

A novel prednisone premedication protocol significantly decreases infusion-related reactions of rituximab in newly diagnosed diffuse large B-cell lymphoma

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Abstract. Rituximab is a widely used anti-CD20 monoclonal antibody with a high incidence of infusion-related reactions (IRRs) during administration. Reducing the incidence of IRRs remains problematic in hematological practices. In the present study, a novel strategy of a prednisone pretreatment regimen was designed similar to the combination of rituximab, cyclophosphamide, epirubicin, vincristine and prednisone (R-CHOP) with the aim of exploring the effect on the incidence of IRRs to rituximab in patients with diffuse large B-cell lymphoma (DLBCL). A prospective, randomized (1:1) and controlled study was conducted in three regional hospitals in two groups (n=44 for each group): i) A control group treated with standard R-CHOP-like regimen; and ii) a group receiving a prednisone-pretreatment, modified R-CHOP-like protocol for newly diagnosed patients with DLBCL. The primary endpoint was to assess the incidence of IRRs to rituximab, as well as the association of IRRs with the efficacy of treatment. The second endpoint involved clinical outcomes. The total incidence of IRRs to rituximab in the treatment group was significantly lower compared with that in the control group (15.9 vs. 43.2%; $P=0.0051$). The different grade incidence of IRRs was lower in the treatment group compared with that in the control group ($P=0.0053$). In total, 29.5% of patients (26/88) experienced >1 IRR episode. The incidence of IRRs in the pre-treatment group was decreased compared with that in the control group in the 1st cycle (15.9 vs. 43.2%; $P=0.0051$) and 2nd cycle (6.8 vs. 27.3%; $P=0.0107$). The overall response rate was similar between the two groups ($P>0.05$). Median progression-free survival and median

overall survival time were not statistically distinct between the two groups ($P=0.5244$ and $P=0.5778$, respectively). Grade \geq III toxicities mainly included vomiting and nausea (<20%), leukopenia and granulocytopenia (<20%), and alopecia (<25%). No death events were reported. Apart from IRRs to rituximab, the incidence of other adverse events was similar in both groups. The novel prednisone-pretreatment R-CHOP-like protocol in the present study significantly decreased the total and different grade incidences of IRRs to rituximab among newly diagnosed patients with DLBCL. This clinical trial was retrospectively registered with the Chinese Clinical Trial Registry (registration number, ChiCTR2300070327; date of registration, 10 April 2023).

Introduction

According to the latest studies, non-Hodgkin lymphoma (NHL) is the most common hematological malignancy worldwide, accounting for ~3% of cancer incidence and mortality (1). CD20⁺ B-cell NHL includes diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL) and marginal zone lymphoma (MZL), accounting for 80% of all NHL cases (2). Despite newly developed therapies and protocols (such as the next-generation anti-CD20 monoclonal antibody obinutuzumab, Bruton's tyrosine kinase inhibitors and chimeric antigen receptor T-cell immunotherapy), rituximab-based regimens such as the combination of rituximab, cyclophosphamide, epirubicin, vincristine and prednisone (R-CHOP) are still the standard first-line therapeutic strategy for treating DLBCL worldwide (3).

Rituximab is a chimeric human/mouse monoclonal antibody that directly targets the CD20 antigen present on the surface of normal and malignant B lymphocytes. Currently, the anti-lymphoma mechanisms of rituximab have been ascribed to antibody-dependent, cell-mediated cytotoxicity and complement-dependent cytotoxicity through the binding of the fragment antigen-binding domain of rituximab to the CD20 antigen (4). Furthermore, R-CHOP regimens improve rates of progression-free survival (PFS) and overall survival (OS) in patients with DLBCL (5). However, the infusion-related reactions (IRRs) of rituximab, which occur particularly after

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the first infusion, with an incidence of 30-50%, have become a major clinical problem for hematologists and patients with DLBCL (6,7). The main symptoms of IRRs vary from mild to life threatening, the latter of which results in discontinued rituximab treatment and, therefore, affects clinical outcome (8). Thus, further exploration of how to reduce the incidence of IRRs to rituximab to improve the quality of life for patients with DLBCL is needed.

