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Research Article

A Study to Evaluate the Safety of Rapid and Conventional Rituximab Infusion in a Tertiary Care Centre

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ABSTRACT

Antibody-based therapy, in particular rituximab, is a promising strategy in the treatment of Non-Hodgkin lymphoma. Rituximab chemotherapy combinations have revolutionised the treatment outcomes in NHL. A major barrier to effective treatment of rituximab is the lengthy infusion time. Hence, by reducing the chair time of one patient from the conventional 4-6 hours to rapid (90 minutes) infusion, more number of patients can be accommodated in outpatient facility. A total of 40 patients who received rapid infusion of rituximab over 90 minutes and 30 patients who received conventional infusion were evaluated for the safety parameter. It was observed that rapid infusion was well tolerated with no grade 3 or 4 reaction and there was no significant difference in the safety analysis between the rapid and conventional infusion. Therefore, it can be concluded that rapid infusion of rituximab can be opted as a safer alternative to conventional infusion and also improves patient satisfaction.

Keywords: Non-Hodgkin lymphoma, infusion-related, diffuse large B-cell, adverse events

INTRODUCTION

Non-Hodgkin lymphomas (NHLs) comprise a heterogeneous group of lymphoid neoplasms and are the fifth most common cancer in the world with the incidence steadily increasing. The introduction of chimeric monoclonal antibody (mAb), rituximab, has been a major breakthrough in the treatment of NHL. It is used in relapse cases[1,] as first line in diffuse large B-cell (DLBCL), low grade or follicular B-cell Cluster of differentiation-20 (CD20) positive NHL, in Chronic Lymphocytic Leukemia (CLL)[2]. It is also used as maintenance therapy for patients with previously untreated follicular CD20- positive B-cell NHL after achieving a response to a chemotherapy regimen including rituximab. It is approved for the treatment of moderate to severe active rheumatoid arthritis (RA)[3]. Rituximab is administered as intravenous (IV) infusion and is associated with infusion-related reactions, with incidence being as high as 77% for the first infusion. The liberation of inflammatory cytokines such as TNF-α and interleukin-6 (IL-6) could be attributed to the occurrence of these reactions[4]. The possibility of such a reaction is maximum with the initial infusion and is considerably reduced with subsequent infusions[5]. Tumor burden, presence of pulmonary infiltrates, age (elderly patients), and type of NHL (CLL or mantle cell lymphoma) are the other risk factors which could be associated with developing an infusion-related reaction[4].

In view of the risks associated with infusion-related toxicity, it is recommended to start at a slow initial rate which can be gradually titrated at intervals of every 30 minutes depending on patient acceptability[6]. On an average, first infusion takes 6 hours and consecutive infusions takes 4 hours. Longer infusion times and frequent infusion rate changes are difficult to manage. It involves longer observation times, increased nursing and administration staff workloads, and also can pose temporal inconvenience to patients[7]. Several studies have been conducted to validate and establish the safety and practicality of rapid infusion rituximab over a period of 90 minutes[4,5]. The 90-minute infusion of rituximab starting in cycle 2 for patients with NHL who did not experience a grade 3 or 4 infusion-related adverse reaction during cycle 1 was approved by the FDA in 2012. However, in view of insufficient data regarding the use of rapid infusion of rituximab in Indian population, this study was conducted to assess the occurrence of grade 3 or grade 4 infusion-related reactions during the administration of rapid infusion and to evaluate the safety of rapid rituximab infusion and conventional rituximab infusion.

MATERIALS AND METHODS

The study was carried out after obtaining Institutional Ethics Committee (IEC) clearance (letter no. IEC 544/2013). It was designed as a prospective and retrospective study and was conducted in the Department of Medical Oncology of a tertiary care hospital. The prospective part of the study included 40 patients and was carried out over a duration of one year (November 2013 to

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Table 1: Age Distribution of the Study Sample.

