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Not Specific Cytokines but B Symptoms or C Reactive Proteins were Related the Infusion Reactions in Rituximab Treated B Cell Non-Hodgkin's Lymphoma

Yutaka Tsutsumi[1]*, Shinichi Ito[1], Ryo Kikuchi[1], Satomi Matsuoka[1] and Takanori Teshima[2]

[1]Department of Hematology, Hakodate Municipal Hospital, Hakodate, Japan
[2]Department of Hematology, Hokkaido Graduate School of Medicine, Sapporo, Japan

Abstract

Purpose: The purpose of this study is to analyze the risk factor for infusion related reaction (IRR) due to the rituximab treatment in patients with B cell non-Hodgkin's lymphoma.

Methods: A retrospective analysis was conducted the newly diagnosed B cell non-Hodgkin's lymphoma patients who have received rituximab contained chemotherapy. Several factors with cytokines in patients were calculated. A P value <0.05 is significant.

Results: 18 patients were included in the analysis. Most of patients were diffuse large B cell lymphoma or follicular lymphoma. Six patients had a IRR. TNF-α, IL6, IL8, sIL-2R, pre-administration of prednisolone were not observed significant differences. B symptom, CRP, gender was showed the significant differences in this analysis (B symptom: P=0.0139, gender: P=0.014, CRP: P=0.0354).

Conclusion: B symptom, CRP, and gender might be important risk factors of the occurrence of IRR. Specific cytokines were not correlation with the IRR. Careful observation for IRR during rituximab administration is necessary for B cell non-Hodgkin's lymphoma with B symptoms, and CRP positive patients.

Keywords: Rituximab; B cell non-Hodgkin's lymphoma; Infusion related reaction; B symptoms

Abbreviations: BL: Burrkit Lymphoma; DLBCL: Diffuse Large B Cell lymphoma; FL: Follicular Lymphoma; IVL: Intravascular Lymphoma; MALT: MALT Lymphoma; MTX-LPD: Methotrexate Associated Lympho-Prolifrative Disease; PCNSL: Primary Central Nervous System Lymphoma; WM: Waldenstrom-Macrogloblinemia

Introduction

Rituximab, which is a chimeric mouse-human antibody that targets CD20, was introduced to treat B-cell non-Hodgkin's lymphoma (NHL) and has improved outcomes in these patients [1,2]. Since the launch in the late 1990s for the follicular lymphoma, the rituximab extended the use of various types of B cell lymphomas and autoimmune disorders, such as diffuse large B cell lymphoma [3], mantle cell lymphoma [4], chronic lymphoid leukemia [5], and rheumatoid arthritis [6]. Rituximab is approved for an intravenous administration in 90-240 min [7]. Common side effects under the infusions are chills, fever, urticarial, hypotension, and respiratory symptoms. These adverse effects are commonly observed in the first administration of rituximab. Infusion related reactions (IRR) of rituximab is a well-known complication especially in the treatment of B-cell NHL patients. Some factors are reported the correlation with the IRR, such as the IgE-mediated reaction, or bone marrow involvement of the B cell lymphoma [8,9]. But still little is known about the factors that may developed the IRR during the rituximab treatment. In this reports, we retrospectively analyzed the several inflammatory factors, such as, procalcitonin, cytokines, B symptoms and CRP in 20 B cell NHL patients treated with rituximab containing chemotherapy.

Patients and Methods

Patients

A retrospective analysis was conducted of patient's newly diagnosed B cell non-Hodgkin's lymphoma that was administered rituximab contained chemotherapy at Hematology in Hakodate Municipal Hospital from January 2012 to December 2014. Patients were eligible if they were greater 18 year old and had histological confirmation of B cell non-Hodgkin' lymphoma according to the World Health Organization criteria. Rituximab was infused from the first cycle of the treatment in all patients. Allergic rhinitis, bronchial asthma, immune thrombocytopenia, and who had an insufficient medical history were excluded in the current analysis. The study was approved by the Hakodate Municipal Hospital Institutional Review Board. Written informed consent according to the Declaration of Helsinki was obtained from the patients.

