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Rituximab Desensitization in Three Patients With Severe Rituximab Allergy

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Abstract

Rituximab is a chimeric monoclonal antibody that targets CD20 positive B cells and has a positive effect on both overall and progression-free survival in B cell lymphoid malignancies. Combination rituximab with chemotherapy treatment provide survival improvement. Although rituximab is an important treatment option in hematological malignancies, the risk of allergic reactions is high. These reactions are usually IgE-mediated and can be varied in regards of severity from urticaria to anaphylaxis. It is an option to interrupt the treatment and omit rituximab therapy who had allergic reactions. Drug desensitization is another option and successful results have been reported by applying desensitization to such reactions. Drug desensitization alters the immune response to induce a state of temporary clinical tolerance to the allergic drug by giving gradual increasing of doses of drug at fixed time intervals. Herein we present 3 cases successfully treated with rituximab desensitization. The cases were using rituximab with the diagnosis of Burkitt lymphoma, follicular lymphoma and marginal zone lymphoma, respectively. Two cases had grade 2, one case had grade 3 systemic allergic reaction with rituximab. There was no known allergy history in all three cases. All patients tolerated the desensitization protocol. The subsequent treatments of the patients were also given by desensitization protocol. A total of 12 desensitizations were administered to 3 cases. No severe or life-threatening reactions were observed in subsequent applications. To date applying desensitization protocols ensure rituximab treatment safely. Rituximab desensitization can be performed at trained allergy centers and it may be an appropriate option for rituximab allergic patients.

Keywords: Biologic, desensitization, drug allergy, Non-Hodgkin's lymphoma, rituximab

Introduction

B cell lymphoproliferative neoplasia are the most common hematological malignancies in adults. Diffuse large B-cell lymphoma, follicular lymphoma and mantle cell lymphoma are the main subtypes of B-cell lymphoma [1]. Monoclonal antibodies targeting CD20 are a key component of therapy for B cell neoplasia. Rituximab is a chimeric monoclonal antibody binding to the CD20 antigen present on B cells, and one of the back-bone treatment option with chemotherapy combinations. The addition of rituximab to chemotherapy has led to a significant improvement in survival of patients with CD20 (+) B-cell neoplasia, especially for chronic lymphocytic leukemia, diffuse large B-cell lymphoma and follicular lymphoma [2-4]. Although rituximab is an effective biological agent in non-Hodgkin's lymphoma it may cause acute infusion-related allergic reactions frequently with the rate of 5-10% [5, 6]. Reactions can vary in regards of severity from urticaria to life-threatening anaphylactic reactions. Up to 77% of the transfusion reactions and 80% of fatal reactions occur with the first dose of the drug [6]. Premedication with acetaminophen, antihistamines, and corticosteroids is typically recommended. However allergic reactions can also occur under premedication and the administration of rituximab in non-Hodgkin's lymphoma may be restricted due to these allergic reactions.

Desensitization is a procedure that alters the immune response to induce a state of temporary clinical tolerance to the allergic drug by giving gradual increasing of doses of drug at fixed time intervals [7]. It is generally preferred by experienced centers when alternative treatment options are not available or significantly risky for the patient's health condition. It is effective in patients presenting with IgE-mediated early onset allergy symptoms including anaphylaxis.

In late drug reactions like Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness or hemolytic anemia drug desensitization cannot be applicable [7]. There is adequate experience on drug desensitization protocols for antibiotic or aspirin allergy. However, the experience with rituximab desensitization is limited. Herein, we report three patients with non-Hodgkin's lymphoma having a history of rituximab related severe allergic reaction who were treated successfully with rituximab in our hematology clinic in collaboration with allergy clinic.

Case 1

A 37-year-old male with Burkitt lymphoma received DA-EPOCH-R (Etoposide, methylprednisolone, vincristine, cyclophosphamide, doxorubicin, rituximab) protocol and developed a pruritus, throat itching, hoarseness and swollen uvula after 1.5 hour of rituximab injection. The reaction occurred at the first injection of rituximab and he had previously received diphenhydramine, acetaminophen and methylprednisolone for premedication. The infusion was stopped and edema of the uvula was relieved after systemic steroid and diphenhydramine treatment. There was no tachycardia, hypotension, hypoxia and fever. He had no any allergic disease and drug allergy in his medical history. His reaction was classified as grade 2 according to the Brown Classification, which indicates a moderate systemic hypersensitivity reaction [8]. There was no alternative therapy to rituximab and a 12-step rapid drug desensitization protocol was planned for the patient. He was premedicated with H1 and H2 blockers, montelukast sodium with systemic steroids and was desensitized by an experienced allergist and nurses according to established protocols (Table 1). No life-threatening allergic reaction occurred during the procedure, and he received his full target dose without any allergic reaction. Future four treatments also were given with rapid desensitization safely.