Rituximab has also been commonly administered to patients with autoimmune disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Notably, the IRR rate of rituximab was higher in patients with B-cell NHL (25.0-35.9%) compared with patients with SLE and RA (9.4-17.5%; $P < 0.0001$) (9,10). Compared with patients with B-cell NHL, patients with SLE and RA are invariably administered concomitant steroid treatment, such as prednisone, prior to rituximab treatment, which might, in part, explain the immunosuppressive status and the resulting lower incidence of rituximab IRRs (11). Inspired by these previous results, a prospective, randomized and controlled study for patients with DLBCL was conducted, which aimed to compare the incidence of rituximab IRRs between standard R-CHOP-like regimens and a prednisone premedication-modified R-CHOP-like protocol.

Materials and methods

Patient selection. Patients with newly-diagnosed DLBCL (age range, 18-70 years; $n=88$) were enrolled between January 2019 and August 2022 in the study at Jiujiang University Affiliated Hospital (Jiujiang, China), Ruichang People's Hospital (Ruichang, China) and Lushan People's Hospital (Lushan, China). Inclusion criteria were as follows: i) All patients were ≥ 18 years old at admission; ii) all the pathological diagnoses of DLBCL were confirmed in the Pathology Department of Jiujiang University Affiliated Hospital; and iii) all patients consented to participate in the study and signed an informed consent form. Exclusion criteria were as follows: i) The patient had a history of rituximab treatment prior to enrollment in the study; ii) the patient refused to participate in the study; and iii) the patient was initially diagnosed with central nervous system DLBCL or HIV-related DLBCL.

The clinicopathological features of all patients at diagnosis were recorded (Table I), including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (12), bulky lesion (i.e., the longest diameter of nodal masses >10 cm in size), number of extra-nodal sites, serum level of lactate dehydrogenase, B symptoms, Lugano stage (version 2014) (13) and age-adjusted International Prognostic Index (i.e. low-, moderate- and high-risk).

Cohort size calculation and randomization. The cohort size was assessed based on the minimum requirement of a 25% reduction in the incidence of rituximab IRRs; that is 40% of standard regimen and 15% of modified protocol. The relative parameters were set as 80% power, 10% α error (based on a one-sided test) and 10% estimated loss rate. According to the calculation formula of cohort size in clinical trials (PASS version 15.0; www.ncss.com), the anticipated total cohort size included 88 cases, with 44 cases per group (14).

According to the random number table method, the 88 patients with DLBCL were divided into two groups with balanced randomization (1:1).

Therapeutic regimens. In the control group, standard R-CHOP-like regimens were administered as follows: 375 mg/m² Rituximab (Roche Diagnostics), intravenously on day 1; 750 mg/m² cyclophosphamide (Jiangsu Hengrui Pharmaceuticals Co., Ltd.), intravenously on day 2; 60 mg/m² epirubicin (Zhejiang Hisun Chemical Co., Ltd.) or 30 mg/m² pegylated liposomal doxorubicin (CSPC Pharmaceutical Group Ltd.), intravenously on day 2; 1.4 mg/m² vincristine (maximum dose of 2 mg; Zhejiang Hisun Chemical Co., Ltd.), intravenously on day 2; and 100 mg/day prednisone (Zhejiang Xianju Pharmaceutical Co., Ltd.), orally on days 1-5.

The treatment group received the modified R-CHOP-like regimen as follows: 100 mg/day Prednisone, orally on days 1-5; 375 mg/m² rituximab, intravenously on day 4; 750 mg/m² cyclophosphamide, intravenously on day 5; 60 mg/m² epirubicin or 30 mg/m² pegylated liposomal doxorubicin, intravenously on day 5; and 1.4 mg/m² vincristine (maximum dose of 2 mg), intravenously on day 5.

For both groups, the treatment cycle was repeated every 21 days and the total number of cycles was 6-8 cycles according to each patient's condition. All patients in the control and treatment groups were given 25 mg diphenhydramine intramuscularly and 25 mg indometacin orally 30 min prior to rituximab treatment. Rituximab was mixed with 500 ml normal saline and infused intravenously with an initial rate of 50 mg/h, increasing gradually by 50 mg/h every 30 min until it reached 400 mg/h.

If no IRRs occurred during the 1st and 2nd cycle, the initial rate of rituximab infusion was 100 mg/h during the 3rd and all subsequent cycles, then increased by 100 mg/h every 30 min up to 400 mg/h for 6-8 cycles.

Incidence of IRR grade to rituximab and chemotherapeutic adverse events. The primary endpoint of the study was the incidence of IRRs to rituximab from the 1st to the 4th cycle. IRRs to rituximab and chemotherapeutic adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) (15). All the episodes of adverse events were recorded in detail, such as vomiting, nausea, leukopenia, granulocytopenia, alopecia, thrombocytopenia and cardiotoxicity.