Rituximab infusion

All analyzed patients were first received 375 mg/m^2 of rituximab as an intravenous infusion on day 1, followed by the combination chemotherapy. 200 mg of ibuprofen and 6 mg of chlorpheniramine were administered for premedication 30 minutes before rituximab treatment. Rituximab was adjusted by 1 mg/1 mL, and administered 25 mg/h at 1 hour intervals up to 100 mg/h at 1 hour, and then up to 150-20 mg/h. If IRR were occurred, infusion was once stopped and administered 100 mg of hydrocortisone and 30 minutes later restarted

***Corresponding author:** Tsutsumi Y, Department of Hematology, Hakodate Municipal Hospital 1-10-1, Minato-cho, Hakodate 041-8680, Japan, Tel: +81-138-43-2000; Fax: +81-138-43-4426; E-mail: yutsutsu@shore.ocn.ne.jp

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the reduction of pre-step infusion dose. IRR was defined rush, chills, fever, urticarial, hypotension, and respiratory symptoms under the rituximab infusions. IRR were graded by the medical records' retrospectively, according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.

Cytokine analysis

C-reactive protein (CRP), Lactate Dehydrogenase (LDH), tumor necrosis factor-alpha (TNF-α), interleukin 6, 1-β, 8, soluble interleukin 2 receptor (sIL2R), and procalcitonin (PCT) were examined 18 hour after the start of rituximab treatment. Analyzed patients' stage, international prognostic index (IPI), B symptoms were calculated before the first rituximab treatment and the treatment effects were calculated after the all treatment courses.

Statistical analysis

Association with cytokine, clinical parameters, and IRR were assessed by chi-square test, Fisher's test, or Mann-Whitney U test, where appropriate. Statistically significant was defined as P value < 0.05.

Results

Patient characteristics

Twenty patients underwent first cycle of rituximab. Half of patients (11 of 20) were diffuse large B cell lymphoma (DLBCL). Four was follicular lymphoma, one was intravascular lymphoma (IVL), Burkitt lymphoma, marginal zone lymphoma (MALT), Methotrexate (MTX) related lymph proliferative disease (LPD), and small lymphocytic lymphoma (SLL). Eleven patients were male, 15 patients were above stage III, 1 2 patients' international prognostic index was high or intermediate-high risk grope. B-symptoms were observed in 5 patients and almost all patients (17 of 20 patients) administered rituximab with CHOP or CHOP like regimens (Table1).

Risk factors for infusion related reactions

International prognostic index (IPI), Disease type, LDH, usage of proton pump inhibitor (PPI), H2-blocker, and under steroid treatment were not related about the development of IRR. Gender (male), B symptom and CRP was only the risk factors of the development of IRR under rituximab treatment (Table 1: P=0.014, P=0.014, and P=0.035). Cytokines, such as IL6, IL1β, TNF-α, IL8, IL12, and PCT were not related with the IRR. Soluble IL2R was some tendency of the correlation with the IRR, but not statistically significant in this analysis (Table 1: P=0.09).

Discussion

Several reports showed the risk factor of IRR in chronic B cell leukemia due to amount of the circulating neoplasm cell [10-12]. Winkler et al. reported the lymphocyte counts exceeding more than 50×10^9/L were risky of the development of IRR. IL6 and TNF-αwere elevated when compared with the lymphocyte counts more than 50×10^9/L and others [10]. On the other hands, the some kind of relation s were not observed between more than the lymphocyte counts exceeding more than 50×10^9/L or not in some reports [13,14]. Above reasons were not necessary reliable, because circulating lymphoid neoplastic cell was rare in NHL patients. Recent studies showed the several reasons for the development of the IRR, for example, IgE or some cytokines hyper sensitivity syndrome such as anti-rituximab antibodies [9]. But in our study not showed the any relations in TNF-α, IL6, IL1β, IL12, Il8, and PCT. So we considered no correlations were observed between IRR and some specific cytokines. On the other hands, although our cases were first line therapy patients analysis, we showed B symptoms, CRP level (the time of the treatment of rituximab) had some correlations and IL2R had the some tendency of the development

