Clinical Trial/Experimental Study

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Efficacy of rituximab combined with CHOP for treating patients with diffuse large B-cell lymphoma

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Abstract

Background: This study aimed to evaluate the efficacy and safety of rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treating patients with diffuse large B-cell lymphoma (DLBCL).

Methods: A total of 144 patients with DLBCL were randomly divided into intervention group and control group, 72 patients in each group. The patients in the control group received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, while the participants in the intervention group received R-CHOP. The primary endpoint was relapse-free survival (RFS) and the secondary endpoints were overall survival rate (OSR) and adverse events (AEs).

Results: One hundred thirty-four patients completed the study. The intervention with R-CHOP did not show greater efficacy than CHOP in the estimated median follow-up time (intervention group 33 months vs control group 29 months, $P = .15$). In addition, no significant differences in the 5-year RFS (intervention group 81% vs placebo group 76%, $P = .28$) or the 5-year OSR (intervention group 93% vs placebo group 91%, $P = .53$) were found between the 2 groups. The AEs were also similar between the 2 groups.

Conclusion: This study demonstrated that R-CHOP, when compared with CHOP alone, could not improve the RFS and OS of patients with DLBCL. Additionally, both groups had similar safety profiles.

Abbreviations: AEs = adverse events, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CR = complete remission, CRu = CR unconfirmed, DLBCL = diffuse large B-cell lymphoma, ECOG = Eastern Cooperative Oncology Group, OSR = overall survival rate, R-CHOP = rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone, RFS = relapse-free survival.

Keywords: clinical trial, diffuse large B-cell lymphoma, efficacy, rituximab, safety

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is one of the most common histological types among malignant lymphomas.[1–5] It accounts for about 30% of lymphomas.[1,6] Fortunately, it is highly chemosensitive and curable. Chemotherapy combined with anti-CD20 antibodies has significantly improved outcomes in patients with DLBCL. However, relapse prevention with such interventions has not been established for DLBCL or other aggressive lymphomas.[7–13]

Because it can improve long-term survival, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy has been selected as the first-line treatment for DLBCL.[14–18] The curative effect of CHOP is supposedly improved by combining rituximab with CHOP (R-CHOP). However, no randomized controlled trial has compared CHOP with R-CHOP in a Chinese population with DLBCL.

In this study, we tested the hypothesis that R-CHOP could improve the curative rate in Chinese patients with DLBCL.

2. Methods

2.1. Design

This randomized controlled trial recruited 144 Chinese patients with DLBCL. It was conducted at Affiliated Tumor Hospital of Xinjiang Medical University from January 2012 to December 2016. It was approved by the Medical Ethical Committee of Affiliated Tumor Hospital of Xinjiang Medical University. All eligible patients were identified and selected by the inclusion/exclusion criteria. All included patients were randomly divided and allocated to the intervention group or the control group in a 1:1 allocation ratio.

2.2. Inclusion and exclusion criteria

The inclusion criteria were previously untreated adults aged from 18 to 75 years. All patients were diagnosed with CD20-positive aggressive DLBCL, according to the World Health Organization classification. In addition, they all had achieved a complete remission (CR) or a CR unconfirmed (CRu) according to the 1999 response criteria for malignant lymphoma.[17] All patients received complete induction treatment 4 weeks before the intervention of this study. This induction treatment included 6 infusions of rituximab (375 mg/m^2 IV) plus four to 6 cycles of chemotherapy with CHOP as first-line treatment. Additionally,

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patients had an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 to 2 at the inclusion time, and all of them provided and signed written informed consent.

Subjects were excluded for pregnancy, transformed lymphoma, serious nervous system diseases, uncontrolled cardiac disease, hematopoietic insufficiency, abnormal renal or liver function, active opportunistic infections, active hepatitis B or C, or positivity for human immunodeficiency virus.

2.3. Randomization and blinding

SAS 8.1 software (SAS Institute, Inc., Cary, NC) was used to perform the randomization by a computerized number generator with the stratified block randomization method. Then, the randomization assignments were concealed in opaque, sequentially numbered, sealed envelopes. The patients, researchers, outcome assessors, and the data analyst were blinded to the treatment allocation.