Clinical outcome evaluation. The secondary endpoint was clinical efficacy, including the short- and long-term outcomes, which were evaluated after every two cycles of treatment according to the 2014 Lugano classification (16). The short-term outcomes included complete remission (CR), partial remission (PR), stable disease and progressive disease (PD). Overall response rate (ORR) included CR and PR. The long-term outcomes comprised PFS and OS; PFS was calculated from the start of treatment until disease progression (i.e. any appearance of a new lesion or enlargement of the remitted targeted lesion), and OS was defined from the date of treatment until death or the end of follow-up. The last follow-up was completed in November 2022.

Statistical analysis. All statistical analyses were performed using SPSS (version 19.0; IBM Corp.) and GraphPad Prism (version 7.0; Dotmatics). Continuous variables are presented as the mean \pm standard deviation, analyzed by unpaired Student's t-test. Categorical variables are presented as counts and percentages, and were assessed by χ^2 or Fisher's exact test. Rank data were analyzed using ridit analysis. Survival data (PFS and OS) were analyzed using the Kaplan-Meier method, and the log-rank test was used to compare the survival outcomes of the two groups. A one-sided test was used in the study, and $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Clinical features. A total of 88 patients with DLBCL were included in this study. As shown in Table I, there were no marked differences in baseline clinicopathological features between the control and the treatment groups ($P > 0.05$).

IRR incidence of rituximab. As presented in Table II, the total incidence of IRRs to rituximab in the treatment group was significantly lower compared with that in the control group (15.9% vs. 43.2%; $P = 0.0051$). In addition, there was a significant difference in incidence between the different grades of IRRs by ridit analysis ($P = 0.0053$). The vast majority of actual IRRs to rituximab were grade I and II in both groups. Grade III or higher IRRs to rituximab were only reported in 9.1% (4/44) and 2.3% (1/44) of patients in the control and treatment groups, respectively. These results strongly indicated that the prednisone premedication modification decreased the total incidence of IRRs to rituximab, but did not affect the incidence of different grades of IRRs to rituximab.

In the present study, 26 out of the 88 total patients (29.5%) experienced >1 IRR episode. As shown in Table III, the incidence of IRRs to rituximab in the treatment group was significantly lower compared with that of the control group in the 1st (15.9 vs. 43.2%; $P = 0.0051$) and 2nd (6.8 vs. 27.3%; $P = 0.0107$) cycle; however, no significant differences were identified in the 3rd and 4th cycle.

Clinical outcomes. The clinical outcomes of both groups were compared. As indicated in Table IV, no significant differences in ORRs were observed between the control and the treatment group by either ridit analysis or χ^2 test. As shown in Fig. 1, the median PFS (mPFS) was 37.4 and 36.4 months in the control and treatment group, respectively ($P = 0.5244$). Additionally, although median OS (mOS) was not reached within the follow up of 47 months, no significant difference in OS was found between the two groups ($P = 0.5878$). These results strongly suggested that the prednisone premedication did not influence the clinical outcomes in patients with DLBCL.

Adverse events. As indicated in Table V, the common adverse events included hematological and non-hematological toxicities. The majority of adverse events were of grade I and II. The grade \geq III toxicities mainly included vomiting and nausea ($<20\%$), leukopenia and granulocytopenia ($<20\%$), alopecia ($<25\%$), thrombocytopenia ($<10\%$) and cardiotoxicity ($<5\%$). The main hematological and non-hematological toxicities

Table I. Baseline clinicopathological features of patients in the control (n=44) and pretreatment (n=44) groups.

