fusion over 2 hours. A longer infusion time should be considered in children weighing less than 20 kg to reduce anxiety and irritability, and to avoid high clofarabine concentrations. The course may be repeated every 2 to 6 weeks, depending on the patient's recovery from bone-marrow depression and other adverse effects. Treatment is usually assessed after 2 treatment cycles.

Clofarabine is under investigation for the treatment of acute myeloid leukaemia, myelodysplastic syndrome, and solid tumours.

◊ References.

1. Kantarjian HM, *et al.* Phase I clinical and pharmacology study of clofarabine in patients with solid and hematologic cancers. *J Clin Oncol* 2003; **21:** 1167–73.
2. Gandhi V, *et al.* Pharmacokinetics and pharmacodynamics of plasma clofarabine and cellular clofarabine triphosphate in patients with acute leukemias. *Clin Cancer Res* 2003; **9:** 6335–42.
3. Kantarjian H, *et al.* Phase 2 clinical and pharmacologic study of clofarabine in patients with refractory or relapsed acute leukemia. *Blood* 2003; **102:** 2379–86.
4. Bonate PL, *et al.* Population pharmacokinetics of clofarabine, a second-generation nucleoside analog, in pediatric patients with acute leukemia. *J Clin Pharmacol* 2004; **44:** 1309–22.
5. Jeha S, *et al.* Clofarabine, a novel nucleoside analog, is active in pediatric patients with advanced leukemia. *Blood* 2004; **103:** 784–9.
6. Faderl S, *et al.* Results of a phase 1-2 study of clofarabine in combination with cytarabine (ara-C) in relapsed and refractory acute leukemias. *Blood* 2005; **105:** 940–7.
7. Curran MP, Perry CM. Clofarabine: in pediatric patients with acute lymphoblastic leukemia. *Paediatr Drugs* 2005; **7:** 259–64.
8. Kline JP, Larson RA. Clofarabine in the treatment of acute myeloid leukaemia and acute lymphoblastic leukaemia: a review. *Expert Opin Pharmacother* 2005; **6:** 2711–18.
9. Kantarjian HM, *et al.* Clofarabine: past, present, and future. *Leuk Lymphoma* 2007; **48:** 1922–30.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Evoltra; ***Fr.:*** Evoltra; ***Port.:*** Evoltra; ***UK:*** Evoltra; ***USA:*** Clolar.

Combretastatin A4 Phosphate

CS-A4 (combretastatin A4); NSC-348103 (combretastatin). 2-Methoxy-5-[(1*Z*)-2-(3,4,5-trimethoxyphenyl)ethenyl]-phenol dihydrogen phosphate.

$C_{18}H_{21}O_8P$ = 396.3.

CAS — 82855-09-2 (combretastatin); 117048-59-6 (combretastatin A4); 222030-63-9 (combretastatin A4 phosphate).

Profile

Combretastatin A4 phosphate is a synthetic derivative of combretastatin compounds originally isolated from the African bushwillow tree (Cape bush-willow; *Combretum caffrum*). It is described as a vascular targeting agent that reduces blood flow to tumours by disrupting the endothelial cells of newly formed blood vessels, and is under investigation for the treatment of thyroid and ovarian cancers.

Corynebacterium parvum

C. parvum; NSC-220537; *Propionibacterium acnes.*

Profile

Inactivated *Corynebacterium parvum* has been used in the treatment of malignant effusions, and has been tried as an adjuvant to cancer chemotherapy for its immunostimulant properties. It has also been used in the treatment of musculoskeletal and joint disorders.

Fever and pain have occurred after intracavitary injection. There have been reports of nephrotoxicity after intravenous use.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: Arthrokehlan A.

Cyclophosphamide *(BAN, rINN)*

B-518; Ciclofosfamida; Ciklofosfamidas; Ciklofoszfamid; Cyclophosphamidum; Cyclophosphamidum Monohydricum; Cyclophosphanum; Cyklofosfamid; Cyklofosfamid monohydrát; NSC-26271; Siklofosfamid; Syklofosfamidi; WR-138719. 2-[Bis(2-chloroethyl)amino]perhydro-1,3,2-oxazaphosphorinan 2-oxide monohydrate.

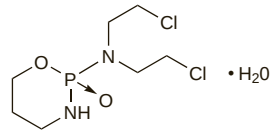
Циклофосфамид

$C_7H_{15}Cl_2N_2O_2P,H_2O$ = 279.1.

CAS — 6055-19-2 (cyclophosphamide monohydrate); 50-18-0 (anhydrous cyclophosphamide).

ATC — L01AA01.

ATC Vet — QL01AA01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Cyclophosphamide). A white or almost white, crystalline powder. Soluble in water; freely soluble in alcohol. A freshly prepared 2% solution in water has a pH of 4.0 to 6.0.
USP 31 (Cyclophosphamide). A white, crystalline powder. It liquefies upon loss of its water of crystallisation. Soluble in water and in alcohol. A 1% solution in water has a pH of 3.9 to 7.1 when determined 30 minutes after preparation. Store in airtight containers at 2° to 30°.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p.635 and p.639. The major dose-limiting effect is myelosuppression. After single doses the nadir of the white cell count may occur in around 1 to 2 weeks with full recovery usually in 3 to 4 weeks. Thrombocytopenia and anaemia may occur but tend to be less common and less severe.

Haemorrhagic cystitis may develop after high or prolonged dosage, and can be life-threatening. Adequate hydration to maintain urine output at 100 mL/hour and use of mesna (see p.1449) are generally recommended in an attempt to reduce urotoxicity. If mesna is used, frequent emptying of the bladder should be avoided. Doses of cyclophosphamide should be given early in the day.

Alopecia occurs in about 20% of patients given low doses and in practically all patients given high doses. Hair loss starts after 3 weeks of treatment but regrowth is usually evident after 3 months, even with continued treatment. Hyperpigmentation of skin, especially that of the palms and soles, and of the nails, has been reported.

Nausea and vomiting commonly occur, and may be reduced by prophylactic antiemetics. Mucositis may also occur.

Other adverse effects include a syndrome resembling inappropriate secretion of antidiuretic hormone (which may require diuretic therapy), disturbances of carbohydrate metabolism, gonadal suppression (common and occasionally resulting in sterility), interstitial pulmonary fibrosis, and, especially at high doses, cardiotoxicity.

Cyclophosphamide, in common with other alkylating agents, has carcinogenic, mutagenic, and teratogenic potential and secondary malignancies have occurred in patients given previous antineoplastic therapy including cyclophosphamide—see p.635.

