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Rituximab

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Contents

Abstract

▲ Rituximab is a chimaeric monoclonal antibody which specifically binds to the CD20 antigen on normal and malignant B lymphocytes. It produces antibody-dependent cell- and complement-mediated cytotoxicity in these cells.

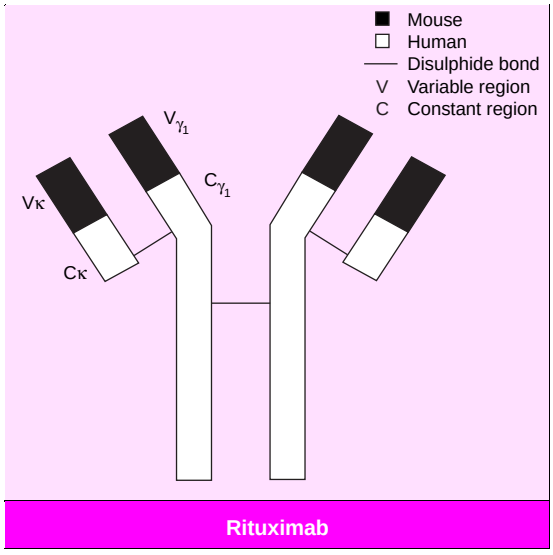
▲ Rituximab reduced peripheral B lymphocyte counts by ≈90% within 3 days in patients with relapsed indolent lymphoma. Counts remained depleted for 6 months and recovered by months 9 to 12 after 4 doses of rituximab 375 mg/m^2 once weekly.

▲ Clinical response rates were 46 and 48% in 2 non-comparative trials in patients with relapsed indolent lymphoma. The rate of response to rituximab appeared to be markedly higher in patients with follicular lymphoma than in those with small lymphocytic disease (56 or 60% versus 13 or 15%).

▲ 85 to 94% of patients reported adverse events during clinical trials of rituximab; 90% of events were mild or moderate. The most common adverse event, a transient set of flu-like symptoms during the first infusion in approximately 50 to 87% of patients, generally resolved completely in <3 hours. Diphenhydramine and/or paracetamol was administered to some patients.

▲ In 10% of patients, the flu-like symptoms during the first infusion were accompanied by bronchospasm and/or hypotension or severe cytokine release syndrome. Patients were generally able to complete treatment after these symptoms resolved.

Features and properties of rituximab (IDEC-C2B8)	
Indication	
Relapsed or refractory indolent non-Hodgkin's lymphoma	
Mechanism of action	
B lymphocyte cytotoxicity	Mouse-human chimaeric antibody specific for CD20 antigen on normal and malignant B lymphocytes
Dosage and administration	
Recommended dose	375 mg/m^2
Route of administration	Intravenous
Frequency of administration	Once weekly for 4 weeks
Concomitant therapy	Paracetamol (acetaminophen) and diphenhydramine before each infusion
Pharmacokinetic profile (after 4 infusions of rituximab 375 mg/m^2 once weekly)	
Peak plasma concentration	465 mg/L
Area under the plasma concentration-time curve	86 125 mg/L • h
Clearance	0.0092 L/h
Terminal elimination half-life	8.6 days
Adverse events	
Most frequent	Transient flu-like symptoms during first infusion
Serious events	Severe cytokine release syndrome during first infusion



Non-Hodgkin's lymphomas are a heterogeneous group of clonal, usually lymphoid, malignancies which arise predominantly from B lymphocytes.[1] These lymphomas are commonly divided into small lymphocytic [International Working Formulation (IWF) category A], follicular (IWF-B, C and D) and intermediate and high grade (IWF-D, G and H) subtypes, with overlap between the follicular and intermediate groups.[2,3] The small lymphocytic and follicular lymphomas are collectively referred to as indolent lymphoma in this article. Approximately 75% of patients with indolent lymphoma present with late stage (stage III or IV of the Ann Arbor classification system) disease.[4] After diagnosis with late stage indolent lymphoma, patients survive for a median of 3 to 7.2 years.[3]

