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Pharmacology for chemotherapy and immunosuppressants

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Introduction

Cancer is the second leading cause of death globally and accounts for 10% of deaths in South Africa.[1,2] Patients with a history of cancer have shown increased survival with the use of treatment. Anaesthetists frequently encounter patients in all stages of cancer and cancer treatment.[3]

There is a global increase in solid organ transplantation. Increased survival amongst transplant recipients is observed due to improved surgical techniques and immunosuppressive therapy. Patients on immunosuppressive treatment therefore present for transplant and non-transplant related surgery.[4]

The majority of chemotherapy targets cancer cells during rapid division and proliferation. However, the disruption of cell division also affects normal functioning cells in organs involved and uninvolved, resulting in acute/chronic injury after exposure. By understanding the mechanisms of chemotherapy drugs on targeted cancer cells, it is possible to predict what injuries might occur in the rest of the body.[3] Consequently, to understand how chemotherapy interferes with cell division, we must revisit the cell cycle.

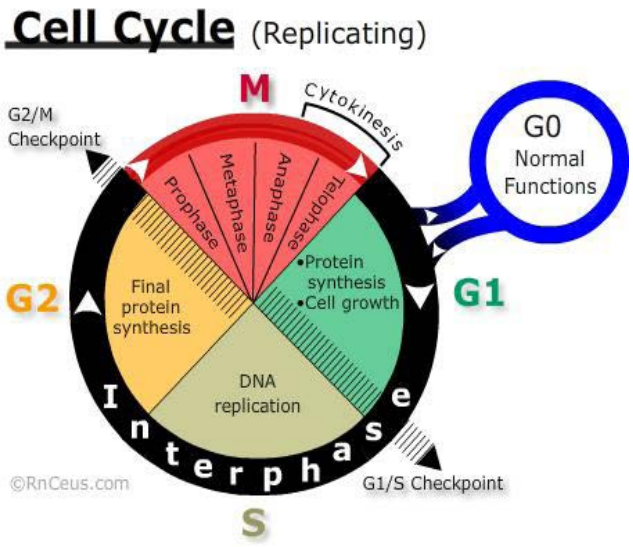

Figure 1: The cell cycle

The cell cycle

The cell cycle is the way cells replicate. It consists of a sequence of cellular events that occur in phases regulated by chemical signals. The eukaryotic cell cycle lasts 24 hours and consists of five phases (Figure 1).[5]

G0/resting stage – Normal metabolic function. Once the cell gets a signal, it starts to replicate.

G1-phase (1st gap) – Involves growth, metabolic activity, and synthesis of ribonucleic acid (RNA).

S-phase – Deoxyribonucleic acid (DNA) synthesis.

G2-phase (2nd gap) – Cell prepares for cell division.

M-phase – Mitosis/cell division occurs.

Proto-oncogenes stimulate cellular growth and division, while tumour suppressor genes restrict the cell cycle progression during G1, before the S-phase.[6] Chemotherapy drugs target cells at different phases of the cell cycle.

Classification of chemotherapeutic agents

Chemotherapeutic agents can be classified based on their mechanism of action (MoA), chemical structure, or relationship to other drugs.[3] Based on the MoA they can be cell-cycle specific (work on specific parts of the cell cycle), cell-cycle nonspecific (effective during all phases of the cell cycle), or hormonal.[6]

Cell-cycle specific

Antimetabolites

Examples: Folate analogue methotrexate (MTX). Purine analogues such as 6-mercaptopurine, azathioprine, and 6-thioguanine. Pyrimidine analogues such as 5-fluorouracil (5-FU), cytarabine, and floxuridine.[3]

MoA: They act as analogues of purine and pyrimidines and inhibit enzymes involved in the cellular metabolism of nucleic acids. They disrupt DNA/RNA synthesis in the S-phase of the cell cycle.[7]

Uses: Treatment of leukaemia, colorectal, bladder, and pancreatic cancers.