Effects on the bladder. *Sterile haemorrhagic cystitis* (p.2178) can occur after high-dose infusions of cyclophosphamide or after prolonged low-dose oral use.[1,2] It is believed to be secondary to renal excretion of alkylating metabolites, particularly the acrolein metabolite, that cause sloughing, thinning, and inflammation of the bladder wall. Damage ranges from minor bleeding to diffuse necrotic ulceration, and can lead to anaemia, constriction of the bladder, bladder perforation, and death.[2] Symptoms may be delayed, and have been reported to occur up to 6 months after stopping the drug.[3] An increased incidence of cystitis when patients on a high-dose cyclophosphamide regimen were transferred from one brand to another has been reported,[4] apparently because one was labelled in terms of the anhydrous substance and one as the monohydrate, resulting in a 6.4% difference in the content of active substance.[5]

Measures used to prevent haemorrhagic cystitis include intravenous hydration with diuresis, frequent voiding, or bladder catheterisation with irrigation, to increase urine output and dilute the excreted metabolites. Mesna may be used as a uroprotectant to reduce exposure to the metabolites.[2] If bleeding occurs, various drugs have been instilled intravesically, including sodium chloride 0.9%, alum, or prostaglandins.[2,6-9] Silver nitrate, formaldehyde, or phenol instillations have been used but are painful and patients require anaesthesia.[2] There is limited information to suggest that conjugated oestrogens given orally or intravenously may be effective.[2,10] Nonpharmacological techniques are reserved for refractory cases and include arterial embolisation or surgery.[2]

In addition to the shorter term effects, cyclophosphamide has been reported to be associated with the development of *bladder carcinoma*.[1,11-14] A history of cyclophosphamide-induced cystitis may be associated with an increased risk of bladder carcinoma[1,11] but some studies have not found a link,[13] and bladder malignancies can develop in patients who have not experienced cystitis while receiving cyclophosphamide.[12] For a discussion of the carcinogenic effects of antineoplastics, including cyclophosphamide, see p.635.

1. Talar-Williams C, *et al.* Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med* 1996; **124:** 477–84.
2. West NJ. Prevention and treatment of hemorrhagic cystitis. *Pharmacotherapy* 1997; **17:** 696–706.
3. Armstrong B, *et al.* Delayed cystitis due to cyclophosphamide. *N Engl J Med* 1979; **300:** 45.
4. Shaw IC, *et al.* Difference in bioactivity between two preparations of cyclophosphamide. *Lancet* 1983; **i:** 709.
5. Hilgard P, *et al.* Bioactivity of cyclophosphamide preparations. *Lancet* 1983; **i:** 1436.
6. Mohiuddin J, *et al.* Treatment of cyclophosphamide-induced cystitis with prostaglandin E . *Ann Intern Med* 1984; **101:** 142.
7. Miller LJ, *et al.* Treatment of cyclophosphamide-induced hemorrhagic cystitis with prostaglandins. *Ann Pharmacother* 1994; **28:** 590–4.
8. Ippoliti C, *et al.* Intravesicular carboprost for the treatment of hemorrhagic cystitis after marrow transplantation. *Urology* 1995; **46:** 811–15.
9. Laszlo D, *et al.* Prostaglandin E2 bladder instillation for the treatment of hemorrhagic cystitis after allogeneic bone marrow transplantation. *Haematologica* 1995; **80:** 421–5.
10. Ordemann R, *et al.* Encouraging results in the treatment of haemorrhagic cystitis with estrogen – report of 10 cases and review of the literature. *Bone Marrow Transplant* 2000; **25:** 981–5.
11. Wall RL, Clausen KP. Carcinoma of the urinary bladder in patients receiving cyclophosphamide. *N Engl J Med* 1975; **293:** 271–3.
12. Plotz PH, *et al.* Bladder complications in patients receiving cyclophosphamide for systemic lupus erythematosus or rheumatoid arthritis. *Ann Intern Med* 1979; **91:** 221–3.
13. Pedersen-Bjergaard J, *et al.* Carcinoma of the urinary bladder after treatment with cyclophosphamide for non-Hodgkin's lymphoma. *N Engl J Med* 1988; **318:** 1028–32.
14. Travis LB, *et al.* Bladder cancer after chemotherapy for non-Hodgkin's lymphoma. *N Engl J Med* 1989; **321:** 544–5.

Effects on the blood. Amifostine has been reported to protect against the myelosuppressive effects of cyclophosphamide, and may be used to reduce neutropenia-related infection associated with the combination of cyclophosphamide and cisplatin (see p.1437).

Effects on carbohydrate metabolism. Acute onset type 1 diabetes occurred in a patient treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), and was thought to be due to the cyclophosphamide.[1]

1. Atlan-Gepner C, *et al.* A cyclophosphamide-induced autoimmune diabetes. *Lancet* 1998; **352:** 373–4.

Effects on electrolytes. Water intoxication has been reported with cyclophosphamide,[1-4] usually in high doses (30 to 50 mg/kg or more) although symptoms have been reported after a dose of 20 mg/kg in a patient with renal disease,[3] and in another patient with SLE but apparently normal renal function who received 10 mg/kg.[4] One case of severe hyponatraemia leading to convulsions and death has been reported.[5] Symptoms resemble the syndrome of inappropriate antidiuretic hormone secretion (SIADH)[5] but plasma concentrations of antidiuretic hormone do not appear to be raised in these patients.[3]

1. DeFronzo RA, *et al.* Water intoxication in man after cyclophosphamide therapy: time course and relation to drug activation. *Ann Intern Med* 1973; **78:** 861–9.
2. Green TP, Mirkin BL. Prevention of cyclophosphamide-induced antidiuresis by furosemide infusion. *Clin Pharmacol Ther* 1981; **29:** 634–42.
3. Bressler RB, Huston DP. Water intoxication following moderate-dose intravenous cyclophosphamide. *Arch Intern Med* 1985; **145:** 548–9.
4. McCarron MO, *et al.* Water intoxication after low dose cyclophosphamide. *BMJ* 1995; **311:** 292.
5. Harlow PJ, *et al.* A fatal case of inappropriate ADH secretion induced by cyclophosphamide therapy. *Cancer* 1979; **44:** 896–8.

Effects on the eyes. Recurrent transient myopia, apparently due to increased hydration of the lens of the eye, was induced by an intravenous bolus of cyclophosphamide in an adolescent with SLE.[1]

CMV retinitis has occurred in patients during or after cyclophosphamide therapy; presenting symptoms included floaters and blurred or decreased vision.[2]

1. Arranz JA, *et al.* Cyclophosphamide-induced myopia. *Ann Intern Med* 1992; **116:** 92–3.
2. Agrawal A, *et al.* Visual symptoms in patients on cyclophosphamide may herald sight threatening disease. *Br J Ophthalmol* 2003; **87:** 122–3.

Effects on reproductive potential. Severe gonadal failure with transient or permanent azoospermia is common in men treated with cyclophosphamide. Suppression of germ-cell function with intramuscular testosterone in 5 men during cyclophosphamide therapy for nephrotic syndrome was associated with a more rapid return of spermatogenesis compared with 10 patients who did not receive the androgen.[1]

1. Masala A, *et al.* Use of testosterone to prevent cyclophosphamide-induced azoospermia. *Ann Intern Med* 1997; **126:** 292–5.

