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ORIGINAL ARTICLE

Addition of rituximab to reduced-dose CHOP chemotherapy is feasible for elderly patients with diffuse large B-cell lymphoma

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Abstract
Purpose The aim of this study was to evaluate the efficacy and toxicity of reduced-dose (RD) RCHOP (rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy for elderly patients with diffuse large B-cell lymphoma (DLBCL).
Methods This study comprised 85 patients, aged ≥60 years, who were diagnosed with DLBCL; patients were enrolled at a single center between June 2004 and December 2009. Patients received either 6 or 8 cycles of RD-RCHOP, spaced 3 weeks apart, at the physician's discretion. The RD-RCHOP regimen consisted of 375 mg/m^2 rituximab, 600 mg/m^2 cyclophosphamide, 30 mg/m^2 doxorubicin, and 1-mg vincristine on day 1 of each cycle, and 40-mg prednisone on days 1–5. The patients received granulocyte colony-stimulating factor if they experienced grade 4 neutropenia or febrile neutropenia during any cycle.
Results The average relative dose intensity was 97.3% for doxorubicin and 97.4% for cyclophosphamide. The complete remission (CR) and overall response rate were 67.1 and 89.5%, respectively. The 3-year event-free survival and overall survival rates were 71.9% ± 5.1% and 83.3% ± 5.1%. By using multivariate analyses, we determined that C-reactive protein levels greater than 1.31 mg/dl and the absence of CR were poor prognostic factors. Grade 3 or 4 neutropenia occurred in 35.3% of patients, and febrile neutropenia occurred in only 3 (3.5%) patients.
Conclusions RD-RCHOP chemotherapy is well tolerated and effective in elderly patients with DLBCL.

Keywords Rituximab · CHOP chemotherapy · Diffuse large B-cell lymphoma · C-reactive protein

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Introduction

More than 60% of patients with diffuse large B-cell lymphoma (DLBCL) are older than 60 years of age at diagnosis. Several trials to decrease the doses of the standard cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) combination chemotherapy or to substitute less toxic drugs in the combination have successfully decreased the treatment toxicity but have not resulted in improved survival [1–3]. Rituximab acts synergistically with chemotherapy to induce lymphoma cell lysis through several mechanisms, including complement-mediated cytolysis, antibody-dependent cell cytotoxicity, and induction of apoptosis. It is possible that addition of rituximab to reduced dose of CHOP chemotherapy can both improve patient outcomes and demonstrate improved toxicities in elderly DLBCL patients.

In several randomized trials, elderly DLBCL patients receiving standard-dose or dose-adjusted CHOP plus rituximab (RCHOP) chemotherapy have demonstrated improved outcomes with manageable toxicities [4, 5]. However, patients in these studies received prophylactic granulocyte

colony-stimulating factors (G-CSF) during all chemotherapy cycles or from the second cycle of chemotherapy if the patients experienced severe hematologic adverse events during first cycle. G-CSF improved the relative dose intensity (RDI) of the CHOP regimen in elderly patients with lymphoma; however, this did not lead to a higher complete remission (CR) rate or better survival. G-CSF also did not prevent serious infections from occurring as a result of the therapy. Moreover, neither the number of hospital admissions nor the duration of hospital stay was reduced [6]. Elderly patients treated with standard CHOP chemotherapy, even when combined with prophylactic use of G-CSF, usually had a higher incidence of febrile neutropenia than younger patients [6–8].

The aim of this study was to evaluate the efficacy and toxicity of reduced-dose RCHOP (RD-RCHOP) chemotherapy without G-CSF prophylaxis in DLBCL patients of over 60 years of age.

Materials and methods

Patients

From June 2004 to December 2009, 85 patients, aged 60 years old and above, were enrolled in this study following diagnosis of DLBCL at Pusan National University Hospital. Patients who had a history of indolent lymphoma or primary central nervous system involvement were excluded. Clinical data and follow-up information were obtained from the patients' medical records. Bulky disease was defined by the presence of a mediastinal mass exceeding one-third of the maximum intrathoracic diameter or a nodal mass larger than 10 cm. Staging procedures included clinical examination, chest and abdominal computed tomography (CT), blood cell count, bone marrow biopsy, and ^{18}F-2-deoxy-2-fluoro-D-glucose positron emission tomography (PET)-CT. Performance status was assessed using the Eastern Cooperative Oncology Group scale [9]. All patients provided written informed consent for RD-RCHOP chemotherapy.

