Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone combined with high-dose methotrexate plus intrathecal chemotherapy for newly diagnosed intravascular large B-cell lymphoma (PRIMEUR-IVL): long-term results of a multicentre, single-arm, phase 2 trial

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Summary

Background **Intravascular large B-cell lymphoma (IVLBCL) is a rare type of extranodal large B-cell lymphoma for which prognosis is typically poor without a timely diagnosis. To explore the safety and efficacy of standard chemotherapy combined with central nervous system (CNS)-directed therapy, we conducted a multicentre, single-arm, phase 2 trial in untreated IVLBCL patients without CNS involvement at diagnosis (PRIMEUR-IVL). In the**

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primary analysis, the PRIMEUR-IVL study demonstrated 2-year progression-free survival (PFS) of 76% and 2-year overall survival (OS) of 92% with a low incidence (3%) of secondary CNS involvement (sCNSi).

Methods We present a prespecified final analysis of the PRIMEUR-IVL study including 5-year PFS, OS and cumulative incidence of sCNSi. Participants were enrolled between June 2011 and July 2016, and the data cutoff date for the final analysis was 16 November 2021. The trial was registered in the UMIN Clinical Trial Registry (UMIN000005707) and the Japan Registry of Clinical Trials (jRCTs041180165).

Findings With a median follow-up of 7.1 years (interquartile range 5.6–8.7), 5-year PFS in all 37 eligible patients was 68% (95% confidence interval [CI] 50%–80%) and OS was 78% (95% CI 61%–89%). No additional sCNSi was observed after the primary analysis. Severe adverse events after the primary analysis were grade 4 neutropenia (n = 1) and grade 4 myelodysplastic syndrome that did not require specific treatment (n = 1). Eight deaths occurred during the observation period after enrolment, due to primary disease (n = 6), sepsis (n = 1) and unknown sudden death (n = 1).

Interpretation Long-term follow-up data demonstrated durable response for PFS and OS, and low cumulative incidence of sCNSi, indicating the efficacy of standard chemotherapy combined with CNS-directed therapy for untreated IVLBCL patients.

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Keywords: Central nervous system-directed therapy; Intravascular large B-Cell lymphoma; R-CHOP; Secondary central nervous system involvement

Research in context

Evidence before this study

A PubMed search for articles published before 17 August 2024 using the terms "angiotropic lymphoma or angioendotheliomatosis or intravascular lymphoma or intravascular large B-cell lymphoma" and "retrospective or prospective" yielded 191 items. We could not find any published prospective studies of IVLBCL except for the primary analysis of this study, which suggests that internationally, this study remains the only published prospective study. However, many retrospective analyses of IVLBCL conducted throughout the world have recently been published. This suggests that IVLBCL has been well recognized following listing of the disease in the World Health Organization (WHO) classification.

Added value of this study

The study treatment of R-CHOP combined with R-high dose methotrexate (HDMTX) plus intrathecal treatment (IT) showed durable response and acceptable toxicity in long-term follow-up. The cumulative incidence of secondary central nervous system involvement (sCNSi) remained low suggesting that CNS-directed therapy comprising HDMTX and IT contributes to improved outcome in patients at high risk of sCNSi.

Implications of all the available evidence

The results of this study suggest that the combination of R-CHOP with HDMTX and IT has durable response and is an effective first-line treatment for IVLBCL without apparent CNS involvement at diagnosis. Further studies are warranted to optimize the first-line treatment of untreated IVLBCL patients.

Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare type of extranodal large B-cell lymphoma characterized by the selective growth of lymphoma cells in the lumina of small vessels of various organs.[1–3] Lymphadenopathy is a common characteristic of malignant lymphomas that is usually lacking in IVLBCL, leading to delay of a timely diagnosis and initiation of treatment, resulting in poor prognosis. Awareness of IVLBCL has improved since its listing as a disease entity in the 4th edition of the World Health Organization (WHO) classification,[4] and patients with IVLBCL have thus received a more accurate and timely diagnosis in recent years.

