ORIGINAL ARTICLE

Clinical characteristics and outcomes in diffuse large B cell lymphoma patients aged 70 years and older: a single-center experience with a literature review

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Background/Aims: Among diffuse large B cell lymphoma (DLBCL) patients, determining the appropriate dose and chemotherapy schedule to balance toxicity and efficacy is harder in elderly than in younger patients. Moreover, there are no currently available clinical factors that consistently identify patients who are unfit to receive chemotherapy. Therefore, the clinical characteristics and outcomes of elderly patients with DLBCL and the causes of treatment-related death were investigated in this study.

Methods: The clinical characteristics and outcomes of 44 elderly (≥ 70 years of age) patients diagnosed with DLBCL between January 2005 and June 2013 were evaluated. Variable clinical data along with the response rate, overall survival (OS), and causes of treatment-related death or treatment interruption were investigated.

Results: The median OS was 18.6 months, and 19 patients completed curative treatment. The mean average relative dose intensity of adriamycin in patients who completed chemotherapy was 0.617, and of these patients, 16 achieved complete remission. Chemotherapy incompletion, infectious complications, extranodal involvement, high lactate dehydrogenase, poor performance status, and low albumin level at diagnosis were related to a shorter OS. However, multivariate analysis revealed that only infections and chemotherapy incompletion were significantly related to poor prognosis. The most common cause of treatment-related death was infection, and patients who had experienced infectious complications tended to have lower albumin levels than those of patients without such complications.

Conclusions: In the treatment of elderly lymphoma patients, the dose intensity of adriamycin is not as important as it is in young patients. However, in elderly patients, infections are particularly dangerous, especially in patients with low albumin levels.

Keywords: Lymphoma, large B-cell, diffuse; Aged; Infection; Albumins

INTRODUCTION

As the life span of human beings extends, the prevalence of elderly lymphoma patients is increasing. Accordingly, the age of those in the "elderly" category, which has been defined in the past as 60 years or older, is increasing,

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and elderly patients with diffuse large B cell lymphoma (DLBCL) account for a significant portion of total elderly lymphoma patients. Although DLBCL has an aggressive nature and poor prognosis, the introduction of rituximab has resulted in better treatment outcomes, and DLBCL is now considered to be a curable disease. Nonetheless, high treatment-related mortality (TRM) and intolerability to standard chemotherapy (rituximab plus cyclophosphamide/adriamycin/vincristine/prednisolone [CHOP]), as well as high comorbidity, still prevent the achievement of favorable outcomes in elderly patients. Currently, comprehensive geriatric assessment (CGA) and other evaluation tools are applied during chemotherapy to assess whether alterations, which may include dose reductions, interval modifications, and the prophylactic administration of granulocyte colony stimulating factor (G-CSF), are needed to improve patient outcome. However, there are no standardized or reliable methods available which allow for the tailoring of chemotherapy treatment to elderly patients, and most physicians still rely on chronologic age, performance status (PS), and comorbidity to determine chemotherapy feasibility in elderly patients.

To address this gap in knowledge, we analyzed the clinical and treatment characteristics, as well as patient outcomes in elderly DLBCL patients. In addition, the prognostic factors and primary causes of treatment-related death and treatment interruptions were analyzed, and the causes of the clinical treatment characteristics were compared.

METHODS

A retrospective review of the clinical characteristics and outcomes of 44 patients aged 70 years or older, who were diagnosed with DLBCL from January 2005 to June 2013 at the Yeouido St. Mary's Hospital, was conducted. Because the majority of patients with DLBCL are over 60 years of age, and because previous studies aimed at elderly patients aged between 60 and 70 years showed favorable outcomes, those over 70 years were targeted in the present study [1]. Clinical characteristics such as age, sex, Eastern cooperative oncology group PS, stage, lactate dehydrogenase (LDH), albumin level at diagnosis, comorbidity status, and extra-nodal involvement were