Side effects: Immunosuppression, nausea and vomiting, ulcerative stomatitis, diarrhoea, and haemorrhagic enteritis with potential intestinal perforation. MTX causes renal and hepatic toxicity, and pulmonary oedema/effusions, and 5-FU causes myocardial ischemia and acute cerebellar syndrome.[8] Mercaptopurine causes cholestatic jaundice, hyperuricemia, and hyperuricosuria.[7]

DNA synthesis enzyme inhibitors

Examples: Topoisomerase I inhibitors topotecan and irinotecan. Topoisomerase II inhibitors epipodophyllotoxins (e.g. etoposide) and anthracyclines (daunorubicin, doxorubicin, epirubicin, and idarubicin).[3]

MoA: They work by inhibiting the enzyme topoisomerase, which cleaves supercoiled DNA strands so they can be copied during the S-phase of the cell cycle. Inhibiting topoisomerase prevents DNA replication and these agents produce oxygen-free radicals. Topoisomerase I inhibitors prevent supercoiling by cleaving one strand while topoisomerase II inhibitors prevent the cleavage of two strands.[3]

Uses: Topotecan is used in leukaemia, lymphoma, ovarian, cervical, renal, and small-cell lung cancers. Irinotecan is for colorectal cancers.[3] Anthracyclines are mostly used in breast, lung, and bladder cancers as well as leukaemia and lymphomas.[7]

Side effects: Topoisomerase I inhibitors cause severe diarrhoea. Topoisomerase II inhibitors are cardiotoxic (oxygen-free radical production and topoisomerase inhibition in the cardiomyocyte alters calcium-channel activity, and causes arrhythmias, restrictive cardiomyopathy, and congestive heart failure).[3]

Enediynes

Examples: Actinomycin D (dactinomycin) and bleomycin.

MoA: These are antineoplastic antibiotics that damage DNA by oxidation and cleave the DNA strands in the G2-phase of the cell cycle. Dactinomycin disrupts DNA transcription by preventing elongation by RNA polymerase. Bleomycin interacts with iron to produce oxygen-free radicals and is inactivated by the amidohydrolase enzyme (found throughout the body except in the skin and the lungs).[3]

Uses: Treatment of cervical, breast, ovarian, skin, penis, rectal, head, and neck cancers as well as lymphomas.[3]

Side effects: Dactinomycin causes hepatic veno-occlusive disease and clotting disorders. Bleomycin causes painless flagellate hyperpigmentation in the skin and accumulates in the lungs, causing pulmonary fibrosis. Exposure to a high oxygen concentration perioperatively in patients on bleomycin can potentiate bleomycin pneumotoxicity and acute respiratory distress syndrome. The use of supplemental oxygen should be limited to < 30% or used as necessary to keep SaO_2 > 90%.[3]

Microtubule-binding agents

Microtubules provide the basic organisation of the cell's cytoplasm. They are critical in actively dividing cells as they create mitotic spindle, which segregates chromosomes during cellular division. Inhibition of microtubule activity prevents cellular proliferation and suppresses cell migration by vascular endothelial cells, leading to antiangiogenesis, and precluding tumour metastasis. There are two classes of anti-microtubular drugs that function by destabilising or stabilising the microtubules in the cell.[3]

i. Microtubule destabilisers

Examples: Vinca alkaloids such as vinblastine, vincristine, and vinorelbine.

MoA: They bind to the microtubular protein tubulin at the end of the microtubule, terminating the assembly and depolymerisation of the microtubules. This causes the arrest of mitosis in metaphase and chromosomes cannot segregate.[3]

Uses: Lymphomas and leukaemia.

Side effects: Nausea, vomiting, bone marrow suppression, and alopecia. Vincristine is neurotoxic (areflexia, muscle weakness, cranial nerve palsy, especially CN VI, sensory and motor peripheral neuropathy, laryngeal nerve paralysis [10% patients], and syndrome of inappropriate antidiuretic hormone secretion [SIADH]).[7] Vinorelbine causes chest pain, dyspnoea, bronchospasm, and pulmonary infiltrates.[8]

ii. Microtubule stabilisers

Examples: Taxanes such as paclitaxel and docetaxel (synthetic taxane).

MoA: They bind to the beta-tubulin subunit, stabilising the microtubule so depolymerisation is prevented, which arrests the cell in metaphase and halts mitosis.[8] Paclitaxel binds to the B-cell lymphoma 2 (Bcl-2) protein, inducing apoptosis and docetaxel inhibits vascular endothelial growth factor (VEGF) in addition to stabilising the microtubule.[3]

Uses: Testicular cancer, lymphoma, and leukaemia

Side effects: Neurotoxicity.

