Profile

Ranpirnase is a ribonuclease reported to have antineoplastic properties. It is under investigation in the treatment of malignant mesothelioma. Ranpirnase has also been investigated in the management of solid tumours. It is also reported to have activity *in vitro* against HIV.

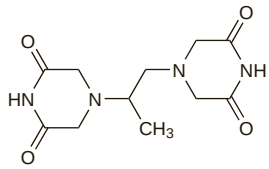
Razoxane *(BAN, rINN)*

ICI-59118; ICRF-159; NSC-129943; Ratsoksaani; Razoxan; Razoxano; Razoxanum. (±)-4,4′-Propylenebis(piperazine-2,6-dione).

Разоксан

$C_{11}H_{16}N_4O_4$ = 268.3.

CAS — 21416-87-5.



Profile

Razoxane is an antineoplastic with inhibitory activity during the pre-mitotic and early mitotic phases of cell growth (G_2-M). It enhances the effects of radiotherapy. It has been used with radiotherapy in the treatment of sarcomas, including Kaposi's sarcoma. Razoxane has also been tried in other malignant diseases including acute leukaemias and non-Hodgkin's lymphomas. However, it is no longer widely used. Razoxane was formerly used in psoriasis, but its carcinogenic properties militate against such use, as discussed below.

In the treatment of sarcomas it has generally been given orally in doses of 125 mg twice daily; higher doses have been given in the management of acute leukaemias and Kaposi's sarcoma. The peripheral blood count should be monitored during treatment.

The principal adverse effects of razoxane include bone-marrow depression, gastrointestinal disturbances, skin reactions, and alopecia. It may enhance the adverse effects of radiotherapy. Razoxane therapy has been associated with the development of secondary malignancies: it is contra-indicated in the treatment of non-malignant conditions.

Dexrazoxane (p.1443) is the (+)-enantiomer of razoxane. It is used to reduce anthracycline-induced cardiotoxicity.

Malignant neoplasms. References to the use of razoxane with radiotherapy.

1. Rhomberg W, *et al.* Radiotherapy vs radiotherapy and razoxane in the treatment of soft tissue sarcomas: final results of a randomized study. *Int J Radiat Oncol Biol Phys* 1996; **36:** 1077–84.
2. Rhomberg W, *et al.* A small prospective study of chordomas treated with radiotherapy and razoxane. *Strahlenther Onkol* 2003; **179:** 249–53.

Skin disorders, non-malignant. Razoxane was formerly used in the systemic treatment of psoriasis, and has been found to be extremely effective, with an initial response rate of 97% overall. It was found to be of use in all forms of cutaneous psoriasis and psoriatic arthropathy.[1] However, the development of acute myeloid leukaemias and other malignancies in patients given razoxane[2-5] has led to its being contra-indicated in non-malignant conditions.

For a discussion of psoriasis and its management, see p.1583.

1. Horton JJ, Wells RS. Razoxane: a review of 6 years' therapy in psoriasis. *Br J Dermatol* 1983; **109:** 669–73.
2. Horton JJ, *et al.* Epitheliomas in patients receiving razoxane therapy for psoriasis. *Br J Dermatol* 1983; **109:** 675–8.
3. Lakhani S, *et al.* Razoxane and leukaemia. *Lancet* 1984; **ii:** 288–9.
4. Caffrey EA, *et al.* Acute myeloid leukaemia after treatment with razoxane. *Br J Dermatol* 1985; **113:** 131–4.
5. Zuiable AG, *et al.* Razoxane and T-cell lymphoma. *Br J Dermatol* 1989; **121:** 149.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Cardioxane.

Rituximab *(BAN, USAN, rINN)*

IDEC-102; IDEC-C2B8; Rituksimab; Rituksimabi; Rituximabum. Immunoglobulin G1 (human-mouse monoclonal IDEC-C2B8 γ1-chain anti-human antigen CD 20), disulfide with human-mouse monoclonal IDEC-C2B8 κ-chain, dimer.

Ритуксимаб

CAS — 174722-31-7.

ATC — L01XC02.

ATC Vet — QL01XC02.