Rituximab is a chimaeric mouse-human monoclonal antibody which has been evaluated in patients with late stage, indolent non-Hodgkin's lymphoma who have relapsed or are resistant to other treatments. Management of indolent non-Hodgkin's lymphomas is not standardised, and some clinicians defer therapy in asymptomatic patients, with no effect on overall survival rates; patients receive chemotherapy if their disease progresses.[5] Approaches such as combination chemotherapy [e.g. cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)], monotherapy with purine analogues (e.g. fludarabine) or interferon-α and radiation therapy produce varying complete response rates (range 25 to 85% of patients); some of the variation reflects differences in patient populations and in response criteria.[4,6,7] Patients who respond invariably relapse, and the magnitude and duration of response are reduced with successive courses of treatment.[4,7] Therapies used in relapsed or refractory patients include alternative chemotherapeutic agents,[4] immunotherapy (e.g. interferon-α)[4,8] and high dose chemotherapy (to ablate lymphoma cells) followed by autologous stem cell transplantation.[4]

1. Pharmacodynamic Profile

Mechanism of Action

• Rituximab selectively binds with high affinity to the CD20 antigen, which is expressed on normal B lymphocytes and on ≥90% of B lymphocyte-derived non-Hodgkin's lymphomas.[9-13] It is thought to deplete CD20-positive cells via antibody-dependent cell- and complement-mediated cytotoxicity.[9] Rituximab has been shown to induce apoptosis (programmed cell death) in B lymphoma cells *in vitro*.[10,14]

Effects on B Lymphocytes

• After a single infusion, rituximab 250 or 500 mg/m^2 reduced peripheral B lymphocyte counts by ≈90% in ≤3 days in patients with relapsed indolent lymphoma (fig. 1). Cell counts began to recover within 90 days.[11] After 4 weekly infusions of rituximab 375 mg/m^2, peripheral B lymphocyte counts were reduced for 6 months; counts recovered after 9 to 12 months.[15]

• Depletion of peripheral B lymphocytes by rituximab correlated with clinical response in patients with refractory indolent lymphoma. Peripheral B lymphocyte counts were not reduced in 10% of 166 patients who received rituximab 375 mg/m^2 once weekly for 4 weeks; 94% of these patients failed to demonstrate a clinical response to the drug (section 3).[15]

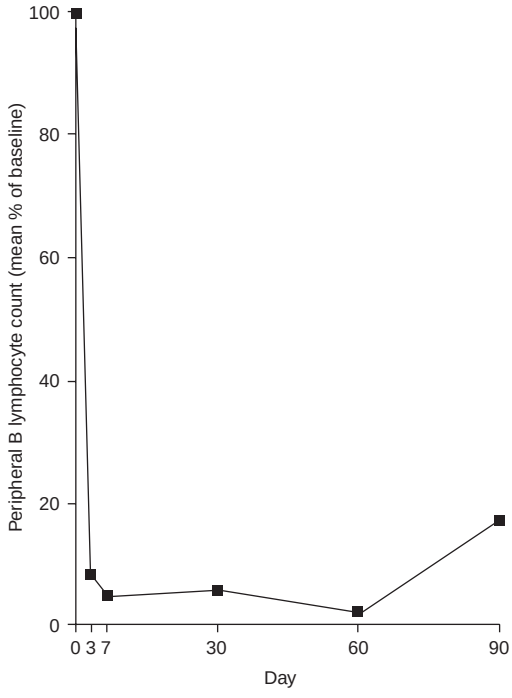


Fig. 1. Depletion of peripheral B lymphocytes after a single dose of rituximab in 5 patients with relapsed indolent lymphoma. Rituximab 250 or 500 mg/m^2 was administered on day 0, and peripheral B lymphocytes were enumerated by flow cytometry. A sixth patient, who received rituximab 250 mg/m^2, had no change in peripheral B lymphocyte counts and was not included in this analysis.[11]

