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Research Article

IMMEDIATE ADVERSE DRUG EVENTS WITH RITUXIMAB THERAPY IN NON-MALIGNANT HEMATOLOGICAL DISORDERS

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ABSTRACT

Objective: Rituximab therapy has become a promising therapeutic option for various non-malignant hematological disorders, after being reported by many case reports. The objective of this study was to evaluate the immediate, infusion-related adverse drug events (ADE) of patients who received rituximab for non-malignant, hematological disorders, in a tertiary healthcare center in India.

Methods: 14 patients (6 with primary immune thrombocytopenia, 4 with autoimmune hemolytic anemia, 3 with thrombotic thrombocytopenic purpura, 1 with acquired hemophilia) were enrolled in the study. Patients were assessable for immediate infusion-related toxicity noted predominately within 5 hrs of administration of rituximab infusion.

Results: Rituximab therapy was tolerated without major ADE. None of the patients experienced high-grade adverse events. The population who experienced ADE (Grades 1-2) frequently had toxicities that suspected to result from infusion-related cytokine release syndrome (IRCRS) and sometimes required cessation of the infusion and supportive intervention. Patients were monitored for 20 types of ADEs associated with IRCRS. 11 types of; mild to moderate (Grades 1 and 2) toxicities resulting from IRCRS were experienced by patients. Mean patients who experienced IRCRS was 1.95 (13.93%), whereas majority of the study population tolerated therapy without IRCRS (86.78%). Among other toxicities, Grade 2 urinary tract infection (UTI) (n=2, 14.29%); Grade 2 hyperglycemia (n=1, 7.14%) and Grade 1 myalgia (n=1, 7.14%) were observed.

Conclusion: Toxicity profile of patients with non-malignant hematological disorders shows that rituximab is a safer biological therapy.

Keywords: Rituximab, Infusion related cytokine release syndrome, Adverse drug events, Immediate toxicities, Benign, Non-malignant, Hematological disorders.

INTRODUCTION

Rituximab is a chimeric mouse-human monoclonal antibody against the CD20 antigen on the surface of B lymphocytes. It binds to CD20 and causes B cell death by antibody dependent cell-mediated cytotoxicity, complement mediated cytotoxicity and apoptosis. It leads to rapid and sustained depletion of B-cells [1]. Although licensed for use in adults with CD20 positive B-cell lymphoma and rheumatoid arthritis, it has also been used in a variety of off-label indications with promising results. It has proved useful as salvage therapy in relapsed/refractory non-Hodgkin's lymphoma and leukemia, and in hematological conditions including chronic immune thrombocytopenic purpura, hemophilia with inhibitors, and autoimmune hemolytic anemia [2]. Rituximab therapy has become a promising therapeutic option for various non-malignant hematological disorders, after being reported by many case reports. However, the toxicity profiles of rituximab among non-malignant hematological disorders were not extensively investigated. The objective of this study was to evaluate the immediate, infusion-related adverse drug events (ADE) of patients who received rituximab for non-malignant, hematological disorders, in a tertiary healthcare center in India.

METHODS

This study was undertaken after obtaining permission from Institutional Thesis Review Committee. Informed consent to the study was obtained from the patients.

Rituximab-related toxicity was assessed during the administration of the drug. All 14 patients enrolled in the study were assessable for immediate infusion-related toxicity noted predominately within 5 hrs of administration of rituximab infusion. The severity of ADE was graded according to the National Cancer Institute common terminology criteria for adverse events (AE) version 3.0.

Fourteen patients (6 with primary immune thrombocytopenia, 4 with autoimmune hemolytic anemia, 3 with thrombotic thrombocytopenic purpura, 1 with acquired hemophilia) treated with rituximab were evaluated.

RESULTS

Rituximab therapy was tolerated without major ADE. None of the patients experienced high-grade AE. The population who experienced ADE (Grades 1-2) frequently had toxicities that suspected to result from infusion-related cytokine release syndrome (IRCRS) and sometimes required cessation of the infusion and supportive intervention. Patients were monitored for 20 types of ADEs associated with IRCRS.11 types of; mild to moderate (Grades 1 and 2) toxicities resulting from IRCRS were experienced by patients. Mean patients who experienced IRCRS was 1.95 (13.93%) whereas the majority of the study population tolerated therapy without IRCRS (86.78%). Among other toxicities, Grade 2 urinary tract infection (UTI) (n=2, 14.29%); Grade 2 hyperglycemia (n=1, 7.14%) and Grade 1 myalgia (n=1, 7.14%) were observed.

