Chapter 8
Malignant disease

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Chapter 8
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1 IMMUNE SYSTEM

Chronic inflammatory and autoimmune diseases, and organ transplant patients are maintained on drug regimens, which may include antiproliferative drugs (azathioprine or mycophenolate mofetil), calcineurin inhibitors (ciclosporin or tacrolimus), corticosteroids, or sirolimus.

The use of azathioprine and ciclosporin should not be discontinued during pregnancy. The use of these drugs during pregnancy needs to be supervised in specialist units.

1.1 ANTIPROLIFERATIVE IMMUNOSUPPRESSANTS

1.1.1 Azathioprine

Azathioprine is used for transplant recipients and auto-immune conditions, it is metabolised to mercaptopurine. Doses should be reduced when allopurinol is given concurrently due to risk of bone marrow suppression.

1.1.1.1 Side effects

Red cell aplasia has been reported with azathioprine *and* mycophenolate mofetil; dose reduction or discontinuation should be considered under specialist supervision.

Hypersensitivity reactions (including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and interstitial nephritis—calling for immediate withdrawal

Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. inexplicable bruising or bleeding, infection.

Nausea, vomiting, and diarrhoea may occur during early stages of treatment, in rheumatoid arthritis treatment can be discontinued if this occurs.

1.1.1.2 Monitoring requirements

Full blood count for 4 weeks then every 3 months; monitor toxicity throughout treatment; blood tests and monitoring for signs of myelosuppression in long-term treatment

1.1.1.3 Pre-treatment screening

Thiopurine methyltransferase (TPMT) metabolises thiopurine drugs (azathioprine, mercaptopurine); the risk of myelosuppression is increased in patients with reduced activity of the enzyme. TPMT activity should be measured before starting azathioprine or mercaptopurine. Patients with absent TPMT activity should not receive thiopurine drugs; those with reduced TPMT activity need specialist supervision.

1.1.2 Mycophenolate

Mycophenolate has a more selective mode of action than azathioprine. It is licensed for the prophylaxis of acute rejection in renal, hepatic or cardiac transplantation when used in combination with ciclosporin and corticosteroids.

1.1.2.1 Bone marrow suppression

Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding.

1.1.2.2 Risk of hypogammaglobulinemia or bronchiectasis

When used in combination with other immunosuppressants risk of recurrent infections (hypogammaglobulinemia), and respiratory symptoms such as cough and dyspnoea (bronchiectasis)

1.1.2.3 Red cell aplasia

Cases have been reported with azathioprine and with mycophenolate mofetil; dose reduction or discontinuation should be considered under specialist supervision.

1.1.2.4 Pregnancy prevention

Congenital malformations and spontaneous abortions reported. Exclude pregnancy immediately before and during treatment. Women should use 2 methods of effective contraception during treatment, and for 6 weeks after discontinuation. Men and their partners should both use contraception during treatment and for at least 90 days after discontinuation.

1.2 CICLOSPORIN (HIGH RISK)

Ciclosporin a calcineurin inhibitor, is a potent immunosuppressant which is virtually non-myelotoxic but markedly nephrotoxic.

Loading doses may be required

1.2.1 Warning signs

(report immediately to a doctor)

- *Neurotoxicity*
  (tremor, headache, encephalopathy (e.g. confusion, convulsions))
- *Blood disorders*
  (signs of infection such as fever, sore throat, mouth ulcers, also unexplained bruising or bleeding)
- *Liver toxicity*
  (jaundice, nausea, vomiting, abdominal discomfort, dark urine)
- *Nephrotoxicity*
  (elevated serum creatinine concentrations)
- *Vomiting, drowsiness, tachycardia*
- *Hypertension*
  (common; monitor blood pressure regularly)
- *Benign intracranial hypertension*
  (headache, visual disturbances; discontinue if occurs)
- *Gingivial hyperplasia*

1.2.2 Monitoring

- *full blood count*
- *liver function*
- *serum electrolytes (K+, Mg2+)*
- *blood lipids*
- *renal function (including creatinine, urea)*
- *blood pressure,*
- *dermatological and physical examination*

1.2.3 Pregnancy

Continue using under specialist supervision

1.2.4 Other points

Avoid excessive exposure to UV light, including sunlight; use a wide spectrum sunscreen (may reduce risk of secondary skin malignancies).

