Chapter 15

Medications used in cancer

Elaine Walls and Leah Rosengarten

Aims

The aim of this chapter is to help the reader understand the pharmacology and pharmaceutical treatment options commonly used in cancer care.

Learning Outcomes

After reading this chapter, the reader will:

1. Understand how cancer occurs in relation to the cell cycle
2. Discuss the use of chemotherapies in the treatment of cancer
3. Appreciate the role of immunotherapies in the management of cancer
4. Recognise how corticosteroids are used in cancer care

Test your knowledge

1. What is the difference between normal cells and cancer cells?
2. What medicines are used in the treatment of cancer?
3. What considerations are relevant when prescribing and administering chemotherapy?
4. How is the immune system used in the treatment of cancer?
5. Why use corticosteroids in cancer care?

Introduction

Over recent years, the NHS has seen a year on year increase in the number of cancer diagnoses but a year on year decrease in the number of people dying from cancer

(Office for National Statistics (ONS), 2019). Consistently statistics have shown that more males in England are diagnosed with cancer than females and just over half (52.6%) of all cancers diagnoses in 2017, were either breast, prostate, lung or colorectal cancer (ONS, 2019).

The goal of cancer treatment in the UK is to cure patients of their cancer through eradication of all cancer cells in their body (Cancer Research UK, 2017). In situations where this is not possible; treatments can be focused on prolonging life or improving the patients' quality of life through symptom management. Treatment options for cancer are not limited to drugs and may include surgery, radiotherapy, bone marrow or stem cell transplants and gene therapies amongst others. This chapter will consider the different drugs used in the treatment of cancer.

First, it is important that we develop a baseline understanding of what cancer is and the process of the normal cell cycle before we can appreciate the roles and mechanisms of drugs used in cancer.

Cancer

Cancer is a condition which occurs when cells in a certain part of the body grow and divide uncontrollably. When these cells grow abnormally, they can form a lump, which is called a tumour. Not all tumours are cancerous; tumours can be benign (not cancerous) or malignant (cancerous). The difference between these is that benign tumours will not spread to other areas of the body, but malignant tumours can spread to other tissues and organs.

Tumours that are benign will still continue to grow but typically only cause problems if they place pressure on nearby organs when they grow. Malignant or cancerous tumours in one part of the body can cast off cells which travel around the body and invade other organs. When these cells invade other organs they may start to grow and form a second tumour, which is called a metastasis. In blood cancer, cancerous cells behave in the same way as other cancer cells and build up in the blood or bone marrow but do not form tumours.

There are certain 'hallmarks' which are said to distinguish cancer cells from normal cells; these are displayed in figure 15.1 (Hanahan and Weinburg, 2011). Though it has been argued that not all cancers can be defined by the same six biological capabilities, appreciation of these common traits can lead to a greater understanding of the difference between cancer cells and normal cells and enhance the quality of care provided.

Figure 15.1. Hallmarks of a cancer cell (Hanahan and Weinburg, 2011).

Sustaining proliferative signalling, describes how a cancer cell ignores signalling to control growth. Where a normal cell's growth is carefully controlled through the production of growth promoting signals, a cancer cell becomes self-sufficient in providing their own growth signals and do not require signalling from external cells to continue to grow. In addition to this, cancer cells also become resistant to anti-growth signals, which is the second hallmark, evading growth suppressors.

Activating tissue invasion and metastasis refers to the cancer cells ability to invade and spread to surrounding tissues and organs rather than remaining in set boundaries as normal cells do. Additionally, cancer cells do not have a limit to how many times they can multiply and grow as a normal cell does; this is termed enabling replicative immortality.

The hallmark inducing angiogenesis identifies that the cancer cell can draw blood cells in to a tumour in order to feed it and ensure it can continue to grow where a normal cell will attract blood vessels only when they need to grow and feed. Lastly, the resisting cell death hallmark recognises that the cancer cell has an ability to ignore signals to die. Where a normal cell has a program of self-destruction named apoptosis which is activated in occasions such as when DNA is damaged, a cancer cell can evade this process.

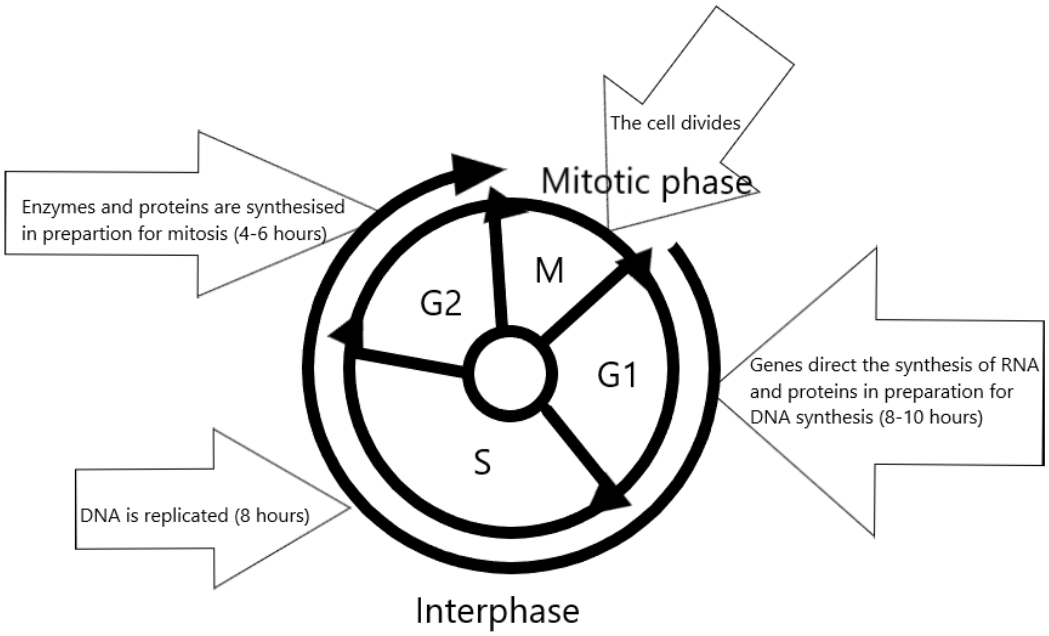
In short, a normal cell will; multiply and divide only when signalled to do so; stop multiplying and dividing when signalled to do so; perform one function that they were designed to perform; reproduce only a set number of times; attract blood vessels only when they need to grow and self-destruct when necessary. A cancer cell will; multiply

and divide uncontrollably; ignore signals to stop growing; invade other tissues and organs; continue to multiply and divide indefinitely; attract blood vessels to nourish itself constantly and resist cell death.

Cell cycle

The purpose of the cell cycle is for cells to reproduce themselves, to replace dead or injured cells and add new ones for tissue growth. The cell cycle is an ordered series of events which consists of two main periods: Interphase, when the cell is not dividing and the Mitotic (M) phase when the cell is dividing. Figure 15.2 below shows the cell cycle.

(Figure 15.2 – The cell cycle - Please insert diagram of cell cycle similar to one below)



The interphase is a period of rapid growth during which the cell replicates its deoxyribonucleic acid (DNA). There are three phases within this period: G1, S and G2.

The G phases are gaps or interruptions in DNA replication and the S phase involves the replication of DNA.

The G1 phase is the gap between the mitotic stage and the S phase, during which the cell is preparing for DNA synthesis through genes directing the synthesis of ribonucleic acid (RNA) and proteins. This stage may last from 8 to 10 hours, though some cells remain in this phase for a longer time and are considered to be in the G0 or resting phase. The S phase is between G1 and G2 and lasts approximately 8 hours, during which time all 46 chromosomes containing genetic DNA are copied, so both new cells that are formed will have matching DNA. Once a cell enters this phase it is committed to going through cell division. The G2 phase is the gap between the S phase and mitosis, this phase may last for 4 to 6 hours, during which time cell growth continues and enzymes and other proteins are synthesised in preparation for cell division.

The M phase or mitosis is characterised by chromosomes passing through phases of change (cytokinesis) to form two genetically identical cells. Mitosis may be broken down into four distinct phases; prophase where chromosomes form identical pairs, called chromotids; metaphase where spindle fibres attach to chromosomes and chromotids begin to separate; anaphase where two sets of new single-stranded chromosomes move to opposite ends of the cell; and telephase where a nuclear membrane forms around each set of chromosomes dividing the cell in two.

Understanding of the process of the cell cycle is important as certain drugs used in the treatment of cancer, impact on specific points in the cell cycle. These drugs interrupt

the process of the cell cycle in order to prevent the cancer from growing further or to kill the cancer cell completely.

