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Chapter 24.

AN INTRODUCTION TO ANTICANCER DRUGS

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Contents

24. An introduction to anticancer drugs

24.1 Introduction

Cancer is defined as a group of diseases which are characterised by uncontrolled cell proliferation and subsequent growth of abnormal tissue leading to profound changes in physiological function. Cancers can arise from both genetic and lifestyle factors that lead to abnormal regulation in the growth of particular stem cell populations or by the dedifferentiation of mature cell types. This aberrant control of cell division can lead to either a benign tumour, which does not spread to other parts of the body and as such is rarely life threatening or to a malignant tumour which can invade other organs, move to other bodily locations (metastasise) and become life threatening.

In the most recent overview of cancer statistics in Australia, it was noted that in 2005, over 100,000 new cases of cancer were diagnosed with over 39,000 deaths recorded in the same period. The major form of cancer affecting females is breast cancer which accounts for some 27% of all diagnoses in 2005. In males, the predominant cancer type is prostate cancer which

accounts for 29% of all diagnoses in 2005. In both sexes, the next biggest killers are colorectal cancer, lung cancer and melanoma. In all, these five types of cancer account for 60% of all cancer deaths in men and women. However, there have been great strides in the development of a raft of treatments which has led to improvement of survival times in sufferers although this has lead to increased disease prevalence. At the end of 2004, over 650,000 living persons had been diagnosed with cancer at some time in the previous 23 years (when national data collection began). This accounts for 1 in every 31 Australians. Indeed, one in three men and one in four women will develop some form of cancer by age 75, a risk that increases to one in two for men and one in three for women by age 85.

There are a number of options available for treatment of cancer with the preferred choice of therapy dependent upon location and type of tumour and the disease stage to which the cancer has progressed. Preferred treatment options include surgery to remove discrete, localised tumours such as those found in prostate and breast cancers; radiation therapy using ionizing radiation to kill cancer cells and shrink tumours (useful in the treatment of most solid tumours as well as leukaemia and lymphoma); and chemotherapy, the treatment of cancer cells with drugs to destroy them.

24.2 The rationale behind anticancer drug therapy

24.2.1 The special characteristics of cancer cells

It is the special characteristics of cancer cells that has been, and is still, the key to the development of pharmacological agents used to treat the disease**.** These characteristics include uncontrolled proliferation, dedifferentiation of cancer cells resulting in loss of function, invasiveness and the development of metastases.

In many cancer cells, the mechanisms of cell proliferation are not subject to the same regulatory processes found in non-cancerous cells. This leads to uncontrolled cell proliferation that usually results in an increase in cell multiplication although a reduction can also occur. Interruption of proliferative control leading to cancer generally occurs as a consequence of genetic changes or mutations. In particular (i) inactivation of genes, known as tumour suppression genes, that have the ability to suppress malignant changes and includes p53, pRB1, PTEN and CD95 and; (ii) activation of genes, known as protooncogenes, which normally control cell division, into tumour producing oncogenes and includes Src, Abl and Ros. Uncontrolled proliferation arising from these gene mutations leads to changes in growth factor signalling, in cell cycle function and in apoptosis (programmed cell death). To date, over 200 tumour suppression genes and protooncogenes have been discovered and shown to be involved in the evolution of cancers such as retinoblastoma, breast carcinoma, colon carcinoma, squamous cell carcinoma and chronic myelogenous leukaemia.

Cellular dedifferentiation occurs when there is a loss in the ability of progeny cells to carry out normal programmed cellular function, as a result of problems caused by faulty parent cells. Cancers caused by dedifferentiating cells are quick growing and have a poorer prognosis than well differentiated cancers.

Under normal conditions, cells tend not to be found outside their designated tissue of origin. Therefore liver cells are restricted to the liver, cortical neurones restricted to the brain and so on. Any cells escaping from their tissue location tend to undergo programmed cell death (apoptosis). However, cancer cell lose the ability to undergo apoptosis and can invade other cells within the tissue. For example, in rectal cancer, cancerous mucosal epithelial cells can

invade other cell layers of the rectum due their ability to secrete metalloproteinase enzymes that destroy the extracellular matrix. These translocated cells, coupled with a loss of apoptotic factors can lead to the formation of aggressive tumours.

