Efficacy and tolerability of rituximab and reduced-dose cyclophosphamide, doxorubicin, vincristine, and prednisolone therapy for elderly patient with diffuse large B-cell lymphoma

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\textbf{ABSTRACT}

\textbf{Objectives:} Chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone combined with rituximab (R-CHOP) is currently the first-line therapy for diffuse large B-cell lymphoma (DLBCL). However, management of elderly patients is challenging and often requires dose reductions or prolonged treatment intervals. We investigated the proper dose of R-CHOP for them.

\textbf{Methods:} At our institute, for DLBCL patients aged 65–79 and ≥80 years, we had reduced CHOP dose to 5/6 and 7/12, respectively, and retrospectively evaluated the reduced-dose R-CHOP.

\textbf{Results:} Although the median age in the standard, 5/6, and 7/12-dose groups was 57, 73, and 84 years, respectively (\(p<0.001\)), the 3-year event-free survival (EFS) rate did not differ between the standard and 5/6-dose groups (60.2 and 56.7\%); however, 7/12-dose group had significantly inferior survival (25.9\%). When patients aged 60–80 were evaluated, no difference in EFS was observed between the standard and 5/6-dose groups using the same international prognostic index. The neutrophil nadir and the frequency of infection were comparable among the three dose groups.

\textbf{Discussion and Conclusions:} Reduced-dose R-CHOP chemotherapy is a promising treatment for elderly patients with DLBCL in terms of efficacy and toxicity.

\textbf{Introduction}

Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin’s lymphoma in adults [1]. The incidence of DLBCL increases with age, such that around 50\% of DLBCL cases occur in patients older than 65 years old, and 40\% in patients older than 70 years of age [2]. Combination chemotherapy with cyclophosphamide (CPA), doxorubicin (DXR), vincristine (VCR), and prednisolone (PSL) combined with rituximab (R-CHOP) is the standard treatment for patients with DLBCL [3]. However, the management of elderly patients with DLBCL remains clinically challenging. Impaired bone marrow function, altered drug metabolism, the presence of comorbidities, and functional status impairment decrease the tolerance to standard-dose treatment and increase treatment-related complications [4]. For these reasons, treatment decisions in elderly patients are often based on individual clinical judgment and lead to arbitrary dose reductions or the use of less-toxic therapy regimen [5-7]. Although these factors are likely to contribute to inferior outcomes in elderly patients compared with younger patients [8], dose reduction has been widely used to increase treatment tolerance to the standard R-CHOP regimen [9,10]. However, standard-dose-intensity R-CHOP has superior efficacy in elderly patients according to large prospective studies [3,11,12]. In the present study, we retrospectively evaluated the efficacy and toxicity of reduced-dose R-CHOP in DLBCL patients of over 60 years of age in real-world clinical practice.

\textbf{Method}

\textbf{Patients}

A total of 89 consecutive patients with CD20 positive DLBCL who were treated with R-CHOP with curative intent at Chiba Municipal Aoba Hospital between January 2004 and March 2015 were retrospectively evaluated. Patients who had a history of indolent lymphoma were excluded. Clinical data were obtained from the patient medical records. Performance status (PS) was assessed using the Eastern Cooperative Oncology Group scale [13]. The median follow-up time was 98.3 months (4.67–372.4 months).

\textbf{Treatment}

At our institution, elderly patients with DLBCL were treated according to the following principles. Patients

