should be stopped at the first signs of microangiopathic haemolytic anaemia. Congestive heart failure, myocardial infarction, or arrhythmias may occur rarely.

Gemcitabine may produce somnolence: patients so affected should not drive or operate machinery. Severe toxicity, in the form of potentially life-threatening oesophagitis and pneumonitis has been seen in patients given radical radiotherapy to the thorax concurrently with gemcitabine.

Effects on the nervous system. A report of autonomic neuropathy associated with gemcitabine therapy.[1] Symptoms resolved 4 weeks after stopping therapy.

1. Dormann AJ, *et al.* Gemcitabine-associated autonomic neuropathy. *Lancet* 1998; **351:** 644.

Effects on the skin. A patient who received gemcitabine 1 week after having had phototherapy developed a severe sunburn reaction in those areas exposed to UVB. The erythema resolved spontaneously, but recurred with each subsequent dose of gemcitabine, and became progressively more intense. A short course of high-dose prednisone was given with topical triamcinolone, and the patient was safely rechallenged with 2 further doses of gemcitabine.[1]

1. Badger J, *et al.* Photo therapy recall with gemcitabine following ultraviolet B treatment. *J Clin Oncol* 2005; **23:** 7224–5.

Peripheral ischaemia. Pain, coldness, colour changes, and distal claudication in the feet have been reported in patients treated with gemcitabine and cisplatin.[1] Pain and colour changes in the fingertips have also been reported after gemcitabine monotherapy.[2]

1. Barceló R, *et al.* Distal ischemic changes related to combination chemotherapy with cisplatin and gemcitabine: description of four cases. *Ann Oncol* 2000; **11:** 1191–4.
2. Yildiz R, *et al.* Digital ischemic changes after gemcitabine therapy in a patient with metastatic non-small-cell lung cancer. *Ann Pharmacother* 2007; **41:** 901–2.

Interactions

Antineoplastics. In a study[1] of 14 patients with lung cancer, the use of *paclitaxel* before gemcitabine caused a decrease in the systemic clearance, volume of distribution, and interpatient pharmacokinetic variability of gemcitabine. This resulted in plasma concentrations of gemcitabine slightly higher than the desired range. However, there was no apparent relationship between pharmacokinetic changes and toxicity, and the clinical significance of this possible interaction is unclear.

A trial investigating a modified chemotherapy regimen in which gemcitabine was substituted for etoposide was stopped because of unexpected pulmonary toxicity. This was considered to be due to the combination of gemcitabine and *bleomycin*, as the adverse effect was apparent in other studies using this combination.[2]

1. Shord SS, *et al.* Gemcitabine pharmacokinetics and interaction with paclitaxel in patients with advanced non-small-cell lung cancer. *Cancer Chemother Pharmacol* 2003; **51:** 328–36.
2. Bredenfeld H, *et al.* Severe pulmonary toxicity in patients with advanced-stage Hodgkin's disease treated with a modified bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, and gemcitabine (BEACOPP) regimen is probably related to the combination of gemcitabine and bleomycin: a report of the German Hodgkin's lymphoma study group. *J Clin Oncol* 2004; **22:** 2424–9.

Pharmacokinetics

After intravenous doses gemcitabine is rapidly cleared from the blood and metabolised by cytidine deaminase in the liver, kidney, blood, and other tissues. Clearance is about 25% lower in women than in men. Almost all of the dose is excreted in urine as 2′-deoxy-2′,2′-difluorouridine (dFdU), only about 1% being found in the faeces. Intracellular metabolism produces mono-, di-, and triphosphate metabolites, the latter two active. The half-life of gemcitabine ranges from 42 to 94 minutes depending on age and gender. The intracellular half-life of the triphosphate is stated to range from 0.7 to 12 hours.

◊ References.

1. Johnson SA. Clinical pharmacokinetics of nucleoside analogues: focus on haematological malignancies. *Clin Pharmacokinet* 2000; **39:** 5–26.
2. Shamseddine AI, *et al.* Comparative pharmacokinetics and metabolic pathway of gemcitabine during intravenous and intra-arterial delivery in unresectable pancreatic cancer patients. *Clin Pharmacokinet* 2005; **44:** 957–67.