Lastly, secondary tumours called metastases are formed by cancer cells that have been released from the initial primary site and transported to other sites via blood or the lymphatic system. Metastases are the principal cause of morbidity (the incidence of a disease) and mortality (death from the disease).

24.2.2 The principles of anticancer chemotherapy

The aim of drug treatment in patients with cancer is to eradicate the presence of malignant cells or, if this is not possible, provide effective palliation to lessen the severity of the symptoms. This may be achieved by causing a lethal cytotoxic event in the cancer cell that will arrest tumour progression. Targets for cytotoxic attack include inhibition of purine and pyrimidine synthesis, inhibition of DNA and RNA synthesis and chemical attack on the integrity of the structure of cellular DNA. Since these treatments inhibit the mechanisms of cell proliferation in general, they are toxic to both tumour cells and normal, non-cancerous proliferating cells. Thus selectivity of cytotoxic drugs has traditionally relied on the fact that in tumour tissue there is a higher proportion of cells undergoing division and proliferation that are susceptible to the effects of the drugs when compared to normal tissue. Proliferating cells in the bone marrow, gastrointestinal tract and hair follicles are particularly sensitive to many of these cytotoxic agents resulting in many of the adverse effects associated with these drugs (leukopaenia/low/loss of white blood cells, thrombocytopaenia/low/loss of platelets, nausea, vomiting, alopecia/hair loss).

However there are a number of problems associated with the use of drugs in chemotherapy. These include cytotoxicity, drug resistance and induction of new tumours. As mentioned above, by their very nature many anticancer drugs will target and kill normal cells as well as tumour cells, thus contributing to the common toxic manifestations of chemotherapy such as vomiting, alopecia and diarrhoea. Although these are generally transient side-effects and symptoms can be alleviated by the use of concomitant drug therapies such as anti-emetics, some more serious, irreversible adverse effects such as myelosuppression (i.e suppression of bone marrow leading to reduced synthesis of blood cells) and cardiac, bladder and pulmonary toxicities can occur.

Another common problem associated with the use of anticancer drugs is resistance of the tumour cells to the drug. Some cancers such as melanoma are inherently resistant to treatment whilst others tumour types may acquire resistance. Design of drug regimens that utilise short term, intensive intermittent therapy with combinations of drugs are effective in minimising drug resistance in most cases. Finally, since most anticancer drugs are mutagens, there is a danger of new cancers (neoplasms) arising following treatment. For example, occurrence of acute non-lymphoblastic leukaemia some ten years after treatment to cure an original tumour has been observed. This is a particular problem with use of the alkylating agent class of anticancer drugs.

24.3 Drugs used in cancer

Anticancer drugs are classified according to their sites of action at specific points in the biosynthetic pathways of important biomolecules. Some drugs are effective during specific parts of the cell cycle and are used in the treatment of high growth fraction malignancies such as blood cancers. The antimetabolites typify this group of drugs. Other anticancer drugs are

cell cycle non specific and are effective in the treatment of low growth fraction malignancies such as solid tumours. The alkylating agents are prime examples of this drug class.

24.3.1 Alkylating agents

Alkylating agents exert their cytotoxic effects through the transfer of their alkyl groups to a variety of cellular targets, the most notable being the nitrogenous bases of DNA, particularly the N7 position of guanine. These covalent additions result in either miscoding of the DNA or strand breakage. Although alkylating agents do not distinguish between proliferating and resting cells, they are most toxic for rapidly dividing cells. These agents are most effective when used in combination with other anticancer agents to treat a variety of lymphatic and solid tumours, however, alkylating agents have been shown to be mutagenic and carcinogenic and treatment with these drugs can lead to a second cancer such as leukaemia. In general, the alkylating agents form into two groups, the **nitrogen mustard agents** and the **nitrosureas** although others do exist.

