

Review

B cell non-Hodgkin's lymphoma: rituximab safety experience

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Abstract

A substantial body of data supports use of rituximab as first-line and maintenance therapy for the treatment of indolent non-Hodgkin's lymphoma. With 7 years of postmarketing surveillance experience and more than 370,000 patient exposures, the safety profile of rituximab is well defined. Several multicenter trials suggest that infusion reactions associated with rituximab administration are well characterized and generally associated with the first infusion; toxicity is reduced with subsequent doses. Since some adverse events are related to circulating tumor loads of non-Hodgkin's lymphoma, fewer events are anticipated in rheumatoid arthritis. Low infection rates in oncology would indicate similar safety in patients with rheumatoid arthritis.

Introduction

The US Food and Drug Administration (FDA) approved the chimeric anti-CD20 monoclonal antibody rituximab in 1997 as a single-agent treatment for relapsed or refractory, low grade or follicular CD20⁺, B cell non-Hodgkin's lymphoma (NHL). In as many as 85% patients, NHL is of B cell origin, and a majority has high affinity expression for CD20. For that reason, rituximab is now widely used in hematologic oncology.

Almost half a million patients have been treated with rituximab, either alone or in combination, from phase II and III of development through postmarketing approval. Although not formally approved for use in combination protocols by the FDA, rituximab is now included in a standard-of-care, in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, for treatment of aggressive lymphomas of B cell origin.

In the original clinical studies, patients received four weekly doses of 375 mg/m²; this dosage schedule increased to eight weekly infusions of 375 mg/m² in subsequent trials. The choice of cumulative dosage was somewhat arbitrarily based on biologic factors. Doctors frequently give extended courses of rituximab (four to eight courses instead of the standard

single 4-week course) to those patients who have not reached dose limiting toxicity.

Overall, rituximab has exhibited very strong and consistent efficacy alone and in combination with virtually all of the chemotherapeutic agents used to treat B cell lymphomas. This has resulted in a very large safety database, permitting accurate assessment of the nature of the specific side effects and risks involved in using this drug.

Safety of rituximab

A substantial and growing body of data illustrates the safety of rituximab when used as first-line treatment and maintenance therapy for NHL. Although responses in a rheumatoid arthritis (RA) population are different from those in NHL patients, knowledge gained in the oncology setting may be of significant relevance to treatment of RA patients.

McLaughlin and coworkers [1] described the safety profile of rituximab monotherapy in a pivotal phase III study conducted in relapsed and refractory indolent NHL. In that trial patients with relapsing low grade or follicular lymphoma received, on an outpatient basis, intravenous rituximab 375 mg/m² weekly for 4 weeks. A total of 166 patients were enrolled in the trial, with an approximately 48% response rate. With a median follow up of 11.8 months, the authors observed that among responders the projected time to progression was 13.0 months.

The majority of adverse events (AEs), which were grade 1 and 2 in severity, occurred during the first infusion period, with fever and chills being the most common symptoms. Only 12% of patients had grade 3 toxicities, and 3% had grade 4 toxicities. A human antichimeric antibody was detected in only one patient. The researchers suggested that the toxicity was mild.

The risk factors for severe AEs associated with use of rituximab are well defined. Moreover, because some of the

rare AEs of rituximab are related to circulating tumor loads in NHL, it can be anticipated that they will be less likely to occur in the RA population.

The AE profile for rituximab has been consistent throughout numerous subsequent studies in both indolent and aggressive NHL. Hainsworth and coworkers [2] enrolled 62 patients with indolent follicular or small lymphocytic subtypes of NHL. These patients, who were previously untreated with systemic therapy, received intravenous rituximab 375 mg/m² weekly for 4 weeks. Patients were restaged at week 6 to assess the response; those with an objective response or stable disease received maintenance rituximab courses (identical dose and schedule) at 6-month intervals. The minimum follow-up period was 24 months. Median actuarial progression-free survival was 34 months.

The study reported that treatment with rituximab was well tolerated. Of the 62 patients who received 245 rituximab doses (four doses per patient), only two developed grade 3 or grade 4 AEs. One patient, the only patient in whom therapy was discontinued because of treatment-related toxicity, had flushing, dyspnea, and ischemic chest pain. One additional patient had severe chills and rigors with the first dose of rituximab but was able to continue treatment without further episodes.

