



Original Article

Intensified First Cycle of Rituximab Plus Eight Cycles of Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone with Rituximab Chemotherapy for Advanced-Stage or Bulky Diffuse Large B-Cell Lymphoma: A Multicenter Phase II Consortium for Improving Survival of Lymphoma (CISL) Study

Yu Ri Kim¹, Jin Seok Kim¹, Won Seog Kim², Hyeon Seok Eom³, Deok-Hwan Yang⁴, Sung Hwa Bae⁵, Hyo Jung Kim⁶, Jae Hoon Lee⁷, Suk-Joong Oh^{8,a}, Sung-Soo Yoon⁹, Jae-Yong Kwak¹⁰, Chul Won Choi¹¹, Min Kyoung Kim¹², Sung Young Oh¹³, Hye Jin Kang¹⁴, Seung Hyun Nam^{15,b}, Hyeok Shim¹⁶, Joon Seong Park¹⁷, Yeung-Chul Mun¹⁸, Cheolwon Suh¹⁹, The Korean Society of Hematology Lymphoma Working Party

*A list of author's affiliations appears at the end of the paper.

Purpose This phase II, open-label, multicenter study aimed to investigate the efficacy and safety of a rituximab intensification for the 1st cycle with every 21-day of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP-21) among patients with previously untreated advanced-stage or bulky diffuse large B-cell lymphoma (DLBCL).

Materials and Methods Ninety-two patients with stage III/IV or bulky DLBCL from 21 institutions were administered 8 cycles of R-CHOP-21 with an additional one dose of rituximab intensification on day 0 of the 1st cycle (RR-CHOP). The primary endpoint was a complete response (CR) rate after 3 cycles of chemotherapy.

Results Among the 92 DLBCL patients assessed herein, the response rate after 3 cycles of chemotherapy was 88.0% (38.0% CR+50.0% partial response [PR]). After the completion of 8 cycles of chemotherapy, the overall response rate was observed for 68.4% (58.7% CR+9.8% PR). The 3-year progression-free survival rate was 64.0%, and the 3-year overall survival rate was 70.4%. Febrile neutropenia was one of the most frequent \geq grade 3 adverse events (40.0%) and five treatment-related deaths occurred. Compared with the clinical outcomes of patients who received R-CHOP chemotherapy as a historical control, the interim CR rate was higher in male patients with RR-CHOP (20.5% vs. 48.8%, $p=0.016$).

Conclusion Rituximab intensification on days 0 to the 1st cycle of the standard 8 cycles R-CHOP-21 for advanced DLBCL yielded favorable response rates after the 3 cycles of chemotherapy and acceptable toxicities, especially for male patients (ClinicalTrials.gov ID: NCT01054781).

Key words Rituximab, Diffuse large B-cell lymphoma, R-CHOP, Response

Introduction

Although the treatment outcomes of diffuse large B-cell lymphoma (DLBCL) have been improved with rituximab [1-3], up to 40% of DLBCL patients with advanced-stage or bulky disease are still resistant to current standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) treatment [1,4,5]. Furthermore, salvage treatment has still yielded unsatisfactory results because > 70% of relapsed or refractory DLBCL patients do not present sustained survival after current salvage therapy, including autologous hematopoietic stem cell transplantation (ASCT)

[6]. Therefore, a more effective first-line treatment strategy is required to overcome the limitations of R-CHOP among high-risk DLBCL patients.

Although R-CHOP every 21 days (R-CHOP-21) is generally used in high-risk DLBCL patients, the optimal dose and schedule of rituximab applications still have been investigated. Previous pharmacokinetic studies have revealed that the concomitant application of CHOP and rituximab does not achieve a plateau trough level of rituximab during the early cycles of chemotherapy, especially for elderly male patients. It was related to the rapid rituximab clearance in elderly male patients [7]. To improve the outcomes of

Correspondence: Cheolwon Suh
Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: 82-2-3010-3209 Fax: 82-2-3010-6961 E-mail: csuh@amc.seoul.kr

Co-correspondence: Jin Seok Kim
Division of Hematology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: 82-2-2228-1972 Fax: 82-2-393-6884 E-mail: hemakim@yuhs.ac

Received January 1, 2023 Accepted March 29, 2023
Published Online March 30, 2023

R-CHOP chemotherapy for high-risk DLBCL patients, it is important to achieve appropriate serum concentrations of rituximab quickly. Here, we hypothesized that appropriate, therapeutic serum rituximab levels can potentially be achieved earlier by increasing the frequency and dose of rituximab applications, and then we can get a better treatment outcome. In this trial, the modifying regimen of rituximab administration with an additional one application on 1 day before (day 0) the 1st cycle of the R-CHOP-21 was tested for patients with high-risk DLBCL. If additional rituximab supplementation can appropriately increase the serum levels of rituximab, it may potentially improve the treatment outcomes of high-risk DLBCL patients.

