Infusion Related Hypersensitivity Reactions with Bio-similar Anti CD-20 Monoclonal Antibody Rituximab in Indian Patients: A Retrospective Study

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Abstract There is paucity of data on infusion related hypersensitivity reactions (IRHR) pattern of bio-similar rituximab in B-cell lymphoma patients. As bio-similar molecules are independently developed monoclonal antibodies, they are likely to differ in immunogenicity and therefore, the hypersensitivity data of the innovator rituximab may not be directly applicable to patients treated with the biosimilar rituximab molecule. We analysed our data of 256 patients of B cell lymphoid neoplasm who received bio-similar rituximab (Reditux) based chemo-immunotherapy for their treatment. Total 56/256 (21.8%) patients had $\geq$ grade II IRHR with first dose of rituximab. Grade II reactions were seen in 32/256 (12.5%) cases, grade III and grade IV reactions were seen in 21/256 (8.2%) and 3/256 (1.2%) cases, respectively. Rituximab was withdrawn from all further therapy in only 2 patients due to grade IV IRHR after attempting re-challenge of the drug under intensive monitoring. There was no difference in complete response rates in patients with or without IRHR during their first rituximab infusion. The IRHRs with bio-similar rituximab noted in our study were comparable with the previously published reactions associated with the original rituximab.

Keywords Biosimilar · Rituximab · Infusion · Hypersensitivity · Lymphoma · Drug reactions · India

Introduction

Rituximab is an anti CD-20 chimeric monoclonal antibody. Rituximab based therapies are current standard of care for most B cell lymphoid neoplasm. Over the past decade, its use has widened to other hematologic and immunologic conditions like autoimmune haemolytic anaemia, post-transplant lympho-proliferative disorders, granulomatous polyangiitis, and rheumatoid arthritis leading to regular use of this drug in clinical practice. Majority of the data on rituximab related adverse events were collected during clinical drug trials with the innovator rituximab molecule (Rituxan, Genentech, Inc./Mabthera, Roche). The most commonly observed adverse event with rituximab is infusion related hypersensitivity reaction (IRHR) [1]. IRHRs are usually defined by signs or symptoms experienced by patients during the infusion of monoclonal antibodies or any related event occurring on the first day of drug administration [2, 3].

Currently, the bio-similar rituximab is used frequently in chemo-immunotherapy for B-lymphoid neoplasms in India. There is paucity of data regarding bio-similar rituximab infusion related hypersensitivity reactions in the real-world scenario. Reditux was the first bio-similar anti CD-20 monoclonal antibody manufactured and launched in India by Dr Reddy's laboratories Ltd. To fill the void in knowledge about IRHRs with bio-similar rituximab, we analysed our data of consecutively treated patients of various B-lymphoid neoplasm with Reditux based therapy for incidence and severity of rituximab related hypersensitivity reactions at the time of the first infusion.

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Methods

- The computerised database of lymphoid malignancies at our institute was searched for all the patients treated with rituximab based regimen from January 2012 to April, 2015. All the adult patients (≥ 18 years) who received at least one dose of bio-similar rituximab (Reditux) for any subtype of B-lymphoid neoplasm were included in the study. Data prior to January 2012 was retrieved from case record files. All such files were reviewed and only the files with information about rituximab related reactions were included in the study. The case files without information regarding IRHR were excluded. Hypersensitivity data was collected for all patients who had received at least one dose of rituximab by 15th April, 2015. Only the IRHRs during first dose of rituximab were noted for the current analysis.
- For survival and outcome analysis, patients who have completed their treatment by 15th, April 2015, were included. IRHR were graded as per National Cancer institute—common toxicity criteria v3.0 (Table 1) [2]. All grade II or more IRHR were noted for further analysis. Temperature of > 100.5 °F was taken as notable fever. Chills and rigors were recorded as per patient's description. Hypoxia and hypotension were noted by the nursing team and were recorded accordingly.

Descriptive statistics were used for demographic details and patient's characteristics. Respective parametric and non-parametric tests were used to analyse correlation in between various categorical and continuous variables.

Table 1 CTC v3.0 for infusion related hypersensitivity reactions [2, 3]

Grade of reaction	Definition
1	Mild reaction; infusion interruption not indicated; intervention not indicated
2	Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h
3	Prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g. renal impairment, pulmonary infiltrates)
4	Life-threatening; pressor or ventilatory support indicated
5	Death

Results

Data of 256 patients were retrieved from computerised database. The median age of the patients was 56 years (range 18–82 years) and the male to female ratio was 1.7:1.

Most common indication of using rituximab was DLBCL (45.7%) followed by CLL/SLL (15.6%) and FL (14.8%). Maximum incidence of IRHR was noted for patients with mantle cell lymphoma, at 29%. Number of patients with IRHR treated for other subtypes of B lymphoid neoplasm was small and the same is represented in Table 2.