Chemotherapies

Chemotherapy is the name given to the group of drugs which are cytotoxic, meaning that they are toxic to cells. Chemotherapy has been used in the treatment of cancer since the 1940's and today there are more than 100 different types of chemotherapy used in the UK. Chemotherapy destroys cancer cells by interrupting the cell cycle and preventing the cells from multiplying further, though chemotherapy cannot distinguish between normal and abnormal cells so healthy cells can also be affected. The point at which a chemotherapy will interrupt the cell cycle differs depending on the type of chemotherapy.

Clinical Considerations
Types of chemotherapy are broken down into groups according to; their chemical structure, how they work and their relationships to other drugs. Some chemotherapies may belong to more than one group as they work in more than one way. Different chemotherapy agents are often given in combination with each other, to interrupt different points within the cell cycle. Table 15.1, 15.2, 15.3 and 15.4 display the commonly used chemotherapy agent for each group.

Preparations of Chemotherapy

Chemotherapy is most commonly given intravenously as either a bolus or infusion but can also be administered through the following routes;

- Orally – swallowed in pill, tablet, capsule or liquid form

- Subcutaneous – into the space between the skin and the muscle
- Intramuscular – into the muscle
- Intrathecal – into the spinal fluid
- Intraperitoneal – into the abdominal cavity
- Intravesicular – into the bladder
- Intrapleural – Into the space between the lung and the lining of the lung
- Intra-arterial – into the artery that is supplying blood to the tumour
- Topical – onto the skin

Types of Chemotherapy

The British National Formulary (BNF) (Joint Formulary Committee, 2019) identifies four classes of chemotherapy;

1. Alkylating Drugs
2. Antimetabolites
3. Anthracyclines and other antibiotics
4. Vinca alkaloids.

Alkylating Drugs

Alkylating drugs or alkylating agents were the first chemotherapy drugs to be used to treat chemotherapy. The use of alkylating drugs to treat cancer were first discovered in the First World War, when sulphur mustards (mustard gas) were used as chemical weapons. As such, alkylating drugs are some of the most studied drugs used to treat cancer and still remain one of the most commonly used group of drugs for this purpose (Almeida et al, 2005).

Alkylating drugs are generally considered non-cell specific as their activity is not restricted to one specific point in the cell cycle (Pires et al, 2018). These drugs work through transferring alkyl carbon groups onto a wide range of biological molecules, prevent the proteins in the DNA from joining together as they should and eventually breaking the strands of DNA, stopping the cell from continuing to multiply and killing the cell (Fu, Calvo and Samson, 2012).

As every aspect of the cell cycle is concerned with the replication of DNA, Alkylating Drugs can impact on every point in the cell cycle, but their biggest impact is thought to be within the S phase of the cell cycle where all 46 chromosomes are copied (Bignold, 2006). Table 15.1, identifies some of the commonly used alkylating drugs in cancer care.

Table 15.1 - Commonly used alkylating drugs (Source: Joint Forumlary Committee, 2019)

Drug	Licensed for treatment of
Cyclophosphamide *Oral or Intravenous*	A wide range of malignancies including leukaemia, lymphomas and solid tumours
Ifosfamide (related to Cyclophosphamide) *Intravenous*	Malignant disease
Melphalan *Intravenous*	Multiple myeloma, polycythaemia vera, childhood neuroblastoma, advanced ovarian adenocarcinoma and advanced breast cancer
Lomustine *Oral*	Hodgkin's disease resistant to conventional therapy, malignant melanoma and certain solid tumours
Carmustine *Intravenous*	Multiple myeloma, non-Hodgkin’s lymphoma and brain tumours
Estramustine phosphate *Oral*	Prostate cancer

Antimetabolites

Antimetabolites structurally resemble normal biological molecules within a cell and work through interfering with the processes that require the use of that normal biological molecule (Gmeiner, 2002). As antimetabolites structurally resemble essential molecules, enzymes will mistake antimetabolites for other essential molecules and combine with them; this results in the exclusion of essential molecules from their normal role and creates a deficiency of that molecule (Woolley, 1959).

Antimetabolites attack cells at specific parts of the cell cycle, but the point at which this occurs in the cycle depends on which substance the antimetabolite interferes with. These drugs tend to be further classified according to which substance they inhibit which can include; dihydrofolate reductase, tetrahydrofolate, purines and pyrimidines (Gmeiner, 2002). Table 15.2, identifies some of the commonly used Antimetabolites in cancer care.

Table 15.2 - Commonly used antimetabolites (Source: Joint Formulary Committee, 2019)

Drug	Licensed for use in
Methotrexate *Intramuscular, Subcutaneous, Intravenous, Oral and Intrathecal*	Neoplastic diseases
6-mercaptopurine *Oral*	Acute leukaemia's and chronic myeloid leukaemia
6-tioguanine *Oral*	Acute leukaemia and chronic myeloid leukaemia
Fludarabine Phosphate *Oral or Intravenous*	Advanced B-cell chronic lymphocytic leukaemia (CLL)
Pentostatin *Intravenous*	Hairy cell leukaemia
Cladribine *Subcutanous, Intravenous or Oral*	Hairy cell leukaemia and chronic lymphocytic leukaemia

5-fluorouracil *Intravenous or Intra-arterial*	Some solid tumours including gastro-intestinal tract cancers and breast cancer and in combination with Folinic acid in advanced colorectal cancer
Cytarabine *Intravenous or Subcutaneous*	Acute myeloid leukaemia
Gemcitabine *Intravenous*	Locally advanced or metastatic non-small cell lung cancer, locally Advanced or metastatic pancreatic cancer and advanced or metastatic bladder cancer

Anthracyclines and other antibiotics

Anthracyclines have been widely used in cancer treatment for over 50 years and are derived from antibiotics.

Though anthracyclines can induce many intracellular effects, their main mechanism of action is inhibition of topoisomerase II (Neilsen, Maare and Skovsgaard, 1996). Topoisomerase II is an enzyme which generates breaks in strands of DNA in order to regulate DNA processes (McClendon and Osheroff, 2007). Anthracyclines inhibit topoisomerase II through intercalating (inserting molecules) between base pairs of adjacent DNA, damaging the DNA and ultimately inducing apoptosis (Hortobágyi, 1997). Table 15.3, identifies some of the commonly used Anthracyclines and other Antibiotics in cancer care.

Table 15.3 - Commonly used Anthracyclines and other Antibiotics (Source: Joint Formulary Committee, 2019)

Drug	Licensed for treatment of
Daunorubicin *Intravenous*	Acute myelogenous leukaemia and acute lymphocytic leukaemia

Doxorubicin Hydrochloride *Intravenous or Intravesical*	Acute leukaemias, Hodgkin's and non-Hodgkin's lymphomas, paediatric malignancies and some solid tumours including breast cancer
Epirubicin Hydrochloride *Intravenous or Intravesical*	Breast cancer
Idarubicin Hydrochloride *Oral or Intravenous*	Haematological malignancies
Mitoxantrone *Intravenous*	Metastatic Breast Cancer, Non-Hodgkin's Lymphoma, Adult Acute Non-Lymphocytic Leukaemia and Non-Resectable Primary Hepatocellular Carcinoma
Pixantrone *Intravenous*	Refractory or Multiply Relapsed Aggressive Non-Hodgkin's B-Cell Lymphomas
Bleomycin *Intramuscular, Intravenous or Intra-arterial*	Metastatic Germ Cell Cancer and Non-Hodgkin's Lymphoma.
Dactinomycin *Intravenous*	Paediatric Cancers
Mitomycin *Intravenous or Intravesical*	Gastro-Intestinal and Breast Cancers and by bladder instillation for Superficial Bladder Tumours.

Vinca alkaloids

Vinca alkaloids are derived from certain types of plant and work through the inhibition of tubulin into microtubules (Zhou and Rahmani, 1992). Microtubules are needed to provide structure and shape to cells and when vinca alkaloids bind to tubulin, they prevent the tubulin from then being able to bind to microtubules (Moudi et al, 2013). This process ultimately blocks the ability of the cell to divide and causes apotosis

(Moudi et al, 2013). Table 15.4, identifies some of the commonly used Vinca alkaloids in cancer care.