Due to the lack of specific signs, the existence of IVLBCL is suspected only when systemic symptoms such as fever, general malaise and weight loss appear due to progression of the disease. Thus, most patients with IVLBCL also have fever, cytopenia, lactate dehydrogenase (LDH) elevation, and poor performance status (PS) and are graded as high-risk by the international

prognostic index (IPI).[5] Moreover, systemic involvement of organs such as the kidneys and adrenal glands is frequently observed in IVLBCL, which means that most IVLBCL patients are also graded as high-risk by the central nervous system (CNS)-IPI.[6,7]

In terms of clinical outcomes, our previous retrospective analysis revealed 2-year progression-free survival (PFS) and overall survival (OS) in patients with IVLBCL receiving rituximab-containing chemotherapies of 56% and 66%, respectively.[8] Subsequent analysis of secondary CNS involvement (sCNSi) revealed that patients with IVLBCL had high risk of sCNSi of up to 25% at 3 years, even in patients without CNS involvement at diagnosis, which is supported by the findings of recent genetic analyses that most patients with IVLBCL harbour *MYD88* and *CD79B* mutations similar to the genetic characteristics of primary CNS lymphoma.[9–12] Based on these findings, we assumed that an R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen combined with any CNS-directed therapy might be useful for untreated IVLBCL patients, and then conducted a phase 2 trial (PRIMEUR-IVL) to explore the safety and efficacy of six cycles of R-CHOP combined with two cycles of R-high dose methotrexate (HDMTX) and four doses of intrathecal treatment (IT) comprising methotrexate, cytarabine, and prednisolone for untreated IVLBCL patients without apparent CNS involvement at diagnosis. The primary analysis demonstrated that 2-year PFS was 76% and 2-year OS was 92% with a median follow-up duration of 3.9 years. The two-year cumulative incidence of sCNSi was 3% and the toxicity of the protocol treatment was acceptable, which suggest that standard treatment combined with CNS-directed therapy is an effective treatment for untreated IVLBCL patients without apparent CNS involvement at diagnosis.[13]

In general, patients with diffuse large B-cell lymphoma (DLBCL) who survive without relapsed disease for 2 years after the end of initial treatment demonstrate comparable survival to that in the general population.[14] However, it is unknown whether the protocol treatment has durable response without remarkable late toxicities and whether it truly contributes to improved clinical outcomes in IVLBCL. Long-term follow-up data regarding late relapse and complications are thus important. Herein we report the prespecified final analysis of 5-year follow-up data of our phase 2 trial of R-CHOP combined with CNS-directed therapy for untreated IVLBCL patients without apparent CNS involvement at diagnosis.

Methods

Study design and participants

The PRIMEUR-IVL study was a multicentre, single-arm, phase 2 trial conducted at 22 hospitals in Japan. The detailed eligibility criteria have been described previously.[13] Briefly, eligible for inclusion were patients aged 20–79 years with histologically confirmed untreated CD20-positive IVLBCL according to the WHO classification, an ECOG performance status of 0–3, no history of antibody therapy or chemotherapy, and adequate organ function. Patients with apparent CNS involvement shown radiographically or in cerebrospinal fluid were excluded. A histological diagnosis of IVLBCL was confirmed at central pathological review by three expert hematopathologists. Prephase steroid treatment was allowed, and if a patient with PS 4 at diagnosis improved to a score of 3 by steroid treatment, the patient was eligible.

Ethics

The protocol complied with the Declaration of Helsinki and domestic ethical guidelines issued by the Ministry of Health, Labour, and Welfare in Japan, and the Clinical Trials Act in Japan. The study was approved by the institutional review board at Aichi Cancer Center (Nagoya, Japan) (approval number 3-14) and each participating centre, and by the central review board of Mie University (Tsu, Japan) (approval number S2018-006) since enactment of the Clinical Trial Act in Japan. All study participants provided written informed consent and the study was registered in the UMIN Clinical Trial Registry (UMIN000005707) and the Japan Registry of Clinical Trials (jRCTs041180165).

Procedures

The procedures have previously been described in detail.[13] Briefly, patients received three cycles of R-CHOP every 3 weeks followed by two cycles of R-HDMTX every 2 weeks, then three additional cycles of R-CHOP. R-CHOP was administered at standard doses of rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), and vincristine (1.4 mg/m^2; maximum 2.0 mg) intravenously. Prednisolone (100 mg/day; patients aged ≥65 years received 40 mg/m^2) was administered orally for 5 days. The dose of HDMTX was 3.5 g/m^2 intravenously for 3 h (patients aged ≥70 years received 2.0 g/m^2). Intrathecal chemotherapy with methotrexate (15 mg), cytarabine (40 mg) and prednisolone (10 mg) was administered before the start of cycles of two, three, seven and eight of R-CHOP, unless contraindicated. Because of concerns about a severe infusion reaction at the initial dose of rituximab, the first dose was administered on day 8 of cycle one. Leucovorin rescue after HDMTX was performed according to approval by the Japanese insurance system. Prophylactic use of sulfamethoxazole and trimethoprim and granulocyte colony stimulating factor was recommended. Treatment response was assessed according to the modified International Working Group response criteria, taking into consideration the characteristics of IVLBCL. In the present study, treatment response was categorized as complete response, no change,

progressive disease and relapsed disease. The detailed treatment response criteria have been reported previously.[13] Symptoms and laboratory abnormalities that were assumed not to be derived from IVLBCL were not considered as tumour-related in this study.

Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Safety was assessed centrally by monitoring and recording of all adverse events and serious adverse events. An independent data and safety monitoring committee assessed serious adverse events when they occurred and reviewed adverse events periodically.

Outcomes

The primary endpoint of this study was 2-year PFS, and the secondary endpoints were complete response rate, OS, cumulative incidence of sCNSi, adverse events and pattern of progression. The protocol prespecified 5-year follow-up analysis as the final analysis, and we assessed PFS, OS, and the cumulative incidence of sCNSi, long-term adverse events and pattern of progression at 5 years after the end of registration.

Source of ad-hoc historical comparison

As an exploratory analysis to investigate whether the present treatment contributed to improved outcomes, we additionally compared the results of this trial with the outcomes of our previous retrospective cohort.[8] Included in this historical comparison were 26 patients with PS <4, creatinine level ≤2.0 mg/dL, and no neurological symptoms at diagnosis (which were eligibility criteria in this trial); and who were receiving R-CHOP or R-CHOP-like therapy without any CNS-directed therapy.

Statistics

To evaluate long-term follow-up data, we descriptively evaluated PFS, OS, and the cumulative incidence of sCNSi in the PRIMEUR-IVL study at 5 years. PFS was defined as the time from trial registration to the last follow-up or event (progression, relapse or death from any cause). OS was defined as the time from trial registration until the date of death due to any cause or to the last date of follow-up. The Kaplan–Meier method was used to estimate survival. For cumulative incidence of sCNSi, death without an event was the competing risk. To control confounding bias for the historical comparison, the confounder factors of patient age, sex, performance status, log LDH, presence of haemophagocytosis, pancytopenia, and B-symptom, and sIL-2R were matched using inverse probability of treatment weighting (IPTW). Balance in covariates between two cohorts before and after IPTW adjustment was assessed using the standardized difference approach. PFS and OS between two cohorts were compared using the

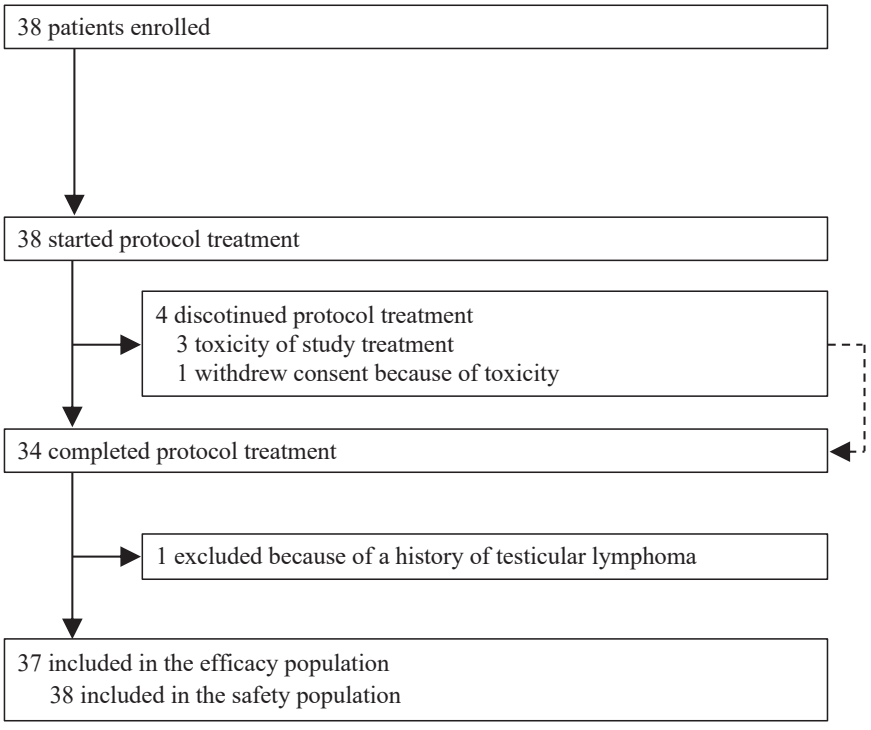

***Fig. 1:* Trial profile**. Trial profile of the study was shown. The profile was previously reported at the primary analysis (Ref[13]).

