

Antineoplastic and immunosuppressive drugs and drugs used in palliative care

Immunosuppressive drugs

Note. WHO advises that this class of drugs is for use only when adequate resources and specialist care are available. Specific expertise, diagnostic precision, individualization of dosage or special equipment are required for their proper use

Immunosuppressive drugs are used in organ transplant recipients to suppress rejection; they are also used as second-line drugs in chronic inflammatory conditions. Treatment should only be initiated by a specialist. Careful monitoring of blood counts is required in patients receiving immunosuppressive drugs and the dose should be adjusted to prevent bone-marrow toxicity. Immunosuppressed patients are particularly prone to atypical infections.

Azathioprine is the most widely used drug in transplant recipients. It is useful when corticosteroid therapy alone has proven inadequate or for other conditions when a reduction in the dose of concurrently administered corticosteroids is required. It is metabolized to mercaptopurine and, as with mercaptopurine, doses need to be reduced when given with allopurinol. The predominant toxic effect is myelosuppression, although hepatic toxicity also occurs.

Ciclosporin is a potent immunosuppressant which is virtually free of myelotoxic effects, but is markedly nephrotoxic. It is particularly useful for the prevention of graft rejection and for the prophylaxis of graft-versus-host disease. The dose is adjusted according to plasma-ciclosporin concentrations and renal function. Dose-related increases in serum creatinine and blood urea nitrogen (BUN) during the first few weeks may necessitate dose reduction.

Corticosteroids such as **prednisolone** (section 8.3) have significant immunosuppressant activity and can also be used to prevent rejection of organ transplants.

Azathioprine

Azathioprine is a complementary immunosuppressive drug

Tablets , azathioprine 50 mg

Injection (Powder for solution for injection), azathioprine (as sodium salt), 100-mg vial

Uses:

to prevent rejection in transplant recipients; rheumatoid arthritis (section 2.4); inflammatory bowel disease (section 17.4)

Contraindications:

hypersensitivity to azathioprine and mercaptopurine; breastfeeding (Appendix 3)

Precautions:

monitor for toxicity throughout treatment; full blood counts necessary every week (or more frequently with higher doses and in renal or hepatic impairment) for first 4 weeks of treatment, and at least every 3 months thereafter; reduce dose in elderly; pregnancy (Appendix 2); renal impairment (Appendix 4); liver disease (Appendix 5); **interactions:** Appendix 1

BONE MARROW SUPPRESSION.

Patients should be warned to report immediately any signs or symptoms of bone marrow suppression, for example unexplained bruising or bleeding, infection

Dosage:

Transplant rejection, *by mouth or by intravenous injection* (over at least 1 minute and followed by 50 ml sodium chloride intravenous infusion) *or by intravenous infusion,* **ADULT** up to 5 mg/kg on day of surgery, then reduced to 1–4 mg/kg daily according to response for maintenance

RECONSTITUTION AND ADMINISTRATION. According to manufacturer's directions

Note. Intravenous injection is alkaline and very irritant; the intravenous route should therefore **only** be used if oral administration is not possible

Adverse effects:

hypersensitivity reactions including malaise, dizziness, vomiting, fever, muscular pains, arthralgia, rash, hypotension or interstitial nephritis call for immediate withdrawal; haematological toxicity includes leukopenia and thrombocytopenia (reversible upon withdrawal); liver impairment, cholestatic jaundice; hair loss; increased susceptibility to infections and colitis in patients also receiving corticosteroids; nausea; rarely pancreatitis, pneumonitis, hepatic veno-occlusive disease

Ciclosporin

Ciclosporin is a complementary immunosuppressive drug

Capsules , ciclosporin 25 mg

Concentrate for infusion (Concentrate for solution for infusion), ciclosporin 50 mg/ml, 1-ml ampoule

Uses:

rejection in kidney, liver, heart or bone-marrow transplantation; graft-versus-host disease

Precautions:

monitor kidney function (dose dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction, exclude rejection if kidney transplant, also Appendix 4); monitor liver function (adjust dosage according to bilirubin and

liver enzymes, also Appendix 5); monitor blood pressure (discontinue if hypertension cannot be controlled by antihypertensives); monitor serum potassium, particularly if marked renal impairment (risk of hyperkalaemia); monitor serum magnesium; hyperuricaemia; measure blood lipids before and during treatment; avoid in porphyria; pregnancy (Appendix 2); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

Note. Lower doses are required when ciclosporin is used with other immunosuppressants

Organ transplantation, *by mouth*, **ADULT** and **CHILD** over 3 months 10–15 mg/kg 4–12 hours before surgery, then 10–15 mg/kg daily for 1–2 weeks, reducing to 2–6 mg/kg daily for maintenance (adjust dose according to blood concentration and kidney function)