Treatment

All patients received the RD-RCHOP regimen. Doses of RD-RCHOP chemotherapy were administered as previously reported [2] and are compared with that of standard RCHOP chemotherapy in Table 1. The cycles were repeated every 3 weeks, accounting to a total of 6 cycles of chemotherapy. If the patients did not achieve CR after the first 3 cycles, they received a total of 8 cycles of chemotherapy.

Patients received G-CSF if they experienced either grade 4 or febrile neutropenia during chemotherapy. Chemotherapy was administered if neutrophil counts were >1,500/l and/or platelet counts were >75,000/l, and all non-hematologic toxicities except alopecia, nausea, and vomiting were alleviated to grade 0 or 1 between cycles. If these results were not achieved, chemotherapy was delayed for up to 2 weeks until the patients recovered from neutropenia, thrombocytopenia, and the non-hematologic toxicities. The dosages of myelosuppressive drugs (cyclophosphamide and doxorubicin) were reduced by 25% if grade 4 neutropenia or thrombocytopenia developed. The development of grade 2 motor or sensory toxicity required a 25% reduction of the original dose of vincristine.

Table 1 Comparison of standard RCHOP and reduced-dose RCHOP chemotherapy regimens

	Standard RCHOP	RD-RCHOP
Rituximab	375 mg/m^2 iv on day 1	375 mg/m^2 iv on day 1
Cyclophosphamide	750 mg/m^2 iv on day 1	600 mg/m^2 iv on day 1
Doxorubicin	50 mg/m^2 iv on day 1	30 mg/m^2 iv on day 1
Vincristine	1.4 mg/m^2 iv on day 1	fixed dose of 1 mg iv on day 1
Prednisone	100 mg orally on days 1–5	40 mg orally on days 1–5

RCHOP rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone; *RD-RCHOP* reduced-dose RCHOP

Measurement of dose intensity

The actual dose intensity of each drug was calculated by dividing the total received dose of the agent by the number of weeks of treatment [10]. The RDI for each drug was calculated by dividing the actual dose intensity by the theoretical dose intensity, as previously described by Hryniuk [11].

Evaluation of response

Tumor responses were assessed after every 3 cycles of chemotherapy and at the end of treatment. PET-CT was performed at the end of chemotherapy to confirm CR. Each patient was re-evaluated every 3 months for the first 2 years after treatment and every 6 months thereafter. Tumor responses were classified according to the Revised Response Criteria for Malignant Lymphoma [10].

Statistical analysis

Event-free survival (EFS) was measured from the start of treatment to the first adverse event (events defined as death from any cause, relapse in complete responders, progression during or after treatment, and changes of therapy during treatment) or to the last follow-up at which the

patient was known to be alive. Overall survival (OS) was measured from the start of treatment to the date of death or the last follow-up at which the patient was known to be alive. EFS and OS were estimated using the Kaplan–Meier method.

Factors that were assessed for their influence on survival included age (≤69 vs. >69), gender, performance status, presence of B symptoms, number of extranodal sites, presence of bulky disease, bone marrow involvement, serum lactate dehydrogenase (LDH), albumin, β2-microglobulin, C-reactive protein (CRP), age-adjusted international prognostic index (IPI) (0–1 vs. 2–3), Ann Arbor disease stage (I–II vs. III–IV), chemotherapy cycles (≥6 cycles vs. <6 cycles), and response to treatment (CR vs no CR). Univariate analysis with the log-rank test was used to evaluate prognostic factors for EFS and OS. Multivariate analysis was performed using the Cox proportional hazards regression model. *P* values less than 0.05 were considered significant. All statistical analyses were completed using SPSS (version 18.0; IBM Corporation, New York, USA) except determination of the cutoff value for continuous variables, which was analyzed using the R statistical software package (version 2.6.0; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Table 2 shows the demographic and disease characteristics of the patients enrolled in this study. The median age of the patients was 69 years (range, 61–85 years), and patients aged 75 years and above accounted for 20% of the study population. One-third of the patients had stage III–IV disease, and fewer than 5% of patients had bulky disease or bone marrow involvement at presentation. Age-adjusted IPI was 2–3 in 35.3% of the patients.