Table 15.4 Commonly used Vinca Alkaloids (Source: Joint Formulary Committee, 2019)

Drug	Licensed for use in
Vinblastine Sulfate *Intravenous*	Variety of cancers including leukaemias, lymphomas and some solid tumours (e.g. breast and lung cancer)
Vincristine Sulfate *Intravenous*	Variety of cancers including leukaemias, lymphomas and some solid tumours (e.g. breast and lung cancer)
Vindesine Sulfate *Intravenous*	Variety of cancers including leukaemias, lymphomas and some solid tumours (e.g. breast and lung cancer)
Vinorelbine *Oral or Intravenous*	Advanced breast cancer and advanced non-small cell lung cancer

Side Effects of chemotherapy

It has been noted that the effects of chemotherapy are not limited to only cancer cells but also impact on healthy cells. As chemotherapy affects the fastest dividing cells in the human body most, side effects of chemotherapy are more likely to occur in areas of the body where cells are fast dividing. Though individual chemotherapies will have differing side effects, common side effects are below;

- Nausea and Vomiting
- Alopecia
- Bone marrow suppression leading to
    - Anaemia (low red blood cell count)
    - Thrombocytopenia (low platelets)
    - Leukopenia (low white blood cell count)
- Mucositis

- Skin changes

As chemotherapy is usually given in cycles or set regimens, patients are clinically assessed before commencing every regimen to ensure that side effects are manageable. These assessments change depending on the point in treatment but frequently include blood tests and a full clinical exam. Healthcare Professionals need to assess the patient to ensure that the impact of the patients' experienced side effects do not outweigh the benefit of the chemotherapy. Some side effects, such as nausea and vomiting, can be managed but others, such as mucositis, require the patient to be given time to recover before commencing more chemotherapy.

Clinical Considerations
According to the Control of Substances Hazardous to Health Regulations 2002 (COSHH), cytotoxic drugs are hazardous substances (HSE, online). Due to this, staff administering these drugs should; control their exposure to the substance, wear Personal Protective Equipment (PPE), monitor exposure in the workplace, use occupational health services to help identify risks if necessary, deal with spillages and contamination appropriately, dispose of waste correctly and report incidents as necessary according and in line with local policy and procedure (HSE, online).

Prescription and Administration of Chemotherapy

The National Chemotherapy Advisory Group (NCAG, 2009) give recommendations on the prescription of chemotherapy. They advise that the decision to initiate a programme of chemotherapy should be made by a consultant and that all patients must have a treatment plan in place for each cycle of chemotherapy they are given.

NCAG (2009) direct that chemotherapy should only be prescribed by appropriately trained staff, according to predefined protocols and should be on pre-printed forms. Practice areas should keep an annually updated list of all staff who can prescribe chemotherapy and an oncology pharmacist should check all chemotherapy prescriptions. Exceptions may be made to the above in emergencies and extraordinary circumstances.

Drug Resistance

It is possible for cancer cells to be or become resistant to chemotherapy treatment. Occasions when cancer does not respond to chemotherapy treatment, may be termed 'refractory'. Some cancer cells may initially respond to chemotherapy, but later develop the ability to prevent chemotherapy drugs from entering the cell, or limit the amount of drug that enters the cell, to stop or minimise the amount of damage the drug can do.

Cyclophosphamide

Using the above categories, cyclophosphamide can be used as an example to gain a deeper insight into the use of a chemotherapy as an anticancer drug. Table 15.5 explains the properties of cyclophosphamide.

Table 15.5 – Properties of cyclophosphamide

Use	Can be used in the treatment of a wide range of malignancies, including some leukaemias, lymphomas and solid tumours (Joint Formulary Committee, 2019).
Dose	Must be individualised. The dose, duration of treatment and treatment intervals are adjusted according to the

	therapeutic indication of the patients scheme of chemotherapy (Electronic Medicines Compendium, EMC, 2017).
Administration	Can be given orally or intravenous (IV) as a bolus or an infusion.
Pharmacodynamics	An alkylating agent which affects the cell at the S or G2 phase of the cell cycle. It is not known whether cyclophosphamide works *only* through the alkylation of DNA but this is the drugs main known method of action (EMC, 2017).
Pharmacokinetics	Cyclophosphamide is inactive at administration but activated in the liver. Absorption – Quickly and almost completely absorbed parenterally and well absorbed orally. Distribution – Distributed widely around the body and can cross the blood-brain barrier, the placental barrier and is found in ascites. The parent compound binds poorly to plasma protein but the active metabolites are significantly protein bound. Metabolism – Activated in the liver. 2-4 hours after administration, the plasma concentrations of the active metabolites are maximal, after which plasma concentrations rapidly decrease. Excretion – The plasma half-life is about 4-8 hours in adults and children. Cyclophosphamide and its metabolites are primarily excreted by the kidneys (EMC, 2016; EMC, 2017).
Side effects (common or very common)	Bone marrow suppression and problems associated low blood counts, alopecia, physical weakness or lack of energy, cystitis, haemolytic uraemic syndrome, hepatic disorders, mucosal abnormalities, sperm abnormalities and progressive multifocal leukoencephalopathy (PML) (Joint Formulary Committee, 2019)

Episode of care (learning disability)

Jasmine

Jasmine was 16 years old when she presented to hospital with a seizure. On admission to hospital Jasmine also identified a month history of dizziness and vomiting. After initial testing, Jasmine was diagnosed with an Ependymoma (a type of brain tumour). Jasmine is now 20 years old and has recently relapsed her Ependymoma.

Jasmine has a moderate learning disability and lives in assisted living where she is visited regularly by her parents and older sister.

Jasmine is being treated with a combination of oral chemotherapies at home. Jasmine was prescribed 50mg/m² of Etoposide orally every day for a period of 3 weeks. She is now due to start taking 2.5mg/kg of Cyclophosphamide orally every day.

Jasmine was given the correct number of tablets of Etoposide to last for 3 weeks but on return to clinic to collect her Cyclophosphamide tablets, Jasmine still has half of her tablets left in the bottle.

Jasmine was previously assessed as having capacity to manage her own medications, but she now seems confused by which medications she should take and when. Jasmine isn't able to remember which days she has taken her medications and which days she may have forgotten.

Before Jasmine can be discharged home, healthcare professionals need to reassess Jasmine's capacity to manage her own medications at home and develop a plan to ensure that she is compliant with her treatment regime.

Immunotherapies in treating cancer

The Immune System

In immunotherapy, it is essential to understand the role of the immune system and how this line of therapy may influence cancer management plans.

The immune system plays a significant role in the development and progression of cancers (Coosemans et al 2019,Hanahan and Weinberg 2011). Natural antibodies within the immune system are proteins that fight infection when the body recognises something harmful, such as viruses and bacteria. In response to these harmful cells, signals are sent by the immune system, to interrupt growth and kill the invading cell (Figure 15.3).

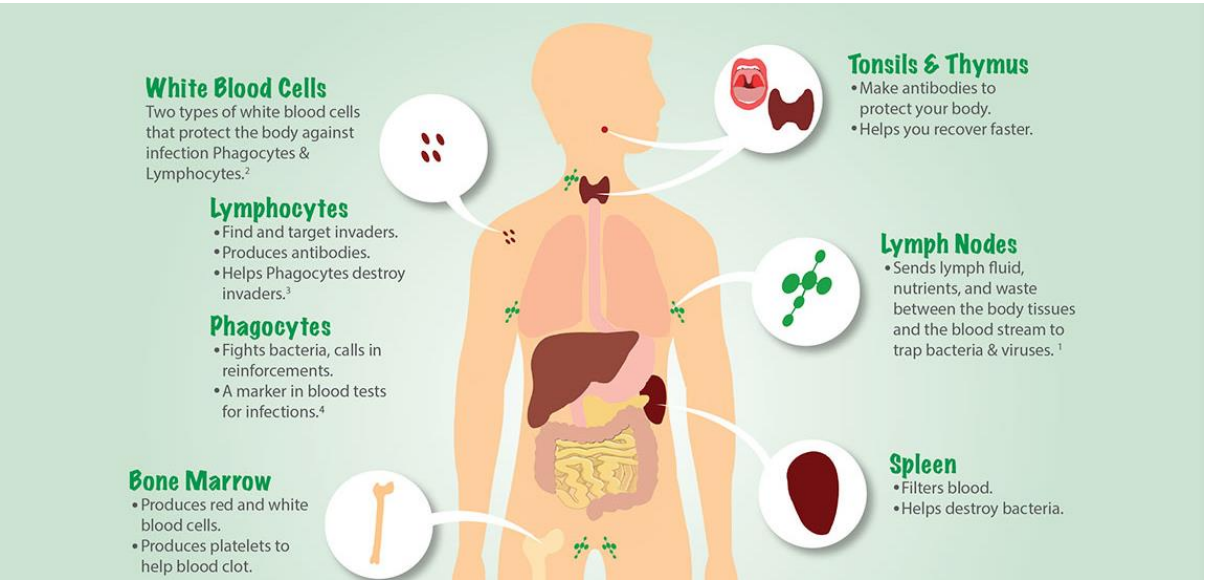
Whilst some of the body's own malformed cells will be destroyed by the immune system responses, many cancers are able to avoid this process, as they act as part of the body's own structure rather than an invading cell. This allows the cancer cell to avoid attack and escape immune system pathways that are in place to block and reduce harm.