investigated. The 19 diseases-weighted Charlson comorbidity index (CCI) was used to assess comorbidity. Response results, overall survival (OS), cause of treatment interruption or deprivation, and cause of death were investigated to evaluate outcomes. Patients with advanced DLBCL were treated with six to eight cycles of rituximab/cyclophosphamide/adriamycin/vincristine/prednisolone (R-CHOP) chemotherapy (rituximab 375 mg/m², cyclophosphamide 750 mg/m², vincristine 1.4 mg/m², adriamycin 50 mg/m², prednisone 40 mg/m² every 3 weeks), and patients with localized disease were treated with three to four cycles of R-CHOP chemotherapy and then with involved field radiation therapy (IFRT), which is the standard at our institute. Doses of chemotherapeutic agents, particularly adriamycin and cyclophosphamide, were modified for patients with poor PS, and cycle duration was modified based on the patient's condition. For example, if bone marrow function was suppressed or PS did not recover, treatment was delayed. The average relative dose intensity (aRDI) of adriamycin was evaluated, since it is a preferentially dose-adjusted agent due to myelosuppression and cardiotoxicity. The aRDI of adriamycin was determined by dividing the actual delivered dose intensity of adriamycin by the dose intensity of the agent in the five-drug standard regimen (R-CHOP) [2]. The aRDI of patients who received only one cycle of chemotherapy was calculated using the mean cycle length (26.8 days). The association between the adriamycin aRDI and outcome was investigated. In addition, patient characteristics were evaluated in terms of treatment characteristics, chemotherapy interruptions, and causes of treatment-related deaths.

Statistical analysis and definitions

OS was defined as the time from the date of diagnosis to the date of death from any cause. Survival data were computed according to the Kaplan-Meier method, and the curves were compared using the log-rank test for univariate analysis. A $p < 0.05$ was considered statistically significant. A multivariate cox proportional hazard regression analysis was used to assess the effects of the prognostic factors on OS. In addition, patient characteristics were compared according to chemotherapy completion using the chi-square test and independent-samples t test. All data were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

A total of 44 patients were investigated in this study. Twenty-four patients (54.5%) were female, and 20 (45.5%) were male. The median age was 75 years (range, 70 to 86), and eight patients older than 80 years were included. Fourteen patients had poor PS scores (> 2). The detailed patient clinical characteristics are summarized in Table 1. There was no significant correlation between age and comorbidity index score, and most patients (n = 32, 72.7%) had a chronic illness such as hypertension or diabetes. The most common comorbidity was hyper-

Table 1. Baseline characteristics of elderly diffuse large B cell lymphoma patients

Characteristic	Value
Age, yr	75 (70–86)
70–74	18 (40.9)
75–79	18 (40.9)
≥ 80	8 (18.2)
Sex	
Male	20 (45.5)
Female	24 (54.5)
Clinical stage	
I–II	14 (31.8)
III–IV	29 (65.9)
Missing	1 (2.3)
Performance status	
0–1	18 (40.9)
2	11 (25)
3	11 (25)
4	3 (6.8)
Missing	1 (2.3)
IPI score	
Low/low-intermediate 0–2	11 (25)
High/high-intermediate 3–5	32 (72.7)
Missing	1 (2.3)
Comorbidities (CCI)	
0–3	21 (47.7)
≥ 4	23 (52.3)

Values are presented as median (range) or number (%).
IPI, International Prognostic Index; CCI, Charlson comorbidity index.

tension (n = 21, 47.7%) followed by diabetes (n = 15, 34.1%). Five patients presented with double primary malignancies (11.3%).

