Journal of clinical and experimental hematopathology
Vol. 65 No. 1, 40-48, 2025

Original Article

Poor outcome of older patients with diffuse large B-cell lymphoma after progression

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One-third of the patients with diffuse large B-cell lymphoma (DLBCL) experience relapse despite receiving standard R-CHOP chemotherapy. We aimed to elucidate the clinical course and prognosis in older patients with relapsed or refractory (R/R) DLBCL in a single-center experience in Japan. We conducted a retrospective survey of 52 older patients with R/R DLBCL (aged >65 years at diagnosis; 54% men) who received R-CHOP chemotherapy, to assess their clinical course and prognosis. The median progression-free survival was 8.5 months. Seventeen patients had central nervous system (CNS) relapse, with 11 receiving high-dose methotrexate or whole-brain irradiation. Briefly, 30 patients underwent salvage chemotherapy, whereas 11 received palliative care only. Overall survival (OS) from initial treatment and progression were 20.8 and 7.8 months, respectively. Patients with disease progression within 12 months from initial treatment had a significantly poorer OS than those with disease progression over 12 months, while CNS relapse did not affect OS. Among the 41 reported deaths, 40 were due to lymphoma. As the prognosis in older patients with R/R DLBCL is poor even after salvage chemotherapy, improved initial treatment strategies to reduce the risk of progression and more effective and feasible treatments after progression are warranted.

Keywords: diffuse large B-cell lymphoma, rituximab contained chemotherapy, older patients, refractory, salvage chemotherapy

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most frequent subtype of non-Hodgkin lymphoma and occurs at a median age of 60 years.[1] Accordingly, its incidence rate is increasing owing to the aging of the population, especially in Japan. Although more than half of the patients with DLBCL can be cured using standard R-CHOP (rituximab [R], cyclophosphamide, doxorubicin, vincristine, and prednisolone) initial chemoimmunotherapy, one-third of them experience relapse.[1] Most young, physically fit patients with DLBCL can be rescued with salvage chemotherapy followed by autologous hematopoietic cell transplantation (ASCT);[2,3] however, older patients without indication for ASCT, especially frail patients, are generally intolerant to conventional salvage chemotherapy, and treatment efficacy is not sufficient. Thus, a standard treatment strategy for this patient population has yet to be established. Recently, polatuzumab vedotin, an antiCD79b monoclonal antibody–drug conjugate agent, chimeric antigen receptor-T cell (CAR-T) therapy, and bispecific T-cell engagers have been approved and available in the clinical setting. Although these strategies increase the number of patients who can be rescued,[4] certain barriers for application to the older population remain, and conventional chemotherapy for disease management is still expected. Here, we conducted a single-center retrospective survey in Japanese older patients with relapsed or refractory (R/R) DLBCL to elucidate their clinical course and prognosis, and to assess the utility of conventional salvage chemotherapy in this population.

PATIENTS AND METHODS

Selection of patients and data collection

The Kanagawa Cancer Center Clinical Research Ethics Board approved this study (2020S-150; date of approval: February 16, 2021). The patients could opt out from being included in this study. This study was performed in accordance with the Declaration of Helsinki.

From 2009 to 2019, 255 older patients (aged > 65 years at diagnosis) who were diagnosed with CD20-positive DLBCL (based on the WHO 2017 criteria[5]) and received the R-CHOP

Received: October 22, 2024. Revised: November 29, 2024. Accepted: December 14, 2024. Online Published: March 28, 2025
DOI: 10.3960/jslrt.24064

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regimen at the Kanagawa Cancer Center (Yokohama, Japan) were screened. Fifty-two (20.4%) of the patients subsequently experienced refractory disease or progression. A flowchart of the patient selection process is shown in Figure 1. The cell-of-origin (COO) subtype was determined using Han's criteria.[6] Patients with distinct forms of DLBCL, such as intravascular lymphoma, primary effusion lymphoma, and pyothorax-associated lymphoma, and those with Burkitt lymphoma or HIV infection, were excluded from the study. Patients with primary central nervous system (CNS) or intraocular lymphoma were also excluded. The decision regarding eligibility for any treatment intervention, selection of regimen, and dose modification was made by each attending physician.