Though the immune system sometimes fails to destroy cancer cells initially, it can still be useful in the management and treatment of cancer. Immunotherapy uses substances that are naturally made by the body or made synthetically in a laboratory,

to improve or restore the immune system in order to elicit or amplify an immune response.

Figure 15.3 – The immune system

(Publisher please redraw a diagram of the immune system like the one below).



Immunotherapy

Immunotherapy is a relatively new form of cancer therapy. Although first recognised by Dr William Coley in the 1800s, it was initially approved as part of cancer treatment in 1990. This was in the form of a cancer based vaccine for tuberculosis (Cancer Research Institute, 2019) and since then advances in research and use of immunotherapy in cancer care has increased exponentially.

Immunotherapy is a form of treatment that can act to support the immune system in recognising specific cancer cells and either destroying them or stopping or slowing growth within the cancer cell (Schreiber and Smith 2011).

Immunotherapy can act to block the pathways that cancer cells often use to avoid immune responses and encourage the immune system to form memory cells against specific types of cancer. In certain cancers, it is thought that immunotherapy relaunches the immune system, allowing it to re-form and therefore producing cancer specific antibodies that will be retained in immune memory and attack any returning cancer cells. Currently immunotherapy has been formulated to be suitable only for certain cancers due to cell composure within these cancer cells. Cancer immunotherapy is an artificial interaction with the immune system in an attempt to fight cancer.

The use of immunotherapy

Immunotherapy may be used independently or as part of a treatment regimen (with chemotherapy and or surgery), both in active and supportive pathways (see below). Using the body's own immune responses allows immunotherapy to respond to cancer only cells, preventing their growth and sparing healthy cells from this invasion, therefore reducing the severe side effects as commonly seen in chemotherapy.

- Active immunotherapy primes the immune system to recognise cancer cells as foreign, encouraging the production of antibodies or cytotoxic T cells to fight cancer, which aims to stop growth within the cancer cell (Yao, Wang and Fung 2018).
- Supportive immunotherapy is nonspecific strengthening of the innate immune system and acts as a secondary treatment line in slowing cancer growth (Vansteenkiste 2012).

Immunotherapy is considered in addition to chemotherapy and radiotherapy for more resistant cancers, as part of an aggressive treatment plan and the effects of such treatment regimens remains under scrutiny (Coosemans et al 2019).

Immunotherapy is used in a variety of treatment methods, including;

- Targeted antibodies
- Checkpoint inhibitors
- Bone marrow/Stem cell transplant
- Adoptive cell transfer
- Cytokines

The role of each of the above are now discussed.

Targeted antibodies

Advances in technology have allowed for the identification of proteins that are uniquely expressed within tumour cells. There are several types of targeted antibodies, each acting on different proteins. Monoclonal antibodies are manufactured antibodies that act by targeting specific proteins so the immune system can destroy these abnormal proteins. The purpose being to return cellular growth, differentiation and proliferation back to its healthy state. Monoclonal antibodies are made up of one protein type and bind to this particular epitope within the cell (Figure 15.4). Some monoclonal antibodies work by stimulating the immune system to respond and attack the cancer, rather than allowing natural immune regulation to see cancer proteins as part of the self and preventing continued antigen assault. Monoclonal antibodies target cancer cells by driving the immune system to release its brakes and remain active in the fight against harmful antigens (National Centre for Biotechnology Information, NCBI, 2019).

Table 15.6, identifies some of the commonly used Monoclonal Antibodies in cancer care.

Figure 15.4 (Publisher please redraw show monoclonal cell activity)

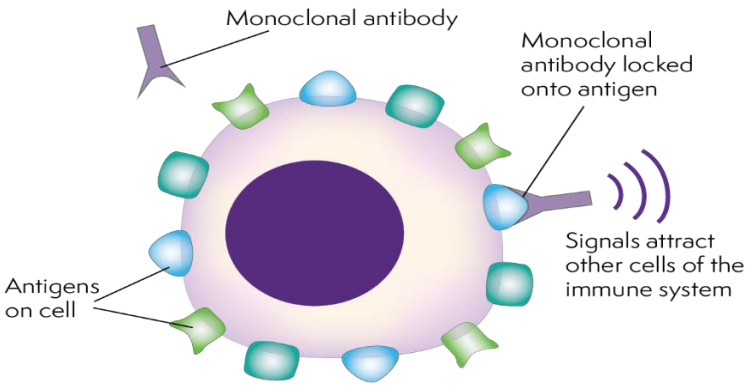


Table 15.6 - examples of monoclonal antibodies (Source: Joint Formulary Committee, 2019)

Drug and route	Indication	Pharmacodynamics
Trasruzumab (Herceptin) *Intravenous infusion*	Breast cancers that over express HER 2	Attach to HER2 cells to block growth signals
Rituximab *Intravenous infusion*	Chronic lymphocytic leukeamina (CLL) Non Hodgkins lymphoma	Targets CD20 on B cells, immune responses then attach and kill CD20 (young cells in the bone marrow do not have CD20)

Checkpoint inhibitors

Check point inhibitors can also be considered a form of monoclonal antibodies. There are pathways in the immune system which are crucial in preventing cancer from being

able to avoid immune responses and continue to grow. These pathways would normally contain a checkpoint to recognise and block invading organisms (such as cancer) and to allow immune responses to identify and destroy harmful cells.

Some cancers are able to fool the immune system and move through these pathways or checkpoints (PD-1/DD-L1, CTLA-4), which is where checkpoint inhibitor drugs may be useful. Checkpoint inhibitors are antibodies that act by stimulating the immune system to block these checkpoints, enticing immune recognition and response to occur, aiming to stop or slow growth of cancer cells (Johnson et al 2019).

Figure 15.5 shows the action that occurs when checkpoint inhibitors such as Anti PD1 occur within the cell. Table 15.7, identifies some of the commonly used Checkpoint Inhibitors in cancer care.

Figure 15.5. – Cell activity with checkpoint inhibitor

(Publisher please redraw to show cell activity with checkpoint inhibitor

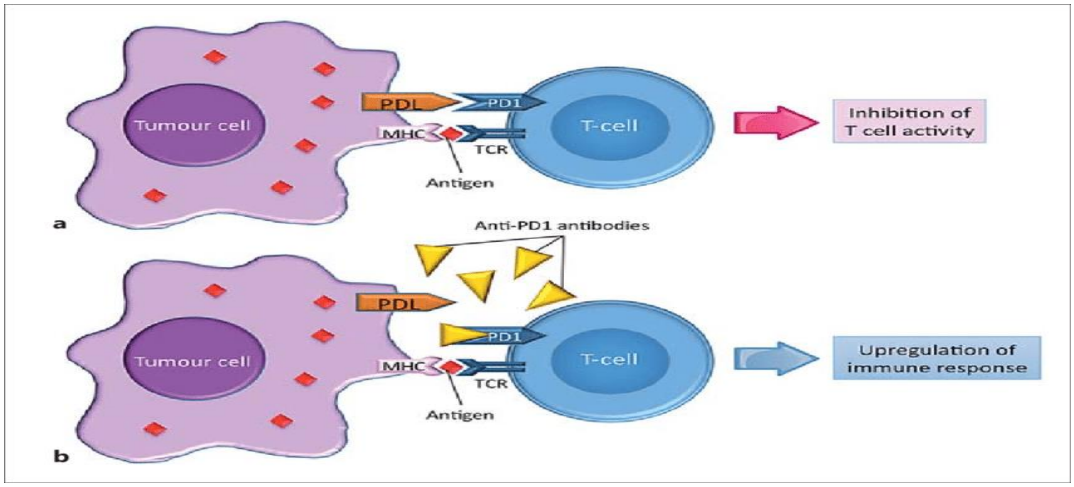


Table 15.7 demonstrates properties of Rituximab as a monoclonal antibody.