Cell-cycle nonspecific

They work on all phases of the cell cycle.

Alkylating agents

Examples: Nitrosoureas like carmustine, alkyl sulfonate such as busulfan, nitrogen mustards such as cyclophosphamide, ifosfamide and platinum drugs such as cisplatin.

MoA: Toxic in all phases of the cell cycle but most effective as antiproliferative drugs. The alkyl group covalently binds to DNA at the N7 position of the guanine nucleotide, forming a crosslinking of the DNA. This prevents subsequent transcription and arrests the cell replication in late G1 and S phases.[7] Platinum

drugs do not alkylate DNA but permanently bind to guanine residues in DNA.[3]

Uses: Treatment of Hodgkin's lymphoma, lymphosarcoma, leukaemia, and bronchogenic sarcomas. Platinum drugs are used in testicular, ovarian, bladder, head and neck, and small-cell lung cancer.[3]

Side effects: They have a dose-dependent toxicity usually targeting rapidly growing tissues. They affect the gastrointestinal tract (nausea, vomiting, diarrhoea) and cause bone marrow suppression (leukopenia, anaemia, thrombocytopenia), pulmonary fibrosis (busulfan, nitrosoureas, cyclophosphamide), neuropathies and nephrotoxicity (platinum drugs), and cyclophosphamide causes alopecia, haemorrhagic cystitis, and inhibits plasma pseudocholinesterase (prolonging the effect of suxamethonium).[3]

Antitumour antibiotics

Most of the antineoplastic antibiotics are produced by *Streptomyces* bacteria. They alter the DNA in cancer cells and prevent replication.[6] They are classified based on the mechanism of DNA damage:

a. Alkylate DNA includes adozelesin, bizelesin, and tallimustine.
b. Alkylate produce oxygen radicals, such as mitomycin C and streptonigrin.
c. Topoisomerase inhibitors produce oxygen radicals, and topoisomerase II inhibitors such as anthracyclines (daunorubicin, doxorubicin, epirubicin, and idarubicin).
d. Other antineoplastic antibiotics such as bleomycin and actinomycin D.[9]

Uses: Treatment of leukaemia, lymphoma, breast, and bladder cancers. Mitomycin C is used for squamous cell cancer of the cervix and adenocarcinomas of the stomach, pancreas, and lungs, and topical intravesical treatment of bladder papillomas.[3]

Side effects: Mitomycin C causes renal toxicity and acute pneumonitis leading to pulmonary fibrosis.[8] The rest have been discussed above.

Hormonal agents

Sex hormones and adrenocortical hormones are used in the management of several neoplastic diseases. Steroid hormones work by binding to receptor proteins in cancer cells, forming a steroid-receptor complex that binds directly to the nuclear nonhistone protein of DNA to activate the transcription of the associated cluster of genes. Most steroid-sensitive cancers have specific receptors.[7] Examples of steroid hormone drugs are discussed below.

Adrenocorticosteroids

Glucocorticoids are produced by zona fasciculata and reticularis, and mineralocorticoids are produced by zona glomerulosa. The main endogenous glucocorticoid is hydrocortisone, and the rest are synthetic with relative potencies indicated in Table I below. They have anti-inflammatory, metabolic, and immunosuppressive effects.[10]

Table I: Relative potencies of glucocorticoids[10]

Drug	Relative potencies	Equivalent doses (mg)
Hydrocortisone	1	100
Prednisolone	4	25
Methylprednisolone	5	20
Dexamethasone	25	4

They are used as prophylaxis for transplant rejection, in the treatment of haematological malignancies, autoimmune diseases, and the management of inflammatory and allergic conditions.

