Uganda demonstrated that the direct and indirect costs of tobacco-related health issues translate to 2.3% of the total national expenditure on health.[19] These data are translatable to most countries on the continent. Taxes and revenues are usually not diverted to health care to offset these costs, and will not cover the full cost of the adverse effects. What is important to resolve is the conflict of interest between government and the tobacco industry and the urgency for intervention from the WHO and global health leaders to reduce consumption and access.[20]

Secondary preventative measures, including mammography screening, cervical smears, HPV-testing and PSA-testing, are all well established in terms of detecting early disease or precursors of disease, but lack of infrastructure and financial backing in struggling health-care systems limit their use in Africa. Innovation with cheap on-site HPV testing and encouraging a culture of breast self-examination are some methods that have been successfully adopted in Africa. In better resourced countries such as South Africa, a variety of screening procedures are provided without co-payment to those who have health insurance. In the public sector, a pap smear at ages 30, 40 and 50 years is freely available at local district clinics, but access to routine PSA-screening and mammography is limited by logistical difficulties and infrastructure availability.

CONCLUSION

With cancer cases projected to increase twofold in the coming decades, it is imperative that there is a focus on prevention and health education to ensure that vaccination is available, early detection is possible and people have access to quality oncological care.

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Treatment Options in Oncology

Chemotherapy: Target Therapy and Immunotherapy

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Chemotherapy is a form of treatment that uses pharmacological agents to stop the growth of cancer cells, either by cell-killing or by stopping them from dividing. Chemotherapy may be administered orally, by injection, infusion, or subcutaneously, depending on the type or stage of the cancer being treated. Chemotherapy may be given alone or in conjunction with other treatment modalities, such as surgery, radiation therapy, or biological therapy.[1]

PRINCIPLES OF CANCER CHEMOTHERAPY

Chemotherapy in the treatment of neoplastic diseases is currently used in three clinical settings:

1. PRIMARY TREATMENT FOR METASTATIC DISEASE

Chemotherapy and other systemic treatments have been the primary approach to treat advanced and metastatic malignant diseases for which there are no other active anticancer treatments. In the majority of patients, the treatment goals are to palliate cancer-related symptoms, improve the overall quality of life, prolong time to disease progression and survival.[2,3] Cancer chemotherapy can be curative in a relatively small subset of patients who present with advanced disease. These curative malignancies are summarised in Table 1.

2. NEOADJUVANT CHEMOTHERAPY TREATMENT

Neoadjuvant chemotherapy is a form of treatment that is administered as a first step to shrink a tumour before the primary therapy, which is usually surgery, is given. This treatment modality is used for patients who present with localised or loco-regional disease.[4] The cancers treated with neoadjuvant chemotherapy are summarised in Table 2.

In certain cancers such as anal cancer, gastro-oesophageal cancer, laryngeal cancer, head and neck malignancy and non-small-cell lung cancer (NSCLC), clinical benefit from chemotherapy is seen when the treatment is administered with radiation therapy either concurrently or sequentially.[5-8]

Table 1. Curative cancers

Adult cancer
Hodgkin's and non-Hodgkin's lymphoma
Germ-cell cancer
Acute leukaemias (acute myeloid leukaemia)
Choriocarcinoma
Childhood cancer
Acute lymphoblastic leukaemia
Burkitt's lymphoma
Wilms' tumour
Embryonal rhabdomyosarcoma

Table 2. Cancers treated with neoadjuvant chemotherapy

Anal cancer
Bladder cancer
Breast cancer
Oesophageal cancer
Laryngeal cancer
Non-small-cell lung cancer (locally advanced disease)
Osteogenic sarcoma

3. ADJUVANT CHEMOTHERAPY TREATMENT

Adjuvant chemotherapy refers to additional treatment given following the primary treatment with the aim to lower the risk of cancer recurrence. Adjuvant anticancer therapy is not restricted to chemotherapy and may include other modalities, including radiation therapy, hormone therapy, targeted therapy, or biological therapy.[1,2]

Malignant tumour recurrence, either locally, regionally or systemically, following surgery or radiation is primarily due to occult micro-metastases spread. The purpose of adjuvant therapy is, therefore, to decrease the incidence of both local and systemic recurrence and to improve the overall survival of cancer patients. It has been shown that chemotherapy treatments with clinical activity in the advanced disease setting may have curative potential following resection of the primary tumour. It has been demonstrated that adjuvant chemotherapy is effective in extending both disease-free survival (DFS) and overall survival (OS) in patients with malignant diseases such as breast cancer, colorectal cancer (CRC), Wilms' tumour, NSCLC, anaplastic astrocytomas and gastric cancer.[1,9-13] The benefit of adjuvant treatment is not limited to chemotherapy agents. Patients with high-risk malignant melanoma have improvement in DFS and OS from adjuvant immunotherapy treatment with alpha-interferon (biologic agent), nivolumab (anti-PD1 immunotherapy) or ipilimumab (anti-CTLA4 immunotherapy).[14-15] The antihormonal agents tamoxifen (anti-oestrogen), anastrozole and letrozole (both aromatase inhibitors) are active agents in the adjuvant therapy of postmenopausal women with hormone receptor-positive breast tumours cancer. Anti-hormone treatment is usually administered for five to 10 years.[16,17] Recent clinical trials have shown that adjuvant imatinib therapy (a targeted therapy against C-Kit/CD117) given to patients with surgically resected gastro-intestinal stromal tumours (GIST) is more effective when given for three years as opposed to one year.[18] Cancers with proven benefit to adjuvant treatment are summarised in Table 3.

Table 3. Cancers treated with adjuvant chemotherapy and other systemic treatments

Chemotherapy
Breast cancer
Colorectal cancer
Gastric cancer
Non-small-cell lung cancer (NSCLC)
Wilms' tumour
Osteogenic sarcoma
Anaplastic astrocytomas
Biological agents
Malignant melanoma: alpha-interferon,
Malignant melanoma: nivolumab (anti-PD1), ipilimumab (anti-CTLA-4)
Breast cancer: transtuzumab (anti-HER2)
Antihormones
Breast cancer (hormone receptor positive)
Tamoxifen (anti-oestrogen)
Anastrozole and letrozole (aromatase inhibitors)
Targeted therapy
GIST: Gastro-intestinal stromal tumour
Imatinib therapy (a targeted therapy against C-Kit/CD117)

COMBINATION CHEMOTHERAPY

Historically, combination chemotherapy started when several active drugs from different classes were used in the treatment of the acute leukaemias and lymphomas. Following the initial success with hematologic malignancies, combination chemotherapy was extended to the treatment of solid tumours.

When several agents of a class are available and are equally effective, a drug should be chosen by a principle of non-overlapping toxicities. This methodology

results in maximisation of the combination chemotherapy dose intensity.

DURATION OF CHEMOTHERAPY TREATMENT

Numerous randomised trials for the adjuvant treatment of breast and colorectal cancer have confirmed that six months is as effective as 12 months of chemotherapy treatment. Ongoing studies are going to determine whether three months of adjuvant chemotherapy will yield the same level of clinical benefit as six months of treatment of early-stage colon cancer.[19]

The potential risk of cumulative adverse effects, such as anthracycline-related cardiotoxicity and taxane and/or platinum neurotoxicity must always be factored into the decision-making process. Additionally, there is no evidence that chemotherapy treatment is of clinical benefit in continuing therapy until disease progression. A randomised clinical study in patients with metastatic CRC comparing continuous and intermittent palliative chemotherapy determined that a policy of drug holiday and re-challenging with the same agents provides a reasonable treatment choice for these patients. Similar observations have been reported in the treatment of metastatic disease of other tumour types, including NSCLC, breast cancer, germ-cell cancer, ovarian cancer, and small-cell lung cancer. The two main problems associated with systemic cancer chemotherapy are the toxicity to the healthy body tissues and the development of cellular drug resistance.

ADVERSE EFFECTS OF CHEMOTHERAPY TREATMENT

The most common side effects of chemotherapy are summarised in Table 4.

Table 4. Common side effects of chemotherapy

Fatigue
Hair loss
Thrombocytopaenia (easy bruising and bleeding)
Neutropaenia and infection
Anaemia (low red-blood-cell counts)
Septicaemia
Chemotherapy-induced nausea and vomiting (CINV)
Appetite changes
Constipation
Diarrhoea
Mucositis
Neuropathy
Skin and nail changes
Urine and bladder changes and kidney problems
Weight changes
Chemo brain (can affect concentration and focus)
Mood changes
Changes in libido and sexual function
Fertility problems

IMMUNOSUPPRESSION AND MYELOSUPPRESSION

Chemotherapy agents have a broad spectrum of side effects that depend on the type of drug, route of administration, and combination used. In general chemotherapy drugs affect rapidly-dividing cells, such as blood cells and the cells of the mucous membranes. Chemotherapy-related toxicities can occur acutely after administration, within hours or days, or chronically, from weeks to years.

Virtually all chemotherapeutic regimens can cause depression of the immune system, myelosuppression leading to leukopaenia, neutropaenia, anaemia, and thrombocytopaenia. Anaemia and thrombocytopaenia, when they occur, are treated with blood transfusion. Neutropaenia (a decrease in the neutrophil granulocyte count below 0.5 x 10^9/litre) can be improved with G-CSF (granulocyte-colony-stimulating factor, e.g., filgrastim, pegfilgrastim). Immunosuppression and myelosuppression may result in dose reductions and dose delays. These dose reductions and delays may compromise cancer-treatment outcome.[20-22]

ANAEMIA AND THROMBOCYTOPAENIA

A combination of factors may contribute to anaemia in cancer patients. These factors include myelosuppressive chemotherapy, and possible cancer-related causes such as haemolysis, bleeding, renal dysfunction, iron deficiency or anaemia of chronic disease. Treatments to mitigate anaemia include iron supplements, blood transfusions, erythropoietin.[23]

Chemotherapy can cause thrombocytopaenia, which can lead to easy bruising and bleeding. Extremely low platelet counts may require platelet transfusions.[24] Chemotherapy treatments may be delayed to allow platelet counts to recover.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Chemotherapy-induced nausea and vomiting (CINV) are the most feared anti-cancer treatment-related side effects. CINV is common with many treatments, including platinum-based regimens (both cisplatin and carboplatin). An additional group at risk is young women with breast cancer receiving combination chemotherapy with doxorubicin- and cyclophosphamide (AC)-based treatment. Several novel classes of antiemetics have been developed, helping to manage these symptoms successfully in a significant portion of patients. Traditional regimens to prevent CINV involved a combination of a corticosteroid plus a 5-hydroxytryptamine receptor antagonist (5HT3-RA) and a neurokinin-1 receptor antagonist (NK1-RA). These agents include ondansetron and granisetron (5HT3-RA) and aprepitant and fosaprepitant (NK1-RA). Successful treatment of these unpleasant and sometimes crippling symptoms results in a significant increase in quality of life and more efficient treatment cycles. Dehydration may occur when patients do not eat or drink enough, due to poor CINV control and gastro-intestinal damage. Poor CINV control may compromise overall anticancer treatment outcome.[25-30]

GASTRO-INTESTINAL SIDE EFFECTS

Mucositis, diarrhoea, abdominal cramps, and constipation are common side effects of chemotherapeutic treatments that kill rapidly-dividing cells.[31]

FATIGUE

Fatigue may be related to cancer or anticancer treatment. Fatigue may last for months following treatment. Anaemia is a cause of fatigue which is usually multifactorial and can be caused by chemotherapy, surgery, radiotherapy, primary, metastatic disease or nutritional depletion. [23-32]

ALOPECIA

Alopecia can be caused by chemotherapy agents that kill hair follicles and can be complete or partial. These are most often temporary side effects: Hair usually starts to regrow during or a few weeks after treatment completion. It can be associated with change of colour, texture, thickness, and style. Severe alopecia occurs most frequently with drugs such as doxorubicin, daunorubicin, paclitaxel, docetaxel, cyclophosphamide, ifosfamide or etoposide. Permanent alopecia can occur, but is not common. Chemotherapy induces alopecia in women more often than men.[33]

SECONDARY NEOPLASM

Development of secondary neoplasia following completion of chemotherapy or radiotherapy treatment can occur. Secondary acute myeloid leukaemia is the most common secondary neoplasm, which appears mainly after treatment with alkylating agents (cyclophosphamide and others) or topoisomerase inhibitors (etoposide).[34] It has been noted that long-term survivors of childhood malignancies have a 13 times higher risk of developing secondary neoplasms during the 30 years after treatment compared to the general population.[35]

INFERTILITY

Some chemotherapy agents are toxic to the gonads and may cause infertility.[36] Drugs with high risk include procarbazine and other alkylating agents, including cyclophosphamide, ifosfamide, busulfan, melphalan and chlorambucil.[37] Agents

with medium risk include doxorubicin and platinum compounds, including cisplatin and carboplatin.[37] Drugs with low risk of gonadal toxicity include vincristine, vinblastine, bleomycin, dactinomycin, and antimetabolites such as methotrexate, mercaptopurine, and 5-fluorouracil.[37, 38] Female infertility as a result of chemotherapy appears to be secondary to premature ovarian failure.[36]

TERATOGENICITY

Chemotherapy treatment is teratogenic during pregnancy, especially during the first trimester. During the second and third trimesters, chemotherapy exposure is not associated with an increase in teratogenic risk.[39]

PERIPHERAL NEUROPATHY

Peripheral neuropathy occurs in approximately 30 to 40 percent of patients treated with chemotherapy agents. Chemotherapy-induced peripheral neuropathy (CIPN), is a progressive, and often irreversible or partially reversible condition. Symptoms include pain, tingling, numbness, and cold sensitivity in the hands and feet.[40] Agents associated with CIPN include vinca alkaloids (vincristine), taxanes (paclitaxel and docetaxel), proteasome inhibitors (bortezomib), and the platinum-based drugs (cisplatin and oxaliplatin). Thalidomide is another anticancer agent used in the treatment of multiple myeloma causing peripheral neuropathy.[40, 41] The severity of CIPN is determined by the particular chemotherapy drug used, the duration of therapy and the total dose. Cisplatin and oxaliplatin neuropathy may deteriorate several months after the treatment completion.[40, 43, 44] Neuropathic pain can be managed pharmacologically. However, treatment of numbness is ineffective.[45]

TUMOR LYSIS SYNDROME

Tumor lysis syndrome is a condition associated with the breakdown of cancer cells that causes the release of chemicals from the intracellular compartment. It is particularly common with leukaemias and lymphomas. Tumour lysis syndrome is associated with high levels of serum uric acid, potassium and phosphate. High levels of phosphate cause secondary hypoparathyroidism, resulting in hypocalcaemia. Complications of tumour lysis syndrome include kidney damage, hyperkalaemia, and cardiac arrhythmias. Tumour lysis syndrome prophylaxis with high fluid intake, alkalisation of the urine, and prophylactic allopurinol is indicated in patients with a significant tumour-cell load, particularly with haematological malignancies. Tumour lysis syndrome is a severe fatal complication if left untreated.[46, 47]

CARDIOTOXICITY

Cardiotoxicity is typically prominent with the use of anthracycline drugs (doxorubicin, epirubicin, and idarubicin). This toxicity is cumulative. The cause of cardiotoxicity is due to the production of free radicals in the cell and subsequent DNA damage.[48-51]

HEPATOTOXICITY

Hepatotoxicity can be caused by commonly used chemotherapy drugs. Risk factors associated with liver damage include the primary malignant condition and metastatic liver disease, viral hepatitis, immunosuppression and nutritional deficiency. Chemotherapy drugs associated with liver toxicity include irinotecan and oxaliplatin. Hepatotoxicity includes damage to hepatocyte, hepatic sinusoidal syndrome, cholestasis and liver fibrosis.[52]

NEPHROTOXICITY

Nephrotoxicity can be caused by tumour lysis syndrome, pre-renal dehydration, direct effects of chemotherapy drug in the kidneys, tubular damage and obstructive uropathy. Cisplatin is particularly nephrotoxic and may induce acute renal failure.[53-55]

OTOTOXICITY

Ototoxicity to the inner ear is a common side effect of platinum-based agents. Ototoxicity symptoms include dizziness and vertigo.[55, 56]

OTHER SIDE EFFECTS

Less common side effects include skin erythema, dry skin, fingernail changes, xerostomia, water retention, and sexual dysfunction and impotence. Specific chemotherapeutic agents cause distinct toxicities, including cardiac toxicity (doxorubicin)[48] and interstitial lung disease (bleomycin).[57]

TARGETED THERAPIES AND IMMUNOTHERAPY

Targeted therapy should be distinguished from chemotherapy. Targeted therapies are a relatively new class of anticancer agents that can overcome many of the effects seen with cytotoxic treatments. Targeted therapies can be classified into two groups: small molecule and antibodies. The toxicity associated with the usage of cytotoxics is primarily due to the lack of cell specificity. Cytotoxic drugs kill any rapidly dividing cells, including tumour or normal cells. Targeted therapies are designed to affect specific cellular proteins, pathways, or processes that are utilised primarily by malignant cells. Although the toxic effects are often less severe than those seen with cytotoxic chemotherapeutics, severe side effects may occur. Initially, the targeted therapies were supposed to be selective for one specific protein. However, there is usually a range of protein targets to which a targeted drug can bind. Some targeted therapies can bind to more than one target (e.g., sorafenib or sunitinib).[58-60] An example target for targeted therapy is the protein produced by the Philadelphia chromosome, a genetic lesion found commonly in chronic myeloid leukaemia. This fusion protein (BCR-ABL protein) can be inhibited by imatinib; a small molecule targeted therapy.[61]

IMMUNOTHERAPY

The human body's immune system can detect foreign bodies, infections and cancer cells and produces antibodies. Antibodies are proteins that fight micro-organisms and cancer. Monoclonal antibodies are a specific type of treatment made in a laboratory. Monoclonal antibodies may be utilised in various forms. As discussed, monoclonal antibodies can be employed as a targeted therapy to block an abnormal protein in a malignant cell. Monoclonal antibodies can also be utilised as immunotherapy. Some monoclonal antibodies, when attached to specific proteins on cancer cells, flag the malignant cells and the immune system can detect and kill those cells.

Other types of monoclonal antibodies work by releasing the brakes on the immune system so it can destroy cancer cells. The PD-1/PD-L1 and CTLA-4 pathways are crucial to the immune system's capacity to control cancer growth. These pathways are often referred to as "immune checkpoints." Many cancers overexpress these pathways to evade the immune system and immune surveillance. Monoclonal antibodies can block immune checkpoint pathways overexpressed in tumours. The following monoclonal antibodies are immune checkpoint inhibitors: ipilimumab (anti-CTLA-4), nivolumab and pembrolizumab (anti-PD1).[62, 63] Checkpoint inhibitor toxicities, referred to as immune-related adverse events, include skin adverse events, gastro-intestinal toxicities (colitis), oral complications, pulmonary toxicities, and endocrinological complications (thyroiditis and hypophysitis).[64, 65]

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Radiation-Therapy Overview

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Global cancer burden is growing and in 2030 alone, about 21.6 million new cancer cases and 13 million cancer deaths are expected to occur, simply due to the growth and ageing of the population. The future burden may be further increased by the adoption of unhealthy behaviours and lifestyle associated with rapid income growth (e.g., smoking, poor diet and physical inactivity) and changes in reproductive patterns (e.g., fewer children, later age of first child birth) in low- and middle-income countries (LMICs). Tobacco use is responsible for almost six million deaths annually, 80% of which are in LMICs; by 2030, this number will reach eight million. By 2030, tobacco-attributable deaths will double in LMIC from 3.4 million to 6.8 million.[1]

Overall, 645 071 new cancer cases and 455 695 cancer deaths were estimated to have occurred in Africa in 2012. Breast cancer was the second most commonly diagnosed cancer and the fifth leading cause of cancer deaths among women in Africa in 2012 (100 000 cases, 49 000 deaths). The incidence of breast cancer among southern African women is among the first five breast cancers of all African regions. Cervical cancer is the fourth most frequently diagnosed cancer (92 000 cases) and the leading cause of cancer deaths (57 000) in African women.[2]

According to the South African Cancer Registry data for the year 2013, prostate cancer accounted for 18.86 % of all male cancers, with the age-standardised rate (ASR) of 44.30/100 000 of the population. Prostate cancers formed 60.4% of the cancers affecting male patients over 65 years of age. Breast cancer was the leading cancer among females (22%), followed by cervical cancer in 15.58% of patients. Breast cancer comprised 32.5% of female cancers in individuals over 65 years of age.[3]

Currently, the top five cancers in South Africa in males are prostate, colorectal, lung, Kaposi sarcoma and bladder. The top five female cancers are breast, cervix, colorectal, uterus and lung. The life-time risk for cancer for South African men is 1:6 and for women it is 1:9.

CANCER DIAGNOSIS

The seven warning signals for cancer include:

1. A change in bowel or bladder habits
2. A sore that does not heal
3. Unusual bleeding or discharge
4. Thickening or a lump in the breast or elsewhere
5. Indigestion or difficulty in swallowing
6. Obvious change in a wart or mole
7. Nagging cough or hoarseness

To make a diagnosis, it is important to have a good history, general physical examination, blood tests, and radiological investigations – x-ray of the specific area, chest x-ray, CT scan, MRI, PET scan and biopsy.

To reduce the risk of cancer, the following behavioural patterns should be followed:

- Do not use tobacco
- Eat a healthy diet[3]
- Maintain a healthy weight and be physically active
- Protect yourself from the sun
- Get immunised
- Avoid risky behaviours
- Regular medical care

RADIATION-THERAPY TREATMENT

When used for the treatment of cancer, ionising radiations such as x-rays or gamma rays work by damaging the DNA of exposed tissue, leading to cellular death. The main aim is to deliver the maximum

dose to the tumour, while preventing the surrounding critical structures from receiving doses above specified dose tolerances. Besides the tumour itself, the radiation fields may also include the draining of lymph nodes if they are clinically or radiologically involved with the tumour or if there is a risk of subclinical malignant spread. It is necessary to include a margin of normal tissue around the tumour to allow for uncertainties in daily set-up (such as movement of external skin marks relative to the tumour position) and internal tumour motion (for example, respiration and bladder-filling). Various techniques have been employed to help ensure the accurate placement of a treatment field. These include ink marks on the skin, tattoo, portal imaging for verification, and electronic portal imaging – the process of creating a digital image with improved quality and contrast over traditional portal imaging. An extra benefit of the system is the ability to capture images digitally for review and guidance.

Various steps in treatment planning are shown in Figure 1.

TYPES OF RADIATION THERAPY

- External beam radiation therapy (EBRT or XRT) or teletherapy
- Brachytherapy or sealed-source radiation therapy
- Systemic radio-isotope therapy or unsealed source radiation therapy

The uncertainties relate to the position of the radiation source: outside the body, sealed radio-active sources placed precisely in the area under treatment, or administered by infusion or oral ingestion (see Figure 2). It is common to combine radiation

Figure 1. Radiation-treatment planning of a patient

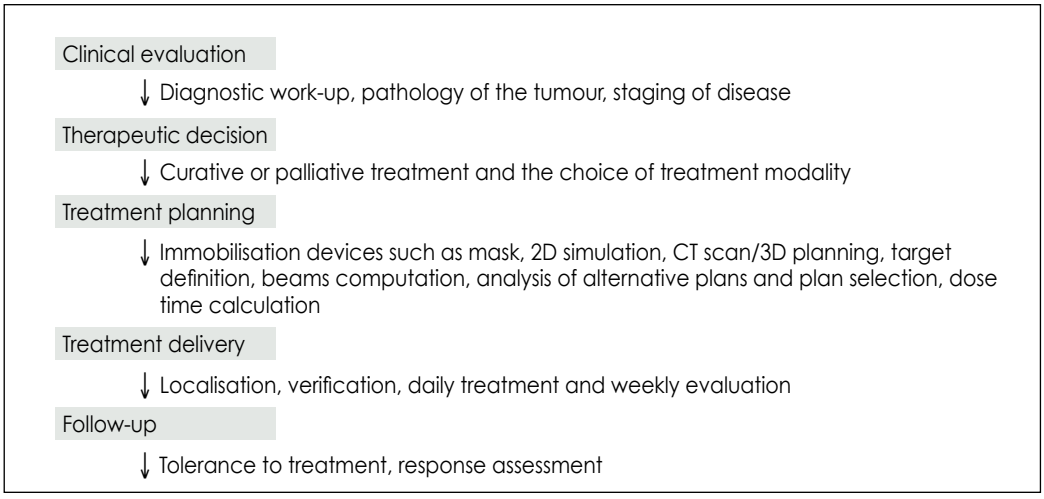
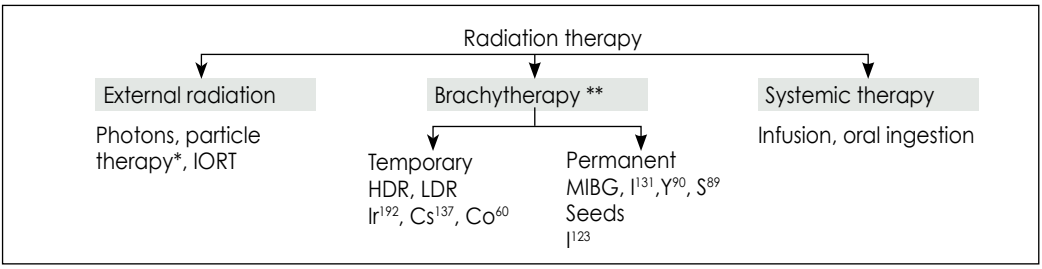


Figure 2. Radiation therapy



* Protons or carbon ions
** Interstitial, intra-cavitary, intra-luminal, surface mould

therapy with surgery, chemotherapy, hormone therapy and immunotherapy or a combination of more than one.

The purpose of radiation therapy is both curative and palliative. The precise treatment intent (curative, adjuvant, neoadjuvant, or palliative) will depend on the tumour type, location, size and stage, as well as the general condition of the patient. Concomitant chemo-radiation improves the effect of radiation by up to 20% and is used as a radiosensitiser. Radiation therapy can also be used in non-malignant conditions such as trigeminal neuralgia, acoustic neuromas, severe thyroid eye disease, pterygium, prevention of keloid scar growth, vascular restenosis and heterotopic ossification.

Brachytherapy, in which the radiation source is placed inside or next to the area requiring treatment, minimises exposure to healthy tissue during treatment of cancers of the cervix, breast, prostate, skin and other organs.

Systemic radio-isotope therapy is the form of targeted therapy in which the chemical properties of the isotope – for example, radio-iodine – are specifically absorbed by the thyroid gland and/or attached to another molecule or antibody to guide it to the target tissue. The radio-isotopes are delivered through infusion (e.g., metaiodobenzylguanidine [MIBG] to treat neuroblastoma) or ingestion (e.g., oral iodine-131 to treat thyroid cancer or thyrotoxicosis, and yttrium-90 to treat neuro-endocrine tumours).

Radiosensitivity determines the response of a cancer to radiation. Highly radiosensitive cancer cells are rapidly killed by modest doses of radiation and include leukaemias, most lymphomas and germ-cell tumours (20-40Gy). The majority of epithelial cancers are only moderately radiosensitive, and require a significantly higher dose of radiation (60-70Gy) to achieve a radical cure (see Table 1). Some types of cancer are notably radio-resistant, and need much higher doses to produce a radical cure than may be safe in clinical practice for cancers such as renal-cell cancer and melanoma. Metastatic cancers are generally incurable with radiation therapy because it is not possible to treat the whole body.

SIDE EFFECTS OF RADIATION THERAPY

The radiation therapy is local treatment and the treatment-related side effects can be acute, defined as happening within 90 days from start of treatment and late after 90 days. These can be general as well as specific to the area of treatment. Side effects occur because radiation therapy can also damage healthy cells and tissues near the treatment area. Major advances in radiation technology now have made it more precise, leading to fewer side effects. They also depend on the site of treatment, radiation-therapy dose, dose per fraction, treatment volume, whether radiation is given alone or in combination with chemotherapy.

Table 1. Cancers curable by radiation

Cancers curable at early stages with radiotherapy alone	Cancers curable with regimens including radiation therapy
■ Prostate carcinoma ■ Head and neck carcinoma ■ Non-small-cell lung carcinomas ■ Squamous- and basal-cell skin cancers ■ Hodgkin's lymphomas ■ Uterine cervix carcinomas	■ Breast carcinomas ■ Locally advanced lung carcinomas ■ Seminoma ■ Endometrial carcinomas ■ CNS tumours, e.g., ependymoma, glioma ■ Soft-tissue sarcomas ■ Rectal and anal carcinomas ■ Lymphomas ■ Advanced head and neck carcinomas ■ Paediatric malignancies, e.g., Wilms' tumour, medulloblastoma

Reactions often start during the second or third week of treatment. They may last for several weeks after the final treatment. Preventing and treating side effects is an important part of cancer treatment. The common general side effects include skin problems, such as dryness, itching, blistering, or peeling. But these side effects often depend on which part of the body received radiation therapy. Patients can also experience fatigue, feeling tired or exhausted almost all the time, and the level of fatigue depends on whether they are having other treatments, such as chemotherapy. Table 2 outlines site-specific side effects.

Coping with side effects: Everyone's experience with cancer treatment is different. There are many options for managing side effects. The patient and general physician should consult with the treating specialist for advice regarding prevention before treatment and how to reduce side effects during treatment and the follow-up period.

DEVELOPMENTS IN RADIATION ONCOLOGY

Considerable developments have occurred over the last decade in all the areas of radiation oncology treatment. The clinical evaluation has been enhanced by improvements in diagnosis with the incorporation of computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET)/CT scans for accurate definition of local, locoregional and metastatic disease.

Information on molecular biomarkers is helping to predict tumour response to a particular treatment. Potential targets for therapy are being identified by using information on genes, proteins and various metabolites.[4] The tumours are being classified based on DNA and RNA with the use of micro-arrays. Personalised treatment is possible – for example, epidermal growth factor receptors (EGFR) are over-expressed in 80% of patients with bronchoalveolar histology and are predominant in women and non-smokers. These tumours are sensitive to erlotinib. Similarly, radiation-induced signalling of EGFR has a pro-survival effect and this can be applied for management. The non-squamous histology has over-expression of vascular endothelial growth factor (VEGF) and denotes poor prognosis. These tumours are sensitive to bevacizumab.

Table 2. Radiation-therapy side effects

Treatment site	Early (up to 90 days from start of treatment)	Late (>90 days from start of treatment)
Head and neck	Dry mouth, mouth and gum sores, painful swallowing and difficulty in swallowing, stiffness of jaw, nausea	Tooth decay, lymphoedema, soft tissue fibrosis in neck
Chest	Difficulty in swallowing, shortness of breath, cough, fever	Oesophageal stricture, ulceration and tracheal oesophageal fistula, radiation lung fibrosis
Abdomen	Nausea, vomiting, abdominal cramps, diarrhoea	Stricture, decreased capacity of stomach
Pelvis	Diarrhoea, bladder irritation, increased urinary frequency, rectal bleeding	Rectal proctitis, rectal strictures, decreased urinary bladder capacity, haematuria
Others	Skin reaction – dry desquamation, moist desquamation. Sexual problems in males – erectile dysfunction, low sperm count and females – vaginal itching, burning, dryness and infertility	Skin fibrosis, vaginal stenosis

With the development of therapeutic agents that interfere with major oncogenes such as KRAS and MYC, treatment will be improved. It is hoped that, with the development of multi-agent protocols, resistance to treatments can be overcome and cancers can be controlled.

Although DNA damage is generally regarded as the primary event for radiation-induced cell lethality, different mechanisms are being studied, such as host-derived blood vessels as a target for radiotherapy in terms of tumour control and complications in normal tissues.[5] The five major biological concepts (intrinsic cellular radiosensitivity; acute/chronic hypoxia and re-oxygenation; differential DNA damage-repair processing; cell-cycle redistribution; and tumour-cell repopulation) are being interpolated for maximising the therapeutic index for particular tumours in particular patients.[4]

Different fractionation schemes such as hyper-fractionation, accelerated fractionation and hypo-fractionation are being employed in addition to conventional fractionation using external-beam radiation. In hyper-fractionation, the low dose per fraction has a sparing effect on late-responding tissues, whereas accelerated fractionation reduces the effect due to accelerated repopulation in the later stages of radiation therapy. With the understanding of radiobiological mechanisms induced by hypo-fractionation, such as abscopal/bystander effect, activation of immune system, endothelial-cell death, no effect of hypoxia in the tumour and differential effect on cancer stem cells,[9] it can be used more judiciously. Improvement in and determination of therapeutic index is complicated by the spatial and temporal interactions of radiation therapy with surgery, conventional chemotherapy, and newer biologics/small molecules.[4]

The supercomputers and imaging modalities, such as CT, MRI, and PET/CT, have become integrated with treatment planning and delivery to undergo transition from two-dimensional (2D) to 3D to 4D treatments.[4] PET-based plans have led to a significant reduction in the volume of high doses, thus limiting the dose delivered to the surrounding normal tissues. The major benefit has been improved definition of the longitudinal extent of the tumour, particularly in the region of gastro-oesophageal junction in cancer of the oesophagus. In the head and neck, target volume was modified in 20% of cases and tumour volumes from PET were 25% greater than CT images.

PET/CT reduces the gross tumour volume (GTV) by down-staging the mediastinal lymph nodes to smaller GTV. This also helps in discriminating tumour tissue from atelectasis or necrosis (22-62%); lowering dose to oesophagus and lung. The treatment strategy was modified in 37% of patients with FDG PET, preventing surgery in 20%.[7]

Virtual simulation, the most basic form of planning, allows more accurate placement of radiation beams than is possible using conventional x-rays, where soft-tissue structures are often difficult to assess and normal tissues are difficult to protect. An enhancement of virtual simulation is three-dimensional conformal radiation therapy (3DCRT), in which the profile of each radiation beam is shaped to fit the profile of the target from a beam's eye view (BEV), using a multileaf collimator (MLC) and a variable number of beams. When the treatment volume conforms to the shape of the tumour, the relative toxicity of radiation to the surrounding normal tissues is reduced, allowing a higher dose of radiation to be delivered to the tumour than in conventional techniques.[8]

Intensity-modulated radiation therapy (IMRT) is an advanced type of high-precision radiation that is the next generation of 3DCRT. IMRT also improves the ability to conform the treatment volume to concave tumour shapes – for example, when the tumour is wrapped around a vulnerable structure, such as the spinal cord or a major organ or blood vessel.[9] The pattern of radiation delivery is determined using highly tailored computing applications to perform optimisation and treatment simulation. The radiation dose is consistent with the 3D shape of the tumour by controlling, or modulating, the radiation beam's

intensity. The radiation-dose intensity is elevated near the GTV, while radiation among the neighbouring normal tissue is decreased or avoided completely. The customised radiation dose is intended to maximise tumour dose, while simultaneously protecting the surrounding normal tissue. This may result in better tumour targeting, reduced side effects, and better treatment outcomes than even 3DCRT. Although 3DCRT is still used extensively for many body sites, the use of IMRT is increasing in more complicated body sites, such as CNS, head and neck, prostate, breast and lung.

Unfortunately, IMRT is limited by its need for additional time from experienced medical personnel. Physicians must manually delineate the tumours one CT image at a time through the entire disease site, which can take much longer than 3DCRT preparation. Then, medical physicists and dosimetrists must create a viable treatment plan. Proof of improved survival benefit from either of these two techniques over conventional radiation therapy (2DXRT) is growing for many tumour sites. The ability to reduce toxicity is generally accepted. Both techniques enable dose escalation, potentially increasing usefulness.

The change in tumour and normal tissue biology during treatment requires adaptive radiotherapy to truly impact on the therapeutic index, and its implementation involves the newer functional imaging (MRI, magnetic resonance spectroscopy [MRS], PET) to monitor spatial variation in tumour-radiation response and normal tissue function during the course of treatment.

Following the advances over the last decade in intensity-modulated radiotherapy (IMRT), namely stereotactic radiosurgery (SRS)/radiotherapy, stereotactic body radiotherapy (SBRT), and image-guided radiation therapy, it has become critical to position patients precisely and reproducibly in the treatment positions.[10] Stereotactic radiation is a specialised type of external-beam radiation therapy and uses focused radiation beams targeting a well-defined tumour, using extremely detailed imaging scans. Radiation oncologists perform stereotactic treatments for tumours in the brain or spine, often with the help of a neurosurgeon for stereotactic radiosurgery (SRS) for a single radiation treatment of the brain. Stereotactic body-radiation therapy (SBRT) refers to several stereotactic radiation treatments for parts of the body, such as the lungs, or for brain.

The advantage of stereotactic treatments is that they deliver the right amount of radiation to the cancer in a shorter time than conventional treatments which can often take six to 11 weeks. The treatments are given with extreme accuracy, which should limit the effect of the radiation on healthy tissues. These treatments are suitable for certain small tumours only.

Tumours located in the pelvis, abdomen and thorax are subject to motion during treatment caused by respiration, inherent bowel mobility and peristalsis, and cardiac motion. This motion is often accounted for by applying a margin to the target of interest to encompass the spatial variability of the target. The use of real-time tracking techniques allows for a reduction in this margin and thus reduces the morbidity associated with unnecessary dose to the surrounding normal tissues. Continuous localisation systems such as Calypso 4D localisation system for prostate[11] and head and neck cancers, radio-cameras for stereotactic radiation for benign and malignant tumours of the central nervous system, and Align RT (a 3D video-based image-guided RT system) for breast cancer have allowed for clinically-relevant reduction in margins. Use of real-time tracking techniques allows for reduced normal-tissue-dose volumes and dose escalation to the target volume, leading to improved tumour control.

Dunscombe[12] has presented a set of recommendations likely to enhance safety and quality in radiotherapy. These include the training of staff in specifically safety-related topics, an adequate number of staff, the proper documentation of standard operating procedures, the sharing of information on incidents (incident-learning), effective and open communication, the development and maintenance of

check-lists, quality control and preventive maintenance, a dosimetric audit, accreditation, the minimisation of interruptions, prospective risk assessment, and the changing of organisational culture.[13]

CONCLUSION

The major challenge in radiation therapy is to broaden the current cross-disciplinary team of radiation oncologists, medical physicists and radiation biologists to include engineers and mathematicians in a systems-science/biology approach. New technologies may reduce costs, as will the development of efficiencies (i.e., class solutions for planning, better plans that reduce treatment time and improve scheduling). Proton therapy with superior dose distribution has an advantage over photons, although the cost at 2.4 times that of IMRT is prohibitive. Expected improvements in target localisation with a higher dose to the target and normal-tissue-dose reduction will result in greater tumour control and a significant reduction in adverse post-treatment morbidity. Trends point to combined (RT+CT) modality treatment, extra-cranial stereotactic radiation, hypo-fractionation protocols and mid-therapy redesign of the radiation dose (adaptive radiation therapy). Use of functional imaging for target definition in addition to the consolidated quality assurance programme will play an important role in the future.

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Recent Advances in Targeted Radionuclide Therapy of Cancers: Moving towards Personalised Care

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Targeted cancer therapy relies on the identification of a biological target in the tumour and optimising it for therapeutic intervention. A candidate biological target should be expressed exclusively by the tumour or must have only low-level expression in non-malignant tissues. A pharmaceutical molecule is designed to target the tumour-expressed biological marker.

For targeted radionuclide therapy of cancers, a radionuclide, which emits a beta, or more recently, an alpha particle, is complexed to the pharmaceutical to form a therapeutic radiopharmaceutical. Beta and alpha particles are two energetic particles that are capable of causing DNA damage, leading to death of the tumour cells. Following *in vivo* administration, the radiopharmaceutical is distributed to the tumour and the radiation released by the radionuclide causes tumour-cell death. Theoretically, any tumour can be treated using targeted radionuclide technique once a suitable biological target that is over-expressed by that tumour is identified and a radiopharmaceutical target is designed for its *in vivo* targeting. Several radionuclide agents have been designed for treatment of different human cancers.

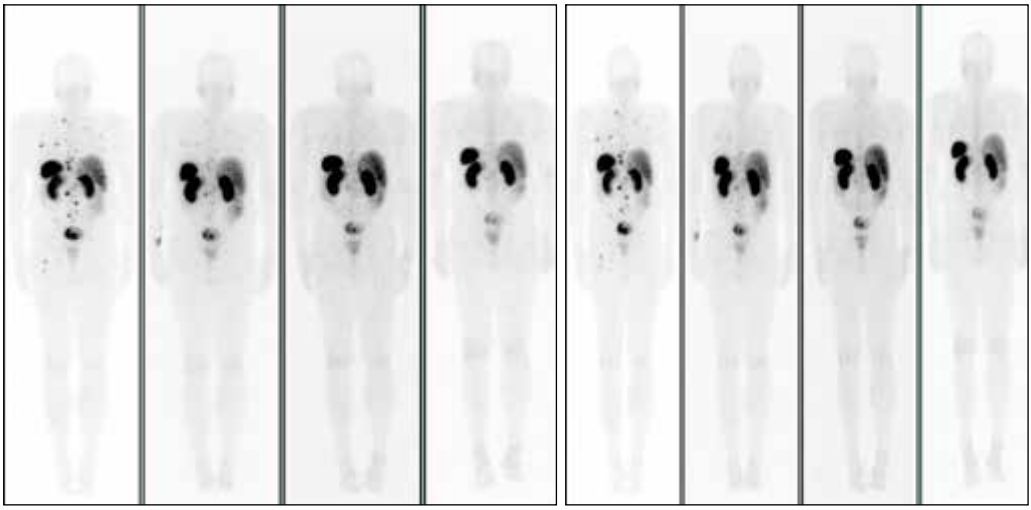
Theranostics is a concept closely related to targeted therapy. Theranostics is a compound word that integrates diagnostics and therapeutics in patient management. In theranostics, a radiopharmaceutical is used for the diagnostic imaging of a disease and a variation of the same molecule is used for the treatment of the disease.

Theranostics involves the following:
- Localisation of site disease and determining its extent (staging)
- Determination of expression of the biological target in the tumour. Only patients whose tumours overexpress the biological target will respond to targeted radionuclide therapy
- Examination of off-target distribution of the agent. This is the cause of side effects
- Determination of the amount of therapeutic radiopharmaceuticals required for treatment in a particular patient
- Monitoring response to treatment after targeted radionuclide therapy

Theranostics epitomises the concept of personalised care in cancer treatment. Only patients who will benefit from radionuclide therapy are treated. This ensures rational use of scarce resources and prevents adverse effects relating to the use of ineffective treatment in patients who may not benefit from it.

Targeted radionuclide therapy started more than 70 years ago with the use of radioactive iodine in the treatment of benign and malignant thyroid diseases.[1] Since then, many other radiopharmaceuticals have been developed and successfully used in the treatment of human cancers. This focus review will briefly elucidate the recent advances in targeted radionuclide therapy of cancers.

Figure 1.[68] Ga-DOTATATE PET/CT images of patient with multi-resistant neuro-endocrine tumour showing good response after fourth therapy with [177]Lu-DOTATATE. Left panel: before therapy; right panel: after the fourth therapy with [177]Lu-DOTATATE



PEPTIDE RECEPTOR RADIONUCLIDE THERAPY OF NEURO-ENDOCRINE TUMOURS

Neuro-endocrine tumours (NETs) are a heterogeneous group of tumours that over-express the somatostatin receptors (SSTs) on the tumour-cell membrane. They most commonly arise from the gastro-enteropancreatic tissues, but can be found in virtually any organ of the body. Liver is a common site of distant metastasis.[2] NETs may be functional or non-functional. Functional NETs produce biologically active substances such as serotonin (as in carcinoid), glucagon (as in glucagonoma) or insulin (as in insulinoma), and so on. Due to the biological effects of these secreted substances, functional NETs come to clinical attention early when the tumour is still very small and presents a diagnostic challenge with anatomic imaging. Non-functional NETs are diagnosed at a more advanced stage, often as a result of pressure symptoms from a large tumour bulk or its metastasis.

Surgical excision with curative intent is the preferred treatment option in localised NETs. Somatostatin analogues with octreotide or lanreotide are first-line agents in metastatic NETs. They provide symptomatic relief in patients with functional NETs and may halt progression of the disease. Chemotherapy offers little benefit in well-differentiated NETs as these tumours are slow-growing.

Peptide receptor radionuclide therapy (PRRNT) has evolved in recent years to be a highly effective therapy option in patients with well differentiated NETs. The SSTs over-expressed on well differentiated NETs are the molecular targets. Theranostic radiopharmaceuticals used consist of three parts; a somatostatin analogue, a radionuclide and a linker molecule connecting the two. For imaging, Gallium 68 (Ga-68) is the radionuclide used for positron emission tomography (PET) imaging, while DOTA is a common linker molecule. Ga-68 DOTATATE, Ga-68 DOTATOC and Ga-68 DOTANOC are the common radiopharmaceuticals for NETs PET imaging. For therapy, Ga-68 is substituted for a radionuclide that emits energetic ionising radiations, such as beta particles. Lutetium 177 (Lu-177) and Yttrium 90 (Y-90) are the two most commonly used beta particle-emitting radionuclides in PRRNT (see Figure 1).

PRRNT is indicated in patients with metastasised, progressive SST-expressing NETs, including gastro-enteropancreatic and bronchial NETs.

Other tumours overexpressing SSTs, such as paraganglioma/pheochromocytoma, neuroblastoma, and medullary thyroid carcinoma may be treated as well. The ideal patients are those with well differentiated tumours, Ki67 ≤20%.

Contra-indications to PRRNT include the following:

- Pregnancy
- Severe acute concomitant illnesses
- Severely compromised renal function, glomerular filtration rate less than 60% of age-adjusted normal values
- Severely compromised bone-marrow function; white blood cell (WBC) <3,000/µL, with absolute neutrophil count <1,000/µL, platelet count <75,000/µL, red cell count <3,000,000/µL

The following must be ensured before a patient is planned for PRRNT:

- Histologically proven NET, ideally with Ki67 ≤20% (WHO grade 1 or 2)
- High expression of SSTs type 2, as demonstrated on a Ga-68 DOTATATE PET/CT scan
- Karnofsky performance status above 60% (ECOG <2)
- Renal scintigraphy documenting good renal function and absence of urinary tract obstruction
- Absence of any contra-indication

PRRNT must be administered in a well-equipped specialised facility with well-trained staff. Therapy is co-administered with amino acid solution to prevent the renal side effects of treatment. Anti-emetics and corticosteroids are given to prevent the side effects associated with amino acid infusion.

The results of NETTER-1 trial; a multicentre, randomised, controlled trial of the efficacy and safety of Lu-177 DOTATATE in patients with advanced, progressive, SSTR-expressing midgut NETs, was recently reported. Patients were randomised to either receive four cycles of Lu-177 DOTATATE plus a monthly intramuscular injection of 30 mg octreotide (Lu-177 DOTATATE group, n = 111) or a monthly injection of 60 mg intramuscular injection of octreotide LAR alone (control group, n = 110). The primary endpoint was progression-free survival. Progression-free survival at 20 months was 65.2% [95% CI, 50.0-76.8] in the Lu-177 DOTATATE group *versus* 10.8% [95% CI, 3.5-23.0] in the control group. The median progression-free survival had not yet been reached in the Lu-177 DOTATATE group and was 8.4 months in the control group. There was 60% lower risk of death in the Lu-177 DOTATATE group than in the control. Eighteen patients in the Lu-177 DOTATATE group had either complete or partial response, compared with three in the control arm. Side effects requiring discontinuation of treatment occurred in 6% in the Lu-177 DOTATATE group, compared with 9% in the control. The commonest side effects in the Lu-177 DOTATATE group were nausea and vomiting related to amino acid infusion. Grade 3 and 4 side effects were similar in both groups. No renal toxicity was seen.[3] Response rate to Lu-177 DOTATATE demonstrated in this study was higher compared with response rates reported in other studies, with similar patients using other treatment options, including everolimus, alpha-interferon and lanreotide.[4-6]

In a report of the long-term toxicity of PRRNT in 807 patients with NETs, Bodei, *et al* reported grade 3/4 renal toxicity in 1.5% of patients, grade 3/4 bone-marrow toxicity in 9.5% of patients, myelodysplastic syndrome in 2.35% and eight patients with acute leukaemia, six of whom converted from myelodysplastic syndrome.[7]

PROSTATE-SPECIFIC MEMBRANE ANTIGEN RADIOLIGAND THERAPY (PRLT)

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein expressed on the cancer cells in metastatic prostate carcinoma. Its level of expression is even higher in metastatic castration-resistant prostate carcinoma (mCRPC). Several small-molecule ligands have been developed, targeting PSMA. Ga-68 PSMA is a diagnostic radionuclide available for PET imaging. PSMA can be

complexed to Lu-177 or an alpha-emitting radionuclide such as Actinium 225 (Ac-225) or Bismuth 213 (Bi-213) for radioligand therapy of mCRPC.[8]

PRLT may be considered in patients with mCRPC who have exhausted or do not tolerate approved therapies.

The following must be ensured before a patient is considered for PRLT.

- Ga-68 PSMA PET/CT showing tracer uptake within lesions
- Sufficient bone-marrow reserve, WBC >3,000/µl, platelets >75,000/µL
- Sufficient renal function reserve defined as serum creatinine <2 times the upper limit of normal
- Renal scintigraphy documenting good renal function and absence of urinary tract obstruction
- Discontinuation of other potentially myelosuppressive therapies for six weeks before commencement of PRLT.

The therapeutic agent in PRLT is administered intravenously with less stringent need for amino acid co-administration due to a lower risk of renal toxicity compared with PRRNT in NETs. Four to six cycles are administered at eight- to 12-week intervals. Concomitant use of androgen deprivation may upregulate the expression of PSMA glycoprotein, hence this therapy can be continued in patients being treated with PRLT.

The efficacy and safety profile of Lu-177 PSMA for PRLT in metastatic prostate cancer were demonstrated in a multicentre German study of 145 patients who had one to four cycles of Lu-177 PSMA. Grade 3/4 anaemia occurred in 15 patients, grade 3/4 thrombocytopaenia in five patients. No therapy-related death was seen. A low pre-therapy blood-cell count was predictive of haematotoxicity. Response was assessed, using a fall in PSA level. 45% of evaluable patients demonstrated a PSA decline of at least 50% – biochemical responders. A PSA decline of any number was seen in 60% of patients.[9] Patient-reported outcome has been evaluated for in multiple studies. PRLT with Lu-177 PSMA led to significant pain relief in 33-70% of mCRPC patients, improvement in quality of life in 60% and an improvement in performance status in 74% of patients.[10]

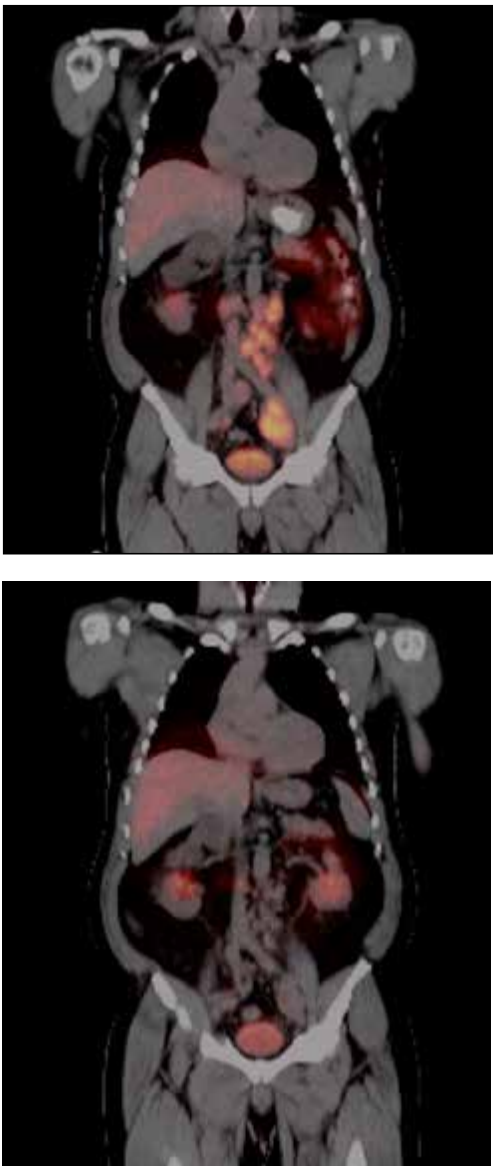
Xerostomia is a potential side effect due to high expression of the PSMA glycoprotein in the salivary glands. Xerostomia is commonly mild and reversible.

Due to the densely ionising ability of alpha particles and their potential to cause more lethal damage to the cancer cells (due to double-stranded DNA damage) than beta particles, interest is now focused on the use of alpha-emitting radionuclides complexed to PSMA ligand for PRLT of metastatic prostate carcinoma. The two most commonly used radionuclides are Bismuth 213 (Bi-213) and Actinium 225 (Ac-225) (see Figure 2). The longer half-life of Ac-225 of 10 days compared with 46 minutes of Bi-213 makes it a more effective therapeutic radionuclide. Alpha particles are heavy and only travel a short distance in the tissue. This accounts for the lower side effects associated with their use. Ac-225 PSMA is now being used in patients whose disease is refractory to Lu-177 PSMA therapy.[11] Several prospective trials are ongoing, evaluating the dosimetry, safety and efficacy of Lu-177 or Ac-255 labelled PSMA for radioligand therapy of mCRPC.[10]

RADIONUCLIDE THERAPY OF BONE METASTASES

Bone is a common site of metastases in several tumours. Presence of skeletal metastases is associated with the occurrence of skeletal-related events (SREs), morbidity, drastic reduction in the quality of life and death. Bone metastases are therefore deserving of prompt institution of effective therapy aimed at alleviating pain and preventing the occurrence of complications. For decades, radionuclides such as Phosphorus-32, Strontium-89, and more recently Samarium-153 EDTMP, Rhenium-186 HEDP and Rhenium 188 HEDP have been successfully used in the targeted therapy of bone metastases, with effective pain control and tolerable side effects. The use of these beta-emitting radionuclides alone, while very effective in pain control, does not confer survival benefit.

Figure 2. Excellent response to therapy after two cycles of ^{225}Ac-PSMA-617. This impressive response in a patient with metastatic castration-resistant prostate cancer was demonstrated by ^{68}Ga-PSMA-11 PET/CT images of before (top panel) and after (bottom panel)



Radium-223 dichloride, an alpha-emitting calcium-mimetic radionuclide, is the first radionuclide for bone metastases therapy with a survival benefit when used in the treatment of bone metastases.

Ra-223 dichloride adsorbs to the hydroxyapatite crystals of the bone matrix. It is concentrated more at sites of increased bone turnover – a feature characteristic of osteoblastic skeletal metastases. It therefore concentrates more at sites of osteoblastic skeletal metastases than normal bone. The emitted alpha particle causes double-stranded DNA damage within a radius of <0.1 mm (*versus* several mm for beta particles), hence has only minimal haematotoxicity.

Radium-223 is indicated in metastatic prostate-cancer patients with symptomatic bone metastases and no known visceral metastases.

The following constitute relative contraindications to the use of Ra-223 for bone-pain therapy:

- Karnofsky score <50% or ECOG performance status >2
- Limited bone-marrow reserve – absolute neutrophil count <1500/µL, platelets <100 000/µL and haemoglobin <10.0 g/dL
- Faecal incontinence

The following must be ensured before a patient is considered for Radium-223 therapy:

- Therapy indication and no contraindications are present
- Exclusion of visceral metastases
- Recent bone scan not older than three months showing increased tracer uptake at sites corresponding to region of bone pain
- Recent blood count not older than 10 days.

The treatment is usually performed on an outpatient basis. Hospitalisation should be considered in patients with faecal incontinence or those with severe debilitation.

The ALSYMPCA trial was a phase III, randomised, double-blind, placebo-controlled study that randomly assigned 921 patients in a 2:1 ratio to receive six injections of Radium-223 or matching placebo. There was a 14.9 months survival benefit in the Radium-223 group, compared to

the placebo group. Radium-223 compared with placebo significantly prolonged time to first symptomatic SRE.[12]

The most frequent side effects of Radium-223 therapy are diarrhoea, nausea, vomiting and thrombocytopaenia. Prior use of chemotherapy or external beam radiotherapy is associated with a higher risk of haematotoxicity.[13]

Bisphosphonates are bone-seeking agents that inhibit bone-resorbing action of osteoclasts. They are commonly used in the treatment of bone metastases. Bisphosphonates have been successfully labelled to diagnostic and therapeutic radionuclides for theranostics of bone metastases. Of all the radio-labelled bisphosphonates, zoledronate appears to have the greatest promise for widespread clinical application due to its high uptake in bone lesions.[14]

RADIOIMMUNOTHERAPY OF B-CELL NON-HODGKIN'S LYMPHOMA

B-cell lymphomas are classified as either aggressive or indolent. Diffuse large B-cell lymphoma typifies aggressive type and responds favourably to chemotherapy. Indolent B-cell lymphoma has a poorer response to chemotherapy, often relapses and may become refractory to re-treatment. Most B-cell lymphomas overexpress CD20 on the tumour-cell membrane. Rituximab is a monoclonal antibody (MAbs) against CD20. Treatment of CD20-expressing B-cell lymphoma with rituximab leads to a modest response rate. Radioimmunotherapy of B-cell lymphoma involves complexing of a therapy radionuclide to a monoclonal antibody against CD20. Binding of a monoclonal antibody to CD20 causes tumour-cell killing via different immunological mechanisms, including apoptosis, antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. When MAbs are labelled with a therapeutic radionuclide, a combination of immunological and radiobiological cytotoxicity leads to better tumour-killing than either alone.

