cholangitis, and biliary sclerosis. Floxuridine infusions have also been associated with a case of fatal progressive cirrhosis of the liver in the absence of overt cholestasis.[4] Pseudoaneurysms of the hepatic artery, leading to serious retroperitoneal or gastrointestinal bleeding, have also been described.[5]

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; **ii:** 440–4.
2. Anonymous. An implanted infusion pump for chemotherapy of liver metastases. *Med Lett Drugs Ther* 1984; **26:** 89–90.
3. Aldrighetti L, *et al.* Extrahepatic biliary stenoses after hepatic arterial infusion (HAI) of floxuridine (FUdR) for liver metastases from colorectal cancer. *Hepatogastroenterology* 2001; **48:** 1302–7.
4. Pettavel J, *et al.* Fatal liver cirrhosis associated with long-term arterial infusion of floxuridine. *Lancet* 1986; **ii:** 1162–3.
5. Samaras P, *et al.* Hemorrhage associated with hepatic artery pseudoaneurysms after regional chemotherapy with floxuridine: case report. *Int Semin Surg Oncol* 2008; **5:** 17.

Interactions

As for Fluorouracil, p.723.

Pharmacokinetics

Floxuridine is poorly absorbed from the gastrointestinal tract and it is usually given by injection. Floxuridine is metabolised mainly in the liver to fluorouracil after rapid injection. When given by slow intra-arterial infusion, more of the drug is metabolised to floxuridine monophosphate (F-dUMP). It is excreted as carbon dioxide via the lungs; some is excreted, as unchanged drug and metabolites, in urine. Floxuridine crosses the blood-brain barrier to some extent and is found in CSF.

Uses and Administration

Floxuridine is an antineoplastic which acts as an antimetabolite, either by conversion to fluorouracil (after rapid injection), or, when given by slow intra-arterial infusion, partly via floxuridine monophosphate (F-dUMP), which produces greater inhibition of DNA synthesis.

Floxuridine is used in the palliative treatment of hepatic metastases of colorectal cancer—see Malignant Neoplasms of the Liver, p.667. It has been tried in some other solid neoplasms. Doses of 100 to 600 micrograms/kg daily are given by continuous hepatic arterial infusion, usually with the aid of an infusion pump, until toxicity occurs.

White cell and platelet counts should be carried out regularly during therapy and treatment should be stopped if the white cell count falls rapidly or if the white cell or platelet count falls below acceptable levels (see also Bone-marrow Depression, p.639), or if major adverse effects occur.

◊ References.

1. Fordy C, *et al.* Hepatic arterial floxuridine as second-line treatment for systemic fluorouracil-resistant colorectal liver metastases. *Br J Cancer* 1998; **78:** 1058–60.
2. Kemeny N, *et al.* Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999; **341:** 2039–48.
3. Lorenz M, Muller HH. Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2000; **18:** 243–54.
4. Fiorentini G, *et al.* Locoregional therapy for liver metastases from colorectal cancer: the possibilities of intraarterial chemotherapy, and new hepatic-directed modalities. *Hepatogastroenterology* 2001; **48:** 305–12.
5. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005; **352:** 734–5.

Preparations

USP 31: Floxuridine for Injection.

Proprietary Preparations (details are given in Part 3)
USA: FUDR.

Fludarabine Phosphate

(BAN, USAN, rINNM)

2-F-ara-AMP; Fludarabiinifosfaatti; Fludarabin Fosfat; Fludarabine Monophosphate; Fludarabine, phosphate de; Fludarabinfosfat; Fludarabin-fosfát; Fludarabini phosphas; Fludarabino fosfatas; 2-Fluoro-ara-AMP; Fosfato de fludarabina; NSC-312887. 9-β-D-Arabinofuranosyl-2-fluoroadenine 5′-dihydrogenphosphate.

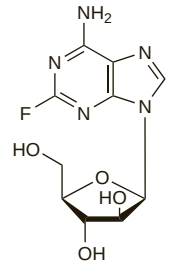
Флударабина Фосфат

$C_{10}H_{13}FN_5O_7P$ = 365.2.