Age group (in years)	Group I No. of patients (%)	Group II No. of patients (%)
< 25	2 (5)	0
26 – 35	1 (2.5)	3 (10)
36 – 45	5 (12.5)	6 (20)
46 – 55	15 (37.5)	7 (23.3)
56 – 65	8 (20)	8 (26.7)
66 – 75	9 (22.5)	6 (20)
TOTAL	40	30

Table 2: Frequencies of Concomitant Diseases.

Comorbidities	Group I No. of patients (%)	Group II No. of patients (%)
Present	9 (22.5)	4 (13.3)
Hypertension	4(10)	0
Diabetes	3(7.5)	3 (10)
Bronchial asthma	2(5)	1 (3.3)

Table 3: Chemotherapy Regimens.

Chemotherapy Regimen	Group I No. of patients (%)	Group II No. of patients (%)
RCHOP	20 (50)	23 (76.7)
BR	13 (32.5)	7 (23.3)
Maintenance rituximab	7 (17.5)	0

RCHOP - Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone; BR - Bendamustine and Rituximab

Table 4: Infusion-related Reactions.

Patient (Age/gender)	Cycle of Rapid Infusion	Event	Management
46/ male	2	Rigor	Infusion interrupted, IV diphenhydramine given, then restarted
59/male	2	Rigor	Infusion interrupted, IV diphenhydramine given, then restarted

Table 5: Comparison of Infusion Related Reactions in Both the Groups.

Infusion Related Reactions	Group I	Group II
Present	2	0
Absent	38	30
Total	40	30

2014) while the retrospective part included 30 patients during the period from January 2011 to December 2012. Permission to access patient records was obtained from the Medical Superintendent for the retrospective part of the study. Non-Hodgkin lymphoma patients with the following criteria were included: Age 18-70 years of both sex and chemotherapy involving rituximab. Pregnant or lactating patients, those getting rituximab infusion for first time or had prior recorded grade 3 or 4 infusion related reactions to rituximab were excluded from the study. After obtaining IEC clearance, the hospital record files of 30 patients satisfying the above inclusion criteria were analysed. The following details were collected using a proforma which included demography (age, gender), clinical details (comorbidities, history of allergy, diagnosis), treatment history (chemotherapy regimen) and adverse events during the infusion in any cycle of chemotherapy (date of the infusion-related reaction, the cycle and the date of the event). For the prospective part, patients fulfilling the study criteria were enrolled after obtaining written informed consent. For the first infusion, rituximab at a dose of 375 mg/m^2 using the standard infusion rate was prescribed and for the subsequent infusions, it was given at a rapid-rate as per the treating doctor's judgement. The enrolled patients received rituximab infusion over a period of 90 minutes (20% of the dose over 30 minutes and the remaining 80% over 1 hour) after premedication with paracetamol 500 mg, pheniramine maleate 45.5 mg and dexamethasone 12 mg. They were observed and patient details (age, gender, body weight, height, comorbidities, history of allergy, diagnosis), treatment details (chemotherapy regimen, details of previous infusion like date, cycle of chemotherapy, any adverse event during the previous cycle) were collected using a proforma. Data pertaining to the current infusion such as date of infusion, baseline vitals (pulse, blood pressure, respiratory rate and temperature), premedications given, time of starting and stopping the infusion, dose of rituximab and details of infusion-related reactions (time of onset, duration, treatment given for the adverse event) were also noted. During the infusion, vitals were monitored every 30 minutes till the end of infusion. Infusion reactions were graded according to the NCI Common Terminology Criteria for Adverse Events[8].

Statistical Analysis

Demographic data was analysed using descriptive statistics. Infusion-related reactions between the two groups were compared using Fishers exact test. Data was analysed using SPSS software version 16.