Y-90 ibritumomab tiuxetan (Zevalin) is presently the only commercially available radio-immunotherapy agent and is indicated in patients with rituximab-relapsed or -refractory CD20+ follicular non-Hodgkin's lymphoma. It may be used as a first-line agent in other CD20+ B-cell lymphomas.

Contra-indications include:

- Pregnancy and continuing breastfeeding
- Known hypersensitivity to any component of the therapy agent
- Patients <18 years old
- Poor bone-marrow reserve, WBC <1500/µl, platelets <100 000/µL
- >25% bone-marrow infiltration by lymphoma cells on bone-marrow biopsy
- Previous bone-marrow or stem-cell transplantation

The following must be ensured before a patient is considered for radio-immunotherapy:

- CD20 positivity on immunohistochemical staining
- Check for correct indication and for absence of any contra-indication
- Life expectancy greater than three months, Karnofsky index >70%

Pre-therapy imaging with Indium-111 ibritumomab to demonstrate bio-distribution of the agent, which used to be mandatory, is no longer mandatory prior to institution of therapy with Zevalin. Zevalin is administered as an intravenous infusion after infusion of cold rituximab to block CD20 expressed of normal circulating B-cells and in the spleen. Zevalin is a pure beta-emitting radionuclide and its administration does not expose caregivers to significant radiation.

The commonest immediate side effects of Zevalin infusion include asthenia, nausea, chills and fever.

The superiority of Zevalin over cold rituximab was demonstrated in a phase III trial that randomised 143 patients with relapsed or refractory low-grade follicular lymphoma or transformed CD20+, transformed non-Hodgkin's lymphoma to either receive

rituximab alone or Zevalin. The overall response rate was 80% for Zevalin, compared with 56% with rituximab alone.[15]

Bone-marrow suppression is a potential side effect of therapy with Zevalin and this may persist for up to 12 weeks post-treatment. Patients should therefore be followed-up with weekly full blood count until recovery.

CONCLUSION

Nuclear medicine is in a prime position to utilise personalised care in cancer management. Targeted therapy ensures that a disease is seen, and a determination is made as to whether the disease will respond to therapy; only then is targeted radionuclide therapy embarked upon. This ensures that treatment is only offered to patients who will benefit from it, prevents unnecessary adverse effects and saves cost. The spectrum of cancers that can be treated with this technique is widening, with an increasing number of biological targets with potential for use in developing therapeutic radiopharmaceuticals for treatment.

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Solid tumours

Lung Cancer

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Carcinoma of the lung is responsible for more deaths than any other cancer. Lung cancer is the cause of death of approximately 18% of all cancer patients. The global incidence rates mirror the smoking prevalence rates. The estimated overall incidence rate for southern Africa is 189.6 per 100 000 population.[1] The estimated overall mortality rate for southern Africa is 133.2 per 100 000 population.[1]

Early stages of the disease are potentially curable, but most patients are diagnosed with advanced disease. A contributing factor is the non-specificity of presenting symptoms, resulting in a delay in diagnosis. Additionally, symptoms may only be experienced at an advanced stage of disease. Further factors are the high prevalence and incidence rates of tuberculosis (TB) in South Africa.

The most significant factor in the aetiology of lung cancer is smoking. Cancer of the lung can be related to smoking (present or past) in 85% of cases. In 5% of cases, cancer of the lung can be related to passive smoking, i.e., exposure to others who smoke. Asbestos or radon exposure may also cause lung cancer. Lung cancers may also develop secondary to radiation therapy to the chest, for example in lymphoma and breast-cancer survivors. Epidemiological studies document an increased incidence of lung cancer in patients who have been previously diagnosed with tuberculosis (TB). Non-smokers most frequently develop adenocarcinoma.

The most important intervention in reducing mortality is smoking-cessation programmes. Screening for lung cancer in high-risk patients has been shown to reduce mortality. High-risk factors are patients between the ages of 55-74 years, ±30 pack-year history and smoking cessation less than 15 years ago. Patients are screened with low-dose computed tomography (CT) scans for two years. Annual CT-scans may be considered until the level of risk reduces. There is no benefit to screening with chest x-rays.[2]

PATHOLOGY AND MOLECULAR BIOLOGY

Lung cancer is divided into two broad histological groups, namely non-small-cell and small-cell lung cancer (SCLC). The histological diagnosis is non-small-cell lung cancer (NSCLC) in 85% of cases, and these are classified further as adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma. SCLC occurs in 15% of cases. These types of cancer have different pathophysiologies and responses to treatment and are discussed separately.[3]

There are many genetic mutations in patients with lung cancer. The epidermal growth factor receptor (EGFR) and the anaplastic lymphoma kinase (ALK) gene mutations predict response to therapy (discussed later). The EGFR and the ALK are transmembrane receptors. When a ligand binds, signal transduction cascade results, which causes cellular proliferation and other hallmarks of malignancy. Tyrosine kinase inhibitors (TKIs) inhibit this pathway.[3]

Tumour cells also express the programmed death ligand (PDL1). PDL1 binds to the programmed death protein (PD1) on the patient's T-cells. This bond inhibits the immune function of the patient, promoting tumour growth. Immune therapy includes antibodies against either PD1 or PDL1.[4]

DIAGNOSIS AND PRE-TREATMENT EVALUATION

Patients with lung cancer usually have a mass on chest radiograph. A tissue diagnosis is mandatory. Fine-needle aspiration and biopsy can be accomplished under CT-guidance or at bronchoscopy,

Lung Cancer

For full prescribing information refer to the package insert approved by the Medicines Regulatory Authority.

S4 CIPLA DOCETAXEL 20 (Solution for infusion). Each single-dose vial contains docetaxel trihydrate equivalent to 20 mg docetaxel (anhydrous) in 0,5 ml polysorbate 80. Inactive ingredients include anhydrous citric acid and polysorbate 80. Reg. No.: 41/26/0162.
Pharmacological classification: A 26 Cytostatic agents.
S4 CIPLA DOCETAXEL 80 (Solution for infusion). Each single-dose vial contains docetaxel trihydrate equivalent to 80 mg docetaxel (anhydrous) in 2,0 ml polysorbate 80. Inactive ingredients include anhydrous citric acid and polysorbate 80. Reg. No.: 41/26/0163.
Pharmacological classification: A.26 Cytostatic agents.
S1 SOLVENT FOR CIPLA DOCETAXEL 20 / 80 (Solvent). Each vial contains 13,0 % m/v ethanol 95 % v/v. Reg. No.: 44/32.2/0393, 94.
Pharmacological classification: A.32.2 Other
S4 CIPLA PACLITAXEL 30 mg / 5 ml, 100 mg / 16.7 ml, 300 mg / 50 ml (Concentrate for dilution for infusion). Each vial contains 30 mg / 100 mg / 300 mg paclitaxel per 5 ml / 16.7 ml / 50 ml. Contains ethanol 49,7 % v/v, polyoxyethylated castor oil and anhydrous citric acid as excipients. Reg. No.: 41/26/0423, 24, 25. Pharmacological classification: A 26 Cytostatic agents.
S4 PCH PACLITAXEL 30 / 100 / 300. Each vial contains 30 mg / 100 mg / 300 mg paclitaxel per 5 ml / 16,7 ml / 50 ml (6 mg/ml).
Reg. No.: A40/26/0609, 10, 11. Pharmacological classification: A 26 Cytostatic agents.
S4 ONCOGEM 200 (Powder for injection). Each vial contains 227,6 mg gemcitabine hydrochloride equivalent to 200 mg of gemcitabine free base.
Reg. No.: 43/26/1171. Pharmacological classification: A 26 Cytostatic agents.
S4 CIPLA-VINORELBINE 10 / 50 (Intravenous injection). Each single dose vial contains 13,85 mg / 69,25 mg of vinorelbine tartrate which is equivalent to 10 mg / 50 mg of vinorelbine base per millilitre / 5 millilitres of solution. Reg. No.: 42/26/0083, 84.
Pharmacological classification: A 26 Cytostatic agents.
S4 CARBOSIN 150 / 450 / 600. Each vial contains 150 mg / 450 mg / 600 mg carboplatin (10 mg/ml). Reg. No.: Z/26/261, 62, A39/26/0170.
Pharmacological classification: A 26 Cytostatic agents.
S4 VINBLASTINE TEVA 10. Each vial contains vinblastine sulphate 1 mg/ml. Reg. No.: 45/26/0373.
Pharmacological classification: A 26 Cytostatic agents.

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dependent on the anatomical location of the tumour. The tissue obtained would be tested for genetic mutations.

A CT-scan of the chest and upper abdomen is indicated to evaluate the extent of disease. A bone scan is indicated for patients with bone pain and an elevated alkaline phosphatase.

Positron emission tomography (PET) is an important investigation in selected patients. It is used to detect occult metastases in patients who have potentially curable disease. However, it can be falsely positive from inflammatory conditions or diseases (e.g., TB and autoimmune diseases). The findings need to be confirmed histologically. It can also be falsely negative in diseases with a low metabolic activity, e.g., minimally invasive adenocarcinoma.

The gold standard for sampling enlarged or FDG-avid lymph nodes is a mediastinoscopy. This confirms that the nodes are large because of metastatic lung cancer. Endobronchial and endoscopic ultrasound-guided biopsies are alternative procedures. These procedures are less invasive, and can be done in-office. Hilar lymph nodes can also be sampled.

The forced expiratory volume in one second (FEV1) is used to assess the patient's ability to tolerate surgery. The post-operative predicted FEV1 needs to be more than 800 ml. The carbon monoxide-diffusing capacity is the best test to evaluate the patient's ability to tolerate chest irradiation.[5]

The performance status (PS) of patients is the most important prognostic factor in lung cancer and informs treatment.

Patients are assessed in terms of the World Health Organization (WHO) scale:

- PS 0 – active and asymptomatic patient
- PS 1 – symptomatic, still active
- PS 2 – in bed less than half of the day
- PS 3 – in bed more than half of the day
- PS 4 – bedridden

Patients who have a performance status of 3 or more are generally not candidates for curative treatment.

STAGING

The stage of the disease determines the prognosis and the intent of treatment. Staging was revised in 2016.

Stages 1,2 and selected stage 3 are usually treated with curative intent. Crude five-year survival rates range from 90% for stage 1 to 0% for stage 4 patients.[6]

STAGE I

Stage 1 includes patients with operable primary tumours of less than or equal to 4 cm in size and no nodal involvement.

The cornerstone of treatment is surgery, most often a lobectomy as this has a lower morbidity and mortality than a pneumonectomy (4% *versus* 9%). Patients with minimally-invasive adenocarcinoma may be treated by focal excision. These tumours spread along the airways rather than through the lymphatics.

Patients who are medically inoperable may be treated by high-dose external-beam radiation. This would comprise the daily course of external-beam irradiation to more than 60 Gray. Whole-body stereotaxis with high-ablatant doses of irradiation given in a few sessions is the preferred therapy. Control rates at two years of more than 90% are being reported.[7]

Patients with the resected stage I disease are at risk of developing a second lung cancer. This risk increases if the patient continues smoking. [8]

STAGE II

Stage II includes patients with potentially operable tumours that are more than 4 cm with or without involvement of the hilar nodes.

Surgery, as described above, remains the cornerstone of treatment for patients in this stage. Patients who have chest-wall involvement should be considered for chest-wall resection.

Adjuvant chemotherapy increases the survival rate in this group of patients by 5% at five years.[9] Patients with stage II and stage IIIA disease derive maximal benefit.[10] The agents most consistently used in trials for adjuvant chemotherapy are one of the platinums and vinorelbine. Carboplatin is

frequently used in the palliative setting in patients with lung cancer because of its tolerability. Data are available for the use of cisplatin in the adjuvant setting.

STAGE IIIA AND IIIB

Stage III consists of patients with locally advanced disease. Tumours are of all dimensions with spread to mediastinal nodes. Tumours are greater than 5 cm with any nodal involvement or more than 7 cm with or without nodal involvement.

The cornerstone of treatment for these patients is combined radiotherapy and chemotherapy. Randomised studies show an improvement in survival with concurrent chemotherapy plus radiation therapy *versus* radiation therapy alone or radiotherapy followed by chemotherapy. There is, however, an increase in severe oesophagitis in patients receiving concurrent treatment. Patients with good PS (0-2) are best so treated.[11]

Surgery has not been found to be beneficial in patients with non-bulky disease. Patients have been randomised to receive either concurrent chemoradiation followed by either surgical resection or continuation of radiation therapy, but no significant difference in overall survival was found. However, there were greater treatment-related mortalities in the surgery arm compared to the chemoradiation-alone arm (8% *versus* 2%), particularly for patients undergoing a pneumonectomy.[12]

STAGE IV

The tumour has spread to the contralateral lung, or the patient has a malignant pleural or pericardial effusion. This stage includes tumours which have spread outside of the thorax.

TREATMENT

FIRST-LINE CHEMOTHERAPY

Chemotherapy results in an increase in survival and quality of life (QoL) in selected patients with metastatic NSCLC. The one-year-survival rate increases from 10% to 30-35%. The median survival increases from eight to 10 months.

Chemotherapy has a documented survival benefit in patients with PS of 0-1.[13] Standard chemotherapy is the platinum-based doublet in which the agent used with one of the platinums are vinorelbine, gemcitabine, paclitaxel, docetaxel or pemetrexed.

Histology is a predictive factor. Pemetrexed is more effective in patients with adenocarcinoma, due to higher thymidylate synthase levels in squamous cell cancers.[14] There is no survival advantage; only increased toxicity from administering more than four to six cycles of chemotherapy. This contrasts with biological and immune therapy, which are given for as long as the patient is responding to treatment. Therapy may be discontinued in the event of unacceptable toxicity.

FIRST-LINE THERAPY WITH BIOLOGICAL AGENTS

Tyrosine kinase inhibitors (TKIs)

Examples are erlotinib and gefitinib. Lung cancers that are EGFR receptor mutation-positive will respond to these agents.[15] The TKIs are taken by mouth daily. Their most frequent toxicities are rash and diarrhoea.[16] A study was undertaken in East Asia where non-smokers or former light smokers with advanced adenocarcinoma were randomised to either gefitinib or doublet chemotherapy as first-line therapy. Among those patients whose tumours harboured EGFR mutations, progression-free survival was significantly longer with gefitinib. Gefitinib was also associated with a better QoL. In the mutation-negative group, gefitinib resulted in significantly shorter progression-free survival.[17]

When the tumour receptor status is unknown, chemotherapy remains first-line therapy.

Vascular endothelial growth factor receptor (VEGFR)

Bevacizumab is an antibody to the ligand of the VEGFR. It is not used in patients with squamous carcinoma because of concerns about increased haemorrhage.

A randomised study evaluated the addition of bevacizumab to carboplatin

and paclitaxel. Bevacizumab was administered every three weeks with chemotherapy and subsequently without for one year until progression of disease. There was a significant increase in median survival from 10.3 months to 12.3 months. A marginal increase in progression-free survival has been reported when bevacizumab is administered with cisplatin and gemcitabine.[18]

FIRST-LINE THERAPY WITH BIOLOGICAL AGENTS

PD1 and PDL1 inhibitors

Pembrolizimab and nivolumab are examples of these drugs. They can be considered for tumours that do not have any of the mutations mentioned previously. These drugs are active in the first-line setting in tumours which express PDL1. Preliminary data show an increase in progression-free survival and overall survival, when compared to standard chemotherapy.[19] Immune-related side effects are the common toxicities. These can occur after cessation of therapy. High-dose steroids may be required to control these side effects. Immunosuppressive therapy is an option in severe cases. Examples are cutaneous vitiligo, lichen planus, colitis, hepatitis and nephritis.[20]

SECOND-LINE THERAPY

- Docetaxel, has shown significantly improved survival and QoL, when compared to best supportive care in patients who have failed first-line therapy.
- Pemetrexed has an antitumour activity similar to docetaxel as a second-line therapy. The response rates for both agents are just under 10% and the median survival around eight months. Pemetrexed has less toxicity with lower rates of neutropaenia and neutropaenic sepsis.[21]
- Erlotinib has been evaluated as a second-line therapy in patients who had not undergone EGFR gene-mutation analysis. There was a statistical increase in response rates (9% *versus* 1%) and survival (6.7 months *versus* 4.7 months) in these patients. The importance of EGFR gene mutation has subsequently been recognised.[22]

SMALL-CELL LUNG CARCINOMA

Small-cell lung carcinoma comprises about 15% of all lung cancers. It is strongly related to smoking. It has neuro-endocrine differentiation and is more commonly associated with paraneoplastic syndromes. It is a rapidly growing tumour and metastasises early. All patients are considered to have micro metastases. Untreated, the median survival of patients will be approximately three months. However, it is sensitive to chemotherapy, which prolongs survival and improves patients' performance status (PS). Patients are rarely cured.

STAGING AND EVALUATION

The 2016 TNM staging system is used. Patients with SCLC can also be staged using a binary staging system, i.e. as having localised or extensive disease (LD and ED). LD can be treated within one radiation port. This includes the hemi-thorax and regional nodes, as well as mediastinal and ipsilateral supraclavicular nodes.

Pre-treatment evaluation includes a complete blood-cell count; liver-function tests, CT of the chest and abdomen and a bone scan. PET-CT scans may have a role in evaluating patients with limited disease.

CHEMOTHERAPY

All patients with SCLC may be considered for chemotherapy, irrespective of PS, unlike patients with NSCLC where chemotherapy is restricted to patients with good PS.

A platinum combined with etoposide is most frequently used nowadays. Cisplatin is the platinum of choice in patients with LD who are candidates for concurrent chemotherapy and irradiation to the chest. Patients who cannot tolerate a platinum agent may be treated with the CAV regimen (cyclophosphamide, doxorubicin, vincristine). This regimen was previously used as standard therapy.

Patients receive between four to six cycles of treatment. There is no gain in increasing the dose intensity of chemotherapy

or adding additional cycles of chemotherapy.

The overall response rate in patients with LD and ED is approximately 75% and 50%, the complete response rate is 50% and 20% and the median survival is 16 and nine months respectively.

Patients will almost always relapse. Such patients may be retreated with the original regimen if they have been off treatment for three months. Alternatively, they may be treated with a regimen to which the patient has not been exposed, e.g., CAV. Single-agent topotecan may also be used with a response rate of approximately 30%.

CHEMOTHERAPY AND IRRADIATION

There is a small but significant improvement in survival in patients who receive concurrent chest irradiation, although this results in an increase in oesophagitis. It should therefore be administered to LD patients with good PS.

SCLC is associated with a high incidence of brain metastases. Prophylactic cranial irradiation decreases this relapse rate and increases the three-year survival rate by 5%. It is indicated for good PS in patients who achieve a complete response to chemotherapy.[23]

REFERRAL

Patients who present with oncological emergencies such as superior mediastinal syndrome, febrile neutropaenia and spinal cord compression require urgent referral. The severe toxicities of therapy should be managed by an oncologist.

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Colorectal Cancer

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Colorectal cancer is a common disease, with approximately 1 360 000 new cases worldwide in 2012. According to the South African National Cancer Registry of 2013, it is the second most common cancer in men and the third most common in women, excluding skin cancers.[1] The incidence increases with age, with the highest number of cases reported in South Africa between 65 and 69 years of age. Approximately 35-40% of patients presenting with colorectal cancer will die from the disease.

The majority of cases of colorectal cancer are sporadic, with only 20% of cases being attributable to familial disease. The two most common inherited conditions are familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome. Patients with FAP develop thousands of colonic polyps which will eventually become carcinomas. Lynch syndrome occurs with mismatch repair gene defects and these patients are at a high risk not only for colorectal cancer, but also for cancers of the uterus, ovary, renal tract, stomach, small bowel and hepatobiliary system. Factors that predispose patients to developing sporadic colorectal cancer are numerous and include inflammatory bowel disease and lifestyle diseases such as obesity, smoking and alcohol consumption.

SCREENING

Most cancers in the large bowel start as adenomas, which then become dysplastic and progress to carcinomas. This process is thought to take place over five to 10 years, which implies that screening for polyps may prevent colorectal cancer and therefore deaths from the disease. A study comparing mortality from colorectal cancer in patients who were referred for colonoscopy with the expected mortality from colorectal cancer according to the surveillance epidemiology and end-results programme (SEER) showed a significant decrease in mortality in the patients who had adenomas removed at colonoscopy.[2] Sigmoidoscopy alone has also been shown to decrease mortality from colorectal cancer.[3] Further effective screening methods include faecal occult blood-testing followed by colonoscopy if the test is positive. The faecal immunochemical test (FIT), either alone or combined with stool DNA, has a high sensitivity for detecting colorectal cancer, but there are no studies to show the effect on mortality. The advantage of FIT is that it does not require the dietary restrictions necessary for accurate interpretation of faecal occult blood tests. Computed tomographic (CT) colonography can also detect polyps, which would then require colonoscopy for removal, but has the risks associated with exposure to radiation. A recent review recommends screening for the average-risk population should start at the age of 50 years and stop at 85 years.[4] The screening method should be that with which the patient is most likely to comply. For patients at higher risk, i.e., those with a family history, previous colorectal cancer, inflammatory bowel disease or one of the inherited syndromes, screening should begin at a younger age and take place at more frequent intervals.

DIAGNOSIS AND STAGING

Presenting symptoms of colorectal cancer include changes in bowel habit, haematochaezia, symptoms of anaemia and abdominal pain. Patients presenting with these symptoms should be referred for colonoscopy. More advanced disease may present with bowel obstruction or perforation or signs of metastatic disease such as hepatomegaly.

The definitive diagnosis of colorectal cancer is made after biopsy and histology confirmation of either the primary site or a

metastasis. Once the diagnosis is made, staging is essential in order to provide optimal treatment. Ideally, the patient should have a full colonoscopy to exclude synchronous lesions, however this procedure may not be possible if the lesion is obstructing the lumen. In this situation, a full colonoscopy should be performed within the first year of diagnosis. Further staging includes a CT-scan of the chest, abdomen and pelvis to detect metastatic disease. For patients with a primary tumour in the rectum, magnetic resonance imaging (MRI) of the pelvis or endoscopic ultrasound (EUS) determines local staging. Serum carcino-embryonic antigen levels (CEA) are useful for prognosis; in general, elevated levels predict worse prognosis. Positron emission tomography (PET) scans are not routinely used for baseline staging. For patients with liver lesions detected on CT, MRI of the liver with gadoxetate disodium (Primovist®), a liver-specific contrast, is useful for defining lesions as well as detecting further lesions that may not be visible on CT. The recommended staging system is the tumour, node, metastasis (TNM) system as defined by the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC), with T describing the depth of invasion, N the number of involved nodes and M the presence of metastases. TNM staging can be determined only after resection of the primary lesion, although it is possible to estimate the clinical stage on imaging.

TREATMENT OF LOCALISED DISEASE

Multidisciplinary team management is important for patients with colorectal cancer, particularly those with advanced disease when the most appropriate combination of surgery, chemotherapy or radiation needs to be established.

SURGERY

Surgery alone is potentially curative for patients with localised early disease. Small polyps containing adenocarcinoma can be removed endoscopically and the patient followed up as long as the margin is clear and there are no concerning features such as lymphovascular invasion or poor differentiation. Lesions confined to the colon in patients who have no contraindications to surgery should be resected with a primary anastomosis according to the blood supply and lymphatic drainage. Surgery for uncomplicated primary tumours in the colon can be performed laparoscopically, allowing for shorter postoperative recovery time.[5]

For patients with a primary tumour involving the rectum, it is important to establish the clinical stage prior to surgery, using both clinical and radiological evaluation. Digital rectal examination for tumours of the distal rectum can determine sphincter involvement as well as possible involvement of surrounding structures. MRI of the pelvis and transrectal ultrasound (TRUS) have been shown to be accurate in assessing the T stage.[6] In general, MRI is recommended since the entire pelvis can then be visualised, as well as the relation of the tumour to the mesorectal fascia, which will ideally be the circumferential resection margin. Lymph-node involvement is difficult to assess since even small nodes have been shown to contain metastases on pathology review and MRI, TRUS and CT seem to have equivalent accuracy for potential nodal involvement. If the primary tumour or a node involves, or is less than 1 mm from, the mesorectal fascia, neoadjuvant treatment is recommended.

The choice of surgical procedure depends on sphincter involvement. In general, if the sphincters are involved, an abdominoperineal resection (APR) will be performed in which the rectum, anus and entire sphincter complex are resected and a permanent end colostomy is fashioned. If the sphincters are spared, then an anterior resection is performed generally with a temporary covering ileostomy to protect the anastomosis. Standard of care for surgery is a total mesorectal excision, ideally performed in a high-volume centre, in which there is sharp dissection around the mesorectal fascia to remove the mesorectal fat and all lymph nodes within the mesorectum. This technique has significantly reduced the local

recurrence rate from approximately 45% to less than 10% .[7]

CHEMOTHERAPY

The decision for adjuvant chemotherapy in adenocarcinoma of the colon is based on the pathological stage of the tumour. In general, stage I and II lesions that are completely resected do not require adjuvant chemotherapy since the risk of recurrence is low. However, stage II lesions that have high-risk features, such as T4-stage, lymphovascular invasion, poor differentiation or tumours that perforate or cause bowel obstruction, may benefit from adjuvant chemotherapy, although the evidence for this is limited. There is a significant decrease in risk of recurrence for patients with stage III disease who receive adjuvant chemotherapy, the standard regimen being a combination of intravenous 5-fluorouracil (5FU), leucovorin and oxaliplatin or oral 5FU (capecitabine) and oxaliplatin.[8] Chemotherapy is generally given for a period of six months and should start within four to six weeks of surgery, although a recent pooled analysis has shown that three months in low-risk stage III patients may be sufficient for patients receiving the combination of 5FU and oxaliplatin, whereas for patients receiving 5FU alone, the full six months of treatment should be given.[9]

RADIATION

Neoadjuvant radiation has been shown in a number of trials to reduce local recurrence in adenocarcinoma of the rectum.[10] In patients with resectable tumours where there is a concern about local control, short-course radiation, i.e., 25 Grey (Gy) in five daily fractions with surgery the following week can be prescribed. For locally advanced tumours in which the mesorectal fascia is threatened by tumour and downstaging is required, chemoradiation is recommended – a dose of 45 to 50.4 Gy in 25 to 28 fractions, given over a period of five to six weeks, with concurrent 5FU as a radiosensitisor. Surgery is then performed six to 10 weeks later. Organ preservation with chemoradiation alone is currently being investigated as a treatment option. Retrospective studies have shown that for patients who have a complete response to neoadjuvant chemoradiation, surgery may be avoided and this treatment option is especially attractive for patients requiring APR.[11] At present, it is recommended that chemoradiation followed by watchful waiting be undertaken only in the context of a clinical trial.

TREATMENT OF METASTATIC DISEASE

Metastatic disease is present in about 25% of patients at initial presentation and a further 25% will develop metastatic disease after treatment of the primary tumour, the most common sites being liver, peritoneum, distant nodes, lung and bone. The prognosis of patients with metastatic disease has improved substantially since the 1980s due to the development of surgical techniques and new systemic agents. In a review of patients treated at two large centres in the US, the median overall survival for patients with metastatic disease increased from 14.2 months in the early 1990s to 29.3 months for the time period between 2004 and 2006.[12]

SURGERY

The only potentially curative treatment for metastatic disease involves surgery. Therefore it is essential that all patients with metastases who are fit for surgery be evaluated for possible metastatectomy, ideally in a multidisciplinary team setting. In general, as long as 25-30% of the original liver volume can be spared, in a liver with normal function, resection of liver metastases is possible. Limited lung metastases are also potentially resectable. Local ablative techniques such as microwave and radiofrequency ablation as well as stereotactic body radiation can be used in patients who are not surgical candidates. Metastases to bone, peritoneum or distant nodes are usually not considered for resection.

CHEMOTHERAPY

Chemotherapy can be used together with surgery to downstage patients with

potentially resectable disease. For patients with unresectable metastatic disease, chemotherapy improves survival over best supportive care.

In the last two decades, a greater understanding of the biology of colorectal cancer has led to the development of a number of new agents effective in the treatment of metastatic disease, allowing for the use of different combinations of drugs, depending on the tumour characteristics as well as the site of the primary tumour. The general condition of the patient and the aim of the treatment must be taken into consideration. For a patient with liver metastases that require downstaging prior to resection or for a patient with significant tumour burden, a combination of agents is prescribed, whereas if the patient is elderly or has a limited tumour burden, a single agent may be prescribed. Patients with a poor performance status, i.e., those who spend more than 50% of the day resting, will generally not benefit from chemotherapy.

The backbone of most regimens is 5FU which can be administered intravenously with leucovorin or orally. There are several oral forms, including capecitabine, S-1 and tegafur. Oxaliplatin and irinotecan are intravenous chemotherapy agents that are prescribed with 5 FU.

The targeted or biological agents have been developed to target certain pathways or molecules that are active in colorectal cancer and thereby inhibit tumour growth. These agents include the anti-angiogenic agents bevacizumab, aflibercept and ramucirumab and the anti-epidermal growth factor receptor (EGFR) agents cetuximab and panitumumab. Together, these agents allow for a number of different regimens for first- and second-line treatments. It is important to establish the molecular profile of the tumour before deciding on the regimen. RAS is one of the many oncogenes involved in colorectal cancer and patients with mutations in RAS will not respond to the anti-EGFR agents. Patients with mutations in the BRAF gene who develop metastatic disease have a poor prognosis and current evidence indicates that they may also not respond to the anti-EGFR agents.

For patients who develop progressive disease after first- and second-line regimens, regorafenib, a tyrosine kinase inhibitor, or trifluridine/tipiracil, a cytotoxic agent, have been shown to have a small survival benefit over best supportive care.

The site of the primary tumour can also influence the treatment regimen. A review of trials incorporating targeted agents has indicated that patients who have metastatic disease from primary tumours arising in the left colon have improved survival with chemotherapy combined with the anti-EGFR agents, providing they are KRAS wild type, whereas for primary tumours arising in the right colon, combination chemotherapy with bevacizumab may improve survival.[13] Immunotherapy is an exciting new development in the treatment of many cancers. For patients with metastatic colorectal cancer with a mismatch repair gene defect who have progressed on chemotherapy, pembrolizumab is a new treatment option.

In summary, the multitude of effective agents has created a variety of different regimens allowing for personalised treatment and improvement in overall survival of patients with metastatic disease.

FOLLOW-UP

For patients with stage II and III disease, most guidelines recommend follow-up to detect recurrence, although the evidence for improved survival after treatment of the recurrence is limited. Since approximately 75% of recurrences occur within the first three years of treatment, patients are examined at three- to six-monthly intervals during this period, CEA levels are monitored and imaging with CT-scans is performed. Colonoscopy can be repeated three years after diagnosis, then five-yearly if no polyps are found. Follow-up is also required for management of possible long-term treatment-related side effects. Patients should be advised to maintain a healthy weight, not smoke and exercise regularly. Recent evidence has shown that aspirin may decrease the risk

of recurrence, but results of randomised trials are awaited.

SUMMARY

Colorectal cancer is a common disease and screening is effective in reducing mortality. Treatment of localised disease in the colon is surgery followed by adjuvant chemotherapy for patients with stage III disease. Neoadjuvant chemoradiation is indicated for locally advanced rectal cancer. The combination of surgical techniques and systemic treatment allows for resection of metastases, offering potentially curative treatment. A number of effective treatment regimens are now available for patients with unresectable metastases, resulting in improved survival.

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Breast Cancer

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According to the CANSA statistics, breast cancer is the most common cancer affecting South African women.

Unfortunately, the national registry has been fraught with challenges, and this has hindered accurate assessment of the burden of disease. This is currently in the process of being updated with NHLS and the Department of Health.

South Africa is among the most unequal societies in the world. This is apparent in the disparate care of patients in the private sector compared to those in the public sector. Breast cancer is unfortunately no different, with the majority of women in the private sector presenting with early stage breast cancer, where the treatment intent is usually curative, compared to the public sector, where women present with advanced stage disease, with subsequent poorer outcomes, against the backdrop of limited resources.

The most common presentation of breast cancer is the finding of a breast lump, or axillary lymphadenopathy. Other symptoms may include thickened skin with an orange-peel appearance (*peau d'orange*), an enlarged node at the base of the neck, a bloody nipple discharge, or ulceration of the breast and surrounding tissues.

The risk of breast cancer increases with age. However, increasingly younger patients are being diagnosed. Only 10-15% of breast cancers are as a result of a genetic aberration, meaning that the majority of breast cancers are sporadic.[1]

The diagnosis is made on a mammogram combined with a breast ultrasound. A core biopsy of the breast mass, rather than a fine-needle aspiration (FNA) is preferred. Core biopsy allows for more accurate assessment of the biology of the cancer, which is important in determining the treatment approach.

STAGING

Breast cancer is staged according to the TNM criteria, which takes into account tumour size, locoregional nodal involvement, and the presence or absence of distant metastasis (see Table 1).

By definition, early breast cancer is cancer that is limited to the breast and/or axilla. However, a tumour in excess of 5 cm, involvement of multiple locoregional lymph nodes, skin changes and/or invasion of the chest wall imply the diagnosis of locally advanced breast cancer.

TUMOUR BIOLOGY

In broad terms, breast cancer biology is divided into *favourable vs unfavourable biology*. The surrogate for this is the IHC 4 test, which includes assessment of oestrogen receptors (ER), progesterone receptors (PR), HER2 neu expression, and Ki67.

HER2 neu overexpression is found in 20-30% of all breast cancers, and portends a poorer prognosis with a propensity for distant spread.

The diagnosis is made on immunohistochemistry, and an equivocal result is confirmed by SISH and reported according the College of American Pathologists (CAP).

Immunohistochemistry is a surrogate for profiling of tumour biology which is best characterised by tumour micro-arrays, which are not readily available.

Tumour biology is divided into luminal A-like, luminal B-like, HER2-enriched, and basal-like.

Luminal A cancers tend to be ER/PR-positive, HER2-negative, with a low Ki 67 of less than or equal to 14%.

Luminal B-like cancers are ER-positive, PR-negative, HER2-negative, with a high Ki 67 of >14%.

HER2-enriched are HER2-overexpressing, and the basal-like cancers include, but are not limited to, triple-negative breast

Table 1. Breast carcinomas TNM staging

Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
Tis (DCIS)	Ductal carcinoma *in situ*
Tis (LCIS)	Lobular carcinoma *in situ*
Tis (Paget's)	Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorised based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted.
T1	Tumour ≤20 mm in greatest dimension
T1mi	Tumour ≤1 mm in greatest dimension
T1a	Tumour >1 mm but ≤5 mm in greatest dimension
T1b	Tumour >5 mm but ≤10 mm in greatest dimension
T1c	Tumour >10 mm but ≤20 mm in greatest dimension
T2	Tumour >20 mm but ≤50 mm in greatest dimension
T3	Tumour >50 mm in greatest dimension
T4	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or oedema (including *peau d'orange*) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph-node metastases
N1	Metastases to moveable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph-node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph-node metastases

Regional lymph nodes (N) (cont.)	
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph-node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph-node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph-node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	No regional lymph-node metastasis identified histologically
pN0(i-)	No regional lymph-node metastases histologically, negative immunohistochemistry (IHC)
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2mm (detected by H&E or IHC including isolated tumour-cell clusters (ITC))
pN0mol-)	No regional lymph-node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR), but no regional lymph-node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph-node biopsy, but not clinically detected
pN1mi	Micrometastases (greater that 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1-3 axillary lymph nodes, at least one metastasis greater than 2 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph-node biopsy, but not clinically detected
pN1c	Metastases in 1-3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph-node biopsy, but not clinically detected
pN2	Metastases in 4-9 axillary lymph nodes; or in clinically detected internal mammary lymph nodes in the *absence* of axillary lymph-node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least one tumour deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes in the *absence* of axillary lymph-node metastases

Regional lymph nodes (N) (cont.)	
pN3	Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph-node biopsy, but not clinically detected, or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumour deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph-node biopsy, but not clinically detected
pN3c	Metastases in ipsilateral supraclavicular lymph nodes
Distant metastasis (M)	
MO	No clinical or radiologic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly- or microscopically-detected tumour cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Anatomic stage/Prognostic groups			
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0

cancer, a particularly aggressive type of breast cancer.

INITIAL WORK-UP AFTER A BREAST-CANCER DIAGNOSIS

Staging tests that should be performed after a breast-cancer diagnosis are a chest x-ray, abdominal ultrasound, blood tests (which must include a liver function test and a calcium level). Tumour markers are not standard tests, but may aid in the overall assessment and monitoring of a patient following diagnosis.

INDICATIONS FOR AN MRI BREAST

An MRI of the breast is not a standard imaging technique in all breast-cancer patients. Doing an MRI pre-operatively increased mastectomy rates and was not shown to reduce re-excision rates.[2] Furthermore, there was no difference in eight-year local recurrence rates (97% *vs* 95%) or disease-free survival rates (89 *vs* 93%)[3] in patients in whom preoperative MRI had been utilised, compared to those who did not undergo preoperative MRI, based on a meta-analysis of in excess of 3 000 patients with newly diagnosed breast cancer.

Indications for an MRI of the breast include lobular cancer, BRCA-positive patients, or patients harbouring other high-risk mutations and multifocal/multicentric breast cancer. Ongoing clinical trials are evaluating the use of breast MRI to assess response to neoadjuvant chemotherapy.

TREATMENT MODALITIES FOR NON-METASTATIC BREAST CANCER

Treatment of non-metastatic breast cancer is best managed in a multidisciplinary team comprising radiologists, breast surgeons, plastic surgeons, medical and radiation oncologists, as well as allied services that include lymphoedema therapists, psychologists and dieticians.

The treatment consists of surgery, which could be a lumpectomy, mastectomy or bilateral mastectomy, chemotherapy with or without HER2-blockade in appropriate patients (HER2-positive), radiation treatment and hormonal blockade in patients whose tumours are endocrine-responsive.

Treatment for breast cancer is personalised, based on patient factors including comorbidities, tumour factors (biology), staging, and so on. A "one-size-fits-all" approach is not appropriate, and each case needs to be evaluated looking at the factors mentioned above.

SURGERY

The choice of surgery is influenced by the size of the tumour, the location within the breast, the presence or absence of deleterious mutations, and patient preferences.

The timing of surgery is determined by the initial stage of the cancer, tumour size, and the use of neoadjuvant chemotherapy.

The trend towards bilateral mastectomies has been increasing across the globe, fuelled by media awareness and celebrities who have undergone this procedure. Contralateral prophylactic mastectomy does not confer a survival benefit, except in patients with a hereditary breast cancer.[4]

CHEMOTHERAPY

Not all patients with breast cancer require chemotherapy. This is based largely on disease biology and chemotherapy sensitivity of a particular type of breast cancer, the intensity of oestrogen receptor and progesterone receptor expression, and HER2 neu status.

Indications for neoadjuvant chemotherapy

Locally advanced breast cancer – Stage IIB-IIIC tumours (see Table 1) must be considered for neoadjuvant chemotherapy, as they are often too large for upfront resection. In addition, smaller tumours with an unfavourable tumour-to-breast ratio are considered for neoadjuvant therapy, as this may improve the likelihood of breast conservation.

Smaller tumours with an unfavourable biology (triple-negative breast cancer, HER2-overexpressors) are often treated with neoadjuvant chemotherapy, as these tumours are chemotherapy-sensitive, and the patients will be candidates

for chemotherapy at some stage in their treatment course.

A large meta-analysis by the Early Breast Trialist Collaborative Group, which included 4 756 patients from 10 clinical trials, found an increased rate of breast conservation among patients treated with neoadjuvant chemotherapy (65% *vs* 49%). There was no difference in the risk of breast-cancer recurrence between the neoadjuvant group and the adjuvant chemotherapy group (15-year rate of 38.2% *vs* 38%) and breast-cancer mortality (34.4% *versus* 33.7%)[5].

The choice of chemotherapy depends on patient factors and physician preferences. The chemotherapy regimens used in this setting are the same as those used in the adjuvant setting.

These largely comprise anthracycline-containing *vs* non-anthracycline-containing regimens.

The most common neoadjuvant chemotherapy schedule in HER2-negative breast cancer is adriamycin, cyclophosphamide 3-weekly x 4, followed by weekly paclitaxel x 12 weeks, or 3-weekly docetaxel x 4.

In patients who cannot tolerate an anthracycline, TC (docetaxel, cyclophosphamide) administered 3-weekly x 4 is a good alternative.

20-30% of cancers overexpress HER2 neu protein. This makes the cancers more aggressive, with a higher propensity for distant spread.

The addition of trastuzumab to neoadjuvant and subsequently adjuvant therapy increases complete pathological response rates, which in turn have been linked to a survival benefit in breast cancer.[6] The duration of trastuzumab is a total of one year.

In 2013, the FDA approved pertuzumab, an anti-HER2 monoclonal antibody that binds HER2/HER3 heterodimers, which is believed to be an important mechanism that is responsible for trastuzumab resistance. The combination of pertuzumab to trastuzumab and chemotherapy improves complete pathological response rates compared to trastuzumab and chemotherapy alone.[7]

ADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy is chemotherapy administered following definitive surgery for breast cancer, with the aim of reducing the risk of local and distant breast-cancer recurrence.

The indications for adjuvant chemotherapy have shifted from the use of clinicpathological factors to genomic profiling of an individual cancer.[8]

The traditional indications for chemotherapy were tumour size of more than 2 cm, positive axillary nodes, triple-negative breast cancer, HER2-positive breast cancer, the presence of lymphovascular invasion, and young age.

Recently, however, a number of genomic profiling tests have received FDA approval, and these quantify the risk of breast-cancer recurrence with or without chemotherapy. In South Africa, two tests, namely the Oncotype DX test and the Mammaprint tests, are in use. The tests are reported as a risk group (low-risk, intermediate-risk or high-risk for Oncotype DX, or low-risk *vs* high-risk for Mammaprint.)

The low-risk group patients do not attain a benefit from chemotherapy, and the high-risk group are managed with chemotherapy. An ongoing clinical trial is underway to assess the benefit of chemotherapy in the intermediate-risk group where Oncotype Dx test is used. (TailoR$_x$)

The tests are indicated in endocrine-responsive, HER2-negative breast cancer, including patients with 1-3 positive axillary nodes, and assist the clinician with decision-making pertaining to the additional benefit of chemotherapy in addition to hormone blockade in patients who have undergone definitive surgery for breast cancer.

This has challenged the traditional indications for chemotherapy, sparing patients from the short- and long-term effects of chemotherapy. Clinical trials have indicated that the use of genomic profiling changes clinician opinion in approximately 25%-30% of cases.

HORMONAL BLOCKADE

Patients whose cancers are hormone-responsive are candidates for adjuvant

hormonal blockade with tamoxifen or aromatase inhibitors. Tamoxifen is used in premenopausal patients with or without luteinising hormone-releasing hormone agonists (LHRH), and aromatase inhibitors are mainly indicated for postmenopausal women. Aromatase inhibitors can also be used in high-risk premenopausal women combined with an LHRH agonist.[9]

In this instance, high-risk disease includes node-positive patients, those who were deemed to require adjuvant chemotherapy, high grade and presence of lymphovascular invasion.

Clinical trials have also supported consideration for 10 years compared to five years of hormonal blockade. This is on the basis of an increased risk of recurrence up to 15 years following completion of five years of adjuvant endocrine therapy.[10] Two large trials have demonstrated the superiority of 10 years *vs* five years of hormonal blockade with tamoxifen.[11] There have been conflicting data on 10 years of aromatase inhibition.

RADIATION

The indications for postoperative radiation are a tumour size of 5 cm or more, positive axillary nodes (including patients with 1-3 positive nodes), and patients who have undergone a lumpectomy.

Radiation can be omitted in elderly women (over 70) following a lumpectomy for a small luminal A-like cancer.

TREATMENT OF METASTATIC BREAST CANCER

The median survival for metastatic breast cancer is two to three years, with 25% of patients being alive at five years. The intention of treatment is to increase survival with a good quality of life. The choice of treatment depends on disease biology, patient factors, tumour burden (including the presence or absence of a visceral crisis), previous treatment, and the rate of disease progression (see Table 2). Patients with a visceral crisis should be treated with combination chemotherapy, provided that their performance status permits.

Table 2. Factors determining choice of treatment in ABC

Disease characteristics	Patient characteristics
Prior adjuvant chemotherapy	Patient preferences (e.g., oral *vs* IV treatment)
Disease burden	Socio-economic and psychological factors (e.g., distance between home and hospital; costs)
Prior therapies and response	Age, PS, comorbidities
Aggressiveness of disease	Menopausal status
ER/PgR, HER2 receptor status	
Disease-free interval	

According to the ABC3 guidelines, visceral crisis is defined as "severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases, but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible."

The first-line treatment for endocrine-responsive metastatic breast cancer is therefore hormonal blockade, and chemotherapy should be considered only once the hormonal-blockade treatment options have been exhausted. It is important to emphasise that the presence of metastatic disease is not an indication for systemic chemotherapy.

A new class of drugs, CDK 4/6 inhibitors, has received regulatory approval in combination with aromatase inhibitors in first-line metastatic breast cancer, or with fulvestrant, an anti-oestrogen that downregulates

the oestrogen receptor (ER) in previously treated patients.

CDK pathway is overactive in a number of cancers, including breast cancer. CDK inhibition leads to activation of the tumour-suppressor gene, Rb, leading to cell-cycle arrest.

For patients in whom chemotherapy is deemed appropriate, single-agent chemotherapy is preferred over combination chemotherapy (in the absence of a visceral crisis), as there is no prospective evidence to demonstrate the survival benefit of combination chemotherapy over single-agent sequential chemotherapy.

Chemotherapy options to be considered for this indication include anthracyclines, taxanes, capecitabine, vinorelbine, gemcitabine, eribulin and cisplatin, among others. The final choice of drug depends on toxicities, previous therapies, and patient preferences.

MALE BREAST CANCER

Male breast cancer is a rare disease, and accounts for 0.5-1% of all breast cancers diagnosed in the US.

The treatment recommendations for male breast cancer are adapted from the guidelines for the management of female breast cancers, as there is a paucity of clinical trials in this patient population.

Male breast cancers are higher in patients who harbour a genetic mutation of BRCA 2 more than BRCA 1. BRCA 2-positive men have a 6% absolute lifetime risk of developing breast cancer, significantly higher than the average man. Other non-BRCA mutations, such as PTEN, PALB2, P53, may also be implicated.

In addition, conditions that increase the oestrogen ratio, e.g., obesity, gynaecomastia, alcohol, marijuana use, and Klinefelter syndrome may increase the risk of male breast cancer.

Patients with non-metastatic breast cancer are managed with surgery, radiation therapy, and adjuvant hormonal blockade with tamoxifen, if indicated. The majority of male breast cancers are endocrine-responsive. There are insufficient data for the use of aromatase inhibitors in male breast cancer, and those patients treated with aromatase inhibitors must either have undergone an orchidectomy, or be treated with an LHRH agonist.

The approach to treatment of metastatic breast cancer in males is similar to the treatment in females.

Overall, the prognosis of males with breast cancer is comparable to females.

WHEN TO REFER

Any patient who presents with a breast lump must be referred for investigation with a mammogram, and at least a breast ultrasound, regardless of age.

A core biopsy, rather than a fine-needle aspiration (FNA), must be performed on the breast mass, and any axillary glands must be cytologically evaluated.

The histology must contain the following:

- The diagnosis
- Grade of the tumour
- Subtype (lobular vs ductal)
- The immnunohistochemistry, that includes oestrogen receptor, progesterone receptor expression, HER2 neu expression and Ki 67

Once the diagnosis is made, the patient should be referred to a breast surgeon, preferably within a multidisciplinary team for further management.

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Female Genital Tract Cancers

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OVARIAN CARCINOMA

GENERAL CONSIDERATIONS

After cervical cancer, ovarian cancer is a leading cause of death from gynaecological malignancies. The current incidence in South Africa is not known, but in 2004, there were 470 cases documented (1.66% of cancers reported in females) by the National Cancer Registry. The disease is diagnosed at an early stage in only a small percentage of women. In the majority, i.e., approximately 85% of patients, the disease is diagnosed at a late stage with a dismal outcome, <30% of women surviving beyond five years. Unfortunately, the symptoms are non-specific, resulting in a delay in diagnosis. The symptoms of early- and late-stage disease are similar.

Ovarian cancer is more commonly seen in the older age groups, with a peak in the seventh and eighth decade of life. Risk factors include early menarche and late menopause, as well as hormonal replacement therapy. A family history and, specifically, associated genetic syndromes such as BRCA mutations are associated with the highest risk for developing the disease.

The importance of histological subtype has become clearer over the past few years.[1,2] This is particularly relevant with regard to prognosis and response to chemotherapeutic agents. Histological subtypes include serous carcinoma, which is the commonest, followed by mucinous, endometrioid and clear-cell carcinomas. Transitional-cell-, mixed-cell- and undifferentiated histology are uncommon.

Staging is best done following a staging laparotomy and is described by the FIGO cancer staging system (see Table 1).

Early stage disease FIGO Stage I-IIa

Surgery alone is still the first and best option for stage Ia and Ib, especially with well-differentiated, non-clear histologies. Adjuvant chemotherapy for poorly-differentiated clear-cell histology stage Ia and Ib can be considered. Stage Ic and stage IIa disease should be treated with adjuvant chemotherapy following surgery.[3,4]

Advanced disease FIGO Stage IIb-IIIc

The standard of care remains maximal debulking surgery by an experienced oncology gynaecologist first. The degree to which debulking is undertaken has been the subject of much research. It has generally been accepted that all visible tumour be bulk-reduced to a maximum size of two cm. However, in recent years, this has changed and the current standard is to bulk-reduce all visible tumour deposits to the extent that there is no visible remaining tumour or a maximum of one cm in diameter.[5]

Following maximum debulking surgery, adjuvant chemotherapy with a platinum and taxane are standard of care.[6] Neoadjuvant chemotherapy or interval debulking surgery is a consideration for those patients who are unable to undergo initial debulking surgery. Generally, three cycles of platinum-based chemotherapy followed by debulking surgery and another three cycles of platinum-based chemotherapy are given.[7] The advantages are easier surgery, less time in theatre, less blood loss and a shorter stay in hospital. The survival rate for patients undergoing primary or interval debulking surgery is the same.

Advanced stage ovarian cancer FIGO Stage IV

Where possible, these patients undergo primary debulking surgery followed by chemotherapy. If this is not possible, chemotherapy with interval debulking surgery can be considered. Unfortunately, in some patients even this is not possible; palliative chemotherapy with single-agent

platinum may be the only choice. Very advanced stage disease, poor performance status (PS), renal dysfunction and comorbidities may preclude even this treatment in some patients.

TREATMENT

INTRAPERITONEAL CHEMOTHERAPY

Intraperitoneal chemotherapy (IP) has been hotly debated in recent years; in fact, it is not a new modality of treatment, and several earlier studies describe this form of treatment. While the results of a recent trial are very promising, there were several methodological issues with the study, including the control arm.[8] Concerns about catheter placement, infection, catheter malfunction and abdominal pain have limited this approach to highly specialised units well-versed in the management of IP catheters and the problem of IP chemotherapy.

CHEMOTHERAPY

Since the 1970s, platinum-based chemotherapy has been used to treat ovarian cancer; initially with cisplatinum and later carboplatinum. The GOG III study demonstrated that cisplatinum and paclitaxel were superior to cisplatinum and cyclophosphamide.[9]

Table 1. FIGO staging of ovarian cancer

Stage I – Tumour is confined to the ovary/ovaries	
Ia	Only one ovary is affected by the tumour, the ovary capsule is intact No tumour is detected on the surface of the ovary Malignant cells are not detected in ascites or peritoneal washings
Ib	Both ovaries are affected by the tumour, the ovary capsule is intact No tumour is detected on the surface of the ovaries Malignant cells are not detected in ascites or peritoneal washings
Ic	The tumour is limited to one or both ovaries, with any of the following: The ovary capsule is ruptured The tumour is detected on the ovary surface Positive malignant cells are detected in the ascites or peritoneal washings
Stage II – Tumour involves one or both ovaries and has extended into the pelvis.	
IIa	The tumour has extended and/or implanted into the uterus and/or the fallopian tubes Malignant cells are not detected in ascites or peritoneal washings
IIb	The tumour has extended to another organ in the pelvis Malignant cells are not detected in ascites or peritoneal washings
IIc	Tumours are as defined in IIa/b, and malignant cells are detected in the ascites or peritoneal washings
Stage III – The tumour involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph-node metastasis. Includes liver capsule metastasis.	
IIIa	Microscopic peritoneal metastasis beyond the pelvis
IIIb	Microscopic peritoneal metastasis beyond the pelvis, 2 cm or less in greatest dimension
IIIc	Microscopic peritoneal metastasis beyond the pelvis, more than 2 cm in greatest dimension and/or regional lymph nodes metastasis
Stage: IV – Distant metastasis beyond the peritoneal cavity and liver parenchymal metastasis.	

Subsequently, carboplatinum was substituted for cisplatinum and the results did not differ. As the incidence of renal toxicity is lower with carboplatinum, the standard of care became carboplatinum and paclitaxel (colloquially known as carbo/taxel). Carboplatinum and docetaxel are equivalent to carboplatinum and paclitaxel.[10] The difference is in the toxicity profile, with more neurotoxicity seen with paclitaxel and more myelosuppression with docetaxel.

The addition of a third or even a fourth chemotherapy agent to the carboplatinum and taxane backbone has not improved outcome, but has merely increased the toxicity. There have been multiple trials of this nature, but none has improved survival rates. The use of single-agent carboplatinum as opposed to the doublet is sometimes recommended in poor PS patients with multiple comorbidities who are unable to tolerate the toxicity of this combination. This follows the results of ICON 3 where carboplatin and paclitaxel as standard of care were compared to single-agent carboplatin or to a third arm of cyclophosphamide, adriamycin and cisplatin.[11] The outcome of all three arms was similar.

ANTI-ANGIOGENIC AGENT

There has been no further improvement in the outcome of patients treated with standard-of-care chemotherapy for the past 15 years. Ovarian cancer, by its nature, is known to be a highly vascular tumour. The addition of bevacizumab as anti-angiogeneic agent has recently been tested in two large phase III studies.

Both the GOG 218 trial and the ICON 7 trial demonstrated no overall survival benefit.[12,13] Both studies added bevacizumab to the carboplatin/paclitaxel backbone, although the dose differed: 15 mg/kg in the GOG 218 and 7.5 mg/kg in ICON 7. Other differences included the cycle at which the bevacizumab was initiated and the number of cycles (months) the bevacizumab was continued (16 cycles in GOG 218 and 12 cycles in ICON 7).

Despite these differences, there was a clear benefit in progression-free survival in both studies, for the arms containing bevacizumab with chemotherapy and followed by maintenance bevacizumab. Unfortunately, there was no clear overall survival benefit.

In a subset of patients with high-risk disease, a survival benefit was seen. Following the results of two trials with bevacizumab, research with multiple new agents, including tyrosine kinase inhibitors (TKIs), is ongoing.

RELAPSED OVARIAN CANCER

The majority (80%) of patients with ovarian cancer will suffer a relapse. The choice of subsequent lines of chemotherapy is then determined by the platinum-free interval. This is defined as the time interval from the last platinum dose until progressive disease. In general, those patients with platinum-refractory or resistant disease have a poor prognosis and do not benefit from the re-introduction of a platinum-containing regimen. The response rates of liposomal doxorubicin, topotecan, paclitaxel and gemcitabine are similar in this setting.

The re-introduction of a platinum-based regimen is, however, recommended in patients with partially-sensitive tumours and especially fully-sensitive tumours. Following the results of the CALYPSO study,[14] pegylated liposomal doxorubicin with carboplatin is often recommended, but other regimens such as carboplatin and gemcitabine also show responses.

Finally, the OCEANS study[13] showed clear progression-free survival benefit of the addition of bevacizumab chemotherapy, as did the AURELIA study,[15] the latter study being in the refractory setting. In both studies, bevacizumab was added to a chemotherapy backbone and continued until disease progression.

CANCER OF THE CERVIX

Squamous carcinoma of the cervix is the most common histological subtype. Other histological subtypes include adenocarcinoma and small-cell carcinoma. The mainstay of cancer of the cervix remains

surgery followed by chemoradiation with the use of cisplatin as a radiosensitiser. The treatment of locally recurrent disease is surgery, if possible, or radiation if this has not been given previously. For advanced or recurrent disease, chemotherapy can be considered. Single agents such as platinum alone, paclitaxel or topotecan all have response rates. Combination chemotherapy with platinum and paclitaxel has been demonstrated with a modest survival benefit of approximately two months with significant toxicity.[16]

Adenocarcinoma of the cervix carries a very poor prognosis. Small-cell carcinoma should be treated in a similar manner to small-cell carcinoma of the lung.

ENDOMETRIAL CANCER

The treatment recommendations for early-stage disease, stages I to III are primarily surgery followed by radiation therapy. The GOG 122 trial[17] compared whole abdominal radiotherapy to adjuvant chemotherapy in patients with stages III to IVa disease. There was both a progression-free as well as an overall survival benefit that favoured the chemotherapy arm of doxorubicin and cisplatin. This form of adjuvant chemotherapy has not been widely used because the control arm in the study was not considered a standard of care. Chemotherapy used as a single agent or in combination has been studied in stage IV disease.