CAS — 21679-14-1 (fludarabine); 75607-67-9 (fludarabine phosphate).

ATC — L01BB05.

ATC Vet — QL01BB05.



(fludarabine)

NOTE. The name FluCam has been used for a regimen of fludarabine with alemtuzumab. Distinguish from Flucam, which is ampiroxicam (p.19).

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Fludarabine Phosphate). A white or almost white, hygroscopic, crystalline powder. Slightly soluble in water; very slightly soluble in dehydrated alcohol; freely soluble in dimethylformamide. Store in airtight containers at a temperature of 2° to 8°. Protect from light.

USP 31 (Fludarabine Phosphate). A white to off-white, hygroscopic, crystalline powder. Slightly soluble in water and in 0.1M hydrochloric acid; practically insoluble in dehydrated alcohol; freely soluble in dimethylformamide. Store at 2° to 8°. Protect from light.

Adverse Effects, Treatment, and Precautions

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

Bone-marrow suppression from fludarabine is dose-limiting, manifesting as neutropenia, thrombocytopenia, and anaemia; the nadir of the white cell and platelet counts usually occurs after about 13 to 16 days. Myelosuppression can be severe and cumulative; prolonged lymphopenia with concomitant risk of opportunistic infections may occur. Bone marrow hypoplasia or aplasia resulting in pancytopenia may sometimes be fatal.

Other common adverse effects include fever, fatigue, chills, cough, weakness, malaise, anorexia, gastrointestinal disturbances, mucositis, stomatitis, oedema, and skin rashes. Pulmonary toxicity, including pulmonary fibrosis, pneumonitis, and dyspnoea can occur. Other adverse effects include dysuria, haematuria, epistaxis, and abnormalities in hepatic or pancreatic enzymes. Tumour lysis syndrome has been reported, especially in patients with large tumour burdens. Autoimmune disorders, including auto-immune haemolytic anaemia, have been reported, and may be life-threatening or fatal. Patients should be monitored for signs of haemolysis and therapy stopped if it occurs. Rarely reported effects include heart failure, arrhythmias, anaphylaxis, and haemorrhagic cystitis. Neurological disturbances include peripheral neuropathy, agitation, confusion, visual disturbances, hearing loss, headache, sleep disorders, and seizures; high doses have been associated with progressive encephalopathy, blindness, coma, and death.

Exacerbation of existing skin cancer lesions as well as new onset of skin cancer has been reported in some patients. Transfusion-associated graft-versus-host disease has been seen after transfusion of non-irradiated blood in patients treated with fludarabine, and fatalities have occurred; patients should only receive irradiated blood.

Dosage should be reduced in renal impairment (see below). It should also be avoided in patients with decompensated haemolytic anaemia.

Carcinogenicity. A study in patients with chronic lymphocytic leukaemia who were treated with fludarabine found that there was no significantly increased risk of secondary malignancy following therapy, despite the immunosuppressive properties of this drug.[1] A review[2] of this and other studies concluded that no significant increase in the risk of secondary malignancy had been shown, but also that long-term follow-up of patients treated with fludarabine was needed.

1. Cheson BD, *et al.* Second malignancies as a consequence of nucleoside analog therapy for chronic lymphoid leukaemias. *J Clin Oncol* 1999; **17:** 2454–60.
2. Van Den Neste E, *et al.* Second primary tumors and immune phenomena after fludarabine or 2-chloro-2′-deoxyadenosine treatment. *Leuk Lymphoma* 2001; **40:** 541–50.

Effects on the eyes. See under Effects on the Nervous System, below.

Effects on the lungs. Pulmonary toxicity manifest as dyspnoea, fever, hypoxaemia, and radiographic evidence of interstitial and alveolar infiltrates was diagnosed in 9 patients of a cohort of 105 treated with fludarabine.[1] Lung biopsies were performed in 6 patients and showed diffuse chronic interstitial inflammation and fibrosis. Patients with chronic lymphocytic leukaemia appeared to be at greater risk of developing this complication than those with non-Hodgkin's lymphoma.