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with limited disease received three cycles of R-CHOP followed by involved field irradiation (IFI, 30–40.1 Gy) or six cycles of R-CHOP without IFI. Whether radiation therapy was performed or not was decided depending on the site of lesions. Patients with advanced disease received six or eight cycles of R-CHOP. Standard doses of CPA (750 mg m\(^{-2}\)), DXR (50 mg m\(^{-2}\)), VCR (1.4 mg m\(^{-2}\), maximum 2 mg), and PSL (100 mg/body, 5 days) with 21-day intervals were reduced according to patient age: patients aged 80 years or older received a 7/12 dose of CPA (438 mg m\(^{-2}\)), DXR (1.2 mg/body), and PSL (42 mg m\(^{-2}\), 5 days), while patients aged 80 years or older received a 7/12 dose of these drugs, CPA (438 mg m\(^{-2}\)), DXR (29 mg m\(^{-2}\)), VCR (0.8 mg/body) and PSL (29 mg m\(^{-2}\), 5 days) [14]. All patients received 375 mg m\(^{-2}\) of rituximab at each cycle without reduction. When the absolute neutrophil count recovered to >1.5 × 10\(^9\) L\(^{-1}\) and platelet count to >100 × 10\(^9\) L\(^{-1}\), the next R-CHOP course was administered. Granulocyte colony stimulating factor (G-CSF; filgrastim) was administered if the physician determined it to be necessary. All patients with newly diagnosed DLBCL were treated in hospitalization until their blood counts recovery. We would prophylactically administer daily G-CSF with a neutrophil count of 1000 μL\(^{-1}\) as a guide and kept dosing G-CSF in out-patient treatment. In the present study period, pegylated G-CSF had not been approved in Japan.

Relative dose intensity

The actual dose intensity of each drug was calculated by dividing the total received dose of the agent by the number of days of treatment [15]. The relative dose intensity (RDI) for each drug was calculated by dividing the actual intensity by the theoretical dose intensity, as previously described [16]. RDI was calculated from cycle #1 even if it was reduced, although there were some newly diagnosed patients who had to receive intensity-reduced CHOP regimen as the first therapy due to a high tumor burden or poor PS.

Assessment of responses and adverse events

Tumor responses were assessed after 3 or 4 cycles of R-CHOP and at the end of treatment. Re-evaluation was performed every 3 or 4 months for the first 2 years after treatment and every 6 months thereafter. Tumor responses were classified according to the National Cancer Institute-sponsored International Workshop Criteria [17] or Revised Response Criteria for Malignant Lymphoma [15]. We evaluated tumor response by using CT in most cases, because PET-CT had not prevailed in this study period.

Statistical analysis

Differences in patient characteristics among the different generation groups were analyzed using Fisher’s exact test or Student’s t-test. Overall survival (OS) was defined as the time from the date of diagnosis until the date of death from any cause. Event-free survival (EFS) was defined as the time from the date of diagnosis until the date of confirmed progression disease (PD), relapse of complete response (CR), change of therapy during treatment, or death from any cause. OS and EFS were estimated according to the Kaplan–Meier method and compared by means of the log-rank test.

Factors that were assessed for their influence on survival included age, gender, PS, presence of B symptoms, number of extranodal sites, lactate dehydrogenase (LDH), RDI, PS, international prognostic index (IPI), and Ann Arbor disease stage. A multivariate analysis using the Cox proportional hazards model was constructed with variables with a p-value of less than 0.1. All tests were two-sided, with p-values ≤ 0.05 considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 1.6-3) [18].

Results

Patient characteristics

In total, 89 patients with DLBCL were treated with R-CHOP during the study period. Patient characteristics are shown in Table 1. Of these, 82 patients received six to eight cycles of R-CHOP. Seven of 30 patients with stage I or II received three cycles of R-CHOP followed by IFI and the others received six cycles of R-CHOP without IFI. In 59 cases with stage III-IV, 53 patients completed all planned 6 to 8 cycles. Twenty-nine, 8 and 16 patients accomplished six, seven and eight cycles of R-CHOP, respectively. The remaining six cases were completed in less than six courses due to patient’s choice (1), poor conditions (4) and progression of the disease (1). Median number of cycles administered was 6 cycles in the patients with stage III–IV. No patient received radiation therapy at the end of treatment.

