Hydroxycarbamide *(BAN, rINN)*

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

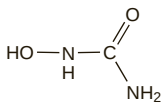
Гидроксикарбамид

$NH_2.CO.NHOH$ = 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-

in did not necessarily correlate with clinical improvement. Conversely, sustained responses have been seen in other studies.[19-22] Use with sodium phenylbutyrate has produced conflicting results.[23-25]

1. Halsey C, Roberts IAG. The role of hydroxyurea in sickle cell disease. *Br J Haematol* 2003; **120:** 177–86.
2. Charache S, *et al.* Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med* 1995; **332:** 1317–22.
3. Steinberg MH, *et al.* Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA* 2003; **289:** 1645–51. Correction. *ibid.*; **290:** 756.
4. Claster S, Vichinsky E. First report of reversal of organ dysfunction in sickle cell anemia by the use of hydroxyurea: splenic regeneration. *Blood* 1996; **88:** 1951–3.
5. Lanzkron S, *et al.* Systematic review: hydroxyurea for the treatment of adults with sickle cell disease. *Ann Intern Med* 2008; **148:** 939–55.
6. Zimmerman SA, *et al.* Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. *Blood* 2004; **103:** 2039–45.
7. Scott JP, *et al.* Hydroxyurea therapy in children severely affected with sickle cell disease. *J Pediatr* 1996; **128:** 820–8.
8. Gulbis B, *et al.* Hydroxyurea for sickle cell disease in children and for prevention of cerebrovascular events: the Belgian experience. *Blood* 2005; **105:** 2685–90.
9. Jayabose S, *et al.* Clinical and hematologic effects of hydroxyurea in children with sickle cell anemia. *J Pediatr* 1996; **129:** 559–65.
10. Ware RE, *et al.* Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with sickle cell disease. *Blood* 1999; **94:** 3022–6.
11. Ware RE, *et al.* Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using hydroxyurea and phlebotomy. *J Pediatr* 2004; **145:** 346–52.
12. Wang WC, *et al.* A two-year pilot trial of hydroxyurea in very young children with sickle-cell anemia. *J Pediatr* 2001; **139:** 790–6.
13. Powars DR. Hydroxyurea in very young children with sickle cell anemia is not a cure-all. *J Pediatr* 2001; **139:** 763–4.
14. Kinney TR, *et al.* Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. *Blood* 1999; **94:** 1550–4.
15. Goldberg MA, *et al.* Treatment of sickle cell anemia with hydroxyurea and erythropoietin. *N Engl J Med* 1990; **323:** 366–72.
16. Rodgers GP, *et al.* Augmentation by erythropoietin of the fetal-hemoglobin response to hydroxyurea in sickle-cell disease. *N Engl J Med* 1993; **328:** 73–80.
17. Hajjar FM, Pearson HA. Pharmacologic treatment of thalassemia intermedia with hydroxyurea. *J Pediatr* 1994; **125:** 490–2.
18. de Paula EV, *et al.* Long-term hydroxyurea therapy in beta-thalassaemia patients. *Eur J Haematol* 2003; **70:** 151–5.
19. Loukopoulos D, *et al*. Hydroxyurea therapy in thalassemia. *Ann N Y Acad Sci* 1998; **30:** 120–8.
20. Rigano P, *et al.* Clinical and hematological responses to hydroxyurea in Sicilian patients with Hb S/β-thalassemia. *Hemoglobin* 2001; **25:** 9–17.
21. Loukopoulos D, *et al.* Reduction of the clinical severity of sickle cell/β-thalassemia with hydroxyurea: the experience of a single center in Greece. *Blood Cells Mol Dis* 2000; **26:** 453–66.
22. Bradai M, *et al.* Hydroxyurea can eliminate transfusion requirements in children with severe β-thalassemia. *Blood* 2003; **102:** 1529–30.
23. Olivieri NF, *et al*. Treatment of thalassaemia major with phenylbutyrate and hydroxyurea. *Lancet* 1997; **350:** 491–2.
24. Hoppe C, *et al.* Hydroxyurea and sodium phenylbutyrate therapy in thalassemia intermedia. *Am J Hematol* 1999; **62:** 221–7.
25. Dover GJ. Hemoglobin switching protocols in thalassemia. *Ann N Y Acad Sci* 1998; **850:** 80–6.

HIV infection and AIDS. Unlike most drugs used to treat HIV, which target viral enzymes, hydroxycarbamide inhibits ribonucleotide reductase, a host cellular enzyme that is less prone to mutation and subsequent development of resistance.[1] The drug acts synergistically with didanosine (p.870). Of 25 HIV-positive patients given didanosine 200 mg twice daily with hydroxycarbamide 15 mg/kg daily in 2 divided doses, all showed a drop in viral load and an increase in CD4+ lymphocyte count.[2] Viraemia was not detectable in 13 of 24 patients evaluated at 6 months and 10 of 20 patients evaluated at 1 year. In 2 of these patients who subsequently received no antiviral treatments for 1 year there was no viral rebound, although some proviral DNA was detected.[3] In another study in 6 patients, didanosine 200 mg twice daily with hydroxycarbamide 250 mg four times daily (suggested to be a better regimen because of the short half-life of the antineoplastic) produced a sharp decrease in viraemia, which was maintained for up to 72 weeks.[4] A rebound occurred in 1 patient on interrupting treatment but viral replication was again suppressed when treatment was restarted.

