Rapid-Infusion Rituximab in Lymphoma Treatment: 2-Year Experience in a Single Institution

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Abstract

Purpose: Rituximab is a chimeric anti-CD20 monoclonal antibody. We aimed to explore the safety and tolerability of rapid infusion rituximab, (over 90 minutes) in patients with non-Hodgkin's lymphoma at Hacettepe University Department of Medical Oncology.

Patients and Methods: Adult patients diagnosed with non-Hodgkin's lymphoma who were to receive rituximab were included in the study. The schedule of administration for cycle 1 was unaltered and delivered according to the product monograph. All subsequent cycles were administered over a total infusion time of 90 minutes (20% of the dose in the first 30 minutes, then the remaining 80% over 60 minutes, total dose delivered in

500 mL). All patients were observed for infusion-related reactions during the rituximab infusion, and vital signs were recorded every 15 minutes.

Results: From July 2006 to December 2008, 75 patients with non-Hodgkin's lymphoma were treated with rituximab-based chemotherapy. A total of 372 infusions were administered. The majority of patients were treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, or rituximab only. The 90-minute rituximab infusion schedule was well tolerated, with no grade 3 or 4 infusion-related adverse events observed.

Conclusion: A rapid infusion rituximab over 90 minutes is well tolerated and safe when administered as the second and subsequent infusions in the course of therapy.

Introduction

Rituximab, a chimeric immunoglobulin G1 monoclonal antibody targeting CD20, has become widely available in the treatment of B-cell lymphoproliferative disorders. Since its approval by the US Food and Drug Administration in 1997 as monotherapy for relapsed follicular or low-grade non-Hodgkin's lymphoma (NHL), indications for its use have continued to expand.¹ Rituximab is now routinely being used in combination with chemotherapy such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or cyclophosphamide, vincristine, and prednisone (CVP) for the treatment of aggressive and indolent lymphomas, and more recently as single-agent maintenance therapy after response to induction therapy for follicular lymphomas.²⁻⁶ Moreover, rituximab is being increasingly used for other nonmalignant conditions, such as immune cytopenias and autoimmune diseases.³

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 tumor necrosis factor alpha and interleukin-6 promoted by the binding of rituximab to tumor cells and normal B cells.^{7,8} The risk of such a 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 infusions, respectively).⁹ As a consequence, a cautious administration schedule has been empirically derived, recom-

mending a slow initial rate of infusion followed by increments every 30 minutes as tolerated by the patient.¹⁰ 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 consecutive infusions. Hence, we sought to assess the practical applicability and safety of a rapid rituximab infusion schedule at our center.

Patients and Methods

In July 2006, we began using a rapid infusion schedule for rituximab in all prospective patients with NHL treated at the Department of Medical Oncology, Hacettepe University (Ankara, Turkey) who were to receive rituximab as part of their corticosteroid-containing chemotherapy or maintenance therapy. All patients provided a written informed consent before their first rituximab infusion at a standard rate, and they were informed about faster infusions to be given thereafter. All patients were monitored closely for safety with an infusion monitoring record. The demographic and clinical characteristics of patients are provided in Table 1.

The schedule of administration for rituximab in cycle 1 was unaltered, and it was delivered according to the product monograph. Patients were excluded from the study if they experienced toxicity grade ≥ 3 during the first cycle. All subsequent 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 500 mL). Patients were encouraged to take their daily corticosteroid dose according to their chemotherapy protocol before receiving rituximab. They also took 500 mg acet-

Table 1. Clinical Characteristics of Patients Treated With Rapid Rituximab Infusion

	No.	%
No. of patients	75	
No. of infusions	372	
Age, years		
Median	60	
Range	20-80	
Diagnosis		
Diffuse large B-cell lymphoma	38	50.7
Follicular lymphoma	22	29.3
Mantle-cell lymphoma	11	14.7
Other lymphomas	4	5.3
Scheme		
Rituximab alone	28	37.3
R-CHOP	34	45.3
R-CVP	5	6.7
R-CNOP	6	8
Other	2	2.7

Abbreviations: R-CHOP, rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab-cyclophosphamide, vincristine, and prednisone; R-CNOP, rituximab-cyclophosphamide, mitoxantrone, vincristine, and prednisone.

Table 2. Administration Schedule and Premedication for Rapid Rituximab Infusion

Diphenhydramine 40 mg IV
Acetaminophen 500 mg orally
Daily oral corticosteroid dose according to chemotherapy protocol
Cycle 1
Rituximab 375 mg/m ² IV infused according to the product monograph
Cycles 2-6
Rituximab 375 mg/m ² IV in 500 mL NS
20% of the dose infused over 30 min
Remaining 80% of the dose infused over 60 min, total infusion time of 90 min
Body temperature, pulse, and blood pressure measured with an interval of 15 minutes after the start of treatment. Any changes in vital signs recorded

Abbreviation: IV, intravenous; NS, normal saline.

aminophen orally the morning before rituximab infusion. Administration and premedication details are given in Table 2. Safety information was monitored prospectively using an infusion monitoring record.