Uses and Administration

Gemcitabine is an analogue of cytarabine (p.705) that is metabolised intracellularly to active diphosphate and triphosphate nucleosides, which inhibit DNA synthesis and induce apoptosis. It is primarily active against cells in S phase. It is given in the management of solid tumours including those of the bladder, breast, lung, ovary, and pancreas (see p.659, p.661, p.668, p.670, and p.671, respectively).

Gemcitabine is given intravenously as the hydrochloride. Doses are calculated in terms of the base; gemcitabine hydrochloride 1.14 g is equivalent to about 1 g of gemcitabine. Doses are reconstituted in sodium chloride 0.9%. The concentration of the infusion solution should not exceed the equivalent of gemcitabine 40 mg/mL. Gemcitabine is given by infusion over 30 to 60 minutes; doses are subsequently adjusted according to response and toxicity.

In the treatment of **pancreatic cancer**, an initial course of gemcitabine 1 g/m^2 once weekly for up to 7 weeks may be given, followed after a one-week recovery period by a regimen of infusions once weekly for 3 consecutive weeks out of 4.

In **non-small cell lung cancer**, gemcitabine may be given as a single agent; 1 g/m^2 once weekly for 3 consecutive weeks out of 4 is recommended. Alternatively, it may be given before cisplatin. Two schedules have been used; gemcitabine 1.25 g/m^2 is given on days 1 and 8 of a 21-day cycle, or gemcitabine 1 g/m^2 is given on days 1, 8 and 15 of a 28-day cycle.

In the treatment of **bladder cancer**, gemcitabine is given before cisplatin. The recommended dose of gemcitabine is 1 g/m^2 on days 1, 8, and 15 of a 28-day cycle.

In **breast cancer**, gemcitabine is usually given after a taxane such as paclitaxel. A dose of gemcitabine 1.25 g/m^2 is given on days 1 and 8 of a 21-day cycle.

In **ovarian cancer**, gemcitabine is given before carboplatin. The recommended dose of gemcitabine is 1 g/m^2 on days 1 and 8 of a 21-day cycle.

◊ References.

1. Stadler WM. Gemcitabine doublets in advanced urothelial cancer. *Semin Oncol* 2002; **29** (suppl 3): 15–19.
2. Hussain M, *et al.* Novel gemcitabine-containing triplets in the management of urothelial cancer. *Semin Oncol* 2002; **29** (suppl 3): 20–4.
3. Hochster HS. Newer approaches to gemcitabine-based therapy of pancreatic cancer: fixed-dose-rate infusion and novel agents. *Int J Radiat Oncol Biol Phys* 2003; **56** (suppl): 24–30.
4. Yardley DA. Gemcitabine and taxanes as a new standard of care in breast cancer. *Clin Breast Cancer* 2004; **4** (suppl 3): S107–S112.
5. Natale R. A ten-year review of progress in the treatment of non-small-cell lung cancer with gemcitabine. *Lung Cancer* 2005; **50** (suppl): S2–S4.
6. Saha A, Rudd R. Gemcitabine and carboplatin: is this the best combination for non-small cell lung cancer? *Expert Rev Anticancer Ther* 2006; **6:** 165–73.
7. Kose MF, *et al.* Gemcitabine plus carboplatin in platinum-sensitive recurrent ovarian carcinoma. *Expert Rev Anticancer Ther* 2006; **6:** 437–43.
8. Wirk B, Perez E. Role of gemcitabine in breast cancer management: an update. *Semin Oncol* 2006; **33** (suppl 2): S6–S14.
9. Pfisterer J, *et al.* Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol* 2006; **24:** 4699–4707.
10. Kiba T, *et al.* Single-agent gemcitabine for biliary tract cancers: study outcomes and systematic review of the literature. *Oncology* 2006; **70:** 358–65.
11. Maki RG. Gemcitabine and docetaxel in metastatic sarcoma: past, present, and future. *Oncologist* 2007; **12:** 999–1006.
12. El Karak F, Flechon A. Gemcitabine in bladder cancer. *Expert Opin Pharmacother* 2007; **8:** 3251–6.
13. Serrano A, Gerson R. Chemotherapy with gemcitabine in advanced biliary tract carcinoma. *Rev Recent Clin Trials* 2008; **3:** 70–8.
14. Hilbig A, Oettle H. Gemcitabine in the treatment of metastatic pancreatic cancer. *Expert Rev Anticancer Ther* 2008; **8:** 511–23.
15. Dent S, *et al.* Gemcitabine in the management of metastatic breast cancer: a systematic review. *Breast Cancer Res Treat* 2008; **108:** 319–31.

