The increasing usage of rituximab in the management of non-Hodgkin lymphoma (NHL) has created huge logistical challenges with respect to the delivery of this time- and labor-intensive drug. To address these challenges, we developed and tested the feasibility of a 90-minute infusion schedule for rituximab (20% of the dose administered in the first 30 minutes, remaining 80% administered over 60 minutes). A safety analysis performed in 150 patients receiving rituximab with corticosteroid-containing chemotherapy and 56 patients receiving rituximab as maintenance therapy demonstrated that this schedule was well tolerated, with no grade 3 or 4 infusion reactions observed. In addition, no increase in minor reactions was noted. More than 1200 patients have been treated with this rapid rituximab infusion schedule in the province of British Columbia (BC), demonstrating its safety in the community setting. The adoption of this 90-minute schedule as standard practice has had a positive impact on resource utilization. (Blood. 2007;109:4171-4173) © 2007 by The American Society of Hematology

Introduction

Rituximab, a chimeric IgG1 monoclonal antibody targeting CD20, has become widely used in the management of B-cell lymphoproliferative disorders. Since its approval by the US FDA in 1997 as monotherapy for relapsed follicular or low-grade non-Hodgkin lymphoma (NHL), its indications have continued to expand. Rituximab is now routinely used in combination with chemotherapy for the treatment of aggressive and indolent lymphomas, and more recently as maintenance therapy after response to induction therapy for follicular NHL. This increase in usage has placed a huge strain on medical resources in many centers, requiring expansion of infusional services and generating treatment waiting times that may negatively affect patient outcomes.

Although generally well tolerated, rituximab administration is associated with a risk of infusion-related toxicity, including hypersensitivity reactions causing fever, rash, cardiovascular, and respiratory compromise and rarely a fatal cytokine release syndrome. The mechanism of this reaction is poorly understood, but it is in part mediated by the release of cytokines such as TNF-α and IL-6 promoted by the binding of rituximab to tumor cells and normal B cells. The risk of reaction is greatest with the first infusion and is significantly diminished with all subsequent infusions (grade 3 or 4 toxicity; 7% with first, 2% with fourth, and 0% with eighth infusion). As a consequence, a cautious administration schedule has been empirically derived, recommending a slow initial rate of infusion followed by increments every 30 minutes as tolerated by the patient. The result is both a time- and labor-intensive process, with an average infusion time of 6 hours for the first infusion and 4 hours for remaining infusions.

Because rituximab is now commonly administered in combination with corticosteroid-containing chemotherapy or as maintenance therapy, settings in which tumor reduction and immunosuppression have been achieved, we hypothesized that lengthy infusions may no longer be necessary. On the basis of previous reports that abbreviated infusions were feasible and safe, we began to use a 90-minute rapid infusion schedule for rituximab in the province of British Columbia (BC). In this report, we present an expanded analysis, including provincial experience and initial data in maintenance therapy.

Patients and methods

In March 2004, we began to use a rapid infusion schedule for rituximab in all prospective patients with NHL planned for treatment with rituximab in combination with corticosteroid-containing chemotherapy at the BC Cancer Agency (Table 1). The schedule of administration for rituximab in cycle 1 was unaltered and delivered according to the product monograph. All further cycles were administered the same day as chemotherapy over a total infusion time of 90 minutes (20% of the dose in the first 30 minutes and the remaining 80% over 60 minutes; total dose delivered in 250 mL). Patients were encouraged to take their daily corticosteroid dose according to their chemotherapy protocol prior to receiving rituximab. Safety information was monitored prospectively using an infusion monitoring record. Clinical characteristics of patients treated in this initial safety analysis are listed in Table 2.

In June 2004, following an initial demonstration of feasibility and safety, this rapid infusion schedule was adopted as the standard administration schedule for all lymphoma treatment protocols combining a corticosteroid-containing chemotherapy regimen with rituximab recommended by the BC Cancer Agency and used throughout the province of British
Table 1. Administration schedule for rapid infusion rituximab in combination with corticosteroid-containing chemotherapy

<table>
<thead>
<tr>
<th>Premedications</th>
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<tbody>
<tr>
<td>Diphenhydramine 50 mg orally</td>
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<tr>
<td>Acetaminophen 375 mg orally</td>
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<tr>
<td>Daily corticosteroid dose</td>
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<td>according to chemotherapy protocol</td>
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**Cycle 1**