Information regarding age, sex, clinical stage (according to the Ann Arbor staging system[7]), level of serum lactate dehydrogenase (LDH) at diagnosis and progression, performance status, presence or absence of bulky mass or B symptoms, International Prognostic Index (IPI) risk score,[8] number of extranodal involvement sites, and treatment regimen were collected from clinical charts and databases and recorded. Additionally, data related to the diagnosis, immunohistochemistry pattern, fluorescence in situ hybridization (FISH) results, and chromosomal analysis using G-banding were collected if available.

Survival analysis

Progression-free survival (PFS) was calculated from the date of salvage therapy commencement to the date of progression, last follow-up, or death from any cause. Overall survival (OS) was calculated from the date of initial therapy commencement (OS1) or progression (OS2) to the date of the last follow-up or death from any cause. In our analysis, primary induction failure was defined as suboptimal response (SD or PD) to initial chemotherapy or early progression within six months, following a previous definition.[1] Survival analysis was performed using the Kaplan–Meier method with the log-rank test. The data from patients who received treatment (n = 41) were subjected to univariate and multivariate analyses. P values < 0.05 in the univariate analysis indicated statistical significance, and factors with $P < 0.1$ were included in the multivariate analysis using COX proportional hazards models. The data were analyzed using EZR (version 1.35; Saitama Medical Center, Jichi Medical University), a graphical user interface of R (The R Foundation for Statistical Computing).[9] The data cut-off date was set as July 31, 2022.

RESULTS

Baseline characteristics

The baseline characteristics of the 52 patients are presented in Table 1. The median age at diagnosis and progression was 74 and 76 years, respectively, and 28 patients were men. We observed that the IPI risk score at diagnosis was low in eight, low-intermediate in seven, high-intermediate in 16, and high in 21 patients. COO data were available for 29 patients; 13 and 16 patients were categorized as germinal center B (GCB) and non-GCB types, respectively. Diagnostic samples from 21 patients were available for FISH analysis

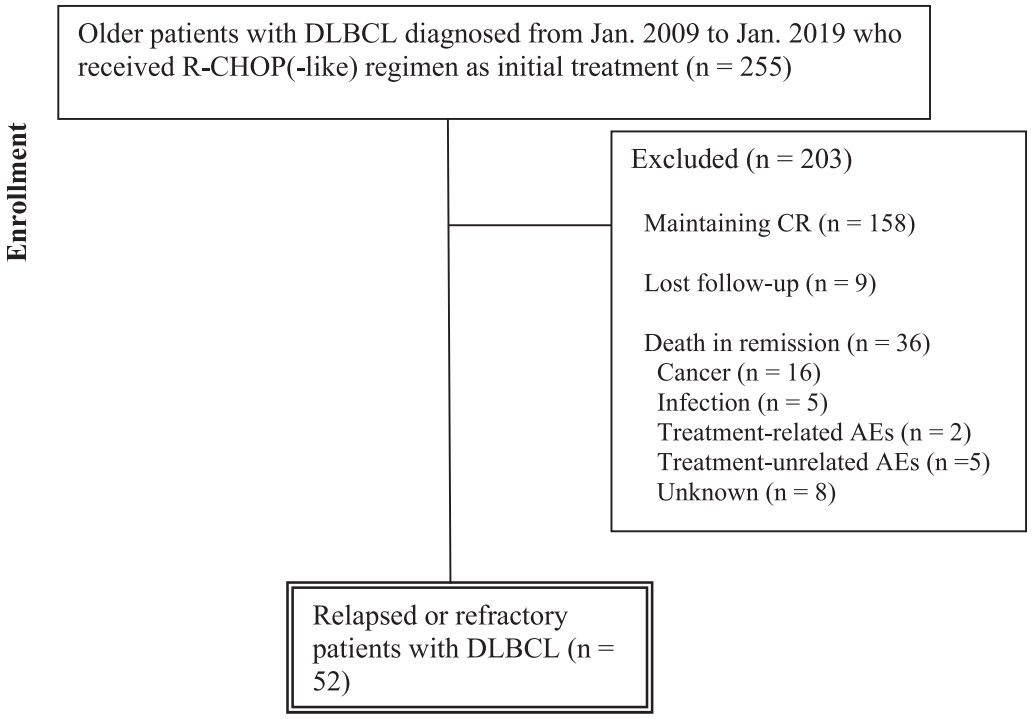

Fig. 1. Selection process of older patients with diffuse large B-cell lymphoma. Among the 255 patients screened, 52 were eligible for the study. DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab+cyclophosphamide+doxorubicin+vincristine+prednisolone; CR, complete response; AE, adverse event.