Randomised trials including doxorubicin alone or in combination have failed to show a survival advantage. The GOG 177 trial[18] compared platinum plus paclitaxel to the same combination together with doxorubicin (TAP). A progression-free and an overall survival benefit were seen, but at the expense of considerable toxicity, including grade 3 symptomatic heart failure. Granulocyte colony-stimulating factor (G-CSF) was required.

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Prostate Cancer

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Second to lung cancer, prostate cancer is the most commonly diagnosed cancer in men 50 years and older. This is true for developed countries as well as developing countries.[1] In the USA, the incidence of prostate cancer is 160 per 100 000.[2]

IMPACT ON SOCIETY

Until 2004, the development of castration-resistant prostate cancer was a uniformly lethal event. These patients mostly developed skeletal-related events. Docetaxel, which prolonged survival, and zoledronic acid, a bisphosphonate, which delays the progression of skeletal-related events had a significant impact on the disease. Since then, findings demonstrating the benefit of early chemotherapy together with three new drugs have added to our ability to curb the impact.

During the last decades, mortality rates have declined sharply, mainly because of improved treatments and earlier diagnosis.

It is not only mortality, but morbidity, lack of productivity (in younger working-age men) and the financial burden of costly treatment that impact on society.

DIAGNOSTIC ISSUES

A number of methods are used in the diagnosis of prostate cancers and there are several diagnostic issues to consider.

These include:

- **PSA** – Prostatic-specific antigen (PSA) for adenocarcinomas of the prostate
- **DRE** – Digital rectal examination (DRE)
- **TRUS** – Transrectal ultrasound (TRUS) and biopsy.

Compared to DRE, the appropriate use of PSA alone can give a diagnostic advantage of five to 10 years. PSA levels of more than 4 ng/ml lead to an approximate 30-35% increase in the likelihood of detecting prostate cancer at prostate biopsy. Men with this level should be encouraged to undergo TRUS-guided biopsy.

- **PSA velocity and free fraction** – velocity is the increase of PSA values over time. A cut-off of 0.75 ng/ml per year increases the sensitivity of PSA testing alone. It is recommended that three levels of PSA be obtained over an 18-month period. Free PSA is significantly lower in men who have prostate cancer compared with men who do not have prostate cancer. A free PSA level of 25% and below in patients with a PSA of 4-10 ng/ml detected 95% of prostate cancers; above this level very few prostate cancers are diagnosed.[3]
- **Screening** – PSA, although very useful in diagnosis, is now challenged as it does not seem to reduce prostate cancer mortality. If it does reduce mortality, the reduction is likely to be small. The European Randomised Study of Prostate Cancer (ERSPC) concluded, however, that PSA screening could reduce prostate cancer mortality. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) showed no or very little reduction in prostate cancer mortality.[4]
- **Imaging** – diagnostic work-up prior to a decision on the treatment modality of choice should include a detailed pelvic MRI to the risk factors (see below).

PATHOPHYSIOLOGY

More than 95% of cancers of the prostate are adenocarcinomas. Most tumours arise in the peripheral zone of the prostate.

GLEASON SCORE

Histological grading is one of the most important variables in prognosis determination. Five distinct patterns, from well- to poorly-differentiated, were described in the original Gleason grading scale. The

sum of the grades of the most common and the second most common growth patterns give the final Gleason Score – e.g., 3 + 4 = 7. The higher Gleason Scores (e.g., 8-10) have the worst prognosis.

PROSTATE RISK-BASED APPROACH TO TREATMENT

RISK FACTORS AND STRATIFICATION

The following factors play a role in selecting the correct initial treatment: anatomic extent of disease (The American Joint Committee on Cancer [AJCC] TNM stage), histological grade (Gleason/Grade group), PSA, expected outcome of each treatment, potential complications of each treatment and patient's general condition: life expectancy and comorbidities.

Since 2014, the International Society of Urological Pathology (ISUP)[5] consensus group has implemented the new Grade Group system which uses the traditional Gleason scoring to classify findings in five groups (see Table 1).

The National Comprehensive Cancer Network (NCCN) guidelines recommend that risk-appropriate treatment should be offered to patients. Very low-, low-, intermediate-, high- and very high-risk groups are identified. For each, group-specific options are recommended. Metastatic disease is set out as a separate entity with different treatment lines.

Table 2 explains the various risks groups. Very-low-risk patients must have disease that is detectable by PSA only (i.e., not on imaging or DRE) with Grade Group 1 disease and PSA <10.

Table 1. International Society of Urological Pathology (ISUP) Grade Group classification system

Grade group	Gleason score and pattern
1	Grade 6 (3+3)
2	Grade 7 (3+4)
3	Grade 7 (4+3)
4	Grade 8 (4+4, 3+5, or 5+3)
5	Grade 9 or 10 (4+5, 5+4, or 5+5)

Source: Adapted from Epstein JI, Egevad L, Amin MB, et al. *The 2014 International Society of Urological Pathology (ISUP), Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System.* Am J Surg Pathol. *2016;40:244*

Table 2. Pretreatment risk stratification for prostate cancer

Risk group	Clinical stage	Gleason Score	Serum PSA
Standard risk groups			
Low-risk	T1c-T2a	≤6	<10 ng/mL
Intermediate-risk	T2b	7	10 to 20 ng/mL
High-risk	T2c	8 to 10	
Risk groupings used by Memorial Sloan-Kettering and Seattle groups[1, 2]			
Low-risk	≤T2a	≤6	<10 ng/mL
Intermediate-risk	One elevated risk factor: Clinical stage ≥T2a disease, Gleason score ≥7, PSA ≥10 ng/mL		
High-risk	Two elevated risk factors		

PSA: prostate specific antigen; T1c: tumour identified by needle biopsy (e.g., because of elevated PSA); T2a: tumour involves one-half of one lobe or less; T2b: tumour involves more than one-half of one lobe, but not both lobes; T2c: tumour involving both lobes

Source: 1. Zelefsky M, et al. Int J Radiat Oncol Biol Phys. *2000;47:1261. 2. Blasko J,* et al. Int J Radiat Oncol Biol Phys. *2000;48:111*

TREATMENT OPTIONS

Traditional thinking such as local, locally advanced and metastatic is useful, but when patients are classified in the risk groups set out in Table 2, treatment options can be better selected.

When a patient suffers metastatic disease, the intent must be clear: prolonged survival, symptom control or supportive care only. See Figure 1 for an algorithm for the treatment of prostate cancer.

ACTIVE SURVEILLANCE

Patients eligible for active surveillance have very low-risk disease.

Advantages of this approach is the delay of interventional treatment – e.g., radical prostatectomy, external beam radiation therapy (EBRT) and hormonal management – deferring the treatment to avoid side effects, but still treating curatively when indicated.

The advantages of active surveillance include prevention, avoidance of danger of anaesthesia and complications during surgery (i.e., erectile dysfunction [ED], incontinence, rectal damage); radiotherapy damage to surrounding organs (i.e., bladder and kidneys and ED in some patients), hormonal issues with ED, osteoporosis, depression and gynaecomastia.

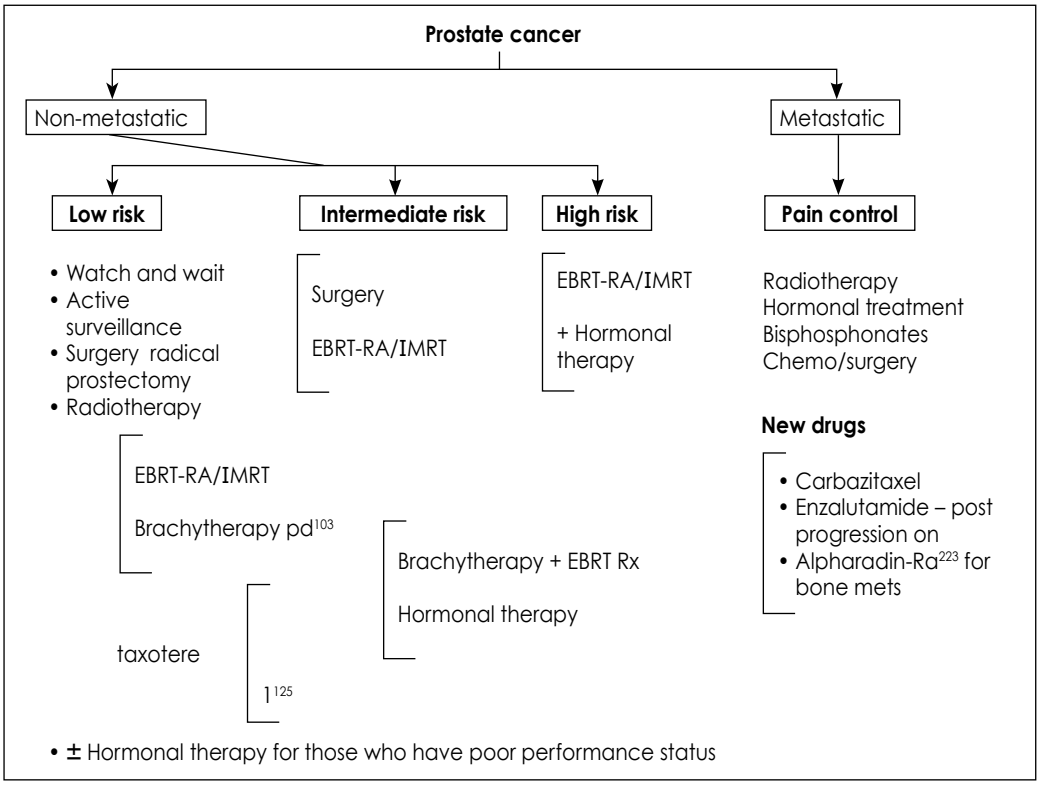
Disadvantages of active surveillance are anxiety and depression from frequent investigations, sepsis and infections from repeated biopsies and higher mortality due to disease progression in some patients.

Surveillance implies PSA evaluation every three to six months, annual DRE and multiparametric MRI, as well as annual biopsy.

The following criteria define clinically significant progression:

- PSA progression: PSA doubling time in less than three years based on multiple PSA readings at three-monthly intervals

Figure 1. Algorithm for the treatment of prostate cancer



IMRT - intensity-modulated radiotherapy; RA - RapidArc; EBRT - external beam radiation therapy

- Clinical progression: doubling of size is determined by TRUS or DRE, local progression or distant metastases
- Gleason Score progression on repeat biopsies.

RADICAL PROSTATECTOMY (PLUS OR MINUS LYMPH-NODE DISSECTION)

Eligible patients include all risk groups if general medical condition, life expectancy and possible complications are justified. (Prostatectomy in metastatic disease is still regarded as experimental and should be done in a clinical trial situation.)

The advantage of radical prostatectomy, plus or minus lymph-node dissection, is the potential of complete cure and/or effective long-term control.

Full pathological staging is possible and gives detail on the spread and character of the tumour. The disadvantages are anaesthetic and other possible complications during surgery, which include bleeding, embolism, mortality risks, incontinence post-surgery, and impaired erectile function. The patient should discuss various procedures, i.e., open (retro-pubic or perineal) or robotic-assisted, with his urologist.

EXTERNAL BEAM RADIOTHERAPY

Eligible patients are from all risk groups, but it is ideal for intermediate-risk groups as all lymph-node groups can be covered in the treatment fields.

The minimal radiotherapy for radical treatment should be conformal radiotherapy (CRT). Intensity-modulated radiotherapy (IMRT) allows for the sparing of other pelvic organs – e.g., bladder and rectum, reducing possible side effects considerably. Image-guided radiotherapy techniques take organ movement into consideration.

The advantages are long-term cancer control; in fact the procedure can be curative. These are non-invasive treatments reducing the risk of urinary incontinence. Erectile function is often preserved. Patients can remain productive at work and attend radiation before or after work.

The disadvantages of these treatments are that they are delivered over a period of six weeks of daily treatment. Acute symptoms appear typically during the third week of radiation and resolve within days or weeks after completion of radiotherapy.

Late toxicities include chronic urethritis in 10% of patients with strictures in 2% of patients. Haemorrhagic cystitis has become uncommon with CRT.

Grade 2 or 3 rectal toxicities at 10 years are 8% for CRT and 1% for IMRT. Impotency rates after EBRT vary in reports between 36% and 68% three years after treatment. The heterogeneity in the population treated with EBRT probably explains the variability of erectile dysfunction.

Newer radiotherapy systems use RapidArc volumetric-modulated arc therapy (VMAT) techniques, delivering high doses in shorter treatment times with high accuracy levels. This allows for dose escalation.

PROSTATE BRACHYTHERAPY

Eligible patients have local disease, thus very low risk, low risk, or by exception intermediate risk.

Ultrasound transperineal image-guided placement of seeds has shown improved long-term outcomes with reduction of treatment-related complications. High doses of radiation delivered directly (and only) result in good tumour outcomes with cancer-control rates equal to surgery and EBRT. However, good results can also be obtained in patients with low risk (varying between 85% and 95%) and in intermediate-risk cases (between 48% and 63%).[3]

For seed implant, the gland size should ideally be below 60 cm^3 (MRI scans, TRUS and DRE).

Types of treatment are:

- Low-dose-rate (LDR) permanent seed implants
- High-dose-rate (HDR) brachytherapy where transperineal catheters are placed in the prostate after loading with high-dose-rate isotope: more than one fraction is used for this technique.
- Brachytherapy plus external beam radiotherapy. In these cases, a lower dose of external beam radiotherapy is delivered to the para-prostatic tissue (45 Gy to 50 Gy) compared to 74 Gy

and higher where only EBRT is used. It can be argued that this will lead to underdosing of para-prostatic spread of the cancer.

Disadvantages of brachytherapy: This is an invasive technique, causing a risk of infections and bleeding, impotence, strictures of the urethra treated with dilatations and gastro-intestinal morbidity – e.g., rectal bleeding, rectal ulcer or prostatorectal fistulae (rare).

HORMONAL MANAGEMENT

Hormone treatment includes androgen deprivation therapy (ADT) which results in medical castration and anti-androgen therapy. Anti-androgen drugs are classified as first- and second-line receptor blockers (such as bicalutamide, enzalutamide cyproterone acetate) or an androgen synthesis inhibitor (abiraterone acetate).

Eligible patients are from intermediate risk-, high- and very high-risk groups, as well as those with metastatic disease.

Androgen-deprivation therapy

Sustained-release luteinising hormone-releasing hormone (LHRH) agonists and antagonists are available in one-month, three-month and six-month formulations. Phase II data indicate equivalence between agonists and antagonists. Antagonists (Degarelix) do not result in the flare-up of symptoms and are therefore indicated in cord compression and cases of severe outflow obstruction.

Androgen-deprivation therapy (ADT) is used:

- In combination with radiotherapy for a limited time period, depending on the risk group. This has shown to increase the radiation effectiveness with better outcomes
- In relapsed patients after radiotherapy and/or surgery
- In metastatic disease
- As the only therapy in frail patients with limited life expectancy.

Intermittent *versus* continuous ADT has been tested in large randomised studies, with the latter showing a reduction in prostate-cancer mortality compared to the intermittent regimen. While ADT has a major role to play in improving results of treatment and managing symptomatic disease, patients who rely on ADT alone will ultimately relapse.[4]

Disadvantages of ADT include hot flushes, libido loss and erectile dysfunction. Later changes in weight, hair, muscle, bone, fat, testicular size, penile length and gynaecomastia have been observed.

Anaemia, hyperlipidaemia and hyperglycaemia have also been recorded. Fatigue, depression and emotion variations may also occur. In castration-resistant prostate cancer, ADT should not be stopped as some prostate-cancer cells remain sensitive.

Abiraterone acetate (Zytiga) is a selective inhibitor of CYP 17, a key enzyme along the biosynthesis of androgens – both in the adrenal glands and in tumour cells. It has demonstrated significant anti-tumour activity (PSA declines by 50% in 50-60% of both chemo-naive and chemo-refractory metastatic castration-resistant prostate cancer). It has demonstrated improved OS (14.8 *vs* 10.9m, HR 0.65, 95%CI0.54-0.77) in the post-docetaxel setting [6] and in the pre-chemo setting [7] (although not statistically significant).

Abiraterone is generally well tolerated, but does cause some fluid retention, and hypokalaemia in rare cases. If hypertension develops, it should be treated, but the drug must be continued as long as there is a clinical benefit.

Enzalutamide (Xtandi) is a novel androgen receptor signal inhibitor. It has shown an overall survival benefit *vs* placebo in the AFFIRM trial in patients' post progression on docetaxel.[8] Median survival was 18.4 *vs* 13.6 months with HR 0.63;95% CI, 0.53-0.75). It was superior in all secondary parameters, namely PSA reduction, time to progression, radiological progression-free survival and time to first skeletal-related event.

Enzalutamide is well tolerated, with later onset of fatigue, mild diarrhoea and hot flushes. It does not require the use of concomitant steroids.

In the pre-chemo setting (Prevail trial)[9], enzalutamide also showed a 29% reduction in the death rate at the time of data cut-off and benefit on the secondary endpoints. The same side effect profile was observed.

Chemotherapy

In patients with metastatic disease showing progression after hormonal management, chemotherapy is indicated.

Docetaxel has been shown to reduce pain, lower PSA levels and increase the survival rate. Docetaxel can be used at three-weekly intervals or at a lower dose at weekly intervals. The addition of prednisone 10 mg daily will improve response.

Cabazitaxel, a second-generation taxane, has been shown to increase survival in patients who have failed docetaxel therapy. In a phase III trial,[10] cabazitaxel plus prednisone significantly increased survival compared with mitoxantrone plus prednisone in men whose disease had progressed on docetaxel. An initial report of a phase III trial found that a dose of 20 mg/m^2 was as effective and less toxic than the approved dose of 25 mg/m^2. This mitigates the side effects typical of taxanes to a level similar to and less than those of docetaxel.

Intravenous radiation: Radium-223 (Xofigo)

Radium-223 (223-Ra), a new intravenously administrated radionuclide (alpha particles), demonstrated improvement in survival in patients with castration-resistant prostate cancer with bone-only metastatic disease. It can also be used to improve pain symptoms.

In the phase III Alsympca trial[11], a monthly infusion was well tolerated, and improved overall survival (14 vs 11.2 months, HR 0.7, 95% CI 0.55-0.88), and assessment of all secondary endpoints (time to first symptomatic skeletal event and biochemical parameters) was positive as well.

Side effects included myelosuppression and mild diarrhoea, however patients generally tolerate these very well. Regrettably, the treatment is costly and few funders will allow access to 223-Ra.

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Kidney and Bladder Cancers

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KIDNEY CANCER

The two most common types of kidney cancer are renal cell carcinoma (RCC) and urothelial carcinoma of the renal pelvis. RCC constitutes approximately 85% of primary renal neoplasms. Urothelial (transitional cell) carcinomas of the renal pelvis account for approximately 8% of kidney tumours, and other parenchymal epithelial tumours are rare. The rest of this discussion will focus on RCC, while urothelial cell carcinomas are covered in the section on bladder cancer.

EPIDEMIOLOGY

The incidence of RCC varies globally from region to region, with the United States having approximately 65 000 new cases annually and approximately 13 500 deaths each year. In South Africa, there are an estimated 500 to 600 new cases per year. RCC is approximately 50% more common in men compared to women, occurring predominantly in the sixth to eighth decade, with the median age of diagnosis at 64 years.

RISK FACTORS

Cigarette-smoking possibly contributes to one-third of cases and is also associated with more advanced disease at presentation. Hypertension and obesity, occupational exposure to toxic compounds such as cadmium, asbestos and petroleum products, analgesic abuse and nephropathy all contribute to the development of RCC. Acquired cystic disease of the kidney, chronic hepatitis C infection and sickle cell disease are also linked to increased incidence of RCC.

Although most RCCs are sporadic, several syndromes associated with RCC have been described. Specific inherited syndromes associated with renal cell carcinoma include von Hippel-Lindau disease, tuberous sclerosis complex, hereditary papillary renal carcinoma, hereditary paraganglioma and pheochromocytoma. Factors that favour a hereditary contribution in patients without a clear genetic disease include first-degree relatives with a tumour, onset before the age of 40, and bilateral or multifocal disease.

PATHOLOGY

All solid renal masses require resection or biopsy for accurate diagnosis unless the presence of a metastatic lesion can be established by biopsy. RCCs are classified to reflect the morphology, growth pattern, cell of origin, and the histochemical and molecular basis of the different types of adenocarcinomas.

The subtypes of RCC include:
- Clear-cell (75-85%)
- Papillary (chromophilic 10-15%)
- Chromophobe (5-10%)
- Oncocytic
- Collecting duct (Bellini's duct)

Clear-cell carcinomas typically have a deletion of chromosome 3p and arise from the proximal tubule. A poor prognosis is associated with a higher nuclear grade or the presence of a sarcomatoid pattern.

TREATMENT

Localised (resectable) RCC

Surgery is potentially curative in the majority of patients with localised RCC and is therefore the preferred treatment for patients with stages I, II and III disease. Treatment can involve either a radical nephrectomy or a variety of renal-sparing approaches (partial nephrectomy or ablative techniques) in carefully selected patients, depending upon the extent of disease.

Patients who are not candidates for surgical resection, such as elderly patients

and those with significant comorbidity, could be considered for non-surgical procedures such as cryoablation, radiofrequency ablation (RFA), embolisation and palliative radiotherapy.

Attempts to improve control after surgery by adding adjuvant therapy is not standard care despite a positive trail (S-TRAC)[1] in which observation was compared to one-year adjuvant sunitinib. (There was a statistical progression-free survival, but no overall survival benefit, and toxicity was such that it is not generally recommended.)

Advanced disease (stage IV)

Almost all patients with metastatic renal cell cancer (mRCC) are incurable. The selection of treatment depends on many factors, including prior treatment and site of recurrence, as well as individual patient considerations, such as performance status (PS).

Options include surgery, immunotherapy, molecular targeted therapy and radiation for the management of metastatic lesions.

Surgery

Nephrectomy can aid in the palliation of symptoms caused by the primary tumour, related ectopic hormone or cytokine production. Two randomised studies have demonstrated an overall survival benefit in selected patients with metastatic disease who have undergone initial cytoreductive nephrectomy prior to the administration of interferon-alpha (IFN).[2,3]

Patients with solitary or a limited number of distant metastases can achieve prolonged survival with nephrectomy and surgical resection of the metastases. This is more likely in patients with a long disease-free interval between the initial nephrectomy and the development of metastases.

Cytokine therapy

Cytokine therapy represents the early days in immunotherapy. Although there are data from the mid-1990s to substantiate the use of interleukin-2 (IL-2), it has not been compared to the new-generation checkpoint inhibitor and is generally not offered any more.

TARGETED THERAPIES AND CHECKPOINT INHIBITORS

A growing understanding of the biology of RCC has led to the development and registration of several targeted therapies and immune checkpoint inhibitors.

Targeted agents either block the mammalian target of rapamycin (mTOR), while a number of agents target the vascular endothelial growth factor (VEGF) pathway through tyrosine kinase inhibitors (TKIs) or monoclonal antibodies (MAB).

Checkpoint inhibitors block the programmed cell-death protein or ligand (PD or PD-L) through monoclonal antibodies.

mTOR target inhibitors

Two mTOR inhibitors, temsirolimus and everolimus, have shown clinical activity in RCC.

Temsirolimus, an intravenously-administered mTOR inhibitor, has resulted in prolonged overall survival (OS) compared with IFN in a phase III randomised controlled trial that enrolled intermediate- and poor-risk patients. The hazard ratio (HR) for death was 0.73 (95% CI, 0.58-0.92, p = 0.008).[4]

Everolimus is an orally administered mTOR inhibitor that was evaluated in a second-line phase III trial in patients with metastatic RCC with a clear-cell component that had progressed during or within six months of stopping treatment with sunitinib or sorafenib.[5]

Based on these results, everolimus is indicated for patients with metastatic clear-cell RCC who have progressed on previous vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs), while temsirolimus is indicated for poor-risk disease. Although the benefit associated with everolimus is significant in comparison to placebo, its value relative to other TKIs remains to be determined.

The most frequent side effects of the mTOR inhibitors were asthenia, rash, anaemia, lymphopaenia, nausea, and anorexia. Severe adverse events were uncommon; the most frequent grade 3 or 4 adverse events were anaemia, asthenia, hyperglycaemia and pneumonitis. Hypersensitivity reactions have been reported

and may be severe or life-threatening and therefore premedication is recommended.

Angiogenesis target inhibition: mAb and VEGF TKIs

Bevacizumab is a mAb that binds circulating VEGF and prevents its interaction with the VEGF receptor. Two phase III trials have demonstrated improved progression-free survival (PFS) with bevacizumab plus IFN compared to IFN alone.[6]

The most important adverse events in the bevacizumab arm included hypertension, thrombo-embolic events, bleeding and gastro-intestinal perforation.

Sunitinib is a multikinase inhibitor targeting VEGFR-1, VEGFR-2, PDGFR and c-Kit. It was more effective compared to IFN in a phase III trial of 750 patients, with good- or intermediate-prognosis metastatic clear-cell RCC, in the first-line setting.[7]

Sorafenib is a small molecule inhibitor of multiple TKs, including VEGF receptor 2, FLT3, PDGF receptor, and fibroblast growth factor receptor-1 (FGFR1), as well as C-RAF and B-RAF. In the phase III TARGET trial, patients with advanced RCC who had failed prior standard therapy were randomly assigned to sorafenib or placebo. The median PFS was significantly longer in those receiving sorafenib compared with placebo.[8]

Axitinib is an orally available inhibitor of the VEGF receptors 1, 2, and 3. Its registration was based on the AXIS phase III trial in second-line metastatic clear-cell RCC patients who were randomly assigned to treatment with either axitinib or sorafenib.[9]

Pazopanib is an oral agent multikinase inhibitor that was approved for patients with previously untreated advanced renal cell carcinoma and for patients who had progressed on cytokine therapy.[10]

Checkpoint inhibitors

Immunotherapy with mAbs directed against PD-1 or cytotoxic T-lymphocyte antigen (CTLA-4) has become an important part of the treatment of mRCC.

Nivolumab (PD-1 inhibitor) has been approved as a second-line therapy following TKI therapy based on a phase III trial[11] where overall survival and response rate was better than everolimus. (Median OS 25 *versus* 19.6m, HR 0.73, 95% CI 0.57-0.93.) The toxicity profile was also more favourable. The combination of nivolumab and ipilumimab (CTLA-4 inhibitor) has been approved in treatment-naïve patients.[12]

Other mAbs (atezoluzimab and pembrolizumab) are also being trialled in this setting, but results are not yet published. Various combinations of PD-1 inhibitors with TKIs are being investigated and seem promising.

Patterns of response differ from those with molecular targeted agents or cytotoxic chemotherapy. Special immune-response criteria were developed for patients in the setting of melanoma and now apply here as well. Lesions may undergo progression before they respond, take long to respond or shrink and become long-term responders.

Toxicity of these mAbs is completely different to that of chemotherapy and typically presents with skin, gastro-intestinal and later endocrine abnormalities. The full clinical picture is still unfolding as follow-up after treatment reflects the long-term side effects.

Price will limit access as all of these drugs are very expensive.

NON-CLEAR-CELL RCC

The activity of agents such as sunitinib, sorafenib and temsirolimus in patients with non-clear-cell RCC still has to be confirmed, although preliminary results and subset analyses suggest that these agents have some activity. Subsets of non-clear-cell tumours occasionally also respond to chemotherapy. Major responses have been reported with various combinations of platinum agents, taxanes, gemcitabine and doxorubicin in patients with collecting-duct tumour and sarcomatoid RCCs. Immunotherapy is being investigated in this setting.

BLADDER CANCER

Bladder cancer is the most common cancer of the urinary tract with a peak incidence in the sixth to eighth decade. An

estimated 1 600 new cases are diagnosed in South Africa each year.

RISK FACTORS

Exposure to tobacco remains the biggest risk factor. Smoking is associated with over half of bladder cancer cases in men and one-third of cases among women. Men are three times more likely to develop bladder cancer than women. Occupational exposure to chemicals may also play a role; metalworkers, mechanics and hairdressers seem to have increased risk.

SIGNS AND SYMPTOMS

Bladder cancer characteristically causes painless macroscopic or microscopic haematuria. Other possible symptoms include dysuria or painful micturition, frequency or urgency.

DIAGNOSIS

The gold standard for diagnosing bladder cancer is biopsy obtained during cystoscopy. It is also important for accurate staging, which determines further management, since the major prognostic factors in carcinoma of the bladder are the depth of invasion into the bladder wall and the degree of differentiation of the tumour.

PATHOLOGY

The most common pathology in bladder malignancy is urothelial or transitional cell carcinoma (85-90%). Other histologies include squamous carcinoma, adenocarcinoma, small-cell cancer, lymphomas and sarcomas.

TREATMENT

The management of bladder cancer can be divided into three broad groups, based on the stage of the disease:

- Non-muscle-invasive disease
- Muscle-invasive disease
- Metastatic disease.

Non-muscle-invasive disease

The initial treatment of non-muscle-invasive bladder tumours is a complete transurethral resection of the bladder tumour (TURBT), which is usually carried out at the time of diagnosis. Many patients can be successfully managed with a localised resection.

Additional intravesical therapy is generally recommended for patients with intermediate- to high-risk, non-muscle-invasive bladder tumours. This option results in high local concentrations of a therapeutic agent within the bladder, decreasing the risk of recurrence and the need for cystectomy. Bacillus Calmette Guerin (BCG) is the most commonly used agent for intravesical immunotherapy for high-grade disease (Ta, Tis, T1). Mitomycin C is the most commonly used chemotherapy agent and is appropriate for the intravesical use for intermediate-risk disease.

Following initial treatment, careful surveillance for secondary tumours of the urinary tract is required for both low- and high-risk patients. Additional primary tumours can develop in the urothelium anywhere along the genito-urinary tract. Subsequent surveillance should include a careful programme of cystoscopy and urine cytology.

Indications for cystectomy include progression to high-grade disease (Tis or T1) or multiple tumours with frequent recurrences within a short period of time, despite treatment or complications such as bleeding with anaemia and any muscle-invasive (T2) disease.

Muscle-invasive disease

Radical cystectomy with a urinary diversion is the mainstay of treatment for muscle-invasive bladder cancer. Radical cystectomy entails removal of the bladder, adjacent organs, and regional lymph nodes.

Neoadjuvant chemotherapy has been shown in randomised clinical trials to result in a survival advantage for patients with muscle-invasive bladder cancer who receive such chemotherapy prior to undergoing cystectomy, and should be considered for all eligible patients. Cisplatin-based chemotherapy (see section on metastatic disease) is the standard in this setting.[11]

Postoperative adjuvant chemotherapy has been studied in several small phase III trials as an alternative to neoadjuvant treatment. Meta-analyses of these trials suggest a survival benefit when patients are given chemotherapy following radical cystectomy. This is a reasonable option for high-risk patients who have not had neoadjuvant chemotherapy.

Most patients with bladder cancer would, if possible, prefer to keep their native bladder. Use of multimodal approaches, including complete TURBT, radiation therapy, and chemotherapy, used together or in sequence, offers an alternative to radical cystectomy, preserving the bladder and its function while providing long-term disease control for carefully selected patients. The pooled analysis of the RTOG (2014)[13] included 468 patients who had chemo-radiation; the response rate was 69% and disease-specific control rates were 71% at five years.

Patients with extensive comorbid disease, or those who are otherwise not candidates for radical cystectomy, could be considered for radiotherapy, with or without chemotherapy, or alternatively chemotherapy alone.

Metastatic disease: chemotherapy and immunotherapy

A cisplatin-based combination chemotherapy regimen is the preferred initial therapy for patients with metastatic urothelial cancer who are cisplatin candidates. Cisplatin-based combination chemotherapy results in superior survival when compared with single-agent cisplatin. Not all patients with urothelial cancer are appropriate candidates for cisplatin therapy.

Other regimens include MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) or GC (gemcitabine and cisplatin). Given the similar efficacy and lesser toxicity, GC rather than MVAC is often considered as the standard first-line regimen for patients with advanced urothelial carcinoma of the bladder.[14]

For those patients who are candidates for chemotherapy, but not able to receive cisplatin, usually because of poor renal function, the combination of gemcitabine and carboplatin is a reasonable alternative.[15]

Single-agent therapy or taxane-based regimens could be considered for these patients. The combination of gemcitabine with a taxane rather than a platinum has been evaluated,[16] with encouraging results.

Since up to 50% of patients with advanced RCC are not candidates for chemotherapy due to age or comorbidities (e.g., renal function, heart failure, neuropathy and so on), immunotherapies were investigated and reported great phase II data.

PD-1 inhibitors (pembrolizumab and nivolumab) and PD-L1 inhibitors (atezolizimab, avelumab and durvalumab) have all shown survival advantage in trials in the second-line setting and acceptable toxicity. Phase III trials are currently being run to test these drugs in the first-line setting, adjuvant and neoadjuvant setting.

SECOND-LINE THERAPY

Although a significant number of patients responds objectively to first-line therapy, most eventually progress (median survival with chemotherapy is 15 months) and may be candidates for second-line chemotherapy. A number of chemotherapy agents has clinical activity after patients have progressed on MVAC or GC.

These agents include paclitaxel, docetaxel, vinflunine, ifosfamide and oxaliplatin. None of these agents can, however, be considered as standard second-line therapy. Patients with advanced bladder cancer who have failed an initial chemotherapy regimen should be encouraged to participate in clinical trials whenever possible.

Immunotherapy has proven survival data in this setting. All five of the mAbs listed above are approved by the FDA. The Keynote-045 trial[17] compared pembrolizumab *versus* platinum-containing chemo and showed a 10.3 *versus* 7.4 m OS, HR 0.7, 95% CI 0.57-0.86. The difference was even bigger at 12 and 18 months, again demonstrating that if the immune system can be correctly activated longer-term response is possible.

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Treatment Options for Inoperable and Metastatic Malignant Melanoma

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Malignant melanoma accounts for less than 5% of all cutaneous malignancies, yet it is responsible for the majority of skin-cancer deaths. The incidence of melanoma has been steadily increasing over the past few decades and is currently the fifth most common cancer in men and the sixth most common cancer in women worldwide, accounting for 6% and 4% of new cancer cases respectively.[1] The average age at diagnosis is 57 years, with the highest incidence occurring between 55 and 74 years of age.[2] In addition, melanoma is the second most common cancer in young adults (age 15 to 29 years).[3]

The vast majority of melanomas (84%) present at an early stage and may be curatively managed with surgical resection. This provides excellent five-year overall survival rates which approach 98%. Locoregional nodal metastases are found in 9% of patients at diagnosis, and here the five-year overall survival rates are around 63%. Four percent of patients will have inoperable or metastatic disease at diagnosis. For these patients, and for those who develop recurrent or metastatic disease following initial definitive therapy, treatment options are limited, and five-year survival rates are less than 20%.[2]

Treatment for metastatic disease comprises systemic therapy with or without radiotherapy. Highly selective patients may be suitable for metastatectomy. Traditional approaches utilising cytotoxic chemotherapy have shown disappointing results. Chemotherapy has not been shown to improve overall survival and response rates are typically less than 20%. Those that do respond, have a median duration of response of less than six months.[3] In an attempt to improve outcomes, recent years have seen the emergence of several novel treatment options. In melanoma, these largely comprise immunotherapies and targeted therapies. Immunotherapy aims to destroy malignant cells by inducing or enhancing immune-system activation.

Immunotherapies fall into three general categories:
- Checkpoint inhibitors
- Cytokines and
- Anti-cancer vaccines.

Targeted therapies act on specific cellular pathways, targets or ligands and mostly result in inhibition of cellular proliferation and tumour growth. The choice, sequencing and combination of these approaches remains essentially undefined and patients should be encouraged to enrol in clinical trials whenever possible. At present, treatment is largely directed by patient-specific factors, drug availability and affordability. This is a rapidly expanding field of oncology and this ever-changing landscape is a daunting one. An overview of currently available systemic options will be briefly discussed.

TREATMENT OPTIONS FOR LOCALLY ADVANCED/UNRESECTABLE AND METASTATIC MELANOMA

IMMUNOTHERAPIES

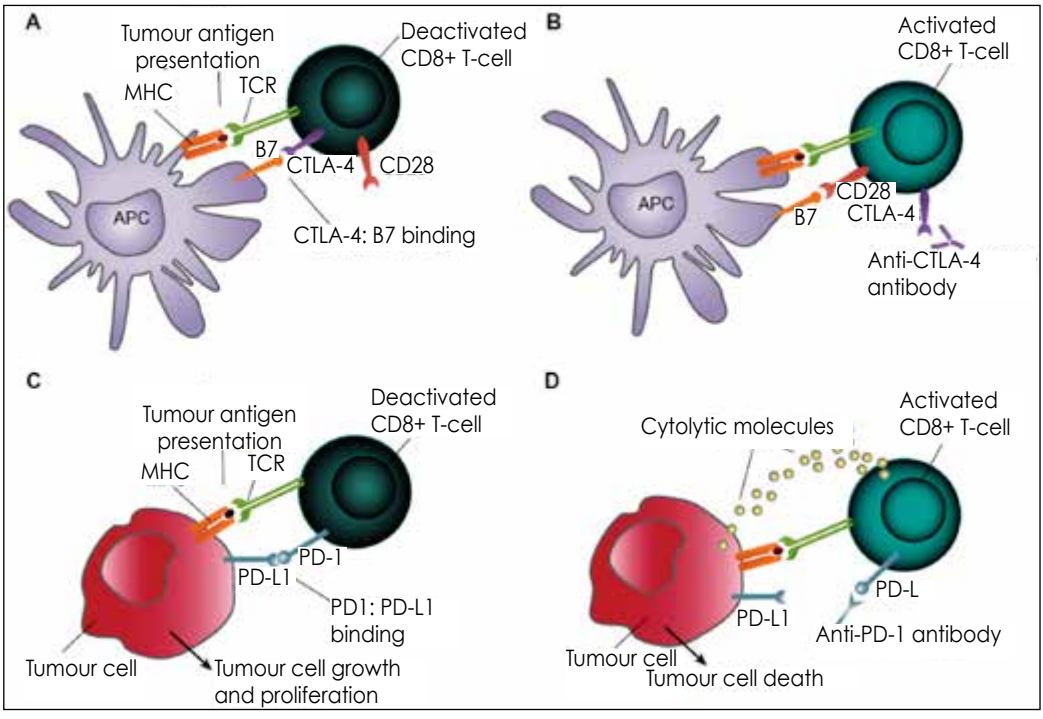
As early as the 1950s, spontaneous tumour regressions have been shown with immune-modulating agents, suggesting a role for these agents in tumour therapeutics. Interleukin-2 was the original therapy utilised and has shown modest response rates of around six to 16%.[9] Use of this agent has been limited by treatment-related toxicities, including acute constitutional symptoms, chronic fatigue, myelosuppression, depression, thyroid dysfunction and multi-organ failure. Its use is thus limited by strict patient selection and preferential use in experienced, high-volume centres.

Continued research in this area has focused on a more-specific immunotherapy approach and has led to the development of the more targeted checkpoint inhibitors.

Immune system activation is brought about by the presentation of intracellular peptide fragments on the surface of antigen-presenting cells (APCs). These peptide fragments are presented in association with the mixed histocompatibility complex (MHC) molecules. These MHC-peptide complexes are recognised by T-cells and result in T-cell activation. This activation also leads to upregulation of the cytotoxic T-lymphocyte antigen 4 (CTLA-4) which functions as a physiological brake via an inhibitory feedback loop (see Figure 1A). Ipilimumab is a monoclonal antibody directed against CTLA-4 (see Figure 1B). Phase III trials, including both previously treated and untreated disease, have shown that ipilimumab provides improved response rates, response duration, progression-free survival and overall survival. Importantly, extended follow-up suggests ipilimumab results in durable remissions with long-term survival approaching 20% (10-year overall survival rate of 21%).[4-6]

A second inhibitory pathway results via programmed cell-death receptor 1 (PD-1). This receptor is present on activated T-cells and binds to its ligand, (PD-L1). Similarly to CTLA-4 above, this interaction serves as a physiological brake and the immune response is down-modulated (see Figure 1 C). Certain tumour cells express PD-L1 and this allows for evasion of the immune system by the tumour cell. Pembrolizumab and nivolumab are monoclonal antibodies directed against the PD-1 receptor and allow for immune-system activation (see Figure 1D). Both agents have shown improved response rates, progression-free survival and overall survival when compared with chemotherapy. In addition, they are associated with a lower risk of adverse events.[7,8] Importantly, data suggest

Figure 1. New modalities of cancer treatment for NSCLC: focus on immunotherapy



Source: Davies M. New modalities of cancer treatment for NSCLC: focus on immunotherapy. Dovepress. Accessed January 2018. https://www.dovepress.com/new-modalities-of-cancer-treatment-for-nsclc-focus-on-immunotherapy-peer-reviewed-fulltext-article-CMAR.

nivolumab may provide long-term survival in up to 50% of patients.

Despite these important clinical benefits, immune-checkpoint inhibitors are associated with a unique spectrum of side effects termed immune-related adverse events (irAEs). These may occur at any time during the course of treatment and may involve any organ system. The most commonly occurring irAEs include dermatitis, enterocolitis, thyroid dysfunction and fatigue. These may also include pneumonitis, hypophysitis and associated endocrinopathies, uveitis, hepatitis, neurological, cardiac, rheumatological and renal toxicities. In certain cases, these reactions have been fatal. Experience with these agents has allowed for effective management of irAEs, with improved patient education, clinical monitoring, early recognition and prompt, algorithm-based initiation of appropriate treatment.

TARGETED THERAPY

Approximately half of patients with metastatic melanoma will show BRAF mutations. BRAF inhibitors vemurafenib and dabrafenib have shown improved response rates, progression-free survival and overall survival when compared with standard chemotherapy.

Patients treated with BRAF inhibitors show median response durations of around five to seven months.[10,11] Treatment is generally well tolerated.

The most frequently occurring toxicities include arthralgia, fatigue and cutaneous events (rash, photosensitivity and the development of squamous cell carcinomas). Small molecule inhibitors of MEK act downstream of BRAF in the MAP kinase pathway, and a combination of these agents with a BRAF inhibitor has resulted in further improvement in progression-free and overall survival when compared with BRAF inhibition alone. Here, a median progression-free survival of between 11 to 14 months and a median overall survival approaching two years has been achieved.[12] Importantly, the combined approach is well tolerated, and the incidence of cutaneous squamous cell carcinoma was significantly decreased. Thus, for patients who are candidates for targeted therapy, a combination of a BRAF and a MEK inhibitor rather than a single agent is recommended.

A small proportion of acral and mucosal melanomas will harbour somatic mutations or amplifications of KIT. Imatinib (small molecule inhibitor of KIT) has demonstrated improved responses in patients with melanoma harbouring KIT mutations. However, these responses were of limited duration and did not translate to an improvement in survival.

CHEMOTHERAPY

At present, the role of chemotherapy is limited to patients who have progressed on immunotherapy or where these treatment options are not clinically appropriate, affordable or available. Chemotherapy agents which have shown activity in melanoma include dacarbazine, temozolomide, nitrosoureas (carmustine and lomustine), platinum compounds (cisplatin and carboplatin) and albumin-bound paclitaxel (nab-paclitaxel). These agents may be used as single agents, or as combination regimens.

CURRENT RECOMMENDATIONS

The mainstay of treatment for inoperable or metastatic melanoma remains systemic therapy, with surgical metastatectomy reserved for a highly select group of patients. Primary systemic therapy approaches include i) immunotherapy (anti-PD-1 antibody alone or in combination with anti-CTLA-4) and ii) targeted therapy (combination of a BRAF and a MEK inhibitor preferred).

The appropriate choice and sequencing of treatments lacks supporting prospective data, and at present, is largely empiric and based on tumour- and patient-specific factors. Patients should be enrolled in a clinical trial wherever possible. Cytotoxic chemotherapy is limited to patients who have progressed on the above options, or where these treatment options are not clinically appropriate, affordable or available.

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Blood, lymph and related conditions

The Acute Leukaemias

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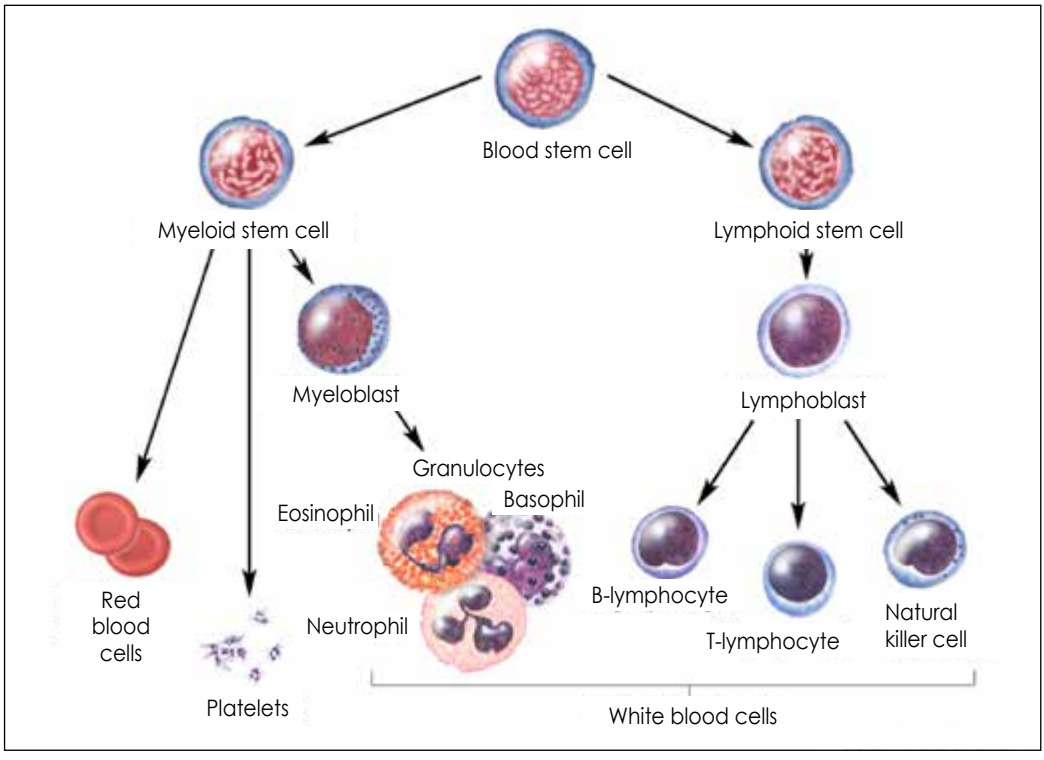
Acute leukaemias are haematological malignancies characterised by uncontrolled proliferation in the bone marrow of myeloid or lymphoid cells associated with a block in their normal differentiation to mature functional elements.[1] The consequence is infiltration of the marrow and other organs by functionally incompetent cells that lead to loss of myeloid and immune function, multiorgan failure and death. Patients often present with clinical symptoms of pancytopaenia (tiredness, infection and bleeding). In Europe, the overall annual incidence has been described as 9.6 per 100 000 population,[2] but there are no community-based statistics for South Africa. Lymphoblastic leukaemia is more frequent in children and young adults, while myelogenous leukaemia may also be seen in younger patients, but is more common among older adults.

ACUTE MYELOGENOUS LEUKAEMIA

Acute myelogenous leukaemia (AML) is a malignancy of an early myeloid/monocytic progenitor cell (see Figure 1) that is able to repopulate its own pool. Immature cells (blasts) accumulate in the bone marrow and spill over into the blood, as well as migrate to soft tissues and other organs, resulting in marrow failure, abnormal coagulation as well as metabolic derangements. While marrow failure leads to symptomatic anaemia and thrombocytopaenia,

Figure 1. Myeloid and lymphoid differentiation. Acute leukaemias seem to result from aberrant differentiation/maturation of myeloid and lymphoid progenitors



uncontrolled proliferation of the malignant blasts may result in extreme leucocytosis and leukostasis with blood hyperviscosity, leading to respiratory failure, uraemia and neurological deficit. Therefore the diagnosis and management of AML is a medical emergency that will require rapid detection and correction of these abnormalities.[2] Depending on risk factors of the blood disorder, the patient performance status and presence of comorbidities, AML can be cured with standard combination chemotherapy or may require other approaches such as allogeneic stem-cell transplantation.

The World Health Organization (WHO) classification of malignancies divides haematological malignancies according to morphology, immunophenotyping and cytogenetic/molecula derangements into distinct groupings.[3,4] While the detailed pathogenesis of AML is not known, genomic instability due to genetic factors (Fanconi anaemia, ataxia telangiectasia), environmental toxins (radiation, benzene) or cytotoxic drugs (alkylators, topoisomerase II inhibitors) has been implicated. These factors lead to loss of genetic material, point mutations or chromosomal translocations that cause cellular gain of proliferative function and clonal expansion of the malignancy. Identification of these aberrant mutations, as well as epigenetic changes in malignant cells, have resulted in better understanding of the disease process and hold promise for the development of specific therapies that may correct these abnormalities.

CLINICAL PRESENTATION

Patients may present with symptoms of marrow failure (anaemia, thrombocytopaenia), respiratory compromise from malignant pleural effusions or multilobar pneumonia and sepsis due to immunosuppression. Metabolic derangements are common, particularly in patients with advanced disease. Hyperuricaemia may result in renal failure due to interstitial nephritis, while hyperphosphataemia, lactic acidosis and hyperkalaemia must all be actively identified and corrected. In addition, patients often have a bleeding tendency due to thrombocytopaenia and thrombosis from disseminated intravascular coagulation (DIC) precipitated by the release of prothrombotic substances from degrading blasts. This is particularly severe in the group named acute promyelocytic leukaemia (APL). Occasionally, paraspinal or other tumour masses (chloromas) may lead to spinal cord compression and paraplegia. Central nervous system (CNS) infiltration by myelogenous leukaemia is not common on presentation, but patients may develop focal signs due to intracranial bleeding or thrombosis.[2]

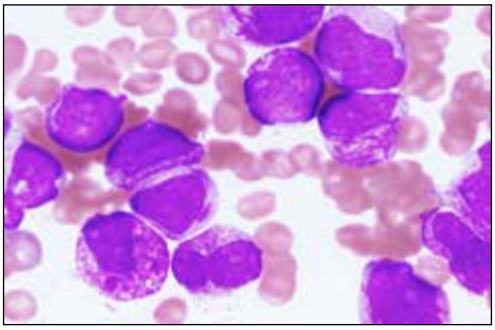
DIAGNOSIS

The diagnosis requires a detailed history and thorough physical examination to determine pre-existence of genetic predisposition, previous exposure to noxious agents and presence of infection, bleeding or masses that may compromise the function of vital organs. The current classification of AML was developed under the auspices of the World Health Organization (WHO) which incorporates clinical features in combination with laboratory findings, including genetics in trying to outline biologically homogeneous entities that have therapeutic and prognostic relevance.[3]

Examination of the peripheral blood smear and of the bone marrow (biopsy) will usually show features of anaemia and thrombocytopaenia with variable morphological abnormalities of the leukocytes and the presence of circulating malignant cells.

By definition, blasts in the bone marrow exceed 20% of nucleated cells. In promyelocytic leukaemia (see Figure 2), patients often have active laboratory features of DIC with clinical bleeding or thrombosis.[4] Cytogenetic analysis provides some of the strongest prognostic information available, predicting outcome of both remission induction and post-remission therapy. Based on the karyotype outcome, three prognostic groups are described with five-year survival of 55-60% in the favourable group, 10-15% in the unfavourable group, and 35-40% in the intermediate group.

Figure 2. Cytological preparation (May-Grünwald-Giemsa) of promyelocytic leukaemia cells. Typical coarse granules and multiple Auer rods in the cytoplasm are shown



More recently, a number of molecular markers have also been associated with prognostication.[2,5,6]

TREATMENT

Treatment of AML is usually divided into induction of remission chemotherapy and post-remission treatment. Induction chemotherapy has the goal of reducing the tumour bulk to undetectable levels (<5% blasts), which is associated with recovery of the blood parameters, a condition named as complete remission (CR). In the first instance, patients will require resuscitation and reversal of all metabolic abnormalities before undertaking intensive combination chemotherapy. During induction therapy, patients will require transfusion with blood products to maintain a haemoglobin level >8 gr/dL and platelet counts >10 x10^9/L.

The treatment of AML remains unsatisfactory and the majority of patients, particularly the older group, are likely to die of the disease. Myelosuppression is a consequence of the treatment so facilities must have capacity for adequate blood-product support (platelets and red cells) and have expertise in the treatment of opportunistic infections.

Clinical trials over the last 30 years have shown that in younger patients (<65 years) one or two cycles of a combination containing cytarabine at 100-200 mg/m^2 for seven days and an anthracycline antibiotic such as daunorubicin (75-90 mg/m^2) or idarubicin (12 mg/m^2) for three days (7+3 regimen) leads to CR in 50-80% (depending on risk factors), particularly in patients with favourable and intermediate-risk cytogenetics.[7] AML in remission is defined as a normal peripheral blood-cell count (absolute neutrophil count >1,000/mm^3 and platelet count >100,000/mm^3) and normocellular bone marrow with less than 5% blasts and no signs or symptoms of the disease. Achieving remission may be adversely affected by clinical factors such as advanced age, poor performance status, leukocyte >30x10^9/L, antecedent haematological disorder (myelodysplasia or myeloproliferative syndrome) and therapy of another malignancy.[8] Alternatively, epigenetic modifications of malignant cells with 5-azacytidine (Vidaza) or decytabine (Dacogen) have also been associated with marrow recovery, particularly if there is an antecedent marrow disorder, and are currently being actively studied in this group.[2,8]

Patients with promyelocytic leukaemia require a different approach both in supportive therapy as well as for the treatment of the malignancy. Due to severe coagulopathy, such patients need aggressive replacement of coagulation factors with blood products to prevent bleeding. Since all trans retinoic acid (ATRA; Vesenoid) can reverse the block in differentiation typical of the disease caused by the chimeric PML-RARa protein product, combination of daily ATRA (40 mg/m^2) with anthracycline chemotherapy has been associated with a nearly 90% remission rate. Prescription of ATRA can lead to hyperleukocytosis and respiratory distress, now known as the differentiation syndrome, which can be prevented by early administration of corticosteroids. Molecular remission (undetectable PML-RARa on PCR) following intensification therapy is associated with favourable long-term outcome.[9] The inclusion of arsenic trioxide (ATO) as part of the induction (ATRA + ATO) or following induction with ATRA and anthracyclines has been associated with improved survival.

Depending on risk factors, following remission induction, treatment is typically with high doses of cytarabine (2 gr/m^2,

twice daily for four days). Patients with intermediate and unfavourable cytogenetics will benefit from intensification with allogeneic stem-cell transplantation from an HLA identical donor. Patients in second remission should also be considered for this procedure. The chance of having an HLA-compatible donor ranges from 20-40% among siblings (same parents) to 1/10000- 1/100000, depending on the genetic diversity of the community. High-dose therapy or immunosuppressive conditioning and stem-cell transplantation are associated with procedure-related mortality of 10-20% and depending on the mentioned risk factors, disease recurrence of 15-30%.[7] Thus, selection criteria from various co-operative groups, such as European Bone Marrow Transplantation Society (EBMT criteria) have been proposed to assist in the selection of patients who will benefit most from this procedure.[10] Haploidentical stem-cell transplantation with post-transplant high-dose cyclophosphamide is emerging as a viable alternative for those who lack HLA-compatible donors, although long-term survival data are still unavailable.

ADULT ACUTE LYMPHOBLASTIC LEUKAEMIA

Adult acute lymphoblastic leukaemia (ALL) is a discrete clonal malignant disorder that affects an early lymphoid progenitor (see Figure 1) and represents a heterogeneous group of diseases that have distinct phenotypes and variable outcomes. Although there are no local data regarding the incidence of ALL, in the US there were 5 960 new cases in 2017.[11] Depending on the lineage, they are classified as precursor T-cell and precursor B-cell leukaemias, implying a thymic or bone-marrow origin of malignant lymphocytes.[3] The pathogenesis of malignant transformation remains unclear, but genomic instability leading to chromosomal translocations and mutations of genes associated with control of cell proliferation and apoptosis are likely. Human T-cell leukaemia virus 1 has also been described in T-cell malignancies in some patients from Asian countries and the Caribbean basin. Epstein Barr virus has also been associated with a B-cell leukaemia in immunocompetent patients and subjects with immunodeficiency virus infection.

CLINICAL PRESENTATION

ALL typically presents in children and young adults, being the most common paediatric cancer, although older patients may also develop this malignancy.[11] Younger patients may present with systemic manifestations of disease, including fever of unknown origin and joint pains, associated with leukopaenia or pancytopaenia. More often they have palpable lymphadenopathy, hepatosplenomegaly and features of marrow failure such as pallor, ecchymoses and petechiae. Less frequently (5-7% of cases), patients may present with cranial nerve abnormalities from meningeal leukaemia. Due to the heterogeneity of this disease, precursor B- and T-cell leukaemias are considered as separate entities. Mediastinal masses are common in T-cell leukaemia and may lead to medical emergency from airway obstruction by lymphoid masses. T-ALL frequently presents with elevated leukocyte count, but is highly responsive to therapy. Occasional, testicular masses may be the initial complaint, or develop later during therapy as both the CNS and testis are sanctuaries with poor tissue penetration of cytotoxic agents.[11]

DIAGNOSIS

The differentiation of AML from acute lymphocytic leukaemia has important therapeutic implications.[3] Investigations should include complete blood count with the differential count, a chemistry panel and coagulation studies as well as careful screening for evidence of active infection. According to WHO, the diagnosis and characterisation of lymphoblastic leukaemia is based on the blood and marrow morphological features, as well as immunophenotyping, cytogenetic analysis and molecular characteristics of the malignant clone.[3] Lymph-node and mediastinal biopsy samples are also useful in some clinical situations, whereas testing of the CSF

is mandatory. While peripheral blood may not demonstrate malignant blasts, bone-marrow biopsy will always show >20% blasts. Immunophenotyping differentiates precursor B (80%) from precursor T (15%) ALL (see Figure 3). Cytogenetic analysis is useful and will show either a favourable pattern or an unfavourable arrangement that also includes the complex karyotypes (five or more abnormalities). The Philadelphia chromosome (Ph1; BCR-ABL p190Kd) is uncommon in paediatric ALL, but occurs in 25-35% of adult ALL.[11] The PH1 chromosome may be detected by reverse transcriptase polymerase chain reaction (RT-PCR) and by fluorescence *in situ* hybridisation (FISH).