Thus, in this prospective phase II study, we attempted to investigate the efficacy and safety of an intensification of rituximab on day 0 of the 1st cycle to the standard 8 cycles of R-CHOP-21 (RR-CHOP) chemotherapy in previously untreated DLBCL patients with stage III/IV or bulky disease.

Materials and Methods

1. Study design

Twenty-one institutions participated in this non-randomized, multicenter, prospective, open-label, phase II study in Korea [8]. This clinical trial was approved by the institutional review boards and ethics committees of each participating institution. The trial is registered on the National Cancer Institute website (trial number NCT01054781).

2. Patient eligibility

Eligible patients were aged > 18 years with histologically confirmed Ann Arbor stage III/IV, CD20-positive, newly diagnosed DLBCL, and/or bulky (largest diameter \geq 10.0 cm) disease regardless of the stage [4]. Patients with primary central nervous system lymphoma, transformed DLBCL from indolent lymphoma, and a history of human immunodeficiency virus and hepatitis C virus infection were ineligible. Patients with hepatitis B virus (HBV)-seropositivity were eligible. However, primary prophylaxis with appropriate antiviral agents (i.e., lamivudine or entecavir) was recommended for HBV carriers to prevent HBV reactivation throughout the treatment period.

3. Treatment regimen

The R-CHOP-21 regimen, comprising rituximab (375 mg/m²; intravenous), cyclophosphamide (750 mg/m²; intravenous), doxorubicin (50 mg/m²; intravenous), and vincristine (1.4 mg/m²; maximum 2.0 mg intravenous) on day 1 and prednisone (100 mg/day; oral) on days 1-5, was administered. Additional rituximab (375 mg/m²; intravenous)

was administered on 1 day (day 0) before the 1st cycle to 8 cycles of R-CHOP-21 (RR-CHOP). Although the granulocyte colony-stimulating factor (G-CSF) administration was not routinely used for primary prophylaxis, the therapeutic purpose of G-CSF was administered at the discretion of individual physicians. Radiotherapy or ASCT was administered after the completion of 8 cycles of R-CHOP at the discretion of each participating institution. Indications for radiotherapy after the completion of chemotherapy included bulky disease (\geq 10 cm) at diagnosis, localized positron emission tomography (PET)-positive lesions, and potential curability via radiotherapy.

4. Baseline evaluation and response assessment

Baseline evaluation was carried out for \leq 28 days before enrollment, and all patients were staged by the Ann Arbor staging system, which included history-taking; physical examination; complete blood count; serum chemistry, including lactate dehydrogenase; bone marrow aspiration and biopsy; computed tomography; and PET imaging. Immunohistochemically defined sub-classification of DLBCL, including germinal center B-cell type (GCB) and non-germinal center B-cell type (non-GCB), was recommended at each institution by the Hans algorithm [9].

All patients underwent response evaluation after 3 cycles, 6 cycles of R-CHOP, and approximately 4 weeks after the completion of treatment, in accordance with the international workshop criteria [10]. Safety profiles were evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 3.0 until the 30th day after the final cycles of chemotherapy. The highest grade during the courses of treatment was considered for analysis. Physical examination and basic laboratory analyses were conducted every 6 months. Tumor assessment was carried out every 3 months during the first 2 years and every 6 months during years 3 to 5.

5. Statistical analysis

The primary endpoint was the rate of complete response (CR) after 3 cycles of R-CHOP chemotherapy, and the secondary endpoints were the overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. PFS was defined as the time from treatment initiation to the first recording of relapse or disease progression or death from any cause. OS was defined as the time from initial treatment to death from any cause or the date of the final follow-up evaluation. To compare the efficacy of RR-CHOP, the clinical outcomes of R-CHOP-treated DLBCL patients as historical controls were analyzed, and propensity score matching was performed using a 1:1 matching protocol without replacement. Among 403 newly diagnosed DLBCL patients

