Avens Publishing Group
J Pharmaceu Pharmacol
March 2023 Vol.10, Issue:1

Open Access Research article

Journal of
Pharmaceutics & Pharmacology

Rituximab's Efficacy in Patients With Hypersensitivity Reactions

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Submission: 04 February 2023
Accepted: 13 March 2023
Published: 15 March 2023

Keywords: Monoclonal antibodies; Rechallenge

Abstract

Background: The B-cell antigen CD20 is expressed on normal B-cells and almost all B-cell lymphomas. This non-modulating agent provides an excellent target for antibody-directed therapeutic regimens. IDEC-C2B8 (rituximab) is a monoclonal antibody (mAb) directed against the B-cell-specific antigen CD20. The monoclonal antibody mediates complement and antibody-dependent cell-mediated cytotoxicity. As its usage has surged, there have been growing concerns about rituximab-related infusion reactions. Approximately 1/4th of the patients receiving first administration show infusion reactions, and most of the time they are re-challenged safely. Since recent studies have reported the presence of serum anti-rituximab antibodies in patients who develop hypersensitivity reactions, we are evaluating the pharmacodynamic response of rituximab in patients re-challenged with it.

Methods: Our study was at HCG, Bangalore, a tertiary care oncology center. The clinical records of lymphoma patients were taken from January 2021 to June 2021. We classified them based on inclusion and exclusion criteria. Patients who developed hypersensitivity were enrolled in Group 1, and those who did not in Group 2. Hypersensitivity was graded as per WAO-SAR criteria. Response assessment after three cycles of a rituximab-based regimen using radiological response: the overall response rate was evaluated and statistically interpreted.

Results: A total of 26 patients were included in the study. 11 patients had hypersensitivity reactions, of which 6 had local reactions, 2 had mild-to-moderate reactions, and 3 had severe reactions. One of these patients had an elevated eosinophil count prior to chemotherapy and an elevated level afterward. The overall response rate was 54.55% in patients with hypersensitivity reactions and 66.66% in patients without hypersensitivity reactions.

Conclusion: It has been established that Rituximab treatment increases the risk of an allergic reaction; our goal was to review the efficacy of Rituximab in patients who developed hypersensitivity reactions as well as the underlying mechanisms.

Abbreviations

HRs (hypersensitivity reactions); IRs (infusion-related reactions); mAbs (monoclonal antibodies); NHL (Non-Hodgkin's Lymphoma); MCL (mantle cell lymphoma); DLBCL (diffuse large B-cell lymphoma).

Introduction

IDEC-C2B8 (Rituximab) is a chimeric murine/human IgG kappa monoclonal antibody against a CD20 molecule that is expressed on human B cells. It binds to the surface antigen CD20 on both malignant and normal B cells, which causes cell death via direct cytotoxicity, competence-dependent toxicity, and antibody-dependent toxicity. Monoclonal antibodies (mAbs) have become mandatory for neoplastic targeted therapy and even in chronic inflammatory and autoimmune disorders.

Rituximab has demonstrated efficacy in patients with various lymphoid malignancies, including indolent and aggressive B-cell non-Hodgkin's lymphomas (NHL) as well as B-cell chronic lymphocytic leukemia. Rituximab is a viable treatment option in patients with relapsed or refractory indolent NHL and as a standard first-line treatment option when combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy in patients with DLBCL (diffuse large B-cell lymphoma) [1].

Mantle cell lymphoma (MCL) has a poor prognosis without cure; the median survival ranges from 3 to 4 years, irrespective of the therapeutic regimens. IDEC-C2D8 induces an evaluable clinical response in patients with mild toxicities. Several clinical trials in the USA have demonstrated high response rates with mild toxic effects in relapsed B-cell lymphoma at a dose of four weekly 375 mg/m^2 infusions. Hence, we conclude that Rituximab is a novel, effective anti-lymphoma agent with acceptable toxicities [2].

Treatment with Rituximab can be associated with moderate-to-severe first-dose side effects, specifically in patients with a greater number of circulating tumour cells. Although adding Rituximab to chemotherapy regimens improves therapeutic outcomes, it is associated with infusion-related toxicities such as fever, rash, urticaria, dyspnea, hypotension, bronchospasms, or other allergic or hypersensitive reactions. Immediate reactions are usually seen in subsequent administrations. We observe a decrease in the frequency of HRs [3,4].