In terms of therapeutic dose, 40 patients received standard-dose R-CHOP (standard-dose group), 40 patients received 5/6 dose R-CHOP (5/6-dose group), 9 patients received 7/12 dose R-CHOP (7/12-dose group). The median age of patients in the standard, 5/6, 7/12-dose groups was 57 years (range, 32–69 years), 73 (range, 60–79 years), and 84 (range, 80–91 years), respectively (p < 0.001). There was a statistical trend toward a greater proportion of patients with PS...
2–4 in the 7/12-dose group (35.0, 47.5, and 77.8% in standard, 5/6, and 7/12-dose group, respectively, p = 0.06). Gender, LDH, stage, number of extranodal lesions, and presence of B symptoms did not significantly differ between the groups. RDI was 90.0% in the standard-dose group, 73.0% in the 5/6-dose (standard-intent 83%) group, 53.0% in the 7/12-dose (standard-intent 58%) group.

Response to treatment

The response at the end of the treatment was as follows: 81 patients (88.9%) achieved a CR, 3 patients (3.4%) archived a partial response, and the remaining 5 patients (5.6%) had PD. There were no significant differences in the CR rate between the groups (92.5, 95.0 and 66.7% in the standard, 5/6, and 7/12-dose groups, respectively, Table 1).

The 3-year OS was 70.4% overall, and 83.2% in the standard-dose group, 63.3% in the 5/6-dose group, and 37.5% in the 7/12-dose group, respectively. Although the 3-year OS was comparable between the standard and 5/6-dose groups (p = 0.294), that of the 7/12-dose group was significantly inferior (versus standard-dose group, p = 0.002; versus 5/6-dose group, p = 0.020; Figure 1(a)). The 3-year EFS rate was 55.7% in all groups, 60.2% in the standard-dose group, 56.7% in the 5/6-dose group and 25.9% in the 7/12-group. Similar to the OS rate, the 3-year EFS in the 7/12-dose group was inferior to that of the standard and 5/6-dose groups (versus standard-dose group; p = 0.024, versus 5/6-dose group; p = 0.019); however, the 3-year EFS between the standard and 5/6-dose groups was equal (p = 0.723, Figure 1(b)).

Prognostic factor

As the survival in the 7/12-dose group was significantly poorer, the following analysis was performed between the standard and 5/6-dose groups. OS and EFS did not significantly differ between patients with RDI 90% or more versus less than 90% (Figure 2(a,b)). On investigating the relationship between chemotherapy dose and survival according to IPI risks in patients aged 60–80 years with IPI low/low-intermediate risk was 63.6% versus 74.6% in standard and 5/6-dose groups, respectively (Figure 3(a)). The 3-year OS rate in patients aged 60–80 years with IPI low/low-intermediate risk was 81.8% versus 66.7% in standard and 5/6-dose groups, respectively (p = 0.379, Figure 3(c)). The 3-year EFS rate in patients aged 60–80 years with IPI low/low-intermediate/high risk was 63.6 and 53.6% in standard and 5/6-dose groups, respectively (p = 0.111, Figure 3(d)).

Regarding OS, univariate analysis revealed that stage (3-year OS, 81.9 and 68.1% for stages I–II and stages III–IV, respectively; p = 0.049) and IPI risks (3-year OS, 84.2 and 64.7% for low/low-intermediate and standard-dose group; p = 0.002; versus 5/6-dose group, p = 0.020; Figure 1(a)). The 3-year EFS rate was 55.7% in all groups, 60.2% in the standard-dose group, 56.7% in the 5/6-dose group and 25.9% in the 7/12-group. Similar to the OS rate, the 3-year EFS in the 7/12-dose group was inferior to that of the standard and 5/6-dose groups (versus standard-dose group; p = 0.024, versus 5/6-dose group; p = 0.019); however, the 3-year EFS between the standard and 5/6-dose groups was equal (p = 0.723, Figure 1(b)).

