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]

Table 1. Classification of DNA-alkylating agents

Nitrogen mustards	Ethyleneimines (aziridine)	Alkyl sulphonates	Nitrosoureas	Triazenes	Platinum co-ordination complexes	New/ other
■ Chlorambucil ■ Cyclophosphamide ■ Estramustine ■ Ifosfamide ■ Melphalan ■ Bendamustine ■ Chlormethine	■ Mitomycin-C ■ Thiotepa	■ Busulfan ■ Treosulfan	■ Carmustine ■ Streptozocin ■ Lomustine	■ Temozolomide	■ Carboplatin ■ Cisplatin ■ Oxaliplatin	■ Trabectedin ■ Dacarbazine

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 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

Chlormethine

- Mycosis fungoides-type cutaneous T-cell lymphoma[144]

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

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 ■ Hepatotoxicity and jaundice ■ Abnormal liver-function tests	■ Tremor ■ Muscle-twitching ■ Myoclonia ■ Confusion ■ Hallucinations ■ 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

- 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.
- 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 crosslink 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]

Table 3. General side effects of ethyleneimines[17]

Haemato-logical	Gastro-intestinal	Central nervous system	Dermato-logical	Respiratory	Miscellaneous
Haemoto-poietic depression	■ Nausea and vomiting ■ Diarrhoea ■ Abdominal pain ■ Anorexia ■ Dysuria ■ Urinary retention ■ Haemorr-hagic cystitis	■ Dizziness ■ Headache ■ Confusion	■ Allergic skin reactions ■ Skin hyper-sensitivity reactions ■ Skin depig-mentation	■ Laryngeal oedema ■ Asthma ■ Wheezing ■ Apnoea	■ Fatigue ■ Weakness ■ Mutagenicity ■ Amenorr-hoea ■ Interference with sperm-atogenesis ■ Pain at injec-tion site ■ Conjunctivitis ■ Increased risk of secondary malignancies

TEPA showed a profound cytotoxic effect, but was chemically too unstable to be used in clinical practice.[5]

ThioTEPA (N,N',N''-triethylenethiophosphoramide), 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 antineoplastic antibiotic produced by *Streptomyces caespitosus* which selectively inhibits the synthesis of DNA and, at higher drug concentrations, RNA and protein synthesis too.[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

Thiotepa

Thiotepa is a conditioning treatment before haematopoietic stem-cell transplantation in the treatment of haematological disease or solid tumours, in combination with other chemotherapy.[144]

Side effects

As with all alkylating agents, ethyleneimines cause myelosuppression.[4]

Table 3 provides general side effects of ethyleneimines.

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]

Treosulfan, structurally related to busulfan, is indicated for the treatment of ovarian cancer, and as a conditioning treatment before allogeneic haematopoietic stem-cell transplantation in patients with both malignant and non-malignant diseases, in combination with other chemotherapy.[144]

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] The cytotoxicity of nitrosoureas 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.

Lomustine

- Indicated for Hodgkin's disease resistant to conventional therapy, malignant melanoma, and certain solid tumours.

Side effects

- Common or very common: leucopaenia
- Frequency unknown: alopecia, anaemia, apathy, decreased appetite, azotaemia, bone-marrow failure (delayed), confusion, abnormal coordination, diarrhoea, hepatic disorders, lethargy, nausea, neoplasms, neurological effects, renal disorders, renal impairment, respiratory disorders, speech impairment, stomatitis, thrombocytopaenia, vision loss (irreversible), vomiting
- Prolonged use of lomustine is associated with an increased incidence of acute leukaemias.

Contra-indications, special precautions and drug interactions: contraindicated in coeliac disease. Manufacturer advises effective contraception during and for at least 6 months after treatment in men or women. Avoid in pregnancy and discontinue breastfeeding. Avoid in severe renal impairment.

Streptozocin

- Indicated for neuro-endocrine tumours of pancreatic origin

Side effects

- Common or very common: Acute kidney injury, diarrhoea, nausea, nephropathy, renal tubular injury, urinary disorder, urine abnormalities, vomiting
- Frequency not known: confusion, depression, extravasation necrosis, fever, glucose-tolerance impairment, hepatotoxicity, hypo-albuminaemia, lethargy

Contra-indications, special precautions and drug interactions: The manufacturer advises women of childbearing potential to use effective contraception during the treatment and for 30 days after the last treatment; male patients should use effective contraception during the treatment and for 90 days after the last treatment if their partner is of childbearing potential. Avoid in pregnancy unless the

potential benefit outweighs the risk. Avoid breastfeeding. Exercise caution in hepatic impairment; dose adjustments may be necessary. Exercise caution in renal impairment, evaluate the benefit/risk ratio if eGFR is 30-45 ml/minute/1.73m^2; avoid if eGFR is less than 30 ml/minute/1.73m^2. The manufacturer advises monitoring renal function, proteinuria, serum electrolytes, liver-function tests, blood-glucose levels, and complete blood counts regularly.

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 intrastrand DNA adducts followed by interstrand 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 anti-tumour 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-HT3) 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]

- Metastatic colorectal cancer, in combination with 5-fluorouracil and folinic acid,
- 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 peri-operative 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.

Dacarbazine is an imidazole carboxamide derivative with structural similarity to certain purines; however, its primary mode of action appears to be alkylation of nucleic acids. Inhibition of DNA synthesis, owing to its action as a purine analogue and interaction with sulfhydryl groups, is also possible. Dacarbazine is indicated for the treatment of metastatic melanoma, soft-tissue sarcomas (in combination therapy), and Hodgkin's disease (in combination therapy). Dacarbazine is also a component of the commonly used combination for Hodgkin's disease known as ABVD, which includes doxorubicin, bleomycin, vinblastine, and dacarbazine.[144]

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 asparagine, 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 anti-tumour 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]

Raltitrexed is a thymidylate synthase inhibitor. It is indicated for the palliation of advanced colorectal cancer, especially in situations where fluorouracil and folinic acid are not suitable treatment options.[144]

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]

Clofarabine is metabolised intracellularly to an active metabolite that inhibits DNA synthesis by acting on ribonucleotide reductase and DNA polymerases. This leads to depletion of the intracellular de-oxynucleotide triphosphate pool and increased incorporation of clofarabine triphosphate into DNA, intensifying DNA-synthesis inhibition. Clofarabine also inhibits DNA repair by incorporating into the DNA chain during repair. Additionally, clofarabine disrupts mitochondrial membrane integrity, releasing pro-apoptotic proteins and inducing programmed cell death.

Nelarabine is a nucleoside analog that, once metabolised into its active form, ara-GTP, accumulates in leukaemic blasts and incorporates into DNA, exerting its cytotoxic effects during the S-phase of the cell cycle, leading to fragmentation and apoptosis. Ara-GTP competes with the endogenous de-oxyGTP (dGTP) for incorporation into DNA. Unlike some other nucleoside analogs, ara-GTP has an intact 3'-OH group, allowing it to be incorporated into the growing DNA strand without causing absolute chain termination. However, the inclusion of ara-GTP in the DNA strand can impair proper DNA repair processes, the exact mechanism of which is not well understood, leading to inhibition of DNA elongation, apoptosis, and cellular destruction. Nelarabine may have additional cytotoxic activities, but these are not fully understood.[144]

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

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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
	Clofarabine	■ Relapsed or refractory acute lymphoblastic leukaemia in patients who have received at least two previous regimens	■ Neutropaenia ■ Nausea and vomiting ■ SCARs
	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
	Nelarabine	■ T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic lymphoma in patients who have relapsed or who are refractory after receiving at least two previous regimens	■ Nausea and vomiting ■ Hepatotoxicity

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-Thioguan-ine	■ 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
	Capecita-bine	■ 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
	Decitabine	■ Treatment of newly diagnosed acute myeloid leukaemia in patients over 65 years of age who are not candidates for standard induction chemotherapy. Administered by intravenous infusion. Dosage should be consulted in local protocol.	Anaemia, diarrhoea, epistaxis, fever, headache, hyper-sensitivity, increased risk of infection, leucopaenia, nausea, neutropaenia, sepsis, stomatitis, thrombocytopaenia, vomiting
	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 adenocarcinoma 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/neo-adjunctive chemotherapy (including an anthracycline-based regimen) unless gemcitabine is contra-indicated ■ Locally advanced or metastatic 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 combination with cisplatin[101]	■ Nausea and vomiting ■ Diarrhoea ■ Myelosuppression with anaemia and thrombocytopaenia ■ Constipation ■ Erythema ■ Ecchymosis ■ Petechiae ■ Rigors ■ Weakness ■ Hypokalaemia

Table 4. (cont.)

