of procarbazine 100 mg/m^2 for 10 to 14 days of each 4- or 6-week cycle. If used as a single agent in adults a dose equivalent to 50 mg of procarbazine daily, increased by 50 mg daily to 250 to 300 mg daily in divided doses has been suggested in the UK, while in the USA the recommended regimen is 2 to 4 mg/kg daily for the first week, subsequently increased to 4 to 6 mg/kg daily, doses being given to the nearest 50 mg. These doses are continued until maximum response is achieved or leucopenia, thrombocytopenia, or other signs of toxicity ensue. Maintenance doses are usually 50 to 150 mg daily, or 1 to 2 mg/kg, daily, until a cumulative dose of at least 6 g has been given. In children, initial daily doses of the equivalent of 50 mg/m^2 have been suggested in the USA (UK product information simply suggests a dose of 50 mg), increased to 100 mg/m^2 and then adjusted according to response.

Blood disorders, non-malignant. Chemotherapy with regimens including procarbazine has been used in a few patients with refractory idiopathic thrombocytopenic purpura (p.1505), and has produced prolonged remission although in most cases of the disease such aggressive therapy is difficult to justify.

Preparations

USP 31: Procarbazine Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)
Austral.: Natulan; ***Canad.:*** Matulane; Natulan†; ***Fr.:*** Natulan; ***Ger.:*** Natulan; ***Gr.:*** Natulan; ***Hung.:*** Natulan†; ***Ital.:*** Natulan; ***Neth.:*** Natulan; ***NZ:*** Natulan†; ***Rus.:*** Natulan (Натулан); ***Spain:*** Natulan; ***USA:*** Matulane.

Raltitrexed *(BAN, USAN, rINN)*

D-1694; ICI-D1694; Raltitreksed; Raltitreksedi; Raltitrexedum; ZD-1694. *N*-{5-[3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl(methyl)amino]-2-thenoyl}-L-glutamic acid.

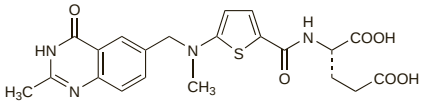
Ралтитрексед

$C_{21}H_{22}N_4O_6S$ = 458.5.

CAS — 112887-68-0.

ATC — L01BA03.

ATC Vet — QL01BA03.



Adverse Effects, Treatment, and Precautions

Raltitrexed produces bone marrow depression, usually mild to moderate, with leucopenia, anaemia, and, less frequently, thrombocytopenia. The nadir of the white cell count usually occurs 7 to 14 days after a dose, with recovery by the third week. Gastrointestinal toxicity is also common, with nausea and vomiting, diarrhoea, and anorexia: mucositis may occur. Reversible increases in liver enzyme values have occurred. Other adverse effects include weakness and malaise, fever, pain, headache, skin rashes, desquamation, arthralgia, muscle cramps, weight loss, dehydration, peripheral oedema, alopecia, increased sweating, taste disturbance, and conjunctivitis. The use of folinic acid 25 mg/m^2 every 6 hours intravenously has been suggested in licensed product information for patients who develop very severe toxicity.

Raltitrexed should be given with care to patients with hepatic impairment and should be avoided if impairment is severe. It should also be avoided in severe renal impairment and be given in reduced doses in moderate impairment. Care is also advisable in debilitated or elderly patients or in patients who have had radiotherapy.

Raltitrexed is teratogenic; pregnancy should be avoided while either partner is receiving the drug and for at least 6 months after treatment. It may impair male fertility.

Toxicity. A large multicentre study comparing raltitrexed with fluorouracil plus folinic acid was suspended in 1999 due to an excess of deaths in the raltitrexed arm.[1] This decision has led to some controversy,[1-3] as in 11 of the 17 deaths in patients taking raltitrexed there was evidence that the dose had not been correctly adjusted to take account of renal function. In addition, and further confusing the issue, the incidence of reported serious adverse effects was lower in raltitrexed-treated patients than in controls. A further study[4] reported an increased rate of raltitrexed-related deaths compared with fluorouracil-based regimens. Almost all of the 18 deaths were caused by gastrointestinal and haematological toxicity, and in 3 of these the dose of raltitrexed had not been adjusted for toxicity.