Effects on the skin. An erythematous pruritic rash, similar to the palmar-plantar erythrodysesthesia syndrome (p.639) but oc-

curring on the dorsal surfaces of the hands and feet, occurred 6 days after the first high dose of cyclophosphamide in a patient being prepared for bone marrow transplantation.[1] Previous cyclophosphamide-containing chemotherapy did not produce this reaction. The symptoms improved somewhat on treatment with triamcinolone ointment, and subsequently desquamation of the hands occurred with decreased purplish discoloration and oedema of the feet. There has also been a report of 2 patients who developed Stevens-Johnson syndrome, with some features suggestive of overlapping toxic epidermal necrolysis.[2]

1. Matsuyama JR, Kwok KK. A variant of the chemotherapy-associated erythrodysesthesia syndrome related to high-dose cyclophosphamide. *DICP Ann Pharmacother* 1989; **23:** 776–9.
2. Assier-Bonnet H, *et al.* Stevens-Johnson syndrome induced by cyclophosphamide: report of two cases. *Br J Dermatol* 1996; **135:** 864–6.

Hypersensitivity. Occasional anaphylaxis has been reported with cyclophosphamide;[1] analysis of data by the Boston Collaborative Drug Surveillance Program detected only one allergic skin reaction among 210 patients given cyclophosphamide, resulting in a calculated incidence of 4.8 reactions per 1000 recipients.[2]

1. Jones JB, *et al.* Cyclophosphamide anaphylaxis. *DICP Ann Pharmacother* 1989; **23:** 88–9.
2. Bigby M, *et al.* Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15 438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; **256:** 3358–63.

Precautions

For reference to the precautions necessary with antineoplastics, see p.641.

Cyclophosphamide should not be given to patients with bone-marrow aplasia, acute infection, or drug- or radiation-induced urothelial toxicity. It should be given with care to those with diabetes mellitus. Care is also needed in elderly or debilitated patients, or those with renal or hepatic impairment or who have undergone adrenalectomy. Liberal fluid intake and frequent micturition are advised to reduce the risk of cystitis but care must be taken to avoid water retention and intoxication. Urine should be examined regularly for red cells, which may precede haemorrhagic cystitis. The haematological profile should be monitored regularly.

The use of cyclophosphamide in pregnancy should be avoided where possible.

Breast feeding. Cyclophosphamide has been detected in breast milk,[1] and there are reports of neutropenia,[2] and leucopenia and thrombocytopenia,[3] in infants who have been breast fed by women receiving cyclophosphamide. The American Academy of Pediatrics considers[4] that cyclophosphamide may interfere with cellular metabolism, causing neutropenia and possibly immune suppression in the infant, and has unknown effects on growth, and an association with carcinogenesis.

1. Wiernik PH, Duncan JH. Cyclophosphamide in human milk. *Lancet* 1971; **1:** 912.
2. Amato D, Niblett JS. Neutropenia from cyclophosphamide in breast milk. *Med J Aust* 1977; **1:** 383–4.
3. Durodola JI. Administration of cyclophosphamide during late pregnancy and early lactation: a case report. *J Natl Med Assoc* 1979; **71:** 165–6.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/06/04)

Handling and disposal. *Residues* of cyclophosphamide or ifosfamide destroyed using alkaline hydrolysis in the presence of dimethylformamide showed no mutagenicity *in vitro*.[1] An alternative method, involving refluxing of cyclophosphamide with hydrochloric acid, neutralising, and then reacting with sodium thiosulfate, was effective for the degradation of cyclophosphamide, but residues from ifosfamide were still highly mutagenic *in vitro* and this second method should therefore not be used to degrade ifosfamide.

Urine and faeces produced for up to 72 hours and 5 days respectively after an oral dose of cyclophosphamide should be handled wearing protective clothing.[2] As cyclophosphamide was present in sweat and saliva, protective clothing was advised for 72 hours after a dose when bathing the patient or carrying out oral procedures.

1. Castegnaro M, *et al.*, eds. Laboratory decontamination and destruction of carcinogens in laboratory wastes: some antineoplastic agents. *IARC Scientific Publications 73*. Lyon: WHO/International Agency for Research on Cancer, 1985.
2. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Porphyria. Cyclophosphamide is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Since cyclophosphamide must undergo hepatic metabolism before it is active, interactions are possible with drugs that inhibit or stimulate the mixed function oxidase enzymes responsible. There may be an increased risk of cardiotoxicity in patients who have also received doxorubicin or other cardiotoxic drugs.

Allopurinol. Although the Boston Collaborative Drug Surveillance Program reported an increased incidence of bone-marrow depression in patients given allopurinol with cyclophosphamide than in those given cyclophosphamide without allopurinol (15 of 26 compared with only 6 of 32),[1] a subsequent study in patients given combination chemotherapy, including cyclophosphamide, for lymphomas failed to find any difference in the nadirs of the platelet and white blood cell counts in cycles in which allopurinol was given.[2] Although allopurinol pretreatment in 4 patients resulted in a longer cyclophosphamide half-life in a study in 26 patients given cyclophosphamide, urinary excretion of cyclophosphamide was unchanged.[3] A longer cyclophosphamide half-life was also seen in a study in children given allopurinol.[4]

1. Boston Collaborative Drug Surveillance Program. Allopurinol and cytotoxic drugs: interaction in relation to bone marrow depression. *JAMA* 1974; **227:** 1036–40.
2. Stolbach L, *et al.* Evaluation of bone marrow toxic reaction in patients treated with allopurinol. *JAMA* 1982; **247:** 334–6.
3. Bagley CM, *et al.* Clinical pharmacology of cyclophosphamide. *Cancer Res* 1973; **33:** 226–33.
4. Yule SM, *et al.* Cyclophosphamide pharmacokinetics in children. *Br J Clin Pharmacol* 1996; **41:** 13–19.

Antibacterials. *Chloramphenicol* given before cyclophosphamide prolonged the mean cyclophosphamide serum half-life from 7.5 to 11.5 hours and reduced the peak activity in all of 5 subjects.[1] Giving *sulfaphenazole* before cyclophosphamide significantly inhibited the rate of biotransformation of cyclophosphamide in 2 of 7 subjects and enhanced it in 2; it remained unchanged in 3. A study in patients with non-Hodgkin's lymphoma found that giving *ciprofloxacin* before cyclophosphamide affected pharmacokinetic parameters of cyclophosphamide. The area under the concentration-time curve (AUC) of cyclophosphamide was increased and clearance was lower; AUC of the active metabolite of cyclophosphamide, 4-hydroxycyclophosphamide, was decreased and clearance increased.[2]

1. Faber OK, *et al.* The effect of chloramphenicol and sulphaphenazole on the biotransformation of cyclophosphamide in man. *Br J Clin Pharmacol* 1975; **2:** 281–5.
2. Afsharian P, *et al.* The effect of ciprofloxacin on cyclophosphamide pharmacokinetics in patients with non-Hodgkin lymphoma. *Eur J Haematol* 2005; **75:** 206–11.

Anticoagulants. For reference to the interaction of cyclophosphamide with *warfarin*, see p.1429.