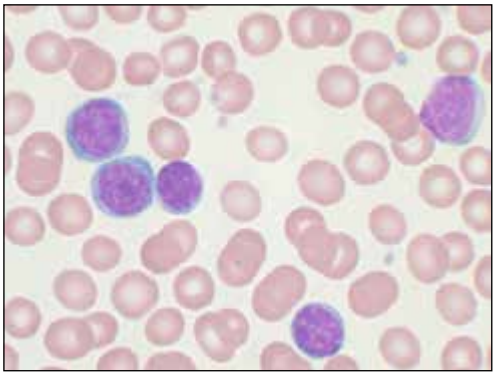
PROGNOSTIC FACTORS

Certain factors at the time of diagnosis or after therapy was commenced have distinct prognostic relevance. Age (<1 year or >9 years in children and <35 and >60 in adults), leukocyte count (>30 x 10^9/L for precursor B-ALL or >100 x 10^9/L in T-ALL) immunophenotype (pro-B), CNS disease, adverse karyotype and molecular abnormalities (BCR-ABL) are all unfavourable factors and are considered in the choice of treatment modality (including referral for allogeneic haemopoietic stem-cell transplantation). Response to treatment with undetectable disease by four weeks of induction therapy defines a biologically more favourable group.[11-13] With standard chemotherapy, there is an inverse relationship between the number of risk factors and survival, with five-year survival in excess of 50% for none, to 20-40% with 1 or 2 and less than 10% in those with cumulative incidence of 3 or 4 risk factors.[11,12] Burkitt's leukaemia (L3 or mature B-cell; 5%) is associated with a variety of translocations that involve translocation of the *c-myc* proto-oncogene to the immunoglobulin gene locus t(2;8), t(8;12), and t(8;22).[11,13]

THERAPY

In children and adolescents, the treatment of ALL has been a significant therapeutic success, with over 80% of children surviving in the long-term. Treatment approaches for adolescents and young adults with ALL have also evolved considerably in the past five to seven years.[12,13] However, in older adults, therapy of this malignancy remains a major challenge. Similar to the treatment of AML, optimal management of patients with ALL requires careful attention to supportive care. Metabolic derangements are frequently encountered, even before chemotherapy is initiated, especially in patients with a high leukaemic cell burden and those with T-cell or mature B-cell ALL. Patients receiving induction therapy develop severe pancytopaenia and require similar supportive care to those with AML. Infections need to be treated aggressively based on empiric and culture-directed antibiotic combinations.

Figure 3. Cytological preparation (May-Grünwald-Giemsa) of lymphoblastic leukaemia cells



The specific treatment of ALL also includes a remission-induction phase and post-remission maintenance therapy. Most induction regimens include combination chemotherapy consisting of vincristine, prednisone, anthracycline, L-asparginase and alkylators such as cyclophosphamide. To avert meningeal leukaemia during induction, all patients should receive CNS prophylaxis with intrathecal chemotherapy (steroids, methotrexate and/or cytarabine).[14] Clinical studies have demonstrated that post-remission consolidation with high doses of methotrexate (with folinic acid rescue), cytarabine with the addition of vinca alkaloids or L-asparginase over a period of six months increases overall survival due to a reduction of disease recurrence.

Clinical trials have shown that oral maintenance chemotherapy (methotrexate and mercaptopurine) for two or three years with periodic reinforcements with vincristine and prednisone leads to long-term, relapse-free survival in the majority of children and 35% of adults, depending on pretreatment risk factors and response to initial therapy.[11-15] A group of interest are patients who develop the BCR-ABL (p190KD) mutation as they are highly responsive to the tyrosine kinase inhibition (TKI), typically more often in the older population. TKIs (imatinib, dasatinib) have shown to have clinical activity as a single agent and led to high responses with extended survival in elderly patients. Their inclusion is recommended in the routine treatment of children and adults with PH1 ALL.[16]

Allogeneic stem-cell transplantation is an important post-remission strategy for certain patients with adverse biological factors (hyperleukocytosis, BCR/ABL, MLL) and can be an effective salvage modality for those who suffer disease recurrence. However, this intense modality is reserved for those who have HLA-identical donors and few comorbidities. Despite these aspects, procedure-related mortality of 15-25% reduces the overall success of this strategy.[17] These options should also be considered for patients with detectable minimal residual disease (MRD) in remission following induction therapy.

CONCLUSION

Thus, the relevant points in patients with acute leukaemia remain early diagnosis in patients with unexplained cytopaenia, pyrexia of unknown origin or persistent leucocytosis, correction of electrolyte, metabolic and coagulation abnormalities, adequate supportive care with transfusion of blood products, prevention of infection and aggressive management of sepsis. Following diagnosis and initial stabilisation of the patient, this group should be referred to a clinical haematologist or medical oncologist with experience in the treatment of these diseases. Delays in specific therapy lead to complications and decreased survival of patients who may otherwise have a curable disease.

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Multiple Myeloma

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Multiple myeloma (MM) is a neoplasm of plasma cells characterised by plasma-cell proliferation in the bone marrow with the production of a monoclonal immunoglobulin. Plasma cells are post-germinal centre B-cells that produce antibodies. The clinical features of myeloma result from bone-marrow invasion, cytokine release with stimulation of osteoclastic activity, and the clinical consequences of excessive immunoglobulin.

The production of a monoclonal immunoglobulin (M-protein) is also seen in lymphoma, other haematological malignancies and two plasma-cell dyscrasias: monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM). MGUS and SMM are considered pre-malignant conditions on the pathway to myeloma, but vary greatly in their risk of progression. The approach to the diagnosis and management of these conditions will be briefly included in the discussion.

An increase in plasma cells and total immunoglobulin is seen in various benign conditions (HIV and chronic inflammation), the distinguishing characteristic from MM is that plasma cells in benign conditions are polyclonal and produce an array of different immunoglobulins.

PREVALENCE OF DISEASE

In South Africa, the incidence rate taken from the latest published National Cancer Registry is 0.5/100 000,[1] however, in the US and Europe the rate is 4-5/100 000 and it accounts for roughly 10% of haematological malignancies.[2,3] The disparity with the global incidence is likely due to underdiagnosis (with earlier death) and underreporting in South Africa.

MM occurs in all races and all geographic locations, but incidence appears to vary with sex and ethnicity. MM is twice as common in blacks compared to Caucasians[4,5] and is slightly more frequent in men than women. MM is typically a disease of older adults, with a median age at diagnosis of 66 years, and only 2% of patients are under the age of 40.[5] In Africa, a five- to 10-year younger median age is described,[6] however newer and large population-based data are needed from southern Africa. A higher incidence of MM is seen in HIV-infected persons.[7,8]

PATHOPHYSIOLOGY

The pathophysiology for the development of MM can be conceptualised as a two-step process: initial production of a plasma cell clone producing a monoclonal immunoglobulin[9] and then a "second-hit" resulting in the proliferation of the malignant clone. While some steps in the process have been elucidated, many remain unknown.

In the first step, a combination of genetic susceptibility with an aberrant response to antigenic stimulation results in cytogenetic abnormalities (usually in the immunoglobulin heavy chain (IgH) locus)[10], which results in the presence of a dominant plasma cell clone. In this stage, a patient would be clinically diagnosed with MGUS (or SMM). The variable rate of progression is evidenced by the fact that MGUS is present in over 3% of the population over the age of 50 but only progresses to MM or a related malignancy at a rate

of 1% per year. Therefore, a "second-hit" is required to progress to MM.[11]

The "second-hit" is due to additional genetic changes (e.g., Ras mutations, p53 mutations), as well as permissive changes in the bone-marrow environment and evasion of immune surveillance.[10] The net result of these changes is an increase in proliferation and survival of the malignant clone.

DIAGNOSTIC ISSUES

DIAGNOSTIC CRITERIA

The diagnosis of MM has been based on demonstrating a clonal plasma-cell population, usually with the production of an M-protein, along with end-organ features. The 2014 International Myeloma Working Group (IMWG) updated these criteria (see Table 1),[12] recognising that a subset of patients previously classified as SMM have near inevitable progression to end-organ damage and for this reason have been included as MM (patients with >60% plasma cells in the bone marrow; involved/uninvolved FLC ratio of >10).

CLINICAL FEATURES

Patients with MM commonly present with symptoms related to end-organ features (often recalled by the acronym CRAB): increased plasma **c**alcium, **r**enal dysfunction, **a**naemia and **b**one pain. An uncommon presentation, but a medical emergency, is that of spinal cord compression.

Anaemia in MM is typically normocytic and normochromic and is present in 73% of cases at diagnosis.[5] Anaemia can be related to bone-marrow infiltration, kidney damage, cytokines affecting erythropoietin release and is dilutional (in the case of a large M-protein). An unexplained normocytic normochromic anaemia in a patient (especially with other "red flags" such as bone pain, weight loss, fatigue and other cytopaenias) warrants further investigation with a bone-marrow examination (BME) and serum electrophoresis (SPEP).

Bone pain is the presenting feature at diagnosis in 60% of cases[5] and is typically in the back or chest. Imaging may show lytic lesions, pathological fractures, vertebral compression fractures, and osteopaenia. Lesions are more sensitively diagnosed by CT, PET CT or MRI than x-ray. Lytic lesions develop as a result of excessive osteoclastic activity driven by cytokines produced by MM cells.

Renal dysfunction occurs in 48% of patients at diagnosis,[5] is often multifactorial in aetiology and is often reversible. Common causes for renal dysfunction in myeloma are light-chain cast nephropathy (deposition of light chains in the tubules, causing tubular damage); hypercalcemia (causing polyuria with subsequent volume depletion which increases toxicity of the filtered light chains) and drugs (especially NSAIDs, intravenous radiocontrast, antimyeloma agents and bisphosphonates). Less commonly, light-chain amyloidosis (AL) and light-chain deposition disease (LCD) result in deposition of light chains at the glomerular basement membrane, which results in nephrotic syndrome.

Hypercalcaemia is present at diagnosis in 28% of patients and in a smaller proportion can be dangerously elevated, requiring immediate management. Symptoms of hypercalcaemia include anorexia, nausea, vomiting, polyuria, polydipsia, weakness, confusion, or a decreased level of consciousness.

Patients with myeloma are at an increased risk for infection due to both immune dysfunction and functional factors and an infection may be the presenting symptom. Immune dysfunction may result from a decrease in normal immunoglobins (hypogammaglobulinaemia) and impaired function or number of neutrophils and lymphocytes.

Neurological disease can result from nerve or spinal cord compression, either from a collapsed vertebra or an extramedullary plasmacytoma. Spinal cord compression should be suspected in patients presenting with severe back pain along with weakness or paraesthesia of the lower limbs, and bladder or bowel dysfunction. This is a *medical emergency* and the patient should be urgently referred for imaging (MRI preferred over CT), with an urgent assessment by a haematologist or oncologist and neurosurgeon. Peripheral

Table 1. Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma

Definition of multiple myeloma
Clonal bone-marrow plasma cells ≥10% of biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma-defining events:
Evidence of end-organ damage that can be attributed to the underlying plasma-cell proliferative disorder, specifically: Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL) Renal insufficiency: creatinine clearance <40 ml per min¶ or serum creatinine >177 µmol/L (>2 mg/dL) Anaemia: haemoglobin value of >2 g/dL below the lower limit of normal, or a haemoglobin value <10 g/dL Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CTΔ
Any one or more of the following biomarkers of malignancy: Clonal bone-marrow plasma cell percentage* ≥60% Involved: uninvolved serum-free light-chain ratio◊ ≥100 >1 focal lesions on MRI studies§
Definition of smouldering multiple myeloma
Both criteria must be met: Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 hours and/or clonal bone-marrow plasma cells 10 to 60% Absence of myeloma-defining events or amyloidosis
Definition of monoclonal gammopathy of undetermined significance
All three criteria must be met: Serum monoclonal protein <30 g/L Bone-marrow plasma cells <10% Absence of myeloma-defining events or amyloidosis (or Waldenström macroglobulinemia in the case of IgM MGUS)

PET-CT: 18F-fluorodeoxyglucose positron emission tomography with computed tomography.
* Clonality should be established by showing kappa/lambda-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone-marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
¶ Measured or estimated by validated equations.
Δ If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
◊ These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.
§ Each focal lesion must be 5 mm or more in size.

Source: Adapted from Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15 (12):e538-e548.

neuropathy rarely occurs; if it does, it is usually in the setting of amyloidosis or POEMS syndrome. Occasionally, patients may present with headaches or blurred vision due to hyperviscosity.

USEFUL LABORATORY TESTS

- Full blood count (FBC) and peripheral smear

Apart from the anaemia as described, other compatible and useful findings on

FBC or smear are: other cytopaenias, rouleaux formation (seen in >50%); occasionally, plasmacytoid lymphocytes or plasma cells can be seen.

■ Bone-marrow examination

A bone-marrow examination (BME) is necessary for the diagnosis of MM and shows an increase in plasma cells which are monoclonal (i.e., they show kappa or lambda light-chain restriction). Plasma cells can usually be readily identified morphologically on an aspirate (see Figure 1) and the trephine (see Figure 2) and may show abnormal malignant features. A flow cytometry plasma-cell panel may be useful to confirm that the plasma cells are clonal, and may be useful for prognostication, but, at present, the plasma-cell percentage on the trephine is the preferred method for the enumeration of plasma-cell burden.[13] At diagnosis, performing cytogenetics on the bone-marrow aspirate is useful for prognostication. Routine karyotyping is typically not useful due to a low number of metaphases, and a myeloma fluorescent *in situ* hybridisation (FISH) panel is preferable.

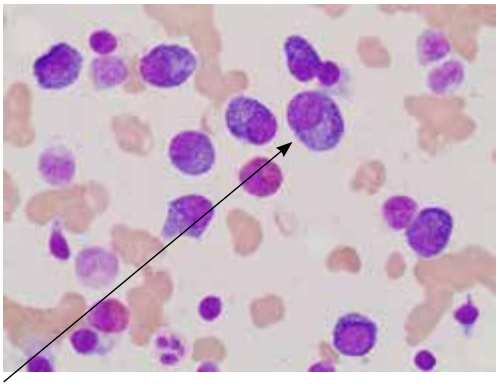
■ Urine analysis

Findings on urine analysis depend on the cause of kidney damage. Myeloma cast nephropathy is characterised by casts formed from precipitated monoclonal light chains in the distal tubule which may be sloughed off and seen on microscopy. The urine dipsticks are often negative for protein despite a raised urine protein: creatinine ratio, because the protein detected is Bence-Jones protein (i.e., light chains) and the dipstick is sensitive only for albumin. In LCCD and amyloidosis AL, the dipsticks will be positive as these conditions cause albuminuria. Thus, for accurate urine light-chain (Bence Jones proteinuria) testing and quantification, a 24-hour urine sample for urine protein electrophoresis (UPEP) and immunofixation is ideally required. However, due to the cumbersome collection and testing method, this test has largely been superseded in clinical utility by the serum free light-chain (FLC) assay.

■ Tests to detect a monoclonal protein

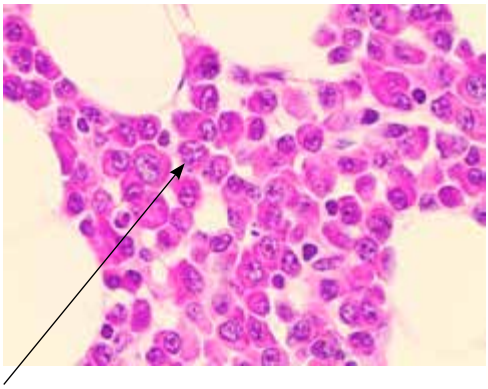
Ninety-three percent of patients with MM will have a monoclonal (M) protein which is detected by serum-protein electrophoresis with serum immunofixation.[14] Serum immunofixation is performed as a secondary test to both confirm the presence of the M-protein, and to determine its type (IgG being the commonest).

Figure 1. Bone-marrow aspirate showing an increase in the number of plasma cells
(These plasma cells have fairly normal morphology, but in many cases the plasma cells show atypical and malignant morphology.)



A plasma cell with an eccentric nucleus, clumped chromatin and a moderate amount of basophilic cytoplasm with a less basophilic Golgi zone adjacent to the nucleus.

Figure 2. Bone-marrow trephine showing a diffusely infiltrated marrow with numerous plasma cells



Plasma cell with an eccentric nucleus with "clock-face" chromatin and a prominent nucleolus.

In patients with a high clinical suspicion of MM but a normal SPEP, the serum-free light-chain (FLC) assay should be performed. The serum FLC test detects light chains (kappa or lambda) and will show abnormality in the ratio of kappa to lambda in 60% of MM patients who do not have an M-protein on SPEP.[15] The SFL has obviated the need for the urine Bence-Jones protein in many patients.[16] There is a small fraction of MM patients who do not have an M protein detectable by any of these methods ("non-secretors").

A total protein test has been aptly called "poor man's SPEP" and in a poor-resource setting is a useful initial screening test when performed in the setting of clinical suspicion for MM (such as back pain or a normocytic anaemia). However, in patients with decreased albumin, early disease or low/non-secretory disease, this may result in a normal total protein level and a falsely normal result. Thus, in any patient with a strong suspicion of myeloma, a full work-up and referral to a specialist centre is required.

- Imaging

Imaging is an important part of the diagnosis of myeloma. Cross-sectional imaging (whole-body, low-dose CT without contrast, PET/CT or MRI) is more sensitive to detect lytic lesions than XR, but due consideration needs to be given to cost and exposure to radiation and drugs that may be nephrotoxic (gadolinium and contrast). Patients for whom cross-sectional imagining should be performed are patients with SMM and solitary plasmacytoma in whom lytic lesions would "up-stage" the diagnosis to MM; and patients with MGUS and bone pain. Whole-body low-dose CT without contrast is preferred for its convenience and lower cost.[17] An important differential cause for lytic bone lesions and hypercalcaemia is metastatic carcinoma, and a subset of these patients may have an incidental MGUS. If the bone-marrow examination is not in keeping with myeloma, a useful investigation is a biopsy of the lytic bone lesion.

PROGNOSIS

The prognosis of myeloma depends on patient factors (age, comorbidities), staging (B2-microglobulin and albumin are used as surrogate markers for tumour burden which in myeloma corresponds to staging), disease biology (cytogenetic abnormalities) and the response to initial treatment. The revised International Staging Score (R-ISS) is the most widely used staging system and combines measures of tumour burden with disease biology to identify three stages with variable overall survival rates (see Table 2).[18]

TREATMENT AND REFERRAL GUIDELINES

GENERAL MANAGEMENT

Patients with MM should be referred for management to an oncologist or haematologist. However, the role of the general practitioner to diagnose, stabilise and appropriately manage the complications of myeloma is of critical importance. Patients with myeloma may be frail and appear terminally unwell at diagnosis (often with a history of deterioration and decreased mobility over months) and yet, despite the incurable nature of the disease, many of them can have a good quality of life for years following diagnosis with therapy.

MGUS does not require treatment. The follow-up of MGUS can be performed by a general practitioner. Current recommendations are to repeat a SPEP in six months in all patients with MGUS and then further follow-up, depending on the risk of the progression of MGUS: patients with low-risk MGUS (an M-protein of <1.5g/dL, IgG subtype and normal FLC ratio) may be followed up with history and examination alone.[19] All other patients with MGUS are followed with annual serum and urinary M-protein, FBC, creatinine and serum calcium. Features considered "red flags" in these patients are bone pain, fatigue, constitutional symptoms, bleeding, lymphadenopathy or splenomegaly.

Patients with SMM and plasmacytoma require a thorough investigation to exclude MM, including cross-sectional imaging studies and FLC assay. These patients

Table 2. The international staging system (R-ISS) for multiple myeloma

Stage	Criteria	5 year overall survival (%)
I	Beta-2-microglobulin <3.5 mg/L and albumin ≥3.5 g/dL	82
II	Not R-ISS I or III	62
III	Beta-2-microglobulin ≥5.5 mg/L and either high LDH or high-risk chromosomal abnormalities by I-FISH (defined as presence of del (17p) and/or translocation t(4;14) and/or translocation t(14;16))	40

I-FISH = interphase fluorescence *in situ* hybridisation; LDH = lactate dehydrogenase

Source: Adapted from Palumbo A, Avet-Loiseau H, Oliva S, et al. *Revised international staging system for multiple myeloma: a report from International Myeloma Working Group.* J Clin Oncol. *33:2863-2869.*

are best followed up by an oncologist or haematologist for close monitoring and a decision for when to initiate therapy.

The complications of MM frequently seen that require specific treatment are hypercalcaemia, renal insufficiency, infection and skeletal lesions. Details on the management of these conditions follows. Patients with MM are at an increased thrombotic risk and when admitted to hospital, prophylactic anticoagulation is advised in the absence of contra-indications.

■ Hypercalcaemia

The treatment depends on the level of calcium, and the patient's symptoms. For mild cases of hypercalcaemia (e.g., calcium <3mmol/ L) hydration (preferably with normal saline) and treatment with corticosteroids is recommended. Note that steroids may affect the findings on bone-marrow biopsy and in these patients with mild hypercalcaemia, a bone-marrow examination is preferably performed before steroid therapy.

In moderate to severe hypercalcaemia, treatment includes hydration, corticosteroids as above, and bisphosphonates such as zoledronic acid or pamidronate. Hydration is critically important as these patients are typically very dehydrated. A reasonable regimen is to give isotonic saline at 200-300 ml/hour that is then adjusted to maintain the urine output at 100-150 ml/ hour. Saline therapy requires careful monitoring, especially in patients with impaired renal function. If a patient becomes oedematous, a loop diuretic may be used. The routine use of loop diuretics in hypercalcaemia (with hyperhydration) has largely fallen out of favour with availability of the bisphosphonates.[20] Zoledronic acid is given IV at a dose of 4 mg over 15 minutes, and pamidronate IV at a dose of 60-90 mg over 2 hours. The dose and/ or duration of administration of zoledronic acid needs to be adjusted for renal failure, and in patients who present with acute renal failure, pamidronate is preferred.

■ Renal insufficiency

The treatment of renal insufficiency depends on the underlying cause, with correction of hydration status and electrolytes and avoidance of nephrotoxins (NSAIDs). Hydration should be carefully monitored and matched to output when a patient is fluid-replete. In the presence of indications for referral, dialysis patients should be referred promptly. Acute renal failure due to light-chain cast nephropathy is best treated by treatment of the myeloma with a dexamethasone-containing regimen.

■ Skeletal lesions

Skeletal lesions can result in bone pain, pathological fractures and spinal cord compression, all of which are best managed by a specialist-led multidisciplinary team. Patients with myeloma should be encouraged to remain as active as possible in order to maintain bone density and take vitamin D supplementation as preventive measures. Bisphosphonate

therapy has been shown to significantly reduce the number of skeletal events (pathological fracture, lytic lesions) and improve pain control from skeletal-related pain.[21]

■ Infection

It is recommended that patients with MM receive the annual flu vaccine as well as a single pneumococcal vaccine at the time of diagnosis, although the evidence for this is weak.[22] Infection should be treated promptly with broad-spectrum antibiotics. Patients with recurrent, severe infections and hypogammaglobulinaemia may benefit from immunoglobulin replacement with IVIG.

DISEASE-SPECIFIC TREATMENT FOR MYELOMA

Disease-specific treatment for MM is performed by oncologists and haematologists. Patients are evaluated pre-treatment for eligibility for autologous haematopoietic cell transplantation (HCT), depending on the age, comorbidities and functional testing. When compared with chemotherapy alone, intensified chemotherapy followed by HCT prolongs both event-free and overall survival in patients with MM and remains the standard of care for younger patients (less than 70 years) with newly diagnosed MM.[22]

Transplant-eligible patients are typically given induction chemotherapy with a two- or three-drug combination that typically includes a corticosteroid, an immunomodulatory agent such as lenalidomide and/or a proteasome inhibitor such as bortezomib and/or a chemotherapeutic agent such as cyclophosphamide or an anthracycline. Patients are typically given four to six cycles of this combination and when an adequate response has been achieved (as determined by the decrease in M-protein) are offered an autologous transplant. Post-transplant, some specialists will treat with maintenance therapy.

Transplant-ineligible patients are given an initial combination of dexamethasone, melphalan and an immunomodulatory agent or proteasome inhibitor. Treatment is continued for 12-18 months until the patient reaches a stable plateau phase as determined by the M-protein; this is followed either by no therapy (with restarting of treatment when the M-protein rises significantly) or with single-agent maintenance therapy.

Although myeloma is presently considered an incurable disease, patients may have a good quality of life for a number of years with treatment and consequently, early diagnosis with appropriate treatment of complications and specialist referral is of critical importance. The development of new drugs that show an enhanced ability to induce a remission, with lower toxicity, is promising and has led to a significant increase in both progression-free and overall survival, but their use is limited by prohibitive costs.

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Myelodysplastic Syndromes

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The myelodysplastic syndromes (MDS) are a group of malignant stem-cell disorders that give rise to inefficient haematopoiesis which results in variable degrees of bone-marrow failure.[1]

This typically manifests in one or more cytopaenias and a variety of dysplastic changes in blood cells in the bone marrow and peripheral blood.[2] This developing bone-marrow insufficiency gives rise to clinical features related to the affected cell lines, namely increased risk of infection if neutropaenic, and symptomatic anaemia and bleeding if thrombocytopaenia.[3] Anaemia is the most common manifestation, with the vast majority of patients developing anaemia and subsequent transfusion-dependence at some stage. The greatest risk of MDS is of transformation to acute myeloid leukaemia (AML), which is difficult to treat, especially in a typically elderly population, who often have many comorbidities.

If no predisposing disorder can be found, it is called *de novo* MDS. If a patient has a predisposing disorder, it is called secondary MDS and in cases where it is thought to be related to prior chemo- and/or radiotherapy, the term therapy-related MDS is used.[4]

PREVALENCE OF DISEASE

The prevalence of MDS in South Africa is unknown.[5] *De novo* MDS is a disease of the elderly, with a slight male predominance, and is unusual in patients under the age of 50 years, although some rare forms have been found in children. The median age at diagnosis is about 70 years.[6] If found in younger people, a secondary cause needs to be excluded. In Western countries, the incidence varies between 1.2 and 4.1 per 100 000.[7,8] This is probably an underestimation, as unexplained cytopaenias in the elderly are not always investigated with a bone marrow aspiration due to other comorbidities.

IMPACT ON SOCIETY

MDS has a dramatic impact on the quality of life of patients, who are often retirees, and are in the phase of their life where they hoped to be enjoying the fruits of their life's labour, travelllng or playing an active role in the lives of loved ones.[9] Frequent doctor's visits, hospitalisations, symptomatic anaemia with or without the need for red-cell and/or platelet transfusion, infections, bleeding symptoms, as well as the constant fear that the disease may transform to AML, all contribute to a decrease in quality of life. Previously, very few treatments were available to these patients. Fortunately, good progress is being made, but often at a high financial cost to the individuals, insurers and society.

DIAGNOSTIC ISSUES

The main challenge diagnostically is a lack of awareness of the disease. As a general rule, all patients with unexplained cytopaenia(s), where common causes have been excluded, should undergo an evaluation of a peripheral blood smear and a unilateral bone-marrow aspirate and trephine biopsy.[2,10,11] Without this, a proper diagnosis and prognostication of MDS are not possible. Most patients will

present with anaemia only, which is usually macrocytic, but often normocytic, while the presence of neutropaenia and thrombocytopaenia is more variable. About 50% of patients will present with a pancytopaenia (leukopaenia, anaemia and thrombocytopaenia). An isolated thrombocytopaenia or neutropaenia is seen in less than 5% of patients. In some rarer subsets, patients may present with a thrombocytosis. Once suspected, it is best to involve a clinical haematologist or haematopathologist to assist with further investigations on the bone marrow, as there are a number of critical cytogenetic tests (e.g., karyotyping, fluorescent *in situ* hybridisation (FISH)) and sometimes others that need to be done upfront to avoid having to repeat the bone-marrow test. The results of these tests form a critical component of the prognostic scoring systems used to estimate the level of risk for transformation to AML, a factor which will have a major impact on the treatment choice for an individual patient. Investigation for the more common cytogenetic abnormalities with karyotyping or FISH has become routine for diagnosis and prognostication, while screening for the now more than 100 known mutations with novel molecular methodologies, (e.g., next-generation sequencing) is not yet widely available.

PATHOPHYSIOLOGY

The pathophysiology of MDS is incompletely understood and is made more difficult due to the large range of mutations found. MDS is caused by a stepwise accumulation of mutations in a haematopoietic progenitor cell, which leads to the formation of a malignant clone. It is considered and classified as a malignancy. These may occur *de novo* with ageing, or may be secondary to exposure to certain environmental factors (e.g., tobacco, benzene, chemotherapy, radiation [accidental or therapeutic], and so on). Some patients have an underlying predisposing condition, such as a congenital genetic disorder (e.g., Fanconi anaemia, Down's syndrome, Bloom's syndrome, and so on) or another predisposing haematological disorder (e.g., paroxysmal nocturnal haemoglobinuria (PNH), aplastic anaemia, myeloproliferative neoplasms, and so on). Whether the presence of autoimmune disorders seen in association with MDS, is causal or not is less clear. Depending on the nature of the stem-cell mutation, different cell lines may be variably affected, with a variable risk of progression to AML. Other factors, such as comorbidities, transfusion needs, the degree of anaemia, transfusion-related iron overload and its complications, may impact negatively on disease progression, bone-marrow function and overall survival.

TREATMENT OF MDS

Treatment of MDS is based on the subtype of MDS, patient-related factors (e.g., age, performance status, patient preferences and comorbidities), and predictive factors for treatment outcome (e.g., classification of an individual patient as *lower* or *higher* risk).

Roughly one-third of patients have a stable, non-progressive course; one-third will die from cytopenic complications (e.g., bleeding or infections) and one-third will die from AML.[11] A range of prognostic scoring systems has been described over the years, with continuous refinement as our understanding of the prognostic impact of certain clinical and pathological features has grown. The most widely used prognostic scoring system used at present is the Revised International Prognostic Scoring System (IPSS-R) (see Table 1).[12] Very-low- and low-risk patients are usually classified and treated as *lower*-risk patients, while high- and very-high-risk patients are considered *higher*-risk and treated as such. Patients who fall in the intermediate category can be treated as either *lower* or *higher* risk, depending on a range of individual factors. Survival varies from weeks to several years, depending on the risk group.

The goal of treatment in patients with *lower*-risk MDS is to improve symptoms related to anaemia and other cytopaenias, improve quality of life and improve haematology, while the goal of therapy in *higher*-risk disease is to either modify the natural history of the disease by delaying disease progression and improving survival

or to completely alter the natural history of disease with a bone-marrow or stem-cell transplantation.[5]

In lower-risk disease, treatment options include growth factors (e.g., erythropoietin, granulocyte colony-stimulating factors [G-CSF]), immune-suppressive treatments and immunomodulatory agents (e.g., lenalidomide).[5] In patients with higher-risk disease, demethylating agents (e.g., azacytidine, decitabine), intensive chemotherapy and stem-cell transplantation

Table 1. Revised international prognostic scoring system (IPSS-R) in myelodysplastic syndrome

Prognostic variable	Score						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics*	Very good		Good		Intermediate	Poor	Very poor
Bone-marrow blast (percent)	≤2		>2 to <5		5 to 10	>10	
Haemoglobin (g/dL)	≥10		8 to <10	<8			
Platelets (cells/microL)	≥100	50 to 100	<50				
Absolute neutrophil count (cells/microL)	≥0.8	<0.8					

This scoring system was applied to an initial group of 7012 patients with primary MDS by the French-American-British classification who had at least two months of stable blood counts, ≤30 percent bone-marrow blasts and ≤19 percent peripheral blood blasts, and who were observed until progression to AML transformation or death (did not receive disease-modifying agents for MDS). Patients could be stratified into five groups with the following estimated overall survival and progression to AML.

Risk group	IPSS-R score	Median overall survival (years)	Median time to 25 percent AML evolution (years)
Very low	≤1.5	8.8	>14.5
Low	>1.5 to 3.0	5.3	10.8
Intermediate	>3 to 4.5	3.0	3.2
High	>4.5 to 6	1.6	1.4
Very high	>6	0.8	0.7

The prognostic value of the IPSS-R was validated in an external cohort of 200 patients with MDS

AML: acute myeloid leukaemia; MDS: myelodysplastic syndrome. *Cytogenetic definitions: Very good: -Y, del(11q).Good: Normal, del(5q), del(12p), del(20q), double including del(5q). Intermediate: del(7q), +8, +19, i(17q), any other single, double not including del(5q) or -7/del(7q), or independent clones. Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities. Very poor: Complex: >3 abnormalities.

Source: This research was originally published in Blood. Greenberg PL, Tuechler H, Schanz J, et al. *Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood 2012. Copyright © 2012 the American Society of Hematology. Graphic 85832 Version 2.0*

are options. Clinical trials should be considered in all patients where available, as there are no curative options as yet, apart from stem-cell transplantation. Despite recent advances in stem-cell transplantation, this remains an option for a minority of patients, due to the frequent presence of multiple comorbidities, the scarcity of matched donors and limitations in performance status.[5]

All patients require supportive care, which may include psychosocial support, clinical and haematological monitoring for disease deterioration or progression, quality-of-life assessment, transfusion, iron chelation therapy (in transfusional iron overload), antibiotics for infections and cytokines (e.g., erythropoietin, G-CSF, etc.). Thrombopoietin-receptor agonists and similar agents are under active investigation for the management of clinically significant thrombocytopaenia. Iron chelators (e.g., deferasirox, deferoxamine) have been shown in non-randomised, but prospective trials to improve survival and improve cell counts in a significant percentage of patients.[13,14]

SPECIALIST REFERRAL

Although very few patients with MDS will be cured, many of the above-mentioned treatments may result in improved quality of life, decreased transfusions, a reduction in complications, decreased progression to AML and increased overall survival. As the diagnostic and therapeutic aspects have become very complex and increasingly individualised, all patients with unexplained cytopaenias and/or diagnosed MDS, should be referred to a clinical haematologist.

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Lymphoma

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Lymphoma is consistently among the top 10 most common malignancies worldwide. It is also among the top 10 malignancies for long-term cure.[1] Moreover, due to treatment advances in developed countries, lymphoma is showing significantly improved outcomes in the past decade compared with earlier data, a trend that is expected to continue.[2] A recent age-standardised incidence rate of all subtypes of lymphoma in Europe was 24.5 per 100 000.[3]

As the incidence and subtypes of lymphoma vary throughout different regions of the world, so the outcome of lymphoma is variable, depending on local factors that impact outcome, such as age on presentation, concomitant HIV, access to treatment and expert referral centres. In sub-Saharan Africa, haematological malignancies are a significant cause of death and disability, but data on the presentation and outcome of lymphoma remain scarce.[4, 5] Lymphoma has a 10 to hundredfold increased incidence in the HIV-infected – in the Johannesburg academic complex an almost 20% increase was seen in the proportion of HIV-positive lymphoma cases in the past decade.[6, 7] However, seeing that South Africa is the epicentre of the HIV pandemic, this increase is modest, suggesting that with the more pressing concerns of HIV and TB, as well as poor access to health care, we are failing to diagnose large numbers of patients with lymphoma.[8] We do know that outcome after lymphoma treatment is poor compared to resource-rich regions where HIV status does not necessarily influence the outcome.[9]

PATHOPHYSIOLOGY

Lymphoma occurs when a specific cell type at various stages along lymphocyte development undergoes malignant dysregulation, resulting in tumour growth. This is analogous to solid cancer types deriving from their organ cell of origin. What makes the lymphoid malignancies unique, are the sheer magnitude of developmental stages and cell types that can give rise to different subtypes of lymphoma (see Table 1 for the current WHO classification of lymphomas).[10] Moreover, lymphoid cells are derived from stem cells in the bone-marrow compartment, and, via the bloodstream, continue their journey, and developmental maturation, through the lymphoid tissues, including thymus, spleen and lymph nodes. Clearly, lymphoid cells form an integral part of the biosystem, pervading every part of the human body, and they are not confined to one anatomical region. It follows that lymphoma can harbour as a tumour in literally every organ of the body, although the diagnostic hallmark of lymphomatous transformation is usually invasion of either bone marrow or lymphoid tissue, or both. This diversity of disease expression leads to diagnostic difficulty, as lymphoma can mimic or be confused with many other disease states.[11]

DIAGNOSTIC ISSUES

Five typical clinical "presentation syndromes" of lymphoma and some common disease confounders:

- **B-symptoms** (consisting of a triad of unexplained temperature >38°C, drenching night sweats and >10% weight loss in previous six months)
  - The obvious clinical confounder is the constitutional symptoms of solid organ cancers, connective tissue diseases, endocrine syndromes, and especially, of infectious diseases such as HIV and TB.
- **Significant lymphadenopathy** that is non-painful, often symmetric, with rubber-hard consistency. Although lymphoma can be present in small nodes, the "index diagnostic" lymph node in lymphoma will be greater than 1,5 cm and be present in excess of two weeks.
  - The endemic occurrence of HIV and TB mandates that firm diagnostic algorithms be followed to ensure that lymphadenopathy related to TB/HIV is successfully differentiated from lymphoma. Empirical TB treatment in the HIV-infected should likewise be subjected to firm guidelines and close follow-up.[12] Lymphadenopathy in the immunocompetent should *never* be subjected to empiric TB treatment. Histological diagnosis is mandatory.
- **Cytopaenias,** especially anaemia, resulting from bone-marrow invasion with failure of normal blood-cell production
  - The differential diagnosis can be another haematological myeloid malignancy, such as AML or MDS.
  - The differential diagnoses of cytopaenias are vast and span across immunological and systemic diseases.
- **Lymphocytosis** due to the above-mentioned lymphomatous bone-marrow invasion with subsequent spill of tumour cells in the bloodstream
  - These blood-borne, or "leukaemic" lymphoma cells can be easily typified and diagnosed as malignant. The pitfall for a missed diagnosis is when the differential count was not requested. Determination of white-cell count should always include a differential count. By the same logic, an abnormal "ward hb" should always be followed by a full blood and differential count (FBC).
- **Tumour masses** that can quietly grow in body cavities, eventually causing symptoms by disturbance of function. These can either grow:
  - **contiguous** to lymph-node sites, such as lymphoblastic lymphoma, causing a mediastinal mass, or mucosa-associated lymphoid tumours, such as MALT lymphoma in the stomach, or diffuse large B-cell lymphoma causing obstruction along the gastro-intestinal tract; or they can be
  - **remote**, such as follicular lymphoma presenting in the humerus or skin, or primary central nervous system lymphoma, presenting as a brain parenchyma tumour.

APPROACH TO DIAGNOSIS BASED ON DISEASE MANIFESTATION

Lymphadenopathy and tumour masses suspicious for lymphoma — in these cases, excision biopsy is the mainstay of diagnosis. Fine-needle aspiration cytology is not sufficient for lymphoma diagnosis and can *never* be used to rule out a diagnosis of lymphoma; "the issue is to get the tissue". Gaining advice from an expert in lymphoma diagnosis is mandatory to avoid time and life lost due to fruitless fine-needle aspiration and aimless biopsies. Increasingly, expert radiologists can employ core biopsy techniques to replace surgical biopsy. In patients with same-size, moderately enlarged lymphadenopathy, the cervical area is always selected before the axillary area and before the inguinal area for diagnostic biopsies. This increases diagnostic yield and avoids false negative results.

Substantial lymphocytosis — in these cases, the diagnosis of a lymphoma can easily be made on flow cytometry of blood. Remember that acute lymphoblastic leukaemia (ALL) can be diagnosed in blood and is the leukaemic counterpart of acute lymphoblastic lymphoma. However, in clinical practice, a sustained lymphocytosis is most often seen with the indolent lymphomas, such as chronic lymphocytic

leukaemia (CLL). The diagnosis becomes more urgent if the lymphocytosis is accompanied by signs of bone-marrow failure such as anaemia and thrombocytopaenia. Bone-marrow examination (BME) will be carried out at the discretion of the haematologist.

HELPFUL NON-FBC BLOOD TESTS WHEN CONSIDERING LYMPHOMA

- **Lactate dehydrogenase** (LDH): The more advanced the stage and the more aggressive the lymphoma, the higher the LDH will be. LDH is not solely connected to red-cell destruction syndromes or acute liver and cardiac states and is a mandatory and useful test when searching for malignancy. Note that normal LDH does not exclude lymphoma.
- **ESR** is usually raised, but is not specific enough to use as screening test.
- **Raised canalicular liver enzymes (alkaline phosphatase [ALP] and gamma-glutamyl transferase [GGT])** are likewise non-specific to lymphoma, but in this setting must prompt consideration of the liver as a site of lymphomatous infiltration.
- **Coombs positivity**, with low haptoglobin, and increased reticulocyte count, is useful when an associated haemolytic anaemia is suspected.

APPROACH TO THE DIAGNOSTIC AND STAGING PROCEDURES OF LYMPHOMA

In some lymphoma cases, the diagnosis is straightforward and the patient can be referred for staging and treatment. On the other hand, many patients are under scrutiny with a possible differential diagnosis of lymphoma. In these cases, it is advised to consult with the clinical haematologist or oncologist early on to guide the diagnostic biopsy of suspicious tissue.

Staging before therapy

Patients with a preliminary/probable diagnosis of lymphoma are best referred for full work-up and staging to a clinical haematologist or oncologist.

Traditional staging procedures include the triad of:

- Imaging, usually computed tomography (CT) of the neck-thorax-abdomen-pelvis or other affected area, but increasingly nuclear study with FDG-PET CT is employed for enhanced metabolic screening of a neoplasm.[13]
- Histology of tumour mass or lymph-node excision biopsy. This includes genetic and molecular techniques to enhance diagnostic differentiation.
- Bone-marrow examination (BME), including cytogenetic and molecular tests.

These procedures are not necessary in all cases – for example, in certain low-grade lymphomas with circulating tumour cells ("leukaemic phase of lymphoma"), flow cytometry on blood and clinical evaluation may be cost-effective and sufficient for diagnosis, whereas a FDG-PET CT has become preferable as a baseline investigation for Hodgkin's lymphoma and may obviate the need for a BME.

Staging after therapy

Investigations are planned based on the following considerations:

- is the treatment non-curative? – then clinical evaluation may trump invasive tests or even imaging.
- is treatment curative? – evaluation of the areas of initial disease is mandatory to re-stage and confirm remission.

TREATMENT AND PROGNOSTIC APPROACH

Based on "cell of origin": tumour histology, lymphoma is divided into Hodgkin's (HL) and non-Hodgkin's lymphoma (NHL).

Hodgkin's lymphoma: Globally, it can be said that HL has a simple classification and a straightforward, excellent prognosis. Classic Hodgkin's lymphoma subtypes exhibit an excellent (>80%) cure rate.[14]

Non-Hodgkin's lymphoma: There are close to a hundred NHL subtypes based on cell of origin, exhibiting extremely

Table 1. The 2016 WHO classification of non-Hodgkin's and Hodgkin's lymphoma

Commonly encountered clinical entities are given in **bold**, *Cell of origin* in margin

Non-Hodgkin's lymphoma: B-cell neoplasms	
Precursor B-cell neoplasm	**Precursor B-lymphoblastic lymphoma/leukaemia**
Mature B-cell neoplasm	**Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL)** Monoclonal B-cell lymphocytosis B-cell prolymphocytic leukaemia **Splenic marginal zone lymphoma** **Hairy cell leukaemia** Lymphoplasmacytic lymphoma → **Waldenström macroglobulinemia** Monoclonal gammopathy of undetermined significance (MGUS), IgM μ heavy chain disease γ heavy chain disease α heavy chain disease Monoclonal gammopathy of undetermined significance (MGUS), IgG/A **Plasma-cell myeloma** Solitary plasmacytoma of bone Extra-osseous plasmacytoma Monoclonal immunoglobulin deposition diseases Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (**MALT lymphoma**) Nodal marginal zone lymphoma **Follicular lymphoma** ■ Duodenal-type follicular lymphoma ■ Paediatric-type follicular lymphoma ■ Primary cutaneous follicle-centre lymphoma **Mantle-cell lymphoma** ■ *In situ* mantle-cell neoplasia **Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)** ■ Germinal centre B-cell-type ■ Activated B-cell-type **T-cell/histiocyte-rich large B-cell lymphoma** Primary DLBCL of the central nervous system (CNS) Primary cutaneous DLBCL, leg type EBV$^+$ DLBCL, NOS DLBCL associated with chronic inflammation Lymphomatoid granulomatosis **Primary mediastinal (thymic) large B-cell lymphoma** Intravascular large B-cell lymphoma ALK$^+$ large B-cell lymphoma

Table 1. (cont.)

Non-Hodgkin's lymphoma: B-cell neoplasms	
Precursor B-cell neoplasm	**Precursor B-lymphoblastic lymphoma/leukaemia**
	Plasmablastic lymphoma Primary effusion lymphoma **Burkitt lymphoma** **High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*** **High-grade B-cell lymphoma, NOS** *B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin's lymphoma

Non-Hodgkin's lymphoma: T- and NK-cell neoplasms	
Precursor T-cell neoplasm	**Precursor T-lymphoblastic lymphoma/leukaemia**
Mature T-cell and *NK-cell* neoplasm	T-cell prolymphocytic leukaemia T-cell large granular lymphocytic leukaemia Aggressive NK-cell leukaemia Systemic EBV$^+$ T-cell lymphoma of childhood Hydroa vacciniforme-like lymphoproliferative disorder Adult T-cell leukaemia/lymphoma Extranodal NK-/T-cell lymphoma, nasal-type Enteropathy-associated T-cell lymphoma Monomorphic epitheliotropic intestinal T-cell lymphoma **Hepatosplenic T-cell lymphoma** Subcutaneous panniculitis-like T-cell lymphoma **Mycosis fungoides** Sézary syndrome Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders: ■ Lymphomatoid papulosis ■ Primary cutaneous anaplastic large cell lymphoma Primary cutaneous γΔ T-cell lymphoma **Peripheral T-cell lymphoma, NOS** **Angio-immunoblastic T-cell lymphoma** **Anaplastic large-cell lymphoma, ALK$^+$** **Anaplastic large-cell lymphoma, ALK$^-$** T-cell prolymphocytic leukaemia T-cell large granular lymphocytic leukaemia
Hodgkin's lymphoma	
Germinal centre B-cell neoplasm	Nodular lymphocyte-predominant Hodgkin's lymphoma Classical Hodgkin's lymphoma: ■ Nodular sclerosis classical Hodgkin's lymphoma ■ Lymphocyte-rich classical Hodgkin's lymphoma ■ Mixed cellularity classical Hodgkin's lymphoma ■ Lymphocyte-depleted classical Hodgkin's lymphoma

Table 1. (cont.)

Non-Hodgkin's lymphoma: T- and NK-cell neoplasms	
Precursor T-cell neoplasm	**Precursor T-lymphoblastic lymphoma/leukaemia**
Post-transplant lymphoproliferative disorders	
Majority *mature B-cell* neoplasm-seldom *T-/NK-cell*	■ Plasmacytic hyperplasia PTLD ■ Infectious mononucleosis PTLD ■ Florid follicular hyperplasia PTLD ■ Polymorphic PTLD ■ Monomorphic PTLD (B- and T-/NK-cell types ■ Classical Hodgkin's lymphoma PTLD
Histiocytic and dendritic cell neoplasms	
Histiocyte and dendritic- cell-type neoplasm	■ Histiocytic sarcoma ■ Langerhans-cell histiocytosis ■ Langerhans-cell sarcoma ■ Indeterminate dendritic cell tumour ■ Interdigitating dendritic cell sarcoma ■ Follicular dendritic cell sarcoma ■ Fibroblastic reticular cell tumour ■ Disseminated juvenile xanthogranulomata ■ Erdheim-Chester disease

diverse predilection for site and degree of disease expression.

Moreover, they display vastly disparate behaviour clinically, which is why it is most useful, from a clinical and treatment point of view, to approach lymphoma based on three clinical presentation patterns (see Table 2).[15]

- The low-grade or indolent lymphoma group
- The high-grade or aggressive lymphoma group
- The very high-grade or very aggressive lymphoma group

Certain upfront characteristics predict the grade of aggressiveness of the lymphoma. Making the correct subtype diagnosis is becoming increasingly important, as treatment for lymphoma is becoming progressively more tailored to subtype. Once the diagnostic subtype is known, treatment can be approached within the framework of one of these three clinical groups.

Lymphoma is treated with classic chemotherapeutic agents and new targeted biological therapies.

Depending on the tumour type, treatment is typically delivered in cycles, with or without radiotherapy, scheduled to recur at two- to four-week intervals. Patients are hospitalised for high-risk or aggressive disease, but mostly treatment is on an out-patient basis. Chemotherapy combinations are used and, increasingly, biological therapy is added (see Tables 3 and 4). The most well-known biological drug in lymphoma and the first among anti-tumour cell antibody therapy in any tumour type, is rituximab, an anti-CD20 humanised monoclonal antibody therapy. Nevertheless, the backbone of most initial chemotherapy schedules for lymphoma remains corticosteroid therapy. Increasingly, the malignant activation pathways in lymphoma growth are being targeted by novel biological drugs, of which a few examples are given, denoted by an *. These drugs are novel in action and hold the promise of revolutionising lymphoma therapy, but this comes at a prohibitive price.

EARLY DIAGNOSIS OF LYMPHOMA AND REFERRAL: FUTURE DIRECTIONS

Lymphoma is high on the list of differential diagnoses of many commonly occurring clinical syndromes. Its incidence increases

Table 2. The three clinical lymphoma groups and the approach to diagnosis

Clinical lymphoma disease expression	Cell-of-origin causing lymphoma	Typical demo-graphics	Typical lymphoma subtypes encountered in clinical practice	Risk to patient if undiagnosed and untreated	Diagnostic urgency
Low-grade or indolent lymphoma	Mature B-cells and less often ma-ture T-cells	Usually a disease of the elderly, peak incidence around 60 years	Chronic lymphocytic leukaemia (CLL) Splenic lymphomas Follicular lymphoma	Not all indolent lymphomas need treat-ment Treatment delay unlikely to impact mortality	Less urgent to diagnose and also easier. Disease often spills into blood-stream ("leukae-mic"), is diagnosed on BME or easily accessible mass, or occurs in large spleen
High-grade or aggres-sive lymph-oma	Mature B-cells and less often ma-ture T-cells, occurring at an interme-diate devel-opmental stage	Wide spectrum of occur-rence across age groups, prognosis better in the young	Diffuse large B-cell lymph-oma Hodgkin's lymphoma Peripheral T-cell lymph-omas	Undiagnosed and untreat-ed patients have a risk of dying within weeks to months	Early diagnosis is crucial, as increased stage of disease decreases cure rate and increases mortality. Tumour lysis syndrome is possible
Very high-grade or very aggressive lymphoma	Immature B-cell or T-cell blastic cells or Burkitt cells with high turnover rate	Wide spectrum of occur-rence across age groups, prognosis better in the young	Acute lympho-blastic lymphoma Burkitt lymphoma	Undiagnosed and untreat-ed patients have risk of dying within days to weeks	Refer with-out delay (attention to hydration and renal protection) High LDH can point to tumour lysis syndrome

Table 3. The three clinical lymphoma groups and the approach to treatment

Clinical lymphoma disease expression	Initial treatment approach and timing of therapy	Common chemotherapy treatment regimens - Note that rituximab forms an integral part of most B-cell lymphoma chemotherapy regimens	Stem-cell and biological* treatment possibilities	Expected treatment outcome
Low-grade or indolent lymphoma	Treat lymphoma symptomatically, i.e., based on effects of disease burden. If asymptomatic, watch and wait	Bendamustine CHOP/CHOEP CVP FC	Ibrutinib* – a bruton kinase inhibitor Curative treatment with allogeneic stem-cell transplant is reserved for young patients with a high burden of disease	Largely non-curative treatment – unless allogeneic stem-cell transplant. Intent is to reduce disease burden and restore to asymptomatic state
High-grade or aggressive lymphoma	Treat aggressively and without delay, even if only a small disease burden	Ist line: CHOP Da-EPOCH ABVD +/- radiotherapy BEACOPP + radiotherapy 2nd line: DHAP ICE GDP IGEV	Nivolumab* and pembroluzimab* – checkpoint inhibitors In patients not achieving remission, autologous stem cells can be used to intensify treatment Allogeneic stem-cell transplant can cure patients with resistant disease	Intent of treatment is curative. Predictors of prognosis include age, disease extent, site of disease, raised LDH, anaemia Typical population survival rates for NHL patients are around 50% and for HL >80%
Very-high-grade or very aggressive lymphoma	Treat aggressively and without delay, high likelihood of tumour lysis syndrome	Intense inpatient chemotherapy regimens such as: hyperCVAD CODOX-M-IVAC Da-EPOCH +/- dose-dense rituximab	High-risk disease qualifies for allogeneic stem-cell transplant. An exciting new therapy for resistant disease is Chimeric Antigen Receptor T (CAR-T)* cells utilising adoptive immunotherapy directed at tumour cells	Intent of treatment is curative and can be achieved in 40-80% of cases, depending on patient age and the growth and genetic characteristics of the tumour

Table 4. Acronyms for and ingredients of common chemotherapy regimens

ABVD	**A**driamycin, **B**leomycin, **V**incristine, **D**acarbazine
BEACOPP	**B**leomycin, **E**toposide, **D**oxorubicin, **C**yclophosphamide, **V**incristine, **P**rocarbazine, **P**rednisone
B-R	**B**endamustine-**R**ituximab
CHOP +/- **R**	**C**yclophosphamide, **H**ydroxydaunorubicin (Doxorubicin), Oncovin (Vincristine), **P**rednisone +/- **R**ituximab
CHOEP +/- **R**	**C**yclophosphamide, **H**ydroxydaunorubicin (Doxorubicin), Oncovin (Vincristine), **E**toposide, **P**rednisone +/- **R**ituximab
CVP	**C**yclophosphamide, Oncovin (Vincristine), **P**rednisone
CODOX-M	**C**yclophosphamide, **O**ncovin (Vincristine), **DOX**orubicin, **M**ethotrexate
IVAC	**I**fosfamide, **V**P-16 (Etoposide), **A**ra-**C** (Cytarabine)
Da-EPOCH-R	**D**ose-**a**djusted **E**toposide, **P**rednisone, **O**ncovin (Vincristine), **C**yclophosphamide, **H**ydroxydaunorubicin (Doxorubicin) with **R**ituximab
DHAP	**D**examethasone, **H**igh-dose **A**ra C (Cytarabine), **P**latinol (Cisplatin)
FC(-R)	**F**ludarabine, **C**yclophosphamide (-**R**ituximab)
GDP	**G**emcitabine, **D**examethasone, **P**latinol (Cisplatin)
HyperCVAD	fractionated **C**yclophosphamide, **V**incristine, **A**driamycin (Doxorubicin), **D**examethasone alternating with Methotrexate and Cytarabine
ICE	**I**fosfamide, **C**isplatin, **E**toposide
IGEV	**I**fosfamide, **G**emcitabine, **V**inorelbine, **P**rednisone

in an ageing and industrialised population, as well as in HIV-infected individuals. However, its elusiveness to diagnosis, and its unpredictable clinical behaviour, complicates and obscures the diagnostic process. The only remedy is for the generalist to become well acquainted with the colleagues at the local haematology laboratory and haemato-oncology clinic to enable timely advice and early referral. This relationship should be reciprocal, in that the haematologist should be able to direct the generalist to the correct diagnostic procedures as carried out by radiologists, surgeons, nuclear-medicine specialists and specialist physicians. The oncological radiotherapist is integral to the therapy of certain aggressive lymphomas such as Hodgkin's lymphoma.

Aggressive lymphoma is a malignancy with high curative potential with early treatment. The many obstacles to lymphoma diagnosis in sub-Saharan Africa, leads to late-stage diagnoses, whereby the excellent cure rates of first-world countries are not yet seen. Increasing awareness, coupled with access to the correct diagnostic techniques, will increase early and accurate diagnoses. Histological diagnosis via biopsy is still essential, but the future lies with newer molecular techniques that have the potential for earlier diagnosis on more readily procurable patient material. Sophisticated approaches to sequencing DNA (analogous to GeneXpert TB assay) are being developed with the potential to detect lymphoma in the blood of patients. Various platforms for next-generation sequencing (NGS) are being developed by which lymphoma subtypes can be detected accurately, thereby enabling earlier and more efficient targeting of therapy.[16]

With a large number of novel agents in development, the future of lymphoma treatment looks better than ever, but the basics of a good clinical diagnostic approach through early and efficient diagnosis, followed by correct treatment, remain foundational to the management of these patients if we want to optimise their outcomes.