1. Anonymous. Drug-company decision to end cancer trial. *Lancet* 1999; **354:** 1045.
2. Ford HER, Cunningham D. Safety of raltitrexed. *Lancet* 1999; **354:** 1824–5.
3. Kerr D. Safety of raltitrexed. *Lancet* 1999; **354:** 1825.
4. Maughan TS, *et al.* Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2002; **359:** 1555–63.

Interactions

Raltitrexed should not be given with folic or folinic acid, which may impair its cytotoxic action. (For the deliberate use of folinic acid to counteract the effects of raltitrexed in patients with severe toxicity, see above.)

Pharmacokinetics

After intravenous doses raltitrexed exhibits triphasic pharmacokinetics, with an initial rapid decline from peak plasma concentrations followed by a slow terminal elimination phase. Raltitrexed is actively transported into cells and metabolised to active polyglutamate forms. The remainder of a dose is excreted unchanged, about 50% of a dose appearing in the urine, and about 15% in the faeces. The terminal elimination half-life is about 8 days. Clearance is markedly reduced in renal impairment.

◊ References.

1. Clarke SJ, *et al.* Clinical and preclinical pharmacokinetics of raltitrexed. *Clin Pharmacokinet* 2000; **39:** 429–43.

Uses and Administration

Raltitrexed is a folate analogue that is a potent and specific inhibitor of the enzyme thymidylate synthase, which is involved in the synthesis of DNA. It has been used in the treatment of advanced colorectal cancer (p.665) and has also been tried in breast cancer (p.661) and other solid neoplasms.

The recommended initial dose of raltitrexed in patients with normal renal function is 3 mg/m^2 given by intravenous infusion over 15 minutes. Subsequent doses, which should be reduced by up to 50% depending on the severity of initial toxicity, may be given at intervals of 3 weeks provided toxicity has resolved.

A full blood count should be performed before each dose and treatment withheld if the white cell or platelet counts are below acceptable levels (see also Bone-marrow Depression, p.639). Hepatic and renal function should also be tested. It is essential that doses be adjusted in renal impairment (see below).

◊ References.

1. Gunasekara NS, Faulds D. Raltitrexed: a review of its pharmacological properties and clinical efficacy in the management of advanced colorectal cancer. *Drugs* 1998; **55:** 423–35.
2. Cunningham D, *et al.* Efficacy, tolerability and management of raltitrexed (Tomudex) monotherapy in patients with advanced colorectal cancer: a review of phase II/III trials. *Eur J Cancer* 2002; **38:** 478–86.
3. Scheithauer W, *et al.* Randomized multicenter phase II trial of oxaliplatin plus irinotecan versus raltitrexed as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2002; **20:** 165–72.
4. Feliu J, *et al.* Raltitrexed in the treatment of elderly patients with advanced colorectal cancer: an active and low toxicity regimen. *Eur J Cancer* 2002; **38:** 1204–11.
5. Comella P, *et al.* Oxaliplatin plus raltitrexed and leucovorin-modulated 5-fluorouracil i.v. bolus: a salvage regimen for colorectal cancer patients. *Br J Cancer* 2002; **86:** 1871–5.
6. Maughan TS, *et al.* Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2002; **359:** 1555–63.
7. van Meerbeeck JP, *et al.* Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005; **23:** 6881–9.
8. Ducreux M, *et al.* FFCD 9601 Collaborative Group. Randomised trial comparing three different schedules of infusional 5FU and raltitrexed alone as first-line therapy in metastatic colorectal cancer. Final results of the Fédération Francophone de Cancérologie Digestive (FFCD) 9601 trial. *Oncology* 2006; **70:** 222–30.
9. Wilson KS, *et al.* Adjuvant therapy with raltitrexed in patients with colorectal cancer intolerant of 5-fluorouracil: British Columbia Cancer Agency experience. *Cancer Invest* 2007; **25:** 711–14.
10. Hind D, *et al.* The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation. *Health Technol Assess* 2008; **12:** 1–182.