Delivered dose intensity

For the 85 patients, a total of 508 therapy cycles were administered, with 66 (77.6%) patients completing the 6–8 cycles of the treatment regimen. The median number of cycles administered per patient was 6 (range 1–8). The average actual dose intensity was 29.2 mg/m^2/day for doxorubicin, 584.2 mg/m^2/day for cyclophosphamide, and 0.95 mg/day for vincristine. The average RDI was 97.3% for doxorubicin, 97.4% for cyclophosphamide, and 95% for vincristine. The doses of chemotherapy were reduced for 17 (20%) patients in 60 of the 508 (12.1%) cycles. The cycle of chemotherapy was delayed for 8 (9.4%) patients and 9 (1.8%) cycles.

Table 2 Patient demographics and characteristics upon enrollment

Factor	*n*	%
Total	85	
Sex		
Men	45	52.9
Women	40	47.1
Age (years)		
60–69	44	51.8
>69	41	48.2
Performance status		
0	37	43.5
1	26	30.6
2	7	8.2
3	15	17.6
Symptom stage		
A	72	84.7
B	13	15.3
Number of extranodal sites		
0	35	41.2
1	45	52.9
>1	5	6.0
Standard international prognostic index risk group		
Low (0 or 1)	25	29.4
Intermediate low (2)	30	35.3
Intermediate high (3)	19	22.4
High (4 or 5)	11	12.9
Age-adjusted international prognostic index risk group		
Low (0)	25	29.4
Intermediate low (1)	30	35.3
Intermediate high (2)	20	23.5
High (3)	10	11.8
Ann Arbor stage		
I	21	24.7
II	39	45.9
III	14	16.5
IV	11	12.9
Bone marrow involvement	4	4.7
Bulky disease	4	4.7
Serum LDH level >624 U/l	38	44.7
Serum albumin level ≤3.0 g/l	15	17.6
β2-microglobulin level >3.18 mg/l	30	35.3
C-reactive protein level >1.31 mg/dl	33	38.8

Response to treatment

The overall response rate (ORR) for the 85 treated patients was 89.5%. After 3 cycles of chemotherapy, 23 (27.1%) patients achieved CR, and 53 (62.4%) achieved partial remission (PR). At the end of the chemotherapy cycles, the

best responses for CR and PR rates were 67.1% (57/85 patients) and 22.4% (19/85 patients), respectively. Overall, the 34 patients who achieved PR after 3 cycles of chemotherapy obtained CR following continued chemotherapy (Table 3).

Survival analyses

The median follow-up duration was 30 months (range 1–71 months), with 16 deaths reported during treatment and follow-up. Disease progression caused the death of 10 patients (during chemotherapy in 4 patients and during the follow-up period in 6 patients). Another 5 (5.9%) patients died during chemotherapy due to chronic hepatitis C reactivation, tumor lysis syndrome, pneumonia, or neutropenic infection. Finally, 1 patient died during chemotherapy due to the aggravation of lung cancer. The 3-year EFS rate was 71.9% ± 5.1%, and the 3-year OS rate was 83.3% ± 5.1% (Fig. 1).

Univariate analyses indicated that serum LDH level >624 U/l; serum albumin level ≤3.0 g/l; β2-microglobulin level >3.18 mg/l; CRP level >1.31 mg/dl; <6 chemotherapy cycles; and the lack of CR following RD-RCHOP chemotherapy were all predictive of shorter survival (Table 4). Sex, age, performance status, symptom stage, number of extranodal sites, bone marrow involvement, bulky disease, age-adjusted IPI, and Ann Arbor stage did not have any apparent prognostic significance (Fig. 2). Multivariate analyses showed that CRP levels >1.31 mg/dl (hazards ratio, 14.1; 95% CI 1.6–126.6; $P = 0.018$) and the absence of CR (hazards ratio, 22.7; 95% CI 2.3–222.0; $P = 0.007$) were predictive factors for reduced OS (Fig. 3).