Table 1. Baseline characteristics of all patients with DLBCL (n = 52)

	n (%)
Age at diagnosis, median [range]	74 [66–87]
Age at progression, median [range]	76 [67–88]
Below or 75	25 (48)
60s / 70s / 80s	5 (9) / 30 (58) / 17 (33)
Sex	
Women	24 (77)
Men	28 (23)
IPI score at diagnosis	
Low	8 (16)
Low-intermediate	7 (13)
High-intermediate	16 (31)
High	21 (40)
Serum level LDH	
Normal	10 (19)
Elevated	42 (81)
Serum level LDH at progression	
Normal	19 (37)
Elevated	32 (62)
ECOG–PS	
0, 1	37 (71)
2 or lower	15 (19)
Ann Arbor clinical stage	
I, II	17 (33)
III, IV	35 (67)
Number of extranodal lesions	
0,1	30 (58)
2 or more	22 (32)
COO	
GCB type	13 (25)
Non–GCB type	16 (31)
Unknown	23 (44)
FISH analysis	
MYC rearrangement+	5 (10)
DHL/THL	2 (both BCL6)/1
Not available	31 (61)
Chromosomal analysis (G-banding)	
BCL2-, BCL6-, MYC-related	8 (15)
Complex karyotype	6 (12)
Normal karyotype	1
Insufficient material	11 (21)
Not available	27 (52)
B symptoms	
Positive	35 (67)
Negative	17 (33)
Bulky mass	
Positive	42 (81)
Negative	10 (19)
Initial treatment	
R–CHOP	52 (100)
Planned dose reduction	
None	20 (38)
80%	18 (35)
50%	14 (27)
Response to initial treatment	
CR	25 (48)
PR	8 (15)
PD	19 (37)
Primary induction failure	22 (42)
Re-biopsy after progression	20 (38)
Biopsy at first progression	14 (27)
Era of progression	
2009–2016	27 (52)
2017–2021	25 (48)
Time from initial treatment to progression, median [range, months]	12.0 [0.8–130.1]
Progression within 12 months	26 (50)
Progression to CNS at first progression	14 (27)
Progression to CNS at any time	17 (33)

DLBCL, diffuse large B–cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; ECOG–PS, Eastern Cooperative Oncology Group performance status; COO, cell of origin; GCB, germinal center B; FISH, fluorescence in situ hybridization; CR, complete response; PR, partial response; PD progressive disease; CNS, central nervous system

(commercially available at SRL inc.), which included five from patients with MYC rearrangement. Data from chromosomal analysis using the G-banding method (commercially available at SRL inc.) were available for 14 patients. Twenty patients received re-biopsy after progression, while the diagnosis was not changed for any of the patients in our cohort. After the initial regimen, we found that 25 patients achieved complete remission (CR), whereas 22 patients met the criteria for PIF. We also observed that 25 patients experienced disease progression after 2017, with the median PFS for the initial regimen being 12 months. Additionally, there was CNS progression in 17 patients, 14 of whom experienced it as first progression.

Clinical course after progression

The treatment course and outcomes after disease progression are presented in Table 2. Eleven patients received palliative care only, whereas among the remaining 41 patients, 11 received CNS-oriented therapy (high-dose methotrexate [HD-MTX]) and whole-brain irradiation (WBI). Of note, one patient underwent ASCT after responding to salvage regimen. During a median observation period of 88.3 months, we determined that the median OS1 and OS2 for surviving 41.7 months from the initiation of the initial regimen or progression were 20.8 [95% CI, 13.8–50.2] and 7.75 [4.2–12] months, respectively (Figure 2A, B). We observed that 41 patients died of lymphoma, with the exception of a single case due to other reasons. We found that the PFS and median OS2 of the patients who received any treatment after progression was 8.5 [3–16] and 11 [6.6–17.8] months, respectively (Figure 2C, D); these patients were included in further subgroup analysis for OS2.