RESULTS

The present study enrolled 70 patients with NHL, 40 patients who underwent rapid infusion of rituximab from 01 Nov 2013 to 01 Nov 2014 (Group I – prospective study group) and 30 patients who underwent conventional rituximab infusion from 01 Jan 2011 to 31 Dec 2012 (Group II – retrospective study group). The following parameters were assessed in both the groups: Age, gender, distribution of types of NHL**,** concomitant diseases, chemotherapy regimens, and infusion-related reactions in both the groups. Patients in the study were divided into 6 groups according to their age. Table 1 shows the age distribution in both the groups. The minimum age of presentation was 19 years and 27 years in group I and II respectively. The maximum age was 70 years and 74 years in group I and II respectively. Mean age was 52.83 ± 12.06 years and 53.30 ± 13.02 years in group I and II

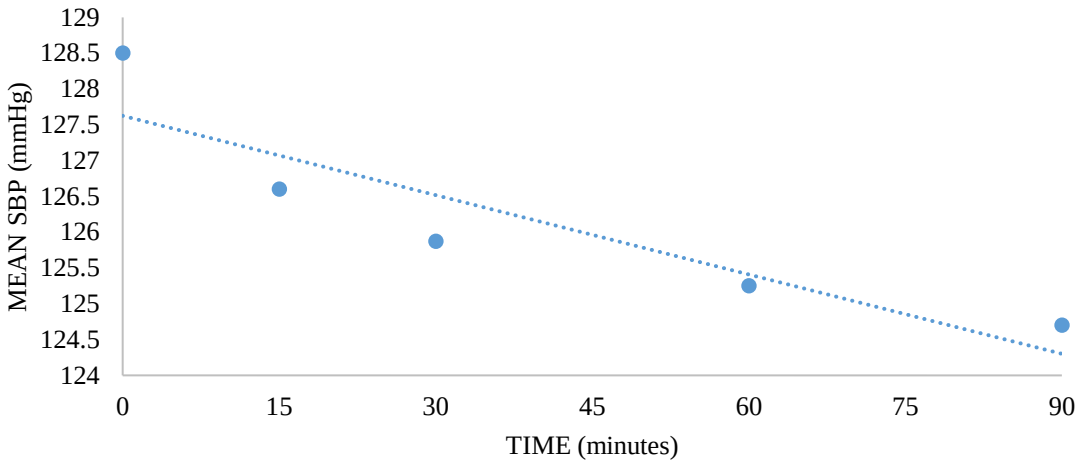

Figure 1: Mean Systolic Blood Pressure at 0, 15, 30, 60, 90 minutes of infusion.

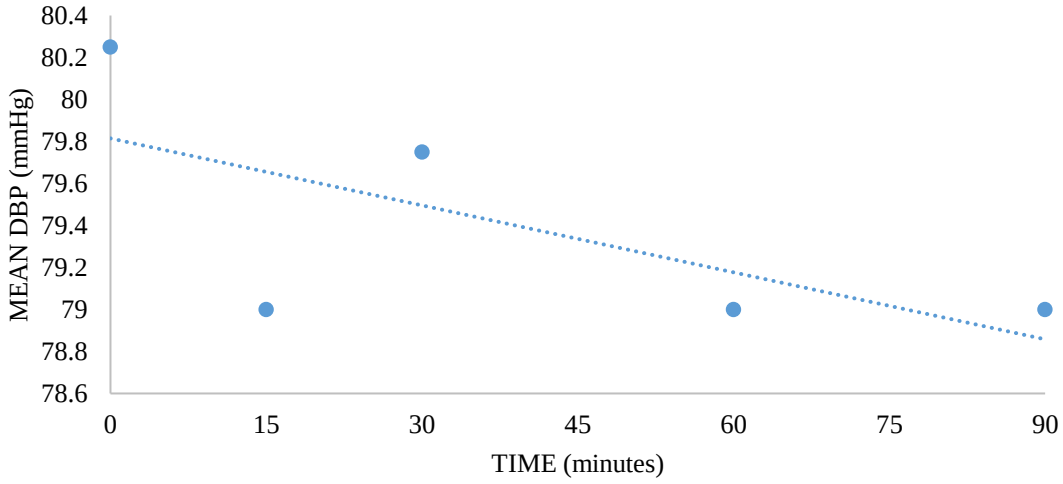

Figure 2: Mean Diastolic Blood Pressure at 0, 15, 30, 60, 90 minutes of infusion.