Table 1. Patient characteristics

	No. (%) (n=92)
Age ≥ 60 yr	52 (56.5)
Sex	
Male/Female	58/34 (63.0/37.0)
Ann Arbor stage	
II/III-IV	7/85 (7.6/92.4)
Bulky disease (≥ 10 cm)	21 (22.8)
B symptom	20 (21.7)
Elevated serum lactate dehydrogenase	70 (76.1)
ECOG performance status	
0/1/≥ 2	35/43/14 (38.0/46.7/15.2)
Extranodal involvement	
0 or 1/≥ 2	38/54 (41.3/58.7)
Bone marrow involvement	13 (14.1)
International Prognostic Index	
Low-risk/Low-intermediate risk	3/23 (3.3/25.0)
High-intermediate risk/High-risk	44/22 (47.8/23.9)
Revised International Prognostic Index	
Good/Poor	26/66 (28.3/71.7)
Cell of origin	
Germinal center B-cell type	25/64 (39.1)
Non-germinal center B-cell type	39/64 (60.9)
Bcl-2 positive	56/76 (73.7)
Bcl-6 positive	47/65 (72.3)

ECOG, Eastern Cooperative Oncology Group.

at Severance Hospital during the period from 2010 to 2013, 14 patients who were transferred to another hospital or did not receive any first-line chemotherapy were excluded. Of the remaining 389 patients, 197 patients with high-risk DLBCL according to the same inclusion criteria of this study were selected for historical control. Actuarial survival analysis and comparisons were carried out using the Kaplan-Meier method and the log-rank test. A Cox regression model was used to determine the hazard ratios and 95% confidence intervals. Statistical analysis was performed using SPSS ver. 25.0 (IBM Corp., Armonk, NY), and a p-value of < 0.05 was considered statistically significant.

Results

1. Patients characteristics

Between January and December 2009, 92 patients with newly diagnosed advanced-stage or bulky DLBCL were enrolled in this study. Fifty-two patients (56.5%) were older than 60 years (median 63, range 20 to 79 years), 14 (15.2%)

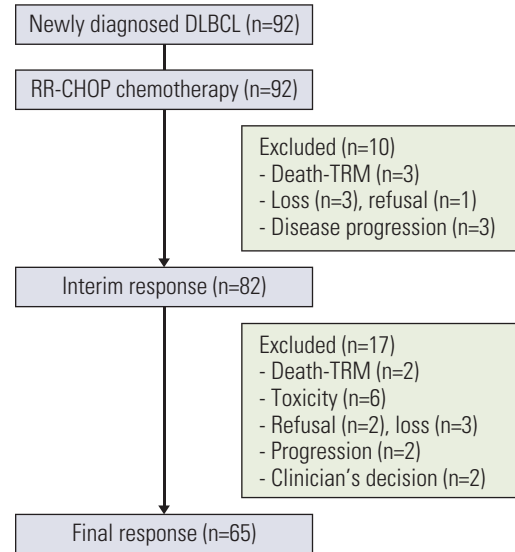


Fig. 1. Diagram of the enrolled diffuse large B-cell lymphoma patients. DLBCL, diffuse large B-cell lymphoma; RR-CHOP, intensified the first cycle of rituximab plus eight cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone with rituximab; TRM, treatment-related mortality.

had a European Cooperative Oncology Group poor performance status ≥ 2 , and 85 (92.4%) had stage III/IV disease. Patient characteristics are summarized in Table 1.

2. Treatment outcomes

The median number of RR-CHOP cycles was 8 (range, 1 to 8). Sixty-five patients (70.7%) completed 8 cycles of treatment following the protocol. CR rate and ORR after 3 cycles of RR-CHOP chemotherapy, were 38.0% (35/92) and 88.0% (81/92) in the full analysis set. Among the 92 patients initially enrolled herein, response data were not available for 10 patients after 3 cycles (3 died early, 3 were transferred to another institution, and 4 progressed disease). Based on the per-protocol analysis, the CR and ORR after 3 cycles of chemotherapy were 42.7% (35/82) and 98.8% (81/82), respectively. After the completion of 8 cycles of chemotherapy, 65 patients were assessed for the final response (Fig. 1).

The reasons for 17 patients with discontinuation of chemotherapy after interim response analysis were as follows: two patients withdrew their consent, two died early, two presented disease progression, six presented treatment-related toxicities, three were lost to follow-up, and two were excluded according to the clinician's discretion (Fig. 1). Fifty-four patients (58.7%) achieved a CR, nine (9.8%) achieved a partial response (PR), one achieved a stable disease and one (1.1%) presented with disease progression after the completion of 8 cycles of treatment (n=65). Based on the per-protocol anal-