- Rituximab 375 mg/m² intravenously infused according to product monograph

**Cycles 2–8**

- 20% of dose infused over 30 minutes
- Remaining 80% of dose infused over 60 minutes, total infusion time of 90 minutes

Columbia. (www.bccancer.bc.ca/HPI/chemotherapyprotocols/lymphoma/default.htm) More recently, in March 2006, patients receiving maintenance rituximab following a response to induction therapy were treated with the rapid infusion schedule beginning with their first infusion of maintenance therapy and monitored closely for safety with an infusion monitoring record. Maintenance rituximab was administered at the standard dose of 375 mg/m² every 3 months for 2 years. Patient characteristics of this second cohort are also listed in Table 2. This review of our experience with rapid infusion rituximab was approved by the Research Ethics Board of the BC Cancer Agency and University of British Columbia. The report was prepared from anonymized information so individualized consent was not required.

**Results and discussion**

A total of 150 patients were treated with 473 rapid infusions of rituximab in combination with corticosteroid-containing chemotherapy in the initial safety analysis. The median number of rapid infusions per patient was 3. The rapid infusion rituximab schedule was extremely well tolerated with no grade 3 or 4 infusion reactions observed. The rate of grade 3 or 4 toxicity was 0% (95% CI, 0.0–0.419%), which is not higher than the expected rate with standard administration. We did not note an increased incidence of minor reactions. Ten patients who had experienced an adverse reaction with their first cycle (administered at the standard rate) subsequently tolerated rapid infusion without event. Eight patients who did not receive any corticosteroids because of a contraindication also tolerated the rapid infusion without event. No patient had an elevated circulating lymphocyte count at the time of rapid infusion rituximab; thus, the safety of rapid infusion of rituximab in this setting remains unknown.

More than 1200 patients have now received rituximab using this rapid infusion schedule in combination with corticosteroid-containing chemotherapy in accordance with BC Cancer Agency protocols in the province of BC. To date, only one patient has been reported to experience a significant (grade 3) reaction. This patient developed a pruritic rash with mild-to-moderate laryngospasm and was successfully managed with parenteral corticosteroids and antihistamines. Overall, this provincial experience confirms the safety of administering the rapid infusion schedule within the community setting.

Fifty-six patients have received a total of 92 rapid infusions of rituximab (median, 2 infusions per patient) in the initial safety analysis performed in the setting of single-agent rituximab maintenance therapy, without coincident corticosteroids, following response to induction therapy. No episodes of grade 3 or 4 infusion reactions have been observed. Two patients experienced transient grade 1 toxicity, one of whom had not received rituximab previously with induction chemotherapy. We have subsequently recommended that rituximab naïve patients receive their first maintenance infusion according to the standard guidelines for first-time infusions. An additional 32 patients have now been treated throughout the province of BC with rapid infusion rituximab in accordance with the BC Cancer Agency maintenance protocol without reported adverse events.

The adoption of this rapid infusion rituximab schedule has had a positive effect on resource utilization in BC. Rituximab administration times have been cut in half or less with a concomitant reduction in nursing workload. Most patients can be conveniently treated with rituximab in a shorter time interval and on the same day as their chemotherapy. As a consequence, patient satisfaction has improved, and treatment waiting times for rituximab have been eliminated.

Several other investigators have reported limited experience with abbreviated rituximab infusions, the majority of which have entailed more complex administration schedules. The advantage of the 90-minute schedule as outlined earlier is the simplicity of its administration and its documented safety in a large population of patients. Since we initially reported the safety of this rapid infusion protocol, it has also been independently confirmed by Salar et al, who investigated its use in 70 patients and observed no grade 3 or 4 toxicity. In their study, 40% of patients were not receiving any corticosteroids; therefore, it is possible that concomitant corticosteroid use is not essential to the administration of this protocol. We have not explored the safety of our rapid infusion protocol with rituximab monotherapy outside of maintenance protocols following initial treatment with chemotherapy plus rituximab; therefore, we cannot recommend its use in this setting.

The availability of rituximab has revolutionized treatment practices for NHL, leading to a marked improvement in outcomes. It has also created substantial logistical challenges. Our rapid infusion rituximab schedule provides a practical and safe solution that has a positive impact on resource utilization.

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Authorship

Contribution: L.H.S. designed research and performed the re-
search, analyzed data, and wrote the manuscript; J.D., A.F., C.F.,
K.K.G., N.R., B.S., S.S., and J.S. performed data acquisition and
reviewed the paper; J.J.S. performed statistical analysis; J.M.C.
designed the research and wrote the paper.

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Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting

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