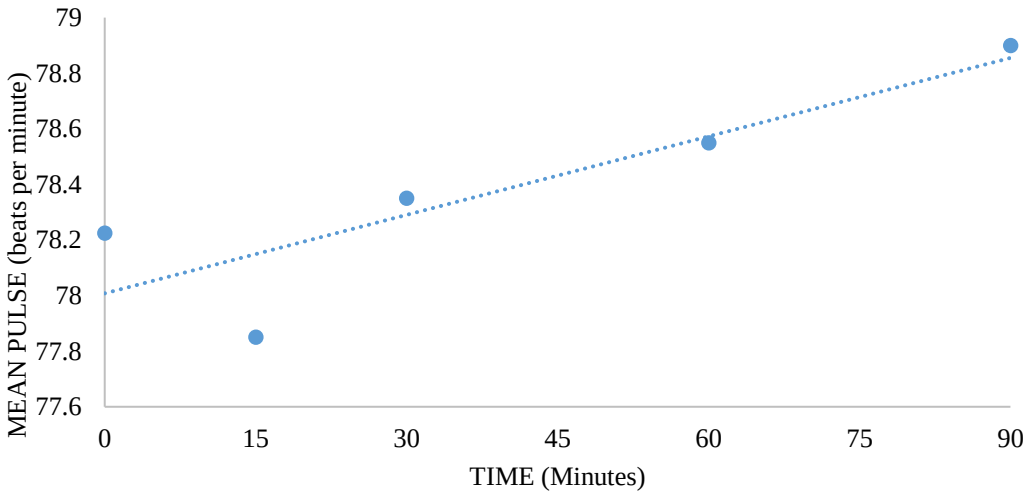

Figure 3: Mean Pulse at 0, 15, 30, 60, 90 minutes of infusion.

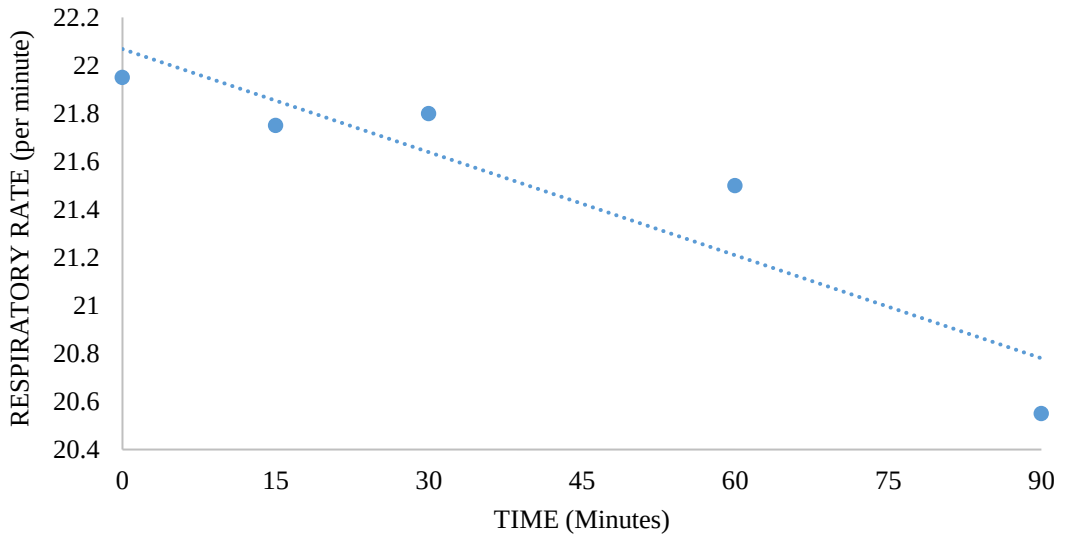

Figure 4: Mean Respiratory Rate at 0, 15, 30, 60, 90 minutes of infusion.