T	Cancers such as: Follicular lymphoma, B cell non-Hodgkins lymphoma, chronic lymphocytic leukaemia (CLL).
Dose	Adults 375mg/m2 body surface. Child dose is strictly guided by individual protocols, weight of child and clinical presentation.
Administration	Always given as IV or Subcutaneous infusion Patients must have close monitoring by a healthcare professional and be in an environment where full resuscitation facilities are available. Pre medication of anti pyretic and antihistamine is required alongside pre hydration.
Pharmacodynmics	Rituximab is a monoclonal antibody that binds to transmembrane antigen CD20 on B cells.CD20 is present on normal

	and malignant B cells, but not on stem cells.
Pharmacokinetics	Absorption- circulating B cells are depleted by rituximab within 3 weeks, effects can last up to 6 months. Distribution-Binding to B cells is seen on lymphoid cells in thymus,spleen,peripheral blood and lymph nodes. Excretion- half life varies depending on disease, with an average of 22 days. This is increased in patients with large tumour mass, in CLL can be up to 32 days.Serum concentrate after 4 doses can be detected after 3-6 months.
Common or very common side effects (a selection only listed)	Decreased appetite Bone marrow disorders Anxiety Myocardial infarction Conjunctivitis Insomnia

	Ear pain Dizziness Migraine Sepsis Multi organ failure

(Source: Joint Formulary Committee 2019, EMC 2019, Drugs.com 2019)

See table 15.8 for examples of checkpoint Inhibitors. (Source: Joint Formulary Committee, 2019; Kirkwood, Lotze and Yaske 2001)

Table 15.8 - other checkpoint inhibitors

Drug and route	Indication	Pharmacodynamics
Ipilimuumab *Intravenous infusion*	Melanoma	Stimulates T cell activation to destroy cancer cell
Avelumab *Intravenous infusion*	Merkel cell carcinoma	Binds to PD1 (programmed death) receptor – at checkpoint to stimulate immune response

Bone Marrow and Stem Cell Transplant

Bone marrow transplants (BMT), also referred to as stem cell transplants, are used to replace diseased bone marrow with new healthy cells. This is a form of immunotherapy, as the transplanted marrow elicits the immune system to re-evaluate and re-launch, making it more able to respond to harmful cells following significant attack from diseases such as cancer. BMT is also used to replace cells within the

immune system which have been permanently destroyed by cancer treatments (such as chemotherapy).

Bone Marrow or Stem cells can be donated from a matched donor or autologous, meaning they have been harvested, cleaned and stored and are later given back to the same person (Figure 15.6).

BMT and stem cell transplantation are used in conjunction with robust pharmaceutical regimens. Treatment to destroy the damaged immune system occurs pre BMT, alongside post BMT therapies which support the new cells to be established and minimise risk of rejection from the bodies original immune system. Table 15.8, identifies the indication for stem cell transplant or BMT Bone in cancer care.

Figure 15.6. Types of bone marrow transplant

(Publisher please redraw representing differentiating types of BMT)

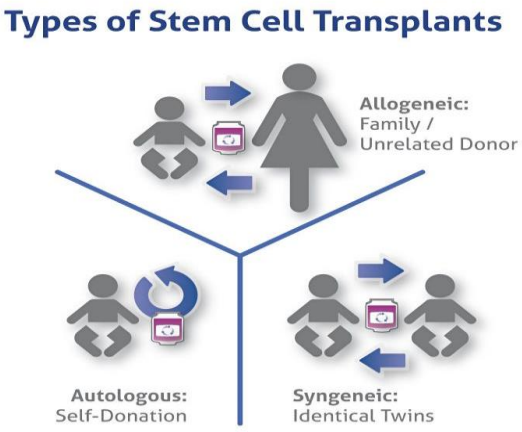


Table 15.8 Indications for use of transplant

Route	Indication
Bone Marrow / Stem Cells *Intravenous infusion*	Leukaemia Lymphoma Multiple myeloma

Adoptive cell transfer (ACT)

Adoptive cell transfer is the autologous use of genetically modified T cells to help activate T cell activity. By stimulating T cells to recognise and target specific proteins on cancer cells. Before ACT can occur, depletion of lymphocytes is required, to support the immune system's ability to accept replaced T cells (Rosenberg et al 2008). This is achieved through chemotherapy agents which destroy lymphocytes.

T cells without tumour activity are harvested via blood from the cancer patient (autologous), the T cell is separated from other components within the blood then genetically modified in vitro and allowed to multiply. A larger collection of stronger T cells now with tumour activity is infused back into the cancer patient. These engineered T cells have an enhanced ability to attack the proteins on the cancer cell (Restifo et al 2012).

Table 15.9 identifies some of the commonly used ACT drugs in cancer care.

Table 15.9. Examples of Adoptive Cell Transfer Drugs (Source: National Institute for Health and Care Excellence, NICE, 2018: NICE 2018b)

Form of ACT	Indication
Tisagenlecleucal	

	Acute lymphoblastic leukaemia in patients up to aged 25 years only
Axicabtagene	T cell lymphomas for patients who have failed conventional treatment twice

Cytokines

Cytokines are memory bound proteins that act as a mediator of intercellular activity. Cytokines are responsible for signalling between cells and maintaining the balance of the Immune system. Cytokines act as messenger cells communicating and co ordinating responses to targeted antigens within the immune system (Lee and Margoln 2011).

Engineered cytokine drugs stimulate the immune system to encourage T cell activity, they are able to interfere with the cancer cell by enticing the cancer cell to produce chemicals that are easily recognised as harmful within the immune system stimulating T cell attack. Cytokines also interfere with the way the cancer cell multiplies, attempting to reduce growth (Castro et al, 2018). Table 15.10 identifies some of the commonly used Cytokines in cancer care.

Table 15.10. Examples of Cytokines (Source: Joint Formulary Committee, 2019).

Drug and Route	Indication	Pharmacodynamics
Interferon alpha *Subcutaneous injection or intravenous injection*	Hairy cell leukaemia Non Hodgkin's lymphoma Myeloma Liver or lymph metastasis of carcinoid tumour	Boosts immune systems response and reduce growth of cancer by interfering with action of proteins that affect growth
Interleukin 2/ proleukin *Subcutaneous injection or Intravenous infusion*	Metastatic renal cancer	Aims to produce tumour shrinkage by inhibiting cell growth

Side effects of immunotherapy

The side effects associated with immunotherapies vary between person to person and differ with each therapeutic agent. Table 15.11 details possible side effects from immunotherapy. The majority of side effects from immunotherapy are mild, due to the composition of immunotherapies in targeting cancer cells, thereby protecting healthy cells within the body. However, there are recorded incidences of severe and life threatening effects from some patients. As immunotherapies stimulate the immune system, certain reactions should be expected (Kirkland, Lotze and Yasko 2001, Joint Formulary Committee, 2018-19).

Immunotherapies (in particular checkpoint inhibitors), take the brakes off the regulation of the immune system, it is therefore crucial when administering immunotherapy that close monitoring of the patient occurs. This monitoring is needed, because releasing the immune system control may entice attack from the immune system, onto healthy functioning parts of the body. This could cause unpredictable, life threatening side effects if early identification and treatment did not occur (Potter 2014). Monitoring of the patient by healthcare professionals should seek to recognise any allergic responses or flu-like symptoms which may occur during or shortly after treatment.

Table 15.11 - Side effects of immunotherapy (Source: (Haanen et al 2017; Kirkwood,Lotze and Yasko, 2001; Joint National Formulary, 19)

Mild side effects	**Severe side effects**
Minor inflammation	Auto immune response
Flu like symptoms	Skin breakdown
Nausea	Mucositis
Headaches	Blood pressure irregularity
Body aches	Vomiting
Fatigue	Colitis
Itching (rash on less than10% of body)	Paralysis

	Myocarditis
	Neurological disorders

Clinical considerations
Immunotherapy treatments are vastly becoming a popular choice in cancer care. They have expended treatment possibilities and are associated with less toxicity than traditional approaches. Guidelines for their use are differentiated by diagnosis, age and prognosis of each patient. Not all cancers and patients are responsive to immunotherapy. The risks and benefits of treatment as always is the priority in any consideration for immunotherapy (Haanen et al 2017).

Episode of care (adult)

Oluchi

Oluchi was 45 years old when she presented to her GP with a lump in her breast. Oluchi was the mother of three girls and lived in the city centre with her husband and children. After initial testing, Oluchi was diagnosed with breast cancer. Further testing showed that Oluchi's cancer staging was 2a and was HER2 positive. Oluchi was initially given Trasruzumab (targeted antibody) to reduce the size of her tumour, before she had surgery to remove the tumour completely.