Total 56/256 (21.8%) patients had $\geq$ grade II IRHR with the first dose of rituximab. Grade II reactions were seen in 32/256 (12.5%) cases, grade III and grade IV reactions were seen in 21/256 (8.2%) and 3/256 (1.2%) cases, respectively. Amongst the 56 cases who developed such reactions, chills and rigors were the most common form of hypersensitivity (80.8%) and fever was noted in only 7 (27%) cases. Both of these hypersensitivity reactions could be controlled with rescue medications like hydrocortisone, H1 and H2 receptor antagonists and paracetamol in all but 2 patients. Respiratory system related hypersensitivity reactions (airway paraesthesias, tightness in the chest, wheezes and hypoxia) were noted in 10 (38%) cases collectively. (For breakup of these reactions—refer to Table 3).

Only two patients developed hypotension during the infusion of rituximab and none of them had underlying cardiac disease. They required immediate high dependency unit hospitalisation and fluid resuscitations. One patient also needed vaso-pressor support. The hypotension improved in both of these patients subsequently. Rituximab was omitted from all further chemotherapy courses for the patient who needed inotropic support for hypotension. In case of the other patient with hypotension, rituximab was re-challenged under intensive care monitoring. There were recurrence of hypersensitivity and chest discomfort. Subsequently this patient was also taken off from further rituximab therapy. Acute anaphylactic reaction leading to discontinuation of treatment with rituximab was observed only in these 2 patients in the whole study cohort.

Median duration of presenting symptoms in patients experiencing IRHR was 3 months while the patients who did not experience IRHR presented with median duration of symptoms of 4.5 months. At the end of the treatment, complete remission rates were 62% in patients with IRHR and 60% in patients without IRHR. Eight percent patients in IRHR patient group died while in the patients without IRHR death rate was 16%. These differences were, however, not statistically significant.

Table 2 Distribution of cases of various B-lymphoid neoplasms

Diagnosis	N	No IRHR, N (%)	> grade I IRHR, N (%)
DLBCL	117	109 (93)	8 (7)
FL	38	34 (89)	4 (11)
CLL/SLL	40	34 (85)	6 (15)
MZL	15	15 (100)	0
MCL	14	10 (71)	4 (29)
BNHL-NOS	12	10 (83)	2 (17)
LPL	7	6 (85)	1 (15)
PTLD	5	5 (100)	0
NLPHL	5	4 (80)	1 (20)
Castleman's disease	3	3 (100)	0
Total	256	230 (89)	26 (11)

BNHL-NOS B cell Non Hodgkin's Lymphoma Not Otherwise Specified, *CLL* Chronic Lymphocytic Leukemia, *DLBCL* Diffuse large B cell Lymphoma, *FL* Follicular Lymphoma, *LPL* Lymphoplasmacytic Lymphoma, *MCL* Mantle cell Lymphoma, *MZL* Marginal Zone Lymphoma, *NLPHL* Nodular Lymphocytic Predominant Hodgkin's Lymphoma, *PTLD* Post Transplant Lymphoproliferative Disorder, *SLL* Small Lymphocytic Lymphoma

Table 3 Incidence and types of IRHRs with bio-similar rituximab

Type of hypersensitivity reactions	N (%)
Chills and rigors	21 (80.8)
Fever > 100 °F	7 (27)
Cutaneous rash	1 (3.8)
Laryngeal paraesthesia	2 (7.6)
Feeling of tightness in the chest	3 (11.5)
Hypoxia (requiring O ₂ supplementation)	5 (19.2)
Hypotension	2 (7.6)

The reactions are not mutually exclusive, often patient had more than one type of reactions

We tested many variables like age, gender, poor PS, presence of B symptoms, differential white cell counts, stage of the disease, biochemical parameters and response to therapy, as a predictive marker for IRHR with rituximab. However, none of these parameters was found to be significantly associated with the higher incidence of IRHRs (Table 4).

Discussion

Rituximab is a genetically engineered chimeric monoclonal antibody and it contains component of both murine and human origin. The variable light- and heavy-chains originate from murine anti-CD20 antibody IDEC-2B8 and the human IgG1 contributes Fc portion, constant parts of the heavy chain and kappa (light-chain) [4]. Xeno-graphic property of the murine part lead to activation of both type 1

or type 2 hypersensitivity reaction at the time of infusion. Apart from immune response, many non-immune mechanisms play their part in pathogenesis of IRHRs and one of them is rapid lysis of B-cells leading to sudden release of pyrogenic triggers.

Due to significant difference in the cost of treatment, the use of bio-similar rituximab is increasing in the developing parts of the world and it has potential to increase even further in the years to come. In a study published from a tertiary care cancer centre in India, only 18% patients received rituximab based therapy between the years 2007 and 2009 [5]. On the contrary, we have noted significant increment in rituximab use for lymphoid malignancies as approximately 58% patients received rituximab based treatment during the 3.5 years of study period. We believe that this significant rise in rituximab use can be attributed to the following two reasons. First, with the availability of many bio-similar rituximab in the last decade there is significant reduction in the cost of treatment with rituximab based regimen, thereby, larger numbers of patients are able to afford rituximab based chemo-immunotherapy. Secondly, with each passing year, wider coverage of medical insurance schemes, government funded patient assistance programs; along with improvement in overall economic status of patients in India has improved access to relatively expensive drugs like rituximab.