	Agent	Indication	Side effects
Pyrimidine analogues (continued)	Tegafur	■ First-line colorectal cancer with calcium folinate	■ Diarrhoea ■ Nausea and vomiting ■ Fatigue ■ Myelosuppression ■ Anaemia ■ Skin and nail changes
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

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 G1-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]

Decitabine is a prodrug that requires transport into cells and phosphorylation by distinct kinases to generate the active molecule 5-aza-2'-deoxycytidine-triphosphate, which is incorporated into DNA during replication. Once incorporated, decitabine is recognised as a substrate by DNA methyltransferase enzymes (DNMTs), specifically DNMT1, but due to the presence of an N5 rather than C5 atom, it traps the DNMT through the irreversible formation of a covalent bond. At low concentrations, this mode of action depletes DNMTs and results in global DNA hypomethylation, while at high concentrations, it additionally results in double-strand breaks and cell death. The therapeutic efficacy of decitabine is hypothesised to be due to the global hypomethylation it induces, resulting in the expression of previously silent tumour-suppressor genes. However, other putative mechanisms related to this change in DNA methylation include indirect alteration of transcription through effects on transcription factors, indirectly altering histone modifications and chromatin structure, and activating pathways involved in DNA-damage response. The overall effect of decitabine is a decrease in neoplastic cell proliferation and an increase in the expression of tumour-suppressor genes.[144]

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.

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 G2-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

Table 5. General side effects of vinca alkaloids[4,35]

Vincristine	Vinblastine	Vinorelbine	Vinflunine	Vindesine
■ 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 ■ Myelosuppression ■ Constipation ■ SIADH	■ Myelosuppression ■ Mucositis ■ Constipation ■ Diarrhoea ■ Loss of fertility	■ Myelosuppression ■ Neurotoxicity

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 damage by the formation of free radicals which bind and break double-stranded DNA.[25,34]

The use of these highly effective antitumour agents 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

Pixantrone

- Treatment of refractory or multiply-relapsed aggressive non-Hodgkin's B-cell lymphomas (monotherapy).

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 G2-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 agents vindesine and 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-G1 phasespecific.[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]

Vindesine

- Acute leukaemia
- Malignant lymphoma
- Hodgkin's disease
- Acute erythraemia
- Acute panmyelosis

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]
- Cervical cancer[99]

Contra-indications, special precautions and drug interactions: See *MIMS Monthly, MDR* or manufacturer's product literature.

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 G2-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 operable 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 anti-tumour 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

CYTOTOXIC ANTIBIOTICS

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 G2-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.

Mitomycin

Mitomycin is an antibiotic that exerts its anti-tumour effect by producing interstrand cross-links in DNA, inhibiting DNA synthesis. It is used for various indications, including recurrent superficial bladder tumours (by intravesical instillation) and several other types of cancer, such as upper gastro-intestinal, breast, non-small-cell lung, and pancreatic cancer (all by intravenous injection). Mitomycin causes delayed bone-marrow toxicity, and prolonged use may result in a cumulative effect. Common or very common side effects include bone-marrow disorders, cystitis, leucopaenia, nausea, respiratory disorders, and thrombocytopaenia. Contraceptive advice is required for those taking mitomycin, and it should be avoided during pregnancy (teratogenic in animal studies). Breastfeeding should be discontinued while taking this drug.[144]

HEDGEHOG PATHWAY INHIBITORS

Glasdegib

Glasdegib is a hedgehog pathway inhibitor used predominantly in the management of acute myeloid leukaemia, particularly when combined with low-dose cytarabine. Common or very common side effects associated with glasdegib encompass a broad spectrum, ranging from alopecia, anaemia, and appetite reduction to gastro-intestinal discomfort, skin reactions, and thrombocytopaenia. Patients taking glasdegib should exercise caution, especially when driving or performing skilled tasks, due to increased risks of fatigue, muscle cramps, pain, or nausea. Special attention must be directed towards conception and contraception: Both females of childbearing potential and male patients with partners who are pregnant or of childbearing potential are advised to use effective contraception methods, inclusive of condoms for males, during the course of treatment and for a minimum of 30 days post the final glasdegib dose.[144]

Vismodegib

Vismodegib is a hedgehog pathway inhibitor primarily used in the treatment of symptomatic metastatic basal cell carcinoma and locally advanced basal cell carcinoma, especially when surgery or radiotherapy is not deemed appropriate. Common or very common side effects associated with vismodegib span a wide range, including alopecia, amenorrhoea, reduced appetite, arthralgia, asthenia, constipation, dehydration, diarrhoea, gastro-intestinal discomfort, abnormal hair growth, muscle complaints, nausea, pain, skin reactions, altered taste, vomiting, and decreased weight. Special precautions must be taken regarding conception and contraception: Women of childbearing potential must confirm the absence of pregnancy before starting the medication and undergo monthly checks during treatment. Such women are required to use two contraceptive methods, one being highly effective and the other a barrier

method, during the treatment and for 24 months after the last dose of vismodegib. Men are advised to use condoms during treatment and for two months post-treatment. Vismodegib holds a significant teratogenic risk, potentially causing severe birth defects and embryo-foetal death. Breastfeeding is to be avoided during the treatment and for 24 months post-final dose. Patients with severe renal impairment should approach vismodegib with caution due to limited available information. Prescribers and pharmacists need to adhere strictly to the manufacturer's Pregnancy Prevention Programme, ensuring patients are well-informed and compliant with its preventive measures.[144]

HISTONE DEACETYLASE (HDAC) INHIBITORS

Panobinostat

Panobinostat is a histone deacetylase inhibitor that induces cell-cycle arrest and apoptosis in tumour cells through multiple pathways. It is prescribed for the treatment of relapsed or refractory multiple myeloma, especially in combination with bortezomib and dexamethasone, in patients who have previously undergone at least two treatments, including bortezomib and an immunomodulatory agent. The side effects of panobinostat can be extensive, the most common of which include anaemia, decreased appetite, arrhythmias, asthenia, gastro-intestinal discomfort, and many others. The manufacturer advises against its use during pregnancy due to animal-study toxicity and recommends avoiding it while breastfeeding. It is essential to employ effective contraception while on this medication. Patients should also be cautious when driving or performing skilled tasks, given the potential for dizziness. Monitoring is crucial, especially concerning full blood count, ECG, electrolytes, and hepatic function.[144]

METHYLHYDRAZINES

Procarbazine

Procarbazine, a mild monoamine oxidase inhibitor, is primarily indicated for the treatment of Hodgkin's lymphoma, administered orally. It is essential to adhere to local dosing protocols to prevent the risks associated with incorrect dosing of oral anti-cancer medications. The drug is contra-indicated in patients with severe leucopaenia and severe thrombocytopaenia. Caution is advised for those with cardiovascular or cerebrovascular diseases, epilepsy or phaeochromocytoma, and given the drug's action, dietary restrictions related to monoamine oxidase inhibition are rarely considered necessary. Common or notable side effects encompass decreased appetite, hepatic disorders, skin reactions, leucopaenia, nausea, and thrombocytopaenia, among others. It is imperative to offer contraceptive advice to individuals on procarbazine, and its use during pregnancy should be avoided due to teratogenic effects noted in animal studies and some human reports. Breastfeeding mothers are advised to discontinue nursing while on this medication, and individuals with significant hepatic or renal impairment should exercise caution or avoid the drug altogether.[144]