The most common grade 1 or 2 toxicities were fever (18%), chills/rigors (26%), and nausea (21%). Almost all AEs occurred during the first rituximab infusion. The infusion reaction also appeared to be related to the tumor load, suggesting that such reactions might be less likely or severe in patients with RA. Hainsworth and coworkers [2] reported that eight patients in the study (13%) had circulating malignant lymphocyte counts greater than 10,000/ μ l upon initiation of treatment. Four of these eight patients experienced grade 1 or 2 infusion related toxicity during the first dose of rituximab, but none developed grade 3 or 4 toxicity. The incidence of toxicity in patients older than 70 years was comparable to that in younger patients.

The other grade 1 or grade 2 AEs related to infusions included flushing (five patients), hypotension (three patients), headache (three patients), and chest pain, angioedema and bronchospasm (one case each). Overall, 18 patients reported fatigue, four had anemia and two developed leukopenia, all grade 1 or 2 AEs. No cumulative or additional toxicities were seen with maintenance courses.

French researchers conducted an open label, randomized, phase II trial to evaluate the clinical efficacy and safety of rituximab in patients with progressive intermediate or high grade NHL [3]. Study participants received one of two dosage schedules of rituximab (all intravenous): 375 mg/m² once weekly for 8 weeks; and 375 mg/m² on day 1 followed by 500 mg/m² on day 8 and once weekly for a further

7 weeks. Rituximab was administered via a peripheral or central intravenous line in an outpatient setting. Infusion was started at an initial rate of 50 mg/hour. If no toxicity was observed during the first hour, then the dosage was escalated by increments of 50 mg/hour every 30 min to a maximum of 300 mg/hour. If the starting dose of rituximab was well tolerated, then the starting flow rate for the administration of the second and subsequent infusions was fixed at 100 mg/hour, with similar increments at 30 min intervals up to 400 mg/hour. The infusion was interrupted if patients experienced severe fever, rigors, edema or mucosal congestion, hypotension, or any other serious AEs. Following resolution of the AEs, the infusion was to be resumed at half the previous rate. The dose was not modified throughout the treatment period. Administration of oral premedication with acetaminophen at 1000 mg and diphenhydramine hydrochloride at 50–100 mg was recommended 30–60 min before each infusion.

Of the 54 patients who were enrolled over a 6-month period, 36 were able to complete the 8-week treatment program. Five patients achieved a complete response and 12 others a partial response. The overall response rate was not statistically significantly different between the two dosage groups.

All patients enrolled in this study received at least one infusion of rituximab. Five patients did not experience any infusion reactions. Altogether, the other 49 patients reported 168 infusion reactions, although nearly 90% of these reactions were termed 'mild to moderate' in severity. In both arms, the majority of AEs occurred during the first infusion and resolved within the same outpatient treatment day. The frequency of AEs and their severity decreased for the subsequent infusions. Grade 3 and grade 4 AEs were seen predominantly during or shortly after the first infusion. Two deaths during the study period were reported, and both were judged secondary to the study disease. Before death, both patients had been withdrawn from the study because of progressive disease.

In another study, Colombat and colleagues [4] recruited 49 patients with grade 1–3, stage II–IV follicular NHL. Ten patients treated with rituximab achieved a complete response rate and, overall, 39 patients (80% of the patients in the study) achieved objective responses to treatment.

All patients in this trial were able to receive the four weekly infusions at full dose. The most common AEs thought to be related to rituximab infusions were grade 1–2 fever, headache, asthenia, pain, rash, laryngitis, rhinitis, paresthesia, hypotension, and nausea. Two cases of grade 3–4 hypotension and hypertension resolved after appropriate pharmacologic management, given in accordance with the protocol procedures. No hematologic toxicity was observed and only one minor infection was reported during the course of the study.

Davis and coworkers [5] administered rituximab to 31 patients with follicular NHL, all of whom had previously undergone therapy. All patients received four rituximab doses. The study found that 43% of patients achieved a response to therapy. The time to response was similar to that observed in patients without bulky disease who had been administered rituximab with different treatment protocols.