The **nitrogen mustard group** of anticancer agents, typified by **cyclophosphamide** and the structurally related **ifosfamide**, are similar to mustard gas, a chemical warfare agent deployed in the First World War. Both drugs share most of the same toxicities and can be considered as prodrugs since they are normally taken orally and become active (and therefore cytotoxic) only after generation of their alkylating species, which are produced by hydroxylation in the liver by cytochrome P450. The hydroxylated intermediates undergo breakdown to form the active ingredients, acrolein and phosphoramide mustard, which interact with DNA to destroy the malignant cells. Cyclophosphamide is particularly useful in the treatment of Hodgkin's lymphoma, various leukaemias, adenocarcinoma of the ovary and retinoblastoma whilst ifosfamide is used to treat germ cell tumours, ovarian, cervical and breast cancers. The most common adverse effects of both drugs (after nausea, vomiting, diarrhoea and alopecia) are bone marrow depression and haemhorragic cystitis which can lead to fibrosis of the bladder. Secondary malignancies may appear years after initial treatment with these drugs.

The second group of alkylating agents, the **nitrosureas**, includes the closely related **carmustine** and **lomustine**. Both of these agents have the ability to penetrate into the central nervous system and, as such, are particularly useful in the treatment of brain cancers. They work in a similar way to the nitrogen mustards and exert their cytotoxic effects through alkylation of DNA bases that results in DNA strand cross-linking that inhibits DNA replication and eventually RNA and protein synthesis. Apart from the usual adverse effects (alopecia, nausea, vomiting, stomatitis), these agents have been demonstrated to cause myelosuppression, leukopaenia, thrombocytopaenia as well as liver, kidney and lung damage.

24.3.2 Cytotoxic antibiotics

Several antibiotics are widely used as anticancer drugs. They include a group of anticancer drugs known as the **anthracycline antibiotics**, typified by **daunorubicin** and its close structural compound **doxorubicin**, both isolated from *Streptomyces*. They owe their cytotoxic action principally to their ability to interact with DNA (intercalation) leading to a disruption of DNA function. The drugs insert non-specifically between adjacent base pairs in the DNA and bind to the phosphate-sugar backbone promoting local uncoiling and blocking DNA and RNA synthesis. In addition, these compounds are also able to inhibit the topoisomerase enzymes causing irreparable breaks in supercoiled DNA, further inhibiting DNA and RNA synthesis. Furthermore, oxygen free radical production by these agents also plays a major role in their cytotoxicity, although chronic administration can lead to cardiotoxicity because the heart lacks the catalase enzyme required to inactivate the oxygen free radicals.

Daunorubicin is used in the treatment of acute myeloblastic and acute lymphoblastic leukaemias, whilst doxorubicin, which is one of the most important and widely used anticancer drugs, is indicated for a number of cancers including breast and lung carcinomas and acute lymphoblastic leukaemia. Both drugs cause irreversible, dose dependent cardiotoxicity which is regarded as the major adverse effect associated with them although transient bone marrow suppression, stomatitis, vomiting and alopecia can also occur.

Another antibiotic used as a cancer therapeutic is **dactinomycin** which is isolated from soil bacteria of the genus *Streptomyces*. Similarly to daunorubicin and doxorubicin, dactinomycin intercalates into the minor groove of DNA forming a stable complex which interferes with RNA polymerase and inhibiting transcription. It is used in the treatment of Wilms' tumour and gestational choriocarcinoma (cancer of the placenta). The major adverse effective is bone marrow suppression, thus the drug is immunosuppressive. In addition, common adverse effects such as nausea, vomiting, diarrhoea, stomatitis and alopecia have been noted.

A final anticancer antibiotic is another *Streptomyces*-derived compound, **bleomycin**. This drug, unlike the other antibiotics described above, is cell-cycle specific and mediates its effects by causing superoxide-mediated single and double stranded breaks in DNA which results in a reduction in DNA synthesis and subsequent inhibition of cell division and growth. Bleomycin is used primarily in the treatment of testicular cancers, as part of a cocktail of other anticancer drugs including cisplatin and vinblastine. It is also effective, although not curative, for squamous cell carcinomas.

24.3.3 Antimetabolites

Antimetabolites are compounds that are structurally similar to normal cellular components. They exert their cytotoxic effects by blocking or subverting the pathways of DNA synthesis. They fall into two main classes; the folate antagonists or antifolates which interfere with nucleotide synthesis and the purine and pyrimidine analogues which are incorporated into DNA and affect the cell cycle.

