Safety and Tolerability of a 90-minute Infusion of Originator and Biosimilar Rituximab in Rituximab-Naïve Patients

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Abstract

This study aimed to investigate the safety and tolerability of 90-min rapid infusion of rituximab, originator or biosimilar (Truxima), for rituximab-naïve patients with hematologic malignancy. We undertook a retrospective review of records of 118 patients (81 originator rituximab and 37 Truxima) with hematologic malignancy who had received rituximab rapid infusion from the first cycle of chemotherapy with corticosteroid premedication administration. Most patients had high Ann Arbor stage (80.9%), high International Prognostic Index risk (69.1%), favorable performance status (98.3%), and high lactate dehydrogenase level (78.8%). The patients received a collective total of 717 rapid rituximab infusions, with an average of 6 infusions per patient (range, 1-8). The incidence of infusion-related reactions (IRRs) of any grade and grade 3/4 during first infusion was 21.2% and 0.8%, respectively. No episode of grade 3/4 IRR was observed during the second and subsequent rituximab infusions. Severity and type of IRRs in Truxima administration were comparable to those of originator rituximab. This study suggests that 90-minute rituximab infusion with the first dose of chemotherapy was well tolerated. In terms of IRR, safety profiles of Truxima were comparable to that of originator rituximab, suggesting that Truxima might replace originator rituximab in a rapid infusion setting.

Introduction

Rituximab is a CD20 monoclonal antibody used in monotherapy or in combination with chemotherapy for treatment of various hematologic diseases, especially non-Hodgkin lymphoma¹. Even though rituximab displays a favorable safety profile, it can cause severe infusion-related reactions (IRRs), occurring mostly during the first infusion of cycle 1. Because of this, infusion of rituximab over a longer time, especially 4–6 hours at first dosing, is recommended by the manufacturer¹.

Currently, to reduce time- and labor-intensive processes and financial burden on hospitals owing to long rituximab infusion time, shorter infusion schedules have been investigated². Among them, the safety and feasibility of a 90-minute infusion of rituximab have been documented in several clinical studies^{2–9}. Based on these studies, the Food and Drug Administration (FDA) approved a 90-minute infusion schedule of rituximab (20% of the rituximab in the first 30 minutes and remaining 80% in the following 60 minutes) from the second treatment cycle for selected patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) or follicular lymphoma (FL) who did not experience severe IRRs with the recommended administration rates during cycle 1⁶. Interestingly, because of the low incidence of grade 3 or higher IRRs during the first 90 minutes of infusion (cycle 2) in the RATE trial, we hypothesized that increasing the infusion rate of the first dose of rituximab during the first cycle would not affect the safety profile. To date, there is no reported study regarding safety and feasibility of rapid infusion of rituximab beginning with the first dose.

Truxima (Celltrion, Incheon, Republic of Korea), a biosimilar rituximab, has been shown to have comparable efficacy and immunogenicity to the originator and has been approved for the same indications as originator rituximab in Europe and South Korea^{10–12}. In our practice, since January 2018,

our institution has used Truxima for all rituximab indications, including for patients with thrombotic thrombocytopenic purpura (TTP). Truxima, like originator rituximab, was administered at the standard infusion rate with premedication. To date, however, data on rapid infusion of Truxima are scarce.

Following results of published studies, we started to use rituximab in the form of rapid infusion in January 2018. Here, we report our experience with a 90-minute rituximab infusion from the first infusion in treatment of various hematologic malignancies. We compared the characteristics related to this rapid infusion rituximab between originator and biosimilar groups.

Results

Baseline characteristics

The characteristics of 118 patients who received the 90-minute rituximab infusion are shown in Table 1. The median age of patients at diagnosis was 65 years (range, 37–90), and 42.4% of patients were older than 70 years. Patients received a 90-minute rituximab infusion with either originator rituximab (68.6%) or Truxima, a biosimilar (31.4%). DLBCL (62.7%) and FL (14.4%) were the most common malignant diseases. Patients with Waldenstrom macroglobulinemia (WM, n = 4), Hodgkin lymphoma (HL, n = 1), and Burkitt lymphoma (n = 1) also were included. Most patients had high Ann Arbor stage (89/110, 80.9%), high IPI risk (69.1%), favorable performance status (ECOG PS $\leq$ 2, 98.3%), and high LDH level (78.8%). Most received either rituximab-CHOP (n = 89, 65.9%) or rituximab-CVP (n = 16, 11.9%) chemotherapy or rituximab monotherapy (n = 19, 14.1%), especially as the maintenance setting for patients with FL (n = 17, 12.4%). Other chemoregimens included R-ABVD for HL (rituximab, doxorubicin, bleomycin, vinblastine, and dexamethasone; n = 1), R-HyperCVAD (rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; n = 2), and VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone; n = 2).