IPTW-adjusted Kaplan–Meier curves and log-rank test. The standard error was calculated by Greenwood's formula with unweighted Kaplan–Meier survivor function. Confidence bands were then drawn as the collection of pointwise confidence intervals of S(t) ± Zα/2*se(t), where Zα/2 is the (1-α/2) quantile of the normal distribution. The cumulative incidence function weighted by IPTW was compared between the present and the retrospective cohorts by univariate Fine and Gray's test. Adjusted cumulative incidence was estimated separately using the 'adjustedcif' function in R utilizing a weighted Aalen–Johansen estimator. Statistical analyses were performed with Stata version 18.0 software (Stata Corp. LP, College Station, TX, USA) or EZR version 1.63[15] and R version 4.3.1.

Role of the funding source

Center for Supporting Hematology-Oncology Studies (C-SHOT) was involved in study design and data collection, but had no role in the final data analysis, data interpretation or writing the report. The other funders had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Thirty-eight patients treated between 16 June 2011 and 21 July 2016 were enrolled in the study. One patient found to have a history of testicular lymphoma after completion of the protocol treatment was excluded from the study. Therefore, 38 patients were included in the safety population and 37 patients were included in the efficacy population (Fig. 1). The final follow-up was conducted in September 2021 and the data cutoff date for the final analysis was 16 November 2021. Patient baseline characteristics are listed in Table 1.

Progression events occurred in 12 patients during the study period: in 11 patients in the primary analysis, and one afterward. The latter patient, a 68-year-old female, developed myelodysplastic syndrome (MDS) 47 months after registration and died of an unknown cause 5 months after the diagnosis of MDS. This patient did not require any specific treatment for MDS prior to the progression event. Regarding the pattern of progression in the 11 patients in the primary analysis, one died of septic shock when in complete remission, five developed progressive disease or relapsed disease at other than the primary site and five developed relapsed disease at the primary site. Eight patients died during the study period: six in the primary analysis and two between the primary and final analyses. Of these two, one died of an unknown cause, as described above, and the other died of refractory IVLBCL 44 months after registration. Three patients who received high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) for relapsed disease remained in remission by the end of the study. Table 2 lists the characteristics of patients with progression or relapse.

Thirty-four of the 38 patients completed the protocol treatment and complete response was achieved in 31 of the 37 (84%) patients. Median follow-up duration in

Characteristics	n	%
Number	37	100
Age at registration, years		
Median (IQR)	66 (59–74)	
>60 years	25	68
Sex, male	16	43
Clinical stage IV	37	100
Performance status		
0	5	14
1	17	46
2	8	22
3	7	19
4	0	0
LDH > ULN	36	97
Extranodal involvement >1	25	68
International prognostic index		
Low	0	0
Low-intermediate	4	11
High-intermediate	12	32
High	21	57
Hypoxemia	10	27
B symptoms		
Fever	27	73
Loss of weight	9	24
Night sweating	7	19
None	7	19
Cytopenia		
Leukocytopenia, WBC <4000/μL	11	30
Anemia, Hb <11 g/dL	30	81
Thrombocytopenia, PLT <10^5/μL	17	46
Pancytopenia	8	22
Haemophagocytosis		
Negative	23	62
Positive	8	22
Uncertain	6	16
CNS symptoms	3	8
Exanthema	4	11
DIC	1	3
Initial treatment response		
Complete response	31	84
No change	5	14
Progressive disease	0	0
Not evaluated	1	3

Abbreviations: IQR, interquartile range; LDH, lactate dehydrogenase; ULN, upper limit of normal; WBC, white blood cell count; Hb, haemoglobin; PLT, platelet count; CNS, central nervous system; DIC, disseminated intravascular coagulation.

Table 1: **Patient characteristics of the present study (n = 37).**

Patient no.	Age/sex	PS	LDH (IU/L)	Initial response	Salvage therapy	Duration from end of protocol treatment to progression/relapse (m)	PFS (m)	OS (m)	Outcome	Note
1	78/M	3	1089	CR	None	5	10	10	DOO	
2	66/M	3	1512	NC	HD-Dexamethasone, MTX/Ara-C	14	19	20	DOD	
3	78/F	1	183	NC	BSC[a]	18	20	21	DOD	
4	78/M	0	1388	NE	GCDR, BSC[b]	20	25	44	DOD	
5	76/M	1	242	NC	VCR/PSL	21	24	29	DOD	
6	77/M	1	885	CR	GCDR, R-EPOCH, R-DeVIC	7	12	25	DOD	
7	38/M	1	750	CR	CHASER, R-MEAM, HD-ASCT	9	14	88	AND	
8	78/F	1	782	CR	R-GDP, BR, R	11	16	85	AND	
9	66/F	2	639	CR	CHASER, MCEC, HD-ASCT, R	12	16	80	AND	
10	67/M	2	503	CR	DA-EPOCH-R/MA, DA-EPOCH-R, CHASER, GCDR, BR, SMILE, R	12	17	38	DOD	
11	69/F	2	1259	CR	CHASE, R-MEAM, HD-ASCT	13	19	104	AND	
12	68/F	3	343	CR	None	48	53	53	Dead of unknown cause	MDS was developed 47 months after enrollment.