Adrenocorticosteroids cause immunosuppression by antiproliferation, and they inhibit T lymphocyte activation by downregulating the expression of cytokines (Interleukin-1, 2 and 6) in macrophages. They reduce plasma antibody levels, decrease capillary permeability, and decrease peripheral lymphocyte counts. Adrenocorticosteroids cause anti-inflammation by inhibiting circulating polymorphs and macrophages from reaching inflamed tissue, hence suppressing the production of inflammatory mediators (prostaglandins and leukotrienes).[10]

Side effects include adrenal suppression, fluid retention, hypertension, diabetes, increased susceptibility to infection, Cushing's syndrome, poor wound healing, bone disease (avascular necrosis and osteopenia), cataracts, muscle wasting, proximal weakness, skin thinning, psychosis, and insomnia.[7,10]

Oestrogens

Fosfestrol and ethinylestradiol are used in oestrogen-sensitive breast and prostate cancer. Side effects include hypercalcaemia and feminisation.[7]

Progestins

Hydroxyprogesterone acetate is used in endometrial, breast, and prostate cancer.

Antioestrogen

Tamoxifen is used in breast and progesterone-resistant endometrial cancer. It functions as a competitive inhibitor of oestrogen, binding to oestrogen-receptor proteins and preventing oestrogen-stimulated increases in oestrogen-sensitive tissues and tumours. It causes hot flushes, deep vein thrombosis, and nausea.[7]

Antiandrogen

Flutamide is used in the treatment of prostate cancer and to antagonise the androgenic effects after orchiectomy. Side effects include feminisation, skeletal muscle weakness, and methemoglobinemia.[7]

5-alpha-reductase inhibitor

Finasteride is used in the treatment of prostate cancer.

Gonadotrophin-releasing hormone agonists

Leuprolide acetate, nafarelin, and goserelin are analogues that inhibit follicle-stimulating hormone and luteinising hormone, causing reduced testicular androgen synthesis. They are used in the treatment of metastatic prostate cancer. Side effects include painful gynaecomastia, nausea, vomiting, oedema, and thromboembolism.[7]

Aromatase inhibitors

Aminoglutethimide (Cytadren) inhibits adrenal steroid synthesis, preventing the conversion of cholesterol to pregnenolone and inhibits the aromatase conversion of adrenal androgen androstenedione to estrone. It is used in treating metastatic breast cancer (oestrogen and progesterone receptor-sensitive). Side effects include dizziness, lethargy, blurred vision, and rash.[7]

Immunosuppressants

These agents play an important role in the prevention and treatment of tissue transplant procedures and the management of certain diseases associated with immunity disorders.[7] Immunosuppressive drugs can be used before transplantation (induction phase), maintenance (long-term drugs), or as anti-rejection therapy. Graft rejection can be hyperacute (< 24 hours), acute (within the first few weeks), or chronic (months to years later).[9] Immunosuppressants are classified according to their mode of action.

Inhibitors of cytokine synthesis

i. Cyclosporine

This is a calcineurin inhibitor. Calcineurin is a protein phosphatase that activates T cells by dephosphorylating a cytoplasmic transcription factor (nuclear factor of activated T cells [NFAT]), which migrates to the nucleus and induces transcription and upregulation of Interleukin-2 (IL-2). IL-2 causes growth and differentiation of T cells. Calcineurin inhibitors blunt signal transduction in T lymphocytes, leading to the suppression of T cell proliferation and response of helper T lymphocytes.[9]

MoA: The calcineurin inhibitor prevents IL-2 T cell proliferation and increases the expression of transforming growth factor (TGF).

Pharmacokinetics: It has 30–90% oral bioavailability, is lipophilic, and has a half-life of 8–27 hours.[11,12]

Uses: Induction and maintenance of immunosuppression in transplant, severe rheumatoid arthritis, and psoriasis.[9]

Side effects: Hypertension, nephrotoxicity (vasoconstriction in the glomerulus leading to renal dysfunction, usually the reason for modifying or stopping the drug), neurotoxicity (tremors, seizures, can prolong the effect of non-depolarising muscle relaxants necessitating a decrease in dose), metabolic problems (hypertriglyceridemia and insulin resistance), gingival hyperplasia (due to increased TGF), and hirsutism. Metabolised by P450, especially CYP3A4, and can have drug interactions with enzyme inducers or inhibitors.[13]

ii. Tacrolimus (FK-506)

MoA: Binds to FK-binding protein 12 (FKBP-12) in the cytoplasm, which interacts and inhibits calcineurin and inhibits the expression of tumour necrosis factor-beta (TNFb). It is highly protein-bound, especially with albumin and alpha-1 glycoprotein, hence close monitoring of blood levels is essential.