Table 1
Baseline characteristics of the patients

	All patients (n = 118)	Originator (n = 81)	Truxima (n = 37)	<i>P</i>
Age, median, (range), yrs	65 (37–90)	64 (37–90)	66 (44–85)	0.898
≥ 70 yrs old	50 (42.4)	33 (40.7)	17 (45.9)	0.596
Sex				0.941
Male	60 (50.8)	41 (50.6)	19 (51.4)	
Female	58 (49.2)	40 (49.4)	18 (48.6)	
Diagnosis				0.215
DLBCL	74 (62.7)	45 (55.6)	29 (78.4)	
FL	17 (14.4)	12 (14.8)	5 (13.5)	
MZL	13 (11)	11 (13.6)	2 (5.4)	
MCL	3 (2.5)	3 (3.7)	0 (0)	
CLL	5 (4.2)	5 (6.2)	0 (0)	
WM	4 (3.4)	3 (3.7)	1 (2.7)	
Other lymphomas	2 (1.7)	2 (2.5)	0 (0)	
Ann Arbor stage ^a				0.402
I	10/110 (9.1)	7/74 (9.6)	3/36 (8.3)	
II	11/110 (10)	5/74 (6.8)	6/36 (16.7)	
III	41/110 (37.3)	30/74 (41.1)	11/36 (30.6)	
IV	48/110 (43.6)	31/74 (42.5)	16/36 (44.4)	
B symptom	28 (23.7)	17 (21)	11 (29.7)	0.300
ECOG PS ≤ 2	116 (98.3)	80 (98.8)	36 (97.3)	0.813

DLBCL diffuse large B-cell lymphoma, *FL* follicular lymphoma, *MZL* marginal zone lymphoma, *MCL* mantle cell lymphoma, *CLL* chronic lymphocytic leukemia, *WM* Waldenstrom macroglobulinemia, *ECOG PS* Eastern Cooperative Oncology Group performance status, *IPI* International Prognostic Index, *LDH* lactate dehydrogenase, *COPD* chronic pulmonary obstructive disease, *R-CHOP* rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone, *R-CVP* rituximab-cyclophosphamide-prednisone, *R* rituximab, *BR* bendamustine-rituximab, *R-FC* rituximab-fludarabine-cyclophosphamide

^aExcluded patients with CLL and WM

*Included maintenance rituximab therapy in patients with FL (n = 17)

	All patients (n = 118)	Originator (n = 81)	Truxima (n = 37)	<i>P</i>
IPI risk ^a				0.577
Low	13/110 (11.9)	6/74 (8.2)	6/36 (16.7)	
Low-intermediate	21/110/ (19.1)	12/74 (16.4)	9/36 (25)	
High-intermediate	44/110/ (40)	32/74 (43.8)	12/36 (33.3)	
High	32/110/ (29.1)	23/74 (31.5)	9/36 (25)	
Elevated LDH level	93 (78.8)	62 (76.5)	31 (83.8)	0.372
Comorbidities				0.568
Hypertension	29 (22.5)	21 (25.9)	8 (21.6)	
Diabetes mellitus	9 (6.6)	7 (8.7)	2 (5.4)	
Arrhythmia	3 (2.2)	2 (2.5)	1 (2.7)	
COPD	4 (3.4)	2 (2.5)	2 (5.4)	
Heart failure	4 (3.4)	3 (3.7)	1 (2.7)	
Others	26 (22.1)	18 (22.2)	8 (21.6)	
Chemotherapy				0.569
R-CHOP	89 (65.9)	57 (61.3)	32 (76.2)	
R-CVP	16 (11.9)	12 (12.9)	4 (9.5)	
R monotherapy*	19 (14.1)	14 (15.1)	5 (11.9)	
BR	3 (2.2)	2 (2.2)	1 (2.4)	
R-FC	3 (2.2)	3 (3.2)	0 (0)	
Others	5 (3.7)	5 (5.5)	0 (0)	
<i>DLBCL</i> diffuse large B-cell lymphoma, <i>FL</i> follicular lymphoma, <i>MZL</i> marginal zone lymphoma, <i>MCL</i> mantle cell lymphoma, <i>CLL</i> chronic lymphocytic leukemia, <i>WM</i> Waldenstrom macroglobulinemia, <i>ECOG PS</i> Eastern Cooperative Oncology Group performance status, <i>IPI</i> International Prognostic Index, <i>LDH</i> lactate dehydrogenase, <i>COPD</i> chronic pulmonary obstructive disease, <i>R-CHOP</i> rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone, <i>R-CVP</i> rituximab-cyclophosphamide-prednisone, <i>R</i> rituximab, <i>BR</i> bendamustine-rituximab, <i>R-FC</i> rituximab-fludarabine-cyclophosphamide				
^a Excluded patients with CLL and WM				
*Included maintenance rituximab therapy in patients with FL (n = 17)				