The most widely used **antifolate** is **methotrexate** which is used in the treatment of acute lymphocytic leukaemia, choriocarcinoma, Burkitt's lymphoma, breast cancer as well as head and neck carcinomas. Methotrexate is an analogue of folic acid, a dietary compound which is a building block precursor for nucleotide (adenine, guanine, thymidine) and amino acid (methionine, serine) synthesis. Folic acid undergoes reduction to the tetrahydrofolate form via an enzymatic reaction catalysed by dihydrofolate reductase (DHFR) and it is this metabolite that undergoes subsequent reactions to form the essential nucleotides and amino acids. Methotrexate is an inhibitor of DHFR. This inhibition deprives the cell of tetrahydrofolate and subsequent metabolite production leading to depressed DNA, RNA and protein synthesis and ultimately cell death. Adverse reactions include renal, liver and pulmonary damage as well as the common adverse effects like nauseas, vomiting, diarrhoea and myelosuppression.

The other main class of antimetabolites are the **purine and pyrimidine analogues** which are inserted into DNA and subvert the cell cycle killing susceptible cells. Amongst the purine analogues are **6-mercaptopurine** which is used in the maintenance of remission of acute lymphoblastic leukaemia. 6-mercaptopurine is converted to 6-thioinosinic acid (TIMP) which blocks the synthesis of cellular purines. Furthermore, TIMP itself can be incorporated into RNA making it non-functional. Bone marrow depression is the common adverse effect

associated with 6-mercaptopurine although jaundice as a result of hepatotoxicity occurs in about one-third of patients. Anorexia, vomiting and diarrhoea have also been reported. A second purine analogue developed as an anticancer agent is **6-thioguanine** which is used in the treatment of acute non-lymphocytic leukaemia (usually in conjunction with other cytotoxic drugs). This drug is converted to nucleotide di- and triphosphate forms which inhibit the synthesis of cellular DNA. Bone marrow suppression is the major adverse effect associated with this drug.

5-fluoruricil (5-Fu) is a pyrimidine analogue indicated for use against slowly growing solid tumours (such as colorectal, breast, ovarian) and in the treatment of superficial basal cell carcinomas. 5-Fu is converted to 5-FdUMP which competes with the precursor of dTMP, dUMP for thymidylate synthase enzyme. This competition results in a decrease in dTMP which affects tumour cell DNA synthesis. As well as the common adverse effects associated with anticancer drugs, 5-Fu can cause severe ulceration of the oral and gastrointestinal mucosa. Other pyrimidine analogues used as anticancer drugs are **capecitabine** (metastatic breast cancer, colorectal cancer), **cytarabine** (acute nonlymphocytic leaukamia) and **gemcitabine** (pancreatic cancer, non-small cell lung cancer).

24.3.4 Microtubule inhibitors

The mitotic spindle is part of a larger intracellular network of microtubules that is formed during prophase in the cell cycle. This role of this larger network, termed the cytoskeleton, is to move cytoplasmic structures around the cell. The mitotic spindles, which comprise chromatin plus a system of tubulin microtubules, attach to the centromeres of the chromosomes and facilitate the equal partitioning of newly replicated DNA from the parent cell into the two daughter cells during anaphase in eukaryotic cell division. A number of plant-derived compounds, the microtubule inhibitors, are able to disrupt the assembly and disassembly mechanism of tubulin polymerisation thereby causing cytotoxicity.

The **microtubule inhibitors** comprise two groups, the **vinca alkaloids** and the **taxanes (taxols),** which can be distinguished by their different modes of action on the microtubule.
The **vinca alkaloids** comprise **vincristine** and **vinblastine**, which are structurally related compounds derived from the periwinkle plant, *Vinca rosa*, and **vinorelbine** which is a newer, less toxic semi-synthetic analogue. All three vinca alkaloids have the same mode of action and are deemed to work in a cell-cycle specific manner. They bind to the microtubule protein tubulin and block its ability to polymerise and form microtubules. Instead aggregates of tubulin dimmers and alkaloid drugs are formed. The resulting dysfunctional spindle apparatus, frozen in metaphase, prevents chromosomal segregation and cell proliferation.