POLY (ADP-RIBOSE) POLYMERASE (PARP) INHIBITORS

Niraparib

Niraparib is a PARP enzyme inhibitor that disrupts cellular homeostasis, leading to cell death, and is predominantly used in the treatment of advanced ovarian, fallopian tube, and peritoneal cancers. Severe hypertension and posterior reversible encephalopathy syndrome (PRES) have been reported, especially in early treatment, necessitating regular blood-pressure monitoring and potential niraparib dose adjustments or discontinuation. Common side effects include anaemia, anxiety, hypertension, and gastro-intestinal discomfort, among others. Females taking niraparib should employ effective contraception during treatment and are advised to avoid pregnancy and breastfeeding. Additionally, patients should be cautious when driving or performing skilled tasks due to increased risks of dizziness and fatigue.[144]

Olaparib

Olaparib is a PARP inhibitor that targets enzymes responsible for repairing damaged DNA in cancer cells. Specifically, in the absence of functional BRCA, inhibiting PARP results in the inability of cancer cells to undergo repair, producing an antineoplastic effect. It is primarily indicated for the treatment of ovarian cancer, fallopian tube cancer, and peritoneal cancer. The drug is also employed for breast cancer, adenocarcinoma of the pancreas, and prostate cancer. Common or very common side effects of olaparib include agranulocytosis, anaemia, decreased appetite, cough, diarrhoea, dizziness, gastrointestinal discomfort, nausea, neutropaenic infection, skin reactions, and vomiting, among others. It is essential to note that females should use two methods of effective contraception during treatment and for one month after the last dose. Similarly, male patients should use effective contraception if their partner is pregnant or of childbearing potential. Pregnant individuals should avoid olaparib due to toxicity observed in animal studies, and breastfeeding should be avoided during treatment and for one month after the last dose. The manufacturer also advises patients to exercise caution when driving or performing skilled tasks due to the potential for malaise and dizziness.[144]

Rucaparib

Rucaparib is a PARP inhibitor that targets enzymes integral to the repair of damaged DNA in cancer cells. Specifically, when there is an absence of functional BRCA, inhibiting PARP leads to the inability of these cancer cells to undergo repair, resulting in a pronounced antineoplastic effect. It is indicated for the treatment of ovarian cancer, fallopian tube cancer, and peritoneal cancer. Common or very common side effects associated with rucaparib encompass a range, including anaemia, decreased appetite, asthenia, reduced leucocyte count, diarrhoea, dizziness, dyspepsia, dyspnoea, fever, hypercholesterolaemia, nausea, neutropaenia, photosensitivity reactions, skin reactions, altered taste, thrombocytopaenia, and vomiting. There are also rarer side effects, such as acute myeloid leukaemia and myelodysplastic syndrome, both warranting discontinuation of the drug, and memory loss. Women of childbearing potential taking rucaparib are advised to use effective contraception during treatment and for six months following the last dose. Due to observed toxicity in animal studies, it is recommended to avoid rucaparib during pregnancy. Additionally, breastfeeding should be halted during treatment and for two weeks after the last dose. It is crucial for patients to be cautious when engaging in driving or other skilled tasks due to increased risks of dizziness and fatigue. Regular monitoring, especially of the full blood count, is advised before starting the treatment and then monthly thereafter.[144]

Talazoparib

Talazoparib is a PARP inhibitor that targets enzymes responsible for repairing damaged DNA in cancer cells. Specifically, when functional BRCA is absent, inhibiting PARP prevents the cancer cells from repairing, resulting in an antineoplastic effect. This drug is primarily indicated for the treatment of breast cancer. Patients taking talazoparib may experience common side effects, such as alopecia, anaemia, reduced appetite, asthenia, decreased leucocytes, diarrhoea, dizziness, gastrointestinal discomfort, headaches, nausea, neutropaenia, stomatitis, altered taste, thrombocytopaenia, and vomiting. There are also cases of bone-marrow depression and neoplasms, although their frequency is not well known. Women of childbearing potential are advised to use effective contraception during treatment and for seven months post-treatment. Similarly, male patients should employ effective contraception during treatment and for at least four months post-treatment if their partner is of childbearing potential or pregnant. Talazoparib is considered toxic in animal studies, so it should be avoided during pregnancy. Furthermore, breastfeeding should

be discontinued during treatment and for one month after the last dose. The drug is not recommended for patients with moderate to severe hepatic impairment or those with a creatinine clearance less than 30 ml/minute, unless the benefits surpass the risks. Before initiating treatment, a full blood count should be monitored, and subsequent checks should be performed monthly or as clinically indicated.[144]

SENSITISERS USED IN PHOTODYNAMIC/ RADIATION THERAPY

Porfimer sodium

Porfimer sodium accumulates in malignant tissue and is activated by laser light to produce a cytotoxic effect. It is indicated for non-small-cell lung cancer and obstructing oesophageal cancer. Porfimer sodium is contraindicated in cases of acute porphyrias, broncho-oesophageal fistula, and tracheo-oesophageal fistula. Common adverse effects include anaemia, anxiety, reduced appetite, arrhythmias, asthenia, chest discomfort, confusion, constipation, cough, diarrhoea, dyspnoea, fever, fluid imbalance, gastro-intestinal discomfort and disorders, haemorrhage, heart failure, hypertension, hypotension, increased risk of infection, insomnia, nausea, oedema, oesophageal disorder, pain, photosensitivity reaction (where sunscreens are ineffective), respiratory disorders, sepsis, difficulty swallowing, tracheo-oesophageal fistula, vomiting, and weight loss. The manufacturer recommends avoiding the drug during pregnancy unless taking it is essential. While there is no specific information on safety during breastfeeding, it is advisable to avoid use. Patients with hepatic impairment should exercise caution; those with mild to moderate impairment may experience extended photosensitivity, and the drug should be avoided entirely in severe impairment cases. Crucially, patients and their caregivers must be aware of the increased risk of photosensitivity. They should avoid exposure of the skin and eyes to direct sunlight or intense indoor light for at least 30 days following treatment.[144]

Temoporfin

Temoporfin accumulates in malignant tissue, and, upon activation by laser light, produces a cytotoxic effect. It is indicated for the photodynamic therapy of advanced head and neck squamous cell carcinoma, especially in cases where other treatments are either refractory or unsuitable. Notably, it is contra-indicated in individuals with acute porphyrias, those undergoing concomitant photosensitising treatments, diseases exacerbated by light, those having elective surgery, and those undergoing ophthalmic slit-lamp examinations within 30 days after temoporfin administration. Common or very common side effects include anaemia, constipation, dizziness, dysphagia, fever, haemorrhage, headache, local infection, nausea, oedema, oral disorders, pain, paraesthesia, photosensitivity reactions (where sunscreens are ineffective), skin reactions, necrotising stomatitis, sunburn, and vomiting. Crucially, patients should be wary of photosensitivity; they should avoid direct exposure of the skin and eyes to sunlight or bright indoor light for at least 15 days post-administration. The injection-site arm should be protected from direct sunlight for up to 6 months after administration, and if extravasation occurs, the affected area should be shielded from light for a minimum of 3 months.[144]

OTHER ANTINEOPLASTIC AGENTS

Amsacrine

Amsacrine is indicated for the treatment of acute leukaemia that is refractory to anthracycline chemotherapy. It can be used either alone or in combination with other chemotherapy agents. Before initiating treatment with amsacrine, it is vital to correct any hypokalaemia due to the heightened risk of ventricular fibrillation. Common or very common side effects of amsacrine encompass a broad range, including abdominal pain, arrhythmias, cardiotoxicity, and vomiting, among others. Due to potential toxicity found in animal studies, it is advised to avoid amsacrine during pregnancy, and its use is also not

recommended while breastfeeding, given the lack of available data. Caution is urged in patients with hepatic or renal impairment because of the increased risk of toxicity. Regular monitoring, including full blood count, liver and renal functions, as well as electrolytes before each treatment, is critical. Additionally, patients should be closely observed for signs of cardiotoxicity during the course of treatment.[144]