Table 3 Objective disease responses

	After 3 cycles	After end of chemotherapy cycles (best response)
	No. (%)	No. (%)
Overall response rate	76 (89.5)	76 (89.5)
Complete remission	23 (27.1)	57 (67.1)
Partial remission	53 (62.4)	19 (22.4)
Stable disease	1 (1.2)	1 (1.2)
Progressive disease	2 (2.4)	2 (2.4)
Not available	6 (7.1)	6 (7.1)

Toxicity

Table 5 lists the incidences of the toxicities according to the NCI-CTC toxicity criteria. Neutropenia was reported in 46 (54.1%) patients, 30 (35.3%) of whom experienced grade 3 or 4 toxicity. Grade 3 or 4 anemia and thrombocytopenia were reported in 8 (9.4%) and 5 (5.9%) patients, respectively. The clinical effects of these hematologic toxicities were limited, with neutropenic fever occurring in only 3 (3.5%) patients.

Severe non-hematologic toxicities were not frequent. Grade 3 or 4 toxicities consisted of asthenia in 11 (13.0%) patients, oral mucositis in 2 (2.4%) patients, and sensory neuropathy in one (1.2%) patient. Two patients experienced increases in liver enzyme levels (grade 2), and one of them died due to chronic hepatitis C reactivation. No severe cardiac events were observed.

Discussion

In the present study, the ORR, 3-year EFS, and OS rates were 89.5, 71.9, and 83.3%, respectively. Table 6 summarizes previous reports of elderly patients with DLBCL who received chemotherapy combined with rituximab as well as the primary results from the current study. The present study showed a similar CR rate and ORR combined with an improved survival, in terms of EFS and OS, as compared to a previous GELA study [11] that enrolled DLBCL patients aged 60–80 years who were treated with the standard RCHOP chemotherapy. Two previously published studies reported data about RD-CHOP-like chemotherapy combined

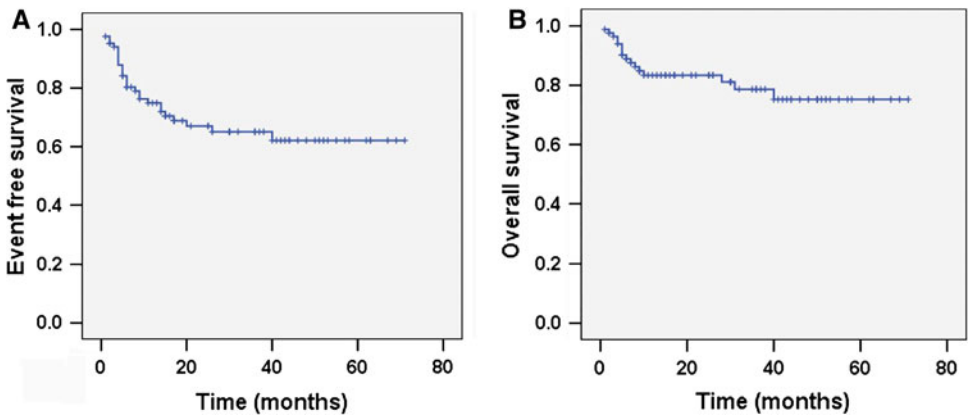

Fig. 1 Event-free survival (**a**) and overall survival (**b**) in 85 elderly patients with diffuse large B-cell lymphoma