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Caring for patients with cancer

Oncological Emergencies

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An oncological emergency is an acute medical problem related to a cancer, or to its treatment, which may result in serious morbidity or mortality unless prompt treatment is initiated.[1] This may occur as a result of structural (obstructive/destructive) or metabolic complications. While the majority will complicate a known cancer diagnosis, occasionally this may be the presenting complaint, and a high index of suspicion is required to allow for rapid recognition, diagnosis and appropriate referral.

This article will focus on the oncological emergencies which commonly present in general practice, and where rapid diagnosis and referral has an important impact on outcome; in the setting of a non-haematological malignancy, unless stated otherwise. These include spinal cord compression, febrile neutropaenia, hypercalcaemia and superior vena cava syndrome.

MALIGNANT SPINAL CORD COMPRESSION AND CAUDA EQUINA SYNDROME

Malignant spinal cord compression is a neuro-oncological emergency that results in a potentially irreversible loss of neurological function due to the loss of integrity of the spine. It is estimated that between five and 40% of patients with malignant tumours will develop spinal metastases,[2] with around 5% of these being complicated by spinal cord compression.[3]

Metastatic tumours from any primary site may result in spinal cord compression, however, those with the highest propensity to metastasise to the spinal column include lung, prostate, breast, kidney, lymphoma and multiple myeloma.

PATHOPHYSIOLOGY

Metastatic spinal cord compression most commonly results from direct extension of vertebral metastatic tumour deposits through the periosteum into the spinal canal. However, in around 25% of cases, injury results from pathological fracture of the vertebra and direct cord damage, retropulsion of a bony fragment or acute tumour haemorrhage. Occasionally, para-spinal tumours or epidural deposits may infiltrate locally, without associated bony destruction. In general, spinal cord compression is a poor prognostic sign, with a median overall survival of six months.[4]

PRESENTING SIGNS AND SYMPTOMS

The single most important determinant of outcome is the severity of neurological compromise at the time of treatment initiation.

Thus, a high index of clinical suspicion is required to detect cases early, while neurological function is intact. Eighty percent of ambulant patients at presentation will retain the ability to walk, whereas only 50% with a transverse myelopathy and less than 5% of those with paraplegia will do so.[5] Patients considered high risk for the development of bone metastases, or those with known bone metastases, should be informed of the associated symptoms, which may allow for early presentation.

Symptoms may be insidious, or occasionally patients may develop rapid paraplegia with few preceding symptoms. The most common early symptom is pain. This is generally localised to the site of tumour and results from periosteal expansion. Common late symptoms include paraesthesia, loss of sensation, loss of motor function, and bladder and bowel incontinence. In adults, the spinal cord ends at the level of L1, and compression below this point results in the cauda equina syndrome (lower back pain, pain radiating down the leg, peri-anal loss of sensation and loss of bowel or bladder control).

MANAGEMENT

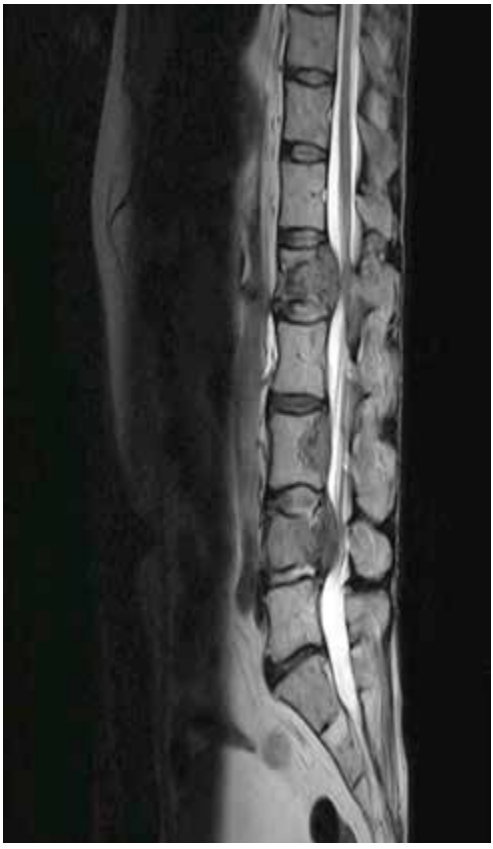
The aim of treatment is to maintain and/or improve neurological function. Definitive treatment should be commenced within 24 hours of diagnosis, and all patients should therefore be rapidly referred for clinical evaluation and spinal imaging. Patients should be nursed in the supine position during transfer due to the possibility of spinal instability. For between eight and 34% of patients, spinal cord compression is the presenting complaint,[2] and a full clinical history, general examination and appropriate investigations will assist to determine the site of primary tumour. Spinal imaging consists of a whole spine MRI, unless contra-indicated. The entire spine must be imaged as patients frequently have multi-level disease.

Definitive management requires a multidisciplinary approach, involving the general practitioner, treating physician/surgeon, radiologist, neurosurgeon, oncologist, as well as specialist physiotherapy and nursing care. Surgical stabilisation followed by radiotherapy has been shown to be associated with superior functional outcomes when compared to radiotherapy alone, with 84% *vs* 57% of patients retaining ambulation.[6] No difference in survival between the two approaches has been shown.

Thus, for select patients with a good prognosis and favourable radiological and clinical features, an initial surgical approach is preferred. Indicators for surgical intervention include:

- patient factors (prognosis, comorbidities, fitness for surgery, functional status)
- tumour factors (tumour type, control of primary, number and site of metastatic deposits, number of spinal levels involved, inherent radio- or chemosensitivity, previous radiotherapy)
- the neurological status of the patient (residual neurological function, complete paralysis with onset of symptoms less than 72 hours, paralysis of rapid onset, vertebral instability, displaced bony fragments and unknown primary tumour).[2]

Figure 1. MRI image of multi-level spinal cord compression



Source: Image courtesy of https://lookfordiagnosis.com/mesh_info.php?term=Spinal+Cord+Compression&lang=1

In patients who are not surgical candidates, radiotherapy alone provides the primary treatment modality. Radiotherapy aims to retain/regain neurological function, and to control pain. For highly chemosensitive tumours, such as lymphomas or small-cell lung carcinomas, chemotherapy may occasionally be commenced as the primary treatment modality, prior to radiotherapy. Prophylaxis against venous thrombo-embolism has not been specifically studied in patients with metastatic SCC, however, anticoagulation should be considered. Supportive care, such as specialised nursing, rehabilitative physiotherapy and pain management, are important aspects of care. This should involve the patient, families and carers and community

support, including primary care and specialist palliative care, as required.

FEBRILE NEUTROPAENIA

International guidelines define febrile neutropaenia (FN) as an oral temperature of >38.3°C, or of >38.0°C on two or more consecutive readings at least one hour apart, and an absolute neutrophil count (ANC) of <0.5 x 10^9/L, or <1.0 x 10^9/L and expected to fall below 0.5 x 10^9/L over the following 48 hours.[7,8] There has been a steady decrease in mortality rates related to febrile neutropaenia, however, this remains an important cause of cancer-related mortality and morbidity, as well as placing financial strain on health-care resources. In addition, dose-delays and reductions may translate to compromised treatment efficacy. All patients should be fully informed of the risk of febrile neutropaenia, the associated symptoms, and how to contact the appropriate services in the event of concerns.

PATHOPHYSIOLOGY

While febrile neutropaenia may complicate any chemotherapy treatment, the risk of febrile neutropaenia increases with the dose-intensity of the chemotherapy regimen utilised. High-risk regimens, defined by ASCO as having a greater than 20% associated risk of febrile neutropaenia,[9] are commonly used in patients with Hodgkin's lymphoma, non-Hodgkin's lymphoma, testicular malignancies and soft-tissue sarcomas (for a detailed list of high-risk regimens see NCCN Guidelines Version 2.2017; Myeloid Growth Factors, MGF-A 1-4).[10] Other factors increasing the risk of febrile neutropaenia include advanced age (>65 years), history of previous febrile neutropaenia, poor performance status, extensive prior therapy, extensive bone-marrow infiltration and significant comorbidities.[7]

Contributory factors to the pathogenesis of febrile neutropaenia include the immunosuppressive effects of chemotherapy, direct effects of chemotherapy on the mucosal barriers with seeding of the bloodstream with endogenous flora, breech in host defences related to the underlying malignancy and obstruction of lymphatics and hollow organs (biliary tract, bronchial, gastro-intestinal or urinary tracts) by tumours or surgical procedures. As a result, infectious pathogens may be bacterial, fungal and occasionally viral.

PREVENTION

Preventive strategies include chemoprophylaxis and/or prophylaxis with G-CSF (filgrastim or pegfilgrastim). Chemoprophylaxis with broad-spectrum antibiotics carries the risk of antibiotic-resistant strains, and current guidelines from the European Organisation for Research and Treatment of Cancer (EORTC) and American Society of Clinical Oncology (ASCO) recommend that clinicians limit the use of antibacterial prophylaxis to patients with >20% risk of febrile neutropaenia, or where specific indications exist (such as valaciclovir for patients receiving bortezomib-containing regimens, and trimethoprim-sulfamethoxazole for patients receiving temozolomide).[9,11]

Similarly, primary G-CSF prophylaxis (initiated with first cycle of chemotherapy) should be limited to those with >20% risk of febrile neutropaenia, while secondary prophylaxis (initiated with the second- or subsequent cycles of chemotherapy) should be commenced in any patient with a history of previous febrile neutropaenia, while on active treatment.

PRESENTING SIGNS AND SYMPTOMS

The magnitude of the neutrophil-mediated inflammatory response may be muted in neutropaenic patients, and thus an increase in temperature is often the earliest sign of infection. It is thus critical to recognise potential neutropaenic fever syndromes and react timeously. Prompt recognition and early initiation of empiric systemic antibacterial therapy are essential in improving outcomes related to febrile neutropaenia, and a delay in initiation of antibiotic treatment has been shown to be associated with a significantly increased hospital stay and increased mortality.[7] See Figure 2 for a consensus-based

time-dependent algorithm.[13] International guidelines for the prevention and management of neutropaenia have been developed, and the approach below is in keeping with these guidelines.[7-12]

MANAGEMENT

When febrile neutropaenia is suspected, body temperature should be determined, and clinical evaluation for haemodynamic stability and an obvious source of infection should follow. A full septic screen, including a full blood count and differential count, blood cultures, urine cultures and sputum cultures, are mandatory. A coagulation screen should be performed in any patient where a septic coagulopathy is suspected. Empiric broad-spectrum antibiotic therapy should be commenced immediately following the above cultures, and before any additional investigation. Subsequent investigations are directed by the clinical findings, but typically include chest radiology and swabs of any open wound or skin lesions.

Patients are grouped according to defined risk criteria into low- or high-risk groupings. The most commonly used scoring system is the Multinational Association of Supportive Care in Cancer (MASCC) index.[8,13] Low-risk patients may be treated with oral antibacterial therapy, on an outpatient basis, as randomised controlled trials have shown this group to have <1% mortality and <6% risk of serious complications.[13] The choice of agent is directed by clinical evaluation, loco-regional bacterial isolate and resistance patterns.

Current local and national guidelines are available, and at present single-agent quinolones, or a quinolone in combination with an extended spectrum penicillin are recommended.

Outpatient parenteral regimens may also be considered. Patients considered as high risk, either due to MASCC criteria or clinical judgement, should be admitted and commenced on broad-spectrum parenteral antibiotics, modified once culture and sensitivity results are available. Current national guidelines promote first-line combination therapy with an extended spectrum penicillin and an aminoglycoside. Antifungals may be added for patients not responding, or those with clinical fungal infections. Oral antibiotics may be substituted safely once the patient has been afebrile for 48 hours. Treatment is discontinued once the ANC is >0.5 x 10^9/L, the patient is asymptomatic, has been afebrile for 48 hours and follow-up blood cultures are negative (see Figures 1 and 2).

HYPERCALCAEMIA

Hypercalcaemia is defined as a corrected serum calcium >2.60 mmol/L. Primary hyperparathyroidism and malignancy comprise the most common causes, combined they account for over 90% of cases.[14] Malignant hypercalcaemia may result from direct displacement of calcium salts due to bony metastases or result as a paraneoplastic phenomenon.

Malignancies with a high propensity to metastasise to bone include lung, prostate, breast, kidney, lymphoma and multiple myeloma. Those associated with the secretion of physiological substances involved in calcium metabolism, such as parathyroid hormone (PTH)-related-peptide, ectopic PTH secretion or calcitriol, include small-cell lung cancers, lymphoma, myeloma and malignancies of the ovary, breast and thyroid.

Mild to moderate hypercalcaemia is defined as a level between 2.60-3.00 mmol/L, while severe hypercalcaemia occurs with corrected serum calcium levels 3.01 mmol/L and above; or is complicated by clinical symptoms. Hypercalcaemia is considered a poor prognostic sign.

PRESENTING SIGNS AND SYMPTOMS

Patients typically present with insidious onset of symptoms consisting of polyuria, polydipsia, anorexia, nausea, vomiting, constipation, muscle weakness, bony pain, renal stones and fatigue. In some cases, patients may present with confusion, focal neurological signs or coma. Physical findings usually confirm the above, and symptoms of the underlying malignancy may be detected.

Figure 1. Risk assessment resources

Using the MASCC risk-index score

- Using the visual analogue score, estimate the patient's burden of illness at the time of the intitial clinical evaluation. No signs or symptoms or mild signs or symptoms are scored as 5 points; moderate signs or symptoms are scored as 3 points. These are mutually exclusive. No points are scored for severe signs or symptoms or moribund.
- Based on the patient's age, past medical history, present clinical features, and site of care (input/output when febrile episode occured), score the other factors in the model and total the sum.

Burden of illnes

How sick is the patient at presentation?

No signs or symptoms	Mild signs or symptoms	Moderate signs or symptoms	Severe signs or symptoms	Moribund

Estimate the burden of illness considering all comorbid conditions

MASCC risk-index score/ model[1,2]

Characteristic	Weight
Burden of illness	
- No or mild symptoms	5
- Moderate symptoms	3
No hypotension	5
No COPD	4
Solid or tumour or haematologic malignancy with no previous fungal infection	4
No dehydration	3
Outpatient status	3
Age <60 years	2

Source: MASCC Index: Courtesy of the NCCN Guidelines Version 1.2018; Prevention and Treatment of Cancer-Related Infections, *FEV-D.*[8,13]

MANAGEMENT

Management is symptomatic, as well as being directed at the underlying cause. Hypercalcaemia should be verified by biochemistry, consisting of corrected serum calcium and serum albumin. Saline diuresis is the cornerstone of management. For patients with adequate renal function, 3-4 L normal saline fluids per 24 hours are required and a urine output of 100-150 ml/hr should be encouraged. Drugs adding to calcium conservation, such as thiazide diuretics and calcium supplementation, should be discontinued. Furosemide may be administered to encourage a calcium diuresis; only once adequate hydration is obtained. Regular monitoring of renal function is required. For patients with calcium levels of 3 mmol/L or higher, or with clinical symptoms due to hypercalcaemia, bisphosphonates should be administered. The dose and choice of agent will depend on the patient's renal function and physician preference. Calcitonin, a physiological PTH antagonist, has been shown to decrease serum calcium in patients with malignant hypercalcaemia, and salmon calcitonin (Miacalcic®) is registered for use for the treatment of hypercalcaemic emergencies, along with other appropriate agents, when a rapid decrease in serum calcium concentration is required.

SUPERIOR VENA CAVA SYNDROME

Superior vena cava (SVC) syndrome results from obstruction of the SVC by invasion or compression of an adjacent pathological process which involves the right lung,

"Bona diagnosis bona curatio"*

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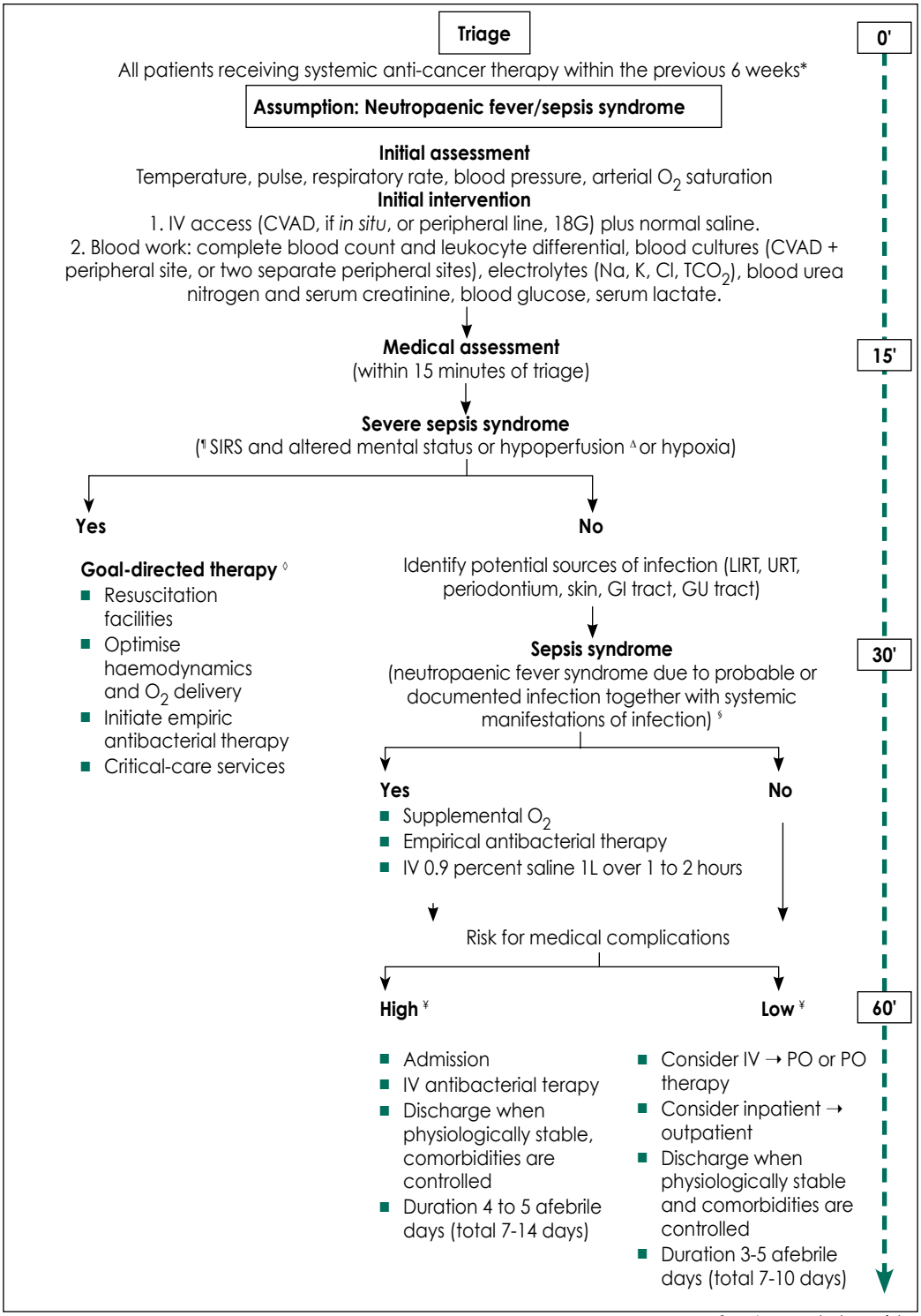
Figure 2. Time-dependent algorithm for the initial assessment and management of cancer patients with neutropaenic fever and suspected sepsis syndrome



See Legend alongside.

Figure 2. Legend

CVAD: central venous access device; Na: sodium; K: potassium; Cl: chloride; TCO2: total carbon dioxide; SIRS: systemic inflammatory response syndrome; LRT: lower respiratory tract; URT: upper respiratory tract; GI: gastrointestinal tract; GU: genito-urinary tract; O2: oxygen; IV: intravenous; MASCC: Multinational Association for Supportive Care in Cancer; PO: per os (by mouth).

* The Northern Ireland Cancer Network states that neutropaenic sepsis is a "time-dependent" condition, the successful management of which is dependent upon the early recognition of the likelihood that the cancer patient's problem represents a neutropaenic fever/sepsis syndrome[1]. Since more than 70 percent of cancer treatment-related syndromes, including neutropaenic fever, manifest within four to six weeks of systemic treatment[2], the Northern Ireland Cancer Network has recommended a history of chemotherapy within the past six weeks as a sensitive discriminator to detect patients with neutropaenic fever/sepsis syndromes by triage services in health-care facilities[1].

¶ SIRS is a clinical syndrome that is a form of dysregulated inflammation. The term SIRS has routinely been associated with both infectious processes (sepsis) and noninfectious insults, such as an autoimmune disorder, pancreatitis, vasculitis, thrombo-embolism, burns, or surgery. SIRS was previously defined as two or more abnormalities in temperature, heart rate, respiration, or white blood cell count.[3] However, in practice, its clinical definition and pathophysiology are nonequivocal such that SIRS and early sepsis cannot be readily distinguished. Thus, when SIRS is suspected it should prompt an evaluation for a septic focus.

Δ Hypoperfusion is defined by hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L.[4] Refer to the UpToDate topic review on the definition of sepsis and SIRS for additional details.

◊ Goal-directed therapy for initial resuscitation includes the following: (a) central venous pressure 8 to 12 mmHg; (b) mean arterial pressure ≥65 mmHg; (c) urine output ≥0.5 mL/kg per hour; and (d) central venous (superior vena cava) oxygen saturation ≥70 percent or mixed venous oxygen saturation ≥65 percent.[4] Refer to the UpToDate topic review on evaluation and management of sepsis for additional details.

§ Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection (eg, temperature >38.3 or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min, altered mental status, leukocytosis, arterial hypotension, arterial hypoxaemia).[4] Refer to the UpToDate topic review on the definition of sepsis and SIRS for the full diagnostic criteria for sepsis.

¥ Patients at low risk for serious complications are defined as those who are expected to be neutropaenic (absolute neutrophil count [ANC] <500 cells/microL) for ≤7 days and those with no comorbidities or evidence of significant hepatic or renal dysfunction. High-risk patients are defined as those who are expected to be neutropaenic (ANC <500 cells/microL) for >7 days; patients with neutropaenic fever who have ongoing comorbidities or evidence of significant hepatic or renal dysfunction are also considered to be high risk, regardless of the duration of neutropaenia. The Multinational Association for Supportive Care in Cancer (MASCC) risk index can also be used for determining risk. A MASCC score of ≥21 predicts a low risk for medical complications of neutropaenic fever syndromes that would require hospitalisation and/or prolonged length of hospitalisation. A score of <21 predicts patients at high risk for such complications.[5] Refer to the text for more details regarding the definitions of low- and high-risk patients based upon clinical criteria and the MASCC risk score.

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lymph nodes or mediastinal structures, or from thrombosis within the SVC, as may result from central venous catheters. An intrathoracic malignancy is responsible for between 60 and 85% of cases, with the remainder resulting from thrombosis, fungal infections, fibrosing mediastinitis and post-radiation fibrosis. The most common malignancies associated with SVC syndrome are small-cell and non-small-cell lung cancers and lymphoma. Together, these account for approximately 95% of cases. Other malignancies which may be associated include any tumour which has metastasised to the mediastinal lymph nodes, mesothelioma, thymoma and germ-cell tumours involving the mediastinum. Importantly, this is the presenting symptom in roughly 60% of patients with SVC syndrome.[15]

PRESENTING SIGNS AND SYMPTOMS

The rate of onset of symptoms is related to the rate of obstruction of the SVC. Obstruction of blood flow within the SVC results in the dilation of venous collaterals. Despite this, pressure within the venous system remains elevated and interstitial oedema of the head, neck and upper limbs develops. This oedema may compromise the upper aerodigestive tract, and accounts for the characteristic symptoms associated with the syndrome. Typical presenting signs and symptoms include swelling of the neck and upper limbs. Oedema of the upper airways results in stridor, cough, hoarseness, dyspnoea and dysphagia. Cerebral oedema typically results in headaches, and may result in cerebral ischaemia, herniation and infrequently death. The diagnosis is made clinically, on the basis of the above characteristic signs and symptoms and is confirmed by chest radiology. The majority of patients with SVC will have an abnormal chest radiograph, however the most useful investigation is a contrast-enhanced CT scan of the chest. This will detail the level and extent of obstruction, and the presence of associated thrombus.

MANAGEMENT

The goals of management are to alleviate symptoms, prevent airway obstruction or cerebral compromise, and treat the underlying malignancy. Patients who present with stridor due to severe laryngeal oedema and occlusion, or with coma, represent a true medical emergency and immediate treatment with stent placement and/or radiotherapy is indicated. For others, emergency radiotherapy may be deferred until a full diagnostic work-up has been concluded. This has not shown to negatively impact on treatment outcomes.[16] Evidence-based guidelines for the management of SVC are not available, and international recommendations support radiotherapy and/or stent placement.[17-19] General measures include nursing the patient in a semi-upright position, and face-mask oxygen may provide symptomatic relief. Intravenous steroids are helpful in steroid-responsive malignancies such as lymphoma and thymoma, and in association with radiotherapy which may result in initial worsening of laryngeal oedema. Diuretics may be used; however, no prospective evidence exists to support their use.

Specific measures include radiotherapy alone, or in combination with placing of an IVC stent. Chemosensitive tumours, such as small-cell lung cancer, lymphoma and germ-cell tumours are generally treated with initial chemotherapy. In these malignancies, radiotherapy may be added and has shown to decrease local recurrence rates and improve OS.

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Childhood Cancer and Its Warning Signs

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Childhood cancer is rare, but highly curable, for which early diagnosis is crucial as cancer is an important cause of death in children past infancy in the USA.[1] In low- and middle-income countries (LMICs), the diagnosis of paediatric cancer is often delayed, resulting in the child presenting with advanced disease, which reduces the chances of cure.[2] For this reason, it is important to ensure that the primary healthcare staff in particular are educated in recognising the warning signs of childhood cancer.

EPIDEMIOLOGY

An estimated 200 000 children are diagnosed with cancer worldwide annually. The world standard population incidence rate (WSR) for all cancers in children aged 0-14 years is 140.6 cases per million person-years, although the WSR is less than 100 for sub-Saharan Africa.[3] This lower WSR in sub-Saharan Africa is probably due to either missed diagnosis or children dying of infectious diseases prior to developing a childhood cancer. Ribeiro, *et al* have reported a marked discrepancy between actual identified childhood-cancer patients and the expected number of paediatric cancers, extrapolated from population-based data in LMICs.[4] The most common cancers in children under 15 years of age are leukaemias, brain tumours, lymphomas neuroblastoma, nephroblastoma and soft-tissue sarcomas. The age-specific incidence rate (ASR) for adolescents 15 to 19 years of age is 185.3 per million person-years, of which the most common is lymphoma with an ASR of 41.8 per million person-years.[3]

SURVIVAL

Childhood cancer is one of the success stories of the 20th Century as childhood-cancer survival rates have improved from poor survival in the first half of the 20th Century to more than 80% survival in high-income countries (HICs).[5,6] It is especially the survival of acute lymphoblastic leukaemia, the most common childhood cancer, that improved from less than 10% five-year survival in the 1960s to more than 80% by 2013 for children under 15 years of age. Adolescents between 15 and 19 years of age, however, still do not have the same improved survival rate as younger children, which is probably due to the presence of more high-risk features at diagnosis, which impacts negatively on prognosis.

It is heartening to note that there has also been a decrease in the childhood-cancer mortality rate of more than 50% from the 1970s to the year 2014, again emphasising the curative potential of childhood cancer.[7,8] Certain cancers, however, still have a poor survival rate, such as brain tumours, particularly pontine gliomas, and metastatic sarcomas.[7,9] More research is needed to understand tumour biology and develop innovative cancer medicines for these tumours.

CHILDHOOD CANCERS *VERSUS* ADULT CANCERS

Cancer in childhood is distinctly different from cancer in adults and therefore needs a different approach to diagnosis and treatment. The majority of childhood cancers has a mesenchymal or neuroectodermal origin *versus* adult cancers, which are usually of epithelial origin.[10] Furthermore, specific childhood cancers are associated with specific age ranges and, in general, the highest incidence is after birth, which declines with the lowest point at about 10 years of age. Childhood solid tumours include particularly embryonal tumours such as neuroblastoma, nephroblastoma and rhabdomyosarcoma, which resemble specific organs' primordial cells. There is a linear increase in incidence of non-embryonal tumours in adolescents,

which extends into adulthood. Males under 15 years of age are more affected than females by the common childhood cancers, such as acute lymphoblastic leukaemia and lymphomas.[6]

CAUSES

Causes of childhood cancer are unknown. There is minimal evidence for environmental factors and other exogenous factors to be involved in the aetiology of childhood cancer. Children born with a congenital malformation are at higher risk to develop a childhood cancer.[6,11] Nephroblastoma or Wilms tumour, for example, is associated with aniridia and Beckwith-Wiedemann syndrome. This is true for both major and minor malformations, as reported by Merks, *et al*.[12]

Risk factors for acute lymphoblastic leukaemia (ALL), the most common childhood cancer, include Down's syndrome, neurofibromatosis type 1, Bloom syndrome and ataxia teleangiectasia.[6,13] Prenatal exposure to x-rays also increases the risk of ALL. SEER data from the USA indicate that more white children will develop ALL than black children.[6] Down's syndrome is also associated with an increased risk of developing acute myeloid leukaemia (AML). Neurofibromatosis type 1 and tuberous sclerosis predispose children to brain tumours. Both Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) are associated with Epstein-Barr virus infections, while both acquired and congenital immunodeficiency are associated with NHL.[6]

About 5% of childhood cancers are caused by an inherited genetic mutation, of which bilateral retinoblastoma is the first described hereditary autosomal dominant cancer.[13] This disease usually presents at a younger age than sporadic unilateral retinoblastoma. Affected individuals carry a germline mutation in the RB1 gene on chromosome 13q14. All siblings of children with bilateral retinoblastoma should have regular ophthalmological surveillance in the first two years of life and preferably also genetics for RB1 gene mutations.[13]

Li-Fraumeni syndrome is a rare familial cancer syndrome, where the proband is diagnosed with a sarcoma before the age of 45 years of age. This syndrome is extremely rare in children.[13] Affected patients will have germline TP53 mutations and may develop any of the following tumours: sarcoma, premenopausal breast cancer, brain tumours, leukaemia, lymphoma, adrenocortical carcinoma and colorectal cancers. Most children with anaplastic sarcomas will have a TP53 mutation.

WARNING SIGNS OF CHILDHOOD CANCER

Early diagnosis is crucial for cure. Limited disease also needs less intense treatment and has a shorter duration with reduced costs.[14] Unfortunately, there is often a time delay in the diagnosis of childhood cancer, which leads to late diagnosis and advanced stage of disease, necessitating more intense therapy and with reduced possibility of cure.[15] It is therefore important for all health-care workers to be able to identify the warning signs of childhood cancer early. These clinical signs are especially persistent, and should alert the health-care worker to identify potentially affected children for referral for specialised investigations.[14]

The warning signs are the following: any abnormal mass or growth, a white spot in the eye, persistent fever, weight loss, pallor, fatigue or lethargy, any abnormal bleeding, persistent or recurrent pain and neurological deterioration.[14] Many of these signs can also be indicative of other chronic infections, and a high index of suspicion is needed when the following systems are affected, i.e., bone marrow, lymph nodes, bone, abdominal and soft tissue masses.

The *abnormal mass* can be either in the abdomen, in a limb or can be enlarged lymph nodes. Tumours presenting in the abdomen include nephroblastoma, neuroblastoma and embryonal rhabdomyosarcoma. It is important to examine the child for hypertension associated with an abdominal mass as both neuroblastoma and nephroblastoma can cause hypertension in a child. If not diagnosed and

treated, this hypertension may result in hypertensive encephalopathy. A *white spot in the eye* before the age of one year should alert the health-care worker to the potential diagnosis of retinoblastoma. Often the parents notice the white spot when photos with a flash are taken and the red reflex is absent.

A child, presenting with general symptoms such as prolonged fever, weight loss and fatigue, may suffer from a childhood cancer. The child, presenting with an *unexplained prolonged fever* for more than two weeks without a clear infection site and not responding to antibiotics, should be investigated for a childhood cancer. *Unexplained weight loss* especially is a presenting sign in solid tumours. The child may also complain of nausea, loss of appetite and night sweats (often present in Hodgkin's lymphoma).

A child with leukaemia may present with *pallor and fatigue* due to the associated anaemia. Leukaemias cause *easy bruising or bleeding*, especially epistaxis, gum bleeding, rectal bleeding or bleeding at any other abnormal site. The bleeding is usually the result of low platelets as platelets are not produced because of abnormal proliferation of the leukaemic blasts in the bone marrow. Metastatic disease can also cause abnormal bleeding as there is invasion of metastasis in the bone marrow.

Persistent pain, especially bone pain, should be deemed pathological, particularly if there is a history of the child being woken by the pain at night. There should be a high suspicion in adolescents, who are often active in sport and who present with persistent bone pain not responding to standard anti-inflammatory medicines, as this may be indicative of an osteosarcoma (bone tumour). There is often a history of trauma and although these adolescents are treated for an injury, the pain does not resolve. Ewing's sarcoma is another bone tumour that can present with bone pain. ALL may present with arthritis and can be wrongly diagnosed as juvenile rheumatoid arthritis. A child with a bone tumour or bone metastasis may also present with pathological fractures.

Another danger sign is *persistent or recurrent headache*, which can present with or without early morning vomiting. The headache with associated vomiting is usually due to the raised intracranial pressure. Other abnormal neurological signs that may be present are ataxia or poor balance, onset of weakness of limbs or trunk, a history of regression of milestones or sudden onset of convulsions. Parents may also complain about a change in the child's temperament.

The abovementioned warning signs are not specific to childhood cancer and health-care systems should have an effective referral system to ensure that children presenting with these signs are identified, referred and appropriately investigated. Poiyaidis, *et al* have described the Saint Siluan warning signs of childhood cancer, which summarise the above-mentioned warning signs, and after undertaking a campaign to educate primary health-care workers in 2001, reported a statistically significant increase (p=0.001) in the referral of new childhood-cancer patients to the Chris Hani Baragwanath hospital thereafter.[16] Such educational programmes, when aimed particularly at primary health-care doctors and nurses, will assist in the early diagnosis of childhood cancer, resulting in improved survival.

OPTIMAL TREATMENT OF CHILDHOOD CANCER

Children should be treated in paediatric oncology units, which are usually attached to the major university teaching hospitals in South Africa as the treatment is complex, necessitating the staff to be experienced in the management of both the treatment, as well as the ability to provide optimal supportive care. The paediatric oncology team usually includes paediatric oncologists, oncology-trained professional nurses, radiation oncologists, paediatric surgeons, social workers, dieticians, physiotherapists and occupational therapists. Psychological services may also be needed. Treatment is usually per the standard international treatment protocol, specific for the type of cancer, and

involves onco-chemotherapy, paediatric surgery and/or radiotherapy, as well as the management of chemotherapy- or radiation-related complications. Common complications are neutropaenic sepsis, bleeding disorders and anaemia. Children with amputations will also need extensive rehabilitation to be able to live as normal a life as possible and to adjust to the use of artificial limbs.

LONG-TERM FOLLOW-UP

Survivors of childhood cancer need lifelong follow-up care, initially in the first five years to ensure that there is no recurrence of the cancer and thereafter for the potential complications of the different treatment modalities. Up to 75% of children may suffer at least one long-term late effect, depending on the type of the cancer, the position of the cancer and the treatment received.[17,18] Radiotherapy, in particular, can cause long-term effects such as the need for joint replacement, congestive heart failure (if the chest was irradiated) and secondary cancers. Onco-chemotherapy can also damage the important target organs such as the heart, kidneys and liver, as well as cause hearing loss.

As the current treatment aims are to minimise long-term side effects, survivors in recent decades suffer fewer long-term adverse effects. It is important that a survivor of childhood cancer should be provided with a cancer-treatment record that includes the following information:[19]

- type and stage of cancer
- date of diagnosis and dates of relapses
- imaging done with dates
- contact details of treating doctors
- list of onco-chemotherapy medicines received, as well as total doses
- types of surgery done, radiotherapy doses and dates with exact description of sites
- any serious complications during treatment and the date of therapy completed.

CONCLUSION

As the majority of children in LMICs are diagnosed late, it is important to sensitise the health-care community to the possibility of a child having developed a cancer. The warning signs are important to share in childhood-cancer awareness campaigns, as this may assist in early identification and diagnosis. Country policy-makers should ensure that there is an effective referral system for these children with adequate treatment facilities, as childhood cancer is curable in the majority of patients.

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Common Childhood Cancers

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Common cancers of childhood include acute lymphoblastic leukaemia (ALL), brain tumours, lymphomas, neuroblastoma and nephroblastoma.[1,2] Retinoblastoma needs mentioning as the cancer may be more common in sub-Saharan Africa. Steliarova-Foucher, *et al*[2] report in their study for the period 2001 till 2010 that the world standard population incidence rate (WSR) for leukaemias is 46.4 per million person-years, followed by brain tumours (WSR 28.2) and lymphomas (WSR 15.2) in children 0-14 years of age.

ACUTE LYMPHOBLASTIC LEUKAEMIA EPIDEMIOLOGY

Acute lymphoblastic leukaemia (ALL) is the most common leukaemia in white children, while the incidence rate is lower for black children. The peak incidence is between two and five years of age with a male predominance.[3]

PATHOGENESIS

As the peak age is between two and five years, there are two hypotheses to explain the observation, namely the "delayed-infection" hypothesis of Greaves and "population-mixing hypothesis".[4] According to Greaves, children who are insulated from exposure to infections at an early age have naïve immune systems and therefore predispose them to a pathological response to an infection.[5] In support of this hypothesis is the evidence that early day-care attendance will protect children against the development of ALL.[6] Kinlen describes in his population-mixing hypothesis,[7] that mixing individuals from developing and industrialised societies may lead to infection exposure in populations previously isolated from such infections, leading to an aberrant immune response and predisposing the individual to develop ALL.[7] Epstein-Barr virus infection is associated with both ALL, as well as endemic Burkitt's lymphoma.[3] Exposure to ionising radiation is a known cause of childhood ALL, as documented after the atomic bomb explosions in Japan during World War II.[3]

CLINICAL PRESENTATION

The history of illness is usually short and presenting signs include pallor, fatigue, fever, generalised lymphadenopathy, hepatosplenomegaly and abnormal bleeding (petechiae, epistaxis, gum-bleeding, bruising).[3] Children may also have headaches if the central nervous system is affected, as well as bone pain with lytic lesions in the bone. The thymus may be enlarged, compressing the superior vena cava, which is known as superior vena cava syndrome (SVCS), a medical emergency.[4] The clinical signs of SVCS include cough, dyspnoea, orthopnoea and cyanosis of the upper body. This syndrome is usually associated with T-cell ALL, but can also occur in Non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma. Emergency treatment includes steroids and chemotherapy as standard of care. Differential diagnosis include juvenile rheumatoid arthritis, idiopathic thrombocytopaenic purpura and other malignancies such as neuroblastoma or non-Hodgkin's lymphoma (NHL).

PROGNOSIS

Age, the initial white cell count, gender, immunophenotype, ethinicity, ploidy and both molecular- and cytogenetics determine prognosis.[3] Younger than one year, older than 10 years, a high initial white cell count of more than 50 000 cells per mm^3 and males have a worse prognosis.

ALL CLASSIFICATION

ALL is classified into either B-cell or T-cell ALL or undifferentiated leukaemia and distinguished from acute myeloid leukaemia

(AML) on the basis of morphology and immunophenotype.[3] The majority of children will have a precursor B-cell ALL, known as common ALL. It is essential to determine the ploidy rate, as hyperdiploidy is associated with a good prognosis. This classification has implications for both treatment protocol and prognosis. For this reason, the child with suspected ALL should be referred to a specialised paediatric oncology unit for the necessary diagnostic investigations. Molecular- and cyogenetics are done to assist in risk stratification, which again determines intensity of onco-chemotherapy. The most common translocation is t(12;21), associated with a favourable prognosis, followed by t(1;19).

TREATMENT AND OUTCOME

Current event-free survival rates for ALL in children is more than 80% in high-income countries.[3] This is because of multi-agent combination onco-chemotherapy, improved supportive care and optimal individual medicine-dosing. The treatment protocol is decided according to risk stratification and appropriate for cell type (either T- or B-cell ALL) with risk stratification and consists of an induction phase, a post-induction phase and maintenance therapy for two years, as well as central nervous system (CNS) preventive therapy. A stem cell transplant may be indicated, especially for relapses.

BRAIN TUMOURS

Brain tumours are the second most common childhood cancer and tumours are heterogenous in pathology.[8,9] More males than females are affected. The WHO classification system classifies brain tumours by histology type, site and degree of malignancy. During childhood, the majority will be located infratentorially in either the cerebellum or brainstem, while the first two years of life (astrocytoma) and late adolescence are associated with supratentorial tumours. Common brain tumours include pilocytic astrocytoma, medulloblastoma, ependymoma, and supratentorial primitive neuro-ectodermal tumours (PNET). Medulloblastoma and PNET are both embryonal tumours.[9] A small number of tumours will be associated with cancer predisposition syndromes such as Li-Fraumeni's syndrome, neurofibromatosis types, tuberous sclerosis 1 and 2 and Gorlin's syndrome.[8] The clinical symptoms and signs include headaches with or without early morning vomiting (due to raised intracranial pressure), cerebellar ataxia, cranial nerve palsies, pyramidal tract signs and/or change in temperament.[8,9] Correct diagnosis is extremely important to ensure the most appropriate treatment and is made after magnetic resonance imaging and biopsy or surgical excision (if possible).[8] Management is according to histological type, site and degree of malignancy. Treatment usually involves a multimodal approach, combining surgery, radiotherapy with or without onco-chemotherapy. There is an improved survival rate if the tumour is completely excised. These children often suffer long-term effects, ranging from neurocognitive disability to seizure disorders and stroke.

LYMPHOMAS

Children can develop either Hodgkin's lymphoma (HL) or non-Hodgkin's lymphoma (NHL).

HODGKIN'S LYMPHOMA

Hodgkin's lymphoma usually presents in adolescence and is rare under five years of age.[10] There is a male predominance and the tumour is associated with increased family size and poor socio-economic circumstances. Epstein-Barr virus infection is a potential causative factor. The most common histology according to the WHO histological classification system is nodular sclerosis subtype, followed by mixed cellularity subtype with nodular lymphocyte-predominant-, lymphocyte-rich- and lymphocyte-depleted subtypes being rare. Clinically, patients present with enlarged lymph nodes in the neck, axilla, groin or with lymph nodes in the mediastinum. They may also have lost weight in the preceding six months, unexplained fever of more than 38°C, fatigue and drenching night sweats, classified as "B" symptoms.

A large mediastinal mass may also cause superior vena cava syndrome (see under ALL). HL is staged according to the Ann Arbor staging classification: Stage I is limited to a single lymph-node region, stage II has two or more involved lymph-node regions on the same side of the diaphragm, stage III has involvement of lymph nodes on both sides of the diaphragm and stage IV has disseminated disease, involving extra-lymphatic tissue. Risk features at diagnosis include the "B" symptoms, bulky disease and extra-lymphatic involvement. Prognosis is good for low-risk disease, but high-risk disease necessitates more intensive therapy. The differential diagnosis is tuberculosis in particular, as the clinical presentation is very similar. Treatment involves onco-chemotherapy with or without radiotherapy. Stem-cell transplant may be indicated for high-risk disease, especially for relapses.

NON-HODGKIN'S LYMPHOMA

The lymphoma originates either from precursor B-cells or thymic T-cells.[11] The most common type in childhood is Burkitt's lymphoma (BL), a B-cell NHL, which occurs in young children under five years of age[11]. There are two distinct clinical presentations, namely endemic BL, which presents with a jaw mass, and sporadic BL, which presents with an abdominal mass. Children with abdominal masses may present with nausea and vomiting, distension, gastro-intestinal bleeding, intestinal perforation and ileocecal intussusception. The disease occurs in the age group four to seven years of age, with a male predominance. Endemic BL is found in the "malarial belt" in Equatorial Africa, associated with both Epstein-Barr virus infection and malaria. HIV-infection is also associated with BL. Diagnosis is made through biopsy as BL is extremely sensitive to onco-chemotherapy, making surgical debulking unnecessary, except if there is obstruction. The current treatment is intensive onco-chemotherapy (e.g., LMB protocol) and supportive care.[12] Cure can be achieved in more than 90% of patients.[11,12]

NEUROBLASTOMA

Neuroblastoma is the most common solid tumour in childhood outside the central nervous system and occurs in infants and children under five years of age, with a median age of about 19 months.[13] Slightly more boys are affected. Aetiology is unknown. The tumour arises from immature nerve cells in either the adrenal gland or any site of the sympathetic chain and is associated with MYCN amplification.[13] There is a varying degree of neuronal differentiation and the fully differentiated ganglioneuroma is benign.

Clinical signs include abdominal mass or thoracic mass, pain (in various locations of the body), inability to walk, changes in the eyes (raccoon eyes: bulging and periorbital ecchymosis), diarrhoea and hypertension. Paraspinal tumours can extend into the neural foramina, causing compression of the spinal cord with acute paraplegia. Investigations should include the determination of tumour markers such as HVA and VMA in the urine, neuron-specific enolase (NSE), ferritin and LDG in serum, as well as bone-marrow aspiration and ^{123}I-MIBG scintigraphy for evaluation of bone and other organ involvement.

Biopsy or primary tumour excision should confirm the diagnosis. Staging is according to localisation, resectability and metastatic involvement. Stage IV needs to be mentioned as this is a stage found in infants under one year of age, characterised by a localised tumour with dissemination to the skin, liver and/or bone marrow but with no bone involvement, which has an excellent survival rate.

Prognosis depends on the stage of disease, the assigned risk, the histology, age at diagnosis, ploidy and MYCN amplification. Treatment consists of tumour excision (if possible) and onco-chemotherapy. Acute spinal compression needs emergency intervention, either through laminectomy or radiotherapy. Autologous stem-cell transplants may be indicated for advanced disease if complete remission is achieved. Targeted delivery of radionuclides or molecularly-targeted agents are being investigated for high-risk disease.[13]

NEPHROBLASTOMA OR WILMS' TUMOUR

Nephroblastoma is a paediatric kidney tumour in children under five years of age, usually present in one kidney, but may rarely affect both kidneys (bilateral disease).[14] Clinically, the children present with an asymptomatic abdominal tumour, but may have fever or pain and loss of appetite. These children may also have hypertension. The disease may be associated with aniridia, Beckwith Wiedeman syndrome and other congenital genitourinary anomalies and is associated with *WT1* gene mutations (11p13).

Of note is that nephroblastoma is seemingly more common in sub-Saharan Africa than neuroblastoma, which differs from Europe and the USA. This is specifically the case for black children.[2,14] Nephroblastoma is classified into low risk, intermediate risk and high risk on the basis of the histology type. Staging is done according to prechemotherapy imaging for metastasis and local operative findings at tumour excision. Prognosis depends on histology risk, age and response to treatment with the current survival rate more than 90% for favourable histology. Treatment consists of pre-operative onco-chemotherapy to shrink the tumour for easier surgical excision. Postsurgical treatment depends on stage at excision with limited disease receiving limited further chemotherapy, while advanced disease and metastasis necessitates intensive chemotherapy and radiotherapy to the tumour bed. Lung metastasis can be excised if persistent.

RETINOBLASTOMA

Retinoblastoma is a rare tumour, but the most common eye tumour in children and usually affects young infants and children under the age of five years.[15] There is an impression that the tumour incidence is higher in Central and South America, India and sub-Saharan Africa. The majority of tumours appear sporadically, but a small group is associated with a germline mutation in the *RB1* gene, leading to the hereditary, often bilateral disease in a younger age group. The clinical presentation is usually leucocoria with an absent red eye reflex. The child may also present with strabismus. Diagnosis is made with either RETCAM or examination under anaesthesia. Local disease has an excellent prognosis if diagnosed early and is amenable to local therapy with vision-saving procedures, while local extension and metastatic disease necessitate onco-chemotherapy. Diagnosis may be delayed in South Africa, as the warning signs may be missed, resulting in metastatic disease with a poor prognosis.[16,17]

CONCLUSION

In conclusion, early diagnosis is crucial for improved survival in children with cancer. Other rare cancers are not discussed in this brief chapter regarding common childhood cancers. These cancers include bone tumours, sarcomas and other embryonal tumours. A high index of suspicion is needed to ensure early referral for specialised investigations in a tertiary centre to diagnose a potential childhood cancer. Both the South African Children Cancer Study Group members (SACCSG) and the Childhood Cancer Foundation of South Africa (CHOC) can provide advice to any health-care worker and/or parent if concerned about potential warning signs of childhood cancer.[18,19]

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HIV-Related Cancers

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People infected with HIV have a substantially higher risk of some types of cancer compared to uninfected people of the same age. The very high incidence of Kaposi's sarcoma was noted early in the AIDS epidemic and in this setting has had a highly aggressive course.

This disease, along with two other cancers, are known as "acquired immunodeficiency syndrome (AIDS)-defining cancers" or ADCs.

These three cancers are:
- Kaposi's sarcoma (KS)
- Non-Hodgkin's lymphoma (NHL)
- Invasive cervical cancer

A diagnosis of any one of these cancers marks the point at which HIV infection has progressed to AIDS.

The pattern of cancers in HIV-infected patients has altered with the increased use of antiretroviral therapy (ART), previously known as highly active antiretroviral therapy (HAART).

In countries where there is a high usage of this medication, the incidence of Kaposi's sarcoma and non-Hodgkin's lymphoma has decreased markedly. However, there has been a persistent increase in cancers that are now called non-AIDS-defining cancers (NADCs) when compared to the general population.

With the longer life expectancy among HIV-positive patients, directly attributable to the use of antiretroviral therapy, an increased risk of cancer in general has been described in industrialised countries and this trend is also seen in South Africa. This is exacerbated locally by the uneven availability, and use, of ART and there is a worrying trend in the incidence of both ADCs and NADCs.

INCIDENCE

Twenty-five to 40 percent of all patients with HIV will develop cancer during their lifetimes.[6]

Some studies indicate that people infected with HIV are 500 times more likely than uninfected people to be diagnosed with Kaposi's sarcoma, at least 12 times more likely to be diagnosed with non-Hodgkin's lymphoma, and, among women, at least three to five times more likely to be diagnosed with cervical cancer.[1]

In addition, people infected with HIV are at higher risk of several other types of cancer. These other malignancies include anal, liver, and lung cancer, and Hodgkin's lymphoma.

People infected with HIV are at least 20 times more likely to be diagnosed with anal cancer, three times as likely to be diagnosed with liver cancer, two to three times as likely to be diagnosed with lung cancer, and at least eight times more likely to be diagnosed with Hodgkin's lymphoma.[1]

An increased risk of testicular cancer (seminomas in particular) and a two to three times increased risk of head and neck cancers (40% related to oral HPV infection) is seen in HIV-infected patients. HPV-related head and neck cancers are known to have a better prognosis than tobacco-related tumours. Castleman's disease (giant or angiofollicular lymph-node hyperplasia, lymphoid hamartoma, angiofollicular lymph-node hyperplasia), a lymphoproliferative disorder that can involve single lymph-node stations or can be systemic, is now seen far more commonly in SA related to HIV infection. Although not a true malignancy, it is sometimes treated with chemotherapy.

People infected with HIV do not seem to have an increased risk of breast, colorectal, prostate, or many other common types of cancer. Thus, screening for these cancers in HIV-infected people should follow guidelines for the general population.

For children diagnosed with AIDS, the risk for developing cancer continues into adulthood even if managed with ART.[10]

In sub-Saharan Africa, Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) incidence and mortality rates have risen dramatically as the HIV/AIDS epidemic has evolved. In the developed world, cervical cancer is also HIV-related, but sub-Saharan Africa had among the world's highest cervical cancer rates even before the HIV/AIDS epidemic. Good data remain sparse.[15]

Access to anti-retroviral therapy in South Africa is improving, but HIV-related malignancies are an increasingly urgent public health problem.

Given its high prevalence, HIV plays a major role in the aetiology, treatment, and outcome of all malignancies in South Africa.

PATHOGENESIS

The immunosuppression associated with HIV reduces the host's ability to fight infections that may lead to cancer. Many people infected with HIV are also infected with other viruses that are known to cause certain cancers.

The following are the most important of these cancer-related viruses:

- Human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma-associated herpes virus (KSHV), is the cause of Kaposi's sarcoma.
- Epstein Barr virus (EBV) causes some subtypes of non-Hodgkin's and Hodgkin's lymphoma.
- Human papillomavirus (HPV) causes cervical cancer and some types of anal, penile, vaginal, vulvar, and head and neck cancer.
- Both hepatitis B virus (HBV) and hepatitis C virus (HCV) can cause liver cancer.

Infection with most of these viruses is more common among people infected with HIV.[2-5]

In addition, studies have shown that some traditional risk factors for cancer, especially smoking (a known cause of lung cancer) and heavy alcohol use (which can increase the risk of liver cancer), has a higher prevalence among people infected with HIV.[4] There is also some indication that the virus may sensitise cells to stimuli such as tobacco.[11]

Compromised immune systems, causing both immunosuppression and inflammation, seem to play a role, both directly and indirectly in the development of certain cancers.[2]

The development of neoplasia in HIV-infected patients mimics that seen in solid organ-transplant patients on chronic immunosuppressive therapy.

People living with HIV seem to develop certain cancers at a younger age, possibly indicating an accelerated disease progression or higher exposure to risk factors. In a US population data study, lung and anal cancer, and myeloma were diagnosed four years earlier and oral cavity and kidney cancer two years earlier in HIV-infected patients compared to the general population.[12]

RISK REDUCTION/SCREENING

There are no particular screening guidelines for HIV-positive patients, but a high index of suspicion for unexplained symptoms should guide investigations. Regular screening for cervical cancer is especially recommended in HIV-infected women.

Taking ART, following current HIV-treatment guidelines, lowers the risk of Kaposi's sarcoma and non-Hodgkin's lymphoma and increases overall survival and is thus a vital part of risk reduction.

The risk of lung cancer can be reduced by stopping smoking. Because HIV-infected people have a higher risk of lung cancer, it is especially important that they do not smoke and that primary health-care workers counsel HIV-infected patients about this.

The higher incidence of liver cancer among HIV-infected people appears to be related to more frequent infection with hepatitis virus (particularly HCV) and alcohol abuse or dependence than among uninfected people. HIV-infected patients should know their hepatitis status and be tested for this. If blood tests show that they

have previously been infected with HBV or HCV, they should be counselled about reducing their alcohol consumption.

In addition, if viral hepatitis is active, HBV- or HCV-suppressing therapy should be considered. Some drugs may be used for both HBV-suppressing therapy and ART.

Because HIV-infected women have a higher risk of cervical cancer, regular screening for this disease is recommended. Studies have suggested that Pap test abnormalities are more common among HIV-infected women. Annual screening for life is generally accepted as a safe approach in this clinical setting.

Some researchers recommend anal Pap-test screening to detect and treat early lesions before they progress to anal cancer. This type of screening may be most beneficial for men who have had sexual intercourse with men.

DIAGNOSIS

The diagnosis and work-up of cancers in HIV-positive patients is the same as for the general population.

With the introduction of ART in the mid-1990s, the incidence of Kaposi's sarcoma and non-Hodgkin's lymphoma among people infected with HIV was greatly reduced. ART lowers the amount of HIV circulating in the blood, thus partially restoring the immune-system function.

Although lower than before, the risk of these two cancers is still much higher among people infected with HIV than the general population. This persistently high risk may be due, at least in part, to the fact that immune-system function remains substantially impaired in people treated with ART. In addition, over time HIV can develop resistance to the drugs used in ART. Many people infected with HIV have had difficulty in accessing medical care or taking their medication as prescribed.

The incidence of cervical cancer, in contrast, has not shown a reduction in incidence with introduction of ART. Also, the incidence of several other cancers, particularly Hodgkin's lymphoma and anal cancer, has been increasing among HIV-infected individuals since the introduction of ART. The influence of ART on the risk of these and other cancer types is not well understood.

As ART has reduced the number of deaths from AIDS, the HIV-infected population has increased and become older. The fastest growing proportion of HIV-infected individuals is the over-40 age group. These individuals are now developing cancers common in older age. In 2003, the proportion of these other cancers exceeded the number of AIDS-defining malignancies in the Western world. However, HIV-infected people do not develop most cancers at a younger age than is typically seen in the general population.

MANAGEMENT: OVERVIEW OF THE MANAGEMENT OF THE THREE AIDS-DEFINING CANCERS

KAPOSI'S SARCOMA

Kaposi's sarcoma (KS) is a vascular tumour associated with human herpes virus 8 (HHV-8).

It is found in four epidemiological forms:

- AIDS-related (epidemic) – prior to ART it was 20 000 times more common in HIV-infected patients
- Endemic or African – endemic in Equatorial Africa
- Organ-transplant-associated – similar to the classic form
- Classic – older men of Mediterranean or Jewish origin

The incidence of AIDS-related Kaposi's sarcoma has declined markedly since ART.

Cutaneous Kaposi's sarcoma is the most common form and affects lower extremities, the face (especially the nose), and genitalia. It is often associated with lympho-oedema.

Visceral Kaposi's sarcoma may include all visceral sites, including oral mucosa, lymph nodes, gastro-intestinal tract, lungs, liver, pancreas, heart, testes, bone marrow, bone and muscle.

Diagnosis, although easy to the clinically trained eye, should be via biopsy/histology.