Adverse Effects, Treatment, and Precautions

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

Infusion of rituximab has been associated with a cytokine release syndrome of fever, chills, and rigors, usually within 2 hours of beginning therapy (see also below). Other reported symptoms include pruritus, urticaria, rashes, dyspnoea, bronchospasm, angioedema, transient hypotension, and flushing. Asthenia, headache, rhinitis, myalgia, dizziness, and hypertension may also be associated with infusion reactions. Severe cases may be associated with tumour lysis syndrome, acute renal failure, respiratory failure, and death. Hypersensitivity reactions manifest similarly to the cytokine release syndrome, but usually occur within minutes of starting infusion. Mucocutaneous reactions, some fatal, and including Stevens-Johnson syndrome or toxic epidermal necrolysis have also occurred.

Patients with an extensive tumour burden, pulmonary tumour infiltration or pulmonary insufficiency may be at increased risk of severe reactions and should be treated with caution and possibly a decreased initial infusion rate. Therapy should be interrupted in patients who develop severe symptoms and only resumed, at half the previous rate, once all signs and symptoms have resolved. Premedication with analgesics, antihistamines, and possibly corticosteroids is recommended in all patients before receiving rituximab.

Reactivation of hepatitis B virus (HBV) has occurred in some patients; fulminant hepatitis, hepatic failure, and fatalities have been reported. Patients at high risk of HBV infection should be screened before starting rituximab therapy and carriers should be monitored for signs of active infection or hepatitis during and for several months after therapy. Rituximab should be stopped if viral hepatitis develops. Other serious infections, which may be fatal, can occur with rituximab. Cases of progressive multifocal leukoencephalopathy, some fatal, have been reported with rituximab.

Haematological adverse effects including lymphopenia, leucopenia, neutropenia, thrombocytopenia, and anaemia have occurred in some patients; effects are considered mild and reversible. Complete blood and platelet counts should be monitored regularly. Exacerbation of heart failure and angina pectoris has also been reported, and other cardiac events include arrhythmias and tachycardia. Gastrointestinal disturbances may also occur. Abdominal pain, bowel obstruction, and perforation, in some cases fatal, have been reported with rituximab combination chemotherapy.

◊ References.

1. Mohrbacher A. B cell non-Hodgkin's lymphoma: rituximab safety experience. *Arthritis Res Ther* 2005; **7** (suppl 3): S19–S25.
2. Kimby E. Tolerability and safety of rituximab (MabThera). *Cancer Treat Rev* 2005; **31:** 456–73.

Effects on the blood. Late-onset neutropenia (defined as neutropenia occurring 30 days after the last dose) has been reported in patients receiving rituximab.[1]

1. Rios-Fernández R, *et al.* Late-onset neutropenia following rituximab treatment in patients with autoimmune diseases. *Br J Dermatol* 2007; **157:** 1271–3.

Effects on the eyes. About 20 minutes after the start of a rituximab infusion, a patient developed bilateral conjunctivitis without pain, lachrymation, or discharge. No other clinical manifestations of a hypersensitivity reaction were apparent, and the conjunctivitis resolved spontaneously, about 30 minutes after the end of the infusion. No recurrence was evident with subsequent rituximab therapy.[1]

1. Marinella MA. Bilateral conjunctivitis due to rituximab. *Ann Pharmacother* 2007; **41:** 1318.

Effects on the gastrointestinal tract. In November 2006 the manufacturer noted that 47 cases of bowel obstruction (9 fatal) and 37 cases of gastrointestinal perforation (4 fatal) had been reported in patients given rituximab.[1] Interpretation of data was difficult due to confounding factors; however, a contributory role of rituximab could not be excluded. The mean time to onset of symptoms was 6 days (range 1 to 77 days) for documented perforation. Complaints of abdominal pain, especially early in a course of rituximab treatment, should prompt thorough diagnostic evaluation and treatment.

1. Roche, Canada. Reports of bowel obstruction and gastrointestinal perforation with RITUXAN (rituximab) (issued 10th November 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2006/rituxan_3_hpc-cps-eng.php (accessed 30/07/08)

Effects on the lungs. Pulmonary reactions have been reported with rituximab use,[1] including reversible interstitial pneumonia[2-4] and interstitial fibrosis.[5] A fatal intra-alveolar haemorrhage in 1 patient was attributed to a hypersensitivity reaction to rituximab.[6]