Although the vinca alkaloids share a related structure, their therapeutic indications are different. Vincristine is used in acute lymphoblastic leukaemia, Hodgkin's and non-Hodgkin's lymphoma and some solid tumours whereas vinblastine, though also used to treat lymphoma, is used to treat metastatic testicular carcinoma. Vinorelbine is beneficial in the treatment of advanced non-small cell lung cancer. Generalised adverse effects such as nausea, vomiting, diarrhoea and alopecia are observed with these drugs whilst more serious adverse reactions such as peripheral neuropathy (including parasthesias and ataxia), phlebitis (inflammation of veins of the legs and arms) and severe myelosuppression have been noted. All of the vinca alkaloids are generally administered with other anticancer drugs.

The second group of microtubule inhibitors are the **taxanes** (also known as the **taxols**). These comprise **paclitaxol** (better known as **taxol**) which is isolated from the Pacific yew tree and **docetaxol**, a semisynthetic structural analogue of paclitaxol.

Although, the taxanes are classified as microtubule inhibitors and are cell-cycle specific, they have a mechanism of action which is distinct from the vinca alkaloids. The taxanes bind to a different site on tubulin from the vinca alkaloids, promoting rather than inhibiting microtubule formation. This results in unusually stable non-functional microtubules that fail to depolymerise, subsequently stopping chromosome desegregation and causing cell death.

The taxanes have been shown to be effective in the treatment of advanced ovarian cancer, metastatic breast cancer and non-small cell lung cancer particularly when used in conjunction with other anticancer drugs. A decrease in the neutrophil blood count (neutropaenia) as a result of taxane administration is the most serious adverse reaction to these drugs and treatment should be discontinued if it occurs. Other adverse effects associated with these drugs include bradycardia (slowing of heart rate), fluid retention, alopecia and, in rare cases, vomiting and diarrhoea. Because of serious hypersensitivity including hypotension, a patient who is to be treated with paclitaxel should be pre-treated with dexamethasone and antihistamines.

24.3.5 Monoclonal antibodies

Most anticancer drugs exert their therapeutic effects by targeting processes that are integral to cell proliferation, a key marker of malignancy. However, since these processes are also occurring in normal cells, non-cancer cells are also a target for these drugs. As discussed earlier, this lack of selectivity often results in the adverse effects associated with anticancer drugs. The use of **monoclonal antibody** (**mAB**) technologies has resulted in an active area of drug development for anticancer therapy and other non-cancerous diseases. The ability of these molecules to specifically identify targets that arise during cancer development provides powerful and selective anticancer treatments that often have fewer adverse effects than conventional treatments.

The basic premise of all antibody treatments is to produce a drug that reacts with an antigen that is specifically expressed on cancer cells. Interaction of the mAB with the antigen, which is usually a component of cell growth and proliferation, leads either to interruption of the normal cellular processes that occur, killing the target cell or activation of the host's immune system resulting in the same conclusion.

mABs are produced from B-lymphocytes isolated from immunised mice or hamsters which have been infused with an immortalised B-lymphocyte tumour cell line. The resultant hybrid cells (or hybridomas) are individually cultured to produce a clonal cell that produces antibodies against a single antigen type. Recent advances in recombinant DNA technology has allowed for the creation of "humanised" antibodies that can overcome previously observed immunological problems associated with administration of animal-derived antibodies. Currently, there are several mABs that are indicated for the treatment of cancer. These exist in the "naked" form where the immunological properties of the antibody alone are enough to disrupt cell function, and the "conjugated" form where the mAB is associated with a cytotoxic element such as a toxin or radioactivity.

The first mAB approved as an anticancer therapy was **rituximab**. This antibody is directed against the CD20 surface antigen found in normal and malignant lymphocytes but absent in other bone marrow derived cells. CD20 plays an important role in the activation process for cell-cycle initiation and cell differentiation. Binding to CD20 by rituximab results in an autoimmune response culminating in complement-mediated and antibody-dependent cytotoxicity of the B cells. The antibody is commonly used in combination with other drug therapies. Severe adverse effects have been noted with administration of rituximab. These

include hypotension, bronchospasm, angioedema (swelling below the skin surface), tumour lysis syndrome resulting in acute renal failure, and blood cell problems including leukopaenia, thrombocytopaenia and neutropaenia.