Advise patient to avoid a high potassium diet and grapefruit juice. The oral solution formulations can be taken with orange or apple juices to improve taste.

Must not receive immunisation with live vaccines.

Stabilise on particular brand

Switching between formulations without close monitoring may lead to changes in blood-ciclosporin concentration. Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent switching. Monitor blood-ciclosporin concentration, serum creatinine, blood pressure, and transplant function if brand is switched.

1.2.5 Interactions

- *Increased plasma concentration with clarithromycin, erythromycin, fluconazole, grapefruit juice, itraconazole, ketoconazole, miconazole, metoclopramide, verapamil, and tacrolimus*
- *Increased risk of nephrotoxicity and myotoxicity with colchicine*
- *Decreased plasma concentration with carbamazepine, orlistat, phenobarbital, phenytoin, rifampicin, St John's wort*
- *Increased risk of hyperkalaemia when ciclosporin given with ACE inhibitors or ARBs, or aldosterone antagonists*
- *Increased risk of nephrotoxicity when ciclosporin given with NSAIDs, plus increases plasma concentration of diclofenac*
- *Ciclosporin increases plasma concentration of digoxin (increased risk of toxicity)*
- *Increased risk of myopathy when ciclosporin given with statins (avoid)*

1.3 Tacrolimus (high risk)

Tacrolimus is also a calcineurin inhibitor with a similar to ciclosporin, however incidence of neurotoxicity is greater; cardiomyopathy has also been reported. Disturbance of glucose metabolism also appears to be significant.

1.3.1 Warning signs

(report immediately to a doctor)

- *Neurotoxicity*
  (tremor, headache)
- *Nephrotoxicity*
  (elevated serum creatinine concentrations)
- *Eye disorders*
  (blurred vision, photophobia)
- *Skin disorders*
  (rash, toxic epidermal necrolysis)
- *Blood disorders*
  (signs of infection such as fever, sore throat, mouth ulcers, also unexplained bruising or bleeding)
- *Hyperglycaemia*
  (diabetes mellitus e.g. increased thirst or excessive urination)
- *Cardiovascular disorders*
  (cardiomyopathy, arrhythmias, hypertension)
- *Liver toxicity*
  (jaundice, nausea, vomiting, abdominal discomfort, dark urine)

1.3.2 Monitoring

- *Blood pressure*
- *ECG (for cardiomyopathy, discontinue is occurs)*
- *Fasting blood glucose concentration*
- *Renal function*
- *Liver function*
- *Serum electrolytes (particularly K+)*
- *Haematological, neurological (including visual) and coagulation parameters*

1.3.3 Pregnancy and breastfeeding

Avoid; risk of premature delivery

1.3.4 Other points

- *Avoid excessive exposure to UV light, including sunlight and to use a wide- spectrum sunscreen (may reduce risk of secondary skin malignancies)*
- *Ensure patient understands the importance of taking immunosuppressants regularly*
- *Tacrolimus may affect performance of skilled tasks (e.g. driving)*
- *Patients must not receive immunisation with live vaccines*
- *Avoid a high potassium diet and grapefruit juice*
- *Switching between oral tacrolimus products has been associated with toxicity and graft rejection, therefore oral tacrolimus should be prescribed and dispensed by brand name only*

1.3.5 Interactions

- *Increased plasma concentration with clarithromycin, diltiazem, erythromycin, fluconazole, grapefruit juice, itraconazole, nifedipine, omeprazole, ranolazine*
- *Reduced plasma concentration with phenobarbital, St. John's Wort, rifampicin, phenytoin*
- *Increased risk of nephrotoxicity when given with aminoglycosides, amphotericin and NSAIDs (especially ibuprofen), certain antivirals (e.g. aciclovir, ganciclovir)*
- *Tacrolimus increases plasma concentration of ciclosporin*
- *Increased risk of hyperkalaemia when given with potassium-sparing diuretics (e.g. amiloride, spironolactone), potassium salts, angiotensin II receptor antagonist*

2 MALIGNANT DISEASE

2.1 CYTOTOXIC RESPONSIVE MALIGNANCY

Cytotoxic drugs have both anti-cancer activity and the potential to damage normal tissue; most cytotoxic drugs are teratogenic.