• In addition to its effects on circulating B lymphocytes, rituximab appears to deplete malignant and normal B lymphocytes from lymph nodes[11] and bone marrow[15,16] in patients with relapsed indolent lymphoma. In biopsies of involved lymph nodes, there was a marked decrease (not quantified) in the number of B lymphocytes relative to T lymphocytes compared with baseline in 6 of 7 patients at 2 weeks after a single infusion of rituximab 100 to 500 mg/m^2.[11] Bone marrow samples from patients with follicular lymphoma were analysed for *bcl-2* gene rearrangement using the polymerase chain reaction (PCR; see below).[15,16]

• Rituximab may be an effective supplement to high dose chemotherapy for *in vivo* purging of lymphoma cells prior to autologous stem cell transplantation. In a study in a total of 20 patients, a combination of standard and high dose chemotherapy and rituximab 375 mg/m^2 (on days 2 and 12 after each course of chemotherapy) produced significantly more lymphoma cell-free progenitor cell harvests than chemotherapy alone (100 *vs* 44 harvests, p = 0.015) [see section 3].[17]

• Rituximab did not usually deplete cell types other than B lymphocytes.[11,15,18,19] Patients who developed non-B lymphocyte cytopenias during clinical trials of rituximab are discussed in section 4.

Effects on Follicular Lymphoma Cells with *Bcl-2* Gene Rearrangement

Bcl-2 gene rearrangement occurs in tumours in 85% of patients with follicular lymphoma.[4,20] After treatment, the presence of residual cells with *bcl-2* gene rearrangement (detected by PCR), particularly in the bone marrow, correlates with significantly increased risk of relapse.[20,21]

• Rituximab eliminated follicular lymphoma cells with *bcl-2* gene rearrangement in 56 or 61% of patients in 2 different trials in 52 or 28 patients, respectively, with relapsed indolent lymphoma[15,22] and, in combination with CHOP, in 88% of 8 patients with previously untreated disease.[16] However, elimination of lymphoma cells did not correlate with clinical response.[22] *Bcl-2* gene rearrangement was assessed by PCR in bone marrow, lymph node and/or peripheral blood samples from relapsed patients 3 months after completion of monotherapy with rituximab 375 mg/m^2/week for 4 weeks[15] or after 6 cycles of a 3-week regimen of CHOP and a total of 6 infusions of rituximab 375 mg/m^2 (see section 3 for dosage details).[16]

2. Pharmacokinetic Profile

• The mean maximum serum rituximab concentration (C_{max}) was 206 mg/L, the area under the concentration versus time curve (AUC) was 16 320 mg/L · h and clearance (CL) was 0.0382 L/h after the first infusion in 14 patients with relapsed indo-

lent lymphoma who received rituximab 375 mg/m^2 once weekly for 4 weeks.[23]

- Clearance of rituximab decreases markedly and accumulation of the drug occurs after multiple infusions. After 4 infusions in the same study,[23] C_{max} was 465 mg/L, AUC was 86 125 mg/L · h and CL was 0.0092 L/h.

- Serum rituximab concentrations correlated positively with clinical response.[15,19] Patients who achieved a clinical response to rituximab 375 mg/m^2 once weekly for 4 weeks had higher median serum concentrations than nonresponders at all timepoints during treatment; the difference was significant immediately before infusions 2 and 4 and after infusion 4 ($p < 0.01$).[15]

- Rituximab CL was markedly faster in nonresponders than responders and correlated directly with baseline peripheral B lymphocyte count ($p = 0.01$) in 14 patients with relapsed indolent lymphoma who received 375 mg/m^2/week for 4 weeks.[15]