Administration in renal impairment. It is essential that doses of raltitrexed be adjusted in renal impairment (creatinine clearance less than 65 mL/minute) as fatalities have been associated with the failure to make such adjustments (see Toxicity, under Adverse Effects, above). The dosage interval should be increased from 3 to 4 weeks and the dose adjusted on the basis of creatinine clearance (CC) as follows:

- CC of 55 to 65 mL/minute, 2.25 mg/m^2
- CC of 25 to 54 mL/minute, 1.5 mg/m^2 (in some countries, adjustment of the dose to a percentage of the full dose equivalent to the value of the CC in mL/minute is suggested in this group, e.g. reduction to 30% in those with a CC of 30 mL/minute, or 40% if CC is 40 mL/minute)
- CC less than 25 mL/minute, treatment contra-indicated

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Tomudex; ***Austral.:*** Tomudex; ***Austria:*** Tomudex; ***Belg.:*** Tomudex; ***Braz.:*** Tomudex; ***Canad.:*** Tomudex; ***Cz.:*** Tomudex; ***Fin.:*** Tomudex†; ***Fr.:*** Tomudex; ***Hong Kong:*** Tomudex†; ***Hung.:*** Tomudex; ***Irl.:*** Tomudex; ***Ital.:*** Tomudex; ***Mex.:*** Tomudex; ***Neth.:*** Tomudex; ***Norw.:*** Tomudex; ***Philipp.:*** Tomudex; ***Port.:*** Tomudex; ***Rus.:*** Tomudex (Томудекс); ***S.Afr.:*** Tomudex†; ***Singapore:*** Tomudex; ***Spain:*** Tomudex; ***Switz.:*** Tomudex; ***Turk.:*** Tomudex; ***UK:*** Tomudex; ***Venez.:*** Tomudex†.

Ranimustine *(rINN)*

MCNU; NSC-0270516; Ranimustina; Ranimustinum; Ranomustine. Methyl 6-[3-(2-chloroethyl)-3-nitrosoureido]-6-deoxy-α-D-glucopyranoside.

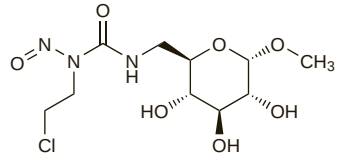
Ранимустин

$C_{10}H_{18}ClN_3O_7$ = 327.7.

CAS — 58994-96-0.

ATC — L01AD07.

ATC Vet — QL01AD07.



Profile

Ranimustine is a nitrosourea derivative with general properties similar to those of carmustine (p.694). It is used intravenously in the treatment of malignant neoplasms in usual doses of 50 to 90 mg/m^2 every 6 to 8 weeks according to haematological response.

◊ References.

1. Wada M, *et al.* Induction therapy consisting of alternating cycles of ranimustine, vincristine, melphalan, dexamethasone and interferon alpha (ROAD-IN) and a randomized comparison of interferon alpha maintenance in multiple myeloma: a co-operative study in Japan. *Br J Haematol* 2000; **109:** 805–14.
2. Hatano N, *et al.* Efficacy of post operative adjuvant therapy with human interferon beta, MCNU and radiation (IMR) for malignant glioma: comparison among three protocols. *Acta Neurochir (Wien)* 2000; **142:** 633–8.
3. Wakabayashi T, *et al.* Initial and maintenance combination treatment with interferon-beta, MCNU (ranimustine), and radiotherapy for patients with previously untreated malignant glioma. *J Neurooncol* 2000; **49:** 57–62.
4. Mizuno H, *et al.* Superior efficacy of MMCP regimen compared with VMCP and MMPP regimens in the treatment of multiple myeloma. *Intern Med* 2002; **41:** 290–4.
5. Takenaka T, *et al.* Phase III study of ranimustine, cyclophosphamide, vincristine, melphalan, and prednisolone (MCNU-COP/MP) versus modified COP/MP in multiple myeloma: a Japan clinical oncology group study, JCOG 9301. *Int J Hematol* 2004; **79:** 165–73.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Cymerin.

Ranpirnase *(USAN, rINN)*

P-30 Protein; Ranpirnasa; Ranpirnasum.

Рапирназа

CAS — 196488-72-9.

NOTE. P-30 protein has been incorrectly stated to contain ergotamine.

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.

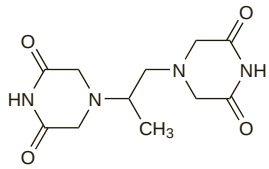
Razoxane *(BAN, rINN)*

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