Currently, new monoclonal antibodies acting against humanised CD20 are replacing Rituximab to reduce infusion-related adverse reactions. Infusion-related reactions can occur in approximately 1/4 of the patients receiving the first administration of Rituximab. In some cases, IRs do not remit after subsequent administrations or despite taking corrective measures. IRs can be seen in 50-70% of cases, and it has been reported that 90% of the cases are mild reactions.

ISSN: 2327-204X

In this study, we aim to analyse the pharmacological response of patients who developed HRs during initial exposure to Rituximab and were rechallenged safely in subsequent cycles.

Rationale of the study

- Rituximab has an incidence of 50–70% in developing HRs, and most of the time it has been re-challenged safely.
- Since recent studies have reported the presence of serum anti-rituximab antibodies in patients developing HRs, we are evaluating the pharmacological response of Rituximab in patients previously exposed to it [5].

Study Design

The study was performed in a single institution, the HCG Cancer Centre, Bangalore, which is a tertiary oncology centre; the study was approved by the Scientific Review Committee and the Ethics Committee. We performed a retrospective review of all lymphoma patients who received rituximab monotherapy (including maintenance therapy) or rituximab combined with chemotherapy. The infusion must begin at a rate of 50 mg per hour. If no toxicity is observed during the first hour, the infusion rate can be escalated by increments of 50 mg/hour every 30 minutes, up to a maximum of 400 mg/hour. If the first treatment is well tolerated, the starting infusion rate for the second and subsequent infusions can be administered at 100 mg/hour, with 100 mg/hour increments at 30-minute intervals up to 400 mg/hour. Despite the improved therapeutic outcomes with the addition of Rituximab to chemotherapy, its administration is associated with infusion-related toxicities. The primary end point of this study was to assess the response of Rituximab in patients who developed HRs to Rituximab [6,7].

Patient's enrolment

Patients 18 and older with histologically proven lymphoma who are eligible for Rituximab-based regimens in the first line were eligible for enrollment, while patients with dual malignancies or Rituximab usage in other indications were excluded [8] (Table 1.1).

All patients received rituximab or rituximab combined therapy; all patients received premedications such as:

- Lorazepam 1mg
- Paracetamol 500 mg, 2 std.
- Hydrocortisone sodium succinate 100 mg IV stat
- Ampule Pheniramine 22.75 mg

Table 1.1: Baseline patient characteristics.

Patient Characteristics	Group I (n = 11)	Group II (n = 15)
Gender, n% Male	7 (63.63%)	8 (53.33%)
Female	4 (36.36%)	7 (46.66%)
Age, mean years (range)	56.64years	58.4years
Diagnosis, n (%)		
Follicular lymphoma	4 (36.36%)	4 (26.6%)
Diffuse large B-cell lymphoma	2 (18.18%)	6 (40%)
Mantle cell lymphoma	1 (9.09%)	1 (6.6%)
NHL, B-cell type	2 (18.18%)	4 (26.6%)
Relapse NHL	1 (9.09%)	
BMT-cell lymphoma	1 (9.09%)	

Hypersensitivity Assessment Scale

The severity of hypersensitivity will be graded according to the World Allergic Organization for Systemic Allergic Reaction (WAO-SAR) criteria (Table 1.2).

The outcome was measured on the basis that patients who develop hypersensitivity reactions in the initial cycle will be classified as Group 1 and not develop hypersensitivity as Group 2. following three doses or cycles of rituximab-based therapy. Response was analysed radiologically (PET CT) using RECIL criteria as complete response (CR), partial response (PR), minor response (MR), stable disease (SD), and progression of disease (PD). The overall response rate (ORR) was calculated.

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Method of Analysis

Patients are enrolled based on inclusion and exclusion criteria. A total of 26 patients who were histologically proven lymphoma patients and were on Rituximab-based regimens in first-line therapy Pre-treatment peripheral markers were evaluated before the first dose of Rituximab-based regimens. Further, patients who developed HRs were classified as Group I, and those who did not develop HRs were classified as Group II. 11 belonged to Group I, and 15 belonged to Group II (Figure 1.1).

Group I was comprised of 7 males (63.63%) and 4 females

Table 1.2: Hypersensitivity reactions graded as per WAO-SAR criteria.

GRADE I (n = 6) 54.55%	GRADE II (n = 2) 18.18%		GRADE III (n = 3) 27.27%		
Local reaction	mild to moderate reaction		Anaphylaxis is a severe systemic reaction.		
GRADE I	Grade II: A (n = 1)	Grade II-B (n = 1)	GRADE IIIA (n = 0)	GRADE IIIB (n = 2)	GRADE IIIC (n = 1)
6	1	1	0	2	1

Table 1.3: Response Evaluation on the Basis of the RESIST Criteria.