Arsenic trioxide

Arsenic trioxide is specifically indicated for the treatment of acute promyelocytic leukaemia. Prior to treatment initiation, it is essential to correct conditions like hypokalaemia and hypomagnesaemia. Common or very common side effects of arsenic trioxide span a wide spectrum, including abdominal pain, arrhythmias, dizziness, and vomiting, among others. There is a notable risk of differentiation syndrome, characterised by symptoms such as unexplained fever and dyspnoea; this requires treatment with high-dose corticosteroids. The manufacturer advises both men and women to use effective contraception during treatment. Due to teratogenic and embryotoxic effects observed in animal studies, its use during pregnancy is discouraged. Breastfeeding should be discontinued while on this medication. Caution is advised in patients with hepatic or renal impairment due to limited available information. Monitoring requirements include an ECG before and during treatment.[144]

Mitotane

Mitotane is primarily indicated for the symptomatic treatment of advanced or inoperable adrenocortical carcinoma. It functions by selectively inhibiting the activity of the adrenal cortex, which necessitates the use of corticosteroid replacement therapy. Treatment with mitotane should be reduced or halted if signs of toxicity emerge, and it is advised to discontinue the drug if there is an inadequate response after 3 months. Common or very common side effects include adrenal insufficiency, anaemia, appetite decrease, dizziness, and nausea, among others. It is crucial to avoid mitotane during pregnancy and to discontinue breastfeeding while on the medication. Caution is also advised for patients with hepatic or renal impairments. Regular monitoring of plasma-mitotane concentration is essential for an optimal response. Furthermore, patients should be informed about the potential risks, including acute adrenal insufficiency, and the possible impact on skilled tasks like driving due to central nervous system toxicity.[144]

Pegaspargase

Pegaspargase is employed for the treatment of acute lymphoblastic leukaemia, often in combination with other antineoplastic drugs. Its mechanism of action involves breaking down the amino acid L-asparagine, which hinders the growth of malignant cells that cannot synthesise L-asparagine on their own. Common or very common side effects include abdominal pain, anaemia, hyperglycaemia, pancreatitis, and vomiting, among others. It is crucial to note that serious hypersensitivity reactions, including life-threatening anaphylaxis, can occur with pegaspargase. Therefore, it should only be administered with immediate access to resuscitation facilities. The manufacturer advises against its use during pregnancy unless essential and recommends avoiding it during breastfeeding. Moreover, those with severe hepatic impairment should avoid pegaspargase. Regular monitoring, such as measuring trough serum asparaginase activity levels and monitoring plasma and urine glucose levels, is essential during treatment. Patients and caregivers should be made aware of the potential risks, including the signs of pancreatitis and the effects on driving and performing skilled tasks due to the increased risk of confusion and somnolence.[144]

Pentostatin

Pentostatin is an antineoplastic agent that is used primarily in the treatment of hairy cell leukaemia, a rare type of chronic

leukaemia. Administered by intravenous injection or infusion, its mechanism of action involves inhibition of the enzyme adenosine deaminase, which leads to accumulation of adenosine and deoxyadenosine, thus impairing DNA synthesis and inducing cell death. Pentostatin is known to cause myelosuppression, immunosuppression, and a range of other side effects that may be severe, including agranulocytosis, anaemia, blood disorders, and bone-marrow disorders. Treatment should be withheld in patients who develop a severe rash and in those showing signs of neurotoxicity. Men should not father children during and for six months after treatment with pentostatin. It should be avoided during pregnancy (teratogenic in animal studies) and breastfeeding should be discontinued. Caution is advised in hepatic impairment, and it should be avoided if creatinine clearance is less than 60 ml/minute.[144]

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 stages III and IV Hodgkin's disease.[144]

Sotorasib

Sotorasib is a selective inhibitor of the kirsten rat sarcoma viral oncogene homolog (KRASG12C), blocks tumour-cell signalling, inhibits cell growth, and promotes apoptosis in tumour cells with a KRAS G12C mutation. It is specifically indicated for the treatment of non-small-cell lung cancer with the KRAS G12C mutation. Common or very common side effects include anaemia, decreased appetite, arthralgia, constipation, and many others. Due to toxicity observed in animal studies, it is advised to avoid sotorasib during pregnancy, and there are no available data for its use during breastfeeding. Monitoring of liver function is essential before treatment initiation, followed by periodic checks.[144]

Venetoclax

Venetoclax is a selective inhibitor of B-cell lymphoma-2 (BCL-2), targeting the anti-apoptotic protein overexpressed in tumour cells to initiate programmed cell death. It is primarily indicated for the treatment of chronic lymphocytic leukaemia and acute myeloid leukaemia. A risk of tumour lysis syndrome (TLS) is associated with venetoclax, even at low doses, emphasising the importance of a TLS risk assessment for all patients. Common or very common side effects include abdominal pain, anaemia, dizziness, and tumour lysis syndrome, among others. Women of childbearing potential are advised to ensure effective, non-hormonal contraception during and for 30 days post-treatment. The drug is not recommended during pregnancy due to observed toxicity in animal studies and when breastfeeding due to the absence of data. Special attention is required for patients with hepatic or renal impairment due to increased toxicity risks. Regular monitoring, including blood chemistry, is essential before starting treatment and after each dose increase. Patients are also advised to maintain hydration and be cautious about activities requiring focus due to the potential for dizziness and fatigue.[144]

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 (IFN-α) and interferon-beta (IFN-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 IFNs.[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), IFN-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-α 2a and IFN-α 2b 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 gastrointestinal stromal tumours has not been demonstrated.

Mifamurtide

Mifamurtide is an immunomodulator with anti-tumour activity, functioning through the activation of macrophages and monocytes. It is indicated for the treatment

of high-grade, resectable, non-metastatic osteosarcoma after complete surgical resection, when used in combination with chemotherapy. There are several cautions associated with mifamurtide, including asthma, chronic obstructive pulmonary disease (where prophylactic bronchodilator therapy should be considered), and a history of auto-immune, collagen, and inflammatory diseases. Common or very common side effects include alopecia, anaemia, anxiety, decreased appetite, arthralgia, asthenia, cancer pain, chest discomfort, chills, confusion, constipation, cough, and many others. Females are advised to use effective contraception during treatment and avoid pregnancy and breastfeeding.[144]

Talimogene laherparepvec

Talimogene laherparepvec is an oncolytic immunotherapy derived from the herpes simplex virus type 1. Its mechanism of action results in tumour lysis and the subsequent release of tumour-derived antigens. It is indicated for the treatment of unresectable metastatic melanoma in patients with no bone, brain, or visceral disease. The manufacturer recommends against the use of this drug in severely immunocompromised patients, such as those with severe congenital or acquired cellular and/or humoral immune deficiencies, due to the increased risk of disseminated herpetic infection. Additional cautions include the administration of antivirals, patients with auto-immune diseases, those who are immunocompromised, and patients with multiple myeloma due to the risk of plasmacytoma at the injection site. Side effects range from common to uncommon and include symptoms such as anaemia, anxiety, arthralgia, dizziness, fever, myalgia, skin reactions, and more. A notable side effect is the potential for necrosis or ulceration of tumour tissue, and if persistent infection or delayed healing develops, reassessment of the continued treatment may be necessary. Patients should be advised on the use of latex condoms during treatment, and the drug is not recommended during pregnancy or breastfeeding. Handling and storage of the drug require specific attention, and it should be stored frozen at temperatures of -90°C to -70°C. Both patients and their carers should be informed about the risks associated with the treatment and given guidelines on managing potential side effects, including risks associated with dizziness and confusion impacting driving and skilled tasks.[144]

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]