Treatment

Among 44 elderly DLBCL patients, 41 (93%) received anti-lymphoma treatment (Table 2). Treatment was not given to three patients (7%) due to objections from the physician, the patient's family, or the patient themselves based on old age or poor PS. Of the 41 DLBCL patients who received anti-lymphoma treatment, 12 completed the full six or eight R-CHOP chemotherapy cycles. An additional seven patients with localized disease completed the intended curative chemotherapy treatment (three or four cycles of R-CHOP) and sequential IFRT. In all, a total of 19 patients (46.3%) completed their initial curative lymphoma treatments; the remaining 22 (53.7%) did not complete their treatment plans for various reasons. A total of 163 cycles of chemotherapy were given to 41 patients. Forty patients received an anthracycline-containing regimen. The median number of received chemotherapy cycles was three for the chemotherapy-incomplete group, not including the chemotherapy-derived patients. The median interval between consecutive chemotherapy cycles was 26 days (range, 18 to 57) in patients who received more than two cycles of chemotherapy. Most patients, those through to be unfit for full doses, received chemotherapy with reduced doses of adriamycin or cyclophosphamide but were mostly given full doses of rituximab and prednisolone. The median aRDI of adriamycin was 0.562 (0 to 1). Although the mean aRDI of adriamycin given to patients in the complete remission (CR) group was slightly higher than that in patients in the non-CR group (0.617 vs. 0.578), there was no statistical significance between groups. In addition, several clinical characteristics were compared between patients who did and did not complete chemotherapy (Table 3). The three chemotherapy-derived patients were not included in these analyses. Patients who completed chemotherapy had a longer median OS than those who did not (30.2 months vs. 5.3 months, $p = 0.004$). Patients in the chemotherapy-incomplete group had a higher average cancer stage, poorer PS, higher CCIs, and lower albumin levels and were overall older than patients who completed chemotherapy. However, only age and albumin level reached statistically significance.

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Table 2. Initial treatment and response summary of elderly diffuse large B cell lymphoma patients

Characteristic	No. (%) (n = 41)	Response				
		CR	PR	PR→PD	PD	ND
Chemotherapy complete group	19 (46.3)	16	0	3	0	0
8 Cycles of R-CHOP	3	2	0	1	0	0
6 Cycles of R-CHOP	9	7	0	2	0	0
4 Cycles of R-CHOP + IFRT	2	2	0	0	0	0
3 Cycles of R-CHOP + IFRT	5	5	0	0	0	0
Chemotherapy incomplete group	22 (53.7)	3	8	4	0	7
5 Cycles of R-CHOP/R-CVP	4	2	2	0	0	0
4 Cycles of R-CHOP	4	1	2	1	0	0
3 Cycles of R-CHOP/R-CVP	6	0	3	3	0	0
1 Cycle of R-CHOP	8	0	1	0	0	7

CR, complete remission; PR, partial remission; PD, progressive disease; ND, not determined; R-CHOP, rituximab/cyclophosphamide/adriamycin/vincristine/prednisolone; IFRT, involved field radiation therapy; CVP, cyclophosphamide/vincristine/prednisolone.

No significant differences were shown for adriamycin aRDI and the cycle length between groups. Two patients received salvage chemotherapy, either ProMACE-CytaBOM (prednisolone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, MTX) or DL-ICE (dexamethasone, L-asparaginase, ifosfamide, carboplatin, etoposide), after the failure of first line R-CHOP. Only one of these patients, who was 71 years old, achieved CR. Among the 14 patients with a poor PS (> 2), 11 received chemotherapy. Ten patients had a PS of three and one a PS of four. Of these patients, three completed treatment (six cycles of R-CHOP chemotherapy in one and three cycles of R-CHOP plus IFRT in two).

Treatment efficacy

The chemotherapy response was evaluated every three cycles using computed tomography (CT) and/or positron emission tomography CT scans. Response to treatment was also assessed in patients who did not complete chemotherapy by performing a follow-up evaluation. Some patients who did not complete chemotherapy were evaluated after the last treatment. Response was defined according to the Revised Response Criteria for Malignant Lymphoma [3]. Of the 19 patients who completed first line chemotherapy, 16 (84.2%) achieved CR. A total of 19 patients achieved CR (46.3%), including three who did not complete the initially planned six cycles of R-CHOP.

Of the 41 patients receiving chemotherapy, 12 achieved partial remission (PR), but the response could not be determined in seven patients who died after only one cycle of chemotherapy (Table 2). Although the CR rate was not great for all 41 patients, that (84.2%) among chemotherapy-completed patients was comparable to the rate seen in younger patients. The mean aRDI of adriamycin was 0.617 in patients who completed chemotherapy.