Preparations

USP 31: Gemcitabine for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Abine; Antoril; Eriogem; Gemtro; Gezt; Gramagen; ***Austral.:*** Gemzar; ***Austria:*** Gemzar; ***Belg.:*** Gemzar; ***Braz.:*** Gemzar; ***Canad.:*** Gemzar; ***Chile:*** Gemzar; ***Cz.:*** Gemzar; ***Denm.:*** Gemzar; ***Fin.:*** Gemzar; ***Fr.:*** Gemzar; ***Ger.:*** Gemzar; ***Gr.:*** Gemzar; ***Hong Kong:*** Gemzar; ***Hung.:*** Gemzar; ***India:*** Gemcite; Oncogem; ***Indon.:*** Gemzar; ***Irl.:*** Gemzar; ***Israel:*** Gemzar; ***Ital.:*** Gemzar; ***Malaysia:*** Gemzar; ***Mex.:*** Gemzar; ***Neth.:*** Gemzar; ***Norw.:*** Gemzar; ***NZ:*** Gemzar; ***Philipp.:*** Gemzar; ***Pol.:*** Gemzar; ***Port.:*** Gemzar; ***Rus.:*** Gemzar (Гемзар); ***S.Afr.:*** Gemzar; ***Singapore:*** Gemzar; ***Spain:*** Gemzar; ***Swed.:*** Gemzar; ***Switz.:*** Gemzar; ***Thai.:*** Gemzar; ***Turk.:*** Gemzar; ***UK:*** Gemzar; ***USA:*** Gemzar; ***Venez.:*** Gemzar.

Gemtuzumab Ozogamicin *(USAN, rINNM)*

CDP-771; CMA-676; Gemtuzumab ozogamicina; Gemtuzumab Ozogamicine; Gemtuzumab Zogamicin; Gemtuzumabum Ozogamicinum; WAY-CMA-676. Immunoglobulin G4 (human-mouse monoclonal hP67.6 κ4-chain anti-human antigen CD 33), disulfide with human-mouse monoclonal hP67.6 κ-chain, dimer conjugate with ozogamicin.

Гемтузумаб Озогамицин

CAS — 220578-59-6.
ATC — L01XC05.
ATC Vet — QL01XC05.

Adverse Effects and Precautions

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

Myelosuppression is common with gemtuzumab ozogamicin, and thrombocytopenia may be prolonged. Infusion-related reactions characteristic of a cytokine release syndrome (including fever, chills, dyspnoea, and hypotension) and hypersensitivity may occur; prophylactic use of an antihistamine and paracetamol is recommended. Pulmonary sequelae may be fatal. Hepatotoxicity, including severe veno-occlusive disease, has also been reported. Electrolyte imbalances, especially hypokalaemia and hypomagnesaemia, and gastrointestinal disturbances may occur.

Blood and platelet counts, electrolytes, and liver function tests should be regularly monitored.

Hypersensitivity. A 75-year-old man with acute myeloid leukaemia developed severe respiratory distress and died after being given gemtuzumab ozogamicin and platelets on the same day. He had previously had the drug and platelets on separate occasions with no untoward effects. It was suggested that this combination contributed to a fatal hypersensitivity reaction.[1]

1. Hanbali A, *et al.* Fatal hypersensitivity reaction to gemtuzumab ozogamicin associated with platelet transfusion. *Am J Health-Syst Pharm* 2007; **64:** 1401–2.