Antifungals. Analysis of cyclophosphamide metabolism in patients enrolled in a study comparing itraconazole with fluconazole found that those given itraconazole had higher exposure to toxic metabolites of cyclophosphamide. Both the antifungals appeared to alter cyclophosphamide metabolism and the authors cautioned against use of azole antifungals with antineoplastics that are metabolised via cytochrome P450 isoenzymes.[1]

1. Marr KA, *et al.* Cyclophosphamide metabolism is affected by azole antifungals. *Blood* 2004; **103:** 1557–9.

Barbiturates. Although patients receiving cyclophosphamide developed higher peak plasma concentrations of active cyclophosphamide metabolites when given enzyme-inducing agents such as barbiturates, the active metabolites also disappeared rapidly.[1]

1. Bagley CM, *et al.* Clinical pharmacology of cyclophosphamide. *Cancer Res* 1973; **33:** 226–33.

Chlorpromazine. The half-life of cyclophosphamide was about 200% greater in 2 children also taking chlorpromazine than in children not given the phenothiazine.[1]

1. Yule SM, *et al.* Cyclophosphamide pharmacokinetics in children. *Br J Clin Pharmacol* 1996; **41:** 13–19.

Ciclosporin. For reference to the effect of cyclophosphamide on ciclosporin concentrations, see Interactions, Antineoplastics, p.1826.

Colony-stimulating factors. Fatal respiratory insufficiency associated with alveolar fibrosis developed in an infant given cyclophosphamide and doxorubicin followed by *filgrastim*.[1] Since pulmonary toxicity with cyclophosphamide is normally associated with high cumulative doses it was suggested that in this case the effects might have been exacerbated by the granulocyte colony-stimulating factor. (The pulmonary toxicity of bleomycin has also been suggested to be exacerbated by colony-stimulating factors, as discussed on p.688).

1. van Woensel JBM, *et al.* Acute respiratory insufficiency during doxorubicin, cyclophosphamide, and G-CSF therapy. *Lancet* 1994; **344:** 759–60.

Corticosteroids. Single doses of *prednisone* have been found to inhibit the activation of cyclophosphamide but after longer-term treatment the rate of activation has increased.[1] A study in children found that pretreatment with *dexamethasone* was associated with increased clearance of cyclophosphamide and a decrease in its half-life relative to children not given the corticosteroid.[2]

1. Faber OK, Mouridsen HT. Cyclophosphamide activation and corticosteroids. *N Engl J Med* 1974; **291:** 211.
2. Yule SM, *et al.* Cyclophosphamide pharmacokinetics in children. *Br J Clin Pharmacol* 1996; **41:** 13–19.

Gastrointestinal drugs. In a retrospective study in patients receiving high-dose cyclophosphamide, cisplatin, and carmustine,[1] the area under the plasma-concentration time curve (AUC) for cyclophosphamide (measured as the parent compound) was 17% lower when *ondansetron* rather than prochlorperazine was added to the antiemetic regimen. In addition, the AUC for cisplatin was 10% higher with the ondansetron regimen. In a similar study,[2] the AUCs for both cyclophosphamide and cisplatin were lower in patients receiving an antiemetic regimen including ondansetron rather than prochlorperazine. The authors of both studies noted that the relevance of these findings to toxicity and antitumour effect of the antineoplastics remained to be determined.

1. Gilbert CJ, *et al.* Pharmacokinetic interaction between ondansetron and cyclophosphamide during high-dose chemotherapy for breast cancer. *Cancer Chemother Pharmacol* 1998; **42:** 497–503.
2. Cagnoni PJ, *et al.* Modification of the pharmacokinetics of high-dose cyclophosphamide and cisplatin by antiemetics. *Bone Marrow Transplant* 1999; **24:** 1–4.

NSAIDs. Acute life-threatening water intoxication was reported in a patient given low-dose cyclophosphamide with *indometacin*.[1] The patient had previously received treatment with cyclophosphamide (for multiple myeloma) without significant adverse effect.

1. Webberley MJ, Murray JA. Life-threatening acute hyponatraemia induced by low dose cyclophosphamide and indomethacin. *Postgrad Med J* 1989; **65:** 950–2.

Suxamethonium. For reference to a possible interaction between cyclophosphamide and suxamethonium, see under Suxamethonium Chloride, p.1911.

Pharmacokinetics

After oral doses, cyclophosphamide is well absorbed from the gastrointestinal tract with a bioavailability greater than 75%. It is widely distributed in the tissues and crosses the blood-brain barrier. It undergoes activation by the mixed function oxidase systems in the liver. The initial metabolites are 4-hydroxycyclophosphamide and its acyclic tautomer, aldophosphamide, which both undergo further metabolism; aldophosphamide may undergo non-enzymatic conversion to active phosphoramide mustard. Acrolein is also produced and may be responsible for bladder toxicity. Cyclophosphamide is excreted principally in urine, as metabolites and some unchanged drug. It crosses the placenta, and is found in breast milk.

◊ Reviews.

1. Boddy AV, Yule SM. Metabolism and pharmacokinetics of oxazaphosphorines. *Clin Pharmacokinet* 2000; **38:** 291–304.
2. de Jonge ME, *et al.* Clinical pharmacokinetics of cyclophosphamide. *Clin Pharmacokinet* 2005; **44:** 1135–64.

Absorption. Cyclophosphamide was detected in the urine of 5 patients after application to intact skin, showing that cyclophosphamide can be absorbed via this route.[1] Absorption continued after the site of application had been cleaned, suggesting that cyclophosphamide had penetrated subcutaneous lipid and was slowly released to the circulation from this depot. Cyclophosphamide was also identified in the urine of 2 oncology nurses but appeared more quickly than in patients, suggesting a faster route of absorption, perhaps by inhalation of aerosols generated during dissolution of the drug.

1. Hirst M, *et al.* Occupational exposure to cyclophosphamide. *Lancet* 1984; **i:** 186–8.

Uses and Administration

Cyclophosphamide is an antineoplastic that is converted in the body to active alkylating metabolites with properties similar to those of chlormethine (p.698). It also possesses marked immunosuppressant properties.

Cyclophosphamide is widely used, often with other agents, in the treatment of malignant diseases as indicated by the cross-references below. It is given for Burkitt's and other non-Hodgkin's lymphomas, multiple myeloma, and mycosis fungoides. It is also used in gestational trophoblastic tumours and malignancies of the brain, breast, endometrium, lung, and ovary; in childhood malignancies such as neuroblastoma, retinoblastoma, Wilms' tumour; and in sarcomas and some leukaemias.

The immunosuppressant properties of cyclophosphamide have been used in organ and tissue transplantation. It has also been used in the management of disor-

ders thought to have an auto-immune component including amyloidosis, Behçet's syndrome, glomerular kidney disease, idiopathic thrombocytopenic purpura, aplastic anaemia, cryptogenic fibrosing alveolitis, polymyositis, scleroderma, SLE, and vasculitic syndromes including the Churg-Strauss syndrome, polyarteritis nodosa, and Wegener's granulomatosis, as indicated by the cross references below.