2.1.1 Guidelines for handling cytotoxic drugs

- Trained personnel should reconstitute cytotoxics;
- Reconstitution should be carried out in designated pharmacy areas;
- Protective clothing (including gloves, gowns, and masks) should be worn;
- The eyes should be protected and means of first aid should be specified;
- Pregnant staff should avoid exposure to cytotoxic drugs (all females of child-bearing age should be informed of the reproductive hazard);
- Use local procedures for dealing with spillages and safe disposal of waste material, including syringes, containers, and absorbent material;
- Staff exposure to cytotoxic drugs should be monitored.

2.1.2 Safe system requirements

- cytotoxic drugs for the treatment of cancer should be given as part of a wider pathway of care coordinated by a multidisciplinary team;
- cytotoxic drugs should be prescribed, dispensed, and administered only in the context of a written protocol or treatment plan;
- injectable cytotoxic drugs should only be dispensed if they are prepared for administration
- oral cytotoxic medicines should be dispensed with clear directions for use

2.1.3 Risks of incorrect oral dosing

Standards to be followed to achieve this include:

- non-specialists should have access to written protocols and treatment plans, and guidance on the monitoring and treatment of toxicity
- staff dispensing oral cytotoxic medicines should confirm that the prescribed dose is appropriate for the patient
- patients should have written information that includes details of the intended oral anti-cancer regimen, the treatment plan, and arrangements for monitoring, taken from the original protocol from the initiating hospital

2.1.4 Doses

Doses are often determined using body-surface area or body-weight. Dose adjustment is common after considering patient's neutrophil count, renal and hepatic function, and history of previous adverse effects. Doses may also differ depending on whether a drug is used alone or in combination. Prescriptions should not be repeated except on the instructions of a specialist.

2.1.5 Side-effects of cytotoxic drugs

Many side-effects of cytotoxic drugs often do not occur at the time of administration, but days or weeks later.

2.1.5.1 Alopecia

Reversible hair loss is a common complication.

2.1.5.2 Thromboembolism

Venous thromboembolism can be a complication of cancer itself, but chemotherapy increases the risk.

2.1.5.3 Tumour lysis syndrome

Large amounts of tumor cells are killed off (lysed) at the same time by the treatment, releasing their contents into the bloodstream. Features include hyperkalaemia, hyperuricaemia (see below), and hyperphosphataemia with hypocalcaemia; renal damage and arrhythmias can follow.

2.1.5.4 Hyperuricaemia

Hyperuricaemia, which may already be present, can be exacerbated by chemotherapy and is associated with acute renal failure. Allopurinol, febuxostat, and rasburicase can be used for treatment and prophylaxis; reduce the dose of mercaptopurine or azathioprine if allopurinol needs to be given (risk of bone marrow suppression).

2.1.5.5 Nausea and vomiting

Mildly emetogenic—fluorouracil, etoposide, methotrexate (less than 100 mg/m^2), vinca alkaloids, and abdominal radiotherapy

Moderately emetogenic—the taxanes, doxorubicin, intermediate and low doses of cyclophosphamide, mitoxantrone, and high doses of methotrexate (more than 100 mg/m^2)

Highly emetogenic—cisplatin, dacarbazine, and high doses of cyclophosphamide

Dexamethasone, Lorazepam, and Metoclopramide are used for the prevention of nausea and vomiting.

2.1.5.6 Bone-marrow suppression

All cytotoxic drugs except vincristine and bleomycin cause bone-marrow suppression; commonly 7-10 days after administration. Blood counts must be checked before each treatment, and doses should be reduced or therapy delayed if bone-marrow has not recovered.