Uses and Administration

Gemtuzumab ozogamicin is a recombinant humanised monoclonal antibody conjugated with calicheamicin, a cytotoxic antibiotic. The antibody binds specifically to the CD33 antigen, which is expressed on leukaemic myeloblasts but not normal haematopoietic stem cells. Gemtuzumab ozogamicin is licensed for the second-line treatment of CD33-positive acute myeloid leukaemia (p.652) in elderly patients who are unable to tolerate conventional chemotherapy. It is given in 100 mL of sodium chloride 0.9% via an in-line 1.2 micron filter. The licensed dose is 9 mg/m^2 given by intravenous infusion over 2 hours, repeated once after 14 days. Lower doses are under investigation as part of combined induction or consolidation regimens.

◊ References.

1. McGavin JK, Spencer CM. Gemtuzumab ozogamicin. *Drugs* 2001; **61:** 1317–22.
2. Dowell JA, *et al.* Pharmacokinetics of gemtuzumab ozogamicin, an antibody-targeted chemotherapy agent for the treatment of patients with acute myeloid leukemia in first relapse. *J Clin Pharmacol* 2001; **41:** 1206–14.
3. Sievers EL, *et al.* Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. *J Clin Oncol* 2001; **19:** 3244–54.
4. Sievers EL, Linenberger M. Mylotarg: antibody-targeted chemotherapy comes of age. *Curr Opin Oncol* 2001; **13:** 522–7.
5. Larson RA, *et al.* Antibody-targeted chemotherapy of older patients with acute myeloid leukemia in first relapse using Mylotarg (gemtuzumab ozogamicin). *Leukemia* 2002; **16:** 1627–36.
6. Buckwalter M, *et al.* Pharmacokinetics of gemtuzumab ozogamicin as a single-agent treatment of pediatric patients with refractory or relapsed acute myeloid leukemia. *J Clin Pharmacol* 2004; **44:** 873–80.
7. Lo-Coco F, *et al.* Gemtuzumab ozogamicin (Mylotarg) as a single agent for molecularly relapsed acute promyelocytic leukemia. *Blood* 2004; **104:** 1995–9.
8. Fenton C, Perry CM. Gemtuzumab ozogamicin: a review of its use in acute myeloid leukaemia. *Drugs* 2005; **65:** 2405–27.
9. Tsimberidou AM, *et al.* The role of gemtuzumab ozogamicin in acute leukaemia therapy. *Br J Haematol* 2006; **132:** 398–409.
10. Stasi R, *et al.* Gemtuzumab ozogamicin in the treatment of acute myeloid leukemia. *Cancer Treat Rev* 2008; **34:** 49–60.
11. Leukaemia Research Fund. AML14: Leukaemia Research Fund Acute Myeloid Leukaemia and High Risk MDS Trial 14. Available at: http://www.download.bham.ac.uk/bctu/aml14/trial%20documentation/amendment%20january%202004/Protocol%20Jan%202004.pdf (accessed 30/07/08)
12. Medical Research Council. AML15: Medical Research Council Working Parties on Leukaemia in Adults and Children Acute Myeloid Leukaemia Trial 15.
Available at: http://www.download.bham.ac.uk/bctu/AML15/Amendment%20Nov%202007/AML15%20protocol%20version%207%20Final%20200704201%20with%20no%20track%20changes.pdf (accessed 30/07/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Mylotarg; ***USA:*** Mylotarg; ***Venez.:*** Mylotarg.

Hydroxycarbamide *(BAN, rINN)*

Hidroksikarbamid; Hidroksikarbamidas; Hidroxicarbamida; Hidroxikarbamid; Hydroksikarbamidi; Hydroksiüre; Hydroxikarbamid; Hydroxycarbamidum; Hydroxymočovina; Hydroxyurea *(USAN)*; NSC-32065; SQ-1089; WR-83799.

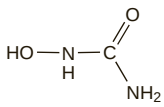
Гидроксикарбамид

$NH_2.CO.NHOH$ = 76.05.