- The terminal elimination half-life of rituximab was 8.6 days after 4 infusions in 14 patients with relapsed indolent lymphoma who received rituximab 375 mg/m^2 once weekly for 4 weeks; this value is similar to that of other mouse-human chimaeric monoclonal antibodies.[23]

3. Therapeutic Trials

The primary efficacy parameter in all trials was clinical response rate, defined as the percentage of patients with complete (disappearance of all signs of disease) or partial responses [>50% decrease in tumour measurements (the sum of the products of tumour diameter and length) and no evidence of progressive disease] for ≥1 month, as assessed by palpation and/or computed tomography.[11,15,18,19]

Indolent Lymphoma

Monotherapy

Rituximab has been evaluated in patients with relapsed or refractory, late stage indolent B cell lymphoma (IWF-A, B, C or D) in 8 noncomparative trials,[11,15,18,19,24-27] some of which are still ongoing.[24-27] Generally, patients had previously received an average of 2 to 3 courses (range 1 to 10) of previous therapy (chemotherapy, radiotherapy or immunotherapy) or had undergone bone marrow transplant.[11,15,18,19] Tumours were always positive for the CD20 antigen and were usually ≤10cm in diameter.[11,15,18,19] Rituximab was administered as an intravenous infusion at a dosage of 375 mg/m^2 once a week for a total of 4 weeks, except where stated otherwise. The duration of infusion was adjusted according to infusion-related adverse events (see section 4).[15,19] In the largest trial, mean duration of the first infusion was 5.2 hours, compared with 3.3 to 3.5 hours for subsequent infusions.[15]

- Rituximab monotherapy achieved a response in nearly half of patients with relapsed indolent lymphoma. In the largest trial, the clinical response rate was 48% of the intent-to-treat population (166 patients) with rituximab 375 mg/m^2/week for 4 weeks (fig. 2);[15] the clinical response rate was 46% of 37 patients in a separate trial of similar design.[19] Complete and partial response rates were, respectively, 6 and 42% in the larger trial[15] and 8 and 38% in the smaller trial.[19] Clinical response rates may be higher with rituximab 375 mg/m^2/week for 8 weeks (57%), according to a pilot study in 37 patients with relapsed indolent lymphoma.[28]

- The rate of clinical response to rituximab appeared to be markedly higher in patients with follicular lymphoma (IWF-B, C and D) than in those with small lymphocytic disease (IWF-A; fig. 2). Clinical response rates with rituximab 375 mg/m^2/week for 4 weeks were 13 or 15% in patients with small lymphocytic lymphoma (n = 30 or 26, respectively),[15,27] versus 56 or 60% in patients with follicular lymphoma (n = 32 or 118).[15,19] However, the clinical response rate in 44 patients with follicular lymphoma was lower (39%) with the same dosage of rituximab in another trial, which is ongoing.[26]

- Other factors positively associated with clinical response were lack of bone marrow involvement of disease, <2 extranodal sites of disease, history of bone marrow transplant (fig. 2)[15] and high natural killer (NK) cell count at baseline.[29]