Neutropenic sepsis is a medical emergency; patients who have symptoms of fever, flu-like symptoms, uncontrolled bleeding or bruising, diarrhoea / uncontrolled vomiting, or severe mouth ulcers, attend their nearest A&E department if they develop signs of neutropenic sepsis and not to take paracetamol without seeking advice

2.1.5.7 Extravasation of intravenous drugs

Severe permanent local tissue necrosis; reduce risk by trained staff administering IV cytotoxics.

2.1.5.8 Oral mucositis

Sore mouth is common and most associated with fluorouracil, methotrexate, and the anthracyclines. Mucositis is self-limiting but with poor oral hygiene it can be a focus for blood-borne infection; therefore, good oral hygiene is beneficial.

2.1.5.9 Anthracyline-induced cardiotoxicity

Anthracyclines are associated with potentially life-threatening cardiotoxic side-effects; Dexrazoxane, an iron chelator, is licensed for the prevention of cardiotoxicity.

2.1.5.10 Urothelial toxicity

Haemorrhagic cystitis is a common manifestation of urothelial toxicity; mesna is useful in preventing toxicity

2.1.5.11 Methotrexate induced mucositis and myelosuppression

Counteracted with folinic acid therapy

2.1.6 Pregnancy and reproductive function

Most cytotoxic drugs are teratogenic and should not be administered during pregnancy, especially during the first trimester. Exclude pregnancy before treatment with cytotoxic drugs. Advice should be given to men and women for contraception before and after cytotoxic therapy. Pretreatment counselling and consideration of sperm storage may be appropriate. Women are less severely affected, though the span of reproductive life may be shortened by the onset of a premature menopause.

2.2 VINCA ALKALOIDS

Neurotoxicity and myelosuppression are dose-limiting side-effects of all vinca alkaloids.

Vinblastine, vincristine, vindesine, vinflunine, and vinorelbine injections are for intravenous administration only. Inadvertent intrathecal administration can cause severe neurotoxicity, which is usually fatal.

2.3 METHOTREXATE (HIGH RISK)

2.3.1 Warning signs

(report immediately to a doctor)

- Gastro-intestinal toxicity
  (inflamed mount or throat may be the first sign)
- Liver toxicity
  (jaundice, nausea, vomiting, abdominal discomfort, dark urine)
- Blood disorders - bone marrow suppression
  (sore throat, bruising, mouth ulcers, fever, rash)
- Pulmonary toxicity – pneumonitis
  (dyspnoea, cough)
- Pregnancy and breast feeding

2.3.2 Monitoring

Full blood count; renal function; liver function

2.3.3 Interactions

- Increased plasma concentration and risk of hepatotoxicity with acitretin (avoid)
- Excretion reduced by NSAIDs and penicillins, therefore increased risk of toxicity; also increased risk of toxicity with ciprofloxacin, doxycycline, tetracycline, ciclosporin, PPIs, and leflunomide
- Increased risk of haematological toxicity when given with trimethoprim or co-trimoxazole

2.3.4 Other points

- Methotrexate tablets are to be taken once a week, on the same day each week, with folic acid as prescribed (to avoid dosing errors, only one strength, usually 2.5mg should be prescribed)
- Counsel the patient on the importance of effective contraception during treatment
- Avoid preparations containing NSAIDs/aspirin
- Folinic acid helps to prevent methotrexate-induced mucositis or myelosuppression
- Methotrexate treatment booklets should be issued where appropriate

2.3.5 Pregnancy and breastfeeding

Avoid; teratogenic

2.4 TAMOXIFEN

Endometrial changes

Increased risk of hyperplasia, polyps, cancer, and uterine tumour. Report the relevant symptoms promptly for urgent investigation; abnormal vaginal bleeding including menstrual irregularities, vaginal discharge, and pelvic pain or pressure.

Risk of thromboembolism

Increased risk of thromboembolism particularly during and immediately after major surgery or periods of immobility; report sudden breathlessness and any pain in the calf of one leg.