Survival and outcome, prognostic factors

Forty-one patients were included in the survival analysis. The 2-year OS rate was 43.8%, and the median survival was 18.6 months (Fig. 1). The 2-year OS rate was significantly worse in patients with extranodal involvement, hypoalbuminemia (albumin < 3 g/dL) at diagnosis, poor PS, high LDH, chemotherapy incompletion, and a history on infections (Table 4). Stage, adriamycin aRDI and cycle length, comorbidity status, and age were not significantly correlated with increased risk of death. Multivariate analysis revealed that infection complications and chemotherapy incompletion were significantly related to shorter OS (Table 5). During the follow-up period, 24 total deaths occurred, and the most common cause of death was infection (10), rather than disease progression (six). Other causes of death were treatment-related complications (hepatic failure in one patient), disease-related complications (gastroin-

testinal bleeding in two), and underlying disease (five) other than lymphoma. Infectious complication was defined as a bacteriologically proven bacterial infection, radiologically proven pneumonia, or a fever over 38ºC with elevated C-reactive protein (> 5 mg/L) and clinically suspected infection. Interestingly, most of the patients who died during the first half of the chemotherapy regimen died from treatment-related complications, such as pneumonia or sepsis, whereas patients who died during the second half of the chemotherapy regimen died from causes unrelated to treatment such as disease progression. In addition, the largest number of patients

Figure 1. Overall survival (OS) of 41 elderly diffuse large B cell lymphoma (DLBCL) patients who received anti-lymphoma treatment. Median survival duration, 18.6 months.

dying from infection (four) during chemotherapy died just after completing the first round of chemotherapy. Most infectious complications presented as pneumonia resulting in multi-organ failure. No deaths were reported to be due to deterioration of cardiac function, which is surprising given the advanced age of the patients, the use of adriamycin, and the comorbidities present.

DISCUSSION

Recently, the treatment of elderly patients in the hematology-oncology field has become an important concern due to population aging. Malignant lymphoma is no exception to this phenomenon, and this disease is curable through chemotherapy. The balance between treatment-related toxicity and efficacy is a particular concern and has been evaluated in many previous studies; however, the methods used to evaluate this balance in elderly patients are lacking. Therefore, more defined criteria other than chronologic age and PS are needed to separate individuals capable of receiving standard chemotherapy from individuals who may require an alternative treatment strategy. Although the International Prognostic Index (IPI) score and age-adjusted IPI have long been considered the most reliable prognostic factors in lymphoma patients, the ability of these factors to predict success has declined since the introduction of rituximab. Moreover, the IPI score has not been defined in terms of chemotherapy application feasibility. Since
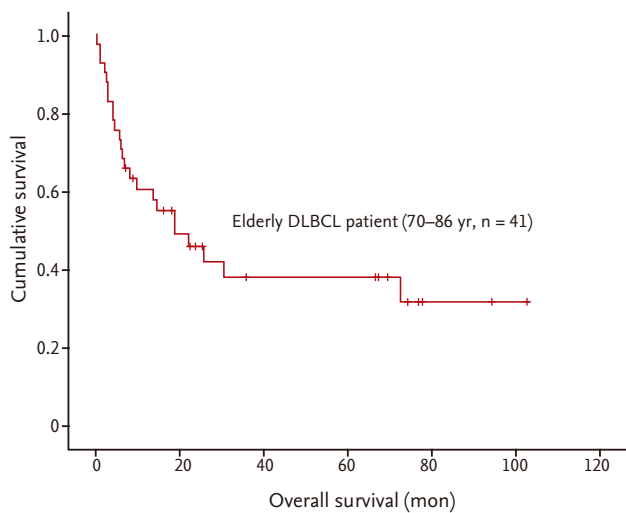
Table 3. Clinical characteristics according to chemotherapy completion

Characteristic	Chemo-incomplete (n = 22)	Chemo-complete (n = 19)	p value[a]
Median OS, mon	5.3	30.2	0.004[b]
Age, yr[c]	76.9 ± 3.95	73.6 ± 3.62	0.008
PS 2–4	15 (68.1)	8 (42.1)	0.093
Stage III–IV	17 (77.2)	8 (42.1)	0.183
Adriamycin aRDI	0.578 ± 0.249	0.617 ± 0.175	0.515
Cycle length	26.3 ± 3.71	26.6 ± 3.27	0.795
Albumin, g/dL	3.12 ± 0.71	3.56 ± 0.54	0.036
CCI ≥ 4	12 (54.5)	10 (52.6)	0.902
Infection	13 (59)	10 (52.6)	0.687

Values are presented as mean ± SD or number of patients (%).
OS, overall survival; PS, performance status; aRDI, average relative dose intensity; CCI, Charlson comorbidity index.
[a]Chi-square test. [b]Log rank test. [c]Independent t test.