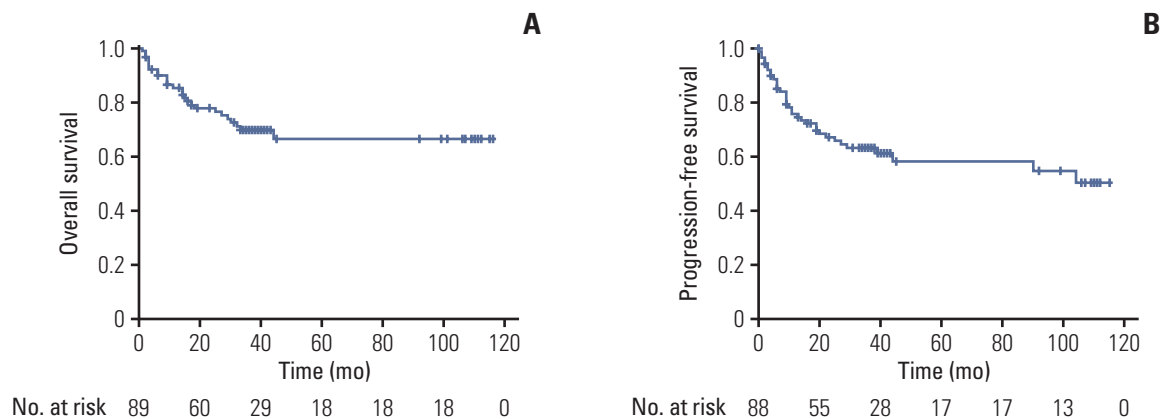


Fig. 2. Kaplan-Meier analyses of overall survival (A) and progression-free survival (B) of patients receiving RR-CHOP chemotherapy. RR-CHOP, intensified the first cycle of rituximab plus eight cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone with rituximab.

Table 2. Univariate analysis for overall survival and progression-free survival

Variable	Overall survival		Progression-free survival	
	p-value	HR (95% CI)	p-value	HR (95% CI)
Age > 60 yr	0.438	1.368 (0.620-3.015)	0.133	1.711 (0.848-3.451)
Male sex	0.920	0.960 (0.435-2.118)	0.655	0.855 (0.429-1.701)
Stage III-IV	0.480	1.433 (0.527-3.894)	0.280	1.729 (0.640-4.675)
ECOG PS \geq 2	0.631	1.299 (0.447-3.776)	0.196	1.732 (0.754-3.977)
LDH > upper normal	0.863	1.084 (0.435-2.700)	0.308	1.579 (0.656-3.806)
Extranodal involvement \geq 2	0.468	0.733 (0.318-1.693)	0.704	0.872 (0.430-1.768)
Bulky disease	0.337	1.505 (0.654-3.463)	0.471	1.310 (0.629-2.728)
GCB vs. non-GCB	0.983	1.010 (0.412-2.473)	0.985	0.992 (0.445-2.215)

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell type; HR, hazard ratio; LDH, lactic dehydrogenase; non-GCB, non-germinal center B-cell type.

ysis, the CR and ORR after 8 cycles of chemotherapy were 58.7% (54/65) and 96.9% (63/65), respectively. Among the 65 patients who completed the 8 cycles of RR-CHOP treatment, consolidative radiotherapy after the RR-CHOP chemotherapy was administered in four patients (6.1%) for the following indications: a bulky disease at initiation of treatment (n=1), consolidation at lymph nodes (n=2), or bone lesions (n=1). Ten patients received ASCT as consolidation: six patients received ASCT in a PR state and four patients received ASCT in a CR state.

3. Survival

The median follow-up duration for all patients was 36 months, and median PFS and OS were not reached. The 2-year and 3-year OS were 77.8% and 69.7%, respectively (Fig. 2A). The 2-year and 3-year PFS were 67.2% and 63.3%, respectively (Fig. 2B). No significant differences were observed according to the international prognostic index (IPI),

and the 3-year OS and PFS of low-risk patients were 100% and 100%, of low-intermediate risk patients were 81.1% and 76.5%, of high-intermediate risk patients was 64.8% and 60.4%, and of high-risk patients was 63.6% and 50.3% (p=0.412 and p=0.084, respectively). The OS of patients with a good revised IPI was not different from that of patients with a poor revised IPI (p=0.110), and PFS was better in patients with a good revised IPI (p=0.038). None of the factors affected the differences in survival via univariate analysis (Table 2). The OS and PFS were not significantly different according to sex (S1 Fig.).