Overall outcomes of rapid rituximab infusion

Overall treatment outcomes of rapid infusion are summarized in Table 2. Patients received a collective total of 717 rapid rituximab infusions, with an average of 6 infusions per patient (range, 1–8). Seventeen patients with FL received rituximab alone as maintenance therapy following induction therapy, with a median of 6 cycles (range, 1–8). Of the total, 81% of rituximab infusions were administered with steroid-containing chemoregimens. The median dose of rituximab per infusion was 603 mg (range, 525–656). Overall response rate after rituximab-containing therapy was 88.1%. During a median follow-up of 631 days (range, 16-5119 days), 5-year progression-free survival (PFS) and overall survival (OS) rate were 63.1% and 80%, respectively. There were no rituximab-induced deaths in this study.

Table 2
Overall outcomes of rapid rituximab infusion

	All (n = 118)	Originator (n = 81)	Truxima (n = 37)	P
Number of R infusion,				
Total number of infusions	717	487	230	0.010
Per patient, median (range)	6 (1–8)	6 (1–8)	6 (1–8)	0.158
Dosage of R per infusion, mg				0.987
Median	603	603	604	
Range	(525–656)	(525–653)	(527–656)	
Concomitant steroid administration, n (%)	81.5	79.5	85.7	0.989
Response after R-containing therapy, n (%)				0.527
Complete response	87 (73.7)	60 (74.1)	27 (73)	
Partial response	17 (14.4)	12 (14.8)	5 (13.5)	
Progressive disease	1 (0.8)	0 (0)	1 (2.7)	
Not evaluable	13 (11)	9 (11.1)	4 (10.8)	
5-year PFS rate, %	63.1	62.2	89.8	0.765
5-year OS rate, %	80	72.4	90.6	0.458
Follow-up duration, days				0.021
Median	631	810	319	
Range	(16–4119)	(29–4119)	(16–688)	
<i>R</i> rituximab, <i>PFS</i> progression-free survival, <i>OS</i> overall survival				

IRRs during first infusion

IRRs during each rituximab infusion are summarized in Table 3. The incidence of IRRs of any grade during first infusion was 21.2% (n = 25). Most of IRRs were grade 1 or 2, except for grade 3 IRRs in one R-CHOP-treated patient with DLBCL (hypotension). No grade 4 IRRs were observed during the first rituximab infusion. Skin rash or urticaria (5.1%) was the most common symptom of IRR. Of patients who experienced IRRs, 17.3% (4/23) had more than two symptoms. Management of IRRs included administration of additional medications (≥ 2 in some cases), fluid hydration, and oxygen supplement.

For one patient experiencing IRR of grade 3, rituximab infusion was temporarily interrupted the infusion. After symptoms resolved, this patient resumed rituximab infusion at a minimum 50% reduction in rate and completed the infusion schedule. No clinical factors such as older age and high LDH level were significantly associated with the occurrence of any grade or grade 3 IRRs.