Oral mucosa is the presenting site in about 15% as the initial site. It is often seen

on the palate and gingiva and is frequently first detected by a dental practitioner.

Prior to ART, 40% of patients had GIT involvement with weight loss, nausea and vomiting, abdominal pain, bleeding, obstruction and diarrhoea.

Treatment

ART is central to the management of Kaposi's sarcoma. The major goals of treatment are symptom palliation, prevention of disease progression, and shrinkage of tumour to alleviate oedema, organ compromise and psychological stress.

Depending on the clinical picture, treatment is either local with intralesional therapies, or localised superficial beam radiation, or systemic chemotherapy for more widespread disease.

The chemotherapies used include doxorubicin (including liposomal versions), paclitaxel bleomycin, the vincaloids and etoposide. Steroids also have a place in the management of Kaposi's sarcoma.

The prognosis has improved with the introduction of ART and often treatment is intermittent and ongoing. The five-year survival in patients with limited stage disease is over 80%, but falls if HIV is not controlled or in extensive disease.

NON-HODGKIN'S LYMPHOMA

Ten percent of HIV-infected patients develop non-Hodgkin's lymphoma (NHL). This disease is more common in males than females.

The three main non-Hodgkin's lymphomas are

i. Systemic NHL (>80%).
   - Diffuse large B-cell (75%)
   - Burkitt's lymphoma (15%)
   - Indolent NHL (<10%)
   - T-cell lymphoma (1-3%)
   - Plasmablastic lymphoma (<1%)

ii. Primary central nervous system (CNS) lymphoma (15%)

iii. Primary effusion lymphoma – rare (<5%)

The general management of non-Hodgkin's lymphoma is identical in the HIV-infected patient to that of the non-infected patient. However, due to various factors, treatment may need to be tailored to co-morbidities found in this population.

Outcomes related to presenting CD4 counts are unclear, but low CD4 counts seem to correlate with more advanced stage (Ann Arbor III and IV) and poorer prognostic features, such as B-symptoms, bone-marrow and extranodal involvement at presentation. Stage and prognostic features are known independent indicators of outcomes.[7]

Treatment

The optimal therapy for HIV-infected patients is still controversial and most studies are based on patients in developed countries who have different risk factors to those locally. The administration of optimal doses (dose frequency and dose intensity) is a challenge and the immunosuppression of HIV-infected patients may limit this. A high rate of dose reduction, treatment delays or treatment interruption is seen in these patients. Low CD4 counts limit the use of bone marrow-suppressive therapies and careful monitoring of blood counts and the higher use of prophylactic neutrophil support using granulocyte colony-stimulating factors is necessary. Patients with very low CD4 counts (<50-100 cells/µl) have a higher risk of infection-related mortality if rituximab, a monoclonal antibody against CD20 protein found on the surface of B-cell non-Hodgkin's lymphomas, is used. Rituximab, commonly used in combination with standard chemotherapy for B-cell non-Hodgkin's lymphomas, reduces CD4 levels which may lead to catastrophic infections. Rituximab is known to offer a 10-15% increase in long-term survival in the general B-cell non-Hodgkin's lymphoma population.

For this reason, HIV-infected patients with non-Hodgkin's lymphoma need to be on ART from the start of the systemic therapy and need careful HIV-monitoring during treatment. Discontinuation of ART is not uncommon in HIV-infected NHL patients due to treatment complications. This further complicates the management and adds to the causes for death in this cohort of patients.[7]

In the era of ART, and despite high-risk features and the treatment limitations highlighted above, the two-year overall survival of HIV-DLBCL patients reaches 75% and is similar to HIV-negative patients with the same risk factors.[7]

For these reasons, HIV-related non-Hodgkin's lymphoma should preferably be managed by experienced specialist oncologists or under their guidance at the very least.

Note: Hodgkin's lymphoma is the most common NADC and is 15- to 30-fold higher than in the non-infected population. Treatment outcomes vary, depending on the cohorts looked at. Although the incidence of this disease has not decreased since the introduction of ART, the prognosis has significantly improved. Some studies show outcomes are similar for patients with similar stages and risk categories as HIV-negative patients. This seems to be mainly because HIV-positive patients tolerate standard chemotherapy regimens well and can be treated in similar ways to their HIV-negative counterparts.[8]

INVASIVE CERVICAL CANCER

The incidence of both cervical dysplasia and neoplasia is significantly increased in HIV-infected women, and the prognosis is worse compared with HIV-uninfected women.[9] Unlike the positive effect of ART on the incidence of NHL and KS, the impact on cervical cancer has been marginal to date.[13] The burden of HIV-related cervical cancer is in sub-Saharan Africa, with the most important risk factor being persistent HPV infection. Cervical cancer is a direct result of this.[14]

Prevention

Studies have shown that HPV vaccines are well-tolerated in HIV-positive HPV-negative women, with high levels (75-100%) of seroconversion for HPV 6, 11, 16 and 18, with the higher rates in women with CD4 counts >200 cells/µl.

Screening

In sub-Saharan Africa, the most important limiting factor to screening is access. The various screening methods – PAP, HPV DNA testing, visual inspection using acetic acid or Lugol's iodine are sporadic, if at all available. In countries with limited resources, various models have been proposed. Most successful seems to be a combination of "see and treat". Pre-malignant lesions are treated on the same-day visit to reduce loss to follow-up.

The age at presentation of changes is on average 10 years younger in HIV-positive *versus* HIV-negative patients.

Treatment

Management of immunosuppression: As per guidelines, ART should be instituted in patients at the appropriate CD4 level count along with other prophylactic measures and vaccinations as per guidelines.

Standard staging in lower- to middle-income countries (LMIC) is pelvic examination (by a suitably trained physician), CXR and ultrasound to exclude hydronephrosis which is indicative of the more advanced stages at presentation. In well-resourced situations, the staging and primary work-up would be the same regardless of HIV-status. The benefit of PET-CT *versus* standard CT-scans in HIV-positive patients is beset with issues of false-positive nodal detection due to HIV/AIDS. CT-scan along with surgical staging seems to be indicated as per the clinical indications.

Surgery and/or chemoradiation are the cornerstones of cervical cancer management and the treatment is as per HIV-negative patients, guided by disease stage and patient factors. Access to trained gynaecological surgeons and to radiation facilities is severely lacking in the areas where this is most needed. Neoadjuvant chemotherapy followed by radical hysterectomy is a common approach in areas without access to radiation.

Palliative care is part of an overall approach to the management of all cancer patients, and often is all that is available in low-resource regions. The lack of access to opioids is problematic. Eighty percent of the global population lack access to appropriate opioid analgesics, based on a WHO estimate.[16]

Outcomes

Data are lacking from both Western and LMICs owing to HIV-positive patients not being included in clinical trials in the West, and poor reporting generally. Some studies have shown poor treatment completion rates and resultant poor outcomes in HIV-positive *versus* HIV-negative patients. However, in sub-Saharan Africa regions where there were good resources, outcomes were comparable stage for stage and showed no difference in outcome by HIV-status. Factors that contribute to outcomes include total radiation dose, the addition of chemotherapy and presenting haemoglobin levels.[13]

CONCLUSION

The incidence and prevalence of HIV-positive patients with cancer can be expected to increase with the extended longevity of HIV-positive patients. In well-resourced settings and in patients where general health is maintained, approaches to HIV-positive patients will mirror that of the HIV-negative population. The importance of risk reduction – reducing tobacco and alcohol exposure, prevention and management of intercurrent bacterial, viral and fungal infections, immune system support and dealing with other general health issues related to HIV – along with appropriate screening, will be central in dealing with this increase.

In South Africa, which has the world's highest burden of this disease, the HIV deaths as a percentage of all deaths has fallen from 42% in 2002 to 25% in 2017, while the prevalence of this disease has increased from just under five million to seven million over the same period.[17]

The impact on the national healthcare budget of managing HIV-related cancers is high and can be expected to continue to rise.

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Medical Ethics in Cancer Care

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Many of the most important medical ethical issues have arisen in oncology first or presented themselves most forcefully in the care of cancer patients. Many of the early, important cases related to informed consent, truth-telling and aspects surrounding end-of-life care pertain to euthanasia and physician-assisted suicide. Unethical research involving cancer patients was also conducted.[1] In the South African scenario of change and complexity of health-care policies and the cost of managing cancer during a time of increased biomedical innovation, a tension between what is good for society as a whole and what is good for the individual patient may become an issue, especially in a resource-constrained environment.

Although the incidence and prevalence of cancer in the South African population is relatively low compared to other non-communicable diseases, the cancer burden in the population in terms of the physical, psychosocial, emotional and financial impact on individual patients, their families and the community at large, is significant. It is for that reason that medical ethical issues feature strongly in oncology and specifically in the care of cancer patients.

Ethical issues in patients with cancer are, as expressed by Holleb and Braun, "complicated by the fact that because cancer is a life-threatening illness, many transactions we have with our patients involve crisis and decision, thus increasing the occasions when these values will come into conflict. Other exacerbating factors are the number of people involved in the care of the cancer patient; the complexity of the disease itself; the intricacy of modern technology; and the multiplicity of answers to questions that once seemed obvious – What is life? What is death? What are the relative values of life and death – and to whom?"[2]

THE MEDICAL PRACTITIONER AS PROFESSIONAL AND PROFESSIONALISM

The term "profession" means "a dedication, promise or commitment publicly made". Medicine is one of the traditional professions and doctors are professionals. In this context, the medical profession presents itself to society as a social benefit and society accepts the profession, expecting it to serve the continuum of heath needs of the population where they work. Doctors, as professionals, have a fiduciary duty towards those they serve. This means that professionals have a particularly stringent duty to ensure that their decisions and actions serve the welfare of their patients, even at some cost to themselves.[3] The profession traditionally issues a code of ethics that specifies the obligations arising from this fiduciary duty. Ethical problems often occur when there appears to be a conflict between these obligations or between fiduciary duties and personal goals.

The building blocks of becomng a good medical practitioner require a lifelong commitment to sound professional and ethical practices and an overriding dedication to the interests of one's fellow human beings and society. The ethos of the practice of medicine is founded on the confidential, trusted doctor-patient relationship.

The fundamental principles that define the fiduciary duty centre around the basic ethical principles of patient autonomy, beneficence and non-maleficence and justice, and translate into professional responsibilities of the doctor that flow from the following principles:[4]

- **Commitment to competence:** Being committed to lifelong learning and being responsible for maintaining the medical knowledge and clinical and

team skills necessary for the provision of quality care

- **Commitment to honesty with patients:** Practitioners must ensure that patients are completely and honestly informed and empowered before they consent to treatment and before treatment occurs.
- **Commitment to confidentiality:** Earning the trust and confidence of patients means that appropriate confidentiality safeguards be applied to disclosure of patient information.
- **Commitment to appropriate relationship with patients**: Given the inherent vulnerability and dependency of patients on medical practitioners, practitioners should never exploit patients for any reason, including for personal financial gain or any other private purpose.
- **Commitment to improving quality of care:** Being dedicated to continuous improvement in the quality of health care means not only maintaining clinical competence, but also working collaboratively with other professionals to reduce medical error, increase patient safety, minimise overuse of health-care resources and optimise the outcome of care
- **Commitment to improving access to care:** A commitment to availability of a uniform and adequate standard of care to all entails the promotion of public health and preventive medicine, as well as public advocacy in support of equity and access without concern for self-interest
- **Commitment to a just distribution of finite resources:** While meeting the needs of individual patients, doctors are required to provide health care that is based on the wise and cost-effective management of limited resources so as to ensure that resources are also available for others.
- **Commitment to scientific knowledge:** The profession is responsible for the integrity of scientific knowledge which is based on scientific evidence and physician experience.
- **Commitment to maintaining trust by managing conflicts of interests**: Physicians have an obligation to recognise, disclose and deal with conflicts of interest that arise in the course of their professional duties and activities
- **Commitment to professional responsibilities:** Doctors are expected to work collaboratively to maximise patient care, be respectful of one another, and to participate in the processes of self-regulation.

Revisiting the principles and responsibilities of professionalism of the physician involved in the treatment of cancer patients is necessary to understand the ethical dilemmas in cancer care within the context of patient-centric care and the framework of the continuum of care throughout the cancer journey. To serve the patient's best interests, the doctors involved need to create an environment founded on trust that facilitates the healing process of the person. The intense need for trust is caused by the patient's dependence on the doctor's skills and judgment when he/she has cancer.

ETHICAL ASPECTS OF CARING FOR PATIENTS WITH CANCER

The social dimensions of ethics include justice, rights, respect of human dignity, autonomy of the individual and respect of the community.

This provides an opportunity to re-emphasise ethics as a tool for titrating the dynamic tension between:

- The interest of the Individual patient
- The interest of the population needs in general and
- The professional ethics of care

INFORMED CONSENT

The fundamental principle that justifies the need for informed consent is respect for the autonomy of the patient. This is also in support of a patient-centric approach in so far as respecting a person's right to determine the course of his or her life. This is

a move away from a doctor-centred and paternalistic approach to a more patient-centric approach.

The role of the doctor is often to provide the cancer patient with sufficient information to be able to make an informed decision or informed refusal to undergo a course of treatment or participate in a research protocol for a new cancer drug.

It requires from the doctor a commitment to the professional values of competence and scientific knowledge to be able to assist the patient to take informed decisions.

Emanuel and Joffe[5] also maintain that although informed consent can be viewed as an event which ends with the patient's decision, it is not adequate for the patient with cancer where interaction and treatment occurs over a period of time. They support the process model which "… is based on the assumption that medical decision-making is a continuous process, and the exchange of information must take place throughout the course of the physician-patient relationship."

The requirement of understanding suggests that the patient should comprehend the information presented and appreciate its relevance for his or her particular situation. This is of particular importance in South Africa with its variety of languages, cultures and levels of education.

The role of the physician includes the early detection of cancer through awareness and screening. In a screening guideline for prostate cancer, the assumption that the prognosis for the cancer patient is better if diagnosed early is disputed based on available evidence. The argument focuses on the impact of routine screening and over-diagnosis of cancer and the substantial harm associated with subsequent treatment. Although screening for cancer has become accepted in medical practice, the practitioner must be aware of the evidence in support of screening programmes when applied in the patient population cared for by the practice. Patients should therefore be properly counselled prior to any screening procedure to ensure a full understanding of the consequences of screening or no screening. This is in support of the ethical principles of beneficence and non-maleficence and the fiduciary duty toward the patient as a professional.

TRUTH-TELLING/DIFFICULT CONVERSATIONS

The treating specialist and sometimes the family practitioner, because of the long-standing relationship with a family or a patient, as well as a member of the care team within the continuum of cancer care, is often consulted by the patient and their family after a diagnosis of cancer has been confirmed, staging established and treatment plan confirmed. But during the cancer journey, there may be instances where the physician needs to engage and have difficult conversations with regard to the prognostic impact of cancer progression or when the treating oncologist has decided to discontinue further active cancer treatment.

In the difficult conversation, the physician is often confronted with the dilemma of whether to tell the truth with regard to the severity and prognosis of the disease. The ethical principle of beneficence suggests that physicians should disclose information in a way that benefits and does not harm the patient.[6] There are two ethical guidelines to be observed in regard to disclosure: appropriate degree of information and humane behaviour.

As with informed consent, it is important that information is given in a way that is meaningful to patients on their own terms. This might mean finding the help of a translator, breaking information down into parts, or revisiting information at different visits. Supplying informational pamphlets or suggesting a support group such as People Living with Cancer is a way to help the patient. The inclusion of the oncology social worker in assisting the patient and his/her familiy in terms of the psychosocial needs during these difficult conversations, supports a patient-centric approach.

As discussions with cancer patients may disclose news that is hurtful, it is important

that doctors communicate with patients in a humane and respectful manner.

Some doctors believe they are entitled to withhold information from patients if they believe the information will have devastating effects on them. Studies, however, have shown that a majority of people say that they want to be told about their diagnosis, even diagnosis of a terminal nature. It may also happen that by withholding this information the trust relationship between patient and the doctors may be compromised.

The important principle here is that patients are ordinarily entitled to full disclosure with regard to their diseases and disorders.

Doctors are sometimes requested by family members to withhold information from the patient for various reasons. This potential conflict can be simply addressed by helping family members to understand that the doctor's primary duty is to the patient. If a patient is able to make decisions about his or her medical care, the doctor has a duty to disclose the information relevant to helping that patient make decisions about exactly what type of care he or she wants.

CARING FOR THE PATIENT WITH ADVANCED DISEASE/PALLIATIVE CARE

Within the continuum of cancer care, after active cancer treatment has been discontinued, the management and coordination of the care of the cancer patient takes place within a multidisciplinary palliative-care team, including the family practitioner, oncologist, palliative-care specialists, nurses, social workers and religious leaders as an essential part of the team to ensure that:

- the patient's symptoms are adequately managed
- the psychosocial needs are being addressed
- care is provided at the most appropriate place
- the patient and the family's wishes are understood and addressed.

This approach is in line with patient-centric care principles that are respectful of, and responsive to, the preferences, the needs and the values of patients and their families.

The medical practitioner may have to deal with a critically ill and fragile patient whose only request is to die at home.

The complexity of end-of-life decisions demands that comprehensive attention be given to the particular patient and his/her life circumstances. These include the patient's unique biology and the pathology of the illness, the patient's clinical condition, functional status, physical needs, desires, life plans, relationships, hopes, sufferings, strengths and limitations, perceptions and understanding of the illness.[7] Consideration should be given to facilitate access to other carers to address the often unmet psychosocial needs of the patient and the family.

End-of-life discussions often revolve around matters where there are no clear-cut answers and require the clinician to be comfortable in dealing with uncertainties and with compassionate truth-telling. The ethical principle involved is the respect for autonomy of the patient and addresses the concept of "self-rule". In these circumstances, patients should be encouraged to take an active part in clinical decision-making as this facilitates their active involvement in care decisions at the end of life.

Beneficence refers to the ethical imperative to ensure that treatment benefits the patient and non-maleficence to the Hippocratic ideal of "first do no harm". Within the objective of palliative care to improve quality of life, a key decision is to be able to identify when active treatment will improve quality of life and prolong life, in contrast to when active care and medical technology will not positively influence the course of the illness, but merely prolong the dying process.

Gwyther[8] draws attention to decisions to withdraw or withhold treatment, when reached in discussion with patient, family members and the clinical team. This respects the essential commitment to the patient. She refers to the booklet *Guidelines for the Withdrawing and Withholding of Treatment* by the Health Professions Council of South Africa which states that

"Health-care practitioners should bear in mind that the decisions of competent adult patients to refuse a particular medical intervention must be respected, even where this would result in serious harm to them or in their own death."

The withholding or withdrawing of treatment must however be distinguished from participating in assisted suicide or active euthanasia which is illegal.

The Telegraph of 26 September 2011 under the heading "Dying cancer patients should not be given 'futile' drugs", refers to current medical practice to continue with new treatments with no thought to their cost or effectiveness because they don't want to disappoint patients, leaving them with "false hope" as some drugs will only lengthen sufferers' lives by a few weeks.

This was based on a detailed report, published in *The Lancet Oncology Journal*, which stated that in some cases it may be better for terminally ill patients to "forgo" these treatments in favour of better end-of-life care. For this purpose, a futile drug or intervention refers to treatment that will not restore a patient to independence or at least to an acceptable quality of life, or which is likely only to prolong the dying phase.

This ethical debate can then be further redirected to the question of waste-avoidance in clinical practice. Wasteful treatment and interventions can cause harm. *Primum non nocere* becomes the strongest argument for eliminating waste through non-beneficial practising.

The doctor may also have to deal with advance directives like a Living Will. These directives can only be a guide and cannot cover all eventualities. The directive should be discussed with the competent patient and family members.

EQUITY, FAIRNESS AND SOCIAL JUSTICE

During 1999, a group of experts in ethics from over the world, the so-called Tavistock group, met in the UK to develop shared ethical principles for those who shape and deliver health care.[9]

This initiative emerged as a consequence of ethical tensions around equity, justice and fairness in the allocation of health-care resources faced by policy-makers to address health-care system design in response to ever-increasing resource consumption and financial constraints.

Although the medical profession has its own codes of ethics, the need for a shared code existed that might bring all stakeholders in health care into a more consistent moral framework. This view is important for the medical practitioner to contextualise the dilemma of policy-makers.

The first ethical principle identified by the Tavistock group was that health care is a human right and the aim of health-care delivery is to maintain and improve health, to alleviate disability and to provide access to appropriate health services to all persons, regardless of their ability to pay.[9]

It is in this context that current medical schemes and the National Health Policy in South Africa should develop. The principles of equity, universal coverage and social solidarity need to be at the core of this reform.[10]

Historically, the allocation of scarce resources in the health-care environment or cost-containment has been dealt with on a policy and business level under the scope of "distributive justice".[11] Within the resource-constrained environment of South Africa, with its developing economy and goal of universal coverage of all citizens in terms of health care, policy decisions inform who will have access to care and the extent or richness of benefits that will be provided.

The private sector medical schemes employ strategies to curb the high cost of cancer treatment within what is provided for in the prevailing legislation and regulations, using medical-scheme rules to determine to which benefits cancer patients are entitled. This may be in the form of financial sub-limits for cancer care for which a patient will be covered – a form of rationing. Provider arrangements and micro-management of health-care encounters are also used to reduce the costs of cancer care.

Although there may be an ethical objection to rationing on the basis that doctors owe an absolute duty of fidelity to each individual patient regardless of cost, it needs to accepted that when resources (money) are exhausted, real patients are deprived of care. The ethical argument therefore shifts to the fairest means of allocating scarce resources within a population served by the practice.

Thus, the ethical challenge of rationing care in South Africa with its inequitable distribution of health-care resources, also needs to translate to a commitment on the part of doctors to protect patients from harmful and wasteful medical care and in so doing unleash the means to serve patients with useful services in an environment devoid of waste.[11]

These ethical principles must help focus physicians to always be mindful of both in the service of their individual patients, as well as the good of society as a whole.

CONCLUSION

The dilemma of doctors treating cancer patients is well summarised by Dr Ezekiel J Emanuel, a leading scholar in bioethics, during an interview in which he stated the following: "Medical ethics is integral to oncology care. When I ran ethics rounds at the Dana-Farber Cancer Institute, I used to say that every single oncology patient faced at least three ethical dilemmas. Informed consent is one. Do patients really understand what they are signing? There's typically a dilemma about allocating resources for treatment because these are very expensive therapies and many of them put a lot of financial pressure on families. And for many patients, there's the dilemma of facing end-of-life care, as there will be for all of us..." [5]

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The Role of Nutrition in Cancer Patients and Cancer Survivors

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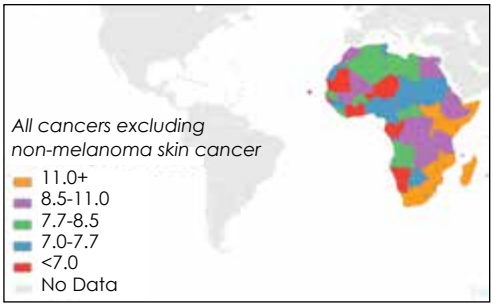
Cancer is a major public health problem. The World Health Organization (WHO) reported that globally cancer accounted for just over one in five deaths from non-communicable diseases. Lung, breast, colorectal, stomach and liver cancers together are responsible for more than half of cancer deaths.[1] The top cancer sites in South Africa are those of the lung, oesophagus, breast, prostate, colorectum, liver and pancreas (see Figure 1).[2]

Fortunately, with advances in medical care and improvements in cancer detection and treatment, cancer-survival rates are improving.[3,4] It is promising that of the leading causes of death, cancer death rates are on the decline. The American Cancer Society (ACS) estimates that the cancer-death rate has declined by 26% from 1991 to 2015, translating into over 2.3 million fewer cancer deaths.[5]

NUTRITIONAL INTERVENTIONS FOR CANCER PATIENTS

It is estimated that one-third of the commonest cancers can be prevented through lifestyle changes, such as adopting a healthy diet and managing weight, as well as being physically active.[6] Interventions targeting these modifiable lifestyle factors could not only prevent cancer, but also encourage healthy behaviour among cancer survivors, influencing the rates of cancer recurrence, and improving the overall health and wellbeing of cancer patients.[4,7] The role of nutrition in cancer survivors will be discussed in more detail.

Figure 1. Estimated cumulative cancer mortality risk in Africa[2]



Source: GLOBOCAN 2012 (IARC)

NUTRITION AND DIET

Cancer survivors are known to want to make healthy dietary changes.[3,8,9,10] Breast-cancer patients modify their eating behaviours after diagnosis by between 30-60%, including increased fruit and vegetable intake, and decreased consumption of red meat, fats and sugary foods.[10] Furthermore, colon cancer patients are disease-free for longer and have greater overall survival rates when they have a healthy body weight, are physically active, and eat a diet rich in whole grains, vegetables and fruit. Compared to cancer patients who do not engage in these behaviours, these cancer patients eat less red and processed meat and consume moderate amounts of alcohol.[11]

Various types of diets have been proposed for cancer management. These include ketogenic diets (80% fat, 8% protein, 2% carbohydrates),[13,14,15,16] vegetarian diets[17,18] and the Mediterranean diet.[19,20] However, much of this research has been done on cancer prevention, and not cancer survivorship. That said, current nutrition guidelines for cancer survivors are consistent with those for cancer prevention.[4,12,21] The guidelines for nutrition for cancer prevention should not be overlooked by patients already diagnosed with cancer.

Table 1. American Cancer Society (ACS) guidelines on nutrition and physical activity for cancer survivors[12]

Achieve and maintain a healthy weight If overweight or obese, limit consumption of energy-dense foods and beverages and increase physical activity to promote weight loss
Engage in regular physical activity Avoid inactivity and return to normal daily activities as soon as possible after diagnosis. Aim to exercise at least 150 minutes per week. Include strength-training exercises at least two days per week.
Achieve a dietary pattern that is high in vegetables, fruit and whole grains Follow the American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention; i.e., limit consumption of processed meat and red meat; eat at least 2.5 cups of vegetables and fruit daily; choose whole grains instead of refined grain products; and, if you drink alcoholic beverages, limit consumption to no more than one drink daily for women or two drinks daily for men

A healthy diet is important for cancer prevention and to improve health outcomes in patients with cancer.[21] Published guidelines for nutrition and diet for cancer survivors by the ACS, National Comprehensive Cancer Network (NCCN) and American Institute for Cancer Research (AICR) recommend that cancer survivors strive to meet their nutritional needs primarily through food rather than supplements. Both AICR and NCCN recommend a diet rich in vegetables, fruit and whole grains (two-thirds of the plate), with less emphasis on animal proteins (one-third part of the plate). Whole grain intake is inversely associated with cancer mortality risk, as confirmed in a recent systematic review and meta-analysis of cohort studies.[22] Recommended sources of dietary fat include plant sources (e.g., olive/canola oil, avocados, nuts) and fatty fish, rather than red meat[3], as saturated fat negatively influences breast-cancer survival rates.[23] The ACS guidelines for nutrition and physical activity in cancer survivors are summarised in Table 1.

NUTRIENT SUPPLEMENTATION

The prevalence of dietary and nutrient supplementation in cancer patients is high[10; 24], with reports of at least one in three (33.3%) cancer survivors using supplements.[25] When investigating supplement use in breast-cancer patients, 50% of participants were taking multivitamin supplementation, yet 70% were overweight/obese and 13% were smokers.[26]

Much of the research in nutrient supplementation has been on the role of polyphenolic compounds acting as antioxidants. An antioxidant is a substance in food that significantly decreases the adverse effect of reactive oxygen species (ROS)/reactive nitrogen species (RNS) on normal physiological functions in humans. In theory, polyphenols are able to scavenge the free electrons of ROS/RNS, protecting against cellular damage related to cancer progression. However, studies on antioxidants, whether dietary or supplementary, in cancer progression remain inconsistent and inconclusive.[27] It is therefore better to encourage the inclusion of a variety of fruit and vegetables to increase antioxidant intake rather than use antioxidant supplements.

Immunonutrition is an emerging field, given the significant role the immune system plays in cancer and cancer treatment.[28] It is suggested that immunonutrition formulae, such as anti-inflammatory omega-3s and probiotics, may aid in improving the immune status of the cancer patient, modulate the acquired immune response, and decrease cancer-treatment toxicity, improving disease outcomes.[28] Results, however, remain inconclusive. Therefore, including omega-3-containing fish (e.g., salmon, pilchards, sardines, trout, and mackerel) and foods containing

RESOURCE® SUPPORT PLUS | Innovative nutrition for your cancer patients

Small volume,

LARGE EFFECT

Flexibility: Complements any existing food or supplement program to help meet patients' nutritional needs.

Quick and Easy Administration: A small amount of high protein, high calorie nutritional supplement is taken with medication.

Simplicity: No extra work required by patients as it fits in with their current medication routine.

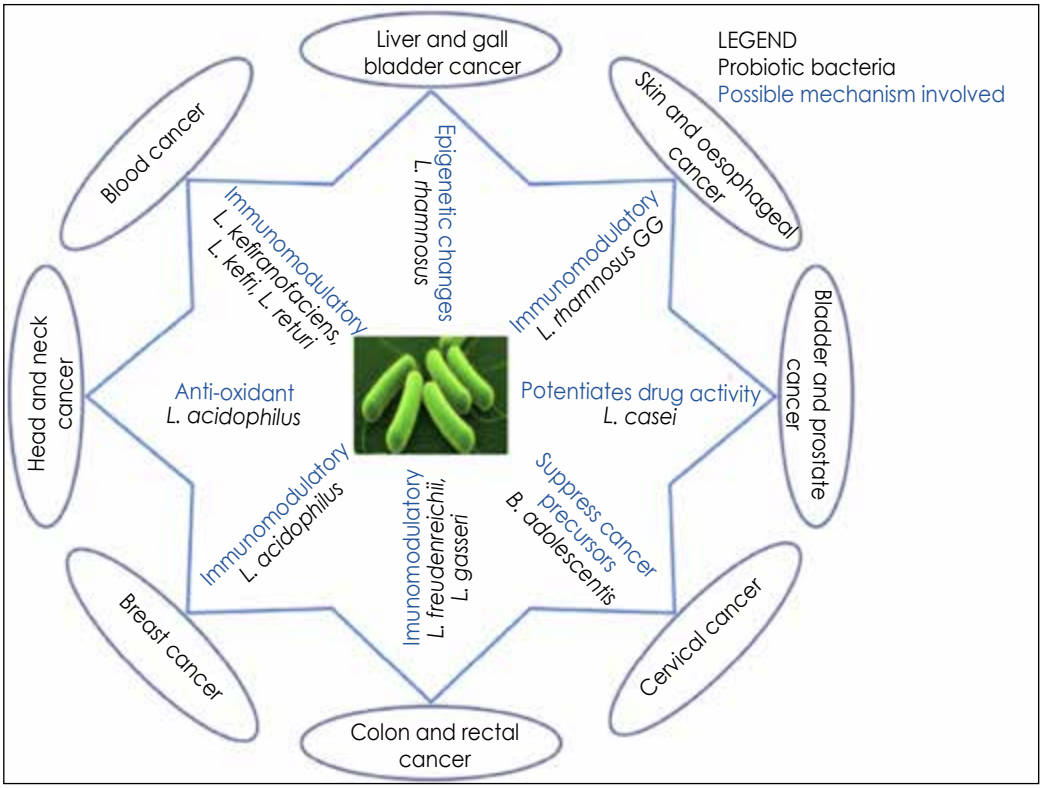
Great Taste: Plum-Mango and Peach-Vanilla.

Nutritional Content:

Volume: **125 ml**	Energy: **255 kcal (2.0 kcal/ml)**
Protein: **11.5g/125 ml**	Flavours: **Plum-Mango and Peach-Vanilla**
Omega-3: **1.7g/125 ml**	Prebiotic dietary fibre: (FOS, GOS): **3.1g**
50% of fat is MCT oil	Osmolarity: **600 mOsm/L**

Nestlé HealthScience

Figure 2. Probiotic bacterial strains and possible mechanisms against various cancers[31]



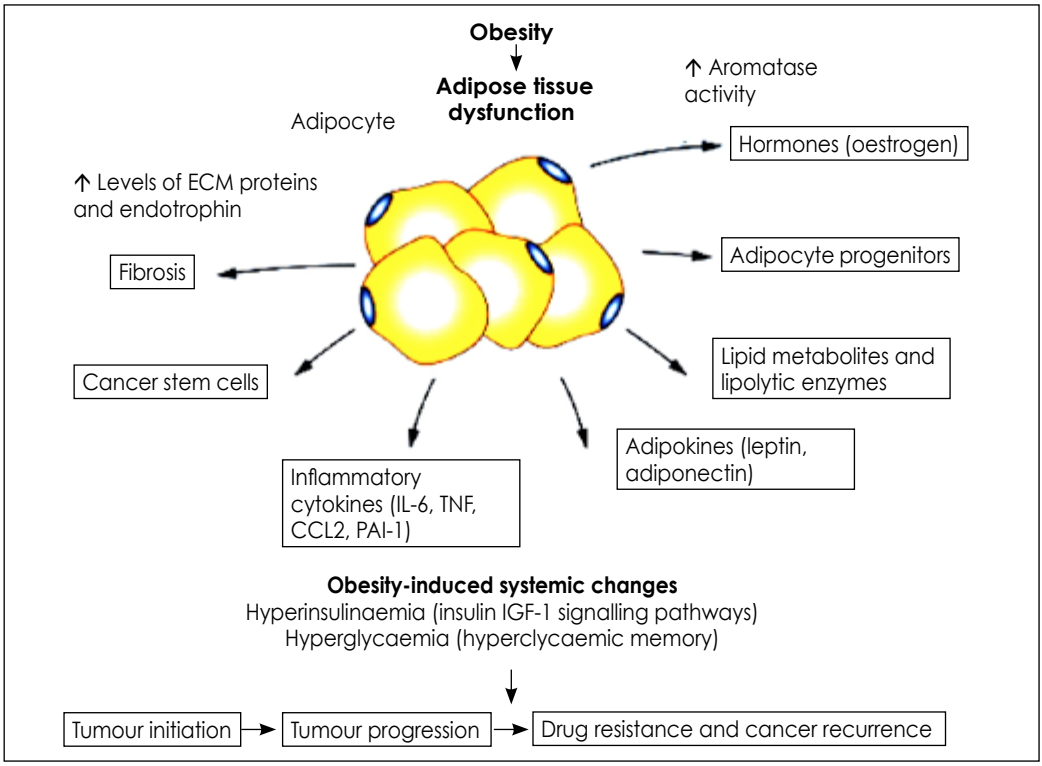
probiotics (e.g., yoghurt, maas) in the diet is advised.

Following from the immune-related effects of cancer, novel research has supported the role of the gut microbiome in the occurrence and progression of intestinal and extra-intestinal cancers.[29,30,31] Anti-cancer drugs are known to trigger an immune response, and certain gut microbiota strains have been shown to synergise with many of these drugs, optimising the immune response against cancers. Strains that have been researched include *Lactobacillus* (*L. plantarum, L. brevis, L. casei*) and *Bifidobacterium* (*B. breve, B. longum*).[30,31] A summary of probiotic strains and potential mechanism of action of probiotics in cancer is summarised in Figure 2. However, it is necessary to progress with caution as most of these studies are conducted on animal models. As such, these benefits may be exaggerated and should not be extrapolated to humans, with further clinical trials needed.[29]

However, the use of multivitamins has not been shown to improve cancer-recurrence risk or cancer mortality in breast-cancer patients,[32,33] nor colon-cancer survivors.[34] A systematic review of the role of nutrient supplements, including vitamins, minerals and protein, confirmed no solid evidence for the uses of supplements in cancer cachexia.[35] There is also evidence of greater risk of death in cancer patients using alternative medicine for cancer treatment.[36] A review of clinical, evidence-based guidelines for nutrition for surgical cancer patients is detailed elsewhere.[37]

The ACS[38] and NCCN[39] do not recommend the routine use of nutrition supplementation, unless indicated to correct a nutrient deficiency. ACS, however, does endorse a daily multivitamin during cancer therapy for those unable to meet their nutrient needs through food alone. Despite evidence to the contrary, many

Figure 3. Potential consequences of obesity-induced dysfunction of adipose tissue on tumour initiation, progression and recurrence[43]



cancer survivors continue to supplement with vitamins and minerals.[4] The concern is that despite limited evidence, a patient's desire for and reliance on supplements may divert their attention from following a healthy and well-balanced diet.[40]

WEIGHT MANAGEMENT

Excess body weight is a known risk factor for many cancers, including bowel, breast (post-menopause), gallbladder, liver, kidney, stomach and oesophageal cancer.[6] Unfortunately, this trend continues post-diagnosis with an increasing number of cancer patients who are overweight or obese at diagnosis gaining additional weight as a side effect of treatment.[3, 41] This is concerning as excess adiposity has been associated with higher rates of cancer-related mortality in men and women.[3, 41, 42] Hyperinsulinaemia, increased IGF-1, hyperglycaemia, dyslipidaemia, and alterations in adipokines, cytokines and the gut microbiome are metabolic changes that may contribute directly or indirectly to cancer progression.[41] See Figure 3.

A multidisciplinary approach to obesity management will help to assist with the development and maintenance of dietary and lifestyle behaviours that are necessary for weight loss and successful weight-loss maintenance. A registered dietician, as part of a multidisciplinary team, can provide support in this regard. A weight-loss goal of 5-10% reduction (current body weight) within six months is recommended.[42] Along with dietary changes, ACS recommends at least 150 minutes of moderate-intensity activity per week for weight loss in cancer patients.[38]

Intentional weight loss may prove to be an effective concurrent treatment in reducing cancer progression.[41, 42, 43] Much of the research on weight gain following cancer diagnosis has been done on breast-cancer patients in particular,[44] but there is

also evidence of weight gain in cancers of the liver and colon.[43] In breast-cancer patients, it is reported that women are unlikely to return to the lower pre-diagnosis weight.[44] Proposed mechanisms of weight gain included changes in eating patterns related to diagnosis- or treatment-related depression, decreased physical activity, a potential role of hormones and menopause in changing metabolism and the development of insulin resistance.[43, 44]

That said, obesity might have a paradoxical protective effect in cancer patients. An observational study (n=175) reported the median survival time for overweight and obese patients was significantly higher compared to those with a low or normal weight, as defined by body mass index (BMI). It is proposed that because BMI does not account for body composition (i.e., fat mass *versus* fat-free mass/lean body mass), BMI itself cannot predict survival in cancer patients.[45] Thus, weight loss measures alone are not sufficient to ignore changes in muscle loss and/or fat gain.[46] Cancer patients are encouraged to maintain good muscle mass as this has been shown to predict better outcomes in cancer patients.[45]

CANCER-RELATED MALNUTRITION AND CACHEXIA

Cancer patients are at high risk for cancer-related malnutrition and cachexia.[4] Weight loss and cachexia are well-defined morbidity and mortality risk factors in cancer patients.[45] Cancer cachexia is defined as more than 5% weight loss within a six-month period.[46] The pathogenesis of cancer cachexia is related to a variable combination of decreased energy intake, increased catabolism of muscle protein and lipolysis, and metabolic and neurohormonal perturbations.[46-49] Symptoms include anorexia, muscle-wasting, fatigue, anaemia, oedema and taste changes (dysgeusia), all of which lead to an increase in treatment toxicity and poor patient prognosis.[4, 46, 49] The health-care practitioner can diagnose cancer-related malnutrition in cancer patients, as summarised in Table 2. Referral to a registered dietician for medical nutrition therapy and support is advised.

Cancerous tumours can affect energy intake due to poor taste, lack of appetite, and difficulties in swallowing.[51] For this reason, the prevalence of malnutrition in cancer patients is considerable: 55% of patients eat less than before the diagnosis of cancer, yet only 41.4% and 50% of these patients receive nutrition counselling and nutritional support, respectively.[52]

Interestingly, cancer cachexia is not always reversible by increasing energy intake, and is distinct from starvation and age-related decreases in lean body mass.[48] Changes in gut function also decrease hunger hormones by altering secretion of gastro-intestinal peptides and stomach-empting. Inflammatory cytokines such as tumour-necrosis factor alpha, interleukin-1 and interleukin-6 are also implicated in decreasing food intake and appetite. Cancer therapies such as chemotherapy and radiation can also alter taste perception and cause nausea, vomiting, mucositis, cramping, bleeding and dysgeusia.[49, 51]

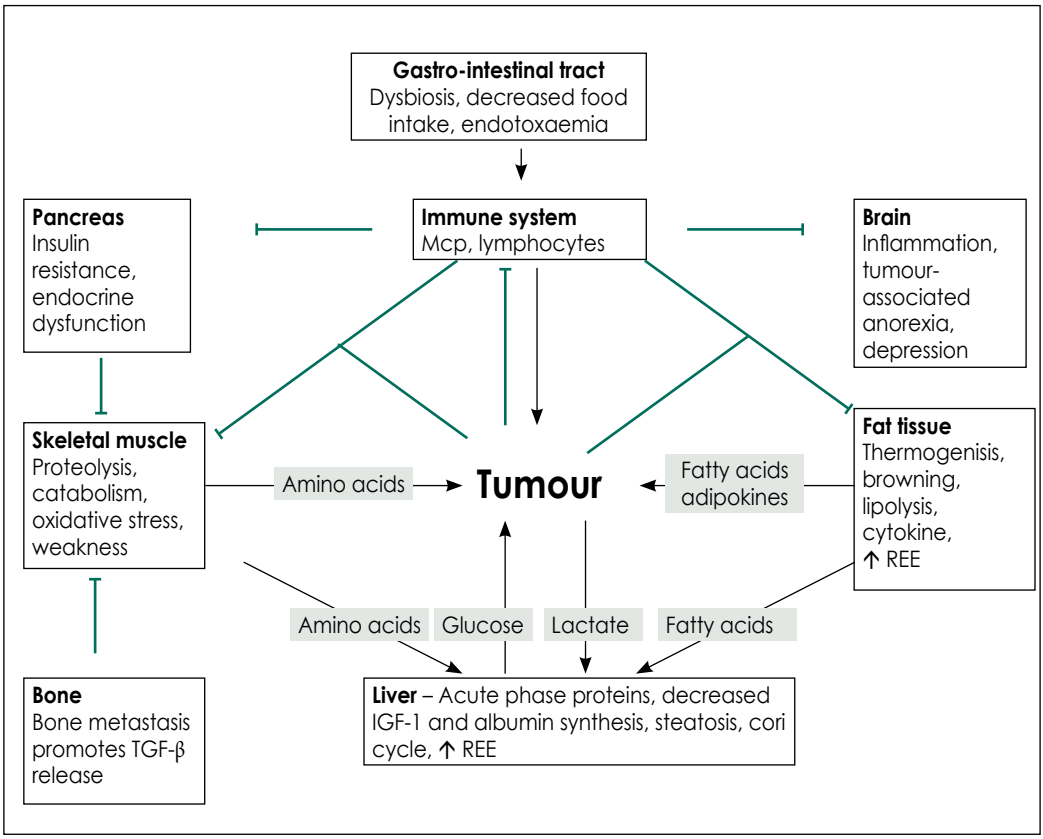
It is well established that nutrition support is a key role in managing cancer cachexia when timeously delivered with adequate

Table 2: Criteria for nutrition diagnosis of malnutrition in adult oncology patients[50]

The presence of **two or more** of the following criteria or characteristics supports a nutrition diagnosis of malnutrition in adult oncology patients:

- Insufficient energy intake
- Unintended weight loss
- Loss of subcutaneous fat
- Loss of muscle mass
- Localised or generalised fluid accumulation (that may mask weight loss)
- Reduced grip strength

Figure 4. Cancer-cachexia pathophysiology [49]



provision of energy as part of a concurrent treatment plan.[47] Referral of cancer patients for nutrition counselling with a registered dietician is highly recommended, given the strong support for the beneficial effects of the prevention and reduction of malnutrition.[53] Table 3 summarises the estimated energy needs of cancer patients. Refer to Table 4 for nutritional intervention guidelines to support side effects and symptoms in cancer patients.

At present, there are no guidelines available for the treatment of cancer cachexia.[48] Cancer patients should be screened using a validated and reliable malnutrition screening tool to identify malnutrition risk.[50] Such screenings can be done by a registered dietician, using validated malnutrition-screening tools, such as the Nutritional Risk Screening 2002 (NRS, 2002), Malnutrition Universal Screening Tools (MUST), and the Mini Nutritional Assessment (MNA), both at diagnosis and at regular points through the disease course.[4, 50, 54-58] These screening tools are available for use by the health-care practitioner.[59]

Patient situations that may benefit from seeking individualised dietary advice include:[60]

- For survivors experiencing anorexia or early satiety, and who are at risk of becoming underweight, consuming smaller, more frequent meals with minimal liquids consumed during meals can help to increase food intake. Liquids can and should be consumed in between meals to avoid dehydration.
- For survivors who cannot meet their nutritional needs through foods alone, fortified, commercially prepared or homemade nutrient-dense beverages or foods (e.g., milk-based drinks, fruit smoothies) can improve the intake of energy and nutrients.

Table 3. Estimating the energy needs of cancer patients[64]

Condition	Energy needs (kJ/kg/day)
Cancer, nutritional repletion, weight gain	126-147
Cancer, inactive, non-stressed	105-126
Cancer, hypermetabolic, stressed	147
Haematopoietic cell transplant	126-147
Sepsis	105-126

Table 4. Nutrition-intervention strategies for patients with cancer

Side effect/ symptom	Strategies
Anorexia (poor, or lack of, appetite)	■ Encourage small, more frequent nutrient-dense meals and snacks. ■ Recommend adding kilojoules in the form of protein (e.g., milk, yoghurt, cheese, egg) and healthy fats (e.g., avocado, nuts, nut butters, olive oil) to favourite foods. ■ Recommend the use of protein- and energy-containing supplements, e.g., whey protein powder, nutritional supplements. ■ Keep nutrient-dense foods nearby and snack frequently, e.g., nuts, dairy, fruit, etc. ■ Advise capitalising on times when feeling best to eat main meals. ■ Recommend eating meals and snacks in a pleasant atmosphere. ■ Suggest viewing eating as part of the treatment. ■ Encourage activities of daily living and physical activity to stimulate appetite, as tolerated.
Nausea and vomiting	■ Recommend eating small, more frequent meals and snacks rather than larger meals. ■ Cold- and room-temperature foods are better tolerated than hot foods with an odour. Advise the avoidance of foods with strong odours. ■ Suggest sipping on cool or room, temperature, clear liquids in small amounts, e.g., tea, apple juice, electrolyte replacement. ■ Advise the avoidance of high-fat, greasy, spicy or overly sweet foods. ■ Adding lemon and ginger to food, tea and water may help manage nausea. ■ Encourage the consumption of bland, soft, easy-to-digest foods on scheduled treatment days. ■ Encourage compliance with medications prescribed to control nausea. ■ Consider changing the timing of medication intake, i.e. before a meal, with a snack, etc.
Diarrhoea	■ Encourage the intake of hydrating liquids such as water, electrolyte replacement, clear juice, broth, popsicles, and sports drinks. ■ Recommend a low-fibre diet and the avoidance of high-fibre foods, such as whole-grain breads and cereals. Include foods rich in soluble fibre such as fibre, oats and stewed apple. ■ Advise the avoidance of sugar alcohol-containing foods, such as sugar-free gum and cooldrinks. ■ Encourage the intake of soluble fibre, e.g., apples, bananas, white rice, pasta. ■ Encourage compliance with medications prescribed to control diarrhoea. ■ Consider changing the timing of medication intake, i.e. before a meal, with a snack, etc.

Side effect/ symptom	Strategies
Constipation	■ Recommend increasing the intake of high-fibre foods, e.g., whole grains, fresh and cooked fruit and vegetables, especially those with skins and seeds, dried fruit, beans, nuts. ■ Encourage the intake of fluid, mostly water. A goal of one glass (250ml) water per kilogram of body weight is estimated. ■ Recommend the use of probiotic-containing foods, e.g., yoghurt and maas or probiotic supplements. (Refer to the probiotic strains for various cancers in Figure 2.) ■ Encourage activities of daily living and physical activity, where possible. Walking can aid in gut peristalsis and improve constipation. ■ Encourage patients to read food labels and choose products that contain 6 g or more of fibre per 100 g product. ■ Encourage compliance with fibre supplements and/or medication that affect bowel function and are prescribed to manage constipation.
Oesophagitis (sore and/ or inflamed throat), sore mouth, mucositis or thrush)	■ Recommend the intake of softer, moister foods with sauces, dressings or gravies. ■ Advise the avoidance of dry, course, rough foods. ■ Avoid alcohol, citrus, caffeine, tomatoes, vinegar and hot peppers. ■ Suggest experimenting with food temperature (e.g., warm, cool, icy, room temperature) to find which temperature is most soothing. ■ Recommend good oral hygiene, e.g., rinse mouth frequently, keep mouth clean. ■ Encourage compliance with medications prescribed to manage oral pain, oral infection oesophagitis and/or painful swallowing.
Fatigue (tiredness)	■ Recommend the intake of small, frequent meals and snacks. ■ Recommend the intake of easy-to-prepare, easy-to-eat foods, e.g., high-fibre cereal with milk, yoghurt and fruit, whole-wheat toast with peanut butter. ■ Advise keeping nutrient-dense snacks nearby and snack frequently, e.g., fresh fruit, raw nuts, yoghurt. ■ Suggest eating when appetite is best. ■ Encourage activities of daily living and physical activity, where possible.
Neutropaenia (low white-blood-cell count)	■ Advise frequent hand-washing and keep kitchen surfaces and utensils clean. ■ Advise the avoidance of raw or under-cooked animal products, including meat, pork, game, poultry, eggs and fish. ■ Advise washing all fruit and vegetables before eating. ■ "When in doubt, throw out" and "No oldy or mouldy".
Dysgeusia (altered taste and altered smell)	■ Recommend good oral hygiene practices, e.g., rinse mouth frequently, keep mouth clean ■ Suggest trying marinades and spices to mask strange tastes. ■ Recommend using plastic utensils if metallic-utensil tastes are a problem. ■ Recommend eating cooler rather than warmer foods.
Thickened saliva	■ Suggest sipping on fluids throughout the day to keep oral cavity moist. ■ Suck on ice cubes. ■ Recommend diluting thickened oral saliva with water or sparkling water. ■ Recommend using a cool mist humidifier when resting and sleeping.

Side effect/ symptom	Strategies
Xerostomia (dry mouth)	■ Suggest sipping on liquids throughout the day to keep the oral cavity most. ■ Suggest trying tart foods to stimulate saliva (if open mouth sores are not present). ■ Recommend alternating bites of food with sips of liquids at meals. ■ Recommend eating soft, moist foods with extra sauces, dressings or gravies. ■ Advise avoidance of alcoholic beverages and alcohol-containing mouthwashes. ■ Recommend good oral hygiene, e.g., rinse more frequently, keep mouth clean. ■ Recommend using a cool mist humidifier when resting and sleeping.

Source: Adapted from Hamilton, 2017

For survivors who are unable to meet their nutritional needs through these measures and who are at risk of becoming malnourished, other means of nutritional support may be needed, such as pharmacotherapy using appetite stimulants, enteral nutrition via tube-feeding, or intravenous parenteral nutrition.

RISK OF CHRONIC DISEASE

There is emerging evidence of shared disease pathways for cardiovascular disease and cancer, the two leading causes of death around the world. Chronic inflammation is a major theme among many diseases, including cardiovascular disease and cancer.[61] Obesity, hyperglycaemia, hypertension and hypertriglyceridemia induce inflammation, all of which are linked to both diseases. Hormones (e.g., leptin), cytokines, growth factors and other metabolic changes have also been linked to both diseases.[62, 63]

Likewise, obesity and type 2 diabetes are associated with an increased incidence and mortality from many cancers.[41] The factors potentially contributing to the progression of cancer in obesity and type 2 diabetes include hyperinsulinemia, increases in IGF-1, hyperglycaemia, dyslipidaemia, increased levels of adipokines and cytokines, and alterations in the gut microbiome. These metabolic changes may contribute directly or indirectly to cancer progression.[41] Therefore, the health-care practitioner is advised to look out for concurrent chronic disease risk in the management of the cancer survivor.

CONCLUSION

The guidelines for nutrition for cancer prevention should not be overlooked for patients with diagnosed cancer, underscoring the importance of consuming a heathy diet for both cancer prevention and to improve health outcomes in cancer patients and cancer survivors.[21] With improved knowledge of the importance of a healthy diet to prevent cancer, survivors are motivated and encouraged to improve their nutrition after diagnosis. Nutritional assessment should be an integral part of a cancer-treatment plan, beginning at diagnosis and extending throughout the post-diagnosis period of treatment.[3]

Cancer survivors report that better patient-provider communication and greater knowledge about how to reduce cancer risk are factors associated with a greater likelihood of attending medical appointments.[7] The health-care provider thus plays a key role in promoting healthy-eating behaviours among cancer survivors.[60] Strategies such as incorporating nutrition as part of the health-care treatment plan of cancer survivors, with the support and guidance of a registered dietician, are advised.[53, 58, 63]

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Palliative care

Palliative Care: an Introduction

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Palliative care (PC) has been practised for many years on the fringes of the South African health-care system. It was marginalised to non-governmental services and sporadic hospital services.

However, due to local needs analyses, the cost-effectiveness of palliative care and international palliative care progress,[1-3] palliative care is globally recognised as a fundamental part of health-care services. These positive palliative care outcomes have been achieved by using effective compassionate communication skills, shared decision-making, holistic pain and symptom control, family involvement and by using a team approach.

The integration of palliative care into global health services was further reinforced in 2014 when the World Health Assembly (WHA) unanimously agreed on resolution 67.19, recognising "that palliative care, when indicated, is fundamental to improving quality of life, wellbeing, comfort and human dignity for individuals, being an effective person-centred health service that values patients' need to receive adequate, personally and culturally sensitive information on their health status, and their central role in making decisions about the treatment received".[4]

The aim of the WHA resolution was to ensure that palliative care was strengthened as part of integrated care within the continuum of care. The integration of palliative care into daily care of patients requires societal understanding of the palliative care approach, the development of health-care workers' competencies to deliver the care, dedicated palliative care services and an attitude that there is "no end to caring".

WHAT IS PALLIATIVE CARE?

Hospices have been around for centuries, but the modern hospice movement was established by Dame Cecily Saunders and her colleagues. In 1967 they opened the world's first modern hospice in London. Dame Saunders introduced the concept of "Total Pain" which details that pain in patients with life-threatening illnesses is caused not only by physical suffering, but also by psycho-social and spiritual suffering.[5] Dr Balfour Mount, who was inspired by Dame Saunders, coined the term "palliative care", derived from the Latin word "pallium" which means "to cloak".[6] Palliative care aims to "cloak" or protect the patient from the suffering caused by a life-threatening illness.

In 2002 the WHO defined palliative care as: "An approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.[7]

Palliative care:

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten nor postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated
- Will enhance quality of life, and may also positively influence the course of illness

- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications."

Core concepts of these principles are that:

- It is a patient- and family-centred approach
- It aims to relieve a bio-psycho-social and spiritual suffering
- It involves a team
- It starts at diagnosis of a life-threatening illness and continues into bereavement
- It is must be integrated in measures that aim to prolong life
- Euthanasia is not a palliative care practice.

It is also generally considered that the term "best supportive care" is essentially equivalent to "palliative care" and is sometimes used because of the misconception around palliative care.[6] Many believe that by introducing palliative care into the care trajectory you are "giving up" on the patient and that palliative care is only for the final stages of life. These misconceptions have been proven wrong, with research proving that palliative care improves quality of life and may lead to longer survival.[3]

INITIATING PALLIATIVE CARE

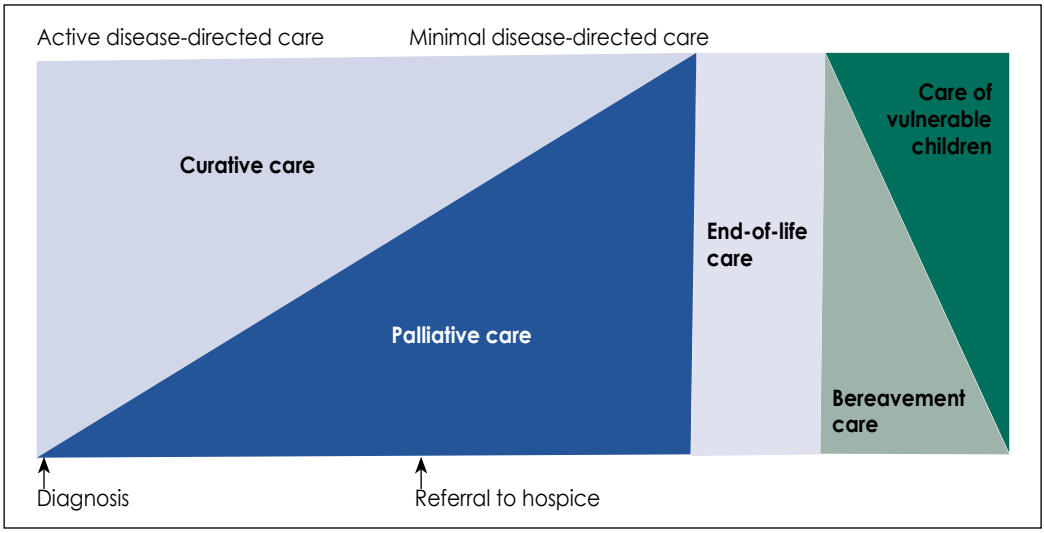
Internationally, there are many disparities and inequalities around when palliative care should be initiated[8] and in response, many indicator tools have been developed to ensure patients are identified for palliative care. The Gold Standard Framework (GSF) indicator tool is a tool developed in the United Kingdom and used to identify patients who are nearing the end of their life and is based on patients' need for palliative care. It uses the well-known "surprise question" *("Would I be surprised if a patient dies within 12 months?"*) and general indicators (e.g, physical decline and poor response to treatment) and specific indicators (e.g., metastatic cancer or stage 4 or 5 kidney disease) to determine who requires palliative care.[9] The Supportive and Palliative Care Indicator Tool (SPICT) (https://www.spict.org.uk/) was designed in Scotland, using a practical, evidence-informed guide to identify patients at risk of dying and who require palliative care alongside curative treatments.[10] These tools were designed in developed countries and do not include communicable diseases such as HIV and TB. Locally, in Groote Schuur hospital, an adapted tool has been used to include these conditions. In cancer care both the GSF framework and the SPICT tool agree that poor performance status and/or progressive metastatic cancer are indicators for palliative care.