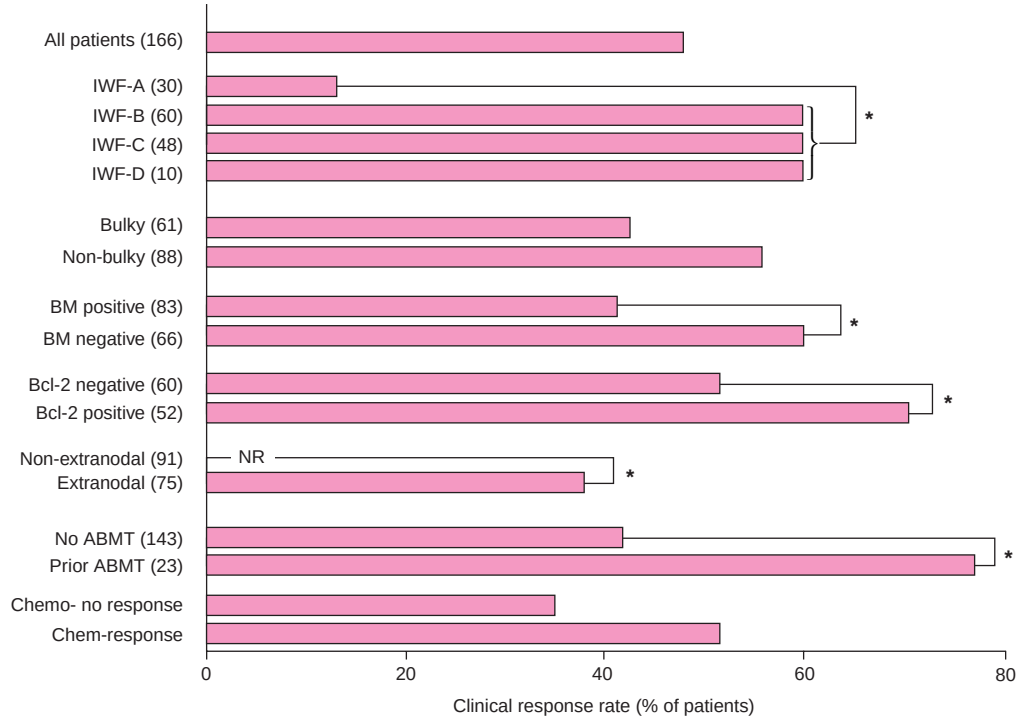


Fig. 2. Clinical efficacy of rituximab monotherapy in patients with relapsed indolent lymphoma. Rituximab 375 mg/m^2 was administered once weekly for 4 weeks; clinical response rates are reported for all patients (intent-to-treat population) and the indicated subgroups (number of patients is shown in parentheses). The clinical response rate in patients with <2 extranodal sites of disease was not reported.[15] **ABMT** = autologous bone marrow transplantation; **bcl-2** = *bcl-2* gene rearrangement in peripheral blood samples; **BM** = disease with bone marrow involvement; **bulky** = disease including ≥1 tumour ≥5cm in diameter; **chemo - no response** = patients with no clinical response to the most recent course of chemotherapy; **chemo - response** = patients with a clinical response to the most recent course of chemotherapy; **extranodal** = disease with ≥2 extranodal tumours; **IWF** = International Working Formulation classification; * $p < 0.05$ between groups as indicated.

- A response to rituximab was evident as early as 1 week after the start of treatment, with a median time to onset of effect of 5 and 7 weeks in 2 clinical trials. Partial or complete responses were first observed after a median of 35.5 (range 7 to 64)[18] and 50 (range 7 to 112)[19] days after 4-week courses of rituximab 125 to 375 mg/m^2/week in trials of 20 and 37 patients with relapsed indolent lymphoma.[18,19]

- The median time to progression of disease (defined as ≥25% increase in tumour measurements or the appearance of any new lesion) was 10.2[19] and 13.0[15] months in patients with partial or complete responses to rituximab 375 mg/m^2/week for 4 weeks.[15] Time to progression was markedly longer (>20.9 to >32.9 months) in 28% of 80 patients with a clinical response to rituximab 375 mg/m^2/week for 4 weeks in another trial, which is ongoing.[15,30]

- The survival rate was 90 to 95% 1 year after treatment with rituximab 375 mg/m^2/week for 4 weeks in patients with relapsed indolent lymphoma;[15,19] the survival rate in rituximab-treated patients after this time-point is not yet known. CD20-negative (rituximab-resistant) disease developed in 2 patients with CD20-positive indolent lym-

phoma at baseline who initially responded to rituximab but subsequently relapsed.[31,32]