Table 3
IRRs during rituximab infusion

	Infusion 1 (n = 118)	Infusion 2 (n = 109)	Infusion 3 (n = 102)	Infusion 4 (n = 92)	Infusion 5 (n = 81)	Infusion ≥ 6 (n = 78)
IRRs						
Rash/urticaria	6 (5.1)	3 (2.7)	3 (2.7)	1 (1.1)	0 (0)	2 (2.6)
Nausea/vomiting	4 (3.2)	2 (1.8)	1 (0.9)	2 (2.2)	2 (2.4)	0 (0)
Pruritus	3 (2.5)	1 (0.9)	2 (1.8)	2 (2.2)	2 (2.4)	1 (1.3)
Nasal congestion	2 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sore throat	2 (1.6)	1 (0.9)	1 (0.9)	0 (0)	0 (0)	0 (0)
Headache	2 (1.6)	1 (0.9)	1 (0.9)	0 (0)	1 (1.2)	0 (0)
Cough	2 (1.6)	1 (0.9)	0 (0)	1 (1.1)	0 (0)	0 (0)
Hypoxia	2 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	2 (1.6)	2 (1.8)	1 (0.9)	1 (1.1)	0 (0)	0 (0)
Chill	2 (1.6)	1 (0.9)	1 (0.9)	2 (2.2)	1 (1.2)	0 (0)
Fever	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Chest discomfort	1 (0.8)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)
Hypertension	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypotension	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade						
Grade 1	16 (13.6)	10 (9)	8 (7.2)	5 (5.5)	4 (4.8)	3 (3.9)
Grade 2	6 (5.1)	3 (2.7)	3 (2.7)	2 (2.2)	1 (1.2)	0 (0)
Grade 3	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

	Infusion 1 (n = 118)	Infusion 2 (n = 109)	Infusion 3 (n = 102)	Infusion 4 (n = 92)	Infusion 5 (n = 81)	Infusion ≥ 6 (n = 78)
Management						
Antihistamine	14 (11.2)	4 (3.6)	5 (4.5)	3 (3.3)	2 (2.4)	3 (3.9)
Antiemesis	4 (3.2)	2 (1.8)	1 (0.9)	2 (2.2)	2 (2.4)	1 (1.3)
Steroid	3 (2.5)	2 (1.8)	2 (1.8)	1 (1.1)	0 (0)	0 (0)
Hydration	3 (2.5)	0 (0)	1 (0.9)	0 (0)	0 (0)	0 (0)
Antipyretics	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Others	6 (5)	7 (6.3)	3 (2.7)	3 (3.3)	3 (3.6)	0 (0)
Slow/interruption	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<i>IRRs</i> infusion-related reactions						

IRRs from second infusion and thereafter

The proportion of patients experiencing IRRs decreased with each rituximab infusion (Table 3). Overall, all reported symptoms regarding IRRs were mild and resolved within 24 hours after infusion. Symptoms of IRRs reported with subsequent rituximab infusions were similar to those of IRRs in the first rituximab infusion. No episode of grade 3 or 4 IRRs were observed during the second and subsequent rituximab infusions. At the second infusion, rituximab infusion rate was temporarily slowed in one patient with DLBCL displaying vague chest discomfort (grade 2). All patients who had IRRs during the first infusion did not have other IRRs during subsequent infusions. Among the patients with FL who received maintenance rituximab, only one experienced IRR (grade 1 urticaria) at the third rituximab infusion and was administered an oral antihistamine.

Comparison between originator rituximab and Truxima regarding IRRs

There was no significant difference in baseline demographic characteristics and treatment outcomes including survival and response rates between originator and Truxima-treated groups, except for total number of infusions (487 vs. 230, $p = 0.01$) resulting from short follow-up duration (810 vs. 319 days, $p = 0.021$) in the Truxima-treated group (Tables 1 and 2). Severity and type of IRRs with Truxima administration were comparable to those of originator rituximab. The incidence of IRRs of each rituximab infusion is summarized in Fig. 2. This incidence was similar between groups during and within 24 hours of infusion 1 (17.2% vs. 24.3%), infusion 2 (12% vs. 11.7%), infusion 3 (10% vs. 12.5%), infusion 4 (6.7% vs. 9.4%), infusion 5 (7.5% vs. 3.7%), and infusion 6 (3.8% vs. 3.8%). During the first rituximab infusion,

grade 3 IRRs were observed in one originator rituximab-treated patient (hypotension). No grade 3 or 4 IRRs occurred in Truxima-treated patients during first or subsequent infusions.

Discussion

This is the first study to provide evidence to support initiation of 90-minute rituximab infusion in rituximab-naïve patients. In this study, first and subsequent infusions of rituximab over 90 minutes can be safely administered in rituximab-naïve patients with hematologic malignancies. Additionally, this study is the first to include patients receiving Truxima, a biosimilar rituximab, in a rapid rituximab infusion protocol.