Amivantamab

Amivantamab is a human monoclonal antibody that targets and disrupts signalling in epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition factor (MET) receptor pathways. This action prevents tumour-cell progression and also causes immune-mediated tumour-cell death. It is indicated for use in non-small-cell lung cancer with activating EGFR exon 20 insertion mutations. Administration is by intravenous infusion, and premedication is recommended to minimse

the development of infusion-related reactions. Common or very common side effects include appetite decrease, asthenia, constipation, diarrhoea, dizziness, dry eye, electrolyte imbalance, eye discomfort, eye disorders, eye inflammation, facial swelling, gastro-intestinal discomfort, hypo-albuminaemia, increased risk of infection, infusion-related reaction, mucositis, myalgia, nail disorders, nausea, oedema, onycholysis, oral disorders, perineal rash, peripheral swelling, respiratory disorders, skin reactions, vertigo, vision disorders, and vomiting. Uncommon side effects include toxic epidermal necrolysis, and side effects where the frequency is unknown include back pain, dyspnoea, fever, muscle weakness, and pulmonary embolism. Females of childbearing potential should use effective contraception during treatment and for at least 3 months after the last treatment. It is advised to avoid use during pregnancy and breast-feeding. Patients should be advised to limit sun exposure during treatment and for 2 months after the last treatment, and to discontinue contact-lens use until worsening eye symptoms are evaluated.[144]

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]

Blinatumomab

Blinatumomab is an anti-lymphocyte monoclonal antibody that causes lysis of B lymphocytes. It is indicated for use in relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukaemia and in Philadelphia chromosome-negative acute lymphoblastic leukaemia in complete remission with minimal residual disease. Administration is by continuous intravenous infusion, and the dose should be consulted in the product literature. Cautions include aphasia, brain injuries (severe), cerebellar disease, dementia, elderly (limited information available), epilepsy, paresis, Parkinson's disease, patients who may need pre-medication to minimize adverse reactions, psychosis, seizure, severe hepatic impairment, severe renal impairment, and stroke.[144]

Cemiplimab

Cemiplimab is indicated for treating metastatic or locally advanced cutaneous squamous cell carcinoma. It is administered by intravenous infusion, and the dose should be consulted in the product literature. Severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients treated with cemiplimab. Healthcare professionals are advised to monitor patients for suspected severe skin reactions and exclude other causes. Patients should be advised to seek urgent medical attention if severe skin reactions occur. If a SCAR is suspected, cemiplimab therapy should be withheld and the patient referred to a specialist for diagnosis and treatment. Cemiplimab should be permanently discontinued for any grade confirmed SJS or TEN, and for any grade 4 SCAR. Caution is recommended when considering the use of cemiplimab in patients with a history of severe or life-threatening SCARs associated with other immunostimulant antineoplastic drugs.[144]

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]

Daratumumab

Daratumumab is a monoclonal antibody that binds to CD38, a cell-surface protein, resulting in tumour-cell death by immune-mediated actions and apoptosis. It is indicated for use in multiple myeloma. Administration can be by intravenous infusion or by subcutaneous injection, and the dose should be consulted in the product literature or local protocols. An EU cumulative review of worldwide data has identified reports of hepatitis B virus (HBV) reactivation in patients treated with daratumumab, including several fatal cases. Healthcare professionals are advised to screen all patients for hepatitis B before starting treatment. Those with positive serology should be monitored for signs of HBV reactivation during, and for at least 6 months after, treatment. Daratumumab should be stopped in patients with HBV reactivation and appropriate treatment initiated, based on expert advice.[144]

Dinutuximab

Dinutuximab beta is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myelo-ablative therapy and stem-cell transplantation, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease. It is administered by infusion, and the dose should be consulted in the product literature. Dinutuximab beta should only be administered when appropriately trained staff and resuscitation facilities are immediately available. Manufacturer advises pre-medication with an antihistamine, and to monitor closely, particularly during the first and second treatment course. Discontinue immediately if a reaction occurs and treat as indicated. The manufacturer advises pre-medication with non-opioid analgesics, gabapentin, and opioids.[144]

Dostarlimab

Dostarlimab is a humanised monoclonal antibody that binds to the programmed death-1 (PD-1) receptor, thereby potentiating an immune response to tumour cells. It is indicated for use in endometrial cancer. Common or very common side effects include adrenal insufficiency, anaemia, arthralgia, auto-immune haemolytic anaemia, chills, diarrhoea, enterocolitis, enterocolitis haemorrhage, fever, gastrointestinal disorders, hyperthyroidism, hypertransaminasaemia, hypothyroidism, infusion-related reaction, myalgia, nausea, pancreatitis, respiratory disorders, skin reactions, and vomiting. Uncommon side effects include diabetic keto-acidosis and eye inflammation.[144]

Elotuzumab

Elotuzumab is a monoclonal antibody that targets the signalling lymphocytic activation molecule family member 7 (SLAMF7) protein, thereby activating natural killer cells and mediating myeloma cell death. It is indicated for use in multiple myeloma in patients who have received at least one prior therapy (in combination with lenalidomide and dexamethasone). Secondary primary malignancies have been reported, and patients should be monitored for the development of secondary primary malignancy before and during treatment with elotuzumab.[144]

Isatuximab

Isatuximab is a monoclonal antibody that binds to the CD38 receptor, thereby potentiating an immune response to cancer cells. It is indicated for use in relapsed and refractory multiple myeloma in combination with pomalidomide and dexamethasone. The manufacturer advises pre-medication with dexamethasone, an antihistamine, and an anti-pyretic. Patients should be closely monitored for signs of infusion-related reactions during and after administration. In the event of a

hypersensitivity reaction, treatment should be stopped immediately and appropriate management initiated The manufacturer advises to monitor for the development of secondary primary malignancy before and during treatment with isatuximab and initiate treatment as indicated.[144]

Mogamulizumab

Mogamulizumab is a monoclonal antibody that binds to the CCR4 receptor, thereby potentiating an immune response to cancer cells. It is indicated for use in mycosis fungoides and Sézary syndrome.. Patients should be closely monitored for signs of infusion-related reactions during and after administration. In the event of a hypersensitivity reaction, treatment should be stopped immediately and appropriate management initiated. The manufacturer advises to monitor for the development of secondary primary malignancy before and during treatment with mogamulizumab.[144]

Obinutuzumab

Obinutuzumab is indicated for the treatment of previously untreated chronic lymphocytic leukaemia in patients for whom full-dose fludarabine-based therapy is unsuitable due to comorbidities. It is also indicated for the treatment of previously untreated advanced follicular lymphoma and for the treatment of follicular lymphoma in patients who did not respond or who progressed during or up to six months after treatment with rituximab or a rituximab-containing regimen. Hepatitis B infection and reactivation (including fatal cases) have been reported in patients taking obinutuzumab. The manufacturer advises screening all patients for hepatitis B before starting treatment. Those with positive serology should be monitored for signs of HBV-reactivation during, and for at least 6 months after, treatment.[144]

Pertuzumab

Pertuzumab is a recombinant humanised monoclonal antibody that acts by inhibiting the human epidermal growth factor receptor 2 protein (HER2) dimerisation. It is indicated for use in HER2-positive early-stage breast cancer (in combination with trastuzumab and chemotherapy) and in HER2-positive metastatic or locally recurrent unresectable breast cancer (in combination with trastuzumab and docetaxel).[144]

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]

Siltuximab

Siltuximab is a monoclonal antibody that inhibits interleukin-6 receptor binding. It is indicated for the treatment of multicentric Castleman's disease (MCD) in patients who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative. Cautions include patients at increased risk of gastro-intestinal perforation and severe infection. Siltuximab therapy should be discontinued permanently in the event of a severe infusion-related reaction, anaphylaxis, a severe allergic reaction, or the occurrence of cytokine-release syndrome. Mild to moderate infusion-related reactions may improve by temporarily reducing the rate or stopping the infusion. When restarting treatment, a reduced infusion rate and the administration of antihistamines, paracetamol, and corticosteroids may be considered.[144]

Tafasitamab

Tafasitamab is a monoclonal antibody that binds to CD19, a cell-surface antigen, resulting in lysis of B lymphocytes by immune-mediated actions and apoptosis. It is indicated for use in diffuse large B-cell lymphoma.[144]