Case 2

A 39-year-old male with follicular lymphoma received treatment with rituximab and bendamustine. Rituximab infusions were premedicated with diphenhydramine, acetaminophen and methylprednisolone. The first infusion was uncomplicated, but during the second infusion, he developed a diffuse erythematous rash, and dyspnea which resolved with diphenhydramine, methylprednisolone. He had no any allergic disease and drug allergy in his medical history. His reaction was defined as grade 2 systemic allergic reaction [8]. For the subsequent infusions, a 12-step rapid drug desensitization protocol was planned for the patient. He was premedicated with H1 and H2 blockers, montelukast sodium with systemic steroids and he desensitized according to protocol safely. At the second day of desensitization he had mild erythema and fatigue which was controlled with antihistamines. He received other 3 rituximab infusions with a 12-step rapid drug desensitization protocol and mild erythema was occurred on the following day of each desensitization.

Case 3

A 60-year-old male received rituximab and chemotherapy combination for marginal zone lymphoma with diffuse large B cell lymphoma transformation. Hypotension, flushing and incontinence occurred at the first injection of rituximab and he had previously received diphenhydramine, acetaminophen and methylprednisolone for premedication. Infusion was stopped and adrenaline was required for anaphylaxis. His reaction was defined as Grade 3 severe systemic allergic reaction. He had diabetes, ischemic heart disease and chronic obstructive lung disease. He was using beta blocker for heart disease which is associated with an increase in the severity and incidence of acute anaphylaxis [9]. He had no additional allergic disease or drug allergy history. There was no alternative therapy to rituximab and a 16-step rapid drug desensitization protocol was chosen and realized in intensive care unit because of the severity of the initial reaction. Additionally, we had to carry on beta blocker during desensitization that may also potentially make anaphylaxis more difficult to treat by

exogenous epinephrine. He was premedicated with H1 and H2 blockers, aspirin, montelukast sodium with systemic steroids (Table 2). He tolerated rituximab desensitization and he also received other 5 rituximab infusions with drug desensitization protocol without any allergic complication.

Discussion

Rituximab is a most important therapeutic option for hematological malignancies and its use is increasing in routine practice. Therefore, anaphylaxis and life-threatening allergic reactions are reported accordingly. This report describes our experience with 12 desensitizations in 3 patients receiving treatment with rituximab. Desensitization was highly successful and safe in moderate to severe allergic reactions and all 3 patients were completed their therapy without omitting rituximab.

We used a 12-step and a 16-step protocols according to severity of allergic reactions described by Castells MC, et al. [5, 10]. All desensitization applications were performed with one-to-one nursing after obtaining informed consent in a chemotherapy inpatient unit or intensive care unit setting. Rescue medications including intramuscular epinephrine, oxygen, intravenous diphenhydramine, methylprednisolone and nebulized albuterol were available at the bedside. Brennan BJ, et al performed 55 rituximab desensitization applications to 14 patients reacted with mild cutaneous reactions. Immediate reactions were observed after the 7th step of desensitization and only one reaction was delayed occurring within 24 hours [5]. The case series in adults and children also did not report any complication after rituximab desensitization [11, 12]. Bavbek S. et al performed 89 desensitization applications to 14 patients who had moderate to severe systemic reactions to rituximab [13]. They observed 12 (13.5%) allergic reactions in 9 patients during desensitization. Except for one grade 3 reaction treated with epinephrine, most of the reactions were grade I. Of the reactions, 55.5% were cutaneous, followed by cardiovascular (33.3%), respiratory (22.2%), and gastrointestinal

(11.1%) symptoms. Reactions mainly occurred between 9th to 12th steps of desensitization. So far, any uncontrolled allergic reaction or death was reported due to desensitization. We only observed a mild delayed erythema in one patient on the day after the completion of desensitization. The same reaction was repeated at subsequent infusions and was well controlled with antihistamine therapy.

Allergy symptoms can occur most commonly during the first administration of rituximab, but sometimes patients can develop allergy after tolerating some infusions. In the Brennan BJ. et al study, 11 of the 14 patients had a reaction during the first administration of rituximab [5]. In the Bavbek S et al study, 12 of 14 patients had reactions during their first infusion of rituximab. Other 2 patients had reactions during their 4th infusion of rituximab [13]. In our report, 2 of 3 patients had reactions during the first administration of the drug and the other one had the reaction during second infusion. The majority of early drug reactions occur within minutes to a few hours after the administration of a drug previously well-tolerated. Sometimes these reactions may happen during the first dose of the drug like rituximab.