Pharmacokinetics: It can be administered orally, sublingual, topical, or intravenously. The half-life is 4–12 hours with a 30 L/kg volume of distribution. It is metabolised by CYP3A4 and about 95% is excreted in bile with 2.4% excreted in the urine unchanged.[12]

Uses: Macrolide antibiotic used for the maintenance of immunosuppression and rescue therapy in acute rejection post-liver transplant.

Side effects: Nephrotoxicity, hypertension, and neurotoxicity (avoid excessive hyperventilation as this can trigger seizures). Drugs inhibiting the CYP3A4 enzyme (like calcium-channel blocker, antifungal, or metoclopramide) or CYP3A4 enzyme inducers, like anticonvulsants, can increase and decrease blood concentrations of tacrolimus respectively.[13]

iii.Sirolimus

MoA: It binds to immunophilin (FKBP-12) in the cytoplasm and the complex inhibits the "target of rapamycin" (mTOR), which is a protein kinase that suppresses the cell division and proliferation of T cells.[13]

Pharmacokinetics: It has rapid gastrointestinal absorption with a peak concentration in one hour (70% of patients) and a half-life of 62 hours.[13] It is hydrophobic and mainly metabolised in the liver, with 92% of metabolites excreted in bile and 1.2% in urine.[12]

Uses: Macrolide antibiotic used as prophylaxis for kidney transplant rejection or in combination with FK-506 and glucocorticoids to decrease their side effects. Also used in drug-eluting stents to prevent endothelial growth over the stent.[9]

Side effects: Pancytopenia, marked hyperlipidaemia (due to inhibition of lipoprotein lipase), and drug interaction with CYP3A enzyme inhibitors/inducers.

iv.Monoclonal anti-CD25 antibodies

Basiliximab (Simulect) and daclizumab (Zenapax) block the IL-2 receptor directly, downregulating the immune system. Daclizumab blocks the CD25 receptor, hence it is used in treating relapsing multiple sclerosis and as an induction immunosuppressive agent. Side effects include anaphylaxis.[8]

Inhibitors of DNA synthesis

i. Mycophenolate mofetil

This is used as a maintenance immunosuppressant and for chronic rejection. It is an ester drug that is hydrolysed to mycophenolic acid (active component), a selective non-competitive inhibitor of inosine monophosphate dehydrogenase (IMPDH), essential for purine synthesis. This causes impaired activity and proliferation of B and T cells.[9] Side effects include pancytopenia, diarrhoea, and vomiting.

ii. Azathioprine

A derivative of 6-mercaptopurine that is subsequently metabolised by xanthine oxidase to 6-thioguanine nucleotides and inhibits purine synthesis. It is used as a maintenance immunosuppressant and autoimmune treatment.[7] It inhibits lymphocyte proliferation and purine synthesis (consequent decreased DNA and RNA synthesis). Side effects include myelosuppression, hepatic dysfunction, pancreatitis, transient antagonism on non-depolarising muscle blockers, and drug interaction with allopurinol (decrease azathioprine dose by one-third to prevent toxicity).[9]

Inhibition of T cell interaction

i. Steroids

Prednisone, dexamethasone, and cortisone are discussed above under adrenocorticosteroids.

ii. Muromonab-CD3 (orthoclone OKT3)

This is a murine monoclonal antibody (mAb) used primarily as induction in patients undergoing a transplant, especially kidney. They bind to the CD3 receptor of T lymphocytes inhibiting its activation. Side effects include pulmonary oedema, anaphylaxis, and cytokine release syndrome (fever, headache, bronchospasm, hypotension, and tachycardia).[9]

Inhibitors of adhesion molecules

i. Antithymocyte globulin (ATG)

This is used as an induction immunosuppressant and in the management of acute rejection in kidney transplants.[9] Antithymocyte globin have cytotoxic antibodies that bind to antigen makers (CD2, CD3, CD4, CD8, CD44, and HLA class I molecules) on the surface of T cells causing the inhibition of T cell function and decreased circulating lymphocytes.[9] Side effects include anaphylaxis, serum sickness, and leukopenia. These are minimised by slow infusion.[9]