Combinations with didanosine and other HIV drugs have also been tried.[1] A controlled study[5] of hydroxycarbamide, didanosine, and stavudine indicated significantly enhanced activity when the antivirals were used with the antineoplastic rather than placebo. However, in a long-term follow-up[6] there was a high withdrawal rate amongst patients receiving this combination, due to virological failure and adverse effects such as peripheral neuropathy and fatigue. Another study[7] (ACTG 5025) was terminated due to the high risk of toxicity, including fatal pancreatitis, in patients receiving the hydroxycarbamide regimens. The authors noted that the use of a higher daily dosage of 1200 mg of hydroxycarbamide (rather than the usual 1000 mg daily) and increased exposure to didanosine (itself associated with pancreatitis) may have contributed to toxicity. An analysis of 2613 patients[8] determined that the use of hydroxycarbamide with didanosine, or didanosine and stavudine, resulted in a fourfold increase in the risk for development of pancreatitis, compared to didanosine alone. In a study of patients who had failed protease-inhibitor based regimens,[9] the addition of the antineoplastic to reverse transcriptase inhibitor-based therapy significantly improved virologic response. Despite an increased incidence of adverse events associated with its use, hydroxycarbamide was considered to be a valuable alternative in these patients. A small randomised study[10] of patients with chronic HIV infection given structured treatment interruptions with cycles of HAART, or HAART and hydroxycarbamide, found that use of the latter decreased viral load. There is some suggestion that a lower dose of hydroxycarbamide (300 mg twice daily) may have better antiretroviral activity, and fewer adverse effects, than higher doses.[11] For further discussion of the management of HIV infection and AIDS, see p.856.

1. Gibbs MA, Sorensen SJ. Hydroxyurea in the treatment of HIV-1. *Ann Pharmacother* 2000; **34:** 89–93.
2. Vila J, *et al.* 1-year follow-up of the use of hydroxycarbamide and didanosine in HIV infection. *Lancet* 1996; **848:** 203–4.
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4. Lori F, *et al.* Long-term suppression of HIV-1 by hydroxyurea and didanosine. *JAMA* 1997; **277:** 1437–8.
5. Rutschmann OT, *et al.* A placebo-controlled trial of didanosine plus stavudine, with and without hydroxyurea, for HIV infection. *AIDS* 1998; **12:** F71–7.
6. Rutschmann OT, *et al.* Long-term hydroxyurea in combination with didanosine and stavudine for the treatment of HIV-1 infection. *AIDS* 2000; **14:** 2145–51.
7. Havlir DV, *et al.* Effects of treatment intensification with hydroxyurea in HIV-infected patients with virologic suppression. *AIDS* 2001; **15:** 1379–88.
8. Moore RD, *et al.* Incidence of pancreatitis in HIV-infected patients receiving nucleoside reverse transcriptase inhibitor drugs. *AIDS* 2001; **15:** 617–20.
9. Lafeuillade A, *et al.* The HYDILE trial: efficacy and tolerance of a quadruple combination of reverse transcriptase inhibitors versus the same regimen plus hydroxyurea or hydroxyurea and interleukin-2 in HIV-infected patients failing protease inhibitor-based combinations. *HIV Clin Trials* 2002; **3:** 263–71.
10. García F, *et al.* A cytostatic drug improves control of HIV-1 replication during structured treatment interruptions: a randomized study. *AIDS* 2003; **17:** 43–51.
11. Lisziewicz J, *et al.* Hydroxyurea in the treatment of HIV infection: clinical efficacy and safety concerns. *Drug Safety* 2003; **26:** 605–24.

Malignant neoplasms. Hydroxycarbamide is used in the treatment of chronic myeloid leukaemia (p.653), and may be used in the myeloproliferative disorders polycythaemia vera (p.654) and primary (essential) thrombocythaemia (p.654). Hydroxycarbamide has been tried, often with radiotherapy, in some solid malignancies such as tumours of the cervix (p.663), head and neck (p.666), and ovary (p.670).

Psoriasis. An immunosuppressant (usually methotrexate or ciclosporin) may be useful in patients with severe refractory psoriasis (p.1583). Hydroxycarbamide has also been tried, although experience is limited.[1,2]

1. Layton AM, *et al.* Hydroxyurea in the management of therapy resistant psoriasis. *Br J Dermatol* 1989; **121:** 647–53.
2. Smith CH, *et al*.. Use of hydroxyurea in psoriasis. *Clin Exp Dermatol* 1999; **24:** 2–6.