Subgroup analysis of OS2

The subgroup univariate and multivariate analyses of the data of patients who received any treatment after progression

Table 2. First salvage treatment and outcomes (n = 52)

	n (%)
Salvage regimen	
HD-MTX±WBI	8 (15)
WBI only	3 (6)
ESHAP±rituximab	15 (29)
DHAP±rituximab	7 (13)
GDP±rituximab	5 (10)
R-CHOP retreatment	1 (2)
Pola-BR	1 (2)
Focal radiotherapy only	1 (2)
Palliative care only	11 (21)
Proceeded to ASCT	1 (2)
Median observation period for surviving patients	88.3 months from initial treatment 41.7 months from salvage treatment
Median PFS (n = 41) [95% CI, months]	8.5 [3–16]
Median OS from initial treatment [95% CI, months]	20.8 [13.8–50.2]
Median OS from salvage treatment [95% CI, months]	7.75 [4.2–12]
Cause of death	
Lymphoma	40 (77)
Accident	1 (2)

HD-MTX, high-density methotrexate; WBI, whole brain irradiation; R-CHOP, rituximab+cyclophosphamide+doxorubicin+vincristine+prednisolone; pola, polatuzumab vedotin; BR, bendamustine and rituximab; ASCT, autologous stem cell transplantation; PFS, progression–free survival; OS, overall survival

are presented in Table 3. With respect to OS2, we found that elevated serum LDH levels at progression (median OS2, 9.8 vs. 24.6; $P = 0.09$), suboptimal response to initial treatment (PD vs. non-PD, 6.4 vs. 16.0; $P = 0.03$), and progression within 12 months (5.6 vs. 17.8; $P < 0.001$) were statistically poor prognostic factors in the univariate analysis (Figure 3); we have thus included them in the multivariate analysis. Based on our multivariate analysis, we determined that elevated LDH serum levels at progression (hazard ratio [HR] = 2.5; $P = 0.03$) and progression within 12 months (HR = 3.7; $P = 0.028$) were significant prognostic factors for patient survival.

DISCUSSION

In the present study, we retrospectively analyzed the characteristics and clinical course of older patients with DLBCL who experienced disease progression after R-CHOP induction. Although 62% of our patients received a reduced dose of R-CHOP according to our daily practice, the progression rate in our cohort was lower than that reported previously.[10] Among the 52 eligible patients, 21% could not receive any subsequent treatment, while the survival of patients who could receive any treatment also remained poor irrespective of CNS involvement. As for CNS prophylaxis, we followed the criteria of the Yokohama City University Hematology Group (YACHT).[11] In our patient cohort, only four patients (three for testis involvement, one for CD5 positivity) received CNS prophylaxis by HD-MTX, whereas the other 49 patients, including 17 who experienced CNS relapse, did not receive prophylaxis. The 17 patients did not receive prophylaxis because four were considered low-risk for CNS relapse, in six, prophylaxis by HD-MTX was not established (before 2014), two were too old to receive HD-MTX, and five experienced progression before reaching the prophylaxis treatment.

Recently, long-term follow-up data have been reported in the LNH03-6B study for older (60–80 years) patients with DLBCL after R-CHOP,[12] in which the 10-year PFS and OS were 40.4% and 50%, respectively, and PFS and OS after progression were poor (37.9% and 55.8% at 1 year after progression). Other studies have reported poor outcomes after relapse for older patients with DLBCL,[13,14] reflecting the frail background to receive the best treatment option available. Our results were generally similar with previous reports, so we focused on second line or later clinical course based on our real-world experience. Our results indicated poor outcomes, potentially reflecting a higher proportion of frail patients than that in clinical trials. Japan is a rapidly aging country,[15,16] and clinical questions regarding how to treat older patients and unmet needs must be answered. Our results might help to improve the outcomes following first-line treatment and prevent progression.