Safety and feasibility of 90-minute rituximab infusion have been evaluated in several studies, in which the low incidence of severe IRRs was observed^{3,5,13,14}. Thus, accelerating the infusion rate of rituximab from the first cycle should not affect the safety profiles by reinforcing premedication before rituximab administration to reduce the risk and severity of IRRs. In the standard infusion method, any grade IRRs were reported in 77% of patients in the first cycle and 33% in the remaining cycles¹. In the RATE trial, grade 3 or higher IRRs occur in 2.4% of patients during the first infusion at a standard infusion rate and in 1.1% of patients for the first rapid infusion⁶. Even though our patients did not receive the first dose of rituximab according to the standard titration scheme, the incidence of any grade or grade 3/4 IRRs during first rapid infusion (19.5% and 0.8%, respectively) was comparable to those of previous studies during first standard infusion, showing no increased IRRs in 90-minute infusion^{3,6,9}. Most IRRs occurred during the first infusion, with a decreased incidence during second and subsequent infusions. The IRRs were generally resolved by temporary pause in the infusion and supportive care, consistent with previous studies^{2,3,5,6,14}. In the present study, patients with older age (≥ 70 years) and high tumor burden, such as high disease stage and high LDH level, received 90-minute rituximab infusion without severe IRRs. Based on our findings, 90-min rituximab infusion from the first cycle of therapy is a feasible and tolerable treatment option for patients with hematologic malignancies. By decreasing the time, the patients need to spend in the infusion center, rapid rituximab infusion can mitigate an important obstacle to patient acceptance of rituximab therapy.

In many studies, premedication usually included acetaminophen and an antihistamine before each rituximab infusion to prevent or minimize serious adverse drug events, but the use of corticosteroid as a part of premedication varies widely^{2-6,9}. In the RATE study, corticosteroid (prednisone or prednisolone) was administered mandatorily prior to rituximab infusion, and only 1.1% of grade 3 IRRs was reported⁶. Similarly, Atay et al. reported a 2-year experience with 90-minute rituximab infusion in which 75 patients were recommended to receive daily corticosteroid prior to rituximab infusion, and no grade 3 or 4 IRRs were observed³. All patients included in the present study also received a corticosteroid (hydrocortisone) 30 minutes prior to each rituximab infusion. Even though there is some controversy about the role of corticosteroid for preventing or reducing the occurrence of IRRs, introduction of corticosteroid premedication might be an important factor that does not increase incidence of severe IRRs during first

rituximab infusion over 90 minutes. Further studies are needed to provide evidence supporting the role of corticosteroid as a premedication in first rituximab infusion.

Truxima, a biosimilar rituximab, has been used for treatment of malignant and autoimmune diseases was shown to be equivalent to originator rituximab in terms of efficacy, safety, and immunogenicity, resulting in potential for significant cost saving¹⁰⁻¹². In this study, the safety profiles of originator rituximab and Truxima were evaluated, with no significant differences identified between groups in term of IRRs. The incidence of IRRs during the first infusion among Truxima-treated patients was 24.3%, which is slightly higher than that in originator rituximab-treated patients (17.2%), though the difference was not significant. One explanation of this result could be the small sample size of the Truxima group. The incidence of any grade and ≥ 3 grade IRRs during the first cycle is similar to previous finding of Truxima treatment in patients with newly diagnosed DLBCL and FL (24.3% vs. 24% and 0% vs. 0%, respectively)¹⁰. Most IRRs following Truxima administration over 90 minutes were mild and manageable, usually observed in the first cycle of treatment. The severity and type of IRRs and treatment outcomes were similar between originator rituximab and Truxima during first and subsequent rapid infusions. Based on our study, safety profiles and efficacy of Truxima administration over 90 minutes were comparable to those of originator rituximab, suggesting that Truxima might replace originator rituximab in a rapid rituximab infusion setting, resulting in reduced time and financial burden for patients.

This study has potential limitations, mostly stemming from the retrospective design. First, some patients receiving rituximab did not meet the inclusion criteria owing to lack of complete information regarding rapid infusion. In addition, any delayed IRRs following rituximab administration in both groups were not evaluated because most patients were discharged after 24 hours of rituximab administration if there were no adverse events. Another limitation of our study is lack of direct comparison data with patients receiving standard duration infusions in our institution. However, our results on safety and tolerability compare favorable to previously reported data regarding 90-minute rituximab infusion. Despite these limitations, we believe that our retrospective study provides clinical findings in that it could be of practical evidence for physicians who consider a 90-min rituximab infusion in their treatment options for hematologic malignancies.