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Table 1. Patient characteristics.

| Characteristics | Standard-dose | 5/6-dose | 7/12-dose | p-value |
|-----------------|--------------|----------|-----------|---------|
| Age             | Median       | 56.5     | 72.9      | 83.8    | <0.001  |
| Age             | Range        | 32–69    | 60–79     | 80–91   |         |
| Gender          | Male         | 19 (47.5%) | 19 (47.5%) | 3 (33.3%) | 0.721   |
| Gender          | Female       | 21 (52.5%) | 21 (52.5%) | 6 (66.7%) |         |
| Treatment       | Stage I, II  | Total    | 17 (42.5%) | 12 (30.0%) | 1 (11.1%) |         |
| Treatment       | R-CHOP 3 + RT | 2 (11.8%) | 4 (33.3%) | 1 (100.0%) | 0.073   |
| Treatment       | R-CHOP 6     | 15 (88.2%) | 8 (66.7%) | 0 (0.0%) |         |
| Treatment       | Stage III, IV| Total    | 23 (57.5%) | 28 (70.0%) | 8 (88.9%) |         |
| Treatment       | R-CHOP <6    | 3 (13.0%) | 1 (3.6%) | 2 (25.0%) | 0.177   |
| Treatment       | R-CHOP 6-8   | 20 (87.0%) | 27 (96.4%) | 6 (75.0%) |         |
| PS              | Negative     | 26 (65.0%) | 21 (52.5%) | 2 (22.2%) | 0.06   |
| PS              | 2, 3, 4      | 14 (35.0%) | 19 (47.5%) | 7 (77.8%) |         |
| PS              | Positive     | 17 (42.5%) | 15 (37.5%) | 3 (33.3%) | 0.835   |
| Extranodal site | 0, 1         | 29 (72.5%) | 28 (70.0%) | 6 (66.7%) | 0.931   |
| Extranodal site | ≥2           | 11 (27.5%) | 12 (30.0%) | 3 (33.3%) |         |
| IPI             | L/LI         | 22 (55.0%) | 13 (32.5%) | 1 (11.1%) | 0.02   |
| IPI             | HI/H         | 18 (45.0%) | 27 (67.5%) | 8 (88.9%) |         |
| CR              | CR           | 37 (92.5%) | 38 (95.0%) | 6 (66.7%) | 0.025   |
| CR              | non CR       | 3 (7.5%) | 2 (5.0%) | 3 (33.3%) |         |

RT: Radiation therapy; RDI: relative dose intensity; LDH: Lactate dehydrogenase; PS: performance status; CR: complete response; IPI: International Prognostic Index; L/LI: low/low-intermediate risk; HI/H: high-intermediate/high risk.
high-intermediate/high risk, respectively; \( p = 0.019 \) were associated with shorter overall survival (Table 2). Multivariate analysis revealed an association between shorter survival and IPI risks (HR, 1.77; 95% CI, 1.10–2.85; \( p = 0.019 \); Table 2).

Considering EFS, univariate analysis revealed that PS (3-year EFS, 65.7 vs. 48.3% for PS 0–1 and PS 2–4; \( p = 0.043 \)), stage (3-year EFS, 79.3 and 43.9% for stages I–II and stages III–IV; \( p = 0.004 \)), the presence of B symptoms (3-year EFS, 65.6 and 48.3% with and without B symptoms respectively; \( p = 0.080 \)), number of extranodal sites (3-year EFS, 65.7 and 38.8% for less than 2 and at least 2; \( p = 0.033 \)), LDH level (3-year EFS, 73.3 and 42.3% for LDH level \(<\text{ULN} \times 2\) and \(\geq \text{ULN} \times 2\), respectively; \( p = 0.010 \)), and IPI risks (3-year EFS, 73.6 and 45.5% for low/low-intermediate and high-intermediate/high, respectively; \( p = 0.005 \)) were associated with shorter survival (Table 3). Multivariate analysis revealed an association between shorter survival and stage (HR, 3.67; 95% CI, 1.50–8.99; \( p = 0.004 \), Table 3). Neither dose nor RDI were associated with shorter OS and EFS.