Abbreviations: no, number; PS, performance status; LDH, lactate dehydrogenase; m, months; PFS, progression-free survival; OS, overall survival; M, male; F, female; BM, bone marrow; PB, peripheral blood; CR, complete response; NC, no change; NE, not evaluable; CNS, central nervous system; HD, high-dose; MTX, methotrexate; Ara-C, cytarabine; BSC, best supportive care; VCR, vincristine; PSL, prednisolone; GCDR, gemcitabine, carboplatin, dexamethasone, and rituximab; R, rituximab; EPOCH, etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin; DeVIC, dexamethasone, etoposide, ifosfamide, carboplatin; CHASER, cyclophosphamide, high-dose cytarabine, dexamethasone, etoposide, and rituximab; MEAM, ranimustine, etoposide, cytarabine, and melphalan; HD-ASCT, autologous stem cell transplantation with high dose therapy; GDP, gemcitabine, dexamethasone, and cisplatin; BR, bendamustine and rituximab; MCEC, ranimustine, carboplatin, etoposide, and cyclophosphamide; DA-EPOCH-R/MA, dose-adjusted, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, rituximab, methotrexate and cytarabine; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide; DOO, dead of other disease; DOD, dead of disease; AND, alive with no evidence of disease; MDS, myelodysplastic syndrome. [a]After Grade 3 intracerebral haemorrhage. [b]After the second relapse of the disease.

Table 2: **Characteristics of patients with progression or relapse.**

survivors was 7.1 years (IQR 5.6–8.7), 5-year PFS was 68% (95% confidence interval (CI) 50–80) and 5-year OS was 78% (95% CI 61–89) (Fig. 2a and b). Median PFS and OS were not reached. No newly relapsed disease occurred between the primary and final analyses. Five-year cumulative incidence of sCNSi was 3% (95% CI 0.2–12), which means that no patient experienced sCNSi after the primary analysis (Fig. 3). Severe late toxicities that occurred after the primary analysis were grade 3 neutropenia (n = 1) and grade 4 MDS (n = 1).

To determine the effectiveness of the protocol treatment, we used the threshold PFS determined from outcomes of patients who received chemotherapies without rituximab in our previous retrospective analysis.[8] However, it remains unclear whether the PRIMUER-IVL protocol treatment contributed to the improved outcomes compared to those of patients who received rituximab-containing chemotherapies without any CNS-directed therapy. As an ad hoc analysis, we compared the present outcomes with those of the previous retrospective analysis.[8] In this ad hoc analysis, we excluded patients with poor performance status, renal failure, neurological symptoms at diagnosis, and those receiving any CNS-directed therapy prior to sCNSi, which were included in the eligibility criteria in the present study. Table S1 lists the characteristics of 26 patients who received CHOP (n = 24) or CHOP-like (n = 2) therapy with rituximab in the previous retrospective cohort.[8] Complete response was achieved in 22 of the 26 (85%) patients. In 5 of the 26 (19%) patients, consolidative high-dose therapy was performed after autologous stem cell transplantation at their first remission. As a standardized mean difference of baseline characteristics between the present and previous cohort was different (Table S2), we performed IPTW adjustment to match confounding factors as much as possible. After the adjustment, three-year PFS and OS were 71% (95% CI 56–86) and 83% (95% CI 72–94), respectively, in the present study, and 50% (95% CI 30–70) and 62% (95% CI 44–81), respectively, in the previous cohort (Figure S1a and b). The weighted cumulative incidence of sCNSi at 2 years was 3.4% (95% CI 0–10) in the present study. In the previous cohort, sCNSi developed in four patients and the cumulative incidence of sCNSi at 2 years was 22% (95% CI 2–42) (Figure S1c).

Discussion

This study presents the analysis of prespecified long-term follow-up data of the PRIMUR-IVL study. No newly relapsed events were observed between the primary and final analyses, resulting in a 5-year PFS of 68%. Only one event was observed after the primary analysis, in a patient who developed secondary

