MJN

SAFETY OF RAPID RITUXIMAB INFUSION POST 72 HOURS OF ADMINISTRATION

Dora SP Lang[1*] & Chng Wee Joo[2]

[1]Nurse Clinician, Oncology Nursing, Oncology Nursing, National University Cancer Institute, Singapore.

[2]Senior Consultant, National University Cancer Institute, Singapore.

**Corresponding Author Email: siew-ping-lang@nuhs.edu.sg*

ABSTRACT

Rapid rituximab infusion, IgG1 monoclonal antibody targeting CD20, at 90-minute is used widely in the treatment of B-cell lymphoproliferative disorders. The aim of the study was to evaluate the safety of application of rapid rituximab at 90-minutes among non-Hodgkin lymphoma. This is a prospective clinical trial using a convenient sampling. Prior to the rapid infusion, the patients received different combinations of pre-medication as per physician's choice. In this case, the patients received 20% of the total volume of rituximab over 30 minutes and the remaining 60% over 60 minutes. The adverse event was monitored using NCI CTCAE version 4 during infusion until 72 hours post infusion. A total of 12 patients participated in the study and received 25 cycles of rapid rituximab infusion. Only one patient experienced grade 2 vomiting at 48 hours post infusion. Thus it was concluded that the rapid rituximab infusion was safe and feasible for non-Hodgkin Lymphoma patient seeking treatment in our institution.

Keywords: *Rapid rituximab infusion, B-cell lymphoproliferative disorders, Non-Hodgkin Lymphoma*

INTRODUCTION

During 1997 Rituximab (Rituxan) also known as Mabthera was approved by Food and Drug Administration for CD-20 positive previously untreated, relapsed, refractory follicular and diffuse large B cell lymphoma (National Cancer Institute, 2010). Since then, the application of Rituximab has extended to other type of non-Hodgkin lymphoma like chronic lymphocytic leukemia and rheumatoid arthritis (National Cancer Institute, 2010). The mechanism of action of rituximab deals with its action on CD-20 positive B-cell, taking into account antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity and apoptosis (Reff *et al.*, 1994; Chow *et al.*, 2002).

Drug manufacturer's guideline has recommended a slow infusion of rituximab at 50mL/hr for the first hour followed by an incremental rate of 50mL/hr every 30 minutes for cycle one. If patient tolerated the first cycle without grade 3 or 4 adverse event, the second cycle will start at the infusion rate of 100mL/hr increasing by 100mL/hr every 30 minutes till the maximum rate of 400mL/hr (National Cancer Institute, 2010). The slower rate of infusion during the first cycle was for the prevention of severe infusion reaction. As reported in the literature 77% and 33% of patients experienced some degree of adverse event during the first infusion and subsequent infusions respectively (National Cancer Institute, 2010). The most frequently reported reactions were hypotension, fever, chills, rigors, urticaria, bronchospasm, angioedema (sensation of tongue and throat swelling), nausea, fatigue, headache, pruitus, dyspnoea, rhinitis, vomiting, flushing and pain at the cancer site (National Cancer Institute, 2010). These reactions is possibly due to a cytokine release syndrome when the drug act on B-cell (Dillman, 1999).

Over the years it was observed that patient's tolerance to rituximab improved tremendously with adequate premedication. Therefore, there was a proliferation of literature on the feasibility and safety of rapid rituximab infusion (Al Zahrani *et al.*, 2009; Chiang *et al.*, 2010).

Many institutions have adopted this new and rapid regimen taking 90 or 60-minute as the standard regimen (Corey *et al.*, 2007; El-Agnaf *et al.*, 2007). However, such infusion was investigational, until the recent FDA approval of 90-minute rapid rituximab infusion on October, 2012 (National Cancer Institute, 2012). Therefore, the study aimed to evaluate the safety of rapid rituximab at 90-minute in our institution.