**Comparison between neutropenia and antibiotics**

There was no difference between the standard, 5/6, and 7/12-dose groups in neutrophil nadir during each

\[ \text{Figure 1. OS (a) and EFS (b) in patients receiving the standard, 5/6 and 7/12-dose R-CHOP.} \]
The median neutrophil nadir was 231–744 µL\(^{-1}\), 390–525 µL\(^{-1}\), and 167–1292 µL\(^{-1}\) in the standard, 5/6 and 7/12-dose groups, respectively, and there were no significant differences between the three dose groups for each chemotherapy course. The incidence of infection was similar among the standard, 5/6, and 7/12-dose groups (47.5, 47.5, and 44.4%, respectively, Table 4). A total of 42 patients were treated with intravenous antibiotics during chemotherapy, with no difference in the duration of antibiotic therapy observed between groups (11.9 days, 21.0 days, and 7.8 days in the standard, 5/6, and 7/12-dose groups, respectively; \(p = 0.099\), Table 4). A total of 66 patients received G-CSF. The dose of G-CSF was similar between the standard, 5/6 and 7/12 dose groups (1611.3, 1816.9 and 900.0 µg, respectively; \(p = 0.475\), Table 4). There were 26 deaths during the treatment and follow-up periods. Of these, 20 patients died of lymphoma, 2 patients of secondary myelodysplastic syndrome or acute myeloid leukemia, 2 patients of other malignant disease, and 2 patients of other disease.

**Discussion**

In the present retrospective study, we demonstrate that CR rate, EFS, and OS in patients treated with 5/6 dose R-CHOP are comparable to those of patients treated with standard-dose R-CHOP, regardless of age, in a population of patients predominantly aged 65–79 years (median, 70 years) treated with 5/6 dose R-CHOP.
The appropriate dose in elderly patients remains unknown in the rituximab era [9]. The RICOVER-60 trial in patients aged over 60 found that age >70 was an adverse factor [12]. In the U.S. intergroup trial E4494, Advani et al. reported that the 3-year OS of patients aged 70 years or older who received standard-dose R-CHOP was significantly inferior to that of 60–69-year-old patients (58 vs. 74%, p = 0.002), largely due to their inability to complete the planned therapy and excessive toxicity [19]. The introduction

![Figure 3](image)

**Figure 3.** The 3-year OS rate in patients aged 60–80 years with IPI low/low-intermediate risk (a) and IPI high-intermediate/high risk (b). The 3-year EFS rate in patients aged 60–80 years with IPI low/low-intermediate risk (c) and IPI high-intermediate/high risk (d).

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**Table 2.** Prognostic factors associated with OS.

| Variables          | Univariate analysis | Multivariate analysis |
|--------------------|---------------------|-----------------------|
|                    | N       | HR     | 95% CI  | 3-year survival (%) | p-value | HR     | 95% CI  | p-value |
| Age                | <65 years | 39     | 1.00    | 86.3 (70.0–94.1) |          |         |         |         |
|                    | ≥65 years | 41     | 2.00    | 0.83–4.86 | 59.8 (40.3–74.7) | 0.125   |         |         |
| Gender             | Male     | 38     | 1.00    | 81.0 (62.0–91.1) |          |         |         |         |
|                    | Female   | 42     | 1.70    | 0.68–4.27 | 67.6 (49.7–80.3) | 0.256   |         |         |
| PS at diagnosis    | 0, 1     | 47     | 1.00    | 75.9 (59.6–86.3) |          |         |         |         |
|                    | 2, 3, 4  | 33     | 1.66    | 0.70–3.93 | 71.3 (50.0–84.7) | 0.246   |         |         |
| Stage              | I, II    | 29     | 1.00    | 81.9 (61.7–92.1) |          |         |         |         |
|                    | III, IV  | 51     | 2.77    | 1.01–7.63 | 68.1 (50.8–80.5) | 0.049   | 1.32    | 0.28–6.33 | 0.726 |
| B symptoms         | Negative | 48     | 1.00    | 80.2 (64.0–89.7) |          |         |         |         |
|                    | Positive | 32     | 1.83    | 0.77–4.34 | 64.1 (42.8–79.1) | 0.172   |         |         |
| Extrananal site    | 0, 1     | 57     | 1.00    | 75.6 (60.9–85.4) |          |         |         |         |
|                    | ≥2       | 23     | 1.90    | 0.78–4.61 | 69.3 (42.7–85.4) | 0.156   |         |         |
| LDH level at diagnosis | <ULN × 2 | 39     | 1.00    | 79.9 (62.9–90.0) |          |         |         |         |
|                    | ≥ULN × 2 | 41     | 2.47    | 0.99–6.15 | 66.9 (47.6–80.4) | 0.051   |         |         |
| Dose               | Standard  | 40     | 1.00    | 83.2 (66.2–92.1) |          |         |         |         |
|                    | 5/6 dose | 40     | 1.59    | 0.67–3.78 | 63.3 (43.9–77.6) | 0.298   |         |         |
| RDI                | <90%     | 23     | 1.00    | 84.8 (59.7–94.9) |          |         |         |         |
|                    | ≥90%     | 57     | 1.88    | 0.63–5.58 | 69.2 (53.8–80.4) | 0.259   |         |         |
| IPI                | L/LI     | 35     | 1.00    | 84.2 (66.0–93.1) |          |         |         |         |
|                    | Hi/H     | 45     | 1.77    | 1.10–2.85 | 64.7 (46.3–78.2) | 0.019   | 1.77    | 1.10–2.85 | 0.019 |