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 G1-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 overexpressed 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 where 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 neo-adjuvant 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 where 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 in patients 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 anti-angiogenic 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 neo-adjuvant 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 neo-adjuvant 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

Cemiplimab

Cemiplimab is indicated for treating metastatic or locally advanced cutaneous squamous cell carcinoma. It is administered by intravenous infusion, and the dose should be consulted in the product literature. Severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients treated with cemiplimab. Healthcare professionals are advised to monitor patients for suspected severe skin reactions and exclude other causes. If a SCAR is suspected, cemiplimab therapy should be withheld and the patient referred to a specialist for diagnosis and treatment. Cemiplimab should be permanently discontinued for any grade confirmed SJS or TEN, and for any grade 4 SCAR. Caution is recommended when considering the use of cemiplimab in patients with a history of severe or life-threatening SCAR associated with other immunostimulant antineoplastic drugs.[144]

Dostarlimab

Dostarlimab is a humanised monoclonal antibody that binds to the programmed death-1 (PD-1) receptor, thereby potentiating an immune response to tumour cells. It is indicated for use in endometrial cancer. Common or very common side effects include adrenal insufficiency, anaemia, arthralgia, auto-immune haemolytic anaemia, chills, diarrhoea, enterocolitis haemorrhage, fever, gastro-intestinal disorders, hyperthyroidism, hypertransaminasaemia, hypothyroidism, infusion-related reaction, myalgia, nausea, pancreatitis, respiratory disorders, skin reactions, and vomiting. Uncommon side effects include diabetic ketoacidosis and eye inflammation.[144]

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 neo-adjuvant 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]

Belantamab

Belantamab mafodotin is an antibody-drug conjugate that contains belantamab linked to mcMMAF, a cytotoxic microtubule disrupting agent. It is indicated for use in multiple myeloma. Common or very common side effects include anaemia, decreased leucocytes, diarrhoea, dry eye, eye discomfort, eye inflammation, fever, increased risk of infection, and infusion-related reactions. Patients should be advised to administer preservative-free artificial tears at least four times daily during treatment and to avoid wearing contact lenses until treatment is completed.[144]

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

Gemtuzumab

Gemtuzumab ozogamicin is a monoclonal antibody that binds to CD33-expressing tumour cells to induce cell-cycle arrest and apoptotic cell death. It is indicated for use in CD33-positive acute myeloid.[144]

Inotuzumab

Inotuzumab ozogamicin is a monoclonal antibody that binds to CD22-expressing tumour cells to induce cell-cycle arrest and apoptotic cell death. It is indicated for use in relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia. Contra-indications include prior confirmed severe or ongoing sinusoidal obstruction syndrome. Cautions include a history of, or predisposition to, QT-interval prolongation, patients who may need pre-medication to minimise adverse reactions, patients undergoing haematopoietic stem-cell transplantation (increased risk of hepatotoxicity).[144]

Polatuzumab

Polatuzumab vedotin is an antibody-drug conjugate that contains polatuzumab covalently linked to MMAE, a cytotoxic microtubule disrupting agent. It is indicated for use in relapsed or refractory diffuse large B-cell lymphoma (in combination with bendamustine and rituximab). Contra-indications include active severe infection. Cautions include a high tumour burden, risk of tumour lysis syndrome, patients who may need pre-medication to minimise infusion-related reactions, peripheral neuropathy, and rapidly proliferating tumours. The manufacturer advises pre-medication with an antihistamine and antipyretic to minimise the development of infusion-related reactions.[144]

Radio-labelled MAbs

The radio-labelled 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.

Sacituzumab

Sacituzumab govitecan is an antibody-drug conjugate. The monoclonal antibody component, sacituzumab, binds to tumour-associated calcium signal transducer 2 (Trop-2) expressing cancer cells to deliver the linked topoisomerase I inhibitor component into the cells, leading to apoptosis and cell death. It is indicated for use in breast cancer. Patients and their carers should be advised to seek immediate medical attention if they have black stools, rectal bleeding, dehydration, or are unable to tolerate oral fluids.[144]

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]

Abemaciclib

Abemaciclib is a selective inhibitor of cyclin-dependent kinases 4 and 6, which leads to disruption of cancer-cell proliferation. It is indicated for the treatment of locally advanced or metastatic breast cancer. Common or very common side effects of abemaciclib include alopecia, anaemia, decreased appetite, decreased leucocytes, diarrhoea, dizziness, embolism and thrombosis, excessive tearing, fatigue, fever, infection, muscle weakness, nausea, neutropaenia, respiratory disorders, skin reactions, altered taste, thrombocytopaenia, and vomiting.[144]

Acalabrutinib

Acalabrutinib is a tyrosine kinase inhibitor indicated for the treatment of chronic lymphocytic leukaemia (CLL). Common or very common side effects of acalabrutinib include abdominal pain, anaemia, arrhythmias, arthralgia, asthenia, constipation, diarrhoea, dizziness, haemorrhage, and headache.[144]

Afatinib

Afatinib is a protein kinase inhibitor used for the treatment of locally advanced or metastatic non-small-cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations, in patients who have not previously been treated with EGFR tyrosine kinase inhibitors. Common or very common side effects of afatinib include decreased appetite, cystitis, dehydration, diarrhoea, dry eye, dyspepsia, epistaxis, eye inflammation, fever, hypokalaemia, muscle spasms, nausea, oral

disorders, paronychia, renal impairment, rhinorrhoea, skin reactions, altered taste, vomiting, and weight decrease.[144]

Alectinib

Alectinib is a tyrosine kinase inhibitor used for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer. Common or very common side effects of alectinib include acute kidney injury, anaemia, arrhythmias, constipation, diarrhoea, eye disorders, eye inflammation, hyperbilirubinaemia, musculoskeletal pain, myalgia, nausea, oedema, oral disorders, photosensitivity reaction, skin reactions, altered taste, vision disorders, vomiting, and weight increase.[144]

Alpelisib

Alpelisib is an alpha-specific class 1 protein kinase inhibitor used for the treatment of locally advanced or metastatic breast cancer (in combination with fulvestrant) in postmenopausal women and men. Common or very common side effects of alpelisib include acute kidney injury and alopecia.[144]

Avapritinib

Avapritinib is a tyrosine kinase inhibitor used for the treatment of gastro-intestinal stromal tumours. Common or very common side effects of avapritinib include abdominal pain, acute kidney injury, alopecia, anaemia, anxiety, decreased appetite, arthralgia, ascites, asthenia, and back pain.[144]

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.

Binimetinib

Binimetinib inhibits the mitogen-activated protein kinase (MAPK) pathway, specifically mitogen-activated extracellular kinases MEK 1 and 2, thereby inhibiting BRAF V600 mutation-positive cell growth. It is indicated for the treatment of unresectable or metastatic melanoma with a BRAF V 600 mutation (in combination with encorafenib).[144]

Bosutinib

Bosutinib is indicated for the treatment of previously treated chronic, accelerated, and blast phase Philadelphia chromosome-positive chronic myeloid leukaemia (CML), as well as newly diagnosed chronic phase Philadelphia chromosome-positive CML.[144]

Brigatinib

Brigatinib is a tyrosine kinase inhibitor used for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer. Common or very common side effects of brigatinib include anaemia, decreased appetite, arrhythmias, arthralgia, asthenia, cataract, chest discomfort, constipation, cough, diarrhoea, dizziness, dry mouth, dyspnoea, electrolyte imbalance, eye disorders, eye inflammation, facial swelling, and fever.[144]

Cabozantinib

Cabozantinib is used for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma. It is also used in combination with nivolumab for the treatment of advanced renal cell carcinoma. Common or very common side effects of cabozantinib include abdominal pain, acute kidney injury, alopecia, anaemia, anxiety, decreased appetite, arthralgia, ascites, asthenia, and back pain.[144]