At our centre, cancer care and treatment is provided free of cost, however the drugs required for the treatment are purchased by the patient. Due to significant difference in the cost of therapy between original and bio-similar rituximab, majority of the patients preferred to receive bio-similar brands of rituximab. The bio-similar monoclonal antibodies are independently developed molecules; they

Table 4 Variables as predictor of higher IRHRs with bio-similar rituximab

SN	Variables	Patients experiencing IRHR	Patients not experiencing IRHR	P-value
1	Age, median (range) years	56 (22–73)	55.5 (18–82)	NS
2	Gender M:F	14:11	147:84	
3	Duration of symptom median (months)	1:180	1:72	
4	PS-ECOG III/IV	24%, 8:34	16%, 38:243	
5	B symptoms	64%	55%	
6	Bulky disease	13.8%	14.1%	
7	Extra-nodal disease	38%	49%	
8	Hemoglobin mean (SD)	10.6 (2.62)	11.0 (2.63)	
9	WBC median	8900	7900	
10	Neutrophil median % (mean)	49.6 (23.3)	57.6 (20.2)	
11	Lymphocyte median % (mean)	46 (25)	33.8 (20.5)	
12	Stage III/IV	84%	70%	
13	Fever	35%	25%	
14	Monocytes median %	4.6%	4.3%	
15	Eosinophil counts median % (mean)	2.7%	2.8%	
16	Albumin mean (SD)	4.0 g/dl (0.88)	4.0 g/dl (0.71)	
17	LDH mean (SD)	733 IU/dl (1354)	509 IU/dl (409)	
18	IPI 3–5	35%	27%	
19	LDH higher than normal	61.7%	58.6%	
20	Interim assessment CR	40%	30%	
21	Final assessment CR	60%	62%	

Table 5 Comparison of IRHRs between original rituximab and bio-similar rituximab

IRHRs	Current study with bio similar rituximab	Published literature with original rituximab [9, 12]
Grade I	Not reported	50–87%
Grade II	13.9%	
Grade III	10.4%	< 10%
Grade IV		
Commonest reaction	Chills and rigors	Fever

differ in bio-chemical structure as well as antigenicity. Thereby, they are also likely to differ in the immune response surmounted by them in a patient which mostly presents as infusion related hypersensitivity reactions. With increasing use of bio-similar monoclonal antibodies, it is imperative to look for patterns of this very common side effect of rituximab.

In literature, most infusion reactions were reported to be mild and self-limiting. As per clinical studies with rituximab, more than half of the patients treated with rituximab develop IRHRs. However, 80–90% of these reactions were either grade I or grade II as per NCI common toxicity criteria. Majority of these reactions occurred during the first hour of starting infusion [6, 7].

One characteristic of IRHR noted in our data was lack of dermatologic reaction. Common, dermatologic hypersensitivity reaction associated with rituximab is

urticarial rash. As per the manufacture, [8] mucocutaneous reactions, can occur in patients treated with Rituxan. These dermatologic reactions include paraneoplastic pemphigus, Stevens–Johnson syndrome, lichenoid dermatitis, vesiculo-bullous dermatitis, and toxic epidermal necrolysis. In the published literature incidence of cutaneous reactions with rituximab is 10–13% [9]. Only one patient in our study had such reaction. We could not point out the exact reason of lesser incidence of dermatologic side effects in our patients. However, the reason may lie in the different immunogenicity of a bio-similar molecule.

Higher incidence of IRHRs are reported in patients with high tumour burden and high TLC [10, 11] But we did not find similar trend in B Lymphoma possibly because the published studies linking high TLC and higher infusion reactions were reported in CLL patients and in our study

CLL patients comprised of only 15% of the total study population.

On comparing our data of IRHR with bio-similar rituximab with the original rituximab brand we found that the grade III/IV IRHR incidence with reditux were at par with the original rituximab (Table 5).

We tried to find any clinical or laboratory predictor of IRHRs with rituximab but none of the clinical features or common lab parameters could correlate with incidence of IRHR, significantly. The small number of patients in our study can be one reason of this lack of significance. However, idiosyncratic nature as well as non-immune reactions as one of the major mechanism behind IRHR may also make it unpredictable in nature.

One limitation of our study is lack of data on grade I IRHRs. Since grade I reactions are mild and self-limiting, their incidence was not optimally captured. Therefore, we omitted that data from our analysis. The limitations associated with a retrospective analysis were also inherent in this study.

Conclusion

Use of bio-similar rituximab in B-NHL Indian patients in the real-world scenario was not associated with higher grade III/IV infusion related hypersensitivity reactions. There is a need of multicentre collection of meticulous data on toxicity of these newer bio-similar monoclonal antibodies to identify their variance with the original drug and to find predictors of IRHRs so that extra caution can be exercised in high risk cases.

Compliance with Ethical Standards

Conflict of interest There are no potential conflict of interest of authors writing this article.

Research Involving Human Participants and/or Animals This is a retrospective data analysis and does not involve any human or animal intervention or experiment.

Informed Consent Informed consent was obtained before data analysis from participating subjects.

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