- A repeat course of rituximab achieved a clinical response rate of 41% in 56 patients with indolent lymphoma who relapsed after receiving rituximab 375 mg/m^2 once weekly for 4 weeks; the complete and partial response rates were 13 and 29%, respectively.[25] 1 patient also responded to a third course of rituximab in this study.[33]

- Rituximab was effective in patients with indolent lymphoma who had not previously received chemotherapy. The overall response rate (complete and partial responses combined) was 67% in 23 patients (35% IWF-A and 65% IWF-B, C or D) who received ≤4 courses of rituximab 375 mg/m^2/week for 4 weeks; courses were administered at 6-month intervals.[34]

Combination Therapy

- Rituximab in combination with CHOP achieved a clinical response rate of 95% in 40 patients (intent-to-treat population) with indolent lymphoma, 78% of whom were previously untreated.[35] 55% of patients achieved a complete response and 40% a partial response,[35] and the median duration of clinical response in this ongoing trial is reported to be >40.5 months.[36] Patients received six 3-week cycles of CHOP and a total of 6 infusions of rituximab 375 mg/m^2 (1 infusion each on days 2 and 7 before starting CHOP, 1 infusion each 2 days before the third and fifth cycle of CHOP and 1 infusion each during the third and fourth week after completion of CHOP) in this trial.[35] CHOP or other chemotherapeutic regimens are reported to produce variable complete remission rates (23 to 84%) in previously untreated patients with indolent lymphoma.[6]

- Preliminary data suggest rituximab is effective in combination with high dose chemotherapy and autologous stem cell transplantation in eradicating PCR-detectable disease in patients with refractory follicular or untreated mantle cell lymphoma. The clinical remission rate was 90% in 10 patients who received 2 to 4 doses of standard chemotherapy followed by a combination of high dose chemotherapy (1 course of cyclophosphamide with granulocyte- or granulocyte-macrophage colony stimulating factor at week 1 and 1 course of cytarabine with stem cells and growth factor at week 3) and rituximab 375 mg/m^2 (on days 2 and 12 after each course of high dose chemotherapy).[17]

- Combination therapy with rituximab and interferon-α achieved a clinical response rate of 58% (8% complete and 50% partial response rate) in patients with relapsed indolent lymphoma, based on an interim analysis of an ongoing trial.[37] The 26 evaluable patients received rituximab 375 mg/m^2/week in weeks 5 to 8 of a 3-month course of subcutaneous interferon-α 5 million units/day 3 times a week in this trial.[37]

Other B Cell Lymphomas

Monotherapy

- Rituximab may be effective in the treatment of relapsed intermediate or high grade lymphomas. The clinical response rate was 31% in 54 patients with late stage, intermediate or high grade lymphoma who received rituximab 375 or 500 mg/m^2 once weekly for 8 weeks; responses to the 2 doses were similar (IWF classifications not stated; 15% of patients had not previously received treatment).[38] The clinical response rate was 86% in 7 patients with relapsed intermediate grade lymphoma and a history of successful autologous stem cell transplantation.[39]

- Rituximab was effective in patients with mantle cell lymphoma, a disease subtype considered to respond poorly to treatment.[40] The clinical response rate was 37% in 23 patients with newly diagnosed disease[27] and 33 or 43%, respectively, in 12[38] or 30 patients[27] with relapsed mantle cell lymphoma who received rituximab 375 mg/m^2/week for 4[27] or 8[38] weeks. In addition, the clinical response rates in 2 small clinical trials were 23% of 26 patients with relapsed lymphoplasmacytoid lymphoma or Waldenström's macroglobulinaemia[27] and 57% of 7 patients with Waldenström's macroglobulinaemia, respectively.[41]

Combination Therapy

• Rituximab in combination with CHOP may be more effective than CHOP alone in patients with previously untreated intermediate or high grade lymphoma (IWF-D, G and H). The clinical response rate was 97% (63% complete and 33% partial) in 30 evaluable patients who received six 3-week cycles of rituximab 375 mg/m^2 and CHOP (starting on day 3) in a noncomparative trial.[42] The complete response rate achieved with CHOP alone in this patient group is reported to be approximately 45 to 55%.[4]