Ceritinib

Ceritinib is a tyrosine kinase inhibitor with particular activity against anaplastic lymphoma kinase (ALK). It is indicated for the first-line treatment of ALK-positive advanced non-small-cell lung cancer and for ALK-positive advanced non-small-cell lung cancer previously treated with crizotinib.[144]

Cobimetinib

Cobimetinib is a mitogen-activated protein kinase (MAPK) inhibitor. It is indicated for the treatment of BRAF V600 mutation-positive unresectable or metastatic

melanoma (in combination with vemurafenib). Common or very common side effects of cobimetinib include anaemia and basal cell carcinoma.[144]

Crizotinib

Crizotinib is a tyrosine kinase inhibitor indicated for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer and ROS1-positive advanced non-small-cell lung cancer. Common or very common side effects of crizotinib include anaemia and decreased appetite.[144]

Dabrafenib

Dabrafenib is a BRAF kinase inhibitor that inhibits BRAF V600 mutation-positive melanoma cell growth. It is indicated for the treatment of unresectable or metastatic melanoma with a BRAF V 600 mutation (as monotherapy or in combination with trametinib), and advanced non-small cell lung cancer with a BRAF V600 mutation (in combination with trametinib). Common or very common side effects of dabrafenib include alopecia, decreased appetite, arthralgia, asthenia, chills, constipation, cough, diarrhoea, fever, headache, hyperglycaemia, hypophosphataemia, influenza-like illness, myalgia, nausea, neoplasms, pain in extremities, photosensitivity reaction, skin reactions, and vomiting.[144]

Dacomitinib

Dacomitinib is a tyrosine kinase inhibitor that inhibits epidermal growth factor receptor (EGFR). It is indicated for the treatment of non-small-cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations. Common or very common side effects of dacomitinib include alopecia and decreased appetite.[144]

Encorafenib

Encorafenib inhibits the mitogen-activated protein kinase (MAPK) pathway, specifically BRAF kinase, thereby inhibiting BRAF V600 mutation-positive cell growth. It is indicated for the treatment of unresectable or metastatic melanoma with a BRAF V 600 mutation (in combination with binimetinib) and metastatic colorectal cancer with a BRAF V 600E mutation (in combination with cetuximab).[144]

Entrectinib

Entrectinib is a tropomyosin receptor kinase inhibitor. It is indicated for the treatment of solid tumours with neurotrophic tyrosine receptor kinase gene fusion and ROS1-positive advanced non-small-cell lung cancer. Common or very common side effects of entrectinib include abdominal pain, anaemia, anxiety, decreased appetite, arthralgia, asthenia, bone fractures, cognitive disorder, impaired concentration, confusion, constipation, cough, delirium, depression, diarrhoea, dizziness, drowsiness, dysphagia, dyspnoea, fever, fluid imbalance, abnormal gait, and hallucinations.[144]

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]

Fedratinib

Fedratinib is a kinase inhibitor with activity against Janus-associated tyrosine kinase JAK2 and FMS-like tyrosine kinase FLT3, thereby reducing the abnormal production of blood cells and associated symptoms. It is indicated for disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis. Common or very common side effects of fedratinib include anaemia, asthenia, constipation,

diarrhoea, dizziness, dyspepsia, dysuria, haemorrhage, headache, hypertension, muscle spasms, nausea, neutropaenia, pain, thrombocytopaenia, urinary tract infection, vomiting, and increased weight.[144]

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]

Gilteritinib

Gilteritinib is a FMS-like tyrosine kinase-3 (FLT3) inhibitor. It is indicated for the treatment of FLT3 mutation-positive acute myeloid leukaemia. Common or very common side effects of gilteritinib include acute kidney injury.[144]

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.

Idelalisib

Idelalisib is indicated for the treatment of chronic lymphocytic leukaemia and refractory follicular lymphoma. It is used in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia who have received at least one prior therapy, or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. It is also used as monotherapy for the treatment of adult patients with follicular lymphoma that is refractory to two prior lines of treatment. Common or very common side effects of idelalisib include colitis, diarrhoea, and fever.[144]

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]

Lorlatinib

Lorlatinib is a tyrosine kinase inhibitor indicated for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer. Common or very common side effects of lorlatinib include anaemia, anxiety, arthralgia, asthenia, abnormal behaviour, cognitive disorder, impaired concentration, confusion, delirium, dementia, depression, diarrhoea, and dyslipidaemia.[144]

Neratinib

Neratinib is a tyrosine kinase inhibitor used for the treatment of HER2-overexpressed/amplified breast cancer. It is indicated for adult patients with early-stage hormone receptor-positive HER2-overexpressed/amplified breast cancer who have completed adjuvant trastuzumab-based therapy less than one year ago. Common or very common side effects of neratinib include colitis, diarrhoea, and fever.[144]

Nintedanib

Nintedanib is a tyrosine protein kinase inhibitor. It is indicated for the treatment of idiopathic pulmonary fibrosis, chronic fibrosing interstitial lung disease with a progressive phenotype, and systemic sclerosis-associated interstitial lung disease. Common or very common side effects of nintedanib include abdominal pain, acute kidney injury, alopecia, anaemia, anxiety, decreased appetite, arthralgia, ascites, asthenia, and back pain.[144]

Osimertinib

Osimertinib is a tyrosine kinase inhibitor that inhibits the epidermal growth factor

receptor (EGFR). It is indicated for the treatment of EGFR T790M mutation-positive advanced non-small-cell lung cancer, untreated EGFR mutation-positive non-small-cell lung cancer, and adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection. Common or very common side effects of osimertinib include diarrhoea, eyelid pruritus, increased risk of infection, nail discolouration, nail disorders, respiratory disorders, skin reactions, and stomatitis.[144]

Palbociclib

Palbociclib is a highly selective inhibitor of cyclin-dependent kinases 4 and 6, which leads to disruption of cancer-cell proliferation. It is indicated for the treatment of locally advanced or metastatic breast cancer. Common or very common side effects of palbociclib include alopecia, anaemia, decreased appetite, asthenia, diarrhoea, dry eye, epistaxis, excessive tearing, fever, infection, leucopaenia, mucositis, nausea, neutropaenia, oral disorders, oropharyngeal complaints, respiratory disorders, skin reactions, altered taste, thrombocytopaenia, blurred vision, and vomiting.[144]

Pemigatinib

Pemigatinib is a protein kinase inhibitor that inhibits fibroblast growth factor receptors (FGFR). It is indicated for the treatment of cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement. Common or very common side effects of pemigatinib include alopecia and arthralgia.[144]

Ponatinib

Ponatinib is indicated for the treatment of chronic, accelerated, or blast-phase chronic myeloid leukaemia in patients who have the T315I mutation or who have resistance to or intolerance of dasatinib or nilotinib, and for whom subsequent treatment with imatinib is not clinically appropriate. It is also indicated for the treatment of Philadelphia-chromosome-positive acute lymphoblastic leukaemia in patients who have the T315I mutation or who have resistance to or intolerance of dasatinib, and for whom subsequent treatment with imatinib is not clinically appropriate. Common or very common side effects of ponatinib include anaemia, asthenia, constipation, diarrhoea, dizziness, dyspepsia, dysuria, haemorrhage, headache, hypertension, muscle spasms, nausea, neutropaenia, pain, thrombocytopaenia, urinary tract infection, vomiting, and increased weight.[144]

Ribociclib

Ribociclib is an inhibitor of cyclin-dependent kinases 4 and 6, which are involved in cancer-cell proliferation. Its inhibition results in the prevention of cancer-cell growth. It is indicated for the treatment of locally advanced or metastatic breast cancer. Common or very common side effects of ribociclib include alopecia, anaemia, decreased appetite, asthenia, diarrhoea, dry eye, epistaxis, excessive tearing, fever, infection, leucopaenia, mucositis, nausea, neutropaenia, oral disorders, oropharyngeal complaints, respiratory disorders, skin reactions, altered taste, thrombocytopaenia, blurred vision, and vomiting.[144]