Other mAbs

i. TNFa inhibitors

Adalimumab, infliximab, and etanercept are used in haematological malignancies and autoimmune conditions (inflammatory bowel disease, rheumatoid arthritis, psoriasis, and sarcoidosis).[7] mAbs are Fc-fusion proteins inhibiting TNFa. Etanercept is not a mAb but works as a decoy TNFa receptor fusion protein at the Fc portion of immunoglobulin G (IgG).[14] Side effects include the reactivation of latent tuberculosis (must test for tuberculosis before commencing this treatment), heart failure, and neurotoxicity (demyelination).[13]

ii. Rituximab

A chimeric mouse/human IgG1-kappa murine mAb. It is used in the treatment of B cell lymphoma, leukaemia, and autoimmune conditions like rheumatoid arthritis and myasthenia gravis. It binds to CD20 and enhances the destruction of B cells leading to decreased B cell levels. Side effects include anaphylaxis, acute kidney injury, bowel obstruction, tumour lysis syndrome, and pulmonary toxicity.[12]

iii.VEGF inhibitors

Bevacizumab selectively binds VEGF and inhibits VEGF from binding to its receptor, hence inhibiting angiogenesis.[13]

Anaesthetic implication of chemotherapeutic and immunosuppressive agents

There are several challenges when faced with patients on cancer treatment or immunosuppressants, from deranged physiology, tumour-associated effects, toxicity of chemotherapy/immunosuppressants, and drug interactions.[15] Various anaesthetic agents interact with chemotherapy and immunosuppressants differently.

Volatile anaesthetics

Volatiles have positive and negative effects when combined with chemotherapeutic agents. Halothane enhances the antitumour effect of IFN-γ when combined in patients with colon cancer. Sevoflurane suppresses cell growth in combination with cisplatin for the management of adenocarcinoma in the lungs but causes chemoresistance in renal cell cancer. Isoflurane causes chemoresistance in prostate cancer while sevoflurane enhances cancer progression in breast cancer.[15]

Intravenous drugs

Propofol enhances the effect of chemotherapy in ovarian and pancreatic cancer but decreases the cytotoxicity of cisplatin when used together. Ketamine causes apoptosis and decreased proliferation in ovarian, gastric, and pancreatic cancer.[15] Anthracycline-based chemotherapeutic agents and mAb agents, like trastuzumab, cause significant cardiotoxicity. In combination with anaesthetics that prolong the QT interval, like halothane, propofol, or beta-2 agonists, it leads to fatal arrhythmias. Renal toxicity of calcineurin inhibitors can have significant interactions with anaesthetic agents and fluid management.

Opioids

Morphine, in particular, decreases the cytotoxic effects of chemotherapeutic agents and causes immunosuppression. Morphine also causes angiogenesis, increased prostaglandins, increased expression of mu receptors and is a natural killer of cell expression in breast and lung cancer, hence it can increase the risk of cancer recurrence.[3] Alpha-2 agonists and nonsteroidal

anti-inflammatory drugs (NSAIDs) have beneficial effects on pain management in cancer patients.

Regional anaesthetics

These have antitumour effects and increase the efficacy of chemotherapy agents when given together. Local anaesthetics, especially lidocaine, have been shown to sensitise tumours to chemotherapy.

Oxygen

Hypoxia causes resistance to radiotherapy and chemotherapy since oxygen is important for DNA damage. However, perioperative use of high concentrations of oxygen in patients on certain medications, like bleomycin, can potentiate bleomycin pneumotoxicity and acute respiratory distress.

Conclusion

Anaesthetics, stress, pain, hypothermia, hyperglycaemia, and other factors that anaesthesiologists encounter are immunomodulators and play a role in increasing or decreasing cancer recurrence. Conducting good clinical history and examination as well as excluding metabolic derangements in patients coming to theatre for surgery on chemotherapy or immunosuppressive drugs is essential. Patients should continue immunosuppressants perioperatively. Meticulous infection control is essential as these patients are prone to infections. Good knowledge of side effects and drug interactions impacts the type of anaesthesia administered and should be known by all anaesthesiologists.

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