About 93% of the clinical AEs were considered mild to moderate, or grade 1 or 2. The majority of patients experienced AEs during the first infusion, and incidence declined with subsequent infusions. The most common related events observed during the treatment period included transient fever (61% of patients), chills (36%), leukopenia (23%), nausea (19%), dizziness (19%), and throat irritation (19%). Grade 3 or 4 related nonhematologic clinical events occurred in four patients: two with pulmonary disorders, one with chills, and one with pain and infusion-related hypotension. The AEs resolved in three of these four patients. No grade 3 or 4 infections were reported, and no patients were hospitalized for infection; however, six infections reported in five patients (pneumonia, rhinitis, sinusitis, herpes zoster, and uncategorized infection) were treated subsequently without incident. None of the patients in this study were forced to discontinue treatment because of AEs.

Foran and colleagues [6] in London treated 131 patients with mantle cell lymphoma, immunocytoma, and small B cell lymphocytic lymphoma; these B cell malignancies express CD20 and historically were incurable with standard therapy. For this study, rituximab 375 mg/m² was administered for 4 weeks as an intravenous infusion in 1 litre normal saline. Of the 120 evaluable patients (11 could not be included in the treatment response assessment because of treatment-related toxicity, including one who died from splenic rupture), 36 (30%) achieved an objective response to rituximab. Although 10 patients achieved a complete response, most of the enrollees had only a partial response to rituximab. Sixty-one patients had stable disease, and 23 had evidence of progressive disease (confirmed during therapy or at the 1 month restaging analysis).

All 131 patients were evaluated for toxicity. The infusions were generally well tolerated, even though infusion-related side effects such as fever, rigors, and nausea were relatively common. These side effects occurred most frequently with the first treatment, and in most cases they were managed with adjustments to the infusion rate. The researchers noted that the average duration of the first infusion was 5.2 hours compared with 3.4 hours for subsequent infusions, reflecting the requirement for fewer interruptions caused by adverse reactions and a more rapid infusion rate in later weeks.

No evident excess in infusional toxicity was observed in the 10 patients presenting with a marked lymphocytosis (i.e. $>25 \times 10^9/l$), although one patient did experience a severe

anaphylactic-type reaction with the first infusion, which necessitated its discontinuation. The latter patient was subsequently able to complete treatment without further reaction.

Eight patients did not finish therapy because of AEs, including three who withdrew due to anaphylaxis/severe allergic reactions. Others were withdrawn because of atrial fibrillation, elevated serum liver function tests, syncope, and urticaria. One patient with underlying diabetes mellitus and extensive chemotherapy refractory mantle cell lymphoma died from splenic rupture several hours after completing the first infusion, which had been complicated by fevers, rigors, and hypoglycemia.

The study uncovered 31 episodes of infection, most of which were deemed mild or moderate in nature. Ten patients suffered arrhythmias, which occurred along with or immediately following infusion.

Long-term objective response

Hainsworth and coworkers selected rituximab for treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) [7]. CLL, the common form of leukemia, is derived from small B lymphocytes in the majority of cases; SLL, which is usually characterized by predominant adenopathy, contains small B lymphocytes that are indistinguishable, histologically and immunologically, from those seen in CLL. Treatment for both of these illnesses is initiated for control of symptomatic or advanced disease, because the disease course is indolent and asymptomatic for long periods in a large percentage of patients. Several cytotoxic agents exhibit activity as first-line therapy, but most patients with CLL/SLL develop progressive resistance with time to subsequent chemotherapeutic agents.

Forty-four patients with previously untreated CLL/SLL received rituximab (375 mg/m² weekly for 4 consecutive weeks). Patients who achieved an objective response or whose disease had stabilized continued to receive identical 4-week courses of rituximab at 6-month intervals, for a total of four full courses of therapy. The first rituximab dose was administered in a slow 6-hour infusion in all patients. The infusion rate was increased beginning with the second dose in 39 out of 44 patients. The infusion rate was begun at a starting rate of 100 mg/hour, with a 100 mg/hour dose escalation every 30 min to a maximum of 400 mg/hour. Many oncologists use this rate only after the first infusion and use half these rates on the first infusion day.

After the first course of treatment with rituximab, 51% of patients achieved an objective response, including 4% who had a complete response. With the inclusion of 28 patients who received one or more additional courses of therapy, the overall response rate reached 58%, with 9% complete responses. At 1 and 2 years of follow up, 62% and 49% of

patients, respectively, had progression-free survival, which compares favorably with combination chemotherapy outcomes.