CAS — 127-07-1.

ATC — L01XX05.

ATC Vet — QL01XX05.



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

Ph. Eur. 6.2 (Hydroxycarbamide). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers. Protect from light.

USP 31 (Hydroxyurea). A white to off-white powder. It is somewhat hygroscopic and decomposes in the presence of moisture. Freely soluble in water and in hot alcohol. Store in airtight containers in a dry atmosphere.

Adverse Effects, Treatment, and Precautions

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

Bone-marrow suppression, including megaloblastic changes, is the main adverse effect of hydroxycarbamide. The erythema caused by irradiation may be exacerbated. Other adverse effects reported have included gastrointestinal disturbances, impairment of renal function, pulmonary oedema, dermatological reactions, alopecia, and neurological reactions such as headache, dizziness, drowsiness, disorientation, hallucinations, and convulsions. There are rare reports of acute pulmonary reactions consisting of pulmonary infiltrates or fibrosis, dyspnoea and fever. Symptoms resembling cutaneous vasculitis, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders treated with hydroxycarbamide, especially in those also given interferon. There are reports of hepatotoxicity and pancreatitis, some fatal, in patients with HIV infection, given hydroxycarbamide and antiretrovirals (see also HIV Infection and AIDS, below); peripheral neuropathy has also occurred.

Pre-existing anaemia should be corrected before beginning therapy with hydroxycarbamide and the haemoglobin concentration, white cell and platelet counts, and hepatic and renal function should be determined repeatedly during treatment. Treatment should be interrupted if the white cell or platelet count fall below acceptable levels (see also Bone-marrow Depression, p.639). If anaemia occurs when hydroxycarbamide is used as an antineoplastic, it may be corrected by transfusions of whole blood without stopping therapy. If anaemia (haemoglobin less than 4.5 g per 100 mL, or reticulocyte count less than 80 000 cells/mm^3 when haemoglobin is less than 9 g per 100 mL) occurs when the drug is used for sickle-cell disease, therapy should be interrupted. Megaloblastic changes are usually self-limiting.

Hydroxycarbamide should be used with caution in patients with impaired renal function. Uric acid concentrations should be monitored, and a high fluid intake maintained during treatment. The elderly may be more sensitive to its adverse effects.

Breast feeding. In breast-milk samples from a woman given hydroxycarbamide 500 mg three times daily, the mean concentration of the drug was found to be about 6 mg/litre. It was estimated that, had the infant been breast-fed, it would have received about 3 to 4 mg daily. Although this amount appears to be low, women are advised not to breast feed while taking hydroxycarbamide.[1]

1. Sylvester RK, *et al.* Excretion of hydroxyurea into milk. *Cancer* 1987; **60:** 2177–8.

Carcinogenicity. Secondary leukaemias have occurred in patients receiving hydroxycarbamide for myeloproliferative disorders, although the extent to which this is due to the treatment or the underlying disorder is unknown.

Skin cancers have also been associated with its use. These are often multiple and include both squamous cell and basal cell carcinomas.

References.

1. Liozon E, *et al.* Is treatment with hydroxyurea leukemogenic in patients with essential thrombocythemia? An analysis of three new cases of leukaemic transformation and review of the literature. *Hematol Cell Ther* 1997; **39:** 11–18.
2. Pearson TC, *et al.* Leukemic transformation in polycythemia vera. *Blood* 1998; **92:** 1837–8.
3. De Simone C, *et al.* Multiple squamous cell carcinomas of the skin during long-term treatment with hydroxyurea. *Eur J Dermatol* 1998; **8:** 114–15.
4. Best PJM, Petitt RM. Multiple skin cancers associated with hydroxyurea therapy. *Mayo Clin Proc* 1998; **73:** 961–3.

Effects on the liver. Fever and hepatitis have been reported[1,2] in patients receiving hydroxycarbamide. Symptoms recurred when patients were rechallenged with the drug.