Although some studies have shown the utility of a curative strategy using conventional salvage chemotherapy with consolidative ASCT even for older patients, this modality is too toxic for most patients, limiting long-term PFS.[17–19] Recently, bendamustine and polatuzumab vedotin (Pola), an antiCD79b monoclonal antibody–drug conjugate, have become available for DLBCL patients in Japan, and their combinational regimen with rituximab,[20–22] BR±Pola are expected to have good efficacy and tolerability for older R/R patients with low sensitivity or tolerability to conventional salvage regimens. Furthermore, several CAR-T therapies or bispecific antibody T-cell engager agent[23–28] are now available, showing satisfactory efficacy even in chemorefractory patients. However, due to neurotoxicity and cytokine release syndrome, the tolerability of CAR-T-cells in older patients remains undetermined,[29,30] and thus its wide application in the general population requires the collection of further data.

In our subgroup analysis, the patients who progressed within 12 months exhibited extremely poor survival, with a median OS of only three months from progression. Poor prognosis for patients with primary refractory or early relapsed disease has also been reported in the international SCHOLAR-1 study[31] and a Japanese single-center study.[32] The multivariate analysis showed that both time to progression and serum level of LDH at progression remained prognostic factors. For this chemo-refractory subgroup, how to apply immune cell therapy, CAR-T, or bispecific antibodies in older patients is an important clinical question remaining to be answered.

Patients with later progression showed limited survival in our cohort, suggesting the need for improvement in initial treatment beyond R-CHOP. Several unsuccessful attempts have been made to improve the outcome of initial regimens.[33–36] Recently, pola-R-CHP (polatuzumab vedotin with