4. Safety

Hematologic toxicities over grade 3 were the most common, with 67.0% neutropenia, 19.3% anemia, and 13.6% thrombocytopenia. Neutropenic fever was reported in 40% of patients, with three patients being grade 5. During RR-CHOP chemotherapy, a total of five treatment-related deaths

Table 3. Grade 3 to 5 AEs

	All events (%)	Grade ≥ 3 (%)
Hematologic AEs		
Anemia	92.0	19.3
Thrombocytopenia	44.3	13.6
Neutropenia	78.4	67.0
Neutropenic fever	40.9	40.9
Non-hematologic AEs		
Generalized weakness	27.2	7.9
Anorexia	39.7	4.5
Nausea	40.9	1.1
Vomiting	18.1	1.1
Stomatitis	23.8	0.0
Abdominal pain	28.4	2.2
Diarrhea	30.6	2.2
Constipation	28.4	0.0
Muscle pain	21.5	1.1
Peripheral neuropathy	36.3	1.1
Liver toxicity	31.8	1.1
Lung toxicity	3.4	2.2
Cardiac toxicity	1.1	1.1

AE, adverse event.

occurred. Grade ≥ 3 non-hematologic toxicities included the following: generalized weakness (7.9%), anorexia (4.5%), abdominal pain (2.2%), diarrhea (2.2%), and lung toxicity (2.2%). Toxicity profiles (grade ≥ 3) during chemotherapy are summarized in Table 3.

5. Comparison with R-CHOP as a historical control

We compared the treatment outcomes of RR-CHOP chemotherapy with those of patients who received R-CHOP chemotherapy. Among 197 high-risk DLBCL patients treated with R-CHOP, 72 age- and IPI-matched patients were selected from each group (S2 Table). The 90.2% (43.1% [31/72] CR+47.2% [34/72] PR) of ORR after 3 cycles of RR-CHOP chemotherapy was superior to 83.3% of ORR (25.0% [18/72] CR and 58.3% [42/72] PR) in patients with R-CHOP ($p=0.042$). After the completion of planned chemotherapy, the final response was able to be assessed in 65 patients with the R-CHOP group. Thirty-four patients (47.2%) achieved CR, 18 (25.0%) achieved PR, and four (5.6%) patients progressed disease in the R-CHOP group. A higher CR rate (59.7%, 43/72) was observed in the patients who received RR-CHOP compared to the patients who received R-CHOP (47.2%, 34/72, $p=0.041$). The interim CR rate for male patients in the RR-CHOP group was significantly higher than that in the R-CHOP group (48.8% [21/43] vs. 20.5% [9/44], $p=0.016$). However, the final CR rate was not different between the two groups (55.8% [24/43] vs. 50.0% [22/44], $p=0.209$) (S3 Table).

The OS and PFS were not significantly different between the two groups (S4 Fig.). The OS and PFS according to the two treatment groups also were not significantly different in both male and female patients (S5 Fig.). The OS and PFS according to the two treatment groups also were not significantly different in both younger (age 18-65 years) and older (age > 65 years) patients (S6 Fig.).

Discussion

This multicenter, prospective, phase II study including patients with newly diagnosed advanced-stage or bulky DLBCL treated with RR-CHOP revealed a favorable CR rate after 3 cycles of chemotherapy in comparison with historical risk-matched patients who were treated with R-CHOP. In particular, the RR-CHOP group displayed higher interim CR rates for male patients compared to the patients who received R-CHOP. These results showed that rituximab intensification on the standard R-CHOP chemotherapy has a meaningful clinical activity for some sub-groups of DLBCL patients.

There is a consensus that improvements in the outcomes of R-CHOP for advanced-stage DLBCL patients would warrant another treatment strategy. Dose-dense regimens, or dose-intense regimens, including additional use of etoposide, did not improve clinical outcomes in DLBCL [11,12]. Additional use of new investigational drugs such as bortezomib, bevacizumab, lenalidomide, and ibrutinib to the R-CHOP chemotherapy also did not improve the survival outcomes of DLBCL patients [13-16]. Early intensification and prolonged rituximab exposure in the SMARTE-R-CHOP-14 trial (6 cycles of CHOP-14 combined with 8 doses of rituximab on days -4, -1, 10, 29, 57, 99, 155, and 239), improved outcomes among elderly poor-prognosis patients compared to the historical control group who received R-CHOP from the RICOVER-60 trial [3,17]. DENSE-R-CHOP-14 trial (12 doses of rituximab was given on days 0, 1, 4, 8, 15, 22, 29, 43, 57, 71, 85, and 99 together with 6 cycles of CHOP-14 cycles) did not show improved outcomes compared to the historical control group from the RICOVER-60 trial and a higher incidence of infection was reported [18]. HOVON-84 study compared the RR-CHOP-14 regimen (R-CHOP-14 with the intensification of rituximab on day 8 of the first 4 cycles) and standard R-CHOP-14 regimen and early rituximab intensification of RR-CHOP-14 regimen did not show the survival benefit [19]. These studies suggest that earlier intensive use and longer exposure of rituximab may achieve the earlier higher and appropriate serum levels of rituximab, but the efficacy and clinical outcomes of additional use of rituximab to the R-CHOP regimen should be re-evaluated in further trials.