2.4. Participants and recruitment

All patients were recruited through the clinic of the Lymphoma Department, Affiliated Tumor Hospital of Xinjiang Medical University, and this study was conducted at the same hospital. All patients were allocated and randomized to either the intervention group or control group after the clinical and patient eligibility evaluation. All investigators were trained in their tasks before the start of this study. The patients were informed about the research and given an information sheet.

2.5. Intervention

The patients in both groups received CHOP chemotherapy. In addition to this therapy, patients in the intervention group also received rituximab by intravenous infusion at a dose of 375 mg/m^2 every 2 months for 1 year.

2.6. Outcome measurements

The primary outcome was progression-free survival (PFS). The secondary outcomes included overall survival rate (OSR) and adverse events (AEs). Overall survival was defined as the time from random assignment or registration to death as a result of any cause. PFS was defined as the time from random assignment or registration to disease progression, relapse, or death as a result of any cause. In patients who did not show disease progression at the time treatment was discontinued, PFS assessment continued until progression was documented.

2.7. Adverse events

All AEs were recorded at each visit. All safety data for all included patients were analyzed and included in the analysis.

2.8. Statistical analysis

The estimated sample size was 60 patients in each group with $\alpha = 0.05$ (2-sided) and $\beta = 0.20$. Assuming a 20% dropout rate, at least 144 patients with 72 in each group needed to be recruited to this study. All outcome data were analyzed by an intention to treat approach. The Kaplan–Meier method was used to analyze the data.

3. Results

Two hundred fifteen patients with DLBCL were initially assessed for eligibility for the study (Fig. 1). Of those 215 patients, 71 were excluded because they did not meet the inclusion criteria, and 12 declined to participate. Finally, 144 patients were randomly assigned to the intervention or control group, 72 patients for each group. At the end of treatment, 134 patients completed the intervention. Ten patients were lost to follow-up (Fig. 1).

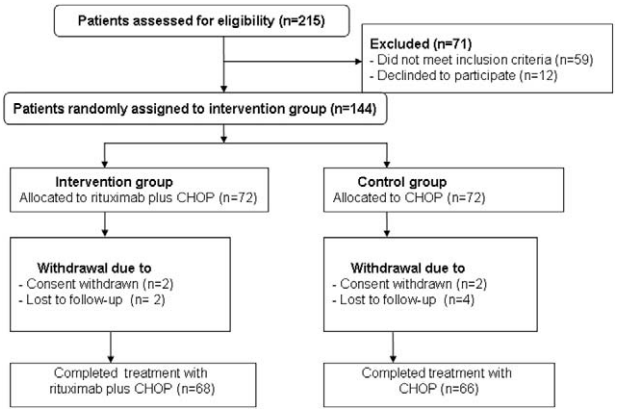

Figure 1. Scheme of patients selection.

The characteristics of the patients in both groups at baseline are shown in Table 1. The patients in the 2 groups did not differ significantly in terms of age, sex, race, education background,

Table 1

Patients characteristics at baseline.