Throughout her treatment, Oluchi's experienced various side effects, including;

- Hot flushes and sweating
- Disinterest in sex
- Vaginal dryness
- Nausea and vomiting
- Pain in her joints

- Mood changes
- Fatigue

Oluchi will continue to receive oral Trasruzumab at 6mg/kg for at least 2 years after her surgery and will continue to see her specialist team in long term follow up clinic.

Healthcare professionals will need to offer ongoing psychological and physical support for Oluchi, monitoring her for side effects of treatment and to ensure that her cancer does not recur.

Corticosteroid use in cancer

Steroids

Steroids are hormones that are naturally produced within the body, these are produced in small amounts during physiological or emotional stress. Stress sends signals to the brain for the pituitary gland to release the adrenocorticotropic hormone (ACTH). ACTH acts by instructing the adrenal glands (located above the kidney) to release cortisol, the body's natural steroid. Cortisol once released is picked up by cell receptors to respond to specific stress issues around the body (Ly and Wen 2017).

Cortisol has several functions, it can help reduce inflammation, help control blood glucose, regulate the metabolism, control salt and water balance, maintain blood pressure and assist memory function. Cortisol receptors are present in a majority of body cells, each using the cortisol in a different way.

Although there is currently limited knowledge on the pharmacodynamics of steroids, it is reported that corticosteroids act in the body by altering transcription and protein

synthesis within cellular activity (Wooldridge, Anderson and Parry 2001), thereby inhibiting the release of specific inflammatory mediators such as arachidonic acid.

Corticosteroids are man made replicas of natural cortisol hormones (steroid). Corticosteroids are used as a means of supplying the body with an increased source of steroid, in order to encourage and produce the same effects within cells of the body, that cortisol stimulates (Twycross 1994). Corticosteroids act through genomic and non genomic mechanisms. Genomic effects occur through gene translation or transcription. These include anti-inflammatory and immune suppression by excretion of anti-inflammatory cytokines and metabolic effects through suppression of the hypothalamic- pituitary -adrenal axis (Czock et al 2005). Non genomic effects occur through interaction with specific receptors such as glucocorticoids within cell membranes (Yu et al 1981; Ly and Wen 2017).

Using corticosteroids to treat cancer

Corticosteroids act in a variety of ways, primarily in cancer they are used for two principal functions, providing important components for modifying the fluid membrane and signalling molecules within the cell. These functions aim to reproduce responses within the immune system that are initiated by steroid activity, such as:

- Reduce inflammation,
- Suppress immunity,
- Reduce allergic reactions,
- Stimulate appetite (metabolic effects),
- Control the balance of water and salt,
- Regulate blood pressure,

- Control mood and behaviour (Walsh et al, 2000, Zhou and Cidlowski 2005).

The use of corticosteroids in cancer is part of well established treatment protocols. The type and stage of cancer often determines how corticosteroids will be used within pharmaceutical therapy plans (table 15.12). Corticosteroids are used in cancer to achieve a variety of effects, such as reduce inflammation, suppress immune responses, treat the cancer (by attacking the cell), help alleviate sickness and improve appetite. Type and stage of cancer often indicates corticosteroid use within treatment or management plans. Corticosteroids can be prescribed from diagnosis, throughout therapy or in palliative care (Ryken at al 2010, Cancer network, 2019). Anti-inflammatory and immune suppression are the main functions that signal use of corticosteroids in cancer patients. Reducing the inflammation around tumours, can help decrease the pressure on nerve endings, brain, spine or bone which are caused by the tumour. The corticosteroids ability to suppress the immune system by altering normal immune responses, although making the patient more susceptible to infection, allows the immune system to be re programmed and other therapeutic agents to fight cancer cells. It is also thought that corticosteroids can induce programmed death within certain cells and help fight cancer (Joint Formulary Committee, 2019).

Table 15.12. Examples of Corticosteroid use in cancer

Therapeutic plan	Desired effect
In conjunction with chemotherapy	Inhibit inflammatory responses, reduce allergic reactions, help reduce sickness, increase appetite Maintain blood pressure Control balance of water and salt
Pre and post surgery	Reduce inflammatory responses
Post Bone Marrow Transplant	Suppress immune system and reduce risk of rejection
Autonomously (advanced cancer)	Reduce inflammatory responses as part of symptom relief.

	Increase appetite

In cancer treatment there are four main corticosteroids in use. These are prednisolone, methylprednisolone, dexamethasone and hydrocortisone as identified in table 15.13.

Corticosteroids can be administered through oral, topical, intravenous and eye drops. Oral tablets or liquids and intravenous methods are the most common routes in cancer care. Each corticosteroid has its own half-life and intermediate acting properties, defining differential indications for use (NICE 2017).

Table 15.13. Examples of corticosteroid

Route	Example of corticosteroid	Indication
Oral	·Prednisolone ·methylprednisolone · dexamethasone	·Acute lymphoblastic leukaemia ·Chronic lymphocytic leukaemia ·Hodgkin's Lymphoma Non Hodgkin's lymphoma Mycosis lymphoma · aplastic anaemia
Intravenous	·Hydrocortisone · methylprednisolone · dexamethasone	· Brain tumours · Spine tumours ·cerebral oedema caused by tumours
Topical	· Dexamethasone · hydrocortisone	· Basal and squamous cell skin cancers
Eye drops	· Dexamethasone	· Prevent eye inflammation in leukaemia and lymphoma patients

Dexamethasone is one of the strongest corticosteroids. Dexamethasone holds 7.5 times greater effect opposed to prednisolone and hydrocortisone. The use of dexamethasone in cancer is a popular choice during initial treatment protocols. Long term use is mainly restricted to palliative care (EMC 2019). Table 15. 14 outlines the properties of oral dexamethasone.

Table 15.14 Dexamethasone

Use	Dexamethsone is a corticosteroid that can be used for its anti inflammatory, immune suppression and membrane stabilising properties within most cancers. It is also often used for the reduction of nausea and vomiting in patients under going chemotherapy (EMC 2019)
Dose	Adult doses range from 0.5-10mg daily, depending on severity of disease. When used to treat nausea and vomiting, doses can range from 8-16mg/day (Joint Formulary Committee 2018-19) Childrens doses are calculated dependant on reason for use, stage of cancer, alongside the child's weight. Each individual child must be prescribed dose accordingly considering how they will manage the treatment.
Administration	Can be given as IV infusion, or oral in tablets and liquid form. Oral treatment should be taken as one dose each morning with or after food. Patients on high doses may require to have doses more than once day (EMC 2019, Joint Formulary Committee 2018-19).

Pharmacodynamics	Dexamethasone activates the transcription of corticosteroid sensitive genes. Effects of anti-inflammatory, immune suppression and cell anti proliferation are caused by a decrease in the formation, release and activity of inflammatory mediators, inhibiting the specific function and migration of inflammatory cells.
Pharmacokinetics	Absorption- oral dexamethasone is rapidly absorbed in the stomach and small intestine. Creating a bio availability of 80%-90%. Distribution- It binds to plasma albumin, high doses give largest portion of drug that circulates within the blood. Metabolism- Partly metabolised by the kidneys. Half life is up to 36 hours. Excretion- Metablities are excreted as gluconates or sulfates and excreted by the kidneys (EMC 2019).
Common or very common side effects	Adrenal suppression, anxiety, appetite increased, abnormal behaviour, cataract, cushings syndrome, electrolyte imbalance,

	fluid retention, headache, increased risk of infection, osteoporosis (Joint Formualry Committee 2018-19)

Side effects of corticosteroids

Corticosteroid use has several mild and severe associated side effects. It is well known that corticosteroids can mask the symptoms of infection and reduce immunity; therefore, stringent procedures should be in place to ensure safe use in cancer patients. Short term use with low doses of corticosteroid have less complicated and more often immediate, short term side effects. Where long term use with high dose of corticosteroids as more common in cancer patients can present severe side effects that may take a prolonged time to resolve once treatment has ceased.

Clinical considerations
High dose and long term use of corticosteroids requires healthcare practitioners to be alert to not only common side effects but also to the more uncommon and rare effects on an individual's physical and mental health, that can be attributed to this form of treatment. The elderly population are at increased risk of osteoporosis and children are more susceptible to retarded growth. Preterm infants may suffer extra complications such as cognitive impairment (EMC 2019).