1. Heddle R, Calvert AF. Hydroxyurea induced hepatitis. *Med J Aust* 1980; **1:** 121.
2. Westerman DA, *et al.* Hydroxyurea-induced fever and hepatitis. *Aust N Z J Med* 1998; **28:** 657–9.

Effects on the skin and nails. Reports of skin reactions with hydroxycarbamide include hyperpigmentation of the skin,[1] and of nails (melanonychia).[2]

Hydroxycarbamide therapy has been associated with scaly erythematous skin lesions often resembling those of dermatomyositis.[1,3,4] Such lesions usually occur after several years of treatment and the course is usually benign. However, withdrawal of the drug is usually necessary for healing or improvement, in which case resolution may take several months.[1,4] Hydroxycarbamide can also cause painful leg ulcers, often on the malleoli, which may require stopping treatment.[1,5,6] Leg ulcers often coexist with dermatomyositis-like eruptions and may be caused by the same mechanism,[7] although mechanical injury may have a role in malleolar ulceration.[5] Licensed product information notes that vasculitic toxicities, including vasculitic ulceration and gangrene, have been associated with hydroxycarbamide use in patients with myeloproliferative disorders (particularly if also given interferon). However, histologically, perivascular lymphocytic infiltration without vasculitis has been reported in both early dermatomyositis-like lesions[1] and in leg ulcers.[5,8]

Skin cancers have also occurred, see Carcinogenicity above.

1. Vassallo C, *et al.* Muco-cutaneous changes during long-term therapy with hydroxyurea in chronic myeloid leukaemia. *Clin Exp Dermatol* 2001; **26:** 141–8.
2. Aste N, *et al.* Nail pigmentation caused by hydroxyurea: report of 9 cases. *J Am Acad Dermatol* 2002; **47:** 146–7.
3. Senet P, *et al.* Hydroxyurea-induced dermatomyositis-like eruption. *Br J Dermatol* 1995; **133:** 455–9.
4. Daoud MS, *et al.*. Hydroxyurea dermopathy: a unique lichenoid eruption complicating long-term therapy with hydroxyurea. *J Am Acad Dermatol* 1997; **36:** 178–82.
5. Best PJ, *et al.* Hydroxyurea-induced leg ulceration in 14 patients. *Ann Intern Med* 1998; **128:** 29–32.
6. Chaine B, *et al.* Cutaneous adverse reactions to hydroxyurea in patients with sickle cell disease. *Arch Dermatol* 2001; **137:** 467–70.
7. Suehiro M, *et al.* Hydroxyurea dermopathy with a dermatomyositis-like eruption and a large leg ulcer. *Br J Dermatol* 1998; **139:** 748–9.
8. Tarumoto T, *et al.* A case of bilateral heel ulcers associated with hydroxyurea therapy for chronic myelogenous leukemia. *Jpn J Clin Oncol* 2000; **30:** 159–62.

Handling and disposal. *Urine* produced for up to 48 hours after a dose of hydroxycarbamide should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Interactions

For a general discussion of antineoplastic drug interactions, see p.642.

Pharmacokinetics

Hydroxycarbamide is readily absorbed from the gastrointestinal tract and distributed throughout the body. Peak plasma concentrations are reached within 2 hours. Up to 50% of a dose is metabolised by the liver; hydroxycarbamide is excreted in urine as metabolites and unchanged drug. Some is excreted as carbon dioxide via the lungs. About 80% of a dose is reported to be excreted in the urine within 12 hours. Hydroxycarbamide crosses the blood-brain barrier and the placenta, and is distributed into breast milk.

◊ References.

1. Gwilt PR, Tracewell WG. Pharmacokinetics and pharmacodynamics of hydroxyurea. *Clin Pharmacokinet* 1998; **34:** 347–58.
2. Gwilt PR, *et al.* Pharmacokinetics of hydroxyurea in plasma and cerebrospinal fluid of HIV-1-infected patients. *J Clin Pharmacol* 2003; **43:** 1003–7.
3. Yan J-H, *et al.* The influence of renal function on hydroxyurea pharmacokinetics in adults with sickle cell disease. *J Clin Pharmacol* 2005; **45:** 434–45.