Organ transplantation, *by intravenous infusion* over 2–6 hours, **ADULT** and **CHILD** one-third of the corresponding dose by mouth

Bone marrow transplantation, graft-versus-host disease, *by mouth*, **ADULT** and **CHILD** over 3 months 12.5–15 mg/kg daily for 2 weeks, starting on day before surgery, followed by 12.5 mg/kg daily for 3–6 months, then gradually tailed off (may take up to 1 year after transplant)

Bone marrow transplantation, graft-versus-host disease, *by intravenous infusion* over 2–6 hours, **ADULT** and **CHILD** over 3 months 3–5 mg/kg daily for 2 weeks, starting on day before surgery, followed by maintenance by mouth

CONVERSION. Any conversion between brands should be undertaken very carefully, and the manufacturer consulted for further information

DILUTION AND ADMINISTRATION. According to manufacturer's directions

Note. Concentrate for infusion contains polyethoxylated castor oil, which has been associated with anaphylaxis; observe patient for 30 minutes after starting infusion, and then at frequent intervals

Adverse effects:

dose-related and reversible increases in serum creatinine and urea unrelated to tissue rejection; burning sensation in hands and feet during initial therapy; electrolyte disturbances including hyperkalaemia, hypomagnesaemia; hepatic dysfunction; hyperuricaemia; hypercholesterolaemia; hyperglycaemia, hypertension (especially in heart transplant patients); increased incidence of malignancies and lymphoproliferative disorders; increased susceptibility to infections due to immunosuppression; gastrointestinal disturbances; gingival hyperplasia; hirsutism; fatigue; allergic reactions; thrombocytopenia (sometimes with haemolytic uraemic syndrome); also mild anaemia, tremors, convulsions, neuropathy; dysmenorrhoea or amenorrhoea; pancreatitis, myopathy or muscle weakness; cramp; gout; oedema; headache

Cytotoxic (antineoplastic) drugs

Note. WHO advises that adequate resources and specialist supervision are a prerequisite for the introduction of this class of drugs. Specific expertise, diagnostic precision, individualization of dosage or special equipment are required for their proper use

The treatment of cancer with drugs, radiotherapy and surgery is complex and should only be undertaken by an oncologist. For this reason, the following information is provided merely as a guide. Chemotherapy may be curative or used to alleviate symptoms or to prolong life. Where the condition can no longer be managed with cytotoxic therapy, alternative palliative treatment (section 8.4) should be considered.

For some tumours, single-drug chemotherapy may be adequate, but for many malignancies a combination of drugs provides the best response. Examples of combination therapy include:

- ‘CHOP’ (cyclophosphamide, doxorubicin, vincristine, prednisolone) for non-Hodgkin disease;
- ‘ABVD’ (doxorubicin, bleomycin, vinblastine, dacarbazine) for Hodgkin disease;
- ‘MOPP’ (chlormethine, vincristine, procarbazine, prednisolone) for Hodgkin disease.

Cytotoxic drugs are often combined with other classes of drugs (section 8.3) in the treatment of malignant conditions. Such drugs include hormone agonists and antagonists, corticosteroids and immunostimulant drugs. Combinations are, however, more toxic than single drugs.

The following information covers drugs that have specific anti-tumour activity. However, they are toxic drugs which should be used with great care and monitoring. The specific doses and details of contraindications, precautions and adverse effects for cytotoxic drugs have been omitted from this section since treatment should be **undertaken by specialists** using agreed regimens. Health authorities may wish to formulate their own regimens on the basis of expert advice.

PRECAUTIONS AND CONTRAINDICATIONS

Treatment with cytotoxic drugs should be initiated only after baseline tests of liver and kidney function have been performed and baseline blood counts established. It may be necessary to modify or delay treatment in certain circumstances. The patient should also be monitored regularly during chemotherapy and cytotoxic drugs withheld if there is significant deterioration in bone-marrow, liver or kidney function.

Many cytotoxic drugs are teratogenic and should not be administered during pregnancy especially in the first trimester. Contraceptive measures are required during therapy and possibly for a period after therapy has ended. Cytotoxic drugs are also contraindicated during breastfeeding.

Cytotoxic drugs should be administered with care to avoid undue toxicity to the patient or exposure during handling by the health care provider. Local policies for the handling and reconstitution of cytotoxic drugs should be strictly adhered to; also all

waste, including patient's body fluids and excreta (and any material contaminated by them) should be treated as hazardous.

Extravasation of intravenously administered cytotoxic drugs can result in severe pain and necrosis of surrounding tissue. If extravasation occurs, aspiration of the drug should first be attempted, then the affected limb is elevated and warm compresses applied to speed and dilute the infusion or it is localized by applying cold compresses until the inflammation subsides; in severe cases, hydrocortisone cream may be applied topically to the site of inflammation. The manufacturer's literature should also be consulted for more specific information.

ADVERSE EFFECTS

Cytotoxic drugs have a considerable potential to damage normal tissue. Specific adverse effects apply, but a number of effects are common to all cytotoxics such as bone-marrow and immunological suppression. Furthermore, the concomitant use of immunosuppressive drugs will enhance susceptibility to infections. Fever associated with neutropenia or immunosuppression requires immediate treatment with antibiotics.

Nausea and vomiting. Nausea and vomiting following administration of cytotoxic drugs and abdominal radiotherapy are often distressing and may compromise further treatment. Symptoms may be acute (occurring within 24 hours of treatment), delayed (first occurring more than 24 hours after treatment), or anticipatory (occurring before subsequent doses). Delayed and anticipatory symptoms are more difficult to control than acute symptoms and require different management.

Cytotoxic drugs associated with a low risk of emesis include etoposide, fluorouracil, low-dose methotrexate, and the vinca alkaloids; those with an intermediate risk include low-dose cyclophosphamide, doxorubicin, and high-dose methotrexate; and the highest risk is with cisplatin, high-dose cyclophosphamide, and dacarbazine.

For patients at a low risk of emesis, pretreatment with an oral phenothiazine (for example chlorpromazine, section 24.1), continued for up to 24 hours after chemotherapy, is often helpful. For patients at a higher risk dexamethasone 6–10 mg by mouth (section 18.1) may be added before chemotherapy. For patients at a high risk of emesis or when other therapies are ineffective, high doses of intravenous metoclopramide (section 17.2) may be used.

NOTE. High doses of metoclopramide are preferably given by continuous intravenous infusion: an initial dose of 2–4 mg/kg is given over 15 to 20 minutes, followed by a maintenance dose of 3–5 mg/kg over 8 to 12 hours; the total dose should not exceed 10 mg/kg in 24 hours.

Dexamethasone is the drug of choice for the prevention of delayed symptoms; it is used alone or with metoclopramide.

Good symptom control is the best way to prevent anticipatory symptoms and the addition of diazepam to antiemetic therapy is helpful because of its sedative, anxiolytic and amnesic effects.

Hyperuricaemia. Hyperuricaemia may complicate treatment of conditions such as non-Hodgkin lymphomas and leukaemia. Renal damage may result from the formation of uric acid crystals. Patients should be adequately hydrated and hyperuricaemia may be managed with allopurinol (section 2.3.2) initiated 24 hours before cytotoxic treatment and continued for 7 to 10 days afterwards.

Alopecia. Alopecia is common during treatment with cytotoxic drugs. There is no drug treatment, but the condition often reverses spontaneously once treatment has stopped.

ALKYLATING DRUGS

Alkylating drugs are among the most widely used drugs in cancer chemotherapy. They act by damaging DNA and therefore interfering with cell replication. However, there are two complications. Firstly, they affect gametogenesis and may cause permanent male sterility; in women, the reproductive span may be shortened by the onset of a premature menopause. Secondly, they are associated with a marked increase in the incidence of acute non-lymphocytic leukaemia, in particular when combined with extensive radiation therapy.

Cyclophosphamide requires hepatic activation; it can therefore be given orally and is not vesicant when given intravenously. Like all alkylating drugs its major toxic effects are myelosuppression, alopecia, nausea and vomiting. It can also cause haemorrhagic cystitis; an increased fluid intake for 24 to 48 hours will help to avoid this complication. Cyclophosphamide is used either as part of treatment or as an adjuvant in non-Hodgkin lymphomas, breast cancer, childhood leukaemia, and ovarian cancer. It is also used in several palliative regimens.

Chlorambucil is used to treat chronic lymphocytic leukaemia, non-Hodgkin lymphomas, Hodgkin disease, ovarian cancer and Waldenstrom (primary) macroglobulinaemia. Adverse effects, apart from bone marrow suppression, are uncommon. However, severe widespread rash can develop and may progress to Stevens-Johnson syndrome or toxic epidermal necrolysis. If a rash occurs, further treatment with chlorambucil is contraindicated.

Chlormethine (mustine) forms part of the regimen for treatment of advanced Hodgkin disease and malignant lymphomas. Its toxicity includes myelosuppression, severe nausea and vomiting, alopecia and thrombophlebitis due to vesicant effect.

Chlorambucil

Chlorambucil is a complementary cytotoxic drug

Tablets , chlorambucil 2 mg

Uses:

chronic lymphocytic leukaemia; some non-Hodgkin lymphomas; Hodgkin disease, ovarian cancer and Waldenstrom (primary) macroglobulinaemia

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; renal impairment (Appendix 4); **interactions:** Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

Chlormethine hydrochloride

Mustine hydrochloride

Chlormethine is a complementary cytotoxic drug

Injection (Powder for solution for injection), chlormethine hydrochloride 10-mg vial

Uses:

Hodgkin disease; some non-Hodgkin lymphomas; polycythaemia vera; mycosis fungoides; brain tumours, neuroblastoma

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; **interactions:** Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

Note. Irritant to tissues

Cyclophosphamide

Cyclophosphamide is a complementary cytotoxic drug

Tablets , cyclophosphamide 25 mg

Injection (Powder for solution for injection), cyclophosphamide 500-mg vial

Uses:

malignant lymphomas including non-Hodgkin lymphomas, lymphocytic lymphoma, Burkitt lymphoma; multiple myeloma; leukaemias, mycosis fungoides; neuroblastoma; adenocarcinoma of the ovary; retinoblastoma; breast cancer

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; renal impairment (Appendix 4) and hepatic impairment (Appendix 5); **interactions:** Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

CYTOTOXIC ANTIBIOTICS

Bleomycin is used in regimens for the treatment of Hodgkin disease and testicular cancer. It has several antineoplastic drug toxicities; it is known to cause dose-related pneumonitis and fibrosis which can be fatal, and is associated with rare acute hypersensitivity reactions. Cutaneous toxicity has also been reported.

Doxorubicin is the most widely used anthracycline antibiotic. It is used for acute leukaemias although other anthracyclines are more commonly used in these circumstances. Doxorubicin also plays a palliative role in the treatment of other malignancies. The primary toxic effects are myelosuppression, alopecia, nausea, vomiting, and dose-related cardiomyopathy. It is also vesicant and can cause severe skin ulceration on extravasation.

Dactinomycin is used to treat paediatric cancers. Its toxicity is similar to that of doxorubicin, but it is not cardiotoxic.

Daunorubicin is used in acute leukaemias. Its toxicity is similar to that of doxorubicin.

Bleomycin

Bleomycin is a complementary cytotoxic drug

Injection (Powder for solution for injection), bleomycin (as sulfate) 15 000-unit vial

Uses:

adjunct to surgery and radiotherapy in palliative treatment of Hodgkin and non-Hodgkin lymphomas; reticulum cell sarcoma and lymphoma; carcinomas of the head, neck, larynx, cervix, penis, skin, vulva, testicles and including embryonal cell carcinoma, choriocarcinoma and teratoma; malignant effusions

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; renal impairment (Appendix 4);
interactions: Appendix 1

Dosage:

Consult specialist literature

Note. Doses of bleomycin are expressed in international units. 1 Bleomycin Unit in the USP is equivalent to 1000 international units

Adverse effects:

see notes above and consult specialist literature

Note. Irritant to tissues

Dactinomycin

Actinomycin D

Dactinomycin is a complementary cytotoxic drug

Injection (Powder for solution for injection), dactinomycin 500-microgram vial

Uses:

trophoblastic tumours, Wilm tumour, Ewing sarcoma, rhabdomyosarcoma

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; **interactions:** Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

Note. Irritant to tissues

Daunorubicin

Daunorubicin is a complementary cytotoxic drug

Infusion (Powder for solution for infusion), daunorubicin (as hydrochloride) 20-mg vial

Uses:

acute leukaemias

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; renal and hepatic impairment (Appendices 4 and 5); **interactions:** Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

Note. Irritant to tissues

Doxorubicin hydrochloride

Doxorubicin hydrochloride is a complementary cytotoxic drug

Injection (Powder for solution for injection), doxorubicin hydrochloride 10-mg vial, 50-mg vial

Uses:

acute leukaemias; carcinomas of the breast, bladder, ovary and thyroid; neuroblastoma; Wilm tumour; non-Hodgkin and Hodgkin lymphomas; soft tissue sarcomas, osteosarcoma

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; hepatic impairment (Appendix 5);
interactions: Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

Note. Irritant to tissues

ANTIMETABOLITES AND RELATED THERAPY

Cytarabine is used in the treatment of acute leukaemia; children may tolerate high doses better than adults. Its effects are highly dependent upon the schedule of administration. It causes myelosuppression, mucositis, and in high doses, central neurotoxicity.

Fluorouracil is primarily used in the adjuvant treatment of colorectal and breast cancer. It is also employed in the palliative treatment of other malignancies. It causes myelosuppression and the palmar-plantar syndrome (erythema and painful desquamation of the hands and feet). When its action is modified by other drugs (such as calcium folinate), its toxicity profile can change; mucositis and diarrhoea may be significant problems. Central neurotoxicity can also occur.

Mercaptopurine is frequently used in the therapy of childhood leukaemia. It can be administered orally and myelosuppression and nausea are the only important toxic effects.

Methotrexate is used to treat a variety of malignancies and it plays a major role as an adjuvant for the treatment of breast cancer. Like fluorouracil, methotrexate is myelotoxic, but nausea and vomiting are minimal. It also causes mucositis. Renal impairment reduces methotrexate excretion and can exacerbate toxicity.

Calcium folinate is used to counteract the folate-antagonist action of methotrexate and thus speed recovery from methotrexate-induced mucositis or myelosuppression. Calcium folinate also enhances the effects of fluorouracil when the two are used together for metastatic colorectal cancer.

Cytarabine

Cytarabine is a complementary cytotoxic drug

Injection (Powder for solution for injection), cytarabine 100-mg vial

Uses:

acute lymphoblastic leukaemia; chronic myeloid leukaemia; meningeal leukaemia; erythroleukaemia; non-Hodgkin lymphomas

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; hepatic impairment (Appendix 5);
interactions: Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

Fluorouracil

5-fluorouracil, 5FU

Fluorouracil is a complementary cytotoxic drug

Injection (Solution for injection), fluorouracil 50 mg/ml, 5-ml ampoule

Uses:

carcinomas of the colorectum, breast, stomach, pancreas, cervix, prostate, ovary and endometrium; liver tumours; head and neck tumours; actinic keratosis (section 13.5)

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; hepatic impairment (Appendix 5); **interactions:** Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

Mercaptopurine

Mercaptopurine is a complementary cytotoxic drug

Tablets , mercaptopurine 50 mg

Uses:

acute leukaemias

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; renal impairment (Appendix 4) and hepatic impairment (Appendix 5); **interactions:** Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

Methotrexate

Methotrexate is a complementary cytotoxic drug

Tablets , methotrexate 2.5 mg

Injection (Solution for injection), methotrexate (as sodium salt) 25mg/ml, 2-ml vial

Uses:

carcinoma of the breast, head and neck, and lung; trophoblastic tumours; acute lymphoblastic leukaemia, meningeal leukaemia; non-Hodgkin lymphomas; advanced cases of mycosis fungoides; non-metastatic osteosarcoma; severe rheumatoid arthritis (section 2.4)

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; renal and hepatic impairment (Appendices 4 and 5); **interactions:** Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

Calcium folinate

Calcium folinate is a complementary drug

Tablets , folinic acid (as calcium folinate) 15 mg

Injection (Solution for injection), folinic acid (as calcium folinate) 3 mg/ml, 10-ml ampoule

Uses:

high-dose methotrexate therapy ('folate rescue'); inadvertent overdose of methotrexate; with fluorouracil in the palliative treatment of advanced colorectal cancer

Precautions:

not for pernicious anaemia or other megaloblastic anaemias due to vitamin B₁₂ deficiency; pregnancy (Appendix 2); breastfeeding; **interactions:** Appendix 1

Dosage:

Antidote to methotrexate (usually started 24 hours after methotrexate), by *intramuscular or intravenous injection or by intravenous infusion*, **ADULT** and **CHILD** up to 120 mg in divided doses over 12–24 hours, then 12–15 mg by *intramuscular injection or 15 mg by mouth* every 6 hours for 48–72 hours

Methotrexate overdosage (started as soon as possible, preferably within 1 hour of methotrexate), by *intravenous injection or infusion*, **ADULT** and **CHILD**, dose equal to or higher than that of methotrexate, at rate not exceeding 160 mg/minute

With fluorouracil in colorectal cancer, consult specialist literature

Reconstitution and administration. According to manufacturer's directions

Note. Intrathecal injection of calcium folinate is contraindicated

Adverse effects:

allergic reactions; pyrexia after parenteral administration

VINCA ALKALOIDS AND ETOPOSIDE

The vinca alkaloids, **vinblastine** and **vincristine**, are primarily used in the treatment of acute leukaemias. Vinblastine is also used for Hodgkin disease and some solid tumours. Vincristine is also used in the management of non-Hodgkin lymphomas. Both can cause neurotoxicity, but this is more of a problem with vincristine. Myelosuppression is more common with vinblastine.

Etoposide is an important component of the treatment of testicular carcinoma, and is also used in several regimens for lung cancers and lymphomas. It causes myelosuppression and alopecia and it can cause hypotension during infusion. It does not produce significant nausea and vomiting.

Etoposide

Etoposide is a complementary cytotoxic drug

Capsules, etoposide 100 mg

Concentrate for infusion (Concentrate for solution for infusion), etoposide 20 mg/ml, 5-ml vial

Uses:

refractory testicular tumours; lung cancer

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; hepatic impairment (Appendix 5);

interactions: Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

Note. Irritant to tissues

Vinblastine sulfate

Vinblastine is a complementary cytotoxic drug

Injection (Powder for solution for injection), vinblastine sulfate 10-mg vial

Uses:

disseminated Hodgkin and non-Hodgkin lymphomas; advanced testicular carcinoma, breast carcinoma; palliative treatment of Kaposi sarcoma; trophoblastic tumours; Letterer-Siwe disease

Contraindications:

see notes above and consult specialist literature; pregnancy and breastfeeding (Appendices 2 and 3)

Important. Intrathecal injection is contraindicated

Precautions:

see notes above and consult specialist literature; hepatic impairment (Appendix 5);

interactions: Appendix 1

Dosage:

Consult specialist literature

Note. Vinblastine is for intravenous administration only. Intrathecal injection causes severe neurotoxicity which is usually fatal

Adverse effects:

see notes above and consult specialist literature

Note. Irritant to tissues

Vincristine sulfate

Vincristine is a complementary cytotoxic drug

Injection (Powder for solution for injection), vincristine sulfate 1-mg vial, 5-mg vial

Uses:

acute lymphoblastic leukaemia; neuroblastoma, Wilm tumour, Hodgkin and non-Hodgkin lymphomas; rhabdomyosarcoma, Ewing sarcoma; mycosis fungoides

Contraindications:

see notes above and consult specialist literature; pregnancy and breastfeeding (Appendices 2 and 3)

Important. Intrathecal injection is contraindicated

Precautions:

see notes above and consult specialist literature; hepatic impairment (Appendix 5);
interactions: Appendix 1

Dosage:

Consult specialist literature

Note. Vincristine is for intravenous administration only. Intrathecal injection causes severe neurotoxicity which is usually fatal

Adverse effects:

see notes above and consult specialist literature

Note. Irritant to tissues

OTHER ANTOINEOPLASTIC DRUGS

The enzyme **asparaginase** is an important component in the management of childhood leukaemia, but is not used in any other malignancy. Its toxicity profile is broad and the drug must be carefully administered because of the risk of anaphylaxis.

Cisplatin is a platinum compound used in the treatment of ovarian and testicular malignancies. It is also a component of regimens used in non-small cell and small cell lung cancer and plays a palliative role in other malignancies. Cisplatin is myelosuppressive and also produces slight alopecia. However, it causes severe dose-related nausea and vomiting. It is also nephrotoxic and neurotoxic. Nephrotoxicity can be reduced by maintaining high urine output during cisplatin administration and immediately afterwards, but neurotoxicity is often dose-limiting.

Dacarbazine, thought to act as an alkylating drug, is a component of a regimen for Hodgkin disease. It is also used in the palliative therapy of metastatic malignant melanoma. Its major toxic effects are myelosuppression, and intense nausea and vomiting.

Levamisole is an anthelmintic with immunostimulating properties; it is used in combination with fluorouracil as adjuvant therapy for colorectal cancer following resection of the tumour. Its major toxic effects are a variety of CNS symptoms, nausea, dermatitis and hypersensitivity reactions.

Procarbazine is used in the treatment of advanced Hodgkin disease. Toxic effects include myelosuppression, nausea, vomiting, CNS symptoms and depression. Procarbazine possesses a weak monoamine oxidase inhibitory effect but dietary restriction is not necessary.

Asparaginase

Crisantaspase

Asparaginase is a complementary cytotoxic drug

Injection (Powder for solution for injection), asparaginase 10 000-unit vial

Uses:

acute lymphoblastic leukaemia

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; **interactions:** Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

Cisplatin

Cisplatin is a complementary cytotoxic drug

Injection (Powder for solution for injection), cisplatin 10-mg vial, 50-mg vial

Uses:

metastatic testicular tumours, metastatic ovarian tumours, advanced bladder carcinoma and other solid tumours

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; renal impairment (Appendix 4);

interactions: Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

Dacarbazine

Dacarbazine is a complementary cytotoxic drug

Injection (Powder for solution for injection), dacarbazine 100-mg vial

Uses:

metastatic malignant melanoma; Hodgkin disease

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; renal and hepatic impairment (Appendices 4 and 5); **interactions:** Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

Note. Irritant to tissues

Levamisole

Levamisole is a complementary drug

Tablets , levamisole (as hydrochloride) 50 mg

Uses:

with fluorouracil for the treatment of colorectal carcinoma after complete resection of primary tumour; intestinal nematode infections (section 6.1.1.2)

Contraindications:

see notes above and consult specialist literature; breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; pregnancy (Appendix 2);

interactions: Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

abdominal pain, nausea, vomiting, dizziness, headache

Procarbazine

Procarbazine is a complementary cytotoxic drug

Capsules , procarbazine (as hydrochloride) 50 mg

Uses:

part of MOPP regimen in Hodgkin and non-Hodgkin lymphomas

Contraindications:

see notes above and consult specialist literature; pregnancy (Appendix 2) and breastfeeding (Appendix 3)

Precautions:

see notes above and consult specialist literature; renal and hepatic impairment (Appendices 4 and 5); **interactions:** Appendix 1

Dosage:

Consult specialist literature

Adverse effects:

see notes above and consult specialist literature

Hormones and antihormones

The corticosteroids **prednisolone**, **dexamethasone** and **hydrocortisone** are synthetic hormones given at pharmacological doses particularly for haematological malignancies. Although there is no evidence for therapeutic superiority, prednisolone is used more commonly than dexamethasone or hydrocortisone (section 3.1); prednisolone is an important component of curative regimens for lymphomas and childhood leukaemias and elsewhere it has a palliative role. However, chronic use leads to the development of a cushingoid syndrome.

Tamoxifen is an estrogen-receptor antagonist. Its important role in breast cancer is use after surgery and for palliative management in patients with advanced disease. When given at recommended doses, it has few adverse effects, although, it can induce uterine endometrial malignancies.

Diethylstilbestrol, a synthetic estrogen, is used to manipulate the hormonal environment in patients with hormone-sensitive tumours (for example breast and testes). It has few significant adverse effects in women but in men it causes gynaecomastia, and, more importantly, increases the risk of cardiovascular disease. For breast cancer diethylstilbestrol has been superseded by tamoxifen but it can be used for its anti-androgen effect in prostate cancer as an adjunct or for palliation.

Prednisolone

Prednisolone is a representative corticosteroid. Various drugs can serve as alternatives

Prednisolone is a complementary drug for the treatment of malignant neoplasms

Tablets, prednisolone 5 mg, 25 mg

Uses:

with antineoplastic drugs for acute lymphoblastic and chronic lymphocytic leukaemias, Hodgkin disease, and non-Hodgkin lymphomas; inflammatory and allergic reactions (sections 3.1 and 18.1); eye (section 21.2)

Contraindications:

untreated bacterial, viral, and fungal infections; avoid live virus vaccines

Precautions:

monitor body weight, blood pressure, fluid and electrolyte balance, and blood glucose concentration throughout treatment; adrenal suppression during and for some months after withdrawal—intercurrent infection or surgery may require increased dose of corticosteroid (or temporary reintroduction if already withdrawn); quiescent amoebiasis, strongyloidiasis, or tuberculosis possibly reactivated; increased severity of viral infections, particularly chickenpox and measles—passive immunization with immunoglobulin required; hypertension, recent myocardial infarction, congestive heart failure; renal impairment; hepatic impairment (Appendix 5); diabetes mellitus; osteoporosis; glaucoma; severe psychosis, epilepsy; peptic ulcer; pregnancy (Appendix 2); breastfeeding (Appendix 3); **interactions:** Appendix 1

Dosage:

Leukaemias and lymphomas, *by mouth*, **ADULT** initially up to 100 mg daily, then gradually reduced if possible to 20–40 mg daily; **CHILD** up to 1 year, initially up to 25 mg, then 5–10 mg; 2–7 years, initially up to 50 mg, then 10–20 mg; 8–12 years, up to 75 mg, then 15–30 mg

Adverse effects:

gastrointestinal effects including dyspepsia, oesophageal ulceration, development of or aggravation of peptic ulcers, abdominal distension, acute pancreatitis; increased appetite and weight gain; adrenal suppression with high doses, leading to cushingoid symptoms (moon face, acne, bruising, abdominal striae, truncal obesity, muscle wasting); menstrual irregularities and amenorrhoea; hypertension; osteoporosis, with resultant vertebral collapse and long-bone fractures; avascular osteonecrosis; ophthalmic effects including glaucoma, subcapsular cataracts, exacerbation of viral or fungal eye infections; diabetes mellitus; thromboembolism; delayed tissue healing; myopathy, muscle weakness of arms and legs; depression, psychosis, epilepsy; raised intracranial pressure; hypersensitivity reactions

Tamoxifen

Tamoxifen is a complementary drug for the treatment of breast cancer

Tablets, tamoxifen (as citrate) 10 mg, 20 mg

Uses:

adjuvant treatment of estrogen-receptor-positive breast cancer; metastatic breast cancer

Contraindications:

pregnancy (exclude before treatment and advise non-hormonal contraception if appropriate, see also Appendix 2); breastfeeding (Appendix 3)

Precautions:

monitor for endometrial changes (increased incidence of hyperplasia, polyps, and cancer); cystic ovarian swellings in premenopausal women; increased risk of thromboembolism when used with antineoplastic drugs; avoid in porphyria;

interactions: Appendix 1

Dosage:

Breast cancer, *by mouth*, **ADULT** 20 mg daily

Adverse effects:

hot flushes; endometrial changes (symptoms such as vaginal bleeding and other menstrual irregularities, vaginal discharge, pelvic pain require immediate investigation); increased pain and hypercalcaemia with bony metastases; tumour flare; nausea and vomiting; liver enzyme changes (rarely cholestasis, hepatitis, hepatic necrosis); hypertriglyceridaemia (sometimes with pancreatitis); thromboembolic events; decreased platelet count; oedema; alopecia; rash; headache; visual disturbances including corneal changes, cataracts, retinopathy; rarely interstitial pneumonitis, hypersensitivity reactions including angioedema, Stevens-Johnson syndrome, bullous pemphigoid

Drugs used in palliative care

Note. The Expert Committee on the Selection and Use of Essential Medicines recommends that all the drugs mentioned in Cancer Pain Relief: with a Guide to Opioid Availability, 2nd edition. Geneva: WHO 1996 be considered essential. These drugs are included in the relevant sections of the Model List according to their therapeutic use, for example analgesics.

Palliative care includes both pain relief and the symptomatic relief of conditions including dyspnoea, restlessness and confusion, anorexia, constipation, pruritus, nausea and vomiting, and insomnia. Health authorities should be encouraged to develop their own palliative care services.

Pain relief can be achieved with drugs and neurosurgical, psychological and behavioural approaches adapted to individual patient needs. If carried out correctly, most patients with cancer pain can obtain effective relief. Pain is best treated with a combination of drug and non-drug measures. Some types of pain respond well to a combination of a non-opioid and an opioid analgesic. Other types of pain are relieved by combining a corticosteroid and an opioid. Neuropathic pains often show little response to non-opioids and opioids, but may be eased by tricyclic antidepressants and anticonvulsants (see below). Cancer patients often have many fears and anxieties,

and may become depressed. Very anxious or deeply depressed patients may need an appropriate psychotropic drug in addition to an analgesic. If this fact is not appreciated, the pain may remain intractable.

In the majority of patients, cancer pain can be relieved with analgesics:

- **by mouth** : if possible analgesics should be given by mouth. Rectal suppositories are useful in patients with dysphagia, uncontrolled vomiting or gastrointestinal obstruction. Continuous subcutaneous infusion offers an alternative route.
- **by the clock** : analgesics are more effective in preventing pain than in the relief of established pain, therefore doses should be given at fixed time intervals and titrated against the patient's pain; if pain occurs between doses, a rescue dose should be given, and the next dose increased.
- **by the ladder** : the first step is to give a non-opioid analgesic such as **acetylsalicylic acid, paracetamol or ibuprofen**, if necessary with an adjuvant drug. If this does not relieve the pain, an opioid for mild to moderate pain such as **codeine** should be added. When this combination fails to relieve pain, an opioid for moderate to severe pain such as **morphine** should be substituted.
- **for the individual** : there are no standard doses for opioid drugs. The range for oral morphine is from as little as 5 mg to more than 100 mg every 4 hours.
- **with attention to detail** : the first and last doses of the day should be linked to the patient's waking time and bedtime. Ideally the drug regimen should be written out in full for the patient and his or her family. The patient should be warned about possible adverse effects.

Drugs for neuropathic pain

Neuropathic pain often responds to a tricyclic antidepressant, such as **amitriptyline** (section 24.2), or to an anticonvulsant such as **carbamazepine** or **sodium valproate** (both section 5.1); **ketamine** (section 1.1.1) or **lidocaine** (section 12.2) by intravenous infusion may be useful in some situations. Neuropathic pain responds only partially to opioids, but they may be considered when other options fail. A corticosteroid may be required, particularly to relieve pressure and therefore pain in patients with nerve compression.