As with NHL patients, the rituximab therapy was well tolerated. During the first course of rituximab two patients experienced grade 3–4 infusion related toxicities during their first infusion. One patient required a brief hospitalization for symptomatic treatment of a severe headache, which subsequently resolved. Grade 1 and 2 infusion related toxicities were relatively common during the first rituximab infusion but were uncommon with subsequent infusions. All treatment-related toxicities were reversible, and no patient was removed from treatment because of toxicity.

Management of infusion-related side effects

Reactions to rituximab are unusual when compared with experiences seen in other drugs. Most of the toxicity occurs immediately and often with the initial dose of the medication. These infusion reactions can be dramatic but are generally easily controlled with additional medication. If clinicians witnessed these reactions with drugs other than rituximab, the usual response would be to withdraw the medication. Those reactions include decreased blood pressure, fever, angioedema, chills, and subjective bronchospasm, although they are not usually accompanied by overt wheezing.

These adverse reactions actually remit rapidly upon discontinuation of the drug infusion. With additional premedication and resumption of the drug infusion, the risk for reactions diminishes dramatically. Data on long-term safety and re-exposure are available and indicate that infusion reactions are well characterized, with a reduction in toxicity with subsequent doses.

An analysis of infusion reactions that take place during the usual four courses of treatment was conducted by McLaughlin and coworkers [8], who looked at data from the pivotal trial of rituximab in NHL. They found that approximately 72% of patients suffered an infusion-related reaction following the initial infusion. About 90% of those infusion reactions were grade 1 or 2 (approximately 45% were grade 2, and 45% were grade 1); 10% were grade 3 or 4. During the second infusion about 28% of patients had reactions, and more than half were grade 1 reactions; fewer than 10% were grade 3 or 4. The percentage of adverse reactions also dropped during the third infusion; 24% of patients suffered reactions, 75% of which were grade 1. Similarly, 22% of patients had a reaction to the fourth treatment, and again 75% were of a mild, grade 1 nature. Grade 3 or 4 reactions in later infusions are very uncommon. In fact, with the continuation of treatment, patients experience less and less toxicity, which is contrary to what one would expect from a traditional anaphylactic-type response. Most symptoms such as bronchospasm, rigor, fever, and drops in blood pressure will resolve if treatment is delayed for just 30 min after additional medications.

In our experience these reactions are easily managed medically, as follows. Patients are premedicated with acetaminophen and diphenhydramine before the first administered dose of rituximab. Additional doses of acetaminophen, hydrocortisone and diphenhydramine are available if the fever or any type of bronchospastic symptom occurs. Although rigors are not medically significant, they may be frightening to patients. If rigors occur, we manage them with meperidine. If a side effect occurs, then the infusion is stopped for approximately half an hour, additional saline is given intravenously, and the infusion resumes at a slower rate. Clinicians may administer diphenhydramine and hydrocortisone at that point to ensure that the infusion is comfortable for the patient. When the patient's condition has returned to baseline the infusion may be resumed. We usually start one step lower than the rate of infusion at the time of the reaction. If there is no reaction at the lower step after resumption of the infusion, then the rate can be increased slowly again. It is often possible to continue to escalate the infusion rate without further incident. It is even possible to increase the rate again beyond the point at which the patient had the initial reaction.

Fewer serious infections

In the original pivotal trial McLaughlin and colleagues [1] followed patients with NHL who received 4 weeks of rituximab therapy, and then subsequently followed them for a year or more. Despite B cell depletion, there was no increase in the incidence of infection, which had been a significant concern when the drug was originally investigated. Researchers suspected that the effectiveness with which rituximab could deplete B cells would lead to an increased risk for serious bacterial infection; however, follow-up data showed that serious bacterial infection did not emerge in these patients. Of 166 patients in the trial, only seven episodes of grade 3 infection occurred, none were grade 4, and the majority were typical of those common in normal hosts (Table 1). Within the lymphoma population, this would not be out of the normal range for infections.