4. Tolerability

First Infusion-Related Events

• Mild to moderate adverse events occurred during the first infusion of rituximab in approximately 50 to 87% of patients in clinical trials,[11,15,18,19,33,38,43] and most commonly included flu-like symptoms (fever, chills, nausea and asthenia)[15,18,19] which were thought to be related to lysis of B lymphocytes by rituximab.[15] Other symptoms which occurred in 5 to 20% of patients during the first infusion were bronchospasm, hypotension, headache, pruritus, rash, vomiting, rigors, urticaria and a sense of tongue or throat swelling.[11,15,18,19]

• Adverse symptoms which occurred during the first infusion were partially relieved by diphenhydramine and/or paracetamol (acetaminophen) and temporary stopping of the infusion. They generally resolved completely in <3 hours.[11,15,18,19,33,38] Adverse events did not usually occur during later infusions.[15,19]

• Approximately 10% of patients developed bronchospasm and/or hypotension in addition to flu-like symptoms during infusion of rituximab; some (percentage not reported) of these patients developed severe cytokine release syndrome (severe dyspnoea, bronchospasm, hypoxia, fever, chills, rigors, urticaria and/or angio-oedema).[44,45] Typically, this adverse event occurred ≤1 to 2 hours after the start of the first infusion, symptoms resolved when the infusion was temporarily slowed or interrupted, and treatment was completed without further incident.[43,46] However, infusion-related events were fatal in 8 of 12 000 to 14 000 patients who received rituximab during postmarketing surveillance; 3 of these patients were treated for unapproved indications.[43,46] Since these events, several precautionary measures have been recommended. These include administration of rituximab in a hospital environment with close monitoring and full resuscitation facilities and premedication with an analgesic, an antihistamine and possibly corticosteroid therapy.[47]

• Infusion-related adverse events were most severe in patients with a high tumour burden and/or a high number of circulating tumour cells (>50 000 cells/ml blood). Thus, rituximab should be used with extreme caution in these patients.[44,45,48-50]

General Adverse Event Profile

• 84 to 95% of patients experienced treatment-related adverse events with rituximab,[15,18,19,38] approximately 90% of which were mild to moderate in severity.[15,18,19,38] Figure 3 shows the incidence of adverse events which occurred up to 1 month after completion of treatment.[15]

• In 2 small dose-ranging studies, there was no apparent relationship between the frequency or severity of adverse events and dose (rituximab 10 to 500 mg/m^2 as a single dose or 125 to 375 mg/m^2 once weekly for 4 weeks).[11,18]

• Cardiac arrhythmias developed in 2% of patients with relapsed indolent lymphoma who received rituximab 375 mg/m^2/week for 4 weeks (fig. 3).[15] Angina pectoris has also been reported in association with rituximab during postmarketing surveillance (incidence not stated).[45,47]

• Adverse events consistent with hypersensitivity were reported in up to 14% of patients and resulted in withdrawal of ≤3% of patients from treatment with rituximab.[15,26,27] As discussed above, rash and pruritus occurred during infusions in 10 and 13% of patients, respectively, and urticaria or angio-oedema were reported in 6 or 14% of 165 patients up to 1 month after completion of treatment