Certain side effects may cause adverse reactions and irreversible damage (Yasir and Sonthalia 2019). Table 15.15 details some of the more common side effects of long and short term use of corticosteroids, this list is not exhaustive. When administering

corticosteroids factors such as dose, duration and route alongside each patient's condition and health status need consideration for potential risk of side effects and adverse reactions.

Table 15.15. Side effects of corticosteroids

Side effects in short term use (often lower dose)	**Side effects in long term and high dose use**
Insomnia	Weight gain
Gastrointestinal ulcers	Thinning of skin
Oral and vaginal candida	Cushingoid appearance
Anxiety	Osteoporosis *This may be permanent*
Glucose intolerance	Proximal myopathy
	Infection
	Impaired wound healing
	Gastrointestinal bleed
	Cardiac arrhythmias *This may be permanent*
	Cataracts *This may be permanent*
	Acne
	Increased risk of bone fracture
	Depression, suicidal thoughts
	Growth deceleration in children

(Yasir and Sonthalia 2019, Sonauke, Docke and Asadullan 2002)

Clinical considerations
NICE (2017) stipulate that consideration for the use of corticosteroids should consider age of person (children and elderly being more susceptible to adverse side effects), certain conditions, (diabetes mellitus, hypertension and hepatic impairment require caution and close monitoring) in conjunction with the indication for use to ensure patient safety.

Episode of care (child) **Alex**

Alex was 3 years old when he presented to hospital with a month history of flu-like symptoms and a recent development of a purpuric rash. After initial testing, Alex was diagnosed with Acute Lymphoblastic Leukaemia (ALL).

Alex lives at home on farm with his mother, father and one sister, aged 2 years. The family are struggling with income due to recent floods.

Alex was treated according to the UKALL 2011 trial guidelines which combines the use of corticosteroids and chemotherapy. As Alex's cancer was low risk, he was assigned to regimen A of the trial.

Alex was initially given a 4 week period of bi-daily, high dose oral dexamethasone, alongside intravenous vincristine (weekly). Following this initial induction period (6 weeks), Alex was given a combination of intravenous and oral chemotherapy and oral corticosteroids over a period of 3 years to cure his leukaemia.

Throughout his treatment, Alex experience various side effects including;

- Initial weight gain
- Nausea and vomiting
- Alopecia
- Mucositis
- Weight loss (later in treatment)
- Decelerated growth

Prior to discharge, a nurse will need to ensure that Alex's family are educated and competent in recognising side effects of treatment and when to seek medical help.

Alex will continue to be followed up after his treatment by his specialist team in long term follow up. Healthcare professionals will need to offer ongoing psychological and physical support for Alex, monitoring him for side effects of treatment and to ensure that his cancer does not recur.

Conclusion

Treatment of cancer can occur using a number of different pharmaceutical options. Understanding of the difference between cancer cells and normal cells, allows for greater appreciation of the pharmacodynamics of each of these treatment options. When caring for patients with cancer, it is important that the nurse understands how each treatment regimen works and the side effects of these. The nurse also needs to be able to provide those receiving cancer treatment and if appropriate, their families with high quality safe and effective care in a compassionate way. A holistic approach is advocated with the patient at the centre of all that is done

Different cancers have different properties and result in different abnormalities during the growth and multiplication of the cell. Not all treatments will be appropriate for all cancers, instead treatment must be tailored to the individual patient's cancer. Whilst one patient may have a single approach to treatment, other patients will require a combination of many different forms of treatment. Cancer care must be managed to ensure that the benefit of treatment outweighs the risk from adverse reactions or side effects.

This chapter has outlined some of the main pharmaceutical treatment options currently used for cancer in the UK. Advances in cancer research are continually developing and improving the care that can be offered to patients with cancer.

References

Almeida, VL., Leitão, A., Reina, LCB., Montanari, CA., Donnici, CL. and Lopes MTP. (2005). 'Cancer and Nonspecific Cycle-Cell and Nonspecific Cycle-Cell Antineoplastic Agents Interacting with DNA: An Introduction'. *New Chemistry*. 28(1), pp118-129.

Bignold, LP. (2006). 'Alkylating Agents and DNA Polymerases'. *Anticancer Research,* 26, pp327-1336.

Cancer Research UK. (2017). 'Treatment'. Available from https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment. Last accessed August 2019.

Cancer research institute (2019) https:www.cancerresearchuk.org accessed 07.08.19

Cancer network (2019) https:www.cancernetwork/steroids.org

Castro F,Cardoso A, Goncalves R,Serne K and Olneiria M. (2018). 'Interferon Gamma at the crossroads of tumour surveillance or evasion'.doi.org/10.3389/fimmu.2018.00847

Chaniyara, R., Kapuriya N, Dong H, Lee PC, Suman S and Marvania B. Novel bifunctional alkylating agents, 5,10-dihydropyrrolo[1,2-b]isoquinoline derivatives, synthesis and biological activity. Bioorganic and Medical Chemistry. 2011;19:275–86. DOI:10.1016/j.bmc.2010.11.030.

Coosemans A, Vankerckhoven A,Baert T,Boon L, Ruts H, Riva M, Blagdon S,Delforge M,Concin N,Mirza M, Ledermann J and Vergote I.(2019).'Combining

convential therapy with immunotherapy: A risky business?'. *European Journal of Cancer.* V113. Pp41-44

Czock D,Keller F,Rasche F and Haussler U. (2005). 'Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids'. doi:10.2165/00003088-200544010-00003.

Drugs.com https://drugs.com/monograph/rituximab.html Last accessed 10.09.19

Electronic Medicines Compendium (EMC). (2016). 'Cyclophosphamide Tablets 50mg'. https://www.medicines.org.uk/emc/product/1813/smpc. Last accessed August 2019.

Electronic Medicines Compendium (EMC). (2017). 'Cyclophosphamide 1000mg Powder for Solution for Injection or Infusion'. https://www.medicines.org.uk/emc/product/3525/smpc. Last accessed August 2019.

Fu, D., Calvo, JA., and Samson, LD. (2012). 'Genomic instability in cancer Balancing repair and tolerance of DNA damage caused by alkylating agents'. *Nature Reviews Cancer*, 12(2), pp104-120.

Gmeiner, WH. (2002). 'Antimetabolite Incorporations into DNA: Structural and Thermodynamic Basis for Anticancer Activity'. *Biopolymers.* 65, pp180-189.

Haanen J,Carbonnel C, Robert C, Kerr K, Larkin J,Peters S and Jordan K. (2017). 'Management of toxicities from Immunotherapy'. doi: 10.1093/annoc/mdx225

Hanahan D and Weinberg RA. (2011). 'The hallmarks of cancer: the next generation' doi.org/10.1016/j.cell.2011.02.013

Health and Safety Executive (HSE). ‘Safe handling of cytotoxic drugs in the workplace’. http://www.hse.gov.uk/healthservices/safe-use-cytotoxic-drugs.htm. Last accessed July 2019.

Hortobágyi,GN. (1997). ‘Anthracyclines in the Treatment of Cancer’. *Drugs.* 54(Supplement 4), pp1-7.

Johnson B, Manoucher A, Haugh A, Quch H, Bako J and Lebrin-Vignes B. (2019). ‘Neurological toxicity associated with immune checkpoint inhibitors: a pharmacoconveince study’. *Journal for Immunotherapy of cancer*. V7(134)

Joint Formulary Committee. (2019) British National Formulary (BNF). (2019). “Cytotoxic Drugs”. https://www.medicinescomplete.com/#/content/bnf/_979237904?hspl=chemotherapy#content%2Fbnf%2F_979237904%23section_979237904-0. Last accessed July 2019.

Kirkwood J, Lotze M and Yasko J.(2001). *Current cancer Therapeutics. 4th edition*. Port City Press. Philadelphia

Lee S and Margoln K.(2011). ‘Cytokines in cancer Immunotherapy’. Journal of Cancer. doi.10.33901/cancers3043856

Ly K and Wen P.(2017). ‘Clinical relevance of steroid use in Neuro-Oncology’. doi:10.1007/s11910-017-0713-6

McClendon, AK., and Osheroff, N. (2007). ‘DNA Topoisomerase II, Genotoxicity, and Cancer’. *Mutation Research.* 623(1-2), pp 83-97.

McEwen B. (1991). ‘Non geonomic and geonomic effects of steroids on neural activity’.*Pharmacology*. V12(4).pp141-7

Moudi, M., Rusea, G., Yien, CYS., and Nazre, M. (2013). ‘Vinca Alkaloids’. *International Journal of Preventative Medicine.* 4(11), pp1231-1235.