1. Helman DL, *et al.* Fludarabine-related pulmonary toxicity: a distinct clinical entity in chronic lymphoproliferative syndromes. *Chest* 2002; **122:** 785–90.

Effects on the nervous system. High doses (of the order of 100 mg/m^2 daily intravenously) of fludarabine are associated with severe, life-threatening neurotoxicity. However, a few cases of progressive multifocal leukoencephalopathy have also been reported in patients given fludarabine in usual doses.[1-4] The prolonged immunosuppression caused by fludarabine might increase the risk of developing this fatal demyelinating disease, which is caused by opportunistic JC virus infection. Ocular toxicity, including irreversible loss of vision, has also been reported occasionally, including with low-dose regimens.[5]

1. Zabernigg A, *et al.* Late-onset fatal neurological toxicity of fludarabine. *Lancet* 1994; **344:** 1780.
2. Gonzalez H, *et al.* Progressive multifocal leukoencephalitis (PML) in three patients treated with standard-dose fludarabine (FAMP). *Hematol Cell Ther* 1999; **41:** 183–6.
3. Cid J, *et al.* Progressive multifocal leukoencephalopathy following oral fludarabine treatment of chronic lymphocytic leukemia. *Ann Hematol* 2000; **79:** 392–5.
4. Vidarsson B, *et al.* Progressive multifocal leukoencephalopathy after fludarabine therapy for low-grade lymphoproliferative disease. *Am J Hematol* 2002; **70:** 51–4.
5. Ding X, *et al.* Ocular toxicity of fludarabine: a purine analog. *Expert Rev Ophthalmol* 2008; **3:** 97–109.

Graft-versus-host disease. Transfusion-associated graft-versus-host disease has been reported when blood products were used in patients treated with fludarabine.[1] Fludarabine-treated patients should receive irradiated red cells and platelets (to inactivate any viable T-cells) if they require a transfusion.

1. Williamson LM, *et al.* Fludarabine treatment and transfusion-associated graft-versus-host disease. *Lancet* 1996; **348:** 472–3.

Infection. A review[1] of patients treated with fludarabine-containing regimens showed that therapy was associated with serious infections including listeriosis, pneumocystis pneumonia, mycobacterial infections, and opportunistic fungal and viral infections. The risk was exacerbated by previous or current corticosteroid therapy. Prophylactic therapy with co-trimoxazole, triazole antifungals, aciclovir, and colony-stimulating factors was recommended in at-risk patients. A high incidence of herpesvirus infections was also found in another review[2] of patients treated with fludarabine. Combination therapy using chlorambucil and fludarabine resulted in more infections than when either was used alone,[3] but single-agent fludarabine was associated with more major infections and herpesvirus infections than chlorambucil alone. The frequency of serious infection has also been reported[4] to be increased in patients after their conditions became refractory to fludarabine and they were being treated with conventional chemotherapy.

For reports of progressive multifocal leukoencephalopathy caused by opportunistic JC virus infection in patients receiving fludarabine, see Effects on the Nervous System, above.

1. Anaissie EJ, *et al.* Infections in patients with chronic lymphocytic leukemia treated with fludarabine. *Ann Intern Med* 1998; **129:** 559–66.
2. Byrd JC, *et al.* Herpes virus infections occur frequently following treatment with fludarabine: results of a prospective natural history study. *Br J Haematol* 1999; **105:** 445–7.
3. Morrison VA, *et al.* Impact of therapy with chlorambucil, fludarabine, or fludarabine plus chlorambucil on infections in patients with chronic lymphocytic leukemia: Intergroup Study Cancer and Leukemia Group B 9011. *J Clin Oncol* 2001; **19:** 3611–21.
4. Perkins JG, *et al.* Frequency and type of serious infections in fludarabine-refractory B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma: implications for clinical trials in this patient population. *Cancer* 2002; **94:** 2033–9.