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Table 4. Clinical outcomes according to clinical characteristics

Characteristic	All patients (n = 41)		p value[a]
	No.	2-Year OS, %	
Infection			0.000[b]
Absent	18	88.9	
≥ 1 episode	23	14.5	
Extranodal involvement			0.003[b]
Absent	26	58	
Present	15	24	
Stage			0.206
I–II	15	57	
III–IV	26	38.3	
aRDI			0.644
≥ 0.56	22	48.1	
< 0.56	19	44.1	
Age			0.782
70–74	17	52.3	
75–79	18	45	
≥ 80	6	33.3	
PS			0.032[b]
0–1	18	71.3	
2–4	23	28.5	
Co-morbidity (CCI)			0.113
0–3	19	63.2	
4–	22	27	
Albumin, g/dL			0.002[b]
≥ 3	28	62.5	
< 3	13	9.6	
LDH, mg/dL			0.044[b]
> 400	32	35	
≤ 400	9	77.8	
Chemotherapy completion			0.001[b]
Complete	19	67.7	
Incomplete	22	26	

Univariate analysis of 2-year overall survival in relation to patient characteristics and treatment characteristics.

OS, overall survival; aRDI, average relative dose intensity; PS, performance status; CCI, Charlson comorbidity index; LDH, lactate dehydrogenase.

[a]Overall survival was compared by log rank test.

[b]Statistically significant.

prognostic factors cannot be the criteria to determine suitability for chemotherapy and whether to modify chemotherapy even though treatment intolerance can affect prognosis. Thus, until recently, chronologic age, comorbidities, and PS have been the principal criteria upon which decisions regarding criteria have been based. However, many studies have suggested that these parameters alone are not sufficient to evaluate the feasibility of chemotherapy in elderly patients, and in particular, age is no longer considered an absolute criteria for the feasibility of chemotherapy [4,5].

The data from the present study suggest that, although PS (favorable, 0 to 1 vs. unfavorable, 2 to 4) was worse in the chemotherapy-incomplete group than in the chemotherapy-complete group, it was not an absolute predictor of chemotherapy completion. Specifically, some patients with favorable PS scores stopped chemotherapy or died from treatment-related complications, and some patients with unfavorable PS scores completed their chemotherapy regimens and achieved favorable responses. This may be due to the inability of PS to predict outcomes in the elderly, or it may be due to additional variables that affect overall outcome. In terms of patient criteria, the insufficiency of PS as a predictive tool has been previously considered, since PS does not exactly reflect clinical variables such as impaired organ function, vulnerability to infection and nutritional status. Moreover, the PS grade definition is somewhat subjective and not well defined. Thus, a CGA tool including comorbidity, functional, cognitive, and psychological statuses was recently introduced and recommended as an alternative, and several studies have demonstrated its usefulness [6-8]. However, the measured patient activity and clinical functions are almost identical to those used for PS, and some researchers believe that CGA is no more useful than PS at predicting chemotherapy feasibility and have suggested that this method is more time consuming. A new and more practical assessment is needed to evaluate the crucial factors that affect the response of elderly DLBCL patients to treatment. For such an assessment method to be developed, the primary causes of treatment-related deaths and treatment interruption must be determined in elderly DLBCL patients. Moreover, the clinical differences between patients that do and do not complete chemotherapy must be evaluated.