MATERIALS AND METHODS

The study was a prospective experimental study using convenience sampling. It was conducted in both inpatient and ambulatory setting. The inclusion criteria included adult patients with non-Hodgkin Lymphoma (NHL) who tolerated 2 cycles of rituximab infusion without grade 3 or 4 adverse events with absolute lymphocytes counts, less than 3.08 x 109/L. Ethic approval was sought from National Healthcare Group Domain Specific Review Board. Written informed consent was obtained from the potential patients prior to the rapid infusion.

The study protocol involved administration of 20% of the total dose of rituximab over 30 minutes followed by the remaining 80% over 60 minutes. Patients' vital signs were monitored prior to starting of the infusion and at 30, 60 and 90 minutes post infusion. The type of premedication could include the combination of any of the following:

i. IV Diphenhydramine 25mg,
ii. IV Hydrocortisone 100mg,
iii. IV Pethedine 25 mg with PO Paracetamol 100mg.

The outcome measurement of adverse events was using National Cancer Institute Common Toxicity Criteria Adverse Event (NCI CTCAE) Version 4. Patients were followed-up via telephone and email 24, 48 and 72 hours post-infusion regarding the presence of any adverse events post infusion. Data analysis involves descriptive and proportion analysis by a statistical software named Stat Directs.

RESULTS

Twelve adult lymphoma patients participated in the study receiving a total of 25 cycles of rapid rituximab infusion at 90-minute. Each patient on average received two cycles (range 1-4 cycles) of rapid rituximab infusion. They were mostly male patients (75%) with a mean age of 53 (SD 10) years old. Six (50%) patients were Malays followed by four (33.3%) Chinese and two (16.6%) Indian. The major types of lymphoma were Diffuse Large B-Cell Lymphoma (50%) followed by other large B-Cell Lymphoma, such as mediatstinal B-cell lymphoma or large cell transformation of a low-grade lymphoma (25%) and other lymphoma (25%). The most commonly used chemotherapy regimen in this study was R-CHOP (50%) (Rituximab, Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisolone).

The patients tolerated the rapid rituximab infusion well. Only one episode of adverse event was reported at 48 hours post-infusion. This patient complained of grade 2 vomiting. The symptoms were resolved with 3 days of continuously oral anti-emetic treatment. The patient who developed grand 2 vomiting was a 51 year-old male Indonesian Malay patient. He developed the grade 2 vomiting during the second cycle of rapid rituximab infusion (cycle 4 of his chemotherapy). The dosage of rituximab administered was 650mg. His absolute lymphocyte count was 0.65 x 109/L prior to that cycle of rapid rituximab infusion. He tolerated another 2 cycles of rapid rituximab infusion without further adverse events.

DISCUSSION

Many publications had reported that rapid rituximab infusion is safe and well-tolerated (Provencio *et al.*, 2006; Atmar, 2010; van Oers *et al.*, 2010). Our study was the first study that extended the duration of follow-up to 72 hours post-infusion. We clearly demonstrated that adverse event related to rapid rituximab infusion might not be limited to the duration of infusion; its effect could possibly extend beyond the completion of infusion. However, the adverse event was mild and was easily treated with medication. Rapid rituximab infusion at 90-minute was safe and feasible for non-Hodgkin Lymphoma patients. Upon completion of this study, our institution has adopted rapid rituximab at 90-minute as a standard regimen for non-Hodgkin lymphoma patients.

As the frequency of adverse event was limited to only one episode of vomiting, the vital signs monitoring could reasonably be kept at a frequency of every 30 minutes or lesser. As the estimated risk of adverse event was very low, it warrants further review of the frequency of monitoring so that the patients are not subjected to unnecessary monitoring, especially blood pressure

monitoring, which could be uncomfortable.

CONCLUSION

The limitation of the study was the small sample size of convenience sampling so that the applicability of the results is limited to the indications used for this study. Thus rituximab improved survival in patients with non-Hodgkin's lymphoma. It improved response and survival in patients with chronic B-cell lymphocytic leukemia. Overall, the results of this study suggest that after the first dose of rituximab has been given in a standard manner, subsequent doses can be safely administered by rapid-infusion protocols.