Response Categories	Group I	Group II
Complete Response	2	6
Partial Response	4	4
Minor Response	1	1
Stable Disease	1	1
Progressive Disease	3	3
Total of Complete Responses and Partial Responses	2 (CR) + 4 (PR)	6 (CR) + 4 (PR)
Overall Response Rate	54.55%	66.66%

ISSN: 2327-204X

(36.36%); the mean age was around 5.64 years. On the other hand, Group II is composed of 8 males (53.33%) and 7 females (46.66%); their mean age was 58.4 years.

Group I had 4 patients with follicular lymphoma (36.36%). 2 patients with diffuse B cell lymphoma (18.18%), 1 patient with mantle cell lymphoma (9.09%), 2 patients with NHL-B cell type (18.18%), 1 patient with relapsed NHL (9.09%), and 1 patient with BMT cell lymphoma

Group II had 4 patients with follicular lymphoma (26.6%), 6 patients with diffuse B cell lymphoma (40%), 1 patient with mantle cell lymphoma (6.6%), and 4 patients with NHL-B cell type (Figure 1.2).

We found six (54.5%) local reactions, such as redness, swelling, and pruritus. 2 (18.18%) had mild to moderate reactions related to the skin or GI tract. 3 (27.27%) had severe systemic reactions with respiratory and cardiovascular involvement.

A radiological response criteria (ORR) evaluation was used to assess response after three cycles of Rituximab-based regimens. The incidence of HRs was statistically analysed against pre-treatment peripheral blood markers.

The overall response rate for Group I was 54.55%, and that for Group II was 66.66% [9-16] (Figures 1.3 & 1.4).

Assessment of Tumor Burden Using Response Evaluation Criteria in Solid Tumors (RESIST) (Table 1.3).

Results

Out of 11 patients, 6 (54.55%) had a local reaction, 2 (18.18%) had a mild to moderate reaction, and 3 (27.27%) had severe systemic reactions. Eosinophil and neutrophil ratios were within the normal range; one of the patients' eosinophil counts seemed to be elevated prior to chemotherapy and further elevated after the therapy despite

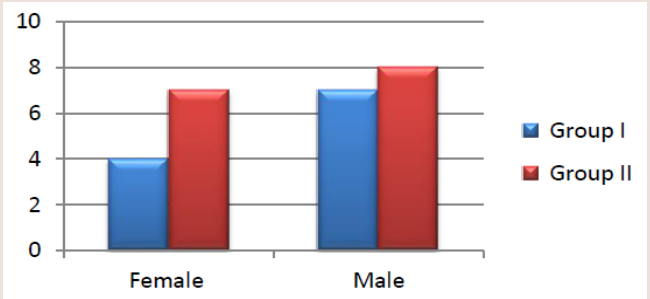

Figure 1.1: Classification on the basis of gender.

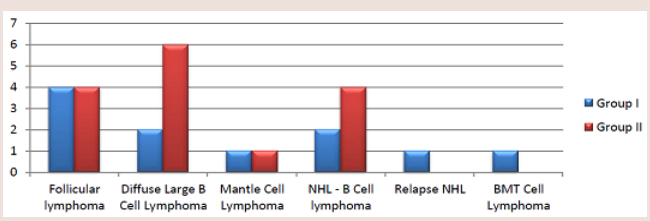

Figure 1.2: Classification on the Basis of Diagnosis.

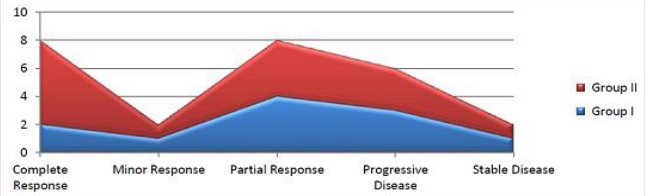

Figure 1.3: Response comparison of Group I and Group II.

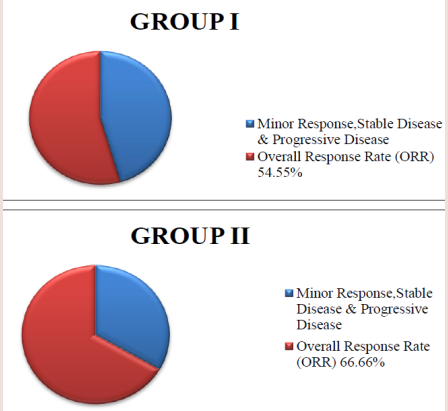

Figure 1.4: Overall response rates of Group I and Group II.

taking all preventive measures. In one case in which a patient had a cardiac arrest, ROSC (return of spontaneous circulation) was achieved within a downtime of 2 minutes; he was intubated, and he subsequently had intermittent prone ventilation. A brain MRI was done and showed hypoxic changes. Neuroprotective measures began. Gradually, the condition worsened. He went into septic shock with triple ionotropic support and refractory hypotension. He had refractory hypoxia. Later, the patient had a cardiac arrest, and he was resuscitated. Despite the best efforts, the patient cannot be revived.