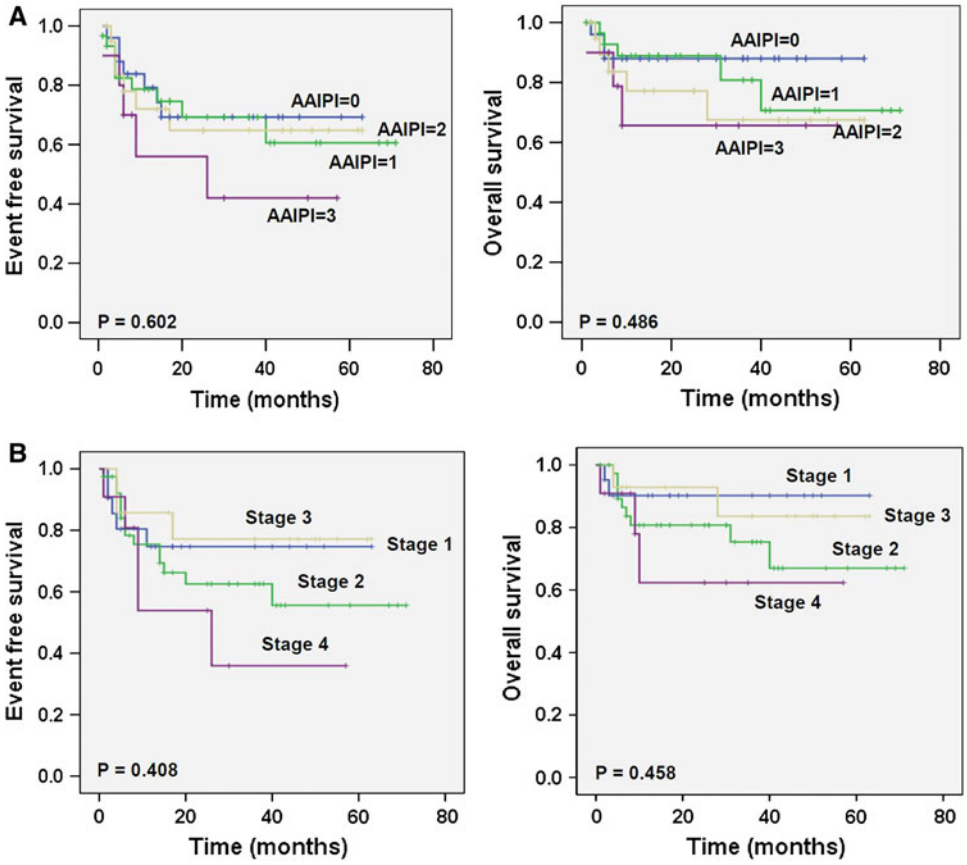

Fig. 2 Event-free survival and overall survival according to age-adjusted international prognostic index (**a**) and Ann Arbor stage (**b**)

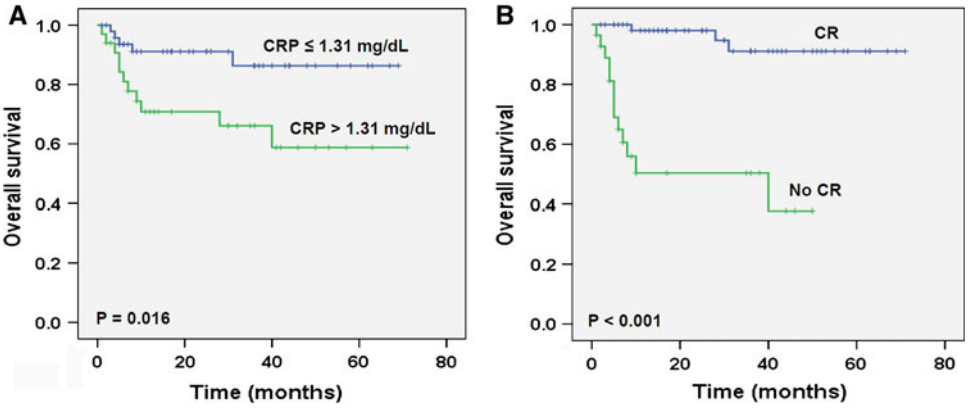

Fig. 3 Comparison of overall survival according to C-reactive protein and responsiveness to chemotherapy

with rituximab in elderly DLBCL patients [4, 5]. The current study demonstrated improved long-term survival compared with dose-adjusted infusions of cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (DA-POCH-R) [5] or rituximab combined with low-dose CHOP (R-miniCHOP) [4] chemotherapy. Our patients were 60 years of age or older, which was younger than that age of subjects involved in the previous 2 studies (DA-POCH-R and R-miniCHOP) where the enrolled patients were over 70 or 80 years old. However, in the current study, subgroup analyses of patients of above 69 years of age were observed to have outcomes similar survival to those below 69 years of age. Considering patients aged over 70 years, the survival of our patients was better than for patients who received either the DA-POCH-R or R-miniCHOP regimens (Table 6). These dose-adjusted RCHOP studies and the current study were similar with regard to hematologic toxicities, especially grade 3 or 4 neutropenia (35–48%), which is important in elderly patients because they are susceptible to increased treatment-related mortality due to life-threatening infections.