IMPLICATION TO CLINICAL PRACTICE

The preliminary safety data on rapid rituximab infusion of this study and the recent approval of Food and Drug Administration for rapid rituximab starting at cycle 2 for patient with non-Hodgkin Lymphoma had led to the adoption the new regimen as standard regimen for the institution. The implementation of new regimen has shorten the duration of patient's stay in the ambulatory cancer centre, better resource allocation and increased patient satisfaction.

IMPLICATION TO RESEARCH

Future research should focus on infusing monoclonal antibodies over a shorter duration and identifying the possible risk factors for predicting the occurrence of adverse events among patients.

ACKNOWLEDGEMENTS

The study team would like to thank all the referral physicians, pharmacists who assisted in dilution of the drug using new regimen and nurses who administered the drug and monitored patients' vital signs closely.

FUNDING

There was funding used to support the research study and the researchers declare no conflict of interest.

REFERENCES

Al Zahrani, A, Ibrahim, N & Al Eid, A (2009). Rapid infusion rituximab changing practice for patient care. Journal of Oncology Pharmacy Practice. 15(3), pp 183-6.

Atmar, J (2010). Review of the safety and feasibility of rapid infusion of rituximab. Journal of Oncology Practice. 6(2), pp 91-93.

Chiang, J, Chan, A, Shih, V, Hee, SW, Tao, M & Lim, ST (2010). A prospective study to evaluate the feasibility and economic benefits of rapid infusion rituximab at an Asian cancer center. International Journal of Hematology. 91(5), pp 826-830.

Chow, KU, Sommerlad, WD, Boehrer, S, Schneider, B, Seipelt, G, Rummel, MJ, Hoelzer, D, Mitrou, PS & Weidmann, E. Anti-CD20 antibody (IDEC-C2B8, rituximab) enhances efficacy of cytotoxic drugs on neoplastic lymphocytes in vitro: role of cytokines, complement, and caspases (2002). Haematologica. 87(1), pp 33-43

Corey, P, Go, R & Schaper, A (2007). A nurse can safely deliver rituximab over 90 minutes.Oncology Nursing Society 32nd Annual Congress, April 24-27, 2007, Las Vegas, NV. Oncol Nurs Forum. 34, pp 493-493.

Dillman, RO (1999). Infusion Reactions Associated with the Therapeutic use of Monoclonal Antibodies in the Treatment of Malignancy. Cancer Metastasis Review. 18(4), pp 465-71.

El-Agnaf, MR, Mccoy, C, Ong, YL, Eswedi, AH, Black, B & Ramadan, KM (2007). Infusion of rituximab over 90 minutes on an out-patient basis is safe and improves resource utilization. Leukemia & Lymphoma. 48(9), 1875-7.

National Cancer Institute (2010). FDA Approval of Rituximab [Online]. U.S National Institutes of Health. Available: http://www.cancer.gov/cancertopics/druginfo/fda-rituximab [Accessed 24 July 2010 2010].

National Cancer Institute (2012). Approved New Dosing and Administration for Certain Non-Hodgkin Lymphoma Patients [Online]. Available: http://www.cancer.gov/cancertopics/druginfo/fda-rituximab [Accessed 10 Jan 2013 2012].

Provencio M, Cerdeira S, Bonilla F, Sánchez A, España P (2006). Rapid-infusion rituximab in lymphoma treatment. Annals of Oncology. 17(6), pp 1027-1028.

Reff, ME, Carner, K, Chambers, KS, Chinn, PC, Leonard, JE, Raab, R, Newman, RA, Hanna, N & Anderson, DR (1994). Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood. 83(2), pp 435-45.

van Oers, MH, Van Glabbeke, M, Giurgea, L, Klasa, R, Marcus, RE, Wolf, M, Kimby, E, van t Veer, M, Vranovsky, A, Holte, H & Hagenbeek, A (2010). Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: longterm outcome of the EORTC 20981 phase III randomized intergroup study. Journal of Clinical Oncology. 28(17), pp 2853-2858