Incidence of Infusion-related Reaction to Monoclonal Antibody Rituximab: A National Kidney and Transplant Institute Experience

Dear Editor,

The advent of rituximab to standard therapy dramatically increased the overall survival of CD20 positive oncologic and haematologic malignancies.[1] Incidence of infusion-related reaction to rituximab is high, as high as 77% for the first infusion.[2] Reactions can be mild from simple rashes, to potentially life-threatening anaphylaxis. The objective of this paper is to determine the incidence of infusion reactions to rituximab, premedications used, and management given for these reactions.

This is a retrospective study involving chart review of patients admitted at the National Kidney and Transplant Institute (NKTI) for rituximab administration from January 2005 to May 2011. Demographic profile and premedications used (dexamethasone, acetaminophen, antihistamines) were obtained. Incidence of infusion reactions was determined, as well as the corresponding management. Infusion reactions were graded according to the National Cancer Institute (NCI) Criteria for Toxicity version 3. Research protocol was approved by the review board of the NKTI. Categorical variables were expressed using descriptive statistics (percentages) and continuous variables were expressed as median and range. Fisher's Exact Test was done to determine whether there exists a difference between those with reactions and those without. Statistical analysis was carried out using SAS version 9 (SAS Institute, NC, USA). *P* value <0.05 was considered significant.

Forty-six patients were included, with a median age of 56 years (range 23 to 83). There were 22 males and 24 females, and the mean performance status was Eastern Co-operative Group (ECOG) 1 (range 0 to 3). Diffuse Large B Cell Lymphoma (DLBCL) was the most common diagnosis with 36 patients (78.27%) followed by Burkitt lymphoma and chronic lymphocytic leukemia (CLL) with 3 patients (6.52%) each.

There were 5 patients who developed infusion reactions with rituximab. Infusion events occurred in 5 out of 46 patients (10.86%) during the study period. All reactions occurred in the first infusion of rituximab. Three out of the 5 patients were diagnosed with DLBCL and were given R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), while the remaining 2 patients were diagnosed with CLL and were given RFC (rituximab, fludarabine, cyclophosphamide) protocol. Four patients had grade II reaction and one patient had grade I reaction according to the NCI Toxicity criteria. All reactions occurred in the first 30 minutes of infusion. Patients experienced chills, fever, and rashes. All symptoms resolved within 30 minutes. Management included infusion interruption, hydrocortisone, acetaminophen, and diphenhydramine. Rituximab rechallenge was successful, with all the patients able to complete infusion.

Table 1 shows the risk profile and premedications given to the patients. Comparing those who developed reactions to those that did not, only the use of ranitidine showed a statistical significant difference (*P* = 0.0199).

Table 1. Demographics and Premedications by Outcome

Variable	With Reaction n = 5 (%)	Without Reaction n = 41 (%)	*P* value
Age (median = 58, range = 23 to 83 years)			
ECOG			0.488
0	2 (4.35)	7 (15.22)	
1	2 (4.35)	26 (56.52)	
2	1 (2.17)	7 (15.22)	
3	0 (0)	1 (2.17)	
Sex			0.659
Female	2 (4.35)	22 (47.83)	
Male	3 (6.52)	19 (41.30)	
Stage			0.438
II	1 (2.17)	12 (26.09)	
III	2 (4.35)	6 (13.04)	
IV	2 (4.35)	23 (50.00)	
Diphenhydramine			0.999
Given	5 (10.87)	39 (84.78)	
Not given	0 (0)	2 (4.35)	
Ranitidine			0.0199
Given	2 (4.35)	37 (80.43)	
Not given	3 (6.52)	4 (8.70)	
Dexamethasone			0.207
Given	4 (8.7)	40 (86.96)	
Not given	1 (2.17)	1 (2.17)	
Acetaminophen			0.999
Given	5 (10.87)	39 (84.78)	
Not given	0 (0)	2 (4.35)	

Table 1. (con't) Demographics and Premedications by Outcome

Variable	With Reaction n = 5 (%)	Without Reaction n = 41 (%)	*P* value
Diagnosis			0.186
CLL	2 (4.35)	1 (2.17)	
DLBCL	3 (6.52)	33 (71.75)	
Burkitt	0 (0)	3 (6.52)	
Follicular	0 (0)	2 (4.35)	
Hodgkin's	0 (0)	1 (2.17)	
Small Cell Lymphocytic	0 (0)	1 (2.17)	

Discussion

The exact cause of infusion reactions is largely undefined, although it may be divided into IgE and non-IgE mediated mechanisms.[3] Infusion reactions to monoclonal antibody may be due to cytokine-dependent reactions. In a study population of patients treated with rituximab, there was elevation of TNFα and IL-6 in the first 90 minutes of treatment. Cytokine elevation was correlated with symptoms fever, chills, and dyspnoea.[4] Monoclonal antibodies react with target cells causing the release of inflammatory cytokines. Another theory is that antibodies cause immunogenicity and produce human anti-human antibody (HAHA) or human anti-chimeric antibody (HACA), which may lead to an immune reaction that may affect the patient's safety.[5]

To decrease the occurrence of infusion reactions, common premedications given include steroids (dexamethasone), acetaminophen, diphenhydramine and ranitidine. Package insert for rituximab mentioned the use of acetaminophen and hydrocortisone prior to administration. Although no specific guideline exists, it is a practice in our institution to give most, if not all, of the above premedications prior to rituximab administration.

In our population, those with reactions were statistically different from those without in terms of the use of ranitidine, an H2 blocker. A combination of Histamine 1 (H1), and Histamine 2 (H2) blockers has been shown to improve outcomes in patients presenting with allergic symptoms.[6] Prophylactic H1 and H2 blockade causes a lesser histamine release, which leads to less anaphylactoid reactions.[7] This can explain the significance of ranitidine in our population.

Conclusion

Infusion reaction incidence to rituximab in our center was 10.9% from January 2005 to May 2011, and this was much lower than what was previously reported. All of the infusion reactions were grades 1 to 2, and occurred in the first 30 minutes of the first infusion. Infusion reactions were managed successfully with supportive care. Rituximab rechallenge was successful in all patients with reactions. Premedications used prior to rituximab include acetaminophen, dexamethasone, diphenhydramine and ranitidine. Of all the premedications used, only use of ranitidine showed a significant statistical difference among patients with reactions compared to those without.

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