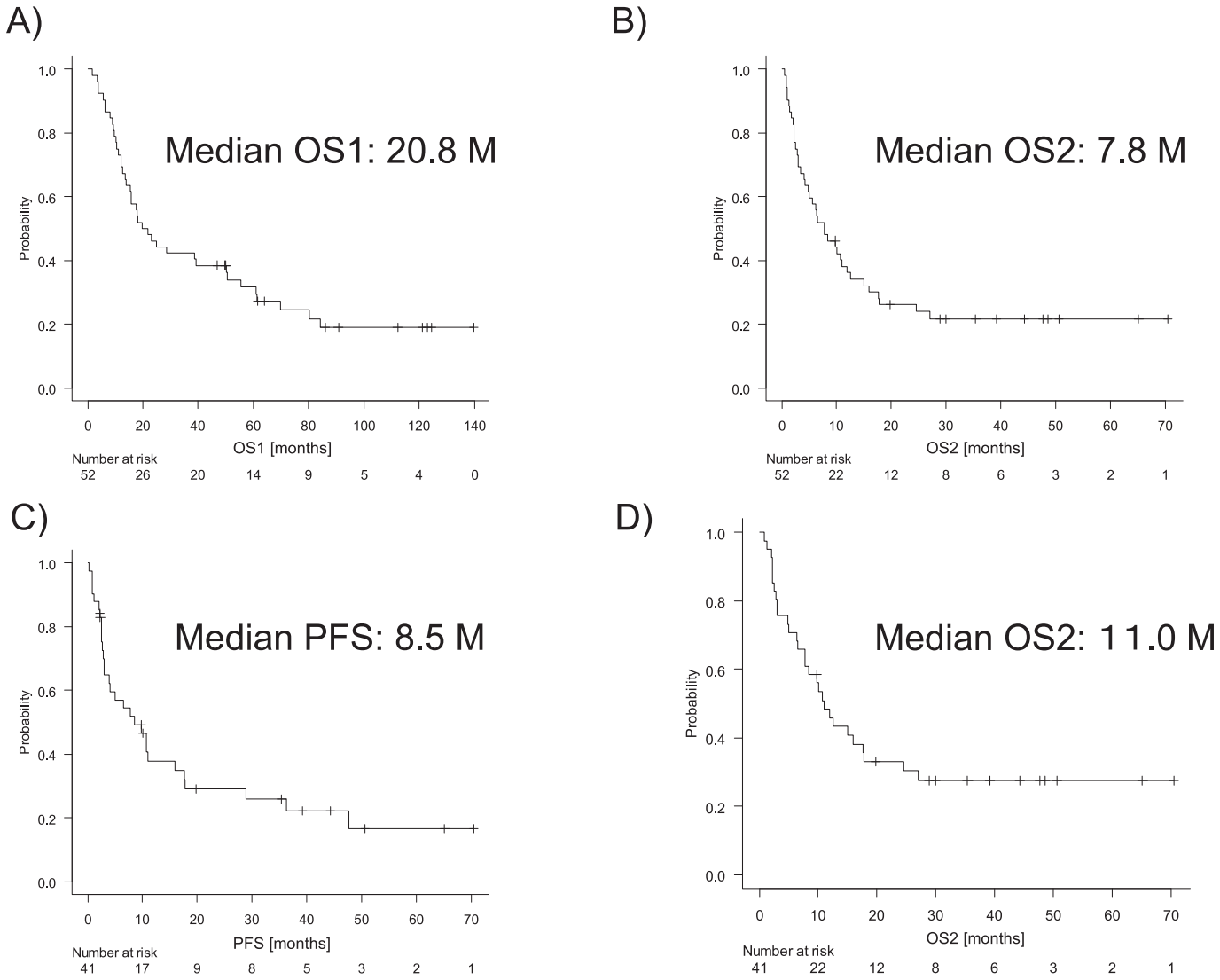

Fig. 2. Overall survival (OS) and progression-free survival (PFS) of 52 patients and those receiving any treatment after progression (n = 41). (***A***) OS from initial treatment (OS1) of all patients. (***B***) OS from progression (OS2) of all patients. (***C***) PFS for treatment after progression in patients receiving any treatment after progression. (***D***) OS2 of patients receiving any treatment after progression.

R-CHOP without vincristine) showed superior PFS in the POLARIX study,[37] which included 70% of older patients, while patients aged > 80 years were excluded from the trial. In the future, specific agents are expected to be introduced to improve the outcome of patients with DLBCL, including older adults.[38]

Notably, two of our patients showed long-term survival over 40 months despite experiencing primary induction failure to initial chemotherapy. One 70-year-old female patient experienced CNS relapse within a month after R-CHOP completion. She received HD-MTX chemotherapy for six cycles and focal irradiation 30 Gy for a residual lesion on the ilium. She presented with another CNS progression in the left frontal lobe within six months from the last HD-MTX, and since the systemic lesion was under control, she received WBI of 40 Gy, resulting in CR without any adverse effects. She remained in CR for four years after WBI until our last follow-up. A second patient (82-year-old male) with a lesion in the right lacrimal sac and nasal cavity received eight cycles of R-mini-CHOP (reduced to 50% dose) and experienced re-progression of the nasal lesion right after the last dose. He received focal irradiation of 40 Gy, resulting in CR. He maintained remission for three years from the end of irradiation to our last follow up. These cases indicate the heterogeneity of DLBCL and necessity for further discussion based on molecular biology.

Our study had several limitations, owing to the single-center retrospective design with a restricted number of participants. Although DLBCL is a molecularly heterogeneous disease with certain reported genetic subclassifications, limited data for COO and lack of data for representative genetic abnormalities (MYC, BCL2, or BCL6) are considerable weaknesses in our study. Secondly, the salvage regimen for each patient and dose intensity were highly heterogeneous due to each physician's decision, and the obtained data are limited to allow comparisons of efficacy and safety.

Table 3. Univariate and multivariate subgroup analysis of OS2 for patients who received any treatment after progression (n = 41)