Clinicopathological feature	Control group	Treatment group	P-value
Age, years ^a	48.5 \pm 6.75	45.9 \pm 5.92	0.0581 ^b
Sex, n (%)			0.1355 ^c
Male	18 (40.9)	25 (56.8)	
Female	26 (59.1)	19 (43.2)	
ECOG score, n (%)			0.1347 ^c
0-1	20 (45.5)	27 (61.4)	
2-4	24 (54.5)	17 (38.6)	
Bulky lesion, n (%)			0.5135 ^c
Present	16 (36.4)	19 (43.2)	
Absent	28 (63.6)	25 (56.8)	
B symptoms, n (%)			0.3754 ^c
Present	14 (31.8)	18 (40.9)	
Absent	30 (68.2)	26 (59.1)	
Number of extra-nodal sites, n (%)			0.2373 ^c
≤ 2	10 (22.7)	15 (34.1)	
> 2	34 (77.3)	29 (65.9)	
LDH, n (%)			0.3858 ^c
Normal	16 (36.3)	20 (45.5)	
Elevated	28 (63.6)	24 (54.5)	
Lugano stage, n (%)			0.3102 ^d
I	7 (15.9)	9 (20.5)	
II	8 (18.2)	11 (25.0)	
III	25 (56.8)	21 (47.7)	
IV	4 (9.1)	3 (6.8)	
aaIPI, n (%)			0.2804 ^d
Low-risk	5 (11.4)	9 (20.5)	
Intermediate-high risk	30 (68.2)	28 (63.6)	
High risk	9 (20.5)	7 (15.9)	

^aAge data are presented as the mean \pm SD, other data are presented as n (%). ^bt-test. ^c χ^2 test. ^dRidit test. aaIPI, age-adjusted International Prognostic Index; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

were manageable with dose adjustment and supportive care. No deaths associated with adverse events were reported. Notably, there was no significant difference in adverse event incidence between the two groups, with the exception of IRRs to rituximab (Table II).

Discussion

Rituximab-based R-CHOP regimens have been broadly administered in patients with DLBCL in China. The issue of IRRs to rituximab has become a major obstacle that cannot be ignored. At present, the mechanisms of IRRs have been mainly attributed to rituximab-induced cytokine release syndrome,

Table II. IRR incidence of rituximab in the two groups (n=44 patients/group).

IRR grade	Control group, n (%)	Treatment group, n (%)	P-value
0 ^a	25 (56.8)	37 (84.1)	0.0053 ^b
I	5 (11.4)	2 (4.5)	
II	10 (22.7)	4 (9.1)	
III	3 (6.8)	1 (2.3)	
IV	1 (2.3)	0 (0.0)	
V	0 (0.0)	0 (0.0)	
Total incidence	19 (43.2)	7 (15.9)	0.0051 ^c

^aNo IRRs to rituximab. ^bRidit test. ^c χ^2 test. IRRs, infusion-related reactions.

Table III. Occurrence cycles of rituximab IRRs between the two groups (n=44 patients/group).

Cycle	Number of IRRs		P-value
	Control group, n (%)	Treatment group, n (%)	
1st	19 (43.2)	7 (15.9)	0.0051 ^a
2nd	12 (27.3)	3 (6.8)	0.0107 ^a
3rd	5 (11.4)	0 (0.0)	
4th	1 (2.3)	0 (0.0)	

^a χ^2 test. IRRs, infusion-related reactions.

which involves the release of TNF- α , IL-1 and IL-6 in the blood (17). Rising levels of cytokines trigger a series of symptoms of inflammatory response, including fever, chills, rigors, rash, headache, hypotension, breathlessness, bronchospasm, nausea, vomiting and even allergic shock (8,18). Additionally, some factors were found to be associated with a risk of IRRs to rituximab. Laudati *et al* (19) demonstrated that female patients exhibited a higher incidence of IRRs to rituximab compared with male patients with CD20+ B-cell NHL (34.1 vs. 21.1%; P=0.04). Cho *et al* (6) reported that B symptoms were independently related to IRRs to rituximab [hazard ratio (HR), 1.850; P=0.036], whereas bone marrow (BM) infiltration was independently linked to re-IRR (>2 repeated experiences) to rituximab (HR, 4.904; P=0.029). Similarly, Ohata *et al* (20) showed that BM involvement was a distinctive risk factor for IRRs to rituximab in patients with CD20+ B-cell NHL. The results indicated that both B symptoms and BM infiltration were the high-risk indicators for IRRs to rituximab in patients with DLBCL.

According to a patient survey, 34.0-49.5% of those with B-cell NHL, including DLBCL, experienced IRRs at least once during treatment with rituximab (6,7,11,20). Generally, the majority of IRRs to rituximab were of mild

Table IV. Clinical outcomes in the two groups (n=44 patients/group).