Table 5. Prognostic factors for overall survival after multivariate analysis (Cox-regression analysis)

Variable	Multivariate		
	HR	95% CI	p value
Infection	10.031	1.979–50.835	0.005[a]
Extranodal involve	1.096	0.412–2.917	0.855
Poor PS	0.636	0.231–1.750	0.636
Low albumin	1.027	0.389–2.715	0.957
High LDH	0.907	0.189–4.361	0.903
Treatment incompletion	6.566	2.183–19.747	0.001[a]

HR, hazard ratio; CI, confidence interval; PS, performance status; LDH, lactate dehydrogenase.
[a]Statistically significant.

In the present study, a total of 23 patients (56%) experienced infectious complications during treatment, and many of these patients had treatment interruptions and treatment-related death. Of the 22 patients who discontinued chemotherapy, 10 (45.5%) discontinued due to infections, most notably pneumonia, and all 10 died due to infection-related complications (n = 6). Interestingly, the number of patients experiencing infection was not significantly different between the chemotherapy-complete and -incomplete groups (52.6% vs. 59%). However, infectious episodes resulted in more fatal outcomes in the chemotherapy-incomplete group. In addition, the majority of infectious complications occurred after the first round of chemotherapy.

A previous study that evaluated treatment-related death and its associated risk factors in elderly patients with aggressive non-Hodgkin's lymphoma found that 63% of deaths occurred after the first cycle, and that infections accounted for 82% of treatment-related deaths [9]. These findings have been consistently discussed in multiple subsequent reports including the Groupe d'Étude des Lymphomes de l'Adulte (GELA) study and NHL-B2 trial, which targeted elderly lymphoma patients with relatively favorable PS grades. Pfreundschuh [10] called this phenomenon the "first cycle effect" and explained that it occurs because the deepest and longest neutropenia usually occurs after the first cycle of chemotherapy. These results suggest that the initial dose of chemotherapy is too high, and that these doses may lead to increased myelotoxicity, poor outcome, and treatment interruptions in elderly lymphoma patients. Furthermore, these findings suggest that age and PS-based assessments cannot precisely reflect impaired

drug metabolism and increased vulnerability to infections in elderly patients and, thus, cannot identify frail patients unable to receive full chemotherapy doses. Consequently, appropriate markers reflecting drug metabolic capacity and immune status should be evaluated to select medically fit elderly patients and determine the initial chemotherapy dose.

The results of the present study revealed that albumin levels were significantly different between patients who did and did not complete chemotherapy, and low albumin levels were associated with shorter OS. Given the high rate of infection mortality in patients with low albumin levels, albumin levels may be a good indicator of susceptibility to infection in elderly patients [11]. To determine the treatment strategy, the dose intensity of CHOP has been a focus of attention, since other regimens are not as superior in terms of OS and response. Previous reports have shown that a reduced relative dose intensity (RDI) can attenuate the efficacy of chemotherapy, and therefore maintaining a RDI, especially for adriamycin and cyclophosphamide, > 0.8 is crucial for positive outcomes, and an insufficient dose intensity has been associated with poor outcome in elderly DLBCL patients [12]. In practice, many studies have shown that less intense regimens achieve poorer results. Meanwhile, based on the analysis report of the GELA non-Hodgkin's lymphoma 98-5 study, Coiffier et al. [13] reported that the addition of rituximab to the CHOP chemotherapy regimen increased the response rate in elderly DLBCL patients without significant toxicity, and R-CHOP was adopted as the standard treatment for elderly lymphoma patients. Many studies have subsequently demonstrated the safety and efficacy of ritux-

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imab in elderly DLBCL patients [13,14]. In addition, the availability of rituximab has enabled physicians to use less-intensive back bone chemotherapy (CHOP) without diminished efficacy.

Fukushima et al. [15] reported no significant difference in OS between elderly DLBCL patients undergoing R-CHOP treatment with an aRDI > 0.85 and an aRDI < 0.85. In the GELA study, R-CHOP did not improve OS compared with CHOP alone when full doses of R-CHOP were administered to a group of high-risk IPI-adjusted patients. The malicious nature of lymphomas and increased TRM in the elderly were used to explain these poor results. Considering that a more aggressive form of chemotherapy is not possible for elderly lymphoma patients, TRM must be improved to improve OS, perhaps by adjusting the RDI.