PALLIATIVE CARE WITHIN THE DISEASE TRAJECTORY

Figure 1, as adapted by the WHO diagram of 1998, illustrates how palliative care should be practised within the continuum of care and highlights a few important factors:

- It should be initiated with the diagnoses of a life-threatening illness and should continue into bereavement care.
- It can be introduced slowly with the diagnosis of a life-threatening illness, and slowly becomes central to care as the illness progresses.
- Palliative care is not an excuse for poor service delivery and should never be a substitute for poor resources.
- Hospice referrals are traditionally done too late in care and thus palliative care cannot be limited to only hospices. This service should be available in all settings where patients present with life-threatening illnesses.
- An imperative part of palliative care is bereavement care and care of vulnerable children. Neglect of these two vital aspects of care can lead to prolonged distress and impairment. It is especially in the South African setting, that we are all responsible for orphans and vulnerable children.[11]

Figure 1. Practising palliative care within the continuum of care



KEY COMPONENTS OF PALLIATIVE CARE SERVICES

Basic palliative care principles can be applied by all health-care workers and all health-care workers should be trained in palliative care. However, the awareness of basic palliative care is not equivalent to a palliative care service. A palliative care service includes the following components:

- **It is delivered by a team**: In most cases, the team will consist of palliative care-trained nurses, social workers, spiritual care workers and doctors. In many oncology settings, allied health-care workers, such as occupational therapists and speech therapists, are integral parts of the team.
- It provides **pain and symptom control to the patient**. Although pain is not just physical pain, the service will ensure that the patient will have access to the necessary drugs to manage his/her pain and symptoms.
- It provides **psycho-social and spiritual care to the patient.** In this context, "spiritual" means the relationship we have with ourselves and the world, and "spiritual care" means the exploration of the individual meaning of life and providing comfort, strength and balance.
- It provides care and education to the **family** in relation to the patient's goals.
- It insures the **continuum of care** for both the patient and the family which includes bereavement care.
- It **collaborates** with other health-care workers, such as oncologists, to ensure the patient receives optimal care.
- It practises and advocates using an **evidence-based palliative care approach.**

Integrating palliative care into current services requires education for all health-care workers, development and implementation of policies for palliative care and collaborative leadership. At Groote Schuur hospital, palliative care services have been slowly incorporated into oncology services and emergency medicine services since 2011, and Groote Schuur hospital currently has a nurse-driven palliative care service across the hospital, initiating palliative care to approximately 80 patients per month. This could not have been achieved without training nurses, social- and allied health-care workers and doctors in palliative care.

CORE COMPETENCIES OF A PALLIATIVE-CARE HEALTH WORKER

Universal access to palliative care will require that all health-care workers undertake

basic training in palliative care. The basic competencies required to work with palliative care patients are:

- To apply the principles of palliative care in the health-care worker's current work setting
- To ensure that the patient receives pain- and symptom control
- To ensure that the patient receives psycho-social and spiritual care
- To respond to the family's need in relationship to the patient's goals
- To function well in an interdisciplinary team
- To ensure that the patient is cared for in an ethical manner
- To effectively communicate with patients, families and colleagues
- To develop self-awareness and positive resilience.

INTEGRATING PALLIATIVE CARE SERVICES INTO HEALTH-CARE SERVICES

As stated previously, palliative care has been practised on the fringe of the South African health-care services for many years. However, Resolution 67.19 underpinned the development of the decision of the South African Minister of Health, Aaron Motsoaledi, to create a national task team to ensure aspects that are covered in the Resolution are implemented in South Africa. The framework of the National Palliative Care Policy was accepted in April 2017 and in the foreword of the policy Minister Motsoaledi states: "*We cannot overlook the importance of integrating palliative care as an essential component in the continuum of health-service delivery*" and continues by stating: "*I am confident that this Policy will translate into services which are responsive, appropriate and ensure universal access on an equitable basis.*"[12]

This National Policy will enable palliative care to be incorporated into National documents such as the Essential Medicine Lists and guidelines to ensure drug availability for pain and symptom control across the spectrum of care. It will also drive the inclusion of palliative care training in both undergraduate and postgraduate training. The Policy speaks to the inclusion of palliative care training for all health-care professionals at a basic level; at an intermediate level for health-care workers whose work includes palliative care indirectly, e.g., oncologists and physicians, and at an advanced level working to palliative care as a speciality in South Africa. All of this speaks to the enabling and the strengthening of palliative care across the whole health-care system and to have the necessary funding to achieve this.[12]

The South African National Policy is an opportunity to develop palliative care in South Africa, however there are still many barriers until full integration. Palliative care is an evidence-based approach, but most of the evidence is being developed in Europe and America, countries which have a different spectrum of illnesses and different resources. There is a huge need to ensure good palliative care-focussed African research in all settings that deal with patients with life-threatening illnesses. We need to ensure a change of mindset in all disciplines which should ensure that there are policies, guidelines and services available for patients in order for patients and their families to receive the best comprehensive care until the very end. Although most health-care workers are involved in the care of patients with life-threatening illnesses, very few have received formal training in palliative care.

Palliative care can be described as an essential human right to improve quality of life and dignity in death.[13] The African palliative care revolution is moving forward; health-care facilities should be able to deliver this service, which cannot be achieved without their having basic palliative care competencies.

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Management of Cancer Pain

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Cancer pain prevalence ranges from 33% in patients after curative treatment to 59% in patients on anticancer treatment and to greater than 70% in patients with metastatic, advanced or terminal phase.[1] No difference in pain prevalence was found between patients undergoing anticancer treatment and those in an advanced or terminal phase of the disease.[1]

It must be noted that pain results not only from the disease itself (25%) but from some of the therapeutic modalities (up to 75%).[2] The resulting pain may become chronic in nature. Treatment may cause peripheral neuropathy due to chemotherapy, radiation-induced brachial plexopathy, chronic pelvic pain secondary to radiation and post-surgical pain.[3]

Examples of treatment-related cancer pain syndromes are: [2]

- Resulting from chemotherapy:
  - Painful peripheral neuropathy
  - Raynaud's syndrome
  - Bony complications of long-term steroids
- Resulting from radiotherapy:
  - Radiation-induced brachial plexopathy
  - Chronic radiation myelopathy
  - Chronic radiation enteritis and proctitis
  - Burning perineum syndrome
  - Osteoradionecrosis
- Resulting from surgery:
  - Post-mastectomy pain syndrome
  - Post-radical neck dissection pain
  - Post-thoracotomy pain syndrome or frozen shoulder
  - Post-surgery pelvic floor pain
  - Stump pain
  - Phantom limb pain

Unrelieved pain continues to be a worldwide problem in patients with either solid or haematological malignancies. Cancer-related pain may be presented as a major issue of health-care systems worldwide if we consider that the incidence of cancer was 12 667 470 new cases in 2008 and, based on projections, it will be greater than 15 million in 2020.[4]

The patient may suffer from pain, but it must be appreciated that pain has other implications, such as the burden that the patient has to bear resulting from the pain. Cancer pain has a significant negative effect on patient quality of life[5,6] Higher levels of pain are associated with poorer quality of life, including decreased social activities, decreased physical functioning and impaired cognitive functioning. Increased psychological distress is associated with higher levels of pain and more than one-third of cancer patients with pain rate their pain as moderate or severe. Increasing cancer pain may be associated with advanced disease with a limited prognosis.[6-9]

Although it is beyond the scope of this article, the need for psychological assessment and help should be emphasised, as psychological issues are a component of the cancer pain experienced and when this is the case, psychotherapy should be considered.[10]

TYPES OF PAIN

When dealing with cancer pain, we must realise that there may be nociceptive pain, neuropathic pain, or a combination of both types of pain, the so-called mixed pain. Distinguishing between these pain types is paramount to treating the pain, as most acute and postsurgical pain is somatic. This type of pain will respond to morphine, paracetamol, nonsteroidal anti-inflammatory agents (NSAIDs), and COX-2 selective inhibitors (coxibs) (see Table 1).

In the case of neuropathic pain, these agents will have no effect on the pain and we would need to employ the sodium channel-blocking anticonvulsants, the alpha-2 delta selective calcium-channel

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Table 1. Examples of nociceptive pain syndromes are listed in the table below: [2]

Origin of Pain	Pain Syndromes
Visceral	■ Hepatic distension syndrome ■ Midline retroperitoneal syndrome ■ Chronic intestinal obstruction ■ Peritoneal carcinomatosis ■ Malignant perineal pain ■ Adrenal pain syndrome ■ Ureteric obstruction
Somatic	■ Tumor-related bone pain ■ Tumor-related soft tissue pain ■ Paraneoplastic pain syndromes (e.g., muscle cramps)

blockers (α2Δ), the serotonin noradrenalin re-uptake inhibitors (SNRIs), and the serotonin-specific re-uptake inhibitors (SSRIs). It follows that in a mixed-pain scenario, a combination of agents would be desirable.

Clinical examples of neuropathic pain are:
- Malignanant painful neuropathies
- Plexopathies
- Metastatic spine compression
- Painful peripheral neuropathies
- Paraneoplastic sensory neuropathies

PHYSIOLOGY OF PAIN MANAGEMENT

Effective pain therapy means using a combination of analgesics and adjuvants that act on appropriate physiological targets. This form of therapy is known as multimodal analgesia.

Clinicians have "six bullets" available to them for pain management and each "bullet" arises because of the six known physiological targets:

1. **The peripheral site of injury**. One of the foremost responses to tissue injury is the formation and release of prostaglandins at the site of injury. In order to stop this process, an antiprostaglandin agent must be used. These agents are collectively known as the NSAIDs and coxibs. It is obvious that the choice of agent depends on the medical status of the patient and the various indications and contra-indications for use of these agents apply.
2. **Conduction of the pain impulse from the site of injury to the spinal cord**. If the "message" does not reach the spinal cord then pain will not be felt. This can be achieved by using sodium-channel blockers. We can clinically achieve this by using some form of local anaesthetic or, in the case of neuropathic pain, an anticonvulsant.
3. **Impulse transfer at the dorsal horn of the spinal cord.** When calcium ions enter the neuron, there is a release of neurotransmitters that will facilitate the passage of the pain impulse to the next neuron. The entry of the calcium can be prevented by the α2Δ blockers. The neurotransmitters released can also be prevented from binding to the N-methyl-D-aspartate (NMDA) receptor by means of an NMDA blocker (ketamine).
4. **Transfer of the impulse from the spinal cord to the brain.** This transfer can be blocked by paracetamol that is thought to bind at COX-3 receptors, as well as by NSAIDs and coxibs that work in the glial cells, blocking COX-2 action.
5. **The brain.** Opioids will alter the pain response by binding at specific opioid receptors in the brain (μ,δ,κ).
6. **Descending inhibition from the brain to the spinal cord.** The brain can "talk back" to the spinal cord and in so doing prevent further painful input. This is achieved by increasing the levels of serotonin and noradrenalin at the spinal cord. Re-uptake of noradrenaline and serotonin can be facilitated by the SNRIs, the SSRIs, and tramadol.

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It is not always necessary to use all of these modalities to manage cancer pain and the clinician will choose those "bullets" that are appropriate for the specific patient. Pain SA's choice is as follows:

- Antiprostaglandins: NSAIDs or coxibs
- Sodium-channel blockers: local anaesthetics or carbamazepine
- Selective calcium-channel blockers: pregabalin and gabapentin
- NMDA receptor antagonists: ketamine
- Spinal-cord conduction modifiers: NSAIDs, coxibs, paracetamol
- μ,δ,κ receptor agonists: opioids
- Noradrenalin and serotonin re-uptake inhibitors: SSRIs, SNRIs, tramadol

PAIN MANAGEMENT

The goal of pain management is to improve patient comfort, function and safety. This involves optimising analgesia and activities of daily living, while minimising adverse effects of the analgesic therapy. This can result in avoidance of aberrant drug-taking and prevention of expected analgesic side effects. To accomplish these goals, a comprehensive pain management regime is needed and it is essential to maximise patient and family education, as well as physical and cognitive integrative interventions. [11]

In 1986, the World Health Organization (WHO) proposed a strategy for cancer-pain treatment based on an analgesic ladder. This is a three-step ladder progressing from non-opioids to weak opioids to strong opioids, according to the pain index (PI) of the patient.[12] It is imperative to "score" the pain of each patient and thereby determine if an intervention reduces the pain score. Such a reduction indicates efficacy and should determine further pain management for that particular patient. The WHO cancer pain-relief programme still, after 20 years, remains the reference point for pain management.[13] According to the WHO guidelines, opioid analgesics are the mainstay of analgesic therapy and are classified according to their ability to control pain from mild to mild-moderate to moderate-severe intensity.[2,15-17] Opioid analgesics may be combined with non-opioid drugs such as paracetamol or NSAIDs and with other adjuvant drugs.[18,19]

Certain principles exist when trying to effectively manage cancer pain.

- Prescribe analgesia for chronic pain on a regular basis and not on an "as required" schedule.
- Prescribe a therapy which can be easily administered and managed by the patient. The oral route is the preferred route of administration.[20-24]
- Assess and treat breakthrough pain (BTP). This can be defined as "a transitory flare of pain that occurs on a background of relatively well-controlled baseline pain".[24] Rescue dose of medications (as required or when necessary) other than the regular basal therapy must be prescribed for BTP episodes.

MILD PAIN

Non-opioid analgesics such as paracetamol, a NSAID or cyclo-oxygenase-2 inhibitors (coxibs, COX-2) are the starting point for the treatment of mild pain. These agents are universally accepted as part of the treatment of cancer pain. It is mandatory to periodically monitor and revise the long-term use of NSAIDs or coxibs[26] because they can induce severe toxicity such as gastro-intestinal bleeding, platelet dysfunction and renal failure.

MILD TO MODERATE PAIN

The use of drugs on the second step of the WHO ladder has several controversial aspects. The controversy stems from the absence of definitive proof of efficacy of the weak opioids. The efficacy when comparing non-opioid analgesics alone, and the combination of these with weak opioids, was not conclusive, but did highlight that the effectiveness of the second step of the WHO ladder has a time limit of 30-40 days for most patients and that the shift to the third step is mainly due to insufficient analgesia achieved, rather than to adverse effects. The problem is that high doses of the second-step drugs were limited by a "ceiling effect". This means that

doses above a certain threshold cannot increase the effectiveness of the drug, and the only result is the appearance of side effects. Many authors have proposed the abolition of the second step of the WHO analgesic ladder, in favour of the early use of morphine at low doses.

It is still recommended that for mild to moderate cancer pain, weak opioids such as codeine and tramadol are given in combination with non-opioid analgesics.

MODERATE TO SEVERE PAIN

Strong opioids are the mainstay of analgesic therapy in treating moderate to severe cancer-related pain. Morphine, oxycodone, hydromorphone, fentanyl, tapentadol and buprenorphine are the most-used strong opioids in Europe.[27] It is debatable whether other opioids are superior to morphine in terms of efficacy and tolerability. Oral morphine is used in hospices and palliative-care units as the drug of choice for this type of pain. It provides effective pain relief, is widely tolerated, simple to administer and inexpensive.

Oral morphine remains the opioid of first choice for moderate to severe cancer pain, but patients presenting with severe pain who need urgent relief should be treated and titrated with parenteral opioids, usually administered by the subcutaneous or intravenous route. A simple conversion for parenteral use is that the equivalent dose is one-third of the oral medication.

Hydromorphone, oxycodone and tapentodol, in both immediate-release and modified-release formulations for oral administration, are effective alternatives to oral morphine.

Transdermal fentanyl and transdermal buprenorphine are best reserved for patients whose opioid requirements are stable. They are usually the treatment of choice for patients who are unable to swallow, those with poor morphine tolerance and patients with poor compliance. Although not recommended in the NCCN Clinical Practice Guidelines in Oncology for Adult Cancer Pain[11] because it is a partial agonist, buprenorphine has a role in analgesic therapy. Strong opioids may be combined with ongoing use of a non-opioid analgesic (as per the WHO analgesic ladder).

In the presence of renal impairment, all opioids should be used with caution and at reduced doses and frequency. Fentanyl and buprenorphine, via the transdermal route or intravenously, are the safest opioids of choice in patients with chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate <30 ml/min).

Opioid-switching is a practice used to improve pain relief and/or drug tolerability. The most frequent switch is among morphine, oxycodone, hydromorphone, and fentanyl.

SCHEDULING AND TITRATION

All patients should receive regular dosing of their medication (so-called by-the-clock dosing) with provision of a "rescue dose" to manage BTP. The "breakthrough dose" is usually equivalent to +10% to 15% of the total daily dose. If more than four "rescue doses" per day are necessary, the total daily prescribed amount is too low and must be upwardly-adjusted until only one to two episodes of BTP occur daily. Opioids with a rapid onset and short duration are preferred as rescue medications. Immediate-release opioids should always be prescribed as a rescue medication in order to eliminate the pain.

The recommended clinical practice is thus to administer individual titration of dosages by means of normal-release morphine administered every four hours plus rescue doses (hourly) for BTP. The regular dose of slow-release opioids can then be adjusted to take into account the total amount of rescue morphine needed per day. The total daily dose can then be divided by the dosage intervals to give a dosage quantum of drug.

MANAGEMENT OF SIDE EFFECTS

The most common adverse effects encountered when treating cancer pain result from opioid therapy. These adverse effects include constipation, nausea/vomiting, urinary retention, pruritus and

signs of central nervous system (CNS) toxicity (drowsiness, cognitive impairment, confusion, hallucinations, myoclonic jerks).

While we can reduce the dosage of the agent responsible for the adverse effect, we may at the same time reduce the analgesic efficacy. The best way to reduce dosages and still achieve analgesic efficacy is by using synergism of more than one analgesic agent. The reduced dosages of the individual agents should decrease the individual drug side effects. Alternative methods of pain control, such as nerve block or radiotherapy, may be needed when dosage reduction and synergism prove ineffective in managing the pain.

Obviously, adverse effects can be managed symptomatically. Suggested therapy would include the continued use of anti-emetics for nausea, laxatives for constipation, major tranquillisers for confusion and psychostimulants for drowsiness. Opioid-switching may aid in resolving symptoms of CNS toxicity.

It is common practice to suggest that laxatives must be routinely prescribed for both the prophylaxis and the management of opioid-induced constipation, while metoclopramide and antidopaminergic drugs should be recommended for treatment of opioid-related nausea and vomiting.

BREAKTHROUGH PAIN (BTP)

The prevalence of BTP is 19% to 95%, depending on the setting in which the patient is being managed.[28, 30]

It is imperative that immediate-release formulation of opioids be used to treat exacerbations of controlled background pain. It is also appropriate to anticipate painful episodes such as pain on moving or on swallowing, and to administer immediate-release oral morphine at least 20 minutes before such potential pain triggers to prevent the BTP.

Intravenous opioids have a shorter onset of analgesic activity in treating BTP episodes compared to oral morphine.

NEUROPATHIC PAIN

As previously stated, cancer pain may be varied in nature, and many cancer patients suffer from neuropathic pain. It has been stated that different types of medications from those previously mentioned are needed to treat neuropathic pain.

An expert panel has published a guideline to the management of neuropathic pain in South Africa.[31] The most commonly recommended agents for the management of neuropathic pain are gabapentin, pregabalin, duloxetine, carbamazepine and amitriptyline. These drugs would be classified as adjuvants in the WHO recommendations and their use does not preclude the use of the other agents described in the WHO pain ladder. It is impossible to discuss the full recommendations at this point, but it should be noted that the recommendation for first-level therapy includes duloxetine, pregabalin, amitriptyline or a combination of those agents. Third-line therapy would include tramadol and other strong opioids. It must be emphasised that these agents need to be prescribed at the correct dosage intervals and at the correct dose.

As a rough guide, prescribe duloxetine 60 mg once daily, pregabalin 150 mg twice daily, amitriptyline up to 50 mg once daily, gabapentin 400 mg three times a day, and tramadol at least 100 mg as needed.

INTERVENTIONAL OR INVASIVE PAIN MANAGEMENT

When cancer pain becomes difficult to manage, it may be necessary to try to improve the situation by using interventional techniques. This can be in the form of regional blocks with either neurolytic agents such as alcohol, phenol or local anaesthesia. Be warned that a neuritis may ensue following neurolysis and the pain from the neuritis may be worse than that for which the block was performed.

Neurolytic blocks are best kept for patients with a short life expectancy. The most effective of these blocks are the coeliac plexus block for pancreatic carcinoma, and the superior hypogastic block for visceral pain. It must be remembered

that opioid therapy may need to be continued after such blocks and that the blocks serve as adjuvant therapy.

Intrathecal drug delivery systems (ITT) may also be used to directly administer drugs into the epidural space or into the cerebrospinal fluid, thereby reducing dosage requirements and obviously side effects of otherwise largely parenterally and orally administered drugs. The drug reduction is approximately 70% if the drugs are epidurally administered and 90% if intrathecally administered. It is imperative that a trial of ITT be performed prior to any system implantation.

The most commonly used agents for ITT are morphine, ketamine, and local anaesthetics.[31,32] Insertion of these devices should only be performed by practitioners trained in managing these devices.

NONPHARMACOLOGICAL THERAPIES

Physiotherapy, psychotherapy and social support services should be used in conjunction with pharmacotherapies to manage the overall pain state. [11]

THE ROLE OF PALLIATIVE CARE

Palliative care should be integrated early in the cancer management strategy. Care should be managed by a specialised, multidisciplinary team of health-care providers with emphasis on the quality of life of the patient and his or her family.

It is a well known fact that early palliative care leads to better patient and caregiver outcomes, improvement in symptoms, quality of life, and patient satisfaction with reduced caregiver burden.[34-37]

SELECTED PAIN MANAGEMENT GUIDELINES

Many guidelines for the management of cancer pain are available in the literature. Here are a selected few for suggested reading or referencing:

- World Health Organization 1996
- French National Federation of Cancer Centres 2002
- Scottish Intercollegiate Guidelines Network (SIGN) 2008
- RAND Corporation 2008
- Cancer Care Ontario's Cancer-related Pain Management Guideline Panel 2012
- European Society for Medical Oncology 2012[6]
- European Association of Palliative Care 2012
- National Comprehensive Cancer Network 2014

CONCLUSION

Cancer pain is a common condition that severely adversely affects quality of life. Cancer pain is a significant burden to the patient and his or her family. It must be understood that a single physician cannot manage cancer pain by himself and that management of cancer pain requires a multidisciplinary approach. Most cancer pain can be managed safely and effectively using combination therapies with opioids. There is no need for a cancer patient to suffer unnecessarily.

The treating physician must be familiar with the available modalities, and when pain management becomes difficult, it is recommended that the patient be referred to a specialised unit used to dealing with cancer pain.

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Drug-Class Overview

CONVENTIONAL CHEMOTHERAPY

Chemotherapeutic agents have a variety of mechanisms whereby they either induce cell death through apoptosis (cytotoxic) or prevent cell division without inducing apoptosis (cytostatic).[1] All cytotoxic chemotherapeutics exert their effects by disrupting the cell cycle in that they directly interfere with the cell DNA or target key proteins required for cell division.[2] The cell cycle, a four-stage cycle (mitosis, Gap 1, synthesis, Gap 2), takes place as the cell prepares to replicate and divide.[2] During mitosis, the chromosomes align and separate as the cell divides, whereas in the synthesis or S-phase, DNA synthesis takes place, replicating the cell's genetic material.[2] The Gap phases serve as checkpoint and repair stations, preventing cell-cycle progression until all requirements have been met.[2] Cancer cells have lost the normal cell-cycle controls, becoming insensitive to growth inhibitory signals and acquiring the ability to evade apoptosis.[2]

As cytotoxic agents cause cell death by disrupting the cell cycle, these agents are also toxic to "normal" cells entering the cell cycle and more so for high-turnover cells such as bone marrow and mucous membranes.[2]

1. DNA-ALKYLATING AGENTS

DNA-alkylating agents are cytotoxic agents used therapeutically as antineoplastic agents. They have a non-specific mechanism of action and are therefore considered non-cell-cycle-specific, although replicating cells are most susceptible to cytotoxicity.[3,4]

As DNA damage can occur at any point in the cell cycle after exposure to an alkylating agent, prolonged exposure to the alkylating agent is not required.[2] Unfortunately, this not the case with cell-cycle-specific agents, as S-phase-specific agents, for example, require prolonged exposure to target cells circulating into the S-phase.[2]

Alkylating agents form the cornerstone of high-dose chemotherapy regimens as they have a steep dose-response curve and anti-tumour activity at standard dose.[5] In high-dose chemotherapy regimens, the dose intensity is important to achieve a cure; the dose can be escalated as the threshold dose is limited only by the toxicity to normal tissues.[2]

Cell-cycle-specific agents, on the other hand, have a dose-response effect up to a threshold. Consequently, increasing the dose does not increase the number of cell deaths.[2]

Electron-deficient alkylating agents react with the electron-rich areas on DNA, RNA and proteins, transferring an alkyl group to these cellular constituents.[3,6] By forming cross-links in and between DNA strands, the DNA strands are unable to uncoil and separate, preventing DNA replication and therefore cellular proliferation.[7]

Alkylating agents are divided into several classes based on their chemical structure. These include nitrogen mustards, ethyleneimines, alkylsulphonates, nitrosoureas and triazenes (see Table 1). They can be

Table 1. Classification of DNA-alkylating agents

Nitrogen mustards	Ethyleneimines (aziridine)	Alkylsulphonates	Nitrosoureas	Triazenes	Platinum co-ordination complexes	New/ other
Chlorambucil Cyclophosphamide Estramustine Ifosfamide Melphalan Bendamustine	Mitomycin-C	Busulfan	Carmustine	Temozolomide	Carboplatin Cisplatin Oxaliplatin	Trabectedin

classified as monofunctional, bifunctional or trifunctional, depending on whether the agent has one, two or three reactive groups capable of interacting with the cellular constituents.[3,5,6]

Therapeutically, the bifunctional agents are the most effective alkylating agents.[6]

DNA-alkylating agents target rapidly dividing cells.

Patients may experience dose-related side effects that lead to myelosuppression which involves bone marrow, lymphoid tissue, intestinal mucosa, hair cells and the reproductive system.[3,6]

Alkylating agents lack cross-resistance and thus combinations can be employed.[5] Combinations may reduce the likelihood of resistance and increase the therapeutic benefit.[5]

NITROGEN MUSTARDS

Sulphur mustard was first synthesised as a vesicant chemical warfare agent in the late 19th century for use by the German army during World War I (WWI).[8-10]

During WWI, physicians observed that soldiers exposed to sulphur mustard or mustard gas had severe bone-marrow suppression.[1]

This observation led to the recognition of the potential cytotoxicity of alkylating agents and the development of nitrogen mustards.[1]

Individuals exposed to nitrogen mustards developed severe irritating symptoms affecting the respiratory tract, mucous membranes, skin, eyes, and endocrine- and immune systems.[10,11]

As lymphocytes are particularly susceptible to the cytotoxic effects of nitrogen mustards, these agents are used in the palliation of chronic lymphatic leukaemias and malignant lymphomas.[12]

Cyclophosphamide is the most frequently used alkylating agent in chemotherapy.[5]

Cyclophosphamide and ifosfamide are prodrugs that require activation via the cytochrome P450 family of drug-metabolising enzymes.[5,6]

Acrolein, a metabolite of cyclophosphamide and ifosfamide, can induce bladder toxicity which can lead to haemorrhagic cystitis. To prevent this side effect, 2-mercaptoethanesulphonate (MESNA) is co-administered in cyclophosphamide and ifosfamide therapy.[5]

Detailed indications for each of the nitrogen mustards follow.

Indications[13-15]

Chlorambucil

- Hodgkin's disease
- Certain forms of non-Hodgkin's lymphoma
- Chronic lymphocytic leukaemia
- Waldenstrom's macroglobulinaemia

Cyclophosphamide

- Alone or in combination with other cytostatic agents for various cancers of the neoplastic disease of the reticulo-endothelial system, such as lymphomas, lymphosarcomas, reticulo-sarcomas, Hodgkin's disease, chronic lymphatic leukaemias, multiple myelomas
- Adjunctive chemotherapy agent in surgery and/or radiotherapy
- As palliative therapy in inoperable malignancies
- Progressive auto-immune disease
- Ovarian cancer[96]

Estramustine

- Advanced prostate cancer

Ifosfamide

- Oat-cell bronchogenic carcinoma
- Ovarian cancer
- Mammary cancer
- Pancreatic cancer
- Testicular tumours
- Hypernephroma
- Malignant lymphoma
- Chondro-osteosarcoma
- Leiomyosarcoma
- Rhabdomyosarcoma

Melphalan

- Multiple myeloma
- Ovarian cancer
- Neuroblastoma in childhood
- Adjunctive in breast cancer

Bendamustine

- First-line CLL treatment (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate
- Indolent CD20-positive non-Hodgkin's lymphoma in combination with rituximab

Table 2. General side effects of nitrogen mustards[4,12,14,16]

Haemato-logical	Gastro-intestinal	Central nervous system	Dermatological	Miscellaneous
Bone-marrow suppression	■ Nausea and vomiting ■ Diarrhoea ■ Anorexia ■ Metallic taste ■ Hepato-toxicity and jaundice ■ Abnormal liver function tests	■ Tremor ■ Muscle-twitching ■ Myoclonia ■ Confusion ■ Halluci-nations ■ Agitation ■ Ataxia ■ Flaccid paresis	■ Allergic skin reactions ■ Skin hyper-sensitivity reactions	■ Pulmonary fibrosis ■ Drug fever ■ Peripheral neuropathy ■ Interstitial pneumonia ■ Sterile cystitis ■ Infertility ■ Tissue damage at injection site ■ Vasculitis ■ Increased risk of secondary malignancies

- Indolent non-Hodgkin's lymphoma as monotherapy in patients who have progressed during or within six months following treatment of multiple myeloma with rituximab or a rituximab-containing regimen
- Front-line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older that 65 years not eligible for autologous stem-cell transplant and who have clinical neuropathy at time of diagnosis precluding use of a thalidomide and bortezomib-containing regimen

Side effects

As with all alkylating agents, the side effects of nitrogen mustards (see Table 2) are generally dose-related and occur in rapidly growing tissues, which results in myelosuppression.[4]

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

ETHYLENEIMINES

Aziridine or ethyleneimines are a group of alkylating agents which contain an aziridine functional group and are chemically and pharmacologically related to the nitrogen mustards.[17] Ethyleneimines cross-link DNA through the release of the aziridine functional group, disrupting the DNA bonds and thereby inhibiting DNA synthesis and function.[17,18]

The first compound synthesised in this class was triethylenemelamine, the synthetic precursor of *N,N',N''*-triethylenephosphoramide (TEPA).[5]

TEPA showed a profound cytotoxic effect, but was chemically too unstable to be used in clinical practice.[5]

ThioTEPA (*N,N',N''*-triethylenethiophosphamide), the major representative of the ethyleneimines, is a more stable sulphur analogue of TEPA with strong alkylating activity.[5]

Following are detailed indications for ethyleneimines.

Indications[5,17-20]

Mitomycin

Mytomycin is an anti-neoplastic antibiotic produced by *Streptomyces caespitosus* which selectively inhibits the synthesis of DNA and, at higher drug concentrations, RNA and protein synthesis as well.[18]

- A broad spectrum cytostatic
- Single therapy: breast cancer and gastro-intestinal cancer
- Combination therapy: gastric, pancreatic, bladder, non-small-cell lung, head and neck squamous cell and colorectal cancer

Side effects

As with all alkylating agents, ethyleneimines cause myelosuppression.[4]

Table 3 provides general side effects of ethyleneimines.

Table 3. General side effects of ethyleneimines[17]

Haemato-logical	Gastro-intes-tinal	Central nervous system	Dermato-logical	Respiratory	Miscellaneous
Haemoto-poietic depression	■ Nausea and vomiting ■ Diarrhoea ■ Abdo-minal pain ■ Anorexia ■ Dysuria ■ Urinary retention ■ Haemor-rhagic cystitis	■ Dizziness ■ Headache ■ Confusion	■ Allergic skin reactions ■ Skin hyper-sensitivity reactions ■ Skin depig-menta-tion	■ Laryngeal oedema ■ Asthma ■ Wheezing ■ Apnoea	■ Fatigue ■ Weakness ■ Mutage-nicity ■ Amen-orrhoea ■ Interference with sperma-togenesis ■ Pain at injection site ■ Conjunc-tivitis ■ Increased risk of secondary malignan-cies

ALKYLSULPHONATES

Busulfan (also known as busulphan) is a highly cytotoxic bifunctional alkylsulphonate with a narrow therapeutic index.[6,21]

Busulfan is not structurally related to the nitrogen mustards.[22]

Busulfan is indicated for the palliative treatment of chronic myelogenous leukaemia as well as for conditioning treatment prior to haematopoietic progenitor cell transplantation in adults.[5,13,21,22]

Side effects

Busulfan can cause dose-related myelosuppression, as well as interstitial pulmonary fibrosis.

- Cardiac tamponade
- Cataracts
- Hyperpigmentation
- Symptoms resembling adrenal insufficiency
- Oesophageal varices
- Jaundice
- Skin complications
- Gynaecomastia
- Myasthenia gravis

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

NITROSOUREAS

Carmustine is the most frequently used member of the nitrosourea class of alkylating agents.[5] Nitrosoureas' cytotoxicity is mediated through the formation of DNA interstrand cross-linking with guanine and cytosine.[5] Nitrosoureas are highly lipid-soluble and easily absorbed through tissues and cell membranes, therefore able to cross the blood-brain barrier for the treatment of brain tumours.[5,6]

Indications[13]

Carmustine

- Surgical adjunctive to prolong survival in recurrent glioblastoma multiforme where surgical resection is indicated
- Adjunct to surgery and radiation in newly diagnosed high-grade malignant glioma patients

Side effects[13]

- Cerebral haemorrhage or infarction
- Peripheral or brain oedema
- Neck, back and chest pain
- Allergic reactions
- Asthenia
- Sepsis
- GI disturbances

- Electrolyte disturbances
- Hyperglycaemia
- CNS effects
- Hyper- or hypotension
- Urinary incontinence
- Blood dyscrasia
- Infections
- Abnormal healing
- Visual disturbances
- Pulmonary embolisms

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

TRIAZENES

Temozolomide is an oral alkylating agent for the treatment of newly diagnosed glioblastoma multiforme, recurrent malignant glioma, refractory anaplastic astrocytoma and advanced metastatic malignant melanoma.[13,23]

Side effects[23]

The main dose-limiting side effect of temozolomide is myelosuppression[5]

- Nausea and vomiting
- Fatigue
- Constipation
- Anorexia
- Headache

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

PLATINUM CO-ORDINATION COMPLEXES

Platinum co-ordination complexes are one of the most widely used chemotherapeutic agents. These agents are used as standard therapy in ovarian, lung, head and neck, oesophageal and cervical cancers and are responsible for the high cure rate in germ-cell tumours.[24]

Platinum co-ordination complexes have two active platinum bonds which, once aquated in the tissues, bind to macromolecules in tissue such as RNA and cellular proteins, and irreversibly to DNA.[1,24] Most of the binding results in the forming of intra-strand DNA adducts followed by inter-strand cross-links.[1,5,24] With the cell unable to divide, it undergoes apoptosis.[5]

Cisplatin was accidentally discovered in 1965 and used in trials for chemo-resistant testicular teratomas and relapsed ovarian cancer.[24] These trials reported a high incidence of toxicities, in particular nausea and vomiting and nephrotoxicity.[24,25] Therefore the cisplatin-related analogues were developed to reduce the side effects experienced by this chemotherapeutic agent.[25]

Cisplatin

Cisplatin has antitumour activity similar to the typical alkylating agents and is highly bound to plasma albumin after intravenous (IV) administration.[5,24] The most common side effect is nausea and vomiting which can be overcome by administering 5-hydroxytryptamine-3 ($5\text{-}HT_3$) receptor antagonists and corticosteroids during therapy.[24] The dose-limiting side effects of cisplatin are nephrotoxicity, neurotoxicity and mild myelosuppression.[24] The risk of nephrotoxicity can be reduced by maintaining good diuresis in the patient.[1]

Cisplatin is indicated for:[13,23]

- Advanced non-seminomatous testicular cancer in combination with bleomycin and vinblastine
- Ovarian cancer in combination with doxorubicin or cyclophosphamide
- Cancer of the bladder, head, neck, endometrium, small-cell-lung cancer
- Lymphomas
- Some childhood neoplasms
- Metastatic breast cancer[94]
- Melanoma[108]

Carboplatin

Carboplatin, a cisplatin-analogue, is less emetogenic, nephrotoxic, neurotoxic and ototoxic than cisplatin, but induces more myelosuppression.[5,24] Carboplatin is a more stable compound with a mechanism of action similar to that of cisplatin, although it requires around a 10-fold higher dose and incubation period.[24]

Carboplatin is indicated for:[13,23,98]

- Advanced ovarian cancer of epithelial origin in first-line therapy or second-line therapy after failure of other treatments
- Small-cell lung cancer
- Squamous cell cancer of head and neck

- Cervical cancer
- Melanoma[110]

Oxaliplatin

Oxaliplatin is a newer analogue to cisplatin.[24] Its mechanism of action is similar to the two other platinum co-ordination complexes, but it forms DNA-adducts 50-times faster than cisplatin.[24] Oxaliplatin is active in cisplatin-resistant cell lines and used in combination with 5-fluorouracil (5-FU) in colorectal cancer.[24] Its main dose-limiting side effect is neuropathy. It does not, however, induce nephrotoxicity.[24]

Oxaliplatin is indicated for:[13]

- In combination with 5-fluorouracil and folinic acid, for metastatic colorectal cancer
- Adjuvant treatment of colon cancer
- Under investigation, the use of the combination of oxaliplatin and S1 over S1 alone or the benefit of docetaxel, oxaliplatin and S-1 (tegafur/gimeracil/oteracil combination) as perioperative regimen over surgery alone[90]

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

NEW/OTHER

Trabectedin is a marine-derived anti-tumoural agent with a unique mechanism of action.[129,130] Trabectedin binds to the minor groove of DNA, interfering with cell division and genetic transcription processes and DNA-repair machinery. Trabectedin is indicated for the treatment of unresectable or metastatic liposarcoma or leiomyosarcoma in patients who have been treated with an anthracycline-containing regimen.

2. S-PHASE-SPECIFIC DRUGS

S-phase-specific drugs are cell-cycle-specific agents that exert their actions when the cell has reached the S-phase of the cell cycle.[26] These agents are grouped as antimetabolites, nucleoside analogues or ribonucleotide reductase inhibitors.

During the S-phase, the DNA of the cell is replicated so each chromosome is passed intact to its two daughter cells during mitosis.[27,28]

The DNA molecule contains a linear sequence of four components, namely nucleotides that code for a specific protein.[27] A process called transcription copies the DNA nucleotides into a nucleic acid messenger, namely RNA. RNA is further translated into the specific amino acid sequence.[27]

Each nucleotide or deoxyribonucleotide consists of a five-carbon sugar, deoxyribose, with a different nitrogenous base for each of the four nucleotides.[28] These four nitrogenous bases are thymine (T), cytosine (C), adenine (A) and guanine (G) and for simplicity each nucleotide in a DNA molecule is referred to by its base.[28]

RNA is similar to DNA, differing only in that its ribonucleotides are slightly different to the deoxyribonucleotides.[28]

Each ribonucleotide in RNA consists of a five-carbon sugar, a nitrogenous base, a phosphase group and a hydroxyl group.[28]

As with DNA, RNA's four nucleotides differ from each other in the composition of the nitrogenous base, with three of the bases being similar to that of DNA – A, C and G.[28] The fourth nitrogenous base in RNA is uracil (U), which is very similar to the T-base of DNA.[28]

ANTIMETABOLITES

L-Asparaginase

L-asparaginase is an enzyme that hydrolyses circulating L-asparagines into aspartic acid and ammonia, thereby rapidly inhibiting protein synthesis.[4,26] L-asparaginase is primarily used for treatment of acute lymphoblastic leukaemia (ALL) and for some mast-cell tumours, as these cells are unable to synthesise the non-essential amino acid asparagines, where normal cells can synthesise their own.[26]

The main side effects are related to hypersensitivity reactions from the agent and manifest as fever, chills, nausea and vomiting, skin rash and urticaria.[4]

DHFR, TS and GARFT inhibitors

Antimetabolites as a group are some of the oldest antitumour agents.[25] These agents' targets are incorporated as false substrates into the DNA or target enzymes such as DNA polymerase, thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT), exploiting the number of quantitative differences in the metabolism between cancer cells and normal cells.[4,25] It is these differences that make cancer cells more sensitive to antimetabolites.[4]

Antifolates

Folic acid (vitamin B_9) is converted in the liver to dihydrofolate which is further converted to its active metabolite, tetrahydrofolate.[26] Tetrahydrofolate is an essential cofactor in numerous bodily functions for nucleotide biosynthesis, DNA synthesis and repair.[26] Methotrexate (MTX) competitively and irreversibly inhibits the enzyme dihydrofolate reductase which has a much higher affinity for MTX than dihydrofolate.[26]

It inhibits the conversion of DHFR to tetrahydrofolate, as well as the synthesis of nucleotides, DNA, RNA, thymidylates and proteins.[26]

Pemetrexed has a similar mechanism of action to that of MTX, but also inhibits the enzymes TS and GARFT, thus inhibiting the synthesis of DNA, RNA and the formation of precursor purine and pyrimidine nucleotides.[26]

PURINE ANALOGUES

A and G are purines as they have a two-ringed nitrogenous base, a six-membered ring fused with a five-membered ring.[28]

Cladribine and fludarabine are purine nucleotide analogues, which are inactive in their parent form and metabolised to cladribine triphosphate or fludarabine triphosphate.[4] These active triphosphate metabolites inhibit DNA polymerase, an enzyme needed for DNA synthesis from nucleotides.[4] Furthermore, these metabolites can also be mistakenly incorporated into DNA, inhibiting DNA synthesis and inducing cell death.[4]

6-Mercaptopurine and 6-thioguanine inhibit purine nucleotide synthesis and metabolism, which alters the function and synthesis of DNA and RNA, leading to cell death.[26]

PYRIMIDINE ANALOGUES

T and C are pyrimidines as they have a single six-membered ring in their nitrogenous base.[28]

As T is needed for the synthesis of DNA and RNA, inhibition in the synthesis would impair DNA and RNA synthesis and eventually lead to cell death.[26] 5-FU and its prodrugs capecitabine and tegafur inhibit the methylation of deoxyuridylic acid to thymidylic acid by serving as a substrate for the enzyme.[26] The effects of RNA and DNA deprivation are most pronounced in rapidly dividing cells as these cells take up more 5-FU.[26]

The cellular metabolism of 5-FU leads to the production of two active metabolites capable of inflicting cell injury.[26] The first metabolite inhibits DNA synthesis by binding to TS, an enzyme that produces thymidylate, which is needed for DNA synthesis, whereas the second metabolite is mistakenly incorporated as an RNA building block, interfering with RNA processing and protein synthesis.[26]

Capecitabine is absorbed from the gastro-intestinal (GI) tract and hydrolysed into 5-FU, but the final conversion of capecitabine to 5-FU by thymidine phosphorylase can only take place in cells or tissue that express this enzyme.[26] Certain types of cancers highly express thymidine phosphorylase, therefore capecitabine is able to target these populations.[26]

Cytarabine inhibits DNA polymerase, thereby preventing the progression of cells from the G_1-phase into the S-phase.[26,28]

Azacitidine or 5-azacitidine is a chemical analogue of the cytosine nucleotide used in DNA and RNA synthesis.[29]

Once taken up by the cells, azacitidine is metabolised to 5-azacitidine diphosphate or 5-azacitidine triphosphate.[29] 5-azacitidine diphosphate is initially reduced to 5-azadeoxycytidine diphosphate and then to 5-azadeoxycytidine triphosphate.[29] 5-azadeoxycytidine triphosphate is incorporated into DNA which leads to the inhibition of DNA synthesis.[29]

5-azacitidine triphosphate is incorporated into RNA, which leads to the disruption of RNA metabolism and inhibition of protein synthesis.[29]

Gemcitabine is a fluorine-substituted deoxycytidine analogue that is phosphorylated to a diphosphate and a triphosphate nucleotide form respectively.[4]

The diphosphate form irreversibly inhibits the ribonucleotide reductase (RNR) as a false substrate.[26]

RNR is responsible for the synthesis of deoxynucleotide triphosphates required for DNA replication and repair. Unable to replicate or repair its DNA, the cell undergoes apoptosis.[26]

The triphosphate form is a defective DNA nucleotide. Once incorporated into the DNA molecule, it prevents the attachment of more nucleotides and the cell is forced to undergo apoptosis.[26]

Table 4 provides a detailed indication and side-effect profile for purine and pyrimidine analogues and antimetabolites.

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

Table 4. General indications and side effects of purine and pyrimidine analogues and antimetabolites[4,13,29,30]

	Agent	Indication	Side effects
Purine analogues	Cladribine	■ Acute hairy cell leukaemia	■ Myelosuppression ■ Nausea and vomiting ■ Immunosuppression
	Fludarabine	■ Initial treatment of B-cell CLL ■ CLL patients with sufficient bone-marrow reserve whose disease has not responded to at least one alkylating-agent-containing regimen ■ Non-Hodgkin's lymphoma	■ Myelosuppression ■ Immunosuppression ■ Fever ■ Myalgias ■ Arthralgias

Table 4. (cont.)

	Agent	Indication	Side effects
Purine analogues (continued)	6-Mercapto-purine	■ Acute leukaemia ■ Value in ALL ■ Acute myelogenous leukaemia (AML) ■ Chronic granulocytic leukaemia	■ Myelosuppression ■ Immunosuppression ■ Hepatotoxicity
	6-Thioguanine	■ AML ■ Chronic myelocytic leukaemia (CML) in combination with other therapy	■ Myelosuppression ■ Immunosuppression ■ Hepatotoxicity
	Dacarbazine (imidazole) [117,118]	■ Metastatic melanoma ■ Hodgkin's lymphoma as part of the ABVD regimen (doxorubicin, bleomycin, vinblastine, dacarbazine)	
Pyrimidine analogues	Azacitidine	■ Myelodysplastic syndrome (MDS) including refractory anaemia ■ Refractory anaemia with ringed sideroblasts if accompanied by: – Neutropaenia – Thrombocytopaenia – Requiring transfusions ■ Refractory anaemia with excess blasts ■ Refractory anaemia with excess blasts in transformation ■ Chronic myelomonocytic leukaemia	■ Nausea and vomiting ■ Diarrhoea ■ Myelosuppression with anaemia and thrombocytopaenia ■ Constipation ■ Erythema ■ Ecchymosis ■ Petechiae ■ Rigors ■ Weakness ■ Hypokalaemia
	Capecitabine	■ Locally advanced or metastatic breast cancer – In combination therapy with docetaxel after failure of cytotoxic therapy, including anthracycline – As monotherapy after failure of taxanes and an anthracycline-containing regimen ■ Colorectal cancer: – Adjuvant after surgery in Dukes C colon cancer – First-line monotherapy when pyrimidine therapy alone preferred ■ Gastric cancer[88]	■ Diarrhoea ■ Hand-foot syndrome ■ Myelosuppression ■ Nausea and vomiting

Table 4. (cont.)

	Agent	Indication	Side effects
Pyrimidine analogues continued	Cytarabine	■ Induction and maintenance of remission in acute myelocytic leukaemia ■ Acute lymphocytic leukaemia	■ Nausea and vomiting ■ Myelosuppression with neutropaenia and thrombo-cytopaenia ■ Cerebellar ataxia
	5-Fluorouracil (5-FU)	■ Palliative treatment of breast and GI-tract cancer ■ Beneficial in hepatoma and cancer of the ovary, cervix, bladder, prostate, pancreas, oropharyngeal areas	■ Nausea ■ Mucositis ■ Diarrhoea ■ Bone-marrow depression ■ Neurotoxicity
	Gemcitabine	■ First-line treatment in locally advanced (non-resected stage II or III) or metastatic (stage IV) pancreatic adeno-carcinoma previously treated with 5-fluorouracil ■ Transitional cell bladder cancer ■ Unresected/locally recurrent or metastatic breast cancer in combination with paclitaxel in patients who have relapsed following adjunctive/neoad-junctive chemotherapy (including an anthracycline-based regimen) unless gemcit-abine is contra-indicated ■ Locally advanced or meta-static non-small-cell lung cancer ■ Alone or in combination for recurrent epithelial ovarian cancer patients who have relapsed following platinum-based chemotherapy ■ Non-Hodgkin's lymphoma ■ Soft tissue sarcoma ■ Cervical cancer in combina-tion with cisplatin[101]	■ Nausea and vomiting ■ Diarrhoea ■ Myelosuppression with anaemia and thrombocytopaenia ■ Constipation ■ Erythema ■ Ecchymosis ■ Petechiae ■ Rigors ■ Weakness ■ Hypokalaemia
	Tegafur	■ First-line colorectal cancer with calcium folinate	■ Diarrhoea ■ Nausea and vomiting ■ Fatigue ■ Myelosuppression ■ Anaemia ■ Skin and nail changes

Table 4. (cont.)

	Agent	Indication	Side effects
Antifolates	Methotrexate (MTX)	■ General oncology ■ Acute lymphoma in children	■ Mucositis ■ Diarrhoea ■ Myelosuppression with neutropaenia and thrombocytopaenia
Antifolates (continued)	Pemetrexed	■ Malignant pleural mesothelioma in combination with cisplatin ■ Initial treatment of locally advanced metastatic non-small-cell lung cancer other than predominant squamous cell histology with cisplatin ■ Monotherapy in locally advanced or metastatic adenocarcinoma of the lung after prior chemotherapy ■ Monotherapy for maintenance treatment of locally advanced or metastatic lung adenocarcinoma when disease has not immediately progressed after standard chemotherapy	■ Myelosuppression ■ Skin rash ■ Mucositis ■ Diarrhoea ■ Fatigue

S-1

S-1 is a combination of three pharmacological compounds, namely tegafur, gimeracil, and oteracil used for the treatment of unresectable advanced gastric cancer in combination with cisplatin.[112] Tegafur is a prodrug of 5-fluorouracil (5-FU), an oral fluoropyrimidine, and it has been developed as a replacement for infusional 5-FU therapy. Gimeracil Is a potent inhibitor of 5-FU degradation and oteracil protects against 5-FU-induced GI toxicity to tegafur.[113]

Trifluridine/tipiracil

Trifluridine/tipiracil is a combination drug for the treatment of metastatic colorectal cancer.[122] Trifluridine is a thymidine-based nucleoside analogue and tipiracil, a thymidine phosphorylase inhibitor, prevents trifluridine degradation by thymidine.

RIBONUCLEOTIDE REDUCTASE INHIBITORS

The precise mechanism of action of hydroxyurea (also known as hydroxycarbamide) is unknown, but it is believed to inhibit retinoic acid receptors (RARs), thereby depleting deoxynucleoside triphosphate and inhibiting DNA synthesis without affecting the synthesis of ribonucleic acids or proteins.[4,31]

Hydroxyurea is indicated for malignant neoplastic disease, recurrent disease, metastatic disease, CML and tumours of the head and neck.[31]

Side effects include bone-marrow suppression, GI upsets such as nausea and vomiting, dermatological effects, drowsiness and elevated serum uric acid, urea and creatinine levels.[31]

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

3. G2-PHASE-SPECIFIC AGENTS

During the G_2-phase, cells continue to grow and prepare for mitosis, increasing the rate of protein synthesis.[27] For DNA replication to take place, the double-stranded DNA coils must be unwound and separated into single strands.[28] The process of unwinding the DNA for replication can result in some sections ahead of the replication fork to supercoil and interfere with the topology of DNA, preventing DNA replication from taking place.[28]

Enzymes called topoisomerases relieve the tension caused by unwinding as they cleave either one strand of the double DNA helix (type I) or both strands (type II) ahead of the replication fork, leaving the DNA molecule to unwind at the cleaved site and relieve the tension.[28] Once the tension has been relieved, these enzymes anneal the stands.[28]

Although these enzymes are similar in some aspects, they differ in their interaction with DNA.[32]

TOPO-I INHIBITORS

The camptothecin analogues are plant-derived compounds extracted from the bark of the Chinese *Camptotheca* trees.[25] These agents inhibit the type I topoisomerase enzymes by binding to the topoisomerase I-DNA complex.[33] This binding prevents annealing of the cleaved strand, resulting in the formation of irreversible DNA breaks that lead to cell death.[25,33] These agents are commonly used in the treatment of gastro-intestinal and pulmonary malignancies.[33]

Detailed indications and side effects of camptothecin analogues follow.

Indications[13,89]

Irinotecan

- Advanced colorectal cancer with WHO performance status of two or lower
  - In combination with 5-FU and folinic acid without prior chemotherapy
  - For advanced disease or as single agent when established 5-FU-containing regimen has failed
- Gastric cancer

Topotecan

- Metastatic ovarian cancer after failure of first-line or subsequent therapy
- In combination with cisplatin for histological confirmed stage IV-B recurring or persistent cervical cancer not amenable to curative treatment with surgical and radiation therapy
- Palliative treatment of small-cell lung cancer as a second-line chemotherapeutic agent in patients who relapse after an initial response to first-line agents
- Cervical cancer[102]

Side effects[4]

- Nausea and vomiting
- Myelosuppression

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

TOPO-II INHIBITORS

Type II topoisomerase, together with type I, regulates the topology of DNA.[32] Topo-II inhibitors block the enzyme, type II topoisomerase, which acts by a different mechanism, preventing annealing of the DNA after it has been cleaved.[32]

Epipodophyllotoxin

Etoposide is a semi-synthetic epipodophyllotoxin analogue.[32] Etoposide inhibits the type II topoisomerase enzyme by binding to the topoisomerase-DNA complex, and thereby prevents annealing of the cleaved DNA.[32]

During replication, the initial DNA break is converted into a permanent double-stranded break which can lead to cell death.[32]

Etoposide is indicated for the treatment of non-small-cell and small-cell lung cancer, non-Hodgkin's lymphoma, gastric cancer, ovarian cancer and cervical cancer.[4,97,100] Its main side effect is haematological toxicity.[26]

Anthracyclines

Anthracyclines, such as doxorubicin and daunorubicin, are antimicrobial isolates from *Streptomyces peucetius* or *Streptomyces galilaeus*, whereas epirubicin and idarubicin are semi-synthetic anthracycline analogues.[25]

These compounds inhibit DNA and RNA synthesis by preventing the action of the type II topoisomerase enzyme by intercalating with the DNA.[25,34] They cause further

Table 5. General side effects of vinca alkaloids[4,35]

Vincristine	Vinblastine	Vinorelbine	Vinflunine
■ Neurotoxicity with peripheral neuropathy ■ Paralytic ileus ■ Myelosuppression ■ Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	■ Nausea and vomiting ■ Myelosuppression ■ Mucositis ■ SIADH ■ Vascular events	■ Nausea and vomiting ■ Myelo-suppression ■ Constipation ■ SIADH	■ Myelosuppression ■ Mucositis ■ Constipation ■ Diarrhoea ■ Loss of fertility

damage by the formation of free radicals which bind and break double-stranded DNA.[25,34]

These highly effective antitumour agents' use is limited by side effects such as cardiotoxicity.[34]

A detailed indication and side-effect profile of anthracyclines follows:

Indications[1,25,89]

Daunorubicin

- Acute lymphocytic and myelocytic leukaemia

Doxorubicin

- Solid tumours, i.e. breast cancer[91]
- Haematological malignancies, sarcomas, embryonal tumours of childhood
- Ovarian cancer in combination with cisplatin or cyclophosphamide

Epirubicin

- Monotherapy for breast cancer (in men and women)
- Monotherapy for gastric cancer
- Malignant lymphoma
- Soft-tissue sarcoma
- Advanced colorectal cancer
- Malignant melanoma
- Combination therapy with other chemotherapeutic agents for lung and ovarian cancer

Idarubicin

- Acute non-lymphocytic leukaemia including acute myeloblastic leukaemia in adults as front-line therapy or remission induction in relapsed or refractory patients.