Characteristics	Intervention group (n = 72)	Control group (n = 72)	*P*
Age, y	48.7 (12.4)	50.1 (13.3)	.51
Sex			
Male	47 (65.3)	51 (70.8)	.71
Female	25 (34.7)	21 (29.2)	.71
Race			
Han ethnicity	36 (50.0)	32 (44.4)	.50
Uighur ethnicity	36 (50.0)	40 (55.6)	.50
Education background			
Primary school	18 (25.0)	21 (29.2)	.57
Secondary school	20 (27.8)	24 (33.3)	.47
High school	23 (31.9)	19 (26.4)	.46
College/university	11 (15.3)	8 (11.1)	.46
ECOG status			
0	19 (26.4)	17 (23.6)	.70
1	24 (33.3)	25 (34.7)	.18
2	29 (40.3)	30 (41.6)	.87
B symptoms			
No	24 (33.3)	27 (37.5)	.60
Yes	48 (66.7)	45 (62.5)	.60
Largest mass diameter >10 cm			
No	6 (8.3)	3 (4.2)	.31
Yes	66 (91.7)	69 (95.8)	.31
Number of extranodal sites			
0–1	63 (87.5)	65 (90.3)	.60
>1	9 (12.5)	7 (9.7)	.60
Bone-marrow involvement			
No	59 (81.9)	62 (86.1)	.50
Yes	6 (8.3)	4 (5.6)	.65
Not assessed	7 (9.7)	6 (8.3)	.77
Histology			
Diffuse large B-cell lymphoma	72 (100.0)	72 (100.0)	1.00
Type of previous therapy			
R-COHP	57 (79.2)	60 (83.3)	.52
Other	15 (20.8)	12 (16.7)	.52

Note: Data are present as mean ± standard deviation or number (%).
ECOG = Eastern Cooperative Oncology Group, R-CHOP = rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone.

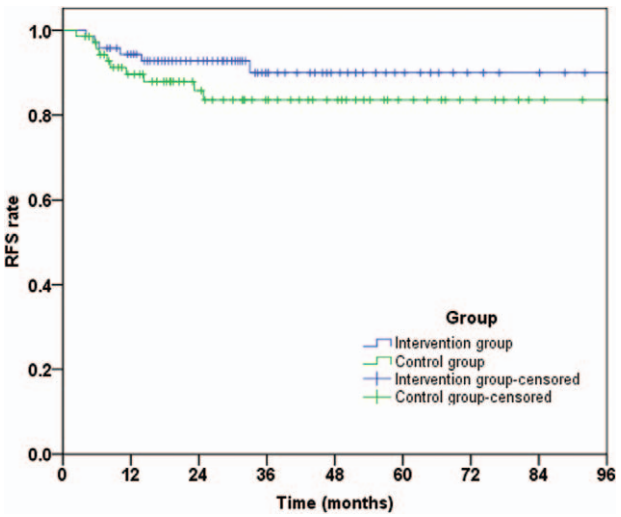

Figure 2. Relapse-free survival rate.

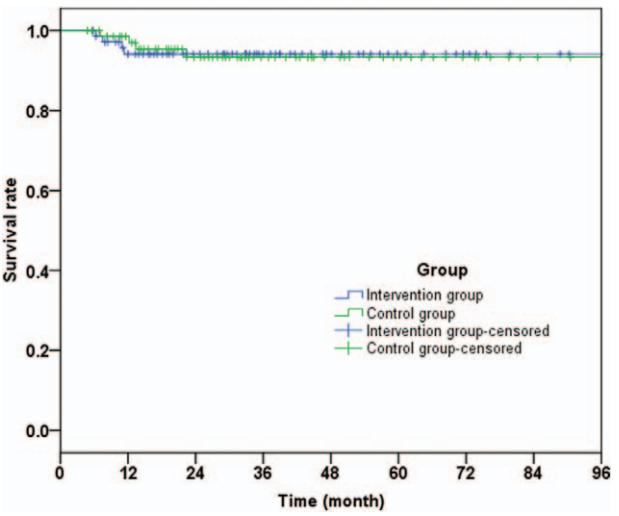

Figure 3. Overall survival rate.

ECOG status, B symptoms, largest mass diameter more than 10 cm, number of extranodal sites, bone-marrow involvement, histology, and types of previous therapy at baseline (Table 1).

The estimated median follow-up time was 33 months in the intervention group and 29 in the control group ($P=.15$). Five-year relapse-free survival (RFS) was 81% in the intervention group and 76% in the control group ($P=.28$, Fig. 2). Five-year OSR was 93% in the intervention group and 91% in the control group ($P=.53$, Fig. 3).