Clinical efficacy	Control group, n (%)	Treatment group, n (%)	P-value
CR	12 (27.3)	14 (31.8)	0.9383 ^a
PR	29 (65.9)	25 (56.8)	
SD	2 (4.5)	3 (6.8)	
PD	1 (2.3)	2 (4.5)	
ORR	41 (93.2)	39 (88.6)	0.7133 ^b

^aRidit test. ^b χ^2 or Fisher's exact test. CR, complete remission; ORR, overall response rate; PD, partial disease; PR, partial remission; SD, stable disease.

to moderate degree, whereas ~10% of patients with B-cell NHL experienced severe or life-threatening IRRs, which greatly affected the patients' compliance and treatment continuity (8). Tsutsumi *et al* (21) established a risk-stratified rituximab protocol for patients with B-cell NHL to minimize IRRs to rituximab. During the 1st cycle of rituximab infusion, the patients in the low- and moderate-risk groups received standard infusions of 25-200 mg/h (total of 4.3 h). The patients in the high-risk group received longer infusions of 25-100 mg/h (total of 6.8 h). The researchers found that the overall incidence of IRRs was 28% and all IRRs were grade \leq II. No severe IRRs of grade \geq III were reported. Notably, only 1% all of patients developed IRRs in the 2nd cycle of rituximab infusion, and no IRR episodes occurred in the 3rd cycle. For some patients with B-cell neoplasia and hypersensitivity to rituximab, a 12-step rituximab desensitization protocol was performed to successfully assist 10 patients in completing the scheduled immunochemotherapy (22). Also, another 16-step rituximab desensitization method was carried out to successfully minimize the IRRs to rituximab in 2 patients with MZL and 1 with RA (23). Thus, the question of how to decrease the occurrence of IRRs to rituximab is still a major clinical issue for hematology and oncology practitioners.

At present, rituximab has been recommended as the main therapeutic agent in autoimmune disorders, including thrombotic thrombocytopenic purpura, SLE, RA and nephrotic syndrome (24-27). A retrospective, multicenter study compared the incidence of IRRs to rituximab in patients with B-cell lymphoproliferative disorders, such as DLBCL, FL, MCL and chronic lymphocytic leukemia, and in patients with autoimmune disorders, such as SLE and RA. Notably, the rate of IRRs was significantly higher in the former group (25.0-35.9%) compared with the rate in the latter group (9.4-17.5%; P<0.001) (11). The history of concomitant steroid use before rituximab treatment has been mainly ascribed to the lower incidence of IRRs to rituximab in autoimmune disorders (28). In the study by Laudati *et al* (19), a low incidence of IRRs was found in patients with B-cell NHL treated with dexamethasone premedication in comparison with no dexamethasone pretreatment (19.1 vs. 36.7%; P=0.005). Hence, the use of steroid pretreatment prompted the design of a novel

Table V. Treatment-related adverse effects in the two groups (n=44 patients/group).

Adverse effect	Control group, n (%)		Treatment group, n (%)		P-value ^a
	All grades	Grade \geq III	All grades	Grade \geq III	
Vomiting and nausea	36 (81.8)	8 (18.2)	33 (75.0)	6 (13.6)	0.437
Leukopenia and granulocytopenia	32 (72.7)	7 (15.9)	34 (77.3)	8 (18.2)	0.6225
Thrombocytopenia	25 (56.8)	4 (9.1)	23 (52.2)	3 (6.8)	0.6686
Cardiotoxicity	14 (31.8)	2 (4.5)	12 (27.2)	1 (2.3)	0.6403
Alopecia	35 (79.5)	10 (22.7)	37 (84.1)	9 (20.5)	0.5804
Hemorrhagic cystitis	4 (9.1)	0 (0.0)	2 (4.5)	0 (0.0)	0.6723

^a χ^2 test.