In conclusion, in our experience, rituximab infusion time of 90 minutes is feasible and well tolerated by patients when administered as the first and subsequent infusions in the course of therapy with corticosteroid premedication, allowing considerable saving of time and cost of the patients and potentially ameliorating their adherence to treatment. In terms of IRR, safety profiles of Truxima, a biosimilar rituximab, were comparable to that of originator rituximab, suggesting that Truxima might replace originator rituximab in a rapid infusion setting. In the future, a comparative, prospective clinical trial is warranted to confirm these findings.

Methods

Patients and study design

In this study, the medical records of 148 patients (≥ 18 years) who received at least one dose of rituximab over 90 minutes for treatment of various diseases between January 2010 and December 2020 in Ewha Womans University Mokdong Hospital were reviewed retrospectively. Thirty patients were excluded because of insufficient data regarding rituximab infusion, central nervous system involvement, or non-malignant diseases such as TTP. Finally, 118 patients (81 originator rituximab and 37 Truxima) were enrolled in this study (Fig. 1). The following clinical data were collected: baseline characteristics (age at diagnosis, sex, underlying comorbidities [especially cardiopulmonary disease], disease type, stage of disease, Eastern Cooperative Oncology Group performance status [ECOG PS], International Prognostic Index [IPI], lactate dehydrogenase [LDH] level, chemotherapy received, number of rituximab infusions, dosage of rituximab infused) and IRR defined as adverse events that occurred during or within 24 hours of infusion^{2,6}. If a patient experienced an IRR, additional data were collected from nursing infusion records, including signs/symptoms of the IRRs and management for the IRRs (administration of additional medication, interruption/resume of rituximab infusion). This study was approved by the Institutional Review Board of Ewha Womans University Mokdong Hospital with a waiver of informed consent owing to its retrospective nature (IRB No. EUMC 2021-03-035) and was performed in accordance with the tenets of the Declaration of Helsinki.

Administration of rituximab

Depending on disease type, rituximab was administered at a standard dose of 375 mg/m^2 (in 250 mL normal saline) as monotherapy or combination with chemotherapy such as CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisolone), CVP (cyclophosphamide, vincristine, and prednisolone), or bendamustine up to eight cycles according to standard practice. Among the patients with FL, rituximab as a maintenance setting was administered at 375 mg/m^2 every 2 months for up to 2 years. Patients were given rapid rituximab infusion at a rate of 166 mL/hr for 90 minutes in total, and most of the infusions were administered in an inpatient setting. Regardless of treatment type, monotherapy or combination with chemotherapy, all patients received premedication with corticosteroid (intravenous hydrocortisone 100 mg), oral acetaminophen (650 mg), H2 antagonists (intravenous), and antihistamine (intravenous pheniramine 4 mg) 30 minutes prior to rituximab infusion with all courses to reduce the risk and severity of IRRs. During each rapid infusion, symptoms and signs including blood pressure, respiratory rate, pulse rate, and body temperature were monitored for IRRs 4 times at every 30 minutes (baseline, 30 min, 60 min, and 90 min) and then every 4 hours for 24 hours. When grade 3 or higher IRRs occurred, rituximab infusion was interrupted or slowed, and additional medications (corticosteroid, antihistamine, antiemetics, antipyretics, hydration) were administered promptly at the physician's discretion. Any adverse events were classified using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analysis

Continuous variables are expressed as median (range) and categorical variables as proportion. Fisher's exact test or chi-square test were used to compare the difference in frequency of categorical variables such as infusion reaction rate between the groups. Continuous variables were compared using Student's *t*

test or the Wilcoxon rank sum test. All p values presented were two-sided, and $P < 0.05$ considered statistically significant. All statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, NY, USA).

Declarations

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Author contributions

Y.H.P.: Writing of the protocol, treatment of patients, data acquisition, analysis and interpretation of the data, and writing of the manuscript; **Y.C.M.:** Treatment of patients, data acquisition, analysis and interpretation of the data; **S.W.L.:** Treatment of patients, data acquisition, analysis and interpretation of the data; **D.Y.K.:** Research design, writing of the protocol, treatment of patients, data acquisition, analysis, interpretation of the data, and writing of the manuscript.

All authors reviewed the manuscript, made edits, and approved the final product.

Conflict of interest

The authors declare no competing interests.

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Figures

Figure 1

Study enrollment flow diagram, *Maintenance therapy for follicular lymphoma

Figure 2

IRRs during or within 24 hours of each rituximab infusion. IRR, infusion-related reaction; Error bars are 95% CI of the percentage.