No significant differences in the anemia, neutropenia, thrombocytopenia, infection, mucositis, nausea or vomiting, diarrhea, cardiac-related toxic effects, aminotransferase elevation, creatinine elevation, lung-related toxic effects, neurological toxic effects, vascular toxic effects, and rash were found between the 2 groups regarding safety at the end of 1-year of treatment ($P>.05$, Table 2).

Table 2

Safety between 2 groups after 1 year treatment.

Safety	Intervention group (n=72)	Control group (n=72)	*P*
Grade 1–2			
Anemia	55 (76.4)	46 (63.9)	.10
Neutropenia	58 (80.6)	49 (68.1)	.09
Thrombocytopenia	22 (30.6)	14 (19.4)	.13
Infection	14 (19.4)	8 (11.1)	.17
Mucositis	10 (13.9)	5 (6.9)	.10
Nausea or vomiting	24 (33.3)	14 (19.4)	.06
Diarrhea	7 (9.7)	3 (4.1)	.20
Cardiac-related toxic effects	1 (1.4)	0 (0.0)	.50
Aminotransferase elevation	18 (25.0)	11 (7.5)	.15
Creatinine elevation	6 (8.3)	2 (2.8)	.17
Lung-related toxic effects	11 (15.3)	4 (5.6)	.07
Neurological toxic effects	17 (23.6)	10 (13.9)	.14
Vascular toxic effects	2 (2.8)	1 (1.4)	.57
Rash	7 (9.7)	3 (4.2)	.20
Grade 3–4			
Anemia	4 (5.6)	3 (4.2)	.70
Neutropenia	39 (54.2)	28 (38.9)	.07
Thrombocytopenia	2 (2.8)	2 (2.8)	1.00
Infection	9 (12.5)	3 (4.2)	.08
Mucositis	0 (0.0)	0 (0.0)	—
Nausea or vomiting	3 (4.2)	1 (1.4)	.33
Diarrhea	1 (1.4)	0 (0.0)	.50
Cardiac-related toxic effects	1 (1.4)	0 (0.0)	.50
Aminotransferase elevation	2 (2.8)	1 (1.4)	.57
Creatinine elevation	0 (0.0)	0 (0.0)	—
Lung-related toxic effects	1 (1.4)	0 (0.0)	.50
Neurological toxic effects	2 (2.8)	1 (1.4)	.57
Vascular toxic effects	1 (1.4)	0 (0.0)	.50
Rash	1 (1.4)	0 (0.0)	.50

Note: Data are present as number (%).

4. Discussion

For patients with DLBCL, it has been reported that the addition of rituximab combined with CHOP may not be helpful.[18] The key finding of this study is that CHOP chemotherapy combined with rituximab cannot improve the OS and PFS compared with CHOP alone. These findings are consistent with those of other studies showing that CHOP chemotherapy combined with rituximab did not prolong event free, progression-free, or overall survival of patients with aggressive B-cell non-Hodgkin lymphoma.[18,19]

A previous systematic review and meta-analysis demonstrated that after first-line chemotherapy, 2 rituximab-combined treatment strategies, including maintenance and salvage therapies, had a survival benefit[20]; however, due to the few included eligible studies and their low methodological quality, they did not reach a firm conclusion that rituximab combined with CHOP could improve the curative rate in Chinese patients with DLBCL.[20]

In this study, we also found that rituximab combined with CHOP could not increase the OS or PFS in Chinese patients with DLBCL, which suggests that the combination of rituximab and CHOP cannot improve the curative rates for patients with DLBCL in China. In addition, both groups had a similar safety profile, with no significant differences in any AEs between groups.

However, this study also had several limitations. First, this study was only performed at the Affiliated Tumor Hospital of Xinjiang Medical University, and most of the participants were of Uyghur ethnicity, which may have had an influence on the

generalizability of our findings to patients of other ethnicities, especially the Han ethnicity, and other hospitals. Furthermore, although all investigators received training before this study, the variety of their experience levels may have resulted in bias during the period of the intervention.

We demonstrated that the administration of rituximab combined with CHOP could not improve the curative rate over CHOP alone in Chinese patients with DLBCL, and both groups had similar AEs.

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