Uses and Administration

Hydroxycarbamide is an antineoplastic that may cause inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor. It is S-phase specific. Hydroxycarbamide is used in the treatment of chronic myeloid leukaemia, and may be used in the myeloproliferative disorders polycythaemia vera and primary (essential) thrombocythaemia. It has also been tried, often combined with radiotherapy, in some solid malignancies (see Malignant Neoplasms, below). Hydroxycarbamide has also produced benefit in the haemoglobinopathies, particularly in sickle-cell disease (see below).

In the treatment of chronic myeloid leukaemia and solid tumours, hydroxycarbamide is given orally, typically in a single dose of 20 to 30 mg/kg daily or in a single dose of 80 mg/kg every third day. Generally, the continuous regimen is used for chronic myeloid leukaemia, and the intermittent regimen for solid tumours. When used with radiotherapy, hydroxycarbamide is started 7 days before radiotherapy. If a beneficial effect is evident after 6 weeks, therapy may be continued indefinitely.

In essential thrombocythaemia, the initial dose of hydroxycarbamide is about 15 mg/kg daily; starting doses of 15 to 20 mg/kg daily are recommended for polycythaemia vera. Doses are subsequently adjusted according to platelet counts.

In sickle-cell disease initial doses of 15 mg/kg daily are suggested, increased if necessary by 5 mg/kg daily every 12 weeks according to response and blood counts, up to a maximum of 35 mg/kg daily. The *BNFC* recommends 10 to 20 mg/kg once daily initially for children aged from 1 to 18 years; increments thereafter are similar to those for adults.

Blood counts and hepatic and renal function should be monitored during therapy; treatment may need to be interrupted if leucopenia or thrombocytopenia occur (see Adverse Effects, Treatment, and Precautions, above).

Administration in renal impairment. Results from a single-dose study in patients with sickle-cell disease indicated that systemic exposure to hydroxycarbamide correlates to renal function.[1] An initial dose of 7.5 mg/kg daily was suggested for patients with sickle-cell disease and a creatinine clearance of less than 60 mL/minute.

1. Yan J-H, *et al.* The influence of renal function on hydroxyurea pharmacokinetics in adults with sickle cell disease. *J Clin Pharmacol* 2005; **45:** 434–45.

Haemoglobinopathies. Hydroxycarbamide is considered a promising treatment for the haemoglobinopathies. It can stimulate fetal haemoglobin production, which in turn can reduce haemoglobin polymerisation and the numbers of deformed, dense, and damaged erythrocytes.[1] In adult patients with **sickle-cell disease** (p.1044), a randomised controlled study produced evidence that initial doses of 15 mg/kg daily, adjusted according to response and tolerance to up to 35 mg/kg daily, reduced the rate of sickle-cell crisis compared with placebo.[2] An observational follow-up study[3] of this group found that patients taking hydroxycarbamide for frequent sickle-cell episodes appeared to have reduced mortality. A report in 2 adults has suggested that it might reverse splenic dysfunction.[4] A systematic review[5] has noted that despite the benefits, the paucity of long-term studies limits conclusions on the toxicity of treatment with hydroxycarbamide.

Despite some concerns about giving a potential carcinogen to children,[6] studies in paediatric populations have also reported evidence of benefit in terms of decreased hospitalisation[7,8] and sickle-cell crisis.[8,9] Hydroxycarbamide may be an alternative to blood transfusions in children who have had a stroke.[8,10,11] Although a small trial[12] has suggested benefit in paediatric patients in terms of splenic preservation, long-term prevention of organ damage remains to be established.[13,14]

It has been suggested that use of the drug with erythropoietin might enhance the production of fetal haemoglobin, but results from studies of the combination have been conflicting.[15,16]

There appear to have been few studies of hydroxycarbamide specifically in **thalassaemia** (p.1045). Initial oral doses of 8.2 to 10.3 mg/kg daily, increased until toxicity occurred, did produce increases in fetal haemoglobin in 3 patients, but these were not sustained.[17] Others have reported[18] that rises in fetal haemoglob-