Corazzelli et al. [12] reported a biweekly rituximab, cyclophosphamide, non-pegylated liposome-encapsulated doxorubicin, vincristine, and prednisone (R-COMP)-14

Table 4 Univariate and multivariate analyses of prognostic factors for overall survival

Parameters	Univariate analyses		Multivariate analyses	
	3-year OS (%)	*P* value	Hazard ratio (95% CI)	*P* value
Serum LDH level >624 U/l	62.9 versus 86.0	0.032	7.102 (0.597–84.454)	0.121
Serum albumin level ≤3.0 g/l	48.6 versus 84.4	0.001	3.478 (0.631–19.170)	0.152
β2-microglobulin level >3.18 mg/l	72.5 versus 90.7	0.028	2.379 (0.315–17.948)	0.401
C-reactive protein level >1.31 mg/dl	66.1 versus 86.3	0.016	14.124 (1.576–126.588)	0.018
Chemotherapy cycles <6	70.4 versus 81.1	0.041	2.970 (0.585–15.084)	0.189
No complete remission	58.0 versus 90.1	<0.001	22.651 (2.311–222.034)	0.007

OS overall survival, *LDH* lactate dehydrogenase

Table 5 Toxicities observed during chemotherapy

Adverse event	Patients, no. (%)	
	All grades	Grades 3/4
Leukopenia	52 (61.2)	27 (31.8)
Neutropenia	46 (54.1)	30 (35.3)
Anemia	34 (40.0)	8 (9.4)
Thrombocytopenia	7 (8.2)	5 (5.9)
Febrile neutropenia	3 (3.5)	3 (3.5)
Anorexia	31 (36.5)	2 (2.4)
Nausea	23 (27.1)	1 (1.2)
Vomiting	5 (5.9)	1 (1.2)
Stomatitis	16 (18.8)	2 (2.4)
Diarrhea	8 (9.4)	0 (0)
Constipation	28 (32.9)	1 (1.2)
Sensory neuropathy	19 (22.4)	1 (1.2)
Motor neuropathy	10 (11.8)	0 (0)
Tinnitus	1 (1.2)	0 (0)
Hearing loss	1 (1.2)	0 (0)
Asthenia	30 (35.3)	11 (13.0)
Skin rash	4 (4.7)	0 (0)
Ataxia	1 (1.2)	0 (0)
Myalgia	5 (5.9)	0 (0)
AST/ALT	2 (2.4)	0 (0)
Bilirubinemia	1 (1.2)	0 (0)
Renal toxicity	1 (1.2)	0 (0)
Dizziness	2 (2.4)	1 (1.2)
Insomnia	5 (5.9)	0 (0)

AST aspartate aminotransferase, *ALT* alanine aminotransferase

regimen that showed a similar CR rate, but a lower survival rate, as compared to the current study. The rituximab, etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisolone, and bleomycin (R-VNCOP-B) combination chemotherapy regimen reported by a Japanese group was a doxorubicin-free combination therapy that was supposed to reduce cardiac toxicity [13]. Despite the favorable outcomes reported, grade 3 or 4 neutropenia (75% vs. 35%) and febrile neutropenia (30% vs. 3.5%) were higher than those reported in the current study. Additionally, febrile neutropenia in our patients was less frequent than that observed in previous studies of CHOP-like chemotherapy for elderly patients where a 27–47% incidence of neutropenic fever was observed [3, 8].

An increased RDI for chemotherapeutic agents is important in the treatment of lymphoma patients; an RDI of more than 70–75% for doxorubicin and cyclophosphamide was associated with better survival in patients treated with CHOP chemotherapy [14–16]. In the current study, the average RDI of doxorubicin and cyclophosphamide was about 97% as compared to the planned doses, in spite of not using prophylactic G-CSF during treatment cycles, and the treatment-related mortality was minimal (5.9%). In the present study, of the 76 patients who achieved ORR, the CR rate (67, 57% patients) at the end of treatment was higher than that observed after the third cycle (27, 23% patients), suggesting that some patients in PR during mid-chemotherapy cycles had a better chance of attaining CR if they continued to receive RD-RCHOP chemotherapy. Despite the absence of prophylactic use of G-CSF, 78% of the patients completed the 6–8 cycles of the treatment. These observations indicate that RD-RCHOP chemotherapy in elderly patients is beneficial because it can eliminate the prophylactic use of G-CSF and increase achievement of CR. This is accomplished by facilitating continued cycles of therapy through reduced chemotherapeutic doses, translating into improved survival.