Interactions

Increased pulmonary toxicity, sometimes fatal, has been reported in patients given fludarabine with pentostatin. Pretreatment with cytarabine may reduce the metabolic activation of fludarabine, but pretreatment with fludarabine results in increased intracellular concentrations of cytarabine—see p.706. The therapeutic efficacy of fludarabine may also be reduced by dipyridamole and other inhibitors of adenosine uptake.

Aminoglycosides. Severe ototoxicity occurred when a short course of *gentamicin* was given to a patient who had recently completed a course of fludarabine.[1]

1. O'Brien RK, Sparling TG. Gentamicin and fludarabine ototoxicity. *Ann Pharmacother* 1995; **29:** 200–1.

Corticosteroids. For a suggestion that use of fludarabine with corticosteroids may increase the risk of infection, see Infection, above.

Pharmacokinetics

Intravenous fludarabine phosphate is rapidly dephosphorylated to fludarabine which is taken up by lymphocytes and rephosphorylated to the active triphosphate nucleotide. Peak intracellular concentrations of fludarabine triphosphate are seen about 4 hours after a dose. Fludarabine has a bioavailability of about 50 to 65% after oral doses of the phosphate.

Clearance of fludarabine from the plasma is triphasic with a terminal half-life of about 20 hours. Elimination is mostly via renal excretion: 60% of a dose is excreted in the urine. The pharmacokinetics of fludarabine exhibit considerable interindividual variation.

◊ References.

1. Johnson SA. Clinical pharmacokinetics of nucleoside analogues: focus on haematological malignancies. *Clin Pharmacokinet* 2000; **39:** 5–26.
2. Gandhi V, Plunkett W. Cellular and clinical pharmacology of fludarabine. *Clin Pharmacokinet* 2002; **41:** 93–103.

Uses and Administration

Fludarabine is a fluorinated nucleotide analogue of the antiviral vidarabine (p.912); it acts as a purine antagonist antimetabolite. It is used for its antineoplastic properties in the treatment of chronic lymphocytic leukaemia. Fludarabine phosphate is given by bolus injection or by intravenous infusion over 30 minutes in a usual dose of 25 mg/m^2 daily for 5 consecutive days. Alternatively it may be given orally in a dose of 40 mg/m^2 daily for 5 consecutive days. Courses may be repeated every 28 days, usually for up to 6 cycles.

Haematological function should be monitored regularly; the dosage may need to be reduced, or further courses delayed, if blood counts indicate severe or persistent myelosuppression (see also Bone-marrow Depression, p.639). Doses should be reduced in renal impairment (see below).

◊ General references.

1. Adkins JC, *et al.* Fludarabine: an update of its pharmacology and use in the treatment of haematological malignancies. *Drugs* 1997; **53:** 1005–37.
2. Plosker GL, Figgitt DP. Oral fludarabine. *Drugs* 2003; **63:** 2317–23.

Administration in renal impairment. Doses of fludarabine phosphate should be reduced by up to 50% in patients with mild to moderate renal impairment (creatinine clearance between 30 and 70 mL/minute); the drug should not be given in more severe renal impairment.

Malignant neoplasms. Fludarabine is the preferred second-line therapy for chronic lymphocytic leukaemia once initial alkylating agent therapy fails,[1] and may also be used for initial therapy (see p.653). It has also been tried in other malignancies. Listed below are some references to the use of fludarabine phosphate for the treatment of chronic lymphocytic leukaemia,[2,3] and its potential activity against a variety of other malignancies, including indolent low-grade non-Hodgkin's lymphoma[4,5] (p.656), mycosis fungoides,[6] heavy chain disease,[7] prolymphocytic leukaemia,[8,9] hairy cell leukaemia,[10] and Waldenström's macroglobulinaemia.[11,12]