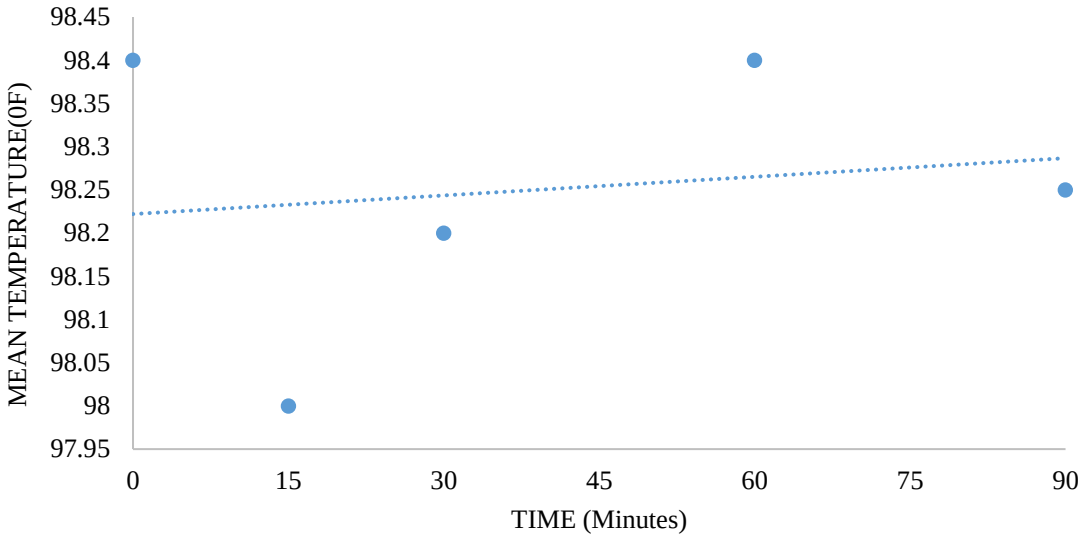

Figure 5: Mean Temperature at 0, 15, 30, 60, 90 minutes of infusion.

respectively. Gender distribution showed male preponderance in both the groups; the percentage of males were 57.5% and 73.3% in group I and group II respectively. In both the groups, DLBCL was the most common type of lymphoma (20 patients in group I and 21 patients in group II). Other types included follicular lymphoma (25% in group I, 20% in group II); mantle cell lymphoma (5% in group I; 6.7% in group II); and others (20% in group I, 3.3% in group II). Others constituted CLL and small lymphocytic lymphoma. Table 2 shows the distribution of concomitant diseases in both the groups. The patients in both the group received chemotherapy regimens such as RCHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone), BR (Bendamustine and Rituximab). Patients on maintenance rituximab were also enrolled in group I. The number of patients who received rituximab in combination with chemotherapy were 33 and 30 in group I and group II respectively (Table 3). A total of 127 rapid rituximab infusions were administered in group I and 180 cycles of conventional rituximab infusion in group II. There were no grade 3 or 4 infusion related adverse events in both the groups. 2 patients in group I as shown in table 4 developed adverse events which were of grade 2 in severity according to NCI Common Terminology criteria for adverse events v4.0. There was no significance (p-value 0.214) in the incidence of infusion related reactions between two groups (Table 5). The trendline of mean systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiratory rate and temperature in group I have been graphically represented (Figure 1, 2, 3, 4, 5).

DISCUSSION

Rituximab has become a mainstay in the treatment of CD20 positive NHL. Since its approval in 1997, the