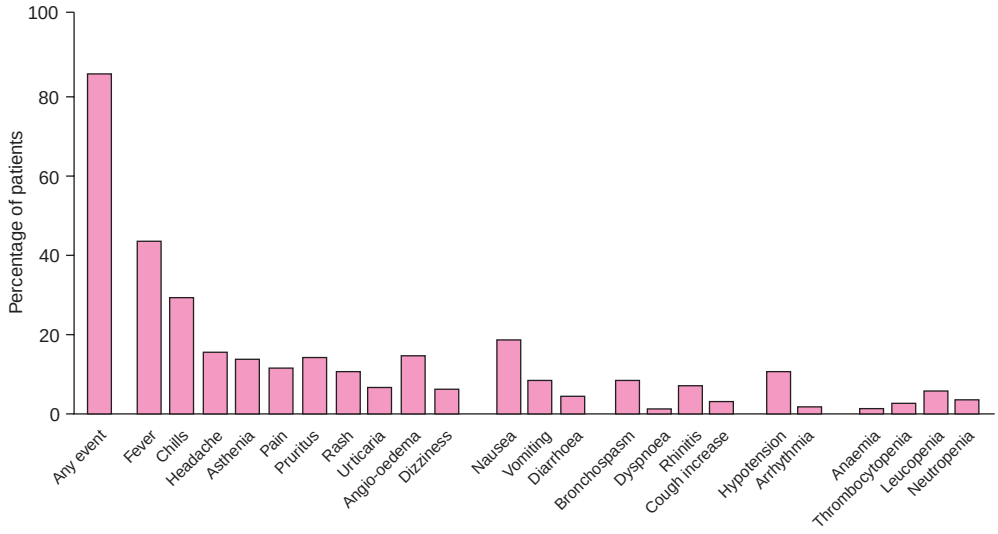


Fig. 3. Adverse events within 1 month after completion of treatment in 165 rituximab-treated patients (safety population) with relapsed indolent lymphoma.[15] Rituximab 375 mg/m^2 was administered once weekly for 4 weeks. Adverse events presented are either those considered to be severe and related to treatment or those with ≥10 occurrences.

(fig. 3).[15] Four of 121 patients were withdrawn from treatment because of syncope (2 patients), anaphylaxis (1) or urticaria (1);[27] 1 of 70 patients was withdrawn from another trial after developing Stevens-Johnson syndrome.[26]

- Human antichimaeric antibodies (HACA) against rituximab were detected in <1% of 355 patients who received rituximab,[45] and 2 patients were successfully re-treated with the drug after developing HACA.[33]

- Because all trials were noncomparative, it was not possible to determine the effect of rituximab on the incidence and severity of infections. However, 68 infections were reported in 165 patients during the year after the start of rituximab monotherapy; 90% of these infections were considered minor (54% of all infections were bacterial and 22% were viral).[15]

Haematological Events

- The incidence of anaemia, thrombocytopenia, leucopenia and neutropenia related to treatment ranged from 1 to 7% of 165 patients up to 1 month after the fourth infusion of rituximab 375 mg/m^2/week (fig. 3).[15] Two to 12 months after the fourth infusion, neutropenia and leucopenia developed in 8 and 6% of patients, respectively, and erythrocyte aplasia developed in a single patient (relationship of these events to treatment was not reported).[15]

- In the largest trial, the incidence of low haemoglobin levels (<10 g/dl) was 10%, that of low neutrophil counts (0.5 to 1.5 × 10^9 cells/L) was 10%, and that of low platelet counts was 2% up to 1 month after the fourth infusion of rituximab.[15] These mild haematological abnormalities resolved spontaneously in 4 to 8 days (relationship to treatment not reported).[15] T lymphocyte and NK cell counts remained stable throughout the study period.[15]

5. Rituximab: Current Status

Rituximab is a chimaeric mouse-human monoclonal antibody which is specific for the CD20 antigen and produces antibody-dependent cell- and complement-mediated cytotoxicity against normal and malignant B lymphocytes. It appears to be ef-

fective in patients with relapsed or refractory indolent lymphoma, particularly those with follicular histology, and has been approved for this indication in the US and Europe. The long term effect of rituximab on survival rates is not yet known. Preliminary studies in patients with intermediate or high grade lymphoma suggest rituximab may be effective after relapse and improve the efficacy of CHOP in the treatment of newly diagnosed disease.

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