1. NICE. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia (issued September 2001). Available at: http://www.nice.org.uk/nicemedia/pdf/NICEfludarab_E_29guidance.pdf (accessed 31/07/08)
2. Zhu Q, *et al.* Fludarabine in comparison to alkylator-based regimen as induction therapy for chronic lymphocytic leukemia: a systematic review and meta-analysis. *Leuk Lymphoma* 2004; **45:** 2239–45.
3. Richards S. Fludarabine increases complete response but not survival compared with conventional alkylator-based regimens for previously untreated chronic lymphocytic leukaemia. *Cancer Treat Rev* 2005; **31:** 332–5.
4. Hiddemann W, Pott-Hoeck C. Fludarabine in the management of malignant lymphomas. *Drugs* 1994; **47** (suppl 6): 50–6.
5. Anderson VR, Perry CM. Fludarabine: a review of its use in non-Hodgkin's lymphoma. *Drugs* 2007; **67:** 1633–55.
6. Scarisbrick JJ, *et al.* A trial of fludarabine and cyclophosphamide combination chemotherapy in the treatment of advanced refractory primary cutaneous T-cell lymphoma. *Br J Dermatol* 2001; **144:** 1010–15.
7. Agrawal S, *et al.* First report of fludarabine in gamma-heavy chain disease. *Br J Haematol* 1994; **88:** 653–5.
8. Smith OP, Mehta AB. Fludarabine monophosphate for prolymphocytic leukaemia. *Lancet* 1990; **336:** 820.
9. Kantarjian HM, *et al.* Efficacy of fludarabine, a new adenine nucleoside analogue, in patients with prolymphocytic leukemia and the prolymphocytoid variant of chronic lymphocytic leukemia. *Am J Med* 1991; **90:** 223–8.
10. Kantarjian HM, *et al.* Fludarabine therapy in hairy cell leukemia. *Cancer* 1991; **67:** 1291–3.
11. Dhodapkar MV, *et al.* Prognostic factors and response to fludarabine therapy in patients with Waldenström macroglobulinemia: results of United States intergroup trial (Southwest Oncology Group S9003). *Blood* 2001; **98:** 41–8.
12. Leblond V, *et al.* Multicenter, randomized comparative trial of fludarabine and the combination of cyclophosphamide-doxorubicin-prednisone in 92 patients with Waldenström macroglobulinemia in first relapse or with primary refractory disease. *Blood* 2001; **98:** 2640–4.

Preparations

USP 31: Fludarabine Phosphate for Injection; Fludarabine Phosphate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Fludakebir; Fludara; Fluradosa; Forclina; ***Austral.:*** Fludara; ***Austria:*** Fludara; ***Belg.:*** Fludara; ***Braz.:*** Fludara; ***Canad.:*** Fludara; ***Chile:*** Fludara; ***Cz.:*** Fludara; Tazumara; ***Denm.:*** Fludara; ***Fin.:*** Fludara; ***Fr.:*** Fludara; ***Ger.:*** Fludara; ***Gr.:*** Fludara; ***Hong Kong:*** Fludara; ***Hung.:*** Fludara; ***India:*** Fludara; ***Indon.:*** Fludara; ***Irl.:*** Fludara; ***Israel:*** Fludara; ***Ital.:*** Fludara; ***Malaysia:*** Fludara; ***Mex.:*** Beneflur; Fludara; ***Neth.:*** Fludara; ***Norw.:*** Fludara; ***NZ:*** Fludara; ***Philipp.:*** Fludara; ***Pol.:*** Fludara; ***Port.:*** Fludara; ***Rus.:*** Fludara (Флудара); ***S.Afr.:*** Fludara; ***Singapore:*** Fludara; ***Spain:*** Beneflur; ***Swed.:*** Fludara; ***Switz.:*** Fludara; ***Thai.:*** Fludara; ***Turk.:*** Fludara; ***UK:*** Fludara; ***USA:*** Fludara; ***Venez.:*** Fludara.