Fisher et al. [17] suggested that the percentage of toxicity-related deaths increased with full-dose CHOP chemotherapy, while the CR rate decreased when the doses were reduced. Standard-dose RCHOP can similarly have more treatment-related toxicities in early cycles of therapy than if the doses are reduced. Indeed, several studies used prophylactic G-CSF or G-CSF support from the second cycle of therapy if the patients experienced severe neutropenia or febrile neutropenia as a result of the first cycle of therapy. Therefore, the introduction of dose-adjusted CHOP chemotherapy from the first cycle in elderly patients can reduce

Table 6 Comparison of elderly, diffuse large B-cell lymphoma patients treated with chemotherapy plus rituximab in previous studies

Study	Drug regimen	Age (years)	No. of patients	CR (%)	ORR (%)	EFS or PFS (years)	OS (years)	G 3–4 neutropenia
GELA study [20]	RCHOP	60–80	202	75	83	47% (5)	58% (5)	NA
Peyrade et al. [4]	R-miniCHOP	>80	150	62	73	47% (2)	59% (2)	40%
Musolino et al. [5]	DA-POCH-R	≥70	23	57	90	54% (3)	56% (3)	48%
Corazzelli et al. [12]	R-COMP-14	>60	41	68	73	77% (4)	67% (4)	NA
Ishii et al. [13]	R-VNCOP-B	>60	23	91	100	83% (3)	76% (3)	75%
Current study	RD-RCHOP	≥60	85	67	90	72% (3)	83% (3)	35%
Current study (Subgroup analysis)	RD-RCHOP	≥70	37	76	87	73% (3)	82% (3)	54%

CR complete response, *ORR* overall response rate, *EFS* event-free survival, *PFS* progression free survival; *OS* overall survival, *RCHOP* cyclophosphamide, doxorubicin vincristine, and prednisone plus rituximab, *R-miniCHOP* rituximab combined with low-dose CHOP, *DA-POCH-R* dose-adjusted infusional CHOP plus rituximab, *R-COMP-14* biweekly rituximab, cyclophosphamide, vincristine, non-pegylated liposome-encapsulated doxorubicin and prednisone, *R-VNCOP-B* etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisolone, and bleomycin plus rituximab, *RD-RCHOP* reduced-dose CHOP plus rituximab

early treatment-related mortality due to hematologic toxicities. The current study showed only 2 cases of treatment-related deaths during the first 3 cycles. Moreover, concurrently infused immunotherapy with rituximab displays an additive effect in both reducing the tumor burden and offsetting the decreased RR expected due to the reduced chemotherapy doses.

The parameters associated with poor outcome in the multivariate analyses were serum CRP concentrations at the time of diagnosis and failure to achieve CR during the RD-RCHOP regimen. The acute-phase protein CRP is used as a prognostic marker in humans with various neoplasias, including non-Hodgkin's lymphoma [18]. Therefore, CRP may also be a valuable prognostic marker in elderly patients with DLBCL.

Standard RCHOP chemotherapy in elderly patients with DLBCL has shown an overall 5-year survival rate of 80% in patients with low risk (age-adjusted IPI, 0–1), but survival in those at a higher risk (age-adjusted IPI, 2–3) was low (5-year OS, 48%) [19]. In the current trial, a subgroup analysis revealed that the OS in patients with low risk was comparable to the GELA study, but slightly higher than those at higher risk (79% vs. 80% in low risk, 67% vs. 48% at higher risk; data not shown). The lack of survival difference among age-adjusted IPI groups reflects the relatively improved survival of patients at a higher risk (Fig. 2a).

In conclusion, RD-RCHOP chemotherapy was found to be well tolerated and effective in elderly patients with DLBCL and was particularly promising, given the fact that the patients in this study did not receive prophylactic G-CSF or routine G-CSF administration after the first cycle of chemotherapy.

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Conflicts of interests The authors declare no competing financial interests.

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