PS: performance status; LDH: Lactate dehydrogenase; RDI: relative dose intensity; CR: complete response; IPI: International Prognostic Index; ULN: upper limit of normal; L/LI: low/low-intermediate risk; Hi/H: high-intermediate/high risk.
Dose reduction may impair the efficacy of chemotherapy and may increase treatment-related mortality due to hematologic toxicities [20]. The neutrophil nadir during each course of chemotherapy is a key parameter associated with the probability of survival. These results suggest that upfront dose reduction of R-CHOP in elderly patients may lead to reasonable treatment outcomes.

Adverse effects were acceptable in the present study. No treatment mortality occurred during chemotherapy. Severity of neutropenia, frequency of infection, and doses of G-CSF did not differ between the standard, 5/6, and 7/12-dose groups. No patients experienced life-threatening infection.

The 7/12 dose of R-CHOP was tolerable in patients with DLBCL who were aged 80 year or older. The CR rate (66.7%) of these patients in the present study was comparable to those in the GELA trial, in which patients aged 80 year or older received six 21-day cycles of R-miniCHOP, with a CR or uncon-fermed CR rate of 62% [21]. Although their survival was not sufficient, it was thought that there were more patients with poor PS in the present study.

The present study was limited by the small sample size and retrospective nature of study design with long-term follow-up from a single institution. These factors may have resulted in selection bias in that only patients with a good physical condition were included. However, such selection bias is inevitable even in prospective studies with specific inclusion criteria, which may exclude patients who are considered to be unable to tolerate chemotherapy. A prospective cohort study that includes all consecutive elderly patients is required to eliminate this bias.

Table 3. Prognostic factors associated with EFS.