Discussion

Our study shows that the ORR would be around 54.55% in patients with hypersensitivity reactions. Among them, 6 had local reactions, 2 had mild to moderate reactions, and 3 had severe hypersensitivity reactions, of which 1 had respiratory distress, 1 had cardiogenic shock, and 1 had cardiac arrest. We initially collected the data of 89 patients, of whom 34 had hypersensitivity reactions. Because of the patients' destitution, we could not get PETCT reports for subsequent cycles.

According to the study conducted by Amy S. Levin, MD, et al. in a retrospective chart review of all rituximab-related safety reports at the outpatient oncology center, clinical notes using electronic health records were used to gather data, which included all patient demographic characteristics, a history of drug allergies, the reason for receiving Rituximab treatment, the Rituximab dose, the cycle number, and any reactions that occurred [2]. From both safety and clinical reports, they assessed the nature and frequency of premedication, symptoms of the Rituximab reaction, and its management with H1 blockers, H2 blockers, steroids, epinephrine, beta-agonists, and/or intravenous fluids. Lorazepam, 1 mg; paracetamol, 500 mg;

ISSN: 2327-204X

hydrocortisone sodium succinate, IV; and pheniramine, 22.75 mg/ampoule, were used in our study.

The National Cancer Institute's modified National Cancer Institute Common Terminology Criteria for Adverse Event Scale was used to grade Rituximab-related reactions. 63% had a cutaneous reaction (Grade 1), 61% had respiratory symptoms (Grade 2), 10% had dyspnea (Grade 3), and 1 patient had hypotension (Grade 4).

Whereas in our study we used WAO-SAR criteria for the classification of HRs, we found 54.55% had a Grade 1 reaction (local reaction), 18.18% had a Grade 2 reaction (mild to moderate), and 27.27% had a severe systemic reaction. According to their findings, most patients in grades 1 and 2 tolerated rechallenge well; grade 1 patients had a discrete outcome on the same day of rechallenge; and grades 3 and 4 had reactions during rechallenge.

According to the study by Masahiro Yokoyama et al., published in 2013, it showed the maximum tolerable infusion rate of rituximab and determined the safety and feasibility of rapid infusion with CD20+ B-cell lymphoma (CD20+ NHL). A total of 18 patients were included in the study, of whom 5 were male. 2 patients (11%) with DLBCL were receiving R-CHOP therapy; 2 (11%) with indolent lymphoma were receiving R-CVP therapy; and 14 (78%) with indolent lymphoma were receiving Rituximab maintenance therapy. Results showed that a total of 88 cycles of Rituximab were administered. Rapid infusion was well tolerated, with only one grade 3 leukopenia and one grade 4 neutropenia being noticed. Four patients developed grade 1 infusion-related toxicities during the first administration of Rituximab. No patients with severe drug-related events were observed. They determined that the maximum tolerable infusion rate of rituximab is 300 mL/h (under 700 mg/h) and even confirmed that administration lasting over 60 minutes was safe and feasible.

According to the study by S. Novelli et al., published in 2020, they described the 12-step desensitisation protocol for intravenous Rituximab in clinical practice. This study was performed prospectively in clinical practise in 10 patients with a history of severe infusion reactions or in patients who had a repeated reaction at subsequent doses despite taking intensive preventive measures. Skin-prick tests were also performed at the time of the reaction and at a later time to eliminate false negatives due to possible drug interference. The results of this study showed that 70% of the patients were able to complete the scheduled immunotherapy; two patients had to discontinue the therapy due to clinical persistence, and a third due to lymphoma progression. Intradermal tests with 0.1% rituximab were positive in only 20% of the cases, which demonstrated the mechanism of HRs.

Acknowledgements

This work was supported by the Rajiv Gandhi University of Health Sciences, Bangalore, to carry out the research project (Project Code: UG21PHA299). I would like to acknowledge and thank Dr. Jyothi Goutham Kumar and Dr. Priyank Tripathi, Dr. Hrishi V, who made this work possible, as well as the staff at HCG, Bangalore, for their assistance.

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