Even when used with chemotherapy, the inclusion of rituximab in the treatment regimen is not associated with greater infection rates. Coiffier and colleagues [9] randomly assigned previously untreated patients (aged 60–80 years) with diffuse, large B cell lymphoma to receive either the standard CHOP regimen or CHOP with rituximab. A total of 197 patients were given eight cycles of CHOP every 3 weeks, and a second group of 202 patients were assigned to receive eight cycles of CHOP plus rituximab given on day 1 of each cycle. The rate of complete response was significantly higher in the group that received CHOP plus rituximab (76%) than in the group that received CHOP alone (63%; $P=0.0005$). Moreover, with a median follow-up period of 2 years, event-free and overall survival times were significantly higher in the CHOP plus rituximab group ($P<0.001$ and $P=0.007$, respectively). The GELA (Groupe

Table 1**Rituximab in non-Hodgkin's lymphoma pivotal trial: infections**

Patients monitored throughout treatment and >1 year follow up
 Despite B cell depletion, incidence of infection was not increased
 Most infections were typical of those common in normal hosts
 Predominantly bacterial
 Seven episodes of grade 3 infections
 No patients experienced grade 4 infections

Data from McLaughlin and coworkers [1].

d'Etude des Lymphomes de l'Adulte) group, which performed the study, did not find any overall difference in the rate of all-cause AEs between those patients receiving CHOP and those receiving CHOP plus rituximab. Further scrutiny revealed no differences in grade 3 and grade 4 infections between the two patient cohorts.

Rare adverse events

Some serious AEs have occurred – even a few fatalities – in patients with infusion reactions in clinical trials, although these are rare (0.01% of patients) [10]. Eighty per cent of the deaths, which occurred following the first infusion, were characterized by more typical anaphylactic-type responses such as hypotension, angioedema, bronchospasm, and hypoxia – adverse reactions that often begin within 30 minutes to 2 hours of the infusion [10].

Some of the rarest serious AEs are not typical anaphylactic reactions but are hematologic in origin. These reactions usually occur in patients with high B cell counts in the range of 20,000/ μ l to 100,000/ μ l, such as CLL patients, and in patients with risk factors for cardiopulmonary disease and who therefore would be more susceptible to bronchospasm or hypotension [10]. Therefore, in patients with heavy disease burden and/or cardiovascular risk factors, the drug is often administered in smaller incremental doses initially. If these infusions are performed safely, the remaining dose can be given 2–3 days later without major risk.

Most rare and severe reactions occur with the first infusion. As B cells clear after the first infusion, the risk factors for AEs decline dramatically with further infusions [10]. Rheumatologists may be concerned about fatal infusion reactions with rituximab treatment; however, the risk factors associated with high B cell counts do not even exist in most RA patients.

There are other serious but not life-threatening AEs such as severe mucocutaneous reactions (0.02%), which occur 1–13 weeks after treatment [10]. These uncommon disorders, including paraneoplastic pemphigus (0.0008%), Stevens–Johnson syndrome, and toxic epidermal necrolysis, may also be manifestations of the patients' underlying malignancies [10].

Prolonged use of rituximab

One of the major differences between use of rituximab in the oncology setting and its use for rheumatologic diseases will be the necessity for long-term, possibly life-long use of rituximab. At present there are several ongoing clinical trials in the USA and worldwide investigating rituximab maintenance therapy from an efficacy and safety perspective. Most patients have tolerated repeat courses of treatment without further accumulated toxicity.

In recent research reported by Hainsworth and colleagues [11] on the use of extended course rituximab for low grade NHL, they demonstrated that prolonged B cell depletion over 2 years was not associated with cumulative toxicity or an increased incidence of serious infections. Forty-one patients with low grade NHL were first administered rituximab at a dose of 375 mg/m² every week for 4 weeks. At 6 weeks patients were followed up for evaluation; if they responded to treatment or their disease had stabilized, then subsequent 4-week cycles of rituximab were initiated at 7, 13, and 19 months. Following the 6-week evaluation period the researchers reported that 25 out of 39 patients (64%) achieved an objective response and 15% a complete response [11]. At a median follow up of 8 months, 32 out of 39 evaluable patients were free of disease progression, and 1-year progression free survival occurred in 77%. When the researchers evaluated the safety of the long-term regimen, they found that grade 1 and 2 infusion related toxicities were the only common side effects. No instances of either grade 3 or grade 4 toxicities or neutropenia were reported in the trial.