indications for rituximab have broadened over the years. However, the conventional administration of rituximab takes longer infusion time (i.e. over a period of 4 hours) and is a disadvantage in this regard. In the present study, we have evaluated the safety of rapid infusion rituximab (over a period of 90 minutes) in patients with NHL who have not developed grade 3 or 4 reactions during the first cycle. In our study, a total of 70 patients with NHL were enrolled. Among the 40 patients who received a total of 127 rapid infusions and 30 patients who received a total of 180 conventional rituximab infusions, the most common type of NHL was DLBCL followed by follicular lymphoma. The incidence of DLBCL is in accordance to previous studies[5,9-11]. The mean age among patients receiving rapid infusion was 52.83 ± 12.06 years with majority of patients belonging to the age group of 46-55 years (Table 1). This is comparable to previous studies by Sehn *et al.*, Gibbs *et al.*, Salar *et al.* wherein the median age was slightly higher[5,10,12] Male preponderance seen in our study group is consistent with previous studies[6,11,12] Thirteen patients with NHL included in the present study had comorbidities like hypertension, diabetes, bronchial asthma; with hypertension being the most common one (Table 2). In a study by Chiang *et al.*, done to evaluate the feasibility and economic benefits of rapid infusion rituximab, hypertension was the most common comorbidity seen[12]. In the present study, majority of the patients received RCHOP followed by BR chemotherapy and the remaining patients received single-agent rituximab maintenance therapy (17.5%) (Table 3). These findings are consistent with the studies done by Atay *et al.* and Chiang *et al*.[9,12]. We have evaluated the safety of 127 rapid infusions and 180 conventional rituximab infusions. Two patients receiving rapid infusion developed grade 2 reactions (Table 4). One patient was a 46 year old male with CLL who was on RCHOP chemotherapy, other was a 69 year old male with mantle cell lymphoma on BR chemotherapy. Both developed rigors during the second cycle of infusion, 30 minutes into the infusion. Infusion had to be interrupted and symptomatic treatment was given. Infusion was restarted at the same rate and it was tolerated well by both patients. They did not develop any reaction during the subsequent cycles with rapid infusion. In the study by Sehn *et al*., one patient had chills and rigors approximately 45 minutes into infusion[5]. The IV infusion was halted and patient was given IV diphenhydramine and infusion was restarted. But further challenge with rapid infusion was not done in that patient. However, the results from our study show that rapid infusion could be continued without compromising patient safety. No grade 3 or 4 infusion-related events were noted in our study. Studies by Sehn *et al*. and Al Zahrani *et al*. have also not reported grade 3 or 4 toxicity[5,13]. Patel *et al*., conducted a study to evaluate the feasibility of rapid infusion in the setting of single-agent rituximab given as maintenance therapy in low grade lymphomas[6]. In a total of 647 infusions, three patients had developed infusion-related reactions. There were two grade 3 reactions in the form of facial flushing, chest tightness and shortness of breath. However, the incidence was too low to assess the correlation between the adverse event and the administration schedule. There was no significant difference in the adverse events between conventional and rapid infusion of rituximab in our study (Table 5). Gibbs *et al*. showed that rapid infusion of rituximab is as effectual and applicable as standard or the conventional infusion in the treatment of DLBCL[11]. No adverse reactions were noted during the administration of 250 rapid infusions in 61 patients with DLBCL. Steroid premedication was given to all the patients prior to infusion. However, Salar *et al*., had concluded that concurrent corticosteroid use was not cardinal to dispensation of rapid infusion rituximab[10]. In our study, we have demonstrated the trend of mean systolic as well as diastolic blood pressure, pulse rate, temperature and respiratory rate in the patients receiving rapid infusion. There was a fall in the mean systolic as well as diastolic blood pressure, respiratory rate, and increase in the mean pulse rate while the mean temperature remained unchanged over the infusion period of 90 minutes as shown in fig. 1, 2, 3, 4, and 5. These were not found to be clinically significant. In the 372 rapid infusions that had been carried out by Atay *et al*., there was rise in body temperature (5.4%), blood pressure (4.8% increase, 8% decrease), pulse rate (1.9% surge, 1% decline)[9]. However, our study had few limitations. The results of the present study cannot be extrapolated to a larger population due to the small sample size used in the present study. Secondly, in our study, all patients had received steroid premedication and 20 patients had received corticosteroid containing chemotherapy. The low incidence of infusion-related reactions could be attributed to concomitant steroid use. In our experience, rituximab administration over 90 minutes seems to be a practical and safe solution in lymphoma patients whether they were receiving steroid-containing chemotherapy or not. This is important since rituximab is given as maintenance therapy in many patients. The results also include patients with CLL, small lymphocytic lymphoma and MCL which further adds to the applicability of rapid infusion in these patients. Our results also show that patients developing grade 2 reactions can be rechallenged with rapid infusion in the subsequent cycles without compromising patient safety. Previous studies that have been reported were conducted in U.S, Canada, Turkey, Saudi Arabia and various other countries[14]. However, there is paucity of data regarding the use of rapid infusion of rituximab in Indian population. Considering the fact that rapid rituximab infusion is gaining importance in the treatment of malignant as well as autoimmune diseases, more studies with a larger sample size are needed to establish its safety in Indian population. Rapid infusion of rituximab in second and subsequent cycles was well tolerated and safe with no grade 3 or 4 reactions. It was also found to be as safe as conventional rituximab infusion in terms of grade 3 or 4 reaction. Given the low incidence of infusion-related reactions and the short administration time with rapid infusion protocol, it should be recommended in all infusion centres across India.