| Variables          | N  | HR   | 95% CI     | p-value | 3-year survival (%) Median (range) | HR   | 95% CI     | p-value |
|--------------------|----|------|------------|---------|-----------------------------------|------|------------|---------|
| Age                |    |      |            |         |                                   |      |            |         |
| <65 years          | 39 | 1.00 | 65.5 (48.0–78.3) | 0.598   |                                   |      |            |         |
| ≥65 years          | 41 | 1.21 | 50.6 (32.1–66.5) |         |                                   |      |            |         |
| Gender             |    |      |            |         |                                   |      |            |         |
| Male               | 38 | 1.00 | 64.3 (45.2–78.2) |         |                                   |      |            |         |
| Female             | 42 | 1.21 | 54.0 (37.0–68.3) | 0.249   |                                   |      |            |         |
| PS at diagnosis    |    |      |            |         |                                   |      |            |         |
| 0, 1               | 47 | 1.00 | 65.7 (49.5–77.9) |         |                                   |      |            |         |
| 2, 3, 4            | 33 | 1.00 | 48.3 (28.7–65.4) | 0.043   | 1.17 (0.50–2.76)                  | 0.722|         |         |
| Stage              |    |      |            |         |                                   |      |            |         |
| L, II              | 29 | 1.00 | 79.3 (59.6–90.1) |         |                                   |      |            |         |
| III, IV            | 51 | 3.67 | 43.9 (27.8–58.9) | 0.004   | 3.67 (1.50–8.99)                  | 0.004|         |         |
| B symptoms         |    |      |            |         |                                   |      |            |         |
| Negative           | 48 | 1.00 | 65.6 (49.3–77.8) |         |                                   |      |            |         |
| Positive           | 32 | 1.86 | 48.3 (28.7–65.3) | 0.080   | 0.95 (0.43–2.09)                  | 0.890|         |         |
| Extranodal site    |    |      |            |         |                                   |      |            |         |
| 0, 1               | 23 | 1.28 | 38.8 (15.9–61.3) | 0.033   | 1.07 (0.41–2.78)                  | 0.889|         |         |
| ≥2                 | 23 | 1.00 | 43.9 (27.8–58.9) | 0.004   | 1.07 (0.41–2.78)                  | 0.889|         |         |
| LDH level at diagnosis |    |      |            |         |                                   |      |            |         |
| <ULN × 2           | 39 | 1.00 | 73.3 (55.9–84.7) |         |                                   |      |            |         |
| ≥ULN × 2           | 41 | 2.65 | 42.3 (24.9–58.7) | 0.010   | 1.82 (0.82–4.07)                  | 0.141|         |         |
| Dose               |    |      |            |         |                                   |      |            |         |
| Standard           | 40 | 1.00 | 60.2 (42.8–73.8) |         |                                   |      |            |         |
| 5/6 dose           | 40 | 0.88 | 56.7 (37.9–71.7) | 0.723   |                                   |      |            |         |
| RDI                |    |      |            |         |                                   |      |            |         |
| ≥90%               | 23 | 1.00 | 66.0 (41.6–82.2) |         |                                   |      |            |         |
| <90%               | 57 | 1.29 | 55.8 (40.9–68.4) | 0.532   |                                   |      |            |         |
| IPI                |    |      |            |         |                                   |      |            |         |
| L/LI               | 35 | 1.00 | 73.6 (55.3–85.3) |         |                                   |      |            |         |
| HI/H               | 45 | 1.74 | 45.5 (28.4–61.1) | 0.005   | 1.21 (0.71–2.04)                  | 0.486|         |         |

PS: performance status; LDH: Lactate dehydrogenase; RDI: relative dose intensity; CR: complete response; IPI: International Prognostic Index; UPN: upper limit of normal; L/LI: low/low-intermediate risk; HI/H: high-intermediate/high risk.

Table 4. Onset of infection and administration of antibiotics and G-CSF.

| Characteristics | Standard-dose | 5/6-dose | 7/12-dose | p-value |
|-----------------|---------------|----------|-----------|---------|
| n               | n = 40        | n = 40   | n = 9     |         |
| Onset of infection | No | 21 (52.5%) | 21 (52.5%) | 5 (55.6%) | 0.985   |
|                 | Yes | 19 (47.5%) | 19 (47.5%) | 4 (44.4%) |         |
| Antibiotics admin. | Median | 11.9 | 21.0 | 7.8 | 0.099 |
| Range (day) | 1–37 | 4–76 | 2–17 |         |
| Dose of G-CSF (μg) | Median | 1611.3 | 1816.9 | 900.0 | 0.475 |
| Range | 75–5325 | 225–6075 | 300–1500 |         |
Conclusion

In conclusion, reduced-dose R-CHOP chemotherapy appeared to be a well-tolerated and effective treatment option for newly diagnosed elderly patients with DLBCL. We believe that appropriate dose adjustments with careful monitoring of adverse events improved the clinical outcome, even for patients with comorbidities. Further studies are warranted to confirm the efficacy of this approach in this population.

Disclosure statement

No potential conflict of interest was reported by the authors.

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