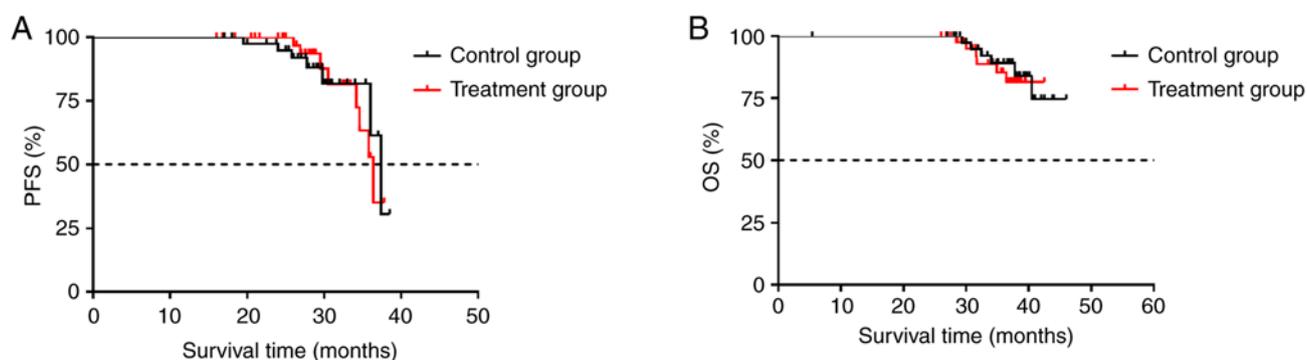


Figure 1. Kaplan-Meier curve analyses of survival between control and treatment groups. (A) PFS curve. (B) OS curve. mPFS, median progression-free survival; mOS, median overall survival.

prednisone premedication modification of the R-CHOP-like protocol in the present study consisting of oral prednisone for 3 days prior to rituximab administration for patients with DLBCL in the treatment group and standard R-CHOP-like regimen in the control group.

In the present study, it was revealed that the total incidence of IRRs to rituximab was significantly lower in the treatment group compared with that in the control group, and that most of the IRRs were of grade \leq II in both groups. Notably, a significant difference in incidence was observed between the different grades of IRRs. These results suggested that the prednisone premedication modification decreased the total incidence and the grade incidence of IRRs to rituximab. The underlying mechanism may be partly ascribed to lower tumor load resulting from prednisone-pretreatment for 3 days, which was presented clinically by the alleviation of B symptoms and shrinkage of superficial lymphadenopathy in most of the patients from the treatment group. To some degree, the usage of prednisone in advance may prevent the occurrence of tumor lysis syndrome, in particular for some patients with DLBCL with bulky lesions, which in turn decreases the incidence of IRRs to rituximab.

Results from the present study confirmed that the strategy of steroid premedication could reduce the risk of IRRs to rituximab, which was consistent with previous study results (7,11,19). Notably, unlike other studies, the innovative point of the current study was to modify the sequence

of prednisone and rituximab treatment in the R-CHOP-like protocol without any additional steroid pretreatment. In the present study, a total of 29.5% patients experienced >1 IRR episode. Importantly, the incidence of IRRs to rituximab in the treatment group decreased significantly compared with that in the control group in the 1st and the 2nd cycle; however, no marked differences were observed in the 3rd and 4th cycles for both groups. These results were in line with previous study results (6,21), highlighting the necessity and importance of monitoring IRRs to rituximab in the first two courses of immunochemotherapy for patients with DLBCL. Clinically, the incidence of IRRs to rituximab gradually reduced over the therapeutic courses and with the decrease of tumor burden in patients with DLBCL. There was no significant association of IRRs to rituximab with clinical outcomes in patients with DLBCL, which was in agreement with previous study results (6). Finally, the hematological and non-hematological toxicities, most of grade I or II, were similar in the two groups in the present study.

In conclusion, the novel strategy of prednisone pretreatment in the R-CHOP-like regimen in the present study significantly reduced the total incidence of IRRs to rituximab in patients with DLBCL. There is a necessity and importance to closely monitor IRRs to rituximab in the first three cycles of immunochemotherapy for patients with DLBCL. Furthermore, IRRs to rituximab did not affect the clinical efficacy of the

R-CHOP-like treatment. Therefore, the novel protocol may be considered a promising method to minimize the incidence of IRRs to rituximab in patients with DLBCL. Owing to the small sample size of the present study, it would be necessary to increase the cohort size and to explore the novel prednisone-premedication regimen for other types of B-cell NHL.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JD conceptualized and wrote the manuscript, and generated the random allocation sequence. ZL collected and analyzed the data, and assigned participants to interventions. HG and XJ provided the data, and enrolled and treated the patients. JD and ZL confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was performed in accordance with The Declaration of Helsinki. All patients signed written informed consent to participate in the study. This study was approved by the Medical Ethical Committee of Jiujiang University Affiliated Hospital (Jiujiang, China) on January 6, 2019 (approval no. jjhmer-a-2019-01), the Medical Ethical Committee of Ruichang People's Hospital on January 8, 2019 (Ruichang, China; approval no. rhmer-2019-01) and the Medical Ethical Committee of Lushan People's Hospital on January 7, 2019 (Lushan, China; approval no. lshmer-2019-02).

Patient consent for publication

All patients signed written informed consent for publication.

Competing interests

The authors declare that they have no competing interests.

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