Cyclophosphamide is usually given orally or by intravenous injection.

In the BP 2008 the content of Cyclophosphamide Injection is expressed in terms of the equivalent amount of anhydrous cyclophosphamide whereas the content of Cyclophosphamide Tablets is given in terms of the monohydrate; the USP 31 expresses content in terms of anhydrous cyclophosphamide for both injection and tablets. Confusion has arisen when patients were changed from a preparation in which the content was expressed as the monohydrate to one in which it was expressed as the anhydrous substance (see Effects on the Bladder, above). 53.45 mg of cyclophosphamide monohydrate is equivalent to 50 mg of anhydrous cyclophosphamide. *Doses below are given in terms of anhydrous cyclophosphamide*.

The dosage given may vary considerably depending on the disease being treated, the condition of the patient including the state of the bone marrow, and use with radiotherapy or other chemotherapy. The white cell count is usually used to guide the dose.

In the UK, examples of licensed regimens are:

- *low-dose*: cyclophosphamide 2 to 6 mg/kg weekly as a single intravenous dose or in divided oral doses
- *moderate-dose*: 10 to 15 mg/kg weekly as a single intravenous dose.
- *high-dose*: 20 to 40 mg/kg as a single intravenous dose every 10 to 20 days, although higher doses have been used

Alternative regimens include:

- 100 to 300 mg daily in divided oral doses
- 80 to 300 mg/m^2 daily as a single intravenous dose
- 300 to 600 mg/m^2 weekly as a single intravenous dose
- 600 to 1500 mg/m^2 as a single intravenous dose or short infusion at 10 to 20 day intervals

The use of mesna is generally recommended with single doses of cyclophosphamide over 2 g, but one manufacturer suggests its use with doses as low as 10 mg/kg.

In the USA, an initial dose of 40 to 50 mg/kg has been licensed for single agent therapy of malignancy, given intravenously in divided doses over 2 to 5 days although in practice treatment of malignancy will generally be with combination regimens. Other licensed regimens include:

- 3 to 5 mg/kg twice weekly intravenously
- 10 to 15 mg/kg every 7 to 10 days intravenously
- 1 to 5 mg/kg daily orally

A daily oral dose of 2 to 3 mg/kg has been used in children with minimal change nephropathy leading to the nephrotic syndrome, in whom corticosteroids have been unsuccessful.

In patients who are to undergo bone marrow transplantation very high doses of cyclophosphamide such as 60 mg/kg daily for 2 days may be given as part of the conditioning regimen.

Cyclophosphamide has also been given intramuscularly, intraperitoneally, and intrapleurally, as well as intra-arterially, and by local perfusion (but passage through the liver is required for its activation—see Pharmacokinetics, above). A liquid preparation of cyclophosphamide for oral use may be prepared using the powder for injection.

Regular blood counts are essential during therapy with cyclophosphamide and treatment should be withdrawn or delayed if leucopenia or thrombocytopenia becomes severe (see also Bone-marrow Depression, p.639). Patients should be adequately hydrated and urine output maintained.

Amyloidosis. Although there is no unequivocally effective treatment for amyloidosis (p.743), cyclophosphamide may reduce the decline in renal function and prolong survival;[1-3] it has also been used with epirubicin and carmustine to suppress the disease in a patient who had undergone heart transplantation for cardiac amyloid.[4] Good responses have also been reported to cyclophosphamide given in a regimen with thalidomide and dexamethasone.[5]

1. Berglund K, *et al.* Alkylating cytostatic treatment in renal amyloidosis secondary to rheumatic disease. *Ann Rheum Dis* 1987; **46:** 757–62.
2. Berglund K, *et al.* Results, principles and pitfalls in the management of renal AA-amyloidosis; a 10-21 year followup of 16 patients with rheumatic disease treated with alkylating cytostatics. *J Rheumatol* 1993; **20:** 2051–7.
3. Chevrel G, *et al.* Renal type AA amyloidosis associated with rheumatoid arthritis: a cohort study showing improved survival on treatment with pulse cyclophosphamide. *Rheumatology (Oxford)* 2001; **40:** 821–5.
4. Hall R, *et al.* Cardiac transplantation for AL amyloidosis. *BMJ* 1994; **309:** 1135–7.
5. Wechalekar AD, *et al.* Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. *Blood* 2007; **109:** 457–64.

Blood disorders, non-malignant. Cyclophosphamide has been used in patients with idiopathic thrombocytopenic purpura (p.1505), but cytotoxic immunosuppressants tend to be a treatment of last resort. Responses generally occur within 8 weeks.[1] In patients with refractory life-threatening disease, high-dose cyclophosphamide[1] may be tried. Combination chemotherapy including cyclophosphamide has also produced responses in a few patients.[2]

In the management of warm auto-immune haemolytic anaemia (p.1043) low-dose cyclophosphamide may be used in patients refractory to corticosteroids and splenectomy. A small number of patients with severe refractory disease have been treated with high-dose cyclophosphamide with some success.[3]

Cyclophosphamide is often used in preparation for bone marrow transplantation in patients with aplastic anaemia (p.1042), and complete remission has also been reported with high-dose cyclophosphamide alone.[4,5] However, a randomised trial[6] of high-dose cyclophosphamide plus ciclosporin compared with conventional immunosuppression was stopped early when a higher mortality was seen in those given cyclophosphamide. Further follow-up[7] also found that relapse rates were no different.

Cyclophosphamide with a corticosteroid has been tried in the rare condition of acquired haemophilia (p.1048).

1. McMillan R. Therapy for adults with refractory chronic immune thrombocytopenic purpura. *Ann Intern Med* 1997; **126:** 307–14.
2. Figueroa M, *et al.* Combination chemotherapy in refractory immune thrombocytopenic purpura. *N Engl J Med* 1993; **328:** 1226–9.
3. Moyo VM, *et al.* High-dose cyclophosphamide for refractory autoimmune hemolytic anemia. *Blood* 2002; **100:** 704–6.
4. Brodsky RA, *et al.* Durable treatment-free remission after high-dose cyclophosphamide therapy for previously untreated severe aplastic anemia. *Ann Intern Med* 2001; **135:** 477–83.
5. Savage WJ, *et al.* Treatment of hepatitis-associated aplastic anemia with high-dose cyclophosphamide. *Pediatr Blood Cancer* 2007; **49:** 947–51.
6. Tisdale JF, *et al.* High-dose cyclophosphamide in severe aplastic anaemia: a randomised trial. *Lancet* 2000; **356:** 1554–9.
7. Tisdale JF, *et al.* Late complications following treatment for severe aplastic anemia (SAA) with high-dose cyclophosphamide (Cy): follow-up of a randomized trial. *Blood* 2002; **100:** 4668–70.

Cogan's syndrome. For reference to the use of cyclophosphamide with corticosteroids for Cogan's syndrome, see p.1502.