Because the clinical outcomes between R-CHOP-14 and R-CHOP-21 were not different, R-CHOP-21 is usually recommended as the first-line treatment in patients with DLBCL [20-22]. Therefore, previously reported intensified rituximab-containing regimens should be re-evaluated in the setting of the R-CHOP-21 backbone. Although the JCOG0601 trial compared the efficacy and safety of CHOP-21 plus dose-dense weekly rituximab (RW-CHOP-21) regimen with standard R-CHOP-21 regimen for DLBCL, the RW-CHOP-21 regimen did not show the improved PFS. This RW-CHOP-21 regimen was just a modification of the rituximab administration schedule (early intensification of rituximab during chemotherapy) and the total dose of rituximab during chemotherapy was the same between the two groups [23].

We added only one dose of rituximab on day 0 of the 1st cycle to the conventional 8 cycles R-CHOP-21 regimen in this trial for promptly achieving the appropriate serum level of rituximab and avoiding the further development of serious infections related to additional intensive use of rituximab. Considering the patients included in this study were high-risk, the CR or ORR after 3 cycles of RR-CHOP was comparable to the previous study [22].

Upon comparing patients receiving R-CHOP therapy in the historical control group, additional rituximab administration on day 0 of the 1st cycle of R-CHOP resulted in a higher interim CR among male patients in this study. Some studies have reported that male patients displayed inferior outcomes of conventional R-CHOP therapy [7,24,25]. Epidemiological studies have suggested that women have a survival advantage over men in various cancers [26,27]. Studies from the United States also have reported that male patients with lymphoma are at a higher mortality risk than female patients [26]. In DLBCL, elderly male patients benefit less from R-CHOP than female patients [7,24,28]. Elderly male DLBCL patients showed low serum levels of rituximab and inferior clinical outcomes of R-CHOP chemotherapy because of the rapid rituximab clearance. Intensified dose of rituximab (500 mg/m²) with CHOP-14 for elderly male patients showed similar PFS and OS to female patients, without increasing the toxicities [29]. The infection rate of RR-CHOP was slightly higher than that previously reported, but most cases were manageable in this study. Because prophylactic pegylated G-CSF is commonly recommended and used for the R-CHOP regimen in most countries, we can reduce the incidence of infection and cytopenia related to the RR-CHOP regimen after applying the prophylactic pegylated G-CSF. Therefore, rituximab intensification on day 0 of the 1st cycle to the standard 8 cycles of R-CHOP therapy is a potentially valuable alternative for advanced-stage high-risk DLBCL patients, especially for male DLBCL patients. This strategy can be easily applied in daily practice before getting the

available newly approved first-line therapy for advanced-stage high-risk DLBCL patients such as polatuzumab vedotin-containing regimens [30].

The limitations of our study include the lack of a central pathological and radiological review. Furthermore, the study also involved inherent limitations associated with single-arm phase II studies having the response rate as the primary endpoint, such as small sample sizes and selection bias, which should be considered when interpreting the results. We stratified high-risk patients only based on clinical factors, not considering gene expression profiles, including those of cells expressing *MYC* or *BCL2*. However, clinical factors are more easily accessible in daily practice. Moreover, we did not carry out a pharmacokinetic analysis; this will be conducted in the future based on the present results.

This phase II study with an additional one dose of rituximab application on day 0 of the 1st cycle to 8 cycles of R-CHOP-21 for advanced-stage DLBCL revealed a favorable response, PFS, and OS, with acceptable toxicity. Moreover, rituximab intensification during early R-CHOP-21 therapy for male high-risk DLBCL patients might be an important treatment alternative.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (<https://www.e-crt.org>).

Ethical Statement

This study was conducted in accordance with the ethical standards of the institutional and national research committee and the Declaration of Helsinki. The study protocols were approved by the institutional review board of each center. This trial was registered on <http://www.clinicaltrials.gov> with the identifier NCT01054781. All participants provided written informed consent before enrollment.

Author Contributions

Conceived and designed the analysis: Kim YR, Kim JS, Suh C.

Collected the data: Kim YR, Kim JS, Kim WS, Eom HS, Yang DH, Bae SH, Kim HJ, Lee JH, Oh SJ, Yoon SS, Kwak JY, Choi CW, Kim MK, Oh SY, Kang HJ, Nam SH, Shim H, Park JS, Mun YC, Suh C.