1. Wagner SA, *et al.* Rituximab-induced interstitial lung disease. *Am J Hematol* 2007; **82:** 916–19.
2. Burton C, *et al.* Interstitial pneumonitis related to rituximab therapy. *N Engl J Med* 2003; **348:** 2690–1.
3. Jullien V, *et al.* Une pneumopathie alvéolo-interstitielle hypoxémiante associée à la prise de rituximab. *Rev Mal Respir* 2004; **21:** 407–10.
4. Swords R, *et al.* Interstitial pneumonitis following rituximab therapy for immune thrombocytopenic purpura (ITP). *Am J Hematol* 2004; **77:** 103–4.
5. Leon RJ, *et al.* Rituximab-induced acute pulmonary fibrosis. *Mayo Clin Proc* 2004; **79:** 949, 953.
6. Alexandrescu DT, *et al.* Fatal intra-alveolar hemorrhage after rituximab in a patient with non-Hodgkin lymphoma. *Leuk Lymphoma* 2004; **45:** 2321–5.

Effects on the nervous system. As of December 2006, the FDA had received a total of 24 reports of progressive multifocal leukoencephalopathy (PML) in patients given rituximab.[1] PML is a fatal demyelinating disease that follows reactivation of latent JC or PK polyomavirus (also known as papovavirus) in the CNS; the virus is present in about 80% of adults. In the first 12 cases reported to the FDA, 10 patients tested positive for the JC virus and 1 had confirmed BK virus.

1. FDA. Rituximab (marketed as Rituxan): progressive multifocal leukoencephalopathy (PML). *FDA Drug Safety Newsletter* 2007; **1:** 3–5. Available at: http://www.fda.gov/cder/dsn/2007_fall/2007_fall.pdf (accessed 07/02/08)

Infusion-related reactions. By November 1998 there had been 74 cases of serious infusion-related reactions to rituximab reported worldwide, with 8 fatal cases.[1] An estimated 12 000 to 14 000 patients had been treated.

The reaction usually occurs within the first 2 hours of infusion and the underlying mechanism is believed to be a severe cytokine release syndrome, with some elements of tumour lysis syndrome.[1-3] In one series of cases tumour necrosis factor-α and interleukin-6 levels were found to peak 90 minutes after the onset of the infusion, and these elevated cytokine levels coincided with infusion-related symptoms.[2] The reaction is usually most marked after the first infusion and subsequent infusions are usually tolerated, emphasising that this is not a true hypersensitivity reaction.[4]

Patients with a high tumour burden (lesions over 10 cm in diameter or more than 500 000 circulating malignant cells/mm^3), a history of pulmonary infiltration or insufficiency, or underlying cardiac disease are believed to be at greater risk of severe reactions.[1,2,4] The UK CSM recommends that premedication with an analgesic and an antihistamine should always be given before rituximab, and corticosteroids should be considered.[1] However, serious or fatal reactions have occurred despite such premedication.[3,4] Alternative infusion schedules and/or combination therapy with chemotherapeutic drugs may be required to decrease the tumour burden before rituximab therapy.[2,4]

1. Committee on Safety of Medicines/Medicines Control Agency. Rituximab (MabThera): serious infusion-related adverse reactions. *Current Problems* 1999; **25:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 26/04/06)
2. Winkler U, *et al.* Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukaemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood* 1999; **94:** 2217–24.
3. Lim L-C, *et al.* Fatal cytokine release syndrome with chimeric anti-CD20 monoclonal antibody rituximab in a 71-year-old patient with chronic lymphocytic leukaemia. *J Clin Oncol* 1999; **17:** 1962–3.
4. Byrd JC, *et al.* Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: association with increased infusion-related side effects and rapid blood tumor clearance. *J Clin Oncol* 1999; **17:** 791–5.

Pregnancy. Giving 4 cycles of rituximab (with doxorubicin, vincristine, and prednisolone) to a pregnant woman with lymphoma, from 21 weeks of gestation until delivery at 35 weeks, resulted in no adverse effects to either the mother or the infant.[1] In another report, a 31-year-old woman was diagnosed with non-Hodgkin's lymphoma during pregnancy. She received 6 cycles of rituximab with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Two months after treatment, she spontaneously delivered a premature but healthy infant. Patient and child were clinically assessed every 3 months; the infant's B cells were severely diminished at birth but recovered over 6 to 12 weeks. Rituximab concentrations in both mother and child also decreased as expected. No adverse effects were seen during 16 months of follow-up.[2] In 2 case reports of rituximab use during the first trimester of pregnancy, no significant adverse effects on the neonates were seen; transient granulocytopenia and lymphopenia were reported.[3,4] A 35-year-old woman diagnosed with Burkitt's lymphoma in week 15 of pregnancy received 4 weekly