Connective tissue and muscular disorders. Cyclophosphamide is one of a number of immunosuppressants that have been tried for disease control in Behçet's syndrome (p.1499); such drugs may permit a reduction in the use of corticosteroids, although they carry their own risks of toxicity. In polymyositis (p.1510) cyclophosphamide may have a role where there is lung disease; the role of immunosuppressants other than azathioprine or methotrexate is poorly defined. In patients with SLE (p.1513), cyclophosphamide has been used with some success for severe disease or disease refractory to corticosteroids alone, and appears to be more effective than corticosteroids for lupus nephritis.

Kidney disorders, non-malignant. Cyclophosphamide is used with corticosteroids in the treatment of some forms of glomerular kidney disease (p.1504). In children with nephrotic syndrome, oral cyclophosphamide 2 to 3 mg/kg daily for 8 weeks may be added to a course of corticosteroid therapy in relapsing disease; intravenous cyclophosphamide 500 mg/m^2 monthly for 6 months also substantially reduces the risk of relapse.[1] Addition of cyclophosphamide to corticosteroid therapy also improves the prospect of remission in focal glomerulosclerosis. Oral cyclophosphamide helps to stabilise progressive disease in patients with membranous nephropathy[2] although intermittent intravenous pulses are reported to be ineffective.[3] Such treatment is usually reserved for those whose disease is severe and progressive enough to justify it, but is probably better tolerated than other alkylating agents such as chlorambucil.[4] Cyclophosphamide has been given with methylprednisolone for rapidly progressive glomerulonephritis,[5] and has been used as part of the aggressive management of renal lesions in Goodpasture's syndrome.

1. Hodson EM *et al.* Non-corticosteroid treatment for nephrotic syndrome in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 24/07/08).
2. Falk RJ, *et al.* Treatment of progressive membranous glomerulopathy: a randomized trial comparing cyclophosphamide and corticosteroids with corticosteroids alone. *Ann Intern Med* 1992; **116:** 438–45.
3. Reichert LJM, *et al.* Preserving renal function in patients with membranous nephropathy: daily oral chlorambucil compared with intermittent monthly pulses of cyclophosphamide. *Ann Intern Med* 1994; **121:** 328–33.
4. Schieppati A, *et al.* Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester; John Wiley; 2004 (accessed 12/05/05).
5. Bruns FJ, *et al.* Long-term follow-up of aggressively treated idiopathic rapidly progressive glomerulonephritis. *Am J Med* 1989; **86:** 400–6.

Liver disorders, non-malignant. For mention of the use of cyclophosphamide in auto-immune hepatitis inadequately controlled by corticosteroids and azathioprine see Chronic Active Hepatitis, p.1501.

Lung disorders, non-malignant. Cyclophosphamide may be useful with corticosteroids in patients with cryptogenic fibrosing alveolitis, as mentioned under Diffuse Parenchymal Lung Disease, p.1502.

Malignant neoplasms. Cyclophosphamide is one of the most widely used drugs for the chemotherapy of malignancy, and mention of its role may be found in the discussions of the management of gestational trophoblastic tumours (p.650); the non-Hodgkin's lymphomas, including AIDS-related lymphoma, Burkitt's lymphoma, and mycosis fungoides (p.656, p.657, p.657, p.657); malignancies of the brain (p.660), breast (p.661), endometrium (p.663), lung (p.668), ovary (p.670) and thymus (p.674); multiple myeloma (p.658); Wilms' tumour, neuroblastoma, and retinoblastoma (p.667, p.674, and p.675 respectively); and sarcomas of bone (p.675) and rhabdomyosarcoma (p.676). Cyclophosphamide is also used in the management of acute lymphoblastic leukaemia (p.651) and chronic lymphocytic leukaemia (p.653).

Neuromuscular disorders. Cyclophosphamide has been tried in myasthenia gravis (p.629) in patients who require immunosuppressants but are intolerant of or unresponsive to corticosteroids and azathioprine. Cyclophosphamide has also been tried in regimens for the management of multiple sclerosis (p.892), but the reported benefits have generally been slight and outweighed by toxicity, such that it is usually reserved for patients with severe disease resistant to standard therapies.

References.

1. De Feo LG, *et al.* Use of intravenous pulsed cyclophosphamide in severe, generalized myasthenia gravis. *Muscle Nerve* 2002; **26:** 31–6.
2. Drachman DB, *et al.* Treatment of refractory myasthenia: "rebooting" with high-dose cyclophosphamide. *Ann Neurol* 2003; **53:** 29–34.
3. Portaccio E, *et al.* Safety and tolerability of cyclophosphamide 'pulses' in multiple sclerosis: a prospective study in a clinical cohort. *Multiple Sclerosis* 2003; **9:** 446–50.
4. Zephir H, *et al.* Treatment of progressive forms of multiple sclerosis by cyclophosphamide: a cohort study of 490 patients. *J Neurol Sci* 2004; **218:** 73–7.
5. La Mantia L, *et al.* Cyclophosphamide for multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 22/04/08).

Ocular disorders, non-malignant. Immunosuppressive agents, including cyclophosphamide, have been used in scleritis and uveitis (see p.1512 and p.1515) unresponsive to corticosteroids in tolerable doses.

Organ and tissue transplantation. Cyclophosphamide is used in high doses, usually with busulfan or irradiation, in conditioning regimens for bone marrow transplantation (see Haematopoietic Stem Cell Transplantation, p.1811). It has been tried as part of immunosuppressant regimens after transplantation of heart grafts (p.1812).

Paraquat poisoning. For reference to the use of cyclophosphamide in paraquat poisoning, see p.2048.

Pemphigus and pemphigoid. Corticosteroids are the main treatment for blistering in pemphigus and pemphigoid (p.1582). Immunosuppressive therapy, including cyclophosphamide,[1,2] has been used with corticosteroids to permit a reduction in corticosteroid dosage. Cyclophosphamide with a corticosteroid is also reported to be of value in ocular mucous membrane pemphigoid,[3] although treatment may not completely prevent cicatrisation.[4] Oral cyclophosphamide is considered an alternative to azathioprine in pemphigus vulgaris and pulsed intravenous doses might be considered in severe or recalcitrant cases.[5] There is less support for cyclophosphamide in bullous pemphigoid and it should only be considered if other treatments have failed or are contra-indicated.[6] However, oral or intravenous cyclophospha-

mide with corticosteroids may be considered for first-line treatment of severe or rapidly progressive mucous membrane pemphigoid.[7]

1. Pandya AG, Sontheimer RD. Treatment of pemphigus vulgaris with pulse intravenous cyclophosphamide. *Arch Dermatol* 1992; **128:** 1626–30.
2. Itoh T, *et al.* Successful treatment of bullous pemphigoid with pulsed intravenous cyclophosphamide. *Br J Dermatol* 1996; **134:** 931–3.
3. Kirtschig G, *et al.* Interventions for mucous membrane pemphigoid/cicatricial pemphigoid and epidermolysis bullosa acquisita: a systematic literature review. *Arch Dermatol* 2002; **138:** 380–4.
4. Elder MJ, *et al.* Role of cyclophosphamide and high dose steroid in ocular cicatricial pemphigoid. *Br J Ophthalmol* 1995; **79:** 264–6.
5. Harman KE, *et al.* British Association of Dermatologists. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003; **149:** 926–37.
   Also available at: http://www.bad.org.uk/healthcare/guidelines/Pemphigus_Vulgaris.pdf (accessed 21/02/07)
6. Wojnarowska F, *et al.* British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002; **147:** 214–21.
   Also available at: http://www.bad.org.uk/healthcare/guidelines/Bullous_Pemphigoid.pdf (accessed 21/02/07)
7. Sacher C, Hunzelmann N. Cicatricial pemphigoid (mucous membrane pemphigoid): current and emerging therapeutic approaches. *Am J Clin Dermatol* 2005; **6:** 93–103.