Preparations

BP 2008: Hydroxycarbamide Capsules;
USP 31: Hydroxyurea Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Dacrodil; Droxiurea†; Hydrea†; ***Austral.:*** Hydrea; ***Austria:*** Litalir; ***Belg.:*** Hydrea; ***Braz.:*** Hydrea; Hydrine†; Oxeron†; Ureax†; ***Canad.:*** Hydrea; ***Chile:*** Hydrea; ***Cz.:*** Litalir; Siklos; ***Denm.:*** Hydrea; ***Fin.:*** Hydrea; ***Fr.:*** Hydrea; Siklos; ***Ger.:*** Litalir; Syrea; ***Gr.:*** Hydrea†; Medroxyurea†; ***Hong Kong:*** Hydrea; ***Hung.:*** Litalir; ***India:*** Cytodrox; Hydab; Neodrea†; Oxyrea; ***Indon.:*** Hydrea; ***Irl.:*** Hydrea; ***Israel:*** Hydrea†; ***Ital.:*** Onco-Carbide; ***Malaysia:*** Hydrea†; ***Mex.:*** Hydrea; ***Neth.:*** Hydrea; ***NZ:*** Hydrea; ***Philipp.:*** Hydab; Krabinex; Litalir; ***Port.:*** Hydrea; Siklos; ***Rus.:*** Gidroksiurea (Гидроксиурея); ***S.Afr.:*** Hydrea; ***Singapore:*** Hydrea; ***Spain:*** Hydrea; ***Swed.:*** Hydrea; ***Switz.:*** Litalir; ***Thai.:*** Hydrea; ***Turk.:*** Hydrea; ***UK:*** Hydrea; ***USA:*** Droxia; Hydrea; Mylocel†.

Ibritumomab Tiuxetan *(BAN, USAN, rINN)*

Ibritumomab tiuxetán; Ibritumomab Tiuxétan; Ibritumomabum Tiuxetanum; IDEC-129; IDEC-Y2B8. Immunoglobulin G1, anti(human CD20 (antigen))(mouse monoclonal IDEC-Y2B8 γ1-chain), disulfide with mouse monoclonal IDEC-Y2B8 κ-chain, dimer tiuxetan conjugate.

Ибритумомаб Тиуксетан

CAS — 206181-63-7.

Adverse Effects and Precautions

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

Myelosuppression is common after doses of ibritumomab tiuxetan, and may be prolonged. Fatal intracranial haemorrhage has occurred. Infections and hypersensitivity reactions may also be severe. As ibritumomab tiuxetan is given with rituximab, severe infusion reactions due to the cytokine release syndrome may occur (see under Rituximab, p.767). Severe cutaneous and mucocutaneous reactions, some fatal, have been reported and therapy should be stopped if they occur. Gastrointestinal disturbances are common. Other adverse effects include anorexia, asthenia, fever, cough, dyspnoea, dizziness, headache, insomnia, anxiety, arthralgia, myalgia, and peripheral oedema. Patients should be monitored for signs of extravasation in order to avoid radiation-associated tissue damage. If extravasation occurs, the infusion should be stopped immediately and restarted in another vein.

Complete blood and platelet counts should be monitored weekly, or more frequently if cytopenia is present, until haematological recovery. Ibritumomab tiuxetan should not be given to patients with extensive marrow involvement, impaired bone marrow reserve, or platelet or neutrophil counts below acceptable levels (see also Bone-marrow Depression, p.639). Care should be taken during and after radiolabelling with indium-111 or yttrium-90 to minimise radiation exposure.

Effects on the skin. Severe cutaneous and mucocutaneous reactions have been reported after use of ibritumomab tiuxetan with rituximab, some of them with a fatal outcome.[1,2] Reactions included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis. Onset was reported to vary from days to months. Treatment should be stopped if any patient experiences such a reaction.

1. Kooijmans-Coutinho M [Biogen Idec (USA)]. Important drug warning (issued October 2005). Available at: http://www.fda.gov/medwatch/safety/2005/Zevalin_dearhcp.pdf (accessed 30/07/08)
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Uses and Administration

Ibritumomab is a murine monoclonal antibody to CD20 antigen, which is conjugated with tiuxetan to provide a chelation site for radioactive isotopes. Radiolabelled ibritumomab tiuxetan is used in the treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (p.656). Patients are pretreated with a low dose of rituximab (p.767). In the USA this is followed by slow intravenous injection of ibritumomab tiuxetan chelated with indium-111 (p.2054) for imaging to confirm that biodistribution of tumour cells is acceptable. A second rituximab treatment is given 7 to 9 days after the first, followed by ibritumomab tiuxetan chelated with yttrium-90 (p.2057) for radio-immunotherapy.

◊ References.

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3. Witzig TE, *et al.* Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2002; **20:** 2453–63.
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6. Witzig TE. Yttrium-90-ibritumomab tiuxetan radioimmunotherapy: a new treatment approach for B-cell non-Hodgkin's lymphoma. *Drugs Today* 2004; **40:** 111–19.
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9. Cheung MC, *et al.* Yttrium 90 ibritumomab tiuxetan in lymphoma. *Leuk Lymphoma* 2006; **47:** 967–77. Correction. *ibid.*; 1719–20.
10. Gisselbrecht C, *et al.* Current status and future perspectives for yttrium-90 (Y)-ibritumomab tiuxetan in stem cell transplantation for non-Hodgkin's lymphoma. *Bone Marrow Transplant* 2007; **40:** 1007–17.