This is certainly true for elderly patients older than 80 years with poor PS grades (3 to 4); since CHOP alone is arduous, they are unlikely to survive more intensive chemotherapy [16-19]. Among the individual drugs included in the R-CHOP regimen, adriamycin, and cyclophosphamide have been the main targets for dose reduction, and most physicians agree that rituximab is well tolerated by elderly lymphoma patients. In the present study, most patients received the full dose of rituximab, while adriamycin and cyclophosphamide were administered at reduced doses in patients with poor PS. Meguro et al. [20] reported that rituximab+ 70% CHOP was more effective in patients 70 years and over, and that this reduced regimen resulted in similar outcomes as the full R-CHOP dose in younger patients. This reduced-toxicity regimen is well tolerated, even by patients older than 80 years [20]. Additional prospective studies have also reported that a modified R-CHOP regimen, consisting of a full dose of rituximab and reduced dose of CHOP, results in good outcomes and is better tolerated in elderly DLBCL patients [21,22]. In all, a reduced CHOP dose may be an acceptable option for elderly patients who are unlikely to tolerate the full regimen, especially in those older than 80 years. The results are similar for patients who have localized disease only, which is treated with fewer cycles plus IFRT [23].

In contrast to these results, the RICOVER-60 trial reported that a bi-weekly dose of CHOP-14 ± rituximab resulted in better outcomes than those of CHOP-21 ± rituximab [24]. However, these results should be interpreted with caution because that study targeted relatively younger patients with better PS (< 2) compared with other studies. In addition, infection was the most common cause of death in this study, even though patients were supported with routine prophylactic G-CSF from day 6 to day 10 during chemotherapy and were treated with a pre-induction regimen of vincristine and prednisone, the latter of which is thought to ameliorate lymphoma-related symptoms and to help improve PS.

The treatment outcomes of the present study were quite good considering the poor PS of the patients and the lack of pre-induction or routine G-CSF treatment, although those are not comparable to the results of previously reported studies about less-intense chemotherapy in elderly lymphoma patients. Overall, the results from the present study support the reduction of cytotoxic drug dosages without having to follow a strict dose interval, and these findings reflect recent changes in the treatment of elderly lymphoma patients [25]. The results also show that OS was not different between patients receiving an adriamycin aRDI ≥ 0.56 and an aRDI < 0.56. Moreover, aRDI was not significantly different between patients with versus without infectious complications.

In contrast, albumin levels were significantly different between patients who did versus did not have infectious complications (3.0 vs. 3.74, p = 0.011), suggesting that the albumin level at the time of diagnosis is an important predictor of infection vulnerability and potential treatment interruption [26]. Given the fact that albumin levels reflect nutritional status, this measure can be considered an important factor when determining the feasibility of chemotherapy in elderly patients vulnerable to infections.

The lack of statistical significance in the present study may be due to the small number of patients included, its retrospective nature, and short follow-up time; however, several important results have been gained. Given the number of infection-related complications in elderly patients, a dose escalation strategy from an initial flat dose, rather than a dose reduction, may be more reasonable and reduce myelosuppression. The chemotherapy dose can then be escalated in patients who respond well to the initial dose. In addition, an additional dose of radiation, or a delay in chemotherapy, should be considered for patients who develop infections. Finally, more tolerable treatment regimens

with more defined criteria should be investigated to distinguish patients who cannot tolerate reduced-intensity R-CHOP [27,28].

In conclusion, infectious complications during neutropenia are more fatal in elderly lymphoma patients compared with younger patients and are closely related to TRM. The albumin level is thought to be a practical and useful clinical predictor of infection vulnerability, poor outcome, and treatment interruption. For the elderly, an R-CHOP regimen in which the initial dose is reduced, and then increased if tolerable, may be the best option for the treatment of lymphoma.

KEY MESSAGE

1. In the treatment of elderly diffuse large B cell lymphoma (DLBCL) patients, conserving the dose intensity of adriamycin is not as important as it is in young patients.
2. Infectious complication during treatment has a significant impact on prognosis in elderly DLBCL patients.
3. The albumin level is thought to be a practical and useful clinical predictor of infection vulnerability, poor outcome, and treatment interruption.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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