Mitoxantrone

- Breast cancer, including locally advanced or metastatic disease
- Adult acute non-lymphocytic leukaemia at relapse and chronic myelogenic leukaemia in blast crisis
- In combination with low-dose oral corticosteroids as initial chemotherapy for symptomatic treatment of intractable pain related to advanced hormone-refractory prostate cancer
- Non-Hodgkin's lymphoma

Side effects[1,25]

- Nausea and vomiting
- Dose-limiting myelosuppression and mucositis
- Cardiotoxicity

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

4. M-PHASE-SPECIFIC AGENTS

The completion of the G_2-phase is marked by the beginning of the M-phase or mitosis.[27] Mitosis is further subdivided into prophase, metaphase, anaphase and telophase.[27] During the prophase-phase, the chromosomes are condensed and attached to the microtubules, to be segregated by the mitotic spindle at the completion of mitosis.[27] Prophase is followed by the alignment of the chromosomes in metaphase.[27] Once aligned, a group of chromosomes moves towards a pole of the cell in anaphase and the events of the prophase are reversed in telophase as two nuclei form and the cell divides into two identical daughter cells.[27]

The M-phase-specific agents are mainly antitubulin agents as they interfere with the normal microtubule dynamics, such as spindle formation and disassembly, blocking the division of the nucleus into two daughter cells.[25]

VINCA ALKALOIDS

Vincristine and vinblastine are vinca alkaloids, derived from the periwinkle plant *Vinca rosea*, whereas vinorelbine and the newer agent vinflunine are semi-synthetic analogues.[1,4] These agents bind tubulin. Tubulin dimers assemble to form microtubules.[1,27]

By binding tubulin, these agents prevent polymerisation of mitotic spindles, thereby blocking cells in mitosis.[1] Vinca alkaloids are highly vesicant and M-G_1 phase-specific.[1,2]

The use of vinca alkaloids is limited by their dose-related side effects (see Table 5), such as neuropathy and bone-marrow suppression for vincristine and vinblastine respectively.[1]

In comparison, vinflunine has a more favourable side-effect profile as it binds relatively weakly to tubulin, and therefore has less ability to cause neurotoxicity.[35]

A detailed indication and side-effect profile of vinca alkaloids follows and Table 5 addresses the side effects.

Indications[4,13,35]

Vincristine

- Acute leukaemia
- Hodgkin's disease and related lymphomas

Vinblastine

- Palliative treatment of malignant non-Hodgkin's lymphoma
- Hodgkin's disease
- Cancer of the testes
- Chorio- and breast cancer
- Melanoma[109]

Vinorelbine

- Palliative treatment of advanced, inoperable non-small-cell lung cancer as monotherapy or as combination therapy (more effective)
- Metastatic breast cancer in patients in whom anthracycline first-line monotherapy has failed or who have relapsed within six months of anthracycline-based adjuvant therapy
- Prostate cancer as palliative treatment.[106]
  Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.
- Cervical cancer[99]

TAXANES

Paclitaxel and its related semi-synthetic compounds docetaxel and cabazitaxel are alkaloid esters derived from the Pacific and European yew trees respectively.[4,36] Paclitaxel and docetaxel are G_2-M phase-specific agents, as they bind to tubulin in the microtubules, causing cell arrest at mitosis, which may lead to apoptosis.[2,36]

Although paclitaxel was isolated in 1966, it did not appear in clinical practice until the 1990s.[25] Today, it is indicated for a variety of cancers, including metastatic breast cancer after combination therapy failure or relapse after six months of adjuvant chemotherapy (including anthracyclines), first-line therapy of advanced or metastatic breast cancer in combination with trastuzumab in patients who overexpress HER2 at a 2+ or 3+ level as determined by immunohistochemistry, palliative treatment of advanced non-small-cell lung cancer when curative surgery and/or radiotherapy is not applicable, palliative treatment of stage 3 or 4 locally advanced ovarian cancer after surgical resection in combination with cisplatin, and palliative management of metastatic ovarian cancer after failure of first-line or subsequent chemotherapy,

as well as gastro-oesophageal cancer, prostate cancer, bladder cancer, cervical cancer and head and neck cancer.[4,13,99] Docetaxal has similar therapeutic and toxic properties as etoposide and is indicated as adjuvant treatment of patients with oper node-positive breast cancer in combination with doxorubicin and cyclophosphamide, locally advanced metastatic breast cancer in combination with doxorubicin in patients who have not received cytotoxic therapy for this condition, locally advanced or metastatic breast cancer after failure of cytotoxic therapy, locally advanced or metastatic breast cancer in combination with capecitabine after failure of cytotoxic chemotherapy where previous therapy did not include an anthracycline, in combination with cisplatin for unresected locally advanced or metastatic non-small-cell lung cancer where chemotherapy has not previously been administered for this condition, locally advanced or metastatic non-small-cell lung cancer even after failure of platinum-based chemotherapy, metastatic ovarian cancer after failure of first-line or subsequent therapy, androgen-independent metastatic prostate cancer in combination with prednisone/prednisolone, in combination with cisplatin and 5-fluorouracil for induction treatment of patients with inoperative locally advanced squamous cell cancer of the head and neck.[4,13] New research has shown that docetaxel in combination with gemcitabine may be considered in the treatment of soft tissue sarcomas.[111] The combination with gemcitabine should be used with caution.

Cabazitaxel is indicated for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxal-containing treatment regimen.[37]

The main side effects of taxanes include:[4]

- Nausea and vomiting
- Hypotension
- Arrhythmias
- Hypersensitivity
- Myelosuppression with neutropaenia
- Peripheral sensory neuropathy
- Neurotoxicity
- Fluid retention

EPOTHILONES

Ixabepilone is an epothilone B analogue from a relatively new class of antitumour agents and a novel microtubule inhibitor.[4,38] The epothilones were developed to overcome tumour-resistant mechanisms. Ixabepilone has activity in drug-resistant tumours that overexpress tubulin mutations.[4,38] Ixabepilone binds to the tubulin during mitosis and thereby stabilises the microtubules, halting the cell cycle.[4]

Ixabepilone is indicated for the treatment of locally advanced or metastatic breast cancer after cytotoxic chemotherapy has failed; as combination therapy with capecitabine in patients who have failed prior therapy with a taxane and an anthracycline or where further anthracycline therapy is not indicated; as monotherapy for patients in whom prior therapy with a taxane or anthracycline has failed.[13]

Ixabepilone's main side effects include: [4]

- Myelosuppression
- Hypersensitivity reactions
- Neurotoxicity in the form of peripheral sensory neuropathy

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

OTHERS

Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into non-productive aggregates.[124] Eribulin exerts its effects via a tubulin-based antimitotic mechanism, leading to G2/M cell-cycle block, disruption of mitotic spindles, and ultimately, apoptotic cell death after prolonged mitotic blockage.

Eribulin is indicated as monotherapy in patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapy regimens for advanced disease.[13] Prior therapy had to include an anthracycline and a taxane unless the patient is not suitable.

5. MISCELLANEOUS

BLEOMYCIN

The exact mechanism of action of bleomycin is unknown. It is believed to be a DNA-cleaving agent that causes single- and doubled-stranded DNA breaks in the region where it binds to the DNA following free radical formation.[4,25,26] Bleomycin is a mixture of cytotoxic glycopeptides isolated from bacteria which specifically target the G_2-phase of the cell cycle.[4,26] As bleomycin accumulates in squamous cells, it is suitable for treating head and neck cancers, Hodgkin's disease, non-Hodgkin's lymphoma and testicular carcinomas.[25] Its main dose-limiting side effect is pulmonary toxicity which may, in rare cases, be fatal.[4]

Other side effects of bleomycin include:[4]

- Allergic reactions
- Fever
- Hypotension
- Skin toxicity
- Pulmonary fibrosis
- Mucositis
- Alopecia

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

CYP17A1 INHIBITORS

Ketoconazole and abiraterone are cytochrome P450 enzyme inhibitors, more specifically they inhibit the enzyme CYP17A1 that mediates androgen precursor synthesis.[114] In castration-resistant prostate cancer, androgen receptors are reactivated, mediating the synthesis of testosterone and dihydrotestosterone from precursor steroids.

Ketoconazole

The antifungal agent ketoconale, is indicated for patients with advanced prostate cancer which progresses after androgen deprivation.[115]

Abiraterone acetate

Abiraterone acetate is a prodrug of abiraterone, an orally available inhibitor of the cytochrome P450 c17 enzyme complex critical to androgen production. Abiraterone acetate Is used in prostate cancer in combination with prednisone.[105]

6. BIOLOGICALS

Signal transduction or biochemical communication in the cell plays an essential role in the normal cell cycle and cell division.[26] Binding of a ligand such as a growth factor to its cell-surface receptor (usually a tyrosine kinase) leads to activation of the receptor.[26] Activation of a receptor involves the transfer of a large phosphate group from adenosine triphosphate (ATP) via a kinase to a protein such as tyrosine which activates a cascade of events.[26] These events may entitle the switching on or off of a particular process.[26]

Growth factors stimulate proliferation, differentiation, interaction with other cells, and growth and survival in cells.[39] In cancer cells, growth factors are involved in invasion, metastasis and angiogenesis as they activate an altered, mutated signalling process.[26, 39]

Certain biological chemotherapeutics such as monoclonal antibodies (MAbs) and small-molecular-weight agents are targeted at cell-surface- and intracellular receptors of the tyrosine kinase family.[1,26]

Specific growth-factor targets include epidermal growth factor (EGF) and its receptors (EGFRs), and vascular endothelial growth factor (VEGF) and its receptors (VEGFRs).[39]

Aflibercept acts as a soluble receptor that binds to human VEGF-A, to human VEGF-B and to human PlGF. By binding to these endogenous ligands, aflibercept can inhibit the binding and activation of their receptors. This inhibition can result in decreased neovascularisation and decreased vascular permeability. Aflibercept is used in combination with 5-fluorouracil, leucovorin and irinotecan-(FOLFIRI), and is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.[119]

EGF belongs to the human epidermal receptor (HER) tyrosine kinase family that is responsible for cell proliferation, growth and survival, whereas VEGF induces endothelial cell proliferation and new blood-vessel formation in the growing tumour.[26,39]

Not all biological chemotherapeutics target tyrosine kinases as some known as immunomodulating agents are often used to boost the ability of the immune system to fight cancer.[26] Immunomodulating agents include certain MAbs, interferons and interleukins.[4,26]

Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumour angiogenesis, metastasis and tumour immunity.[125] Regorafenib is indicated for metastatic colorectal cancer previously treated with or contra-indicated for fluoropyrimidine-based chemotherapy, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy.[13] Regorafenib is furthermore indicated for the treatment of GIST previously treated with two tyrosine kinase inhibitors and hepatocellular carcinoma (HCC) which has been previously treated with sorafenib.

Vemurafenib inhibits some mutated forms of BRAF serine threonine kinase, including BRAF V600E, and has been shown to inhibit CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5, and FGR *in vitro*.[131] Some mutations in the BRAF gene including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. Vemurafenib is indicated for the treatment of unresectable or metastatic melanoma with BRAF V600E mutation, Erdheim Chester Disease with BRAF V600 mutation.

INTERFERONS

Interferons (IFNs) are cytokines produced naturally by host cells in the presence of a pathogen such as a tumour cell, bacteria, virus or parasite. IFNs bind to specific cell-membrane receptors and initiate a complex sequence of events, facilitating communication between immune cells, enabling them to destroy a pathogen.[4,26] The immunomodulating activities of IFNs include the direct antiproliferative effects on tumour cells, enhancement of the phagocytic activity of macrophages, up-regulating tumour antigen presentation to cytotoxic T-lymphocytes and activation of natural killer cells.[4,26,39]

Interferon-alpha and beta

Interferon-alpha (INF-α) and interferon-beta (INF-β) are cytokines which form part of a large subclass of interferons better known as type I IFNs.[41,42] The host cells, in response to a pathogen, produce cytokines such as

type I INFs.[42] Type I IFNs bind to type I interferon receptors, which in turn activate certain tyrosine kinase receptors.[42-45]. Activation of the tyrosine kinase receptors leads to enhanced activation of CD8-positive T-cells that are the precursors for cytotoxic T-lymphocytes, activation of macrophages and natural killer cells and upregulating of MHC expression.[42-45]

The best clinical responses of type I IFNs are observed mainly, but not exclusively, in haematological malignancies and cancers linked to viral infections.[42] Until the discovery of tyrosine kinase inhibitors (TKIs), INF-α was the treatment of choice in CML and is indicated in the treatment of hairy cell leukaemia, low-grade lymphoma, myeloma, cutaneous T-cell lymphoma, as well as some solid tumours such as melanoma, renal cell carcinoma and Kaposi sarcoma.[41,42] Interferon alfacon-1, IFN-α2a and IFN-α2b are recombinantly produced IFNs, whereas IFN-β is a human interferon produced in mammalian cells.[43-45] INF-β has a greater antiproliferative effect on melanoma cells when compared to INF-α; it is mainly used in the treatment of multiple sclerosis.[40,42]

Side effects of type I INFs include:[39,40]
- Flu-like symptoms
- Lethargy
- Auto-immune disease
- Myelosupression with neutropaenia
- Weight loss
- Myalgias or arthralgias
- Depression
- Pulmonary complications
- Pulmonary arterial hypertension

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

INTERLEUKIN-2

Native human interleukin-2 (IL-2) is a cytokine-signalling molecule of the immune system secreted by T-cells.[46] IL-2 is capable of enhancing lymphocyte mitogenesis and cytotoxicity, activation of natural killer cells and production of interferon-gamma.[46,47]

Aldesleukin

Aldesleukin (also known as proleukin) is a recombinantly produced human IL-2 with the same biological activities of native IL-2.[44,45] Aldesleukin binds to the IL-2 receptor and activates certain tyrosine kinase complexes which leads to a series of events to activate the cellular immune system to kill tumour cells.[46,47]

Aldesleukin is indicated for the treatment of metastatic renal cell carcinoma and melanoma.[47,107]

The side effects of aldesleukin include:[47]
- Flu-like symptoms
- Asthenia
- Pain
- Hypotension and tachycardia
- Confusion
- Bilirubinaemia and an increase in creatinine levels
- Peripheral oedema
- Nausea and vomiting
- Diarrhoea
- Respiratory effects
- Rash
- Thrombocytopaenia and anaemia
- Oliguria

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

OTHERS

Pazopanib

Pazopanib is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma and advanced soft tissue sarcoma who have received prior chemotherapy.[116] The efficacy of pazopanib for the treatment of patients with adipocytic soft tissue sarcoma or gastro-intestinal stromal tumours has not been demonstrated.

MONOCLONAL ANTIBODIES

Monoclonal antibodies (MAbs) are biological agents that usually target specific antigens which are highly expressed on cancer cells, but not on normal cells.[48]

MAbs are subdivided into naked or conjugated MAbs.[39]

Naked MAbs are not attached to any drug or radio-active material, whereas conjugated MAbs are joined to a toxin or radio-active isotope.[39]

Naked MAbs

Alemtuzumab

Alemtuzumab is a humanised MAb directed against the glycoprotein CD52, a

cell-surface protein expressed on normal and cancerous B- and T-lymphocytes.[48] By binding to CD52, alemtuzumab causes lysis to the lymphocytes via complemented fixation and antibody-dependent, cell-mediated cytotoxicity.[48] Alemtuzumab is used in the treatment of chronic lymphocytic leukaemia and in fludarabine-refractory patients.[48,49] Side effects include transient neutropaenia, the risk of opportunistic infection, fever, rigors, chills, bronchospasm, hypotension, angio-oedema and acute lung injury.[48]

Bevacizumab

Bevacizumab binds to VEGF and blocks its biological activities by preventing it from binding with its receptor, VEGFR, on the vascular endothelium.[26,39] Bevacizumab inhibits vascular permeability, but increases tumour blood flow and therefore drug delivery.[4] Bevacizumab is indicated in the treatment of colorectal cancer, breast cancer, non-small-cell lung cancer and renal cancer.[4] Side effects of MAbs include hypertension, infusion reactions, arterial thrombo-embolic events, GI perforations, wound-healing complications and proteinuria.[4]

Cetuximab

Cetuximab is a recombinant, human/mouse chimeric MAb that binds specifically to the extracellular domain of the EGFR, preventing binding of EGF.[26,39] Binding to the receptor blocks phosphorylation and activation of receptor-associated kinases, which results in inhibition of cell growth, motility, invasiveness, metastasis and promotes apoptosis.[26,39] Cetuximab decreases the production of VEGF and enhances the response to radio- or chemotherapy.[4,26] Unfortunately, it targets EGFR on both normal and cancer cells.[26]

Cetuximab is indicated for the treatment of colorectal cancer, as an adjunct to radiotherapy in head and neck cancer and non-small-cell lung cancer.[4] Side effects of cetuximab include infusion reactions, skin rash, hypomagnesaemia, fatigue and interstitial lung disease.[4]

Rituximab

The immunomodulating MAb, rituximab, is a cytotoxic MAb that binds to CD20, a cell-surface marker expressed by mature B-lymphocytes, some leukaemias and non-Hodgkin's lymphomas.[1,4,26] Binding of the MAb to CD20 leads to apoptosis of the CD20-positive cells.[26] Side effects of rituximab are rare, with most patients only developing a rash after the initial treatment.[4]

Trastuzumab

Trastuzumab is a recombinant MAb that binds to the extracellular segment of the HER2.[26] Binding of the antibody to the receptor inhibits DNA repair and cell proliferation, arresting the cell cycle at the G_1-phase, which leads to the induction of apoptosis in the cell.[39] Furthermore, trastuzumab suppresses angiogenesis as it has anti-angiogenic properties preventing new vessel formation required for tumour growth.[26,39] Trastuzumab is indicated for the treatment of metastatic breast cancer with HER2 overexpression (in men and women).[39,92] Side effects of trastuzumab therapy may include a degree of cardiotoxicity, dermatitis and acute oesophagitis toxicity.[39]

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

Ramucirumab

Ramucirumab is a recombinant human IgG1 monoclonal antibody that specifically binds to VEGFR2 and therefore Inhibits ligand-induced proliferation, and migration of human endothelial cells.[120] Ramucirumab is indicated as a single agent or in combination with paclitaxel, for treatment of advanced gastric or gastro-oesophageal junction adenocarcinoma, with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy, in combination with docetaxel and for treatment of metastatic non-small-cell lung cancer with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab. Ramucirumab may be used in combination with the FOLFIRI (folinic acid, 5-FU and irinotecan) regimen, for the treatment of metastatic colorectal cancer with disease progression with or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

Panitumumab

Panitumumab is a recombinant, human IgG2 kappa monoclonal antibody that binds specifically to the human EGFR.[121] The EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases, including EGFR, HER2, HER3, and HER4. EGFR is constitutively expressed in normal epithelial tissues, including the skin and hair follicle and over-expressed in certain human cancers, including colon and rectal cancers. Binding of ligands to EGFR ultimately results in transcription of genes involved with cellular growth and survival, motility, and proliferation.

Panitumumab binds specifically to EGFR on both normal and tumour cells, and competitively inhibits the binding of ligands for EGFR.

Panitumumab is indicated as a single agent for the treatment of metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy regimens.[121]

PD-1 inhibitors

Pembrolizumab, nivolumab, atezolizumab, avelumab and durvalumab all have a similar mechanism of action. These agents are humanised monoclonal antibodies that block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.[123] Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T-cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours, and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. Inhibition of PD-1 and ligand interaction releases the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response.

Pembrolizumab

Pembrolizumab is indicated for the treatment of[123]

- Unresectable or metastatic melanoma
- Non-small-cell lung cancer
  - as a single agent for the first-line treatment of patients with metastatic non-small-cell lung cancer with tumours having high PD-L1 with no EGFR or ALK genomic tumour aberrations
  - as a single agent for the treatment of patients with metastatic non-small cell lung cancer whose tumours express PD-L1 (TPS ≥1%) with disease progression on or after platinum-containing chemotherapy
  - in combination with pemetrexed and carboplatin, as first-line treatment of patients with metastatic non-squamous non-small-cell lung cancer
- Head and neck squamous cell cancer
  - recurrent or metastatic head and neck squamous cell cancer with disease progression on or after platinum-containing chemotherapy
- Hodgkin's lymphoma
  - adult and paediatric patients with refractory Hodgkin's lymphoma, or who have relapsed after three or more prior lines of therapy
- Urothelial carcinoma
  - locally advanced or metastatic urothelial carcinoma in patients who are not eligible for cisplatin-containing chemotherapy
  - locally advanced or metastatic urothelial carcinoma in patients whose disease has progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
- Microsatellite instability-high cancer
  - adult and paediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch-repair-deficient
    - solid tumours that have progressed following prior treatment and which have no satisfactory alternative treatment options, or
    - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

- Gastric cancer
  - recurrent locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 [Combined Positive Score (CPS) ≥1], with disease progression on or after two or more prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy

Nivolumab

Nivolumab is indicated for the treatment of:[133]

- BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent
- BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent
- unresectable or metastatic melanoma, in combination with ipilimumab
- melanoma with lymph-node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting
- metastatic non-small-cell lung cancer and progression on or after platinum-based chemotherapy. EGFR or ALK genomic tumour aberrations should have disease progression
- advanced renal cell carcinoma in patients who have received prior antiangiogenic therapy
- adult patients with classical Hodgkin's lymphoma that has relapsed or progressed after:
  - autologous haematopoietic stem-cell transplantation (HSCT) and brentuximab vedotin, or
  - three or more lines of systemic therapy that includes autologous HSCT
- recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy
- locally advanced or metastatic urothelial carcinoma in patients who:
  - have disease progression during or following platinum-containing chemotherapy
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
- adult and paediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch-repair-deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan
- hepatocellular carcinoma in patients who have been previously treated with sorafenib

Atezolizumab

Atezolizumab is indicated for the treatment of:[135]

- Locally advanced or metastatic urothelial carcinoma in patients who:
  - are not eligible for cisplatin-containing chemotherapy, or
  - have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy
- Metastatic non-small-cell lung cancer in patients who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression

Avelumab

Avelumab is indicated for the treatment of:[137]

- metastatic Merkel cell carcinoma in adult and paediatric patients older than 12 years of age

Durvalumab

Durvalumab is indicated for the treatment of:[138]

- Locally advanced or metastatic urothelial carcinoma patients who:
  - have disease progression during or following platinum-containing chemotherapy
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
- Unresectable, stage III non-small-cell lung cancer patients whose disease has not progressed following

concurrent platinum-based chemotherapy and radiation therapy

Ipilimumab

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and inhibits the interaction of CTLA-4 with its ligands, CD80/CD86.[128] Inhibition of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumour-infiltrating T-effector cells. Inhibition of CTLA-4 signalling can also reduce T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumour immune response.

Ipilimumab is indicated for previously treated unresectable or metastatic melanoma.[13]

Conjugated MAbs

Conjugated MAbs have a different mechanism of action to that of the naked MAbs, as the interaction between the MAb and the antigen is either to facilitate the delivery of the toxin or to specifically target cancer cells with radiation therapy.[39]

Brentuximab vedotin

Brentuximab vedotin is a CD30-directed antibody-drug conjugate indicated for treatment of[134]:

- Previously untreated Stage III or IV Hodgkin's lymphoma, in combination with chemotherapy
- Hodgkin's lymphoma at high risk of relapse or progression as post-autologous haematopoietic stem-cell transplantation (auto-HSCT) consolidation
- Hodgkin's lymphoma after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates
- Systemic anaplastic large-cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen
- Primary cutaneous anaplastic large-cell lymphoma or CD30-expressing mycosis fungoides (MF) in patients who have received prior systemic therapy

Radiolabelled MAbs

The radiolabelled antibody, ibritumomab tiuxetan, is a monoclonal mouse antibody conjugated with the chelator tiuxetan to which a radio-isotope indium-111 is added.[48] The monoclonal antibody section of ibritumomab tiuxetan is capable of binding to B-lymphocytes; it therefore delivers a dose of radiation to the cell and the antibody binds to its neighbouring cells as well.[48]

Ibritumomab tiuxetan is deliberately kept as a monoclonal mouse antibody to ensure rapid elimination from the body.[48] The main side effect of ibritumomab tiuxetan is myelosuppression.[48]

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

7. SMALL-MOLECULE KINASE INHIBITORS

Dasatinib, imatinib and nilotinib

Imatinib is a two-phenylaminopyrimidine derivative tyrosine kinase inhibitor, which inhibits the tyrosine kinase domain of the Bcr-Abl oncoprotein in CML.[4,26] Imatinib is also capable of inhibiting tyrosine kinase receptors such as PDGF, stem-cell factor and c-Kit in GI stromal tumours (GIST).[4,26]

CML is a clonal pluripotent haematopoietic stem-cell disorder.[42] CML contains a derivate chromosome known as the Philadelphia chromosome.[42] Here, a balanced translocation between the c-Abl gene on chromosome 9 and the Bcr gene on chromosome 22 is found on a single chromosome as a chimeric Bcr-Abl gene which is responsible for CML.[4,42]

Similar to imatinib, dasatinib and nilotinib inhibit the same tyrosine kinase and kinase receptor, but differ from imatinib in that they bind to the active and inactive conforms of the Abl kinase domain, overcoming imatinib resistance due to mutations in the Bcr-Abl kinase.[4,26] Furthermore, research has shown that dasatinib is much more potent compared to imatinib against Bcr-Abl-expressing cells.[26]

In adults and paediatric patients, imatinib is indicated for CML, CML in blast crisis or accelerated or chronic phase after interferon-alpha therapy failure.[13] In adult patients, imatinib is indicated for patients with Philadelphia-chromosome-positive ALL (Ph+ALL) integrated with chemotherapy relapse or Ph+ALL as monotherapy, myelodysplastic or myeloproliferative disease (MDS/MPD) associated with PDGF-receptor gene rearrangement, systemic mastocytosis (SM) without the D816V c-Kit mutation and eosinophilia, hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1-PDGF-receptor alpha rearrangement, unresected and/or metastatic malignant GI stromal tumours (GIST), adjuvant treatment following resection of Kit-positive GIST, unresected or recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

Dasatinib is indicated for Ph+ CML in chronic phase, chronic-accelerated- or myeloid- or lymphoid blast-phase chronic myeloid leukaemia in adults resistant or intolerant to prior therapy, including imatinib.

Nilotinib is indicated for the treatment of adult patients newly diagnosed with Ph+ CML in chronic phase, treatment of chronic or accelerated Ph+ CML in adult patients resistant or intolerant to at least one prior therapy, including imatinib.[4,13]

Side effects of these agents include nausea and vomiting, fluid retention with ankle and peripheral oedema, myalgias and congestive heart failure.[4]

Erlotinib

Erlotinib inhibits the EGFR and EGFR tyrosine kinase, preventing autophosphorylation of the kinase and thereby inhibiting the EGF-signalling pathway.[4,26] Erlotinib is used in the treatment of locally advanced or metastatic non-small-cell lung cancer after failure of at least one prior chemotherapy regimen, first-line treatment of locally advanced or metastatic (stage IV) bronchial adenocarcinoma demonstrating EGF-receptor-activated mutation in patients who have never smoked and with ECOG performance status of 0-1, and first-line treatment of locally advanced unresectable or metastatic pancreatic cancer in combination with gemcitabine.[4,13] Its side effects include hypertension, diarrhoea, skin rash, anorexia and interstitial lung disease.[4]

Gefitinib

Gefitinib has a similar mechanism of action to erlotinib and is indicated as first-line treatment of patients with metastatic non-small-cell lung cancer (NSCLC) with tumours having epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.[139]

Lapatinib

Lapatinib, a TKI, is indicated as combination therapy for HER2-positive metastatic breast cancer.[50] Lapatinib combinations include:[50]

- Use with capecitabine in patients who have received prior therapy, including an anthracycline, a taxane and trastuzumab
- Use with letrozole in postmenopausal women in whom hormonal therapy is indicated

Side effects of lapatinib combination therapy include diarrhoea, palmar-plantar erythrodysesthesia, nausea and vomiting, rash and fatigue.[50]

Sorafenib and sunitinib

Sorafenib and sunitinib are small molecular TKIs involved in cellular pathways such as the Raf/MEK/ERK pathway (MAP kinase pathway) as well as cell-surface kinases such as the VEGFRs and platelet-derived growth factor (PDGF) receptor-beta.[4] These kinases are involved in angiogenesis, invasion of the tumour and tumour metastasis, all of which are inhibited by sorafenib and sunitinib.[4] Sorafenib is indicated for the treatment of advanced renal cell cancer and advanced inoperable hepatocellular cancer and locally advanced or metastatic differentiated thyroid cancer, whereas sunitinib is indicated for the treatment of metastatic renal cell cancer after failure of cytokine-based therapy (interferon-alpha and IL-2) and GIST after failure of imatinib treatment due to resistance or intolerability.[4,13]

Side effects of the small molecular inhibitor include nausea and vomiting, skin rash, fatigue, asthenia and bleeding complications.[4] The use of sorafenib can further lead to hypophosphataemia, whereas sunitinib use may lead to cardiotoxicity or congestive heart failure.[4]

Axitinib

Axitinib is a TKI including VEGFR-1, VEGFR-2 and VEGFR-3.[132] Axitinib is indicated for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.

Ibrutinib

Ibrutinib is a small-molecule inhibitor of BTK as it forms covalent bonds with a cysteine residue in the BTK active site, inhibiting enzyme activity.[140] BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. Ibrutinib inhibits malignant B-cell proliferation, survival, cell migration and substrate adhesion.

8. PROTEASOME INHIBITORS

A proteasome is an enzyme complex that plays an important role in the degradation of proteins involved in the cell cycle and other cellular processes.[26] Bortezomib is a reversible proteasome inhibitor capable of disrupting cellular processes involved in the growth and survival of cancerous cells, leading to apoptosis.[26] Bortezomib is indicated for:[13,51]

- Primary treatment of multiple myeloma in combination with melphalan and prednisone
- Monotherapy for multiple myeloma in patients who have received at least one prior treatment and who have progressive disease
- Treatment of patients with mantle-cell lymphoma who have received at least one prior therapy which includes an anthracycline or mitoxantrone and/or rituximab as part of a chemotherapy regimen

Side effects of bortezomib include nausea, diarrhoea, thrombocytopaenia, neutropaenia, peripheral neuropathy, fatigue, neuralgia, anaemia, leukopaenia, constipation, vomiting, lymphopaenia, rash, pyrexia, and anorexia.[51]

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

9. MOTOR INHIBITORS

The mammalian target for rapamycin (mTOR) is a mediator of tumour progression and forms part of the PI3K/AKT/mTOR pathway.[52] Activation of the mTOR kinase activity by phosphorylation results in the interpretation of a variety of growth and survival signals received by the cancer cells and the upregulation of proteins needed for the cell's survival.[26,52]

Everolimus and temsirolimus are inhibitors of mTOR.[26,52] These agents prevent mTOR-mediated phosphorylation of key kinases by binding with high affinity to the intracellular receptor FKBP12.[26,52] The inhibitor-FKBP12 complex binds to mTOR and prevents downstream signalling.[52] The cancer cell's cell cycle is arrested at the G_1-phase and angiogenesis is inhibited.[52]

Everolimus and temsirolimus are indicated for palliative monotherapy treatment of advanced renal cell cancer.[13]

Side effects[13]

- Infections
- Rhinitis
- Folliculitis
- Pneumonia
- Anaemia, thrombocytopaenia
- Neutropaenia, leukopaenia, lymphopaenia
- Allergic reactions
- Dyspnoea, cough, epistaxis
- Anorexia
- Hyperlipidaemia, hyperglycaemia, hypercholesterolaemia
- Hypokalaemia, hypophosphataemia
- Dysgeusia
- Conjunctivitis
- Hypertension, venous thrombo-embolism

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

10. IMiDs

Thalidomide was developed in the first half of the 1950s as a sedative and hypnotic anti-emetic drug to treat morning sickness in the first trimester of gestation, but was removed from the market after discovery of its teratogenic effects.[53,54] Since then, findings of thalidomide's anti-angiogenic properties have led to the investigation of thalidomide as an anticancer agent in patients with vascular tumours.[53,54] Although the precise mechanism of action is not understood, thalidomide as an anti-angiogenic agent leads to the development of new immunomodulatory agents (IMiDs), with thalidomide as the parent compound with possibly fewer side effects.[53,54] The use of thalidomide is restricted to patients and/or doctors and pharmacists in the Pharmion Risk Management Programme (PRMP) and indicated for use in multiple myeloma.[13]

Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties.[142] Lenalidomide is indicated for the treatment of multiple myeloma, in combination with dexamethasone, in patients who have received at least one prior therapy. It is also indicated for transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a 5q deletion abnormality with or without additional cytogenetic abnormalities and mantle-cell lymphoma patients whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

Side effects[13]

- Teratogenesis
- Sedation
- Constipation
- Asthenia
- Peripheral neuropathy
- Orthostatic hypotension
- Neutropaenia
- Severe skin reactions
- Leukopaenia
- Increased appetite
- Mood changes
- CNS effects, cardiac arrhythmias
- Bradycardia/tachycardia
- Thrombo-embolisms
- GI disturbances

- Allergic reactions
- Facial oedema
- Photosensitivity
- Menstrual irregularities
- Peripheral oedema

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or Manufacturer's product literature.

11. HORMONES

Hormonal therapy is considered as effective as chemotherapy in hormone-sensitive cancers as it involves the manipulation of the endocrine system through administration of specific hormones or drugs that alter the production or activity of these hormones, and therefore influences the growth and survival rate of sensitive cancers.[26]

ANTI-OESTROGENS

Selective oestrogen receptor modulators (SERMs)

Selective oestrogen receptor modulators (SERMs), such as tamoxifen and toremifene, competitively bind to oestrogen receptors, opposing the peripheral effects of oestrogen on receptive tissues such as oestrogen-sensitive tumours, breast and other tissue.[4,26]

Steroid hormones, such as oestrogen, influence normal physiology by regulating cell growth and differentiation by influencing gene transcription and DNA synthesis.[38] The SERM-receptor nuclear complex prevents DNA synthesis and therefore inhibits oestrogen's effects on hormone-sensitive tissues.[26]

SERMs halt cancerous cells in the G_0 and G_1 phases of the cell cycle, preventing cell growth.[26]

Tamoxifen and toremifene are indicated for the treatment of metastatic breast cancer in postmenopausal patients with oestrogen-receptor positive or unknown tumours.[4,55] Recent studies indicate that tamoxifen may counteract drug resistance mechanisms in drug-resistant ovarian cancer.[95]

Side effects[4,55]

- Hot flushes
- Oedema
- Vaginal bleeding
- Pruritus vulvae
- GI disturbances
- Dizziness
- Rashes
- Hypercalcaemia
- Tumour pain
- Thrombocytopaenia and leukopaenia
- Headache
- Depression
- Fatigue

- Confusion
- Leg cramps
- Alopecia
- Dry skin

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

Pure oestrogen receptor antagonists

Fulvestrant is a pure oestrogen receptor antagonist, therefore competing with oestrogen for the receptor.[56] Unlike the SERMs, fulvestrant downregulates the oestrogen receptor itself.[56] Fulvestrant is indicated for the treatment of hormone-receptor-positive metastatic breast cancer in postmenopausal women with disease progression following anti-oestrogen therapy.[57]

Side effects of fulvestrant include injection-site pain, musculoskeletal pain, nausea and vomiting, arthralgia, headache, fatigue, hot flushes, anorexia, asthenia, cough, dyspnoea and constipation.[57]

AROMATASE INHIBITORS

In premenopausal women, most of the oestrogen is synthesised in the ovaries.[58] In postmenopausal women, oestrogen is mainly synthesised in the adrenal, muscle and adipose tissue.[58,59] Breast adipose tissue is able to synthesise a significant amount of oestrogen, a potent inducer of tumour proliferation in women with oestrogen-receptor-positive breast cancer.[59] Adipose oestrogen biosynthesis is catalysed by the enzyme aromatase where androgens (androstenedione and testosterone) are converted into oestrogens (oestrone and oestradiol).[58,59] Aromatase inhibitors prevent the conversion of androgens into oestrogens and have demonstrated efficacy in patients with breast cancer resistant to anti-oestrogens.[59]

Aromatase inhibitors are categorised as steroidal or nonsteroidal inhibitors.[59] Steroidal-type aromatase inhibitors irreversibly bind to the active site of the enzyme, whereas nonsteroidal aromatase inhibitors bind competitively and reversibly to aromatase enzymes.[59]

Nonsteroidal aromatase inhibitors

Indications[60,61]

Anastrozole

- Adjuvant treatment of postmenopausal women with hormone-receptor-positive early breast cancer
- First-line treatment of postmenopausal women with hormone-receptor-positive or hormone-receptor-unknown locally advanced or metastatic breast cancer
- Second-line treatment of advanced breast cancer in postmenopausal women with disease progression, following tamoxifen therapy

Letrozole

- Adjuvant treatment of postmenopausal women with hormone-receptor-positive early breast cancer
- Extended adjuvant treatment of early breast cancer in postmenopausal women, who have received five years of adjuvant tamoxifen therapy
- First-line treatment of postmenopausal women with hormone-receptor-positive or unknown locally advanced or metastatic breast cancer
- Treatment of advanced breast cancer in postmenopausal women with disease progression following anti-oestrogen therapy

Side effects[60,61]

- Hot flushes
- Asthenia
- Arthritis
- Pain
- Arthralgia
- Pharyngitis
- Hypertension
- Depression
- Nausea and vomiting
- Rash
- Osteoporosis
- Fractures
- Musculoskeletal pain
- Headache
- Peripheral oedema
- Increased cough
- Dyspnea
- Pharyngitis
- Lymphoedema

Steroidal aromatase inhibitors

Indications[62]

Exemestane

- Treatment of advanced breast cancer in postmenopausal women in

whom disease has progressed following tamoxifen therapy

Side effects[62]

- Increased sweating
- Fatigue
- Hot flushes
- Pain
- Flu-like symptoms
- Oedema
- Hypertension
- CNS effects
- Nausea and vomiting
- GI disturbances
- Dyspnoea and coughing

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

GNRH AGONISTS

Gonadotropin-releasing hormone (GnRH) agonists mimic the hormone GnRH, which in turn controls human reproductive physiology.[4,63] Binding of the GnRH to its receptor results in the release of the gonadotropin hormones, namely luteinising hormone (LH) and follicle-stimulating hormone (FSH), which in turn are responsible for spermatogenesis and testosterone production in males, and ovulation and oestradiol production in females.[4]

The potency, dose and duration of treatment with a GnRH agonist will determine whether gonadotropin hormones are released (a pro-fertility effect) or the release prevented (antifertility effect) a decrease in LH and FSH and decreased serum testosterone and oestradiol levels.[63]

Intermittent administration of a GnRH agonist, increases LH and FSH, but chronic administration of a potent GnRH agonist (such as the GnRH agonists listed below) results in inhibition of GnRH secretion and suppression of ovarian and testicular steroidogenesis.[4,64,65]

Indications[64-67]

Leuprolide

- Palliative treatment of advanced prostate cancer
- Adjuvant therapy to surgery in breast cancer

Buserelin

- Palliative treatment of hormone-dependent advanced prostate cancer

Goserelin

- In combination with flutamide for the management of locally confined carcinoma of the prostate
- Palliative treatment of advanced prostate cancer
- Palliative treatment of advanced breast cancer in pre- and perimenopausal women

Triptorelin

- Palliative treatment of hormone-dependent prostate cancer

Side effects[64,66,67]

- A transient increase in serum concentration of testosterone during the first weeks of treatment may occur in patients with prostate cancer, with worsening of symptoms or onset of new symptoms such as bone pain, neuropathy, haematuria, ureteral- or bladder-outlet obstruction
- CNS effects
- Cardiovascular risk
- Reduced glucose tolerance
- Anaemia
- Hepatic impairment
- Hypersensitivity reactions
- Decreased bone-mineral density
- Hot flushes
- Sexual dysfunction
- Lethargy
- Oedema
- Upper respiratory infection and chronic obstructive pulmonary disease
- Sweating
- Anorexia

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

ANTI-ANDROGENS

Anti-androgens compete with endogenously produced and exogenously supplied androgens for the androgen receptors at the target organs. Stimulating effects of the androgens on receptive tissue are therefore prevented and further production of androgens is diminished due to a reduction in GnRH release.[68-70]

Indications[68-70]

Cyproterone acetate

- Anti-androgen treatment in inoperable prostate cancer

Flutamide

- Use in combination with GnRH agonists for the management of locally confined stage B_2-C and stage D_2 metastatic prostate cancer

Bicalutamide

- Use in combination therapy with GnRH agonists for the treatment of stage D_2 metastatic prostate cancer

Side effects[68-70]

- Hepatic toxicity
- Impotence
- Gynaecomastia
- Reduction in the functioning of the adrenal cortex
- Lethargy
- Mood changes and CNS effects
- Weight gain
- Hot flushes
- Hypertension
- GI disorders
- Anaemia, leukopaenia and thrombocytopaenia

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

Enzalutamide

Enzalutamide is an androgen-receptor inhibitor that acts on different steps in the androgen-receptor signalling pathway.[127] Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen-receptor nuclear translocation and interaction with DNA. Enzalutamide is indicated for the treatment of patients with metastatic castration-resistant prostate cancer.

PROGESTOGENS

The anticontraceptive, medroxyprogesterone acetate, is a progesterone derivative.[71] Medroxyprogesterone acetate is indicated for use as adjunctive therapy and palliative treatment of inoperable, recurrent, and metastatic endometrial or renal cancers or metastatic breast cancer.[71,93]

Medroxyprogesterone acetate decreases the release of GnRH and thus the secretion of FSH, LH and oestradiol.[71] Side effects of medroxyprogesterone acetate include menstrual irregularities and amenorrhoea, CNS effects, oedema, weight changes, cervical changes, cholestatic jaundice, breast tenderness and galactorrhoea, hypersensitivity and allergic reactions, nausea, somnolence and insomnia, acne, alopecia and hirsutism.[71]

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's drug literature.

SOMATOSTATIN

Lanreotide

Lanreotide is a somatostatin analogue indicated for long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy and treatment of patients with unresectable, well- or moderately differentiated, locally advanced or metastatic gastro-enteropancreatic neuro-endocrine tumours (GEP-NETs) to improve progression-free survival.[143] Lanreotide binds to the same receptors as the naturally occurring somatostatin with higher affinity. The inhibitory hormone somastatin inhibits the release of growth hormone, TSH, insulin and glucagon.

12. CORTICOSTEROIDS

Corticosteroids have a variety of applications in adjunctive cancer management. The clinical applications are mainly dependent on their pro-apoptotic properties, but these agents are also able to reduce inflammation, reduce the immune response, act as an anti-emetic and improve the overall wellbeing in critically ill patients.[103] Corticosteroids typically used include prednisone, prednisolone, dexamethasone and methylprednisolone.

CORTICOSTEROIDS IN COMBINATION WITH CHEMOTHERAPY

Research has shown that pharmacological doses of corticosteroids can inhibit growth of various tumour systems, with lymphoid cells being the most sensitive to their pro-apoptotic effects. Although the mechanism of action is not completely understood, these agents can be used in combination treatment for endocrine-responsive cancers.[103,104]

Cancers treated with corticosteroids include:

- ALL
- AML
- CLL
- CML
- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma
- Multiple myeloma
- Breast cancer
- Prostate cancer

CORTICOSTEROIDS AND ANTI-EMETICS

The basis for the anti-emetic potential of corticosteroids is unknown.[4] Methylprednisolone and prednisolone are usually combined with other anti-emetics such as the $5HT_3$ antagonists and NK1 antagonists for prevention of acute and delayed nausea and vomiting in patients receiving emetogenic chemotherapy regimens.[4,72]

CORTICOSTEROIDS IN PALLIATIVE CARE

Corticosteroids improve symptoms such as fever, sweating, lethargy and weakness. They are responsible for mild euphoria, improved appetite and an overall improvement in wellbeing. However, because of the side effects, only short-term treatment is possible.[103]

CORTICOSTEROIDS IN CENTRAL NERVOUS SYSTEM TUMOURS

Corticosteroids reduce peritumoral oedema from primary and metastatic brain and spinal cord tumours, alleviating symptoms in most cases.[103] The corticosteroid of choice is dexamethasone as it has no mineralocorticoid activity and is highly potent. It is important to note that corticosteroids may decrease capillary permeability and therefore the dose of a cytotoxic drug at the tumour site.

13. OTHERS

TRETINOINS

All-trans retinoic acid or tretinoin induces cytodifferentiation and decreased proliferation of acute promyelocytic leukaemia (APL) cells and is therefore indicated for the induction of remission in APL. It is also suitable for prevention in untreated patients or those who relapse after, or are refractory to, standard chemotherapy.[13,126]

VACCINES

Bacillus Calmette-Guérin (BCG) vaccine

The BCG is an attenuated, live culture preparation of the Bacillus of Calmette and Guérin (BCG) strain of *Mycobacterium bovis*.[136] Although the precise mechanism is unknown, BCG induces a granulomatous reaction at the local site of administration and is therefore used as treatment and prophylaxis against recurrent tumours in patients with carcinoma *in situ* of the urinary bladder, and to prevent recurrence of Stage TaT1 papillary tumours of the bladder at high risk of recurrence.

PROCARBAZINE

The precise mechanism of action of procarbazine is not known, but it has been shown to inhibit DNA, RNA and protein synthesis.[141]

Procarbazine is used as part of the MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) regimen in the treatment of stage III and IV Hodgkin's disease.

RADIUM-223 DICHLORIDE

The alpha particle-emitting isotope radium-223 (radium Ra-223 dichloride) mimics calcium and forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases.[143]

The high linear energy transfer of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in an anti-tumour effect on bone metastases. The alpha particle range from radium-223 dichloride is less than 100 micrometres (less than 10 cell diameters), which limits damage to the surrounding normal tissue.

Radium-223 dichloride is indicated for the treatment of men with castration-resistant prostate cancer and symptomatic bone metastases and no known visceral metastatic disease.

14. SUPPORTIVE CARE

ANTI-EMETICS

Nausea and vomiting are among the most common and unpleasant side effects of chemotherapy.[72]

The vomiting centre, located in the medulla, controls the act of vomiting.[4] The vomiting centre receives input from the chemoreceptor trigger zone situated outside the blood-brain barrier and is therefore accessible to emetogenic stimuli in the blood or cerebrospinal fluid.[4] Neurotransmitters involved in emesis in the vomiting centre include muscarinic, histamine, neurokinin and serotonin, whereas the chemoreceptor trigger zone is rich in dopamine, opioid, serotonin and neurokinin.[4]

Identification of these neurotransmitters involved with emesis has led to the development of anti-emetic agents with affinity for the various receptors involved.[4]

5HT3 antagonists

Serotonin is the most important neurotransmitter in the initiation of chemotherapy-induced nausea and vomiting mainly due to stimulation of the peripheral 5-HT_3 receptors on extrinsic intestinal vagal and spinal afferent nerves.[4,72] 5-HT_3 receptor antagonists such as granisetron and palonosetron, not only prevent vagal and spinal input in the vomiting centre, but block the 5-HT_3 receptors in the vomiting centre and chemoreceptor trigger zone.[4]

Side effects[4,72]

- Headache
- Dizziness
- Constipation
- Prolongation of the QT-interval

NK1 antagonists

The neurokinin 1 (NK1)-receptor antagonist aprepitants' anti-emetic potential is due to the blockage of the NK1 receptors in the vomiting centre.[4] Aprepitant can be used in combination with 5-HT_3 blockers and corticosteroids for the prevention of acute and delayed nausea and vomiting from highly emetogenic chemotherapeutic regimens.[4]

Side effects[4,72]

- Fatigue
- Dizziness
- GI disturbances
- Hiccups

Dopamine antagonists

Dopamine antagonists are not very efficient as single agents in the prophylaxis of chemotherapy-induced nausea and vomiting and are rarely helpful in severe nausea and vomiting.[4,72] Dopamine antagonists such as metoclopramide and domperidone only block the D_2 dopamine receptors in the chemoreceptor trigger zone situated outside the blood-brain barrier.[4] These agents cannot readily cross the blood-brain barrier and therefore do not have the ability to act on the vomiting centre and have fewer extrapyramidal effects.[4] Prochlorperazine, an anti-psychotic, multi-potent receptor blocker, exhibits anti-emetic potential due to blockage of chemoreceptor trigger zone dopamine receptors and the central muscarinic receptors.[4] As prochlorperazine can cross the blood-brain barrier, it has more CNS effects.[4] The antipsychotic, droperidol, also possesses anti-emetic potential due to dopaminergic blockage and is highly sedating.[4]

Side effects[4,72]

- Extrapyramidal side effects
- Restlessness
- Drowsiness
- Insomnia
- Anxiety
- Agitation
- Hypotension

G-CSFs

Granulocyte-colony stimulating factors (G-CSFs) are haematopoietic growth factors indicated to prevent or treat neutropaenia in patients receiving chemotherapy for myelosuppressive cancers.[4] The recombinantly produced G-CSFs act on haematopoietic cells in the bone marrow and induce proliferation, differentiation, survival and activation of the phagocytic activity of neutrophils.[4,73] Filgrastim, lenograstim and pegfilgrastrim are all recombinantly produced G-CSFs indicated for accelerating the neutrophil counts following a variety of chemotherapy regimens.[4,73]

Side effects[4,74]

- Spleen rupture
- Allergic reactions
- Acute respiratory distress syndrome
- Bone pain

THROMBOPOIETINS

Romiplostim is a thrombopoietin peptibody indicated for the treatment of thrombocytopaenia in patients with chronic immune thrombocytopaenia who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy.[4,75]

Romiplostim is covalently linked to two antibody fragments and two Mpl- peptides.[4,75] The Mpl-peptide fragment of romiplostim is able to bind and activate the thrombopoietin receptor which activates intracellular transcriptional pathways and thereby increases platelet production.[4,75]

Side effects[75]

- Arthralgia
- Dizziness
- Insomnia
- Myalgia
- Pain in extremities
- Abdominal pain
- Shoulder pain
- Dyspepsia
- Paraesthaesia
- Headache

ERYTHROPOIETINS

Erythropoietin (EPO) interacts with erythropoietin receptors on red cell progenitors and stimulates erythroid proliferation and differentiation.[4]

Epoetin alfa and beta are forms of recombinant human EPO produced in a mammalian cell-expression system.[4,76] Epoetin alfa is indicated for the treatment of anaemia and reduction of transfusion in patients with non-myeloid malignancies where anaemia develops as a result of concomitantly administered chemotherapy.[76] Epoetin beta is indicated for the prevention and treatment of anaemia in adults with solid tumours and treated with platinum-based chemotherapeutics prone to induce anaemia, as well as treatment of anaemia in patients with multiple myeloma, low-grade non-Hodgkin's lymphoma or CCL with a relative erythropoietin deficiency receiving anti-tumour therapy.[77]

Side effects[4,76]

- Hypertension
- Thrombotic complications
- Allergic reactions
- Pure red cell aplasia accompanied by neutralising antibodies to erythropoietin

15. PAIN MANAGEMENT

There are two types of pain, namely nociceptive or somatic pain and neuropathic pain. Neuropathic pain includes a group of disorders with a variety of origins and symptoms.

NARCOTIC ANALGESICS

Narcotic analgesics are the drugs of choice in chronic and malignant pain, as they are able to alleviate intense pain, as well as the anxiety that sometimes accompanies it.[78] Narcotic analgesics mimic the effects of endogenous endorphins by binding to the opioid receptors in the central nervous system important in both acute and chronic pain.[78,79]

Narcotic analgesics interact mainly with three opioid receptors, namely mu, kappa and delta in the CNS, nerve terminals in the periphery and gastro-intestinal cells.[78,79] The analgesic properties of these agents are mainly attributable to their interaction with the mu receptors in the CNS and to a lesser extent, the kappa receptors in the dorsal horn.[78]

Narcotic analgesics can be classified according to their affinity for the mu receptors as either full or partial agonists (see Table 6).[78]

Side effects[78]

- Respiratory depression
- Euphoria
- Nausea and vomiting
- Sedation
- Sweating
- Urinary retention and constipation
- Chronic use can lead to dependence and tolerance
- Pinpoint pupils

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

COMBINATION ANALGESICS

For pain relief, nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are usually combined with paracetamol and/or weak opioid analgesics, such as codeine.[80,81] NSAIDs prevent the production of prostaglandins responsible for pain and inflammation by reversibly inhibiting cyclooxygenase (COX) enzyme 2.[80]

Ibuprofen is a commonly prescribed medication and is used in a variety of chronic painful states. Ibuprofen possesses anti-inflammatory, analgesic and antipyretic activity and can alter platelet function, but unlike aspirin does not irreversibly bind to COX enzyme.[80,81] Ibuprofen is therefore one of the preferred NSAIDs in the treatment of chronic conditions as its gastro-intestinal side effects are generally less when compared to aspirin.[4]

The mechanism of action of paracetamol is not entirely understood.[81] What is known is that it does not have the same mechanism of action as the other NSAIDs as it does not significantly inhibit prostaglandin synthesis.[81] Due to the lack of effective prostaglandin-synthesis inhibition, paracetamol does not have the ability to prevent or reduce inflammation and furthermore does not exhibit side effects associated with the reduction in prostaglandin synthesis.[81] A possible serious side effect of paracetamol which can occur with large doses is hepatotoxicity, which occurs when the glutathione stores in the liver are depleted and unable to bind the cytotoxic phase I metabolite of paracetamol. This may lead to liver damage.[81]

Codeine's analgesic properties are mainly attributable to its conversion of the prodrug (codeine) into its active form, morphine.[78] Although codeine is considered a strong opioid analgesic, only around 10% of codeine is metabolised into morphine.[78]

Table 6.78 Classification of narcotic analgesics

Full agonist at mu opioid receptors		Partial agonist at mu opioid receptors	Other
Strong Hydromorphone Morphine Fentanyl Oxycodone	**Moderate** Methadone Tilidine Tapentadol	Buprenorphine Pentazocine	Tramadol

Side effects[80]

General side effects are mainly due to COX-1 inhibition and prolonged use. The side effects are primarily gastro-intestinal, haematological and renal in nature.

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

ANTICONVULSANTS

Anti-epileptic drugs have proven to be effective in the treatment of diabetic neuropathy, post-herpetic pain, trigeminal neuralgia and other types of neuropathic pain disorders, such as cancer-related neuropathic pain.[82,83] It is important to note that complete pain relief is rarely achieved with anti-epileptic drugs alone and the addition of an anti-epileptic or antidepressant in addition to an existing opioid analgesic is likely to result in modest analgesia, with the risk of more adverse effects.[82,83]

Anti-epileptic agents are classified as either first- or second-generation. The second-generation or newer drugs such as gabapentin and pregabalin are better tolerated, have fewer side effects and drug-drug interactions and cause less sedation compared to the first generation or older drugs.[82]

Research has shown a correlation between the pathophysiology of epilepsy, neuropathic pain and migraine and it is therefore believed that the mechanism of action responsible for the management of epileptic seizures is also responsible for analgesia.[82,83]

Gabapentin and pregabalin bind to the specific sites on voltage-dependent calcium channels located in the spinal cord. These agents inhibit the release of excitatory neurotransmitters and reduce glutamate availability at N-methyl-D-aspartate (NMDA) and non-NMDA receptors, reducing pain.[82]

Side effects[4]

- CNS effects
- Nausea
- Drowsiness
- Blurred vision
- Somnolence
- Ataxia
- Peripheral oedema
- Leukopaenia
- Impairment of liver function
- GI complications
- Dermatological complications
- Bleeding and platelet disorders
- Respiratory depression
- Reduction of plasma-sodium levels

16. OTHER

BISPHOSPHONATES

With cancer cells present in bone, accelerated osteoclast-mediated bone resorption can occur.[84] Bisphosphonates are stable synthetic analogues of pyrophosphate (PPi,) with their main function being to inhibit bone resorption, preventing loss of bone mass.[84,85] Bisphosphonates are therefore used to treat bone metastasis and multiple myelomas.[85]

Although bisphosphonates target the osteoclast-mediated bone resorption, new evidence suggests that bisphosphonates have anti-cancer properties as they are able to decrease cancer-cell adhesion and invasion, induce cancer-cell apoptosis, reduce cancer-cell viability and proliferation and exhibit anti-angiogenic effects.[84]

Bisphosphonates are divided into two classes, namely non-nitrogen-containing bisphosphonates (clodronate) and the more potent nitrogen-containing bisphosphonates (pamidronate, ibandronate and zoledronate).

Bisphosphonates bind to, and accumulate in, mineralised bone matrix after administration where they are released during resorption and are selectively internalised by osteoclasts, inducing apoptosis in these cells.[84,85]

Side effects

- Hypocalcaemia
- Lactic acid dehydrogenase elevations
- Increase in serum parathyroid hormone associated with bisphosphonate drug holiday
- Decrease in serum calcium
- Increase in serum alkaline phosphatase
- Increase in transaminases
- Reversible proteinuria
- Serum creatinine elevations
- Renal dysfunction
- Musculoskeletal pain
- Atrial fibrillation
- GI disorders
- Osteonecrosis of the jaw

IMIQUIMOD

Imiquimod is an immune-response modifier.[4,86] Imiquimod is indicated for the treatment of biopsy-proven primary basal cell carcinomas on the trunk, neck, and extremities.[4] Imiquimod is thought to stimulate peripheral mononuclear cells to cytokines, activating the local immune cells when applied topically. Side effects of imiquimod treatment are mainly localised inflammatory reactions to the applied areas.[4]

MESNA

Sodium-2-mercaptoethane sulphonate (MESNA) is a prophylactic agent given to reduce the risk of haemorrhagic cystitis induced by ifosfamide.[5,87] In the kidneys, MESNA interacts with the toxic ifosfamide metabolites, detoxifying the metabolites.[87] Side effects of MESNA therapy include headache, injection-site reactions, flushing, dizziness, nausea and vomiting, somnolence, GI upsets, fever, pharyngitis, hyperaesthesia, flu-like symptoms and coughing.[87]

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