Ruxolitinib

Ruxolitinib is a selective inhibitor of the Janus-associated tyrosine kinases JAK1 and JAK2. It is indicated for the treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis, or post-essential thrombocythaemia myelofibrosis. It is also indicated for the treatment of polycythaemia vera in patients resistant to, or intolerant of, hydroxyurea. Common or very common side effects of ruxolitinib include anaemia, bruising, constipation, dizziness, dyslipidaemia, flatulence, haemorrhage, headache, hypertension, increased risk of infection, intracranial haemorrhage, neutropaenia, sepsis, thrombocytopaenia, and increased weight.[144]

Selpercatinib

Selpercatinib is a protein kinase inhibitor that inhibits rearranged during transfection

(RET) fusion-positive proteins. It is indicated for the treatment of advanced thyroid cancer with RET alterations, previously treated RET fusion-positive advanced non-small-cell lung cancer, advanced RET-mutant medullary thyroid cancer, advanced RET fusion-positive thyroid cancer, and advanced RET fusion-positive non-small-cell lung cancer. Common or very common side effects of selpercatinib include abdominal pain and decreased appetite.[144]

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]

Tepotinib

Tepotinib is a kinase inhibitor that targets mesenchymal-epithelial transition (MET) factor gene, including variants with exon 14 skipping alterations, thereby inhibiting tumour-cell proliferation. It is indicated for the treatment of non-small-cell lung cancer with mesenchymal-epithelial transition factor gene (MET) exon 14 skipping alterations. Common or very common side effects of tepotinib include asthenia, constipation, diarrhoea, gastro-intestinal discomfort, hepatic disorders, hypoalbuminaemia, nausea, oedema, respiratory disorders, and vomiting.[144]

Tivozanib

Tivozanib is a tyrosine kinase inhibitor indicated for the treatment of advanced renal cell carcinoma. Common or very common side effects of tivozanib include alopecia, anaemia, and angina.[144]

Trametinib

Trametinib is a mitogen-activated protein kinase (MAPK) inhibitor. It is indicated for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma, in combination with dabrafenib. Common or very common side effects of trametinib include anaemia, basal cell carcinoma, and hypertension.[144]

Tucatinib

Tucatinib is a tyrosine kinase inhibitor that inhibits human epidermal growth factor receptor-2 (HER2). It is indicated for the treatment of HER2-positive breast cancer. Common or very common side effects of tucatinib include arthralgia, diarrhoea, epistaxis, hyperbilirubinaemia, nausea, oral disorders, oropharyngeal pain, rash pustular, skin reactions, vomiting, and decreased weight.[144]

Vandetanib

Vandetanib is a tyrosine kinase inhibitor. It is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Common or very common side effects of vandetanib include alopecia, anxiety, and decreased appetite.[144]

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.

Carfilzomib

Carfilzomib is an irreversible selective proteasome inhibitor that disrupts tumour-cell turnover and induces apoptosis. It is indicated for the treatment of multiple myeloma. Common or very common side effects of carfilzomib include anaemia, anxiety, decreased appetite, arrhythmias, arthralgia, asthenia, cataract, chest pain, chills, confusion, constipation, cough, decreased leucocytes, dehydration, diarrhoea, dizziness, dysphonia, dyspnoea, electrolyte imbalance, embolism and thrombosis, fever, flushing, gastro-intestinal discomfort, haemorrhage, headache, heart failure, hyperbilirubinaemia, hyperglycaemia, hyperhidrosis, hypertension, hyperuricaemia, hypo-albuminaemia, hypotension, increased risk of infection, influenza-like illness, infusion-related reaction, insomnia, malaise, muscle complaints, muscle weakness, myocardial infarction, nausea, neutropaenia, oropharyngeal pain, pain, palpitations, peripheral neuropathy, peripheral oedema, pulmonary hypertension, pulmonary oedema, renal impairment, respiratory disorders, abnormal sensation, sepsis, skin reactions, thrombocytopaenia, tinnitus, toothache, blurred vision, and vomiting.[144]

Ixazomib

Ixazomib is a proteasome inhibitor indicated for the treatment of multiple myeloma in patients who have received at least one prior therapy, in combination with lenalidomide and dexamethasone. Common or very common side effects of ixazomib include back pain, constipation, diarrhoea, increased risk of infection, nausea, neutropaenia, peripheral neuropathy (monitor for symptoms), peripheral oedema, skin reactions, thrombocytopaenia, and vomiting. Rare or very rare side effects include posterior reversible encephalopathy syndrome (PRES) (discontinue), Stevens-Johnson syndrome, thrombotic micro-angiopathy, transverse myelitis, and tumour lysis syndrome. Side effects of unknown frequency include decreased appetite, conjunctivitis, dizziness, dry eye, fatigue, hepatic disorders, and hypokalaemia.[144]

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 G1-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, anti-angiogenic, 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.

Pomalidomide, which is structurally related to thalidomide, is another drug that has shown promise in treating multiple myeloma. Pomalidomide possesses immunomodulatory properties and exhibits direct anti-myeloma tumoricidal activity. It is indicated for the treatment of relapsed and refractory multiple myeloma in patients who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and who have experienced disease progression during the last treatment. It is important to note

that pomalidomide can cause hepatitis B reactivation, and therefore hepatitis B virus status should be established in all patients before treatment initiation. Patients are also advised to monitor for signs and symptoms of thrombo-embolism, cardiac failure, and respiratory symptoms.[144]

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 G0 and G1 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
- 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
- Lympho-oedema

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 B2-C and stage D2 metastatic prostate cancer

Bicalutamide

- Use in combination therapy with GnRH agonists for the treatment of stage D2 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.

Apalutamide

Apalutamide is an androgen receptor inhibitor that decreases tumour cell proliferation and increases apoptosis. It is indicated in patients with hormone-relapsed non-metastatic prostate cancer who are at high risk of developing metastatic disease.

Darolutamide

Darolutamide is an androgen receptor inhibitor that decreases tumour-cell proliferation. It is indicated in patients with hormone-relapsed non-metastatic prostate cancer who are at high risk of developing metastatic disease.

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.

OESTROGENS

Diethylstilbestrol is synthetic nonsteroidal oestrogen used in the treatment of breast cancer in postmenopausal women and 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 gastroenteropancreatic neuro-endocrine tumours (GEPNETs) 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.

Octreotide

Octreotide is a somatostatin analogue indicated for the treatment of symptoms associated with carcinoid tumours with features of carcinoid syndrome, VIPomas, and glucagonomas. Octreotide is also indicated for acromegaly, short-term treatment before pituitary surgery, or long-term treatment in those inadequately controlled by other treatment or until radiotherapy becomes fully effective.

Pasireotide

Pasireotide is a somatostatin analogue indicated for the treatment of Cushing's disease when surgery has failed or is inappropriate. Pasireotide is also indicated for acromegaly when surgery has failed or is inappropriate, and control with another somatostatin analogue is inadequate.

OTHER HORMONE ANTAGONISTS AND RELATED AGENTS

Degarelix

Degarelix is a synthetic peptide derivative drug which binds to gonadotropin-releasing hormone (GnRH) receptors in the pituitary gland and blocks interaction with GnRH. This antagonism reduces luteinising hormone (LH) and follicle-stimulating hormone (FSH) which ultimately causes testosterone suppression. It is indicated for advanced hormone-dependent prostate cancer.

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]

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 5HT3 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/micrometre) 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-HT3 receptors on extrinsic intestinal vagal and spinal afferent nerves.[4,72] 5-HT3 receptor antagonists, such as granisetron and palonosetron, not only prevent vagal and spinal input in the vomiting centre, but block the 5-HT3 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-HT3 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 D2 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 cyclo-oxygenase (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

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

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]

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, injectionsite reactions, flushing, dizziness, nausea and vomiting, somnolence, GI upsets, fever, pharyngitis, hyperaesthesia, flu-like symptoms and coughing.[87]

REFERENCES AVAILABLE ON REQUEST