Rheumatoid arthritis. Cyclophosphamide has been used as a disease-modifying antirheumatic drug in rheumatoid arthritis (p.11), usually in patients with severe disease unresponsive to other drugs; its severe toxicity limits its usefulness.[1] It is of most value in controlling antibody-mediated systemic complications of the disease such as vasculitis[2] through inhibition of B-cell function.

1. Suarez-Almazor ME, *et al.* Cyclophosphamide for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 12/05/05).
2. Choy E, Kingsley G. How do second-line agents work? *Br Med Bull* 1995; **51:** 472–92.

Sarcoidosis. Where drug therapy is required for sarcoidosis (p.1512), corticosteroids are the usual treatment. Cyclophosphamide is one of a number of cytotoxic immunosuppressants that have been tried, with variable results, as a second-line therapy; its use has been limited by toxicity.

Scleroderma. As discussed on p.1817 the role of drug treatment for scleroderma is not well determined, but cyclophosphamide may be useful with or without a corticosteroid for patients with lung involvement.

Vasculitic syndromes. Treatment of the systemic vasculitides has revolved around the use of corticosteroids and cyclophosphamide. The benefits are uncertain in polyarteritis nodosa (p.1510) and Takayasu's arteritis (p.1514), but the benefits of combined therapy are generally accepted in Churg-Strauss syndrome (p.1501) and microscopic polyangiitis (p.1510), and cyclophosphamide is the mainstay of effective treatment of Wegener's granulomatosis (p.1515). A number of regimens are in use; in particular intermittent high-dose intravenous ('pulsed') use is being evaluated in comparison with continuous therapy.[1]

1. Richmond R, *et al.* Optimisation of cyclophosphamide therapy in systemic vasculitis. *Clin Pharmacokinet* 1998; **34:** 79–90.

Preparations

BP 2008: Cyclophosphamide Injection; Cyclophosphamide Tablets; ***USP 31:*** Cyclophosphamide for Injection; Cyclophosphamide Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Ciclokebir; Endoxan†; Genoxal†; ***Austral.:*** Cycloblastin; Endoxan; ***Austria:*** Endoxan; ***Belg.:*** Endoxan; ***Braz.:*** Ciclodrax†; Cyclan†; Fosfaseron†; Genuxal; ***Canad.:*** Cytoxan; Procytox; ***Chile:*** Endoxan; Ledoxina; ***Cz.:*** Cytoxan†; Endoxan; ***Denm.:*** Carloxan†; Sendoxan; ***Fin.:*** Sendoxan; ***Fr.:*** Endoxan; ***Ger.:*** Cyclostin†; Endoxan; ***Gr.:*** Endoxan; ***Hong Kong:*** Endoxan; ***Hung.:*** Cytoxan; Endoxan; ***India:*** Cycloxan; Endoxan; Oncophos; ***Indon.:*** Endoxan; ***Irl.:*** Endoxana; ***Israel:*** Cytophosphan; Cytoxan†; Endoxan; ***Ital.:*** Endoxan; ***Jpn:*** Endoxan†; ***Malaysia:*** Endoxan†; ***Mex.:*** Genoxal†; Hidrofosmin; Ledoxina; ***Neth.:*** Endoxan; ***Norw.:*** Sendoxan; ***NZ:*** Cycloblastin; Cytoxan; Endoxan; ***Philipp.:*** Cytoxan; Endoxan; Ledoxan; Xyclomed; ***Pol.:*** Endoxan; ***Port.:*** Endoxan; ***S.Afr.:*** Cycloblastin; Endoxan; ***Singapore:*** Alkyloxan†; Endoxan; ***Spain:*** Genoxal; ***Swed.:*** Sendoxan; ***Switz.:*** Endoxan; ***Thai.:*** Endoxan; Ledoxan; ***Turk.:*** Alkyloxan; Endoxan; ***UK:*** Endoxana†; ***USA:*** Cytoxan†; Neosar; ***Venez.:*** Biodoxan.

Cytarabine *(BAN, USAN, rINN)*

Arabinosylcytosine; Ara-C; Citarabin; Citarabina; Citarabinas; Cytarabin; Cytarabina; Cytarabinum; Cytosine Arabinoside; NSC-63878 (cytarabine hydrochloride); Sitarabin; Sytarabiini; U-19920; U-19920A (cytarabine hydrochloride); WR-28453. 1-β-D-Arabinofuranosylcytosine; 4-Amino-1-β-D-arabinofuranosylpyrimidin-2(1*H*)-one.

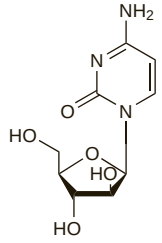
Цитарабин

$C_9H_{13}N_3O_5$ = 243.2.

CAS — 147-94-4 (cytarabine); 69-74-9 (cytarabine hydrochloride).

ATC — L01BC01.

ATC Vet — QL01BC01.



Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Chin. includes the hydrochloride.

Ph. Eur. 6.2 (Cytarabine). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Cytarabine). An odourless, white to off-white, crystalline powder. Freely soluble in water; slightly soluble in alcohol and in chloroform. Protect from light.

Incompatibility. Although cytarabine has been stated in the literature to be incompatible with solutions of fluorouracil[1,2] and methotrexate[2] some studies have reported it to be stable for some hours when mixed with the latter.[3]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; **33:** 1010–13.
2. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.
3. Cheung Y-W, *et al.* Stability of cytarabine, methotrexate sodium, and hydrocortisone sodium succinate admixtures. *Am J Hosp Pharm* 1984; **41:** 1802–6.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

The major dose-limiting adverse effect of cytarabine is bone-marrow depression, manifest as leucopenia (particularly granulocytopenia), thrombocytopenia, and anaemia, sometimes with striking megaloblastic changes. Myelosuppression appears to be more evident after continuous infusions. Leucopenia is biphasic, with a nadir at 7 to 9 days after a dose and another, more severe, at 15 to 24 days. The nadir of the platelet count occurs at about 12 to 15 days. Recovery generally occurs in a further 10 days.