Results and Discussion

A total of 75 patients were treated with rapid infusions of rituximab either along with chemotherapy or alone. Most of the patients received either rituximab alone (37.3%) or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP; 45.3%) chemotherapy regimen. During a total number of 372 rapid infusions, 5.4% increase in body temperature, 1% decrease in pulse rate, 1.9% increase in pulse rate, 8%

Table 3. Most Common Toxicities in Patients Treated With Rituximab*

Toxicity	No.	%
Fatigue	195	52.4
Alopecia	138	37.1
Sensory problems	105	28.2
Cortical problems	88	23.7
Constipation	85	22.8
Change in taste sensation	80	21.5
Anemia	80	21.5
Headache	64	17.2
Insomnia	58	15.6
Mucositis/stomatitis	51	13.7

* During a total of 372 infusions.

decrease in blood pressure, and 4.8% increase in blood pressure were recorded. The rapid-infusion rituximab schedule was extremely well tolerated, with no grade 3 or 4 infusion reactions observed.

After the rapid rituximab infusions, toxicity was evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. The most common toxicities are presented in Table 3.

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, treatment waiting times for rituximab have been largely eliminated. We think that shortening the rituximab infusion time also improves patient satisfaction.

Several other investigators have reported limited experience with abbreviated rituximab infusions, the majority of which have entailed more complex administration schedules.¹¹⁻¹⁶ 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. Salar et al,¹⁷ who investigated rapid-infusion rituximab in 70 patients, observed no grade 3 or 4 toxicities. In their study, 40% of the patients did not receive any corticosteroids; therefore, it was possible to assume that concomitant corticosteroid use was not essential to the administration of this protocol. Sehn et al¹⁸ investigated 150 patients who had been treated with 473 rapid infusions of rituximab in combination with corticosteroid-containing chemotherapy in the initial safety analysis. 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% to 0.019%). In addition, Al Zahrani et al¹⁹ reported a study in which 84 (67%) rituximab infusions were administered with corticosteroid-containing regimens and 42 (33%) of the infusions were given without steroids. Again, no grade 3 or 4 adverse events were observed.

Although there are some reports that favor the use of corticosteroids as premedication for rituximab,^{15,16} our study and most of the published articles in the literature emphasize that

corticosteroids are not needed before the administration of rituximab. Thus, corticosteroids may be reserved for patients who are at high risk for infusion-related reactions.

The availability of rituximab has revolutionized the 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 use. Overall, this provincial experience confirms the safety of administering the rapid infusion schedule in the community setting.

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Authors' Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

References

- McLaughlin P, Grillo-López AJ, Link BK, et al: Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: Half of patients respond to a four-dose treatment program. *J Clin Oncol* 16:2825-2833, 1998
- van Oers MH, Klasa R, Marcus RE, et al: Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin's lymphoma, both in patients with and without rituximab during induction: Results of a prospective randomized phase III intergroup trial. *Blood* 108:2395-3301, 2006
- Rastetter W, Molina A, White CA, et al: Rituximab: Expanding role in therapy for lymphomas and autoimmune diseases. *Ann Rev Med* 55:477-503, 2004
- Feugier P, Van Hoof A, Sebban C, et al: Long term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: A study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 23:4117-4126, 2005
- Coiffier B, Lepage E, Briere J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 346:235-242, 2002
- Marcus R, Imrie K, Belch A, et al: CHOP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood* 105:1417-1423, 2005
- Byrd JC, Murphy T, Howard RS, et al: Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. *J Clin Oncol* 19:2153-2164, 2001
- Winkler U, Jensen M, Mancke O, et al: Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood* 94:2217-2224, 1999
- MabThera [product monograph]. www.mabthera.com, 2011
- MabThera: Administration. www.mabthera.com/portal/mabthera/administration
- Sehn L, Donaldson J, Filewich A, et al: Rapid infusion rituximab in combination with steroid containing chemotherapy can be given safely and substantially reduces resource utilization. *Blood* 104 (abstr 1407), 2004
- Sehn L, Donaldson J, Filewich A, et al: Rapid infusion rituximab can be safely administered and has a positive impact on resource utilization. *Ann Oncol* 16 (abstr 107), 2005
- Aurran-Schleinitz T, Gravis G, Vittot M, et al: One hour rituximab infusion is safe and improves patient care and outpatient unit management. *Blood* 106 (abstr 4759), 2005
- Ghielmini M, Negretti L, Lerch E, et al: Infusion speed-escalation trial to give full dose rituximab in one hour without steroid pre-medication. *Blood* 106 (abstr 2451), 2005
- Middleton H, Mollee P, Bird R, et al: Accelerated delivery of rituximab is safe on an out-patient basis. *Blood* 106 (abstr 4777), 2005
- Tuthill M, Crook T, Corbet T, et al: Rapid infusion of rituximab over 60 min. *Eur J Haematol* 82:322-325, 2009
- Salar A, Casao D, Cervera M, et al: Rapid infusion of rituximab with or without steroid-containing chemotherapy: 1-yr experience in a single institution. *Eur J Haematol* 77:338-340, 2006
- Sehn LH, Donaldson J, Filewich A, et al: 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. *Blood* 109: 4171-4173, 2007
- Al Zahrani A, Ibrahim N, Al Eid A: Rapid infusion rituximab changing practice for patient care. *J Oncol Pharm Pract* 15:183-186, 2009

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