Infusion reaction		Negative	Positive	P
n		14	6	
Age		62 (43-81)	58 (22-68)	0.214
Sex (%)	Female	9 (64.3)	0 (0.0)	0.014
	Male	5 (35.7)	6 (100.0)	
Disease Type (%)	BL	0 (0.0)	1 (16.7)	0.567
	DLBCL	7 (50.0)	2 (33.3)	
	FL	3 (21.4)	1 (16.7)	
	FL+DLBCL	0 (0.0)	1 (16.7)	
	IVL	1 (7.1)	0 (0.0)	
	MALT	1 (7.1)	0 (0.0)	
	MTX-LPD	1 (7.1)	0 (0.0)	
	PCNSL	1 (7.1)	0 (0.0)	
	WM	0 (0.0)	1 (16.7)	
Stage (%)	I	2 (14.3)	1 (16.7)	1
	II	2 (14.3)	0 (0.0)	
	III	1 (7.1)	1 (16.7)	
	IV	9 (64.3)	4 (66.7)	
B.symtom positive (%)		1 (7.1)	4 (66.7)	0.0139
IPI (%)	Low	4 (28.6)	1 (16.7)	0.143
	Low-Int	2 (14.3)	1 (16.7)	
	High-Int	1 (7.1)	3 (50.0)	
	High	7 (50.0)	1 (16.7)	
IPI (%)	Low, Low-Int	6	2	1
	High-Int, Hjgh	8	4	
Chemotherapy (%)	R-CHOP	3 (21.4)	1 (16.7)	
	R-THP-COP	9 (64.3)	4 (66.7)	
	CODOX-M-R	0 (0.0)	1 (16.7)	
	R-Bend	1 (7.1)	0 (0.0)	
	R-MPV	1 (7.1)	0 (0.0)	
LDH		226.5 (133-476)	205.00 (133-504)	0.68
sIL-2R (average(range))		819.5 (176-5930)	6510 (353-12100)	0.0913
H2 blocker or PPI (%)	no	2 (14.3)	0 (0.0)	1
	yes	12 (85.7)	6 (100.0)	
Steroid treatment before	no	5 (35.7)	1 (16.7)	0.613
rituximab administration	yes	9 (64.3)	5 (83.3)	
IL.1beta (%)	negative	10 (71.4)	5 (83.3)	1
	positive	4 (28.6)	1 (16.7)	
IL.8 (%)	negative	6 (42.9)	2 (33.3)	0.653
	positive	6 (42.9)	4 (66.7)	
	NA	2 (14.3)	0 (0.0)	
IL.12 (%)	negative	13 (92.9)	6 (100.0)	1
	positive	1 (7.1)	0 (0.0)	
PTC (%)	negative	10 (71.4)	3 (50.0)	0.376
	positive	4 (28.6)	2 (33.3)	
	NA	0 (0.0)	1 (16.7)	
CRP (time of rituximab treatment)		0.63 (0.10-4.53)	3.32 (0.58-6.58)	0.0354
IL.6 (average(range))		3.95 (0.20-17.10)	14.70 (1.80-69.20)	0.216
TNF-α (average(range))		11.40 (2.00-82.00)	16.15 (3.90-58.50)	0.741
Alival (%)	died	2 (14.3)	0 (0.0)	0.529
	alrival	12 (85.7)	6 (100.0)	

Table 1: Patients characteristics.

of IRR. Because these factors might be showed the activity, progression of the lymphoid neoplasm or some cytokines release, disease status of the lymphoid neoplasm was important factor in the development of IRR. Some report showed the IRR was often observed in the bone marrow involvement of lymphoid neoplasm, complement activation, tumor-cell agglutination of blood vessel, marked lymphocytosis and also several lines of previous treatments were affect [9-12,15-18]. These factors also showed the status of the highly active and progression of disease. Some report explain the poor survival of patients who experienced IRR was higher probability of BM involvement and its relevant higher tumor burden and a high tumor load leads to a worse survival and to more IRR caused by rituximab treatment [9]. Although BM involvement of lymphoma was not observed, no strong correlations were observed between prognosis and the development of IRR. In this report, male patients were often developed IRR. But another reports not showed any correlations between male gender and IRR [9,19]. Our cases were small and not enough to define the correlation of between gender and IRR. In conclusion, B symptom, CRP, and gender might be important risk factors of the occurrence of IRR. Specific cytokines were not correlation with the infusion related reactions. Careful observation for IRR during rituximab administration is necessary for B cell non-Hodgkin's lymphoma with B symptoms, CRP positive, and male patients.

Conflict of Interest

The authors report no conflicts of interest.

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