Contributed data or analysis tools: Kim YR, Kim JS, Kim WS, Eom HS, Yang DH, Bae SH, Kim HJ, Lee JH, Oh SJ, Yoon SS, Kwak JY, Choi CW, Kim MK, Oh SY, Kang HJ, Nam SH, Shim H, Park JS, Suh C.

Performed the analysis: Kim YR, Kim JS, Suh C.

Wrote the paper: Kim YR, Kim JS.

Critical revision of the manuscript for important intellectual content: Kim JS, Suh C.

ORCID iDs

Yu Ri Kim  : <https://orcid.org/0000-0001-5505-0142>

Jin Seok Kim  : <https://orcid.org/0000-0001-8986-8436>

Cheolwon Suh  : <https://orcid.org/0000-0002-9178-4431>

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

Acknowledgments

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. NRF-2022R1A2C1013495).

Author Details

¹Division of Hematology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, ²Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, ³Hematology-Oncology Clinic, National Cancer Center, Goyang, ⁴Department of Hematology/Oncology, Chonnam National University Hwasun Hospital, Hwasun, ⁵Department of Internal Medicine, Daegu Catholic University Medical Center, Daegu, ⁶Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, ⁷Department of Internal Medicine, Gachon University Gil Medical Center, Incheon,

⁸Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, ⁹Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, ¹⁰Department of Internal Medicine, Jeongbuk National University Medical School, Jeonju, ¹¹Department of Internal Medicine, Korea University College of Medicine, Seoul, ¹²Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, ¹³Department of Internal Medicine, Dong-A University College of Medicine, Busan, ¹⁴Department of Internal Medicine, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Seoul, ¹⁵Department of Internal Medicine, Veterans Health Service Medical Center, Seoul, ¹⁶Department of Internal Medicine, Wonkwang University School of Medicine, Iksan, ¹⁷Department of Hematology-Oncology, Ajou University School of Medicine, Suwon, ¹⁸Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, ¹⁹Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Present address

^{a)}Department of Hematology and Oncology, Hanyang University Seoul Hospital, Seoul, Korea

^{b)}Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Seoul, Korea

References

1. Coiffier B, Thieblemont C, Van Den Neste E, Lepage G, Planter I, Castaigne S, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood*. 2010;116:2040-5.
2. Pfreundschuh M, Trumper L, Osterborg A, Pettengell R, Trneny M, Imrie K, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2006;7:379-91.
3. Pfreundschuh M, Schubert J, Ziepert M, Schmits R, Mohren M, Lengfelder E, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol*. 2008;9:105-16.
4. Pfreundschuh M, Ho AD, Cavallin-Stahl E, Wolf M, Pettengell R, Vasova I, et al. Prognostic significance of maximum tumour (bulk) diameter in young patients with good-prognosis diffuse large-B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: an exploratory analysis of the MabThera International Trial Group (MInT) study. *Lancet Oncol*. 2008;9:435-44.
5. Yoo KH, Lee H, Suh C; CISL. Lymphoma epidemiology in Korea and the real clinical field including the Consortium for Improving Survival of Lymphoma (CISL) trial. *Int J Hematol*. 2018;107:395-404.
6. Stiff PJ, Unger JM, Cook JR, Constine LS, Couban S, Stewart DA, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 2013;369:1681-90.
7. Muller C, Murawski N, Wiesen MH, Held G, Poeschel V, Zeynalova S, et al. The role of sex and weight on rituximab clearance and serum elimination half-life in elderly patients with DLBCL. *Blood*. 2012;119:3276-84.
8. Suh C, Park BB, Kim WS; CISL. The Consortium for Improving Survival of Lymphoma (CISL): recent achievements and future perspective. *Blood Res*. 2017;52:3-6.
9. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103:275-82.
10. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25:579-86.
11. Delarue R, Tilly H, Mounier N, Petrella T, Salles G, Thieblemont C, et al. Dose-dense rituximab-CHOP compared with

- standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. *Lancet Oncol.* 2013;14:525-33.
12. Pfreundschuh M, Kuhnt E, Trumper L, Osterborg A, Trnety M, Shepherd L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol.* 2011;12:1013-22.
 13. Leonard JP, Kolibaba KS, Reeves JA, Tulpule A, Flinn IW, Kolevska T, et al. Randomized phase II study of R-CHOP with or without bortezomib in previously untreated patients with non-germinal center B-cell-like diffuse large B-cell lymphoma. *J Clin Oncol.* 2017;35:3538-46.
 14. Seymour JF, Pfreundschuh M, Trnety M, Sehn LH, Catalano J, Csinady E, et al. R-CHOP with or without bevacizumab in patients with previously untreated diffuse large B-cell lymphoma: final MAIN study outcomes. *Haematologica.* 2014;99:1343-9.
 15. Nowakowski GS, LaPlant B, Macon WR, Reeder CB, Foran JM, Nelson GD, et al. Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-Cell lymphoma: a phase II study. *J Clin Oncol.* 2015;33:251-7.
 16. Younes A, Sehn LH, Johnson P, Zinzani PL, Hong X, Zhu J, et al. Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non-germinal center B-cell diffuse large B-cell lymphoma. *J Clin Oncol.* 2019;37:1285-95.
 17. Pfreundschuh M, Poeschel V, Zeynalova S, Hanel M, Held G, Schmitz N, et al. Optimization of rituximab for the treatment of diffuse large B-cell lymphoma (II): extended rituximab exposure time in the SMARTE-R-CHOP-14 trial of the german high-grade non-Hodgkin lymphoma study group. *J Clin Oncol.* 2014;32:4127-33.
 18. Murawski N, Pfreundschuh M, Zeynalova S, Poeschel V, Hanel M, Held G, et al. Optimization of rituximab for the treatment of DLBCL (I): dose-dense rituximab in the DENSE-R-CHOP-14 trial of the DSHNHL. *Ann Oncol.* 2014;25:1800-6.
 19. Lugtenburg PJ, de Nully Brown P, van der Holt B, D'Amore FA, Koene HR, de Jongh E, et al. Rituximab-CHOP with early rituximab intensification for diffuse large B-cell lymphoma: a randomized phase III trial of the HOVON and the Nordic Lymphoma Group (HOVON-84). *J Clin Oncol.* 2020;38:3377-87.
 20. Gleeson M, Counsell N, Cunningham D, Lawrie A, Clifton-Hadley L, Hawkes E, et al. Prognostic indices in diffuse large B-cell lymphoma in the rituximab era: an analysis of the UK National Cancer Research Institute R-CHOP 14 versus 21 phase 3 trial. *Br J Haematol.* 2021;192:1015-9.
 21. Li X, Huang H, Xu B, Guo H, Lin Y, Ye S, et al. Dose-dense rituximab-CHOP versus standard rituximab-CHOP in newly diagnosed Chinese patients with diffuse large B-cell lymphoma: a randomized, multicenter, open-label phase 3 trial. *Cancer Res Treat.* 2019;51:919-32.
 22. Cunningham D, Hawkes EA, Jack A, Qian W, Smith P, Mouncey P, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet.* 2013;381:1817-26.
 23. Ohmachi K, Kinoshita T, Tobinai K, Ogawa G, Mizutani T, Yamauchi N, et al. A randomized phase 2/3 study of R-CHOP vs CHOP combined with dose-dense rituximab for DLBCL: the JCOG0601 trial. *Blood Adv.* 2021;5:984-93.
 24. Hedstrom G, Peterson S, Berglund M, Jerkeman M, Enblad G; Swedish Lymphoma Study Group. Male gender is an adverse risk factor only in young patients with diffuse large B-cell lymphoma: a Swedish population-based study. *Acta Oncol.* 2015;54:924-32.
 25. Pfreundschuh M, Muller C, Zeynalova S, Kuhnt E, Wiesen MH, Held G, et al. Suboptimal dosing of rituximab in male and female patients with DLBCL. *Blood.* 2014;123:640-6.
 26. Cook MB, McGlynn KA, Devesa SS, Freedman ND, Anderson WF. Sex disparities in cancer mortality and survival. *Cancer Epidemiol Biomarkers Prev.* 2011;20:1629-37.
 27. Micheli A, Ciampichini R, Oberaigner W, Ciccolallo L, de Vries E, Izarzugaza I, et al. The advantage of women in cancer survival: an analysis of EURO CARE-4 data. *Eur J Cancer.* 2009;45:1017-27.
 28. Riihijarvi S, Taskinen M, Jerkeman M, Leppa S. Male gender is an adverse prognostic factor in B-cell lymphoma patients treated with immunochemotherapy. *Eur J Haematol.* 2011; 86:124-8.
 29. Pfreundschuh M, Held G, Zeynalova S, Zwick C, Haanel M, Truemper L, et al. Increased rituximab (R) doses and effect on risk of elderly male patients with aggressive CD20+ B-cell lymphomas: results from the SEXIE-R-CHOP-14 trial of the DSHNHL. *J Clin Oncol.* 2014;32(15 Suppl):8501.
 30. Tilly H, Morschhauser F, Sehn LH, Friedberg JW, Trnety M, Sharman JP, et al. Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. *N Engl J Med.* 2022;386:351-63.