In an effort to determine whether the clinical and pharmacokinetic characteristics of rituximab could be improved with prolonged exposure to the drug, Ghielmini and coworkers [12] enrolled 202 patients with newly diagnosed or resistant/relapsed follicular NHL. After a standard induction phase with rituximab 375 mg/m² every week for 4 weeks, patients who exhibited a response or whose disease had stabilized at week 12 were randomly assigned to either observation or a maintenance protocol of rituximab 375 mg/m² every 8 weeks at months 3, 5, 7, and 9. At a median follow up of 35 months from the initial induction treatment, Ghielmini and colleagues noted that the median event-free survival was 12 months and 23 months for the observational and maintenance arms, respectively ($P=0.02$). For patients who responded at week 12, 56% were still in remission at 12 months in the observational arm as compared with 80% in the maintenance arm ($P=0.01$). Patients receiving standard therapy experienced a 17% rate of hematologic toxicity, as compared with 18% among those in the maintenance protocol. Two per cent of patients had anemia, 3% leukocytopenia, 4% thrombocytopenia, and 9.4% experienced neutropenia.

Even though these patients were very effectively depleted of their B cells for more than 6 months, they maintained normal

Table 2

Rituximab maintenance versus retreatment: comparison of efficacy

	Maintenance	Retreatment	<i>P</i>
Overall response rate (%)	52%	35%	0.14
Complete response rate (%)	27%	4%	0.007
% in continuous remission	45%	24%	0.05
% remaining in continuous remission	23%	2%	0.03
Median progression-free survival (months)	31.7	7.4	0.007
Median duration of rituximab benefit (months)	31.7	27.4	0.94

IgA and IgG levels, and only had an approximate 28% drop in IgM levels. That drop, in our experience, does not appreciably increase the risk for bacterial infection. A 20% decline in IgM is considered within the normal range.

The study demonstrated that, in follicular NHL patients whose condition remained stable or responded after standard rituximab treatment, the addition of single doses at 2-month intervals for four total doses significantly improved the chances of remaining in remission at 1 year, without inducing additional toxicity.

Hainsworth and colleagues [13] also studied the efficacy of rituximab maintenance therapy versus retreatment at progression among patients with indolent NHL. The study participants – rituximab naïve patients with previously treated follicular or small lymphocytic lymphoma – were treated with a standard induction course of rituximab 375 mg/m² weekly for 4 weeks. Patients who responded or achieved stabilization of disease were then randomly assigned to receive either rituximab retreatment – another standard 4 week course of therapy – at the time of progressive disease or maintenance therapy, defined as a 4-week course of treatment every 6 months for 2 years. Of the 114 patients who entered the trial, 90 (79%) patients achieved clinical benefit with the first course of treatment, allowing 44 patients to be randomized to maintenance therapy and the other 46 to the rituximab retreatment arm.

The final overall response rates were 52% in the maintenance arm and 35% in the retreatment arm. The median progression-free survival, however, was 31.7 months for maintenance patients versus 7.4 months for retreatment, which was statistically significant (*P* = 0.007; Table 2). The improvement seen with maintenance therapy also appears to have been achieved without increases in AEs. This database of patients who received rituximab for extended periods of time and completed B cell depletion for extended periods suggests that rituximab is effective at clearing malignant B cells, with no significant additional toxicity. In addition, the retreatment trial conducted by Hainsworth and coworkers demonstrated

Table 3

Reasons why oncology experience with rituximab is most helpful

- Non-Hodgkin's lymphoma and autoimmune diseases have similarities
- Provides information on chronic use
- Provides a large safety database of >370,000 patient exposures
- Provides 7 years of postmarketing experience
- Extensive experience allows us to predict and manage infusion reactions
- Low infection rate in oncology provides information on potential for infection in rheumatoid arthritis

a lack of cumulative toxicity and no increase in opportunistic or bacterial infections.

Conclusion

The data from these clinical trials provide clinicians with insight into the role of rituximab in the management of NHL and autoimmune diseases. Although there is still controversy regarding the ideal maintenance schedule, treatment data from more than 370,000 treated patients attest to the long-term safety of rituximab therapy (Table 3). These pivotal trials conducted with rituximab revealed that most of the adverse side effects occur with the first infusion and grow less frequent with subsequent infusions. Also, the findings yield an improved awareness of the correlation between AEs and a high number of circulating malignant cells and heavy tumor burden. In addition, toxicity decreases with subsequent treatment doses.

In light of the low infection rates (including no increased risk for opportunistic infection) observed in oncology patients taking rituximab, there is preliminary evidence to suggest that this agent will be acceptably safe for use in rheumatologic diseases such as RA.

Competing interests

AM is on the Speaker's Bureau for Genentech.

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