	n (%)	Median OS2 (months)	95% CI	Univariate *P*	HR	95% CI	Multivariate *P*
Age at progression							
Below or 75	23 (56)	12.0	6.6–NA	NS			
Over 75	18 (44)	10.7	3.0–17.6				
Sex							
Women	21 (54)	9.8	4.8–17.6	NS			
Men	20 (46)	12.6	3.0–NA				
IPI score at diagnosis							
Low, low–intermediate	12 (29)	15.1	3.0–27	NS			
High, high–intermediate	29 (71)	10.1	3.0–NA				
Serum level LDH at diagnosis							
Normal	12 (29)	11.7	2.2–NA	NS			
Elevated	29 (71)	9.0	5.0–16				
Serum level LDH at progression							
Normal	17 (41)	24.6	4.8–NA	0.09	1	1.09–5.69	0.03
Elevated	24 (59)	9.8	3.0–16		2.5		
ECOG–PS							
0, 1	31 (76)	12.6	7.8–NA	NS			
2 or lower	10 (24)	7.2	2.0–15				
Ann Arbor clinical stage							
I, II	14 (34)	11.8	3.0–27	NS			
III, IV	27 (66)	10.7	4.8–24.6				
Number of extranodal lesions							
0, 1	25 (61)	12.0	6.6–27	NS			
2 or more	16 (39)	9.8	2.2–24.6				
COO							
GCB type	12 (29)	22.3	6.6–NA	NS			
Non–GCB type	12 (29)	13.4	2.2–NA				
Unknown	17 (42)	-	-				
B symptoms							
Positive	35 (67)	8.2	2.0–15	NS			
Negative	17 (33)	12.6	7.7–NA				
Bulky mass							
Positive	8 (20)	5.7	1.3–NA	NS			
Negative	33 (80)	12.0	7.8–17.8				
Response to initial treatment							
CR	22 (54)	16.0	8.4–NA	0.03	1	0.31–3.47	NS
PR	6 (15)						
PD	13 (31)	6.4	2.2–10.1		1.04		
Era of initial treatment							
2009–2014	19 (46)	12.6	4.8–NA	NS			
2014–2019	22 (54)	10.9	3.0–17.6				
Initial treatment to progression							
Over 12 months	25 (61)	17.8	10.7–NA	<0.001	1	1.15–11.9	0.028
Within 12 months	16 (39)	5.6	2.2–9.8		3.7		
Progression to CNS							
Yes	14 (34)	10.0	2.3–17.8	NS			
No	27 (66)	12.0	5.0–27				

DLBCL, diffuse large B–cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; ECOG–PS, Eastern Cooperative Oncology Group performance status; CR, complete response; PR, partial response; PD progressive disease; CNS, central nervous system; NS, not significant

Therefore, we cannot determine a preferred regimen from our available treatment options. Thirdly, assessments of patients' feasibility only by chronological age are challenging, and evaluating frailty via comprehensive geriatric assessment has been recently preferred.[39] Dose modifications in our patient cohort were applied in line with each physician's decision and not performed systematically. However, our single-center real-world findings revealed poor prognoses for all older