Fluorouracil *(BAN, USAN, rINN)*

5-Fluorouracil; Fluorouracilas; Fluorouracile; Fluorouracilo; Fluorouracilum; Fluorouracyl; Fluorourasiili; Fluorourasil; 5-Fluorourasil; Fluoruracil; 5-FU; NSC-19893; Ro-2-9757; WR-69596. 5-Fluoropyrimidine-2,4(1*H*,3*H*)-dione.

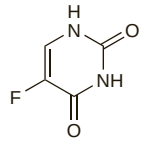
Флуороурацил

$C_4H_3FN_2O_2$ = 130.1.

CAS — 51-21-8.

ATC — L01BC02.

ATC Vet — QL01BC02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Fluorouracil). A white or almost white, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 5.0. Protect from light.
USP 31 (Fluorouracil). A white to practically white, practically odourless, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Incompatibility. Preparations of fluorouracil are alkaline, and compatibility problems may be expected with acidic drugs and preparations, or those which are unstable in the presence of alkali. Fluorouracil is reported to be incompatible with cytarabine,[1] diazepam,[2] doxorubicin[2] (and presumably other anthracyclines that are unstable at alkaline pH), and calcium folinate.[3] Although fluorouracil has been stated to be incompatible with methotrexate[1] a study of the long-term stability of an admixture of the 2 drugs in sodium chloride 0.9% injection suggests otherwise.[4]

1. McRae MP, King JC. Compatibility of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. *Am J Hosp Pharm* 1976; **33:** 1010–13.
2. Dorr RT. Incompatibilities with parenteral anticancer drugs. *Am J Intravenous Ther* 1979; **6:** 42–52.
3. Trissel LA, *et al.* Incompatibility of fluorouracil with leucovorin calcium or levoleucovorin calcium. *Am J Health-Syst Pharm* 1995; **52:** 710–15.
4. Vincké BJ, *et al.* Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; **54:** 181–9.

Stability. Despite one report[1] that fluorouracil had limited stability when dissolved in glucose 5% at room temperature (10% loss from solution in 43 hours when stored in PVC and in only 7 hours when stored in glass), others[2] found such a solution to be stable for at least 16 weeks when stored in PVC at 5°. When stored at room temperature in PVC, solutions of fluorouracil may lose water by evaporation, which slowly increases their concentration.[2,3] Results of a study of fluorouracil and methotrexate admixtures in sodium chloride 0.9% suggest that extended stability (up to 13 weeks) is possible in this diluent at 5° in PVC bags.[3] Commercial solutions of fluorouracil for injection have been reported to be stable for 7 days at 37° in a portable infusion pump, although at 25° one brand showed evidence of precipitation.[4] Fluorouracil solutions may be incompatible with synthetic elastomers: microscopic precipitation has been reported as soon as 4 hours after placement into polyisoprene reservoirs of elastomeric infusers and in polypropylene syringes with an elastomeric joint.[5] Some have questioned the validity of this finding.[6,7]

1. Benvenuto JA, *et al.* Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; **38:** 1914–18.
2. Quebbeman EJ, *et al.* Stability of fluorouracil in plastic containers used for continuous infusion at home. *Am J Hosp Pharm* 1984; **41:** 1153–6.
3. Vincké B, *et al.* Extended stability of 5-fluorouracil and methotrexate solutions in PVC containers. *Int J Pharmaceutics* 1989; **54:** 181–9.
4. Stiles ML, *et al.* Stability of fluorouracil administered through four portable infusion pumps. *Am J Hosp Pharm* 1989; **46:** 2036–40.
5. Corbrion V, *et al.* Precipitation of fluorouracil in elastomeric infusers with a polyisoprene reservoir and in polypropylene syringes with an elastomeric joint. *Am J Health-Syst Pharm* 1997; **54:** 1845–8.
6. Trissel LA. Fluorouracil precipitate. *Am J Health-Syst Pharm* 1998; **55:** 1314–15.
7. Allwood MC. Fluorouracil precipitate. *Am J Health-Syst Pharm* 1998; **55;** 1315–16.