Trastuzumab (marketed as Herceptin) targets human epidermal growth factor receptor 2 (HER2) and is used in the treatment of early breast cancer and metastatic breast cancer. Activation of HER2 by mitogen agonists promotes cell proliferation. The HER2 gene is amplified in some 25-30% of early breast cancers leading to an overexpression of the receptor and subsequent increased sensitivity of the malignant tissue to the mitogen, an effect blocked by administration of trastuzumab. The most serious adverse effect associated with trastuzumab administration is congestive heart failure. Other adverse effects such as infusion-related fever and chills, headache, dizziness, vomiting, nausea and back pain are well tolerated.

Bevacizumab is the first in a new class of anticancer drugs known as anti-angiogenesis agents and is indicated for use in the treatment of metastatic colorectal cancer. This antibody binds to vascular endothelial growth factor A (VEGFA) neutralising its ability to stimulate the formation of new blood vessels thus depriving tumours of oxygen and nutrients essential for growth and proliferation. Among the rare serious side effects of bevacizumab are bowel perforation and stroke. A second mAB also used to treat metastatic colorectal cancer, cetuximab, exerts its anticancer effect by targeting the epidermal growth factor receptors on the surface of cancer cells and retarding their growth. Cetuximab has been reported to cause breathing difficulties during the first treatment and interstitial lung disease has been reported.
Other "naked" mABs used in the treatment of cancers are **alemtuzumab** (chronic lymphocytic leukaemia) and **panitumumab** (metastatic colorectal cancer). It is expected that many more will be developed over the next few years.

A second group of mAB therapies being developed are the **"conjugated" mABs** which comprise couopling the antibody to a cytotoxic element ,usually a toxin or a radioactive isotope. The most successful of these is **ibritumomab tiuxetan** which is an antibody directed against the CD20 antigen coupled with a molecule called tiuxetan which contains a radionucleotide (either yttrium-90 or indium 111). The antibody binds to the CD20 antigen found on the surface of normal and malignant B cells (but not B cell precursors), allowing radiation from the attached isotope (mostly beta emission) to kill it and some nearby cells. It is primarily used in the treatment of non-Hodgkin lymphoma. A second mAB directed against the CD20 antigen tagged with Iodine-131, **tositumomab** is also available as a therapy for non-Hodgkin lymphoma. However, **gemtuzumab**, an antibody directed against the CD33 surface antigen found in 80% of all patients with acute myelocytic leukaemia, and conjugated with the plant toxin, ozogamicin has recently been withdrawn from clinical use due to toxicity problems.

24.3.6 Steroid hormones and their antagonists

The growth of a number of tumours have been demonstrated, in part, to be positively or negatively regulated by the presence of various steroid hormones. This has afforded the opportunity to develop treatments specifically targeted to these cancers. For example, many breast cancers depend on proliferative signals produced by oestrogens to support their growth. Indeed, oestrogen receptors are over-expressed in some 70% of all breast cancers making these tissues especially sensitive to the action of the steroids (oestrogen receptor positive breast cancer). Treatment involves either the use of agents to inhibit the pathways of endogenous oestrogen synthesis (aromatase inhibitors) or SERMs (**s**elective o**e**strogen **r**eceptor **m**odulator**s**) that subvert the actions of the steroid. The aromatases are a group of enzymes involved in the synthesis of steroids from precursor cholesterol. Principal amongst

these reactions is the first stage conversion of cholesterol to pregnenolone which inturn gets converted to mineralocorticoids, glucocorticoids, androgens as well as oestrogens. The aromatase inhibitors (**anastrazole, exemestane, letrozole**) block this first step reducing the oestrogen biosynthesis and removing proliferative signals to the hormone-sensitive cancer tissues. Normal chemotherapeutic adverse effects are seen with these compounds though rare instances of thrombosis have been noted with administration of letrozole. SERMs are drugs that act specifically on oestrogen receptors where they can behave as agonists or antagonists depending on the tissue targeted. **Tamoxifen** is a SERM indicated for use in oestrogen receptor positive breast cancers where it acts as antagonists to the breast tissue oestrogen receptors blocking activation of oestrogen-responsive genes stopping RNA synthesis. The result is a depletion of oestrogen receptors and suppression of the steroid's proliferative effects. Adverse effects include hot flushes, nausea, vomiting, skin, rash and vaginal bleeding and discharge. However, tamoxifen acts as oestrogen receptor agonists is other tissues including bone, thereby avoiding the increased risk of osteoporosis that accompanies the removal of endogenous oestrogen.