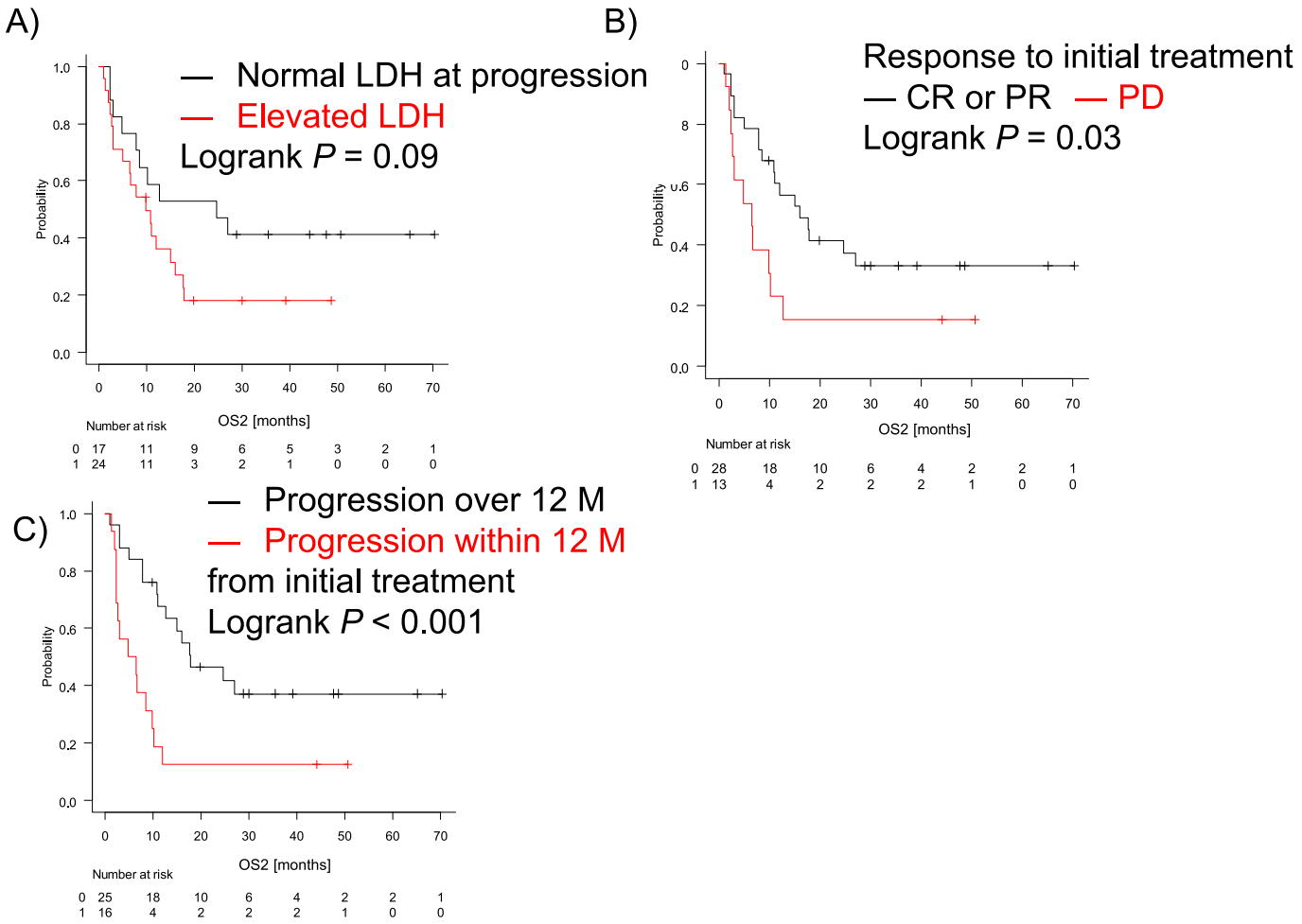

Fig. 3. Subgroup analysis for OS2. (***A***) Normal or elevated level of lactate dehydrogenase (LDH) at progression. (***B***) Response to initial treatment. (***C***) Time from initial treatment, within 12 months or over 12 months. CR, complete response; PR, partial response; PD progressive disease.

patients with progressing DLBCL after R-CHOP, regardless of which treatment was selected, suggesting unsolved clinical questions for this cohort.

In conclusion, older patients with R/R DLBCL have a poor prognosis, even if administered conventional salvage chemotherapy. Development of novel treatment strategies, which will incorporate more effective and less toxic novel agents, based on detailed molecular subclassification and comorbidities and frailty of each patient is warranted.

ACKNOWLEDGMENTS

We would like to thank Editage (www.editage.com) for English language editing.

FUNDING

This work was supported by “a grant from Kanagawa Cancer Foundation” (approved on 2nd Dec. 2021).

AUTHORSHIP CONTRIBUTIONS

HT designed the study, contributed to data collection, analysis, and interpretation, performed the statistical analyses, and wrote the manuscript; RS designed the study, and contributed to data collection, analysis, and interpretation; NH, YH, and MT participated in data collection; and HN approved the study.

CONFLICT OF INTEREST

HT received honoraria from AstraZeneca plc, Bristol Myers Squibb, Chugai Pharma, Janssen, Kyowa Kirin, Meiji Seika Pharma, Nippon Shinyaku, Mundipharma, Ono Pharmaceutical, SymBio pharmaceuticals, Takeda Pharmaceutical, Eisai, and Sanofi S.A. RS received honoraria from Bristol Myers Squibb, Chugai Pharma, Janssen, Kyowa Kirin, Meiji Seika Pharma, Nippon Shinyaku, Mundipharma, SymBio pharmaceuticals, Takeda Pharmaceutical, CSL Behring K.K, Eisai, AstraZeneca plc, Nihon Medi-Physics, Sanofi S.A., Towa Pharmaceutical, and research funding from Chugai Pharma, Kyowa Kirin, and

TAIHO Pharmaceutical. YH received honoraria from Nippon Shinyaku and Chugai Pharma. HN received honoraria from Novartis and Daiichi-Sankyo, and research funding from Daiichi-Sankyo, Celgene, Chugai pharmaceuticals, Astellas, Asahikasei pharma, Takeda pharmaceuticals, Pfizer, and Eizai. No other potential conflicts of interest are reported.

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