Adverse Effects and Treatment

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

The main adverse effects of fluorouracil are on the bone marrow and the gastrointestinal tract, and may be dose-limiting. Toxicity is schedule dependent: reducing the rate of injection to a slow infusion is associated with less haematological toxicity but does not decrease gastrointestinal toxicity. With protracted continuous infusion in particular, the palmar-plantar erythrodysesthesia syndrome (erythema and painful desquamation of the hands and feet) may occur. Gastrointestinal toxicity may be exacerbated if fluorouracil is given with folinic acid.

Leucopenia, thrombocytopenia, stomatitis, gastrointestinal ulceration and bleeding, diarrhoea, or haemorrhage from any site, are signs that treatment should be stopped. The nadir of the white cell count may occur from 7 to 20 days after a dose, and counts usually return to normal after about 30 days. Thrombocytopenia is usually at a maximum 7 to 17 days after a dose. Anaemia may also occur. Nausea and vomiting, rashes, and alopecia are common. Ocular irritation, central neurotoxicity (notably cerebellar ataxia), and myocardial ischaemia have occurred.

Local inflammatory and photosensitivity reactions have occurred after topical use. Dermatitis and, rarely, erythema multiforme have been reported.

Effects on the eyes. Systemic fluorouracil therapy has been associated with various types of ocular toxicity including several cases of excessive lachrymation and watering of the eyes.[1] In one patient this was associated with symptoms suggesting fibrosis of the tear duct,[1] and possibly representing local irritation due to the presence of fluorouracil in tear fluid,[2] although symptoms have not always resolved on stopping the drug.[1] More seriously a case of bilateral total corneal epithelial erosion has been described.[3] Optic neuropathy, culminating in near blindness, has also occurred in a patient given fluorouracil as part of a combination regimen.[4] Severe ulceration and corneal abscess with hyopyon has followed local injection of fluorouracil into the eye in a diabetic patient with idiopathic band keratopathy.[5]

1. Haidak DJ, *et al.* Tear-duct fibrosis (dacryostenosis) due to 5-fluorouracil. *Ann Intern Med* 1978; **88:** 657.
2. Christophidis N, *et al.* Lacrimation and 5-fluorouracil. *Ann Intern Med* 1978; **89:** 574.
3. Hirsh A, *et al.* Bilateral total corneal epithelial erosion as a side effect of cytotoxic therapy. *Br J Ophthalmol* 1990; **74:** 638.
4. Adams JW, *et al.* Recurrent acute toxic optic neuropathy secondary to 5-FU. *Cancer Treat Rep* 1984; **68:** 565–6.
5. Hickey-Dwyer M, Wishart PK. Serious corneal complication of 5-fluorouracil. *Br J Ophthalmol* 1993; **77:** 250–1.

Effects on the heart. Life-threatening cardiotoxicity (arrhythmias, ventricular tachycardia, and cardiac arrest, secondary to transmural ischaemia) has been reported to occur in 0.55% of patients given fluorouracil,[1] although the incidence of angina and less severe cardiotoxicity associated with coronary artery spasm may be higher.[1-3] Possible risk factors include pre-existing heart disease or mediastinal radiotherapy, and prolonged infusion of the drug, but symptoms can also occur in patients without these risk factors.[2-4] Therefore, at present, it is not possible to reliably predict patients at risk.[5] Some suggest that the use of a trometamol buffer in the fluorouracil formulation may contribute to the formation of cardiotoxic degradation products.[6]

1. Keefe DL, *et al.* Clinical cardiotoxicity of 5-fluorouracil. *J Clin Pharmacol* 1993; **33:** 1060–70.
2. McLachlan SA, *et al.* The spectrum of 5-fluorouracil cardiotoxicity. *Med J Aust* 1994; **161:** 207–9.
3. Anand AJ. Fluorouracil cardiotoxicity. *Ann Pharmacother* 1994; **28:** 374–8.