Progression of prostate cancer is under sophisticated hormonal control. Gonadotropin releasing hormone (GnRH) is secreted by the hypothalamus and interacts with specific receptors on the anterior pituitary gland which in turn facilitates the release of the gonadotropic hormones, follicle stimulating hormone (FSH) and luteinising hormone (LH) which are responsible for the secretion of testosterone and oestrogen. Exposure of the prostate to testosterone is implicit for the growth and survival of certain prostate cancers and so blocking the production or action of this hormone presents an important opportunity for therapy. **Leuprolide** and **goserelin** are analogues of GnRH and act as agonists at the GnRH receptor on the anterior pituitary gland. Chronic activation of these receptors by these drugs results in downregulation of the receptors and consequent inhibition of gonadotropin release resulting in a decrease in tumour growth and survival. These drugs also have some benefit in the treatment of advanced breast cancer. Adverse effects include impotence and hot flushes.

Synthetic, non-steroidal, antiandrogens (**flutamide, bicalutamide**) are also used in the treatment of prostate cancer. These drugs bind to androgen receptors (particularly testosterone receptors) on the prostate, competing with the endogenous steroid, impairing tumour growth. Adverse effects include gynecomastia (abnormal development of mal breast tissue) and gastrointestinal problems. Liver failure has been noted in rare cases with flutamide.

Prednisone is a potent, synthetic glucocorticoid that inhibits cell division by interfering with DNA synthesis. It is widely used in the treatment of acute lymphocytic leukaemia and Hodgkin and non-Hodgkin lymphoma. Adverse reactions are those primarily associated with glucocorticoid treatmentweight gain, ulcers, pancreatitis, cataract and glaucoma formation, osteoporosis and mood change (euphoria, psychosis).

24.3.7 Other treatments

A number of other agents that fall outside the regular classifications are used as anticancer treatments. Included in this group are the platinum coordination complexes such as **cisplatin** and **carboplatin** (both used in the treatment of metastatic testicular cancer, ovarian cancer and bladder carcinoma) and **oxaliplatin** (used in treatment of advanced colorectal cancer). All of these agents work in a similar way although cisplatin has severe toxicity issues. They crosslink with DNA through a guanine nucleobase and the resulting cytotoxic lesion inhibits both DNA replication and RNA synthesis. Adverse effects include severe, persistent

vomiting (so anti-emetic agents should be used in conjunction), nephrotoxicity and ototoxicity.

Irinotecan (treatment of colorectal carcinoma) and **topotecan** (treatment of metastatic ovarian cancer, small-cell lung cancer) exert their actions by inhibition of topoisomerase I, an enzyme essential for the replication of DNA in human cells. In contrast, **etopside** (treatment of acute lymphoblastic leukaemia, lung cancer, testicular cancer) targets a second topisomerse enzyme, topoisomerase II and results in arrest of the cells in the late S to G2 phase of the cell cycle. These compounds cause the common adverse effects associated with anticancer drugs, however, etopside may cause leukaemia to develop.

Imatinib belongs to a new class of anticancer agents. These perturb intracellular signalling pathways. Imatinib, which is used to treat chronic myeloid lymphoma and gastrointestinal stromal tumours, works by blocking the unregulated expression of tyrosine kinases associated with tumour growth thus inhibiting cell proliferation. Unusual adverse effects associated with this drug include thrombocytopaenia, neutropaenia, oedema and gastrointestinal bleeding. Very rare instances of stroke and congestive heart failure have been reported with the use of this drug.

Recombinant DNA technology has proved particularly useful in producing usable quantities of low abundant biomolecules for use as treatments. In particular, production of interferons has proved particularly useful. These are proteins released by lymphocytes in response to pathogens or tumour cells. Two subtypes, **interferon α2a** and **α2b** have been shown to be particularly effective in the treatment of leukaemia, melanoma and AIDS-related Kaposi's sarcoma.