DISCUSSION

Patients enrolled in our study demonstrated an acceptable toxicity profile with rituximab administration. Adverse effects to rituximab can be classified as immediate, acute and delayed. Immediate reactions are infusion reactions. Their incidence is about 25% [2]. Despite the

Table 1: Immediate toxicities in benign hematological disorders

S. No	Toxicity	n (%)			
		Frequency and percentage of ADE (Grading of ADE by CTCAE scale)			Overall patients (Grades 1-5) who
		Grade 1	Grade 2	Grades 3-5	Experienced ADE
	ADE related to IRCRS				
1	Shivering	4 (28.6)	0 (0)	0 (0)	4 (28.6)
2	Rashes	0 (0)	2 (14.3)	0 (0)	2 (14.3)
3	Itching	0 (0)	2 (14.3)	0 (0)	2 (14.3)
4	Cough	0 (0)	0 (0)	0 (0)	0 (0)
5	Breathing difficulty	1 (7.1)	0 (0)	0 (0)	1 (7.1)
6	Fatigue	1 (7.1)	4 (28.8)	0 (0)	5 (35.7)
7	Dizziness	0 (0)	0 (0)	0 (0)	0 (0)
8	Tachycardia	0 (0)	0 (0)	0 (0)	0 (0)
9	Chest pain	1 (7.1)	0 (0)	0 (0)	1 (7.1)
10	Chills	7 (50)	0 (0)	0 (0)	7 (50)
11	Rigor	3 (21.4)	0 (0)	0 (0)	3 (21.4)
12	Fever	2 (14.3)	2 (14.3)	0 (0)	4 (28.6)
13	Hypotension	0 (0)	0 (0)	0 (0)	0 (0)
14	Rhinitis	5 (35.7)	1 (7.1)	0 (0)	6 (42.9)
15	Dyspnoea	0 (0)	0 (0)	0 (0)	0 (0)
16	Sweating	0 (0)	0 (0)	0 (0)	0 (0)
17	Erythema	0 (0)	0 (0)	0 (0)	0 (0)
18	Throat discomfort	4 (28.6)	0 (0)	0 (0)	4 (28.6)
19	Hot flushes	0 (0)	0 (0)	0 (0)	0 (0)
20	Body pain	0 (0)	0 (0)	0 (0)	0 (0)

ADE: Adverse drug events, IRCRS: Infusion related cytokine release syndrome, CTCAE: Common terminology criteria for adverse events

fact that rituximab is a safer biological therapy, there were odd reports of patients with high-grade AE [3]. In contrast, none of our patients experienced any type of high-grade ADE.

Monitoring for ADE among our patients showed that most ADE associated with therapy arise due to the development of infusion-related cytokine release syndrome which was manageable (Table 1). The first infusion often causes a syndrome of chills, fever, headache, and occasional dyspnea, nausea, pruritis, angiedema, or hypotension [4,5]. Although not always mentioned in the different reports, the incidence of infusion-related side effects seems to be comparable in immune-mediated disorders [6]. In the systematic review by Arnold *et al*., 21.6% of the patients showed mild to moderate AE, of which 83.3% were infusion-related [7]. Although rare, life-threatening symptoms such as bronchospasm, angioedema, hypoxia, and shock have been described. However, in our patients' high-grade toxicities related o IRCRS were not observed.

A few patients had moderate grade UTI, hyperglycemia, and myalgia (Table 2). Infectious AE reported in post-marketing surveillance include an increase in the incidence of UTI by 6%. Musculoskeletal AE have been reported with rituximab, although it should be noted that myalgia has been associated with reactions related to the infusion that can be severe and/or fatal. In clinical trials, AE reported include asthenia (26%; 2% combination trials), myalgia (10%), arthralgia (10-13%; 6-12% combination trials), and muscle spasms (17%) [1].

Table 2: Immediate toxicities in benign hematological disorders

S. No	Toxicity	n (%)			
		Frequency and percentage of ADE (Grading of ADE by CTCAE scale)			Overall patients (Grades 1-5) who
		Grade 1	Grade 2	Grades 3-5	Experienced ADE
	Other adverse drug events				
21	Nausea	0 (0)	0 (0)	0 (0)	0 (0)
22	Vomiting	0 (0)	0 (0)	0 (0)	0 (0)
23	UTI	0 (0)	2 (14.3)	0 (0)	2 (14.3)
24	Ulcers	0 (0)	0 (0)	0 (0)	0 (0)
25	Blisters	0 (0)	0 (0)	0 (0)	0 (0)
26	Skin peeling	0 (0)	0 (0)	0 (0)	0 (0)
27	Head ache	0 (0)	0 (0)	0 (0)	0 (0)
28	Seizure	0 (0)	0 (0)	0 (0)	0 (0)
29	Hypoglycemia	0 (0)	0 (0)	0 (0)	0 (0)
30	Hyperglycemia	0 (0)	1 (7.1)	0 (0)	1 (7.1)
31	Myalgia	1 (7.1)	0 (0)	0 (0)	1 (7.1)
32	Cyanosis	0 (0)	0 (0)	0 (0)	0 (0)
33	Abdominal cramps	0 (0)	0 (0)	0 (0)	0 (0)

ADE: Adverse drug events, UTI: Urinary tract infection, CTCAE: Common terminology criteria for adverse events

However, reactivation of hepatitis B infection, as mentioned by some case reports, was not observed in our patients.

CONCLUSION

Toxicity profile of non-malignant hematological disorders treated with rituximab reveals that this chimeric monoclonal antibody may be a relatively safer biological therapy. Immediate, infusion-related toxicities were low grade, without requiring interruption of infusion administration. The majority of the observed AE were attributed to cytokine release syndrome associated with administration of therapeutic monoclonal antibodies.

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