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REFERENCES

1. Gurcan HM, Keskin DB, Stern JN, Nitzberg MA, Shekhani H, Ahmed A. A review of the current use of rituximab in autoimmune diseases. Int Immunopharmacol 2009; 9:10-25.
2. FDA approval for rituximab [Internet] [updated 2013 Jul 3; cited 2015 Jun 29]. Available from: http://www.cancer.gov/about-cancer/treatment/drugs/fda-rituximab.
3. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, *et al*. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006; 54:2793–806.
4. Atmar J. Review of the safety and feasibility of rapid infusion of rituximab. J Oncol Pract 2010; 6:91–3.
5. Sehn LH, Donaldson J, Filewich A, Fitzgerald C, Gill KK, Runzer N, *et al*. Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting. Blood 2007; 109:4171-3.
6. Patel J, Ho M, Ho V, Bello C, Djulbegovic B, Sokol L, *et al*. Rapid infusion rituximab for maintenance therapy: is it feasible? Leuk Res Treatment [Internet]. 2013 [cited Nov 4]; 2013:[4 p.]. Available from: http://www.hindawi.com/journals/lrt/2013/629283/
7. Pritchard CH, Greenwald MW, Kremer JM, Gaylis NB, Rigby W, Zlotnick S, *et al*. Safety of infusing rituximab at a more rapid rate in patients with rheumatoid arthritis: results from the RATE-RA study. BMC Musculoskelet Disord 2014; 15:177.
8. Grading of infusion reactions according to the NCI Common Terminology Criteria for Adverse Events v4.0 [Internet] [cited 2015 Jun 29]. Available from: http://cursoenarm.net/UPTODATE/contents/mobipreview.htm?8/18/8491
9. Atay S, Barista I, Gundogdu F, Akgedik K, Arpaci A. Rapid-infusion rituximab in lymphoma treatment: 2-year experience in a single institution. J Oncol Pract 2012; 8:141-3.
10. Salar A, Casao D, Cervera M, Pedro C, Calafell M, Abella E, *et al*. Rapid infusion of rituximab with or without steroid-containing chemotherapy: 1-yr experience in a single institution. Eur J Haematol 2006; 77:338-40.
11. Gibbs S, Pout G, Wimperis J. Rapid infusion rituximab is a clinically effective and safe as conventional infusion regimes in the treatment of diffuse large B-cell lymphoma: A 2-year prospective study. Haematologica 2007; 92:264.
12. Chiang J, Chan A, Shih V, Hee SW, Tao M, Lim ST. A prospective study to evaluate the feasibility and economic benefits of rapid infusion rituximab at an Asian cancer center. Int J Hematol 2010; 91:826-30.
13. Al Zahrani A, Ibrahim N, Al Eid A. Rapid infusion rituximab changing practice for patient care. J Oncol Pharm Pract 2009; 15:183–86.
14. Lang DS, Hagger C, Pearson A. Safety of rapid rituximab infusion in adult cancer patients: a systematic review. Int J Nurs Pract 2011; 17:357-69.