Neilsen, D., Maare, C., and Skovsgaard T. (1996). ‘Cellular resistance to anthracyclines’. *General Pharmarcology: The Vascular System.* 27(2), pp251-255.

NICE (2017). National Institute for Health and Care Excellence. https:www.nice.uk/corticosteroids

NICE. (2018) National Institute for Health and Care Excellence. https:www.nice.uk/ngTA554

NICE (2018b) National Institute for Health and Care Excellence. https:www.nice.uk/ngTA559

Office for National Statistics (ONS). (2019). ‘Cancer registration statistics, England: 2017’. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2017. Last accessed July 2019.

Pires, J., Kreutz, OC., Sayuri Suyenaga, E., and Perassolo, MS. (2018). ‘Pharmacological Profile and Structure-Activity Relationship of Alykylating Agents used in Cancer Treatment’. *International Journal of Research in Pharmacy and Chemistry,* 8(1), pp6-17

Restifo N, Dudley M and Rosenberg S.(2012). ‘Adoptive immunotherapy for cancer: harnessing the T cell response.’ *Nature Reviews Immunology*. V12. Pp269-281

Rosenberg S, Restifo N, Yang J, Morgan R and Dudley M.(2008).'Adoptive cell transfer : a clinical path to effective cancer immunotherapy'. *Nature Reviews Cancer.*V8.pp299-308

Ryken Tc, McDermott M, Robinson P,Ammirati M, Andrews D, Asher A, Burri S.(2010).'The role of steroids in management of brain metastases: A systemic rerview. doi:10.1007/s11060-009-0057-4

Sanauke H, Dacke W and Asadullah K. (2002). 'Mechanisms involved in the side effects of glucocorticoids'. Pharmacology.V961.pp23-43

Schrieber RD and Smyth MJ.(2011).'Cancer immunoediting: integrating immunity's role in cancer suppression and promotion'.doi.org/10.1126/science.1034864

Twycross R.(1994).'Risks and benefits of corticosteroids in advanced cancer'. National Library of Medicine. V11(3).pp163-8

Vansteenkiste J.(2012).'Immunotherapy'. https://dx.doi.org/10.1016/j.lungcan.2012.05.029

Walsh D, Doona M, Molnar M and Lipnickey V.(2000).'Symptom control in advanced cancer:important drugs and routes of administration'. Oncology. V27(1).pp69-83

Wooldridge J,Anderson M and Parry M.(2001).'Corticosteroids in advanced cancer'. Cancer Network. V15(2). Pp225-234.

Woolley, D. (1959). 'Antimetabolites'. *Science.* 129, pp3349.

www.ncbi.nih.gov.uk (2019)

Yao H, Wang and Fang JY.(2018).'Cancer cell intrinisic PD-1 and implications in combinatorial immunotherapy'. Doi.org/10.3389/fimmu.2018.01774

Yasir M and Sonthalia S.(2019).'Corticosteroids adverse effects'.www.ncbi.nlm.nih.gov

Yu Z, Wrange O, Baethius J, Hatam A, Granholm L and Gustafsson J.(1981).'A study of glucocorticoid receptors in intracranial tumours'. doi:10.3171/jns.1981.55.5.0757.

Zhou J and Cidwlowski J.(2005). 'The human glucocortoid receptor: one gene multiple proteins and diverse responses'. doi:10.1016/j.steroids.2005.02.006

Zhou, XJ., and Rahmani R. (1992). 'Preclinical and Clinical Pharmacology of Vinca Alkaloids'. *Drugs.* 44(Supplement 4) pp1-16.

Further Reading

National Cancer Peer Review-National Cancer Action Team

The NCAT have written a Manual for Cancer Services which supports the National Cancer Peer Review quality assurance programme for cancer services to enable quality improvement, in terms of both clinical and patient outcomes.

NICE guidelines

The National Institute for Health and Care Excellence (NICE) write evidence-based recommendations for healthcare in England. They provide a number of guidelines for the care and services suitable for most patients with certain types of cancer.

SIGN Guidelines

The Scottish Intercollegiate Guidelines Network (SIGN) develop and disseminate clinical guidelines for evidence based healthcare practice in Scotland. They have developed a range of guidelines for use in cancer care.

Royal Pharmaceutical Society

The RPS provides pharmaceutical guidance for all healthcare practitioners in the UK. Information is available on current treatments for cancer.

Multiple Choice Questions

1. Over recent years, the UK has seen….
    a. A decrease in the number of females diagnosed with cancer.
    b. An increase in the number of people dying from cancer.
    c. A decrease in the number of people dying from cancer.
    d. No change in the number of people diagnosed with cancer.
2. Which of these is a ‘Hallmark of a cancer cell’?
    a. Inducing angiogenesis
    b. Apoptosis
    c. Activating growth suppressors
    d. Limited multiplication
3. At what stage in the cell cycle, does the cell completely divide?
    a. M
    b. G1
    c. G2
    d. S
4. What does cytotoxic mean?
    a. Nourishes the cell

b. Stops the cell receiving messages

c. Stimulates the cell to grow

d. Poisonous to cells

5. Which of these is **not** a route that chemotherapy can be administrated?

a. Oral

b. Intravenous

c. Intrafollicular

d. Intrathecal

6. How does an antimetabolite work?

a. Inhibits topoisomerase II

b. Creates a deficiency of essential molecules

c. Transfers alkyl carbon molecules

d. Binds to tubulin

7. What are vinca alkaloids derived from?

a. Plants

b. Hormones

c. Horse urine

d. Synthetic compounds

8. Which of these is a **common** side effect of chemotherapy?

a. Changes to eye colour

b. Death

c. Hair loss

d. Perforated ear drum

9. What are the two main functions of the immune system?

a. Increase bone strength and fight infection

b. Fight infection and reduce inflammation

c. Stimulate growth and reduce inflammation

d. Control hair growth and support vision

10. Which one of the following is **not** part of the immune system?

a. White blood cells

b. Spleen

c. Lymph Nodes

d. Liver

11. How does immunotherapy work?

a. Targets proteins on cancer only cells

b. Suppresses the immune system

c. Attracts cancer cells

d. Opens checkpoints in cancer cells

12. What is the role of supportive immunotherapy?

a. To prime the immune system

b. To stop growth within the cancer cell

c. To reduce growth in the cancer cell

d. To reduce inflammation

13. Who is the donor for an autologous bone marrow transplant?

a. Identical twin

b. Unrelated

c. Family

d. Self

14. Where are steroids naturally produced in the body?

a. The adrenal glands

b. Lymphocytes

c. The bone marrow

d. Testes

15. Why are corticosteroids used in the treatment of cancer?

a. To regulate heart and kidney function

b. Increase immunity and inflammatory responses

c. Reduce inflammation and allergic reactions

d. Support bone strength and growth

The following is a list of some of the cancers that are included in this chapter. Take some time and write notes about the treatment of each of the cancers and be specific about the pharmacodynamics and possible side effects of the medicines that would be used to treat this.	
Acute Lymphoblastic Leukaemia (ALL)	
Myeloma	
Hodgkin's lymphoma	
Breast Cancer	
Melanoma	

Glossary

Alopecia	The partial or complete loss of hair from areas of the body where it normally grows.
Antibodies	A blood protein produced in response to and counteracting a specific antigen.

	Antibodies combine chemically with substances which the body recognizes as alien, such as bacteria, viruses and foreign substances in the blood.
Antigen	A toxin or other foreign substance which induces an immune response in the body, especially the production of antibodies.
Auto immune	Relating to disease caused by antibodies or lymphocytes produced against substances naturally present in the body, producing the body's own auto immune response.
Differentiation	The process by which cells, tissue and organs acquire specialized features, especially during embryonic development.
Epitope	The part of an antigen molecule to which an antibody attaches itself.
Molecule	A group of atoms bonded together, representing the smallest fundamental unit of a chemical compound that can take part in a chemical reaction.
Mucositis	Inflammation of a mucous membrane, especially that caused by cytotoxic therapy (radiation or chemotherapy).
Organism	An individual animal, plant, or single-celled life form.
Proliferation	Rapid reproduction of a cell, part, or organism.
Protein	Proteins are large molecules, composed of one or more chains of amino acids in a specific order, and are required for the structure, function, and regulation of the body's cells, tissues, and organs.
T cell	A lymphocyte of a type produced or processed by the thymus gland and actively participating in the immune response.
Toxic	Relating to or caused by poison.