Most of the IgE-sensitized patients presenting reactions to drugs have a positive skin test to this medication [7]. Skin testing helps to confirm the diagnosis and to risk stratification of desensitization. They are recommended at least 3 weeks after the initial reaction to avoid false-negative results [5]. However, skin testing was not performed on our patients. Because the treatment with rituximab for malignancy was urgent and the waiting period would interrupt the patient's treatment. The increase in the tryptase level indicates a hypersensitivity reaction due to IgE and obtaining tryptase level immediately following the reaction might be helpful in diagnosing IgE mediated allergy. But tryptase level were not obtained by the physicians taking care of our patients during the acute reaction. Absence of skin testing and tryptase level of our patients is the limitation of our report.

Most patients treated with monoclonal therapeutics require interval drug administration. The patient's hypersensitivity to the medication returns back after discontinuation of medication. So, each treatment should be administrated by desensitization protocols. We used a single-day desensitization for each treatment and completed 12 desensitizations for 3 patients safely. We used the initial protocols for the subsequent infusions and all patients were desensitized by an experienced allergist and nurses. Levin ES et al rechallenged 51 of 67 patients at the same day as their initial rituximab reaction [14]. Most patients with a grade 1 reaction tolerated the rechallenge. But four patients with a grade 3 reaction had a reaction during rechallenge. Our patients had moderate or severe allergic reactions with rituximab and we did not rechallenge our patients at the same day. We waited for at least 48 hours to start desensitization in our patients.

In conclusion, rituximab is an important drug for the treatment of B cell lymphoma and desensitization protocols can be used in experienced allergy centers. Rituximab desensitization provides a safe and effective treatment option to patients with non-Hodgkin's lymphoma who had hypersensitivity reactions to rituximab.

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Table 1: A 12 step rituximab desensitization protocol

Step	Solution	Rate(ml/h)	Time (min)	Dose (ml)	Dose (mg)	Total Dose (mg)
1	1	2	15	0.5	0.0148	0.0148
2	1	5	15	1.25	0.037	0.0518
3	1	10	15	2.5	0.074	0.1258
4	1	20	15	5	0.148	0.2738
5	2	5	15	1.25	0.37	0.6438
6	2	10	15	2.5	0.74	1.3838
7	2	20	15	5	1.48	2.8638
8	2	40	15	10	2.96	5.8238
9	3	10	15	2.5	7.3418	13.166
10	3	20	15	5	14.684	27.849
11	3	40	15	10	29.367	57.216
12	3	80	173.36	230.5325	682.78	740
Target dose : 740 mg rituximab Total Time : 339.4 minutes Solution 1 : 250mL, 5% dextrose, at 0.0296 mg/mL concentration. Solution 2 : 250mL, 5% dextrose, at 0.296 mg/mL concentration. Solution 3 : 250mL, 5% dextrose, at 2.96 mg/mL concentration. Premedication : 20 minutes before pheniramine 45.5mg IV, methylprednisolone 80 mg IV, montelukast Na 10 mg 1x1 po, levocetirizine 5 mg 1x1 po and ranitidine 50mg IV.						

Table 2: A 16 step rituximab desensitization protocol

Step	Solution	Rate (ml/h)	Time (min)	Dose (ml)	Dose (mg)	Total dose (mg)
1	1	0.5	15	0.125	0.00035	0.00035
2	1	1	15	0.25	0.0007	0.00105
3	1	2	15	0.5	0.0014	0.00245
4	1	4	15	1	0.0028	0.00525
5	2	1	15	0.25	0.007	0.01225
6	2	2	15	0.5	0.014	0.02625
7	2	4	15	1	0.028	0.05425
8	2	8	15	2	0.056	0.11025
9	3	2	15	0.5	0.14	0.25025
10	3	4	15	1	0.28	0.53025
11	3	8	15	2	0.56	1.0902
12	3	16	15	4	1.12	2.2102
13	4	4	15	1	2.7912	5.0014
14	4	10	15	2.5	6.9779	11.979
15	4	20	15	5	13.956	25.935
16	4	40	362.25	241.5	674.06	700
Target dose :700 mg rituximab Total Time :587 minutes Solution 1 : 250mL, 5% dextrose, at 0.0028mg/mL concentration. Solution 2 : 250mL, 5% dextrose, at 0.028 mg/mL concentration Solution 3 : 250mL, 5% dextrose, at 0.28 mg/mL concentration Solution 4 : 250mL, 5% dextrose, at 2.7912 mg/mL concentration Premedication: 20 minutes before pheniramine 45.5mg IV, aspirin 300 mg 1x1 pomethylprednisolone 80 mg IV, montelukast Na 10 mg 1x1 po, levocetirizine 5 mg 1x1 po and ranitidine 50mg IV.						