Gastrointestinal disturbances may occur: nausea and vomiting may be more severe when doses are given rapidly (but other adverse effects are reported to be worse when the drug is given by infusion). Other adverse effects reported include hepatic dysfunction, renal dysfunction, neurotoxicity, bleeding complications, rashes, oral and anal ulceration, gastrointestinal haemorrhage, oesophagitis, and conjunctivitis. A syndrome of bone and muscle pain, fever, malaise, conjunctivitis, and rash, sometimes described as flu-like, has been reported 6 to 12 hours after cytarabine doses, and may be treated or prevented with corticosteroids. Anaphylactoid reactions and pancreatitis have occurred rarely. There may be local pain, cellulitis, and thrombophlebitis at the site of injection.

Intrathecal use of the liposomal cytarabine formulation commonly causes chemical arachnoiditis manifesting as neck stiffness or pain, nausea, vomiting, headache, and fever. Dexamethasone should be used prophylactically to reduce the incidence and severity of this complication. Other rare adverse effects include encephalopathy, and focal seizures. Intrathecal use of conventional cytarabine formulations has rarely been associated with severe spinal cord toxicity, necrotising encephalopathy, blindness, and other neurotoxicities. If given intrathecally, preservative-free diluents must be used.

High-dose therapy has been associated with particularly severe gastrointestinal and CNS effects, including severe ulceration of the gastrointestinal tract, pneumatosis cystoides leading to peritonitis, necrotising colitis and bowel necrosis, peripheral neuropathy, and cerebral and cerebellar dysfunction, with personality changes, somnolence, and coma. There may also be corneal toxicity leading to punctate keratitis and haemorrhagic conjunctivitis, sepsis, liver abscess, severe skin rash leading to desquamation, alopecia, and cardiac disorders including pericarditis and fatal cardiomyopathy. Pulmonary oedema, sometimes fatal, has occurred.

Cytarabine is teratogenic in *animals* (but see Pregnancy, below).

In addition to frequent white blood cell and platelet counts, blood-uric acid should be monitored because of the risk of hyperuricaemia secondary to lysis of neoplastic cells, and renal and hepatic function should be periodically assessed. Cytarabine should be given with care to patients with impaired liver function; dosage reduction may be necessary.

◊ The toxicity of cytarabine has been reviewed.[1] The principal toxicity of standard dosage regimens is myelosuppression but bleeding complications and gastrointestinal toxicity are also major problems at standard doses. With the high-dose regimens neurological toxicity may be dose-limiting: severe and sometimes irreversible symptoms have been seen in some 6 to 10% of patients receiving a cumulative dose of 36 g/m^2. Ocular toxicity may occur in up to 80% of patients at the highest doses. Since cytarabine toxicity is largely dose-related, low-dose cytarabine is generally well tolerated, even in elderly patients (who are more susceptible): its only significant toxicity is myelosuppression.

1. Stentoft J. The toxicity of cytarabine. *Drug Safety* 1990; **5:** 7–27.

Effects on the nervous system. Although paraplegia has been reported with intrathecal cytarabine[1] (see also under Benzyl Alcohol, p.1631) and peripheral neuropathy has occurred in a patient who had received only conventional intravenous doses,[2] the majority of cases of neurotoxicity associated with cytarabine appear to be in patients given high-dose regimens.[3-7] Although some cases have manifested as demyelinating peripheral neuropathy,[3,4] including a syndrome of painful legs and involuntary movements in the toes which showed some response to carbamazepine,[3] most studies have reported in particular a syndrome of cerebellar toxicity,[5-8] with symptoms such as dysarthria, nystagmus, and ataxia. Toxicity appears to be dose-related: in one series[5] CNS toxicity occurred in none of 12 patients given total doses of up to 24 g/m^2 of cytarabine, 3 of 19 receiving 36 g/m^2, and 1 of 12 given 48 g/m^2, none of which were life-threatening or irreversible, whereas 4 of 6 given 54 g/m^2 (as 4.5 g/m^2 every 12 hours for 12 doses) developed neurotoxicity, which was fatal in one and irreversible in another. However, persistent, severe cerebellar toxicity has also been reported in a patient who had received a total dose of only 36 g/m^2 (as 3 g/m^2 every 12 hours).[8] There is some evidence[6] that patients aged over 50, and those who have recently received conventional-dose cytarabine[7] may be at increased risk. Intracranial hypertension (pseudotumor cerebri) has occurred rarely.[9]

1. Saleh MN, *et al.* Intrathecal cytosine arabinoside-induced acute, rapidly reversible paralysis. *Am J Med* 1989; **86:** 729–30.
2. Russell JA, Powles RL. Neuropathy due to cytosine arabinoside. *BMJ* 1974; **4:** 652–3.
3. Malapert D, Degos JD. Jambes douloureuses et orteils instables: neuropathie induite par la cytarabine. *Rev Neurol (Paris)* 1989; **145:** 869–71.
4. Openshaw H, *et al.* Acute polyneuropathy after high dose cytosine arabinoside in patients with leukemia. *Cancer* 1996; **78:** 1899–1905.
5. Lazarus HM, *et al.* Central nervous system toxicity of high-dose systemic cytosine arabinoside. *Cancer* 1981; **48:** 2577–82.
6. Graves T, Hooks MA. Drug-induced toxicities associated with high-dose cytosine arabinoside infusions. *Pharmacotherapy* 1989; **9:** 23–8.
7. Barnett MJ, *et al.* Neurotoxicity of high-dose cytosine arabinoside. *Prog Exp Tumor Res* 1985; **29:** 177–82.
8. Dworkin LA, *et al.* Cerebellar toxicity following high-dose cytosine arabinoside. *J Clin Oncol* 1985; **3:** 613–16.
9. Fort JA, Smith LD. Pseudotumor cerebri secondary to intermediate-dose cytarabine HCl. *Ann Pharmacother* 1999; **33:** 576–8.

Effects on the skin. A syndrome of pain and erythema of the palms and soles, progressing to bullae and desquamation, has been seen in patients receiving intermediate- or high-dose cytarabine.[1-3] The syndrome is similar to the palmar-plantar erythrodysesthesia syndrome (p.639) reported in patients receiving chemotherapy not including cytarabine,[4] although some considered the two forms of toxicity distinct.[5] Cutaneous small vessel necrotising vasculitis has been reported after high-dose therapy with cytarabine.[6]

1. Baer MR, *et al.* Palmar-plantar erythrodysesthesia and cytarabine. *Ann Intern Med* 1985; **102:** 556.
2. Peters WG, Willemze R. Palmar-plantar skin changes and cytarabine. *Ann Intern Med* 1985; **103:** 805.
3. Calista D, Landi C. Cytarabine-induced acral erythema: a localized form of toxic epidermal necrolysis? *J Eur Acad Dermatol Venereol* 1998; **10:** 274–5.
4. Lokich JJ, Moore C. Chemotherapy-associated palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med* 1984; **101:** 798–800.
5. Vogelzang NJ, Ratain MJ. Cancer chemotherapy and skin changes. *Ann Intern Med* 1985; **103:** 303–4.
6. Ahmed I, *et al.* Cytosine arabinoside-induced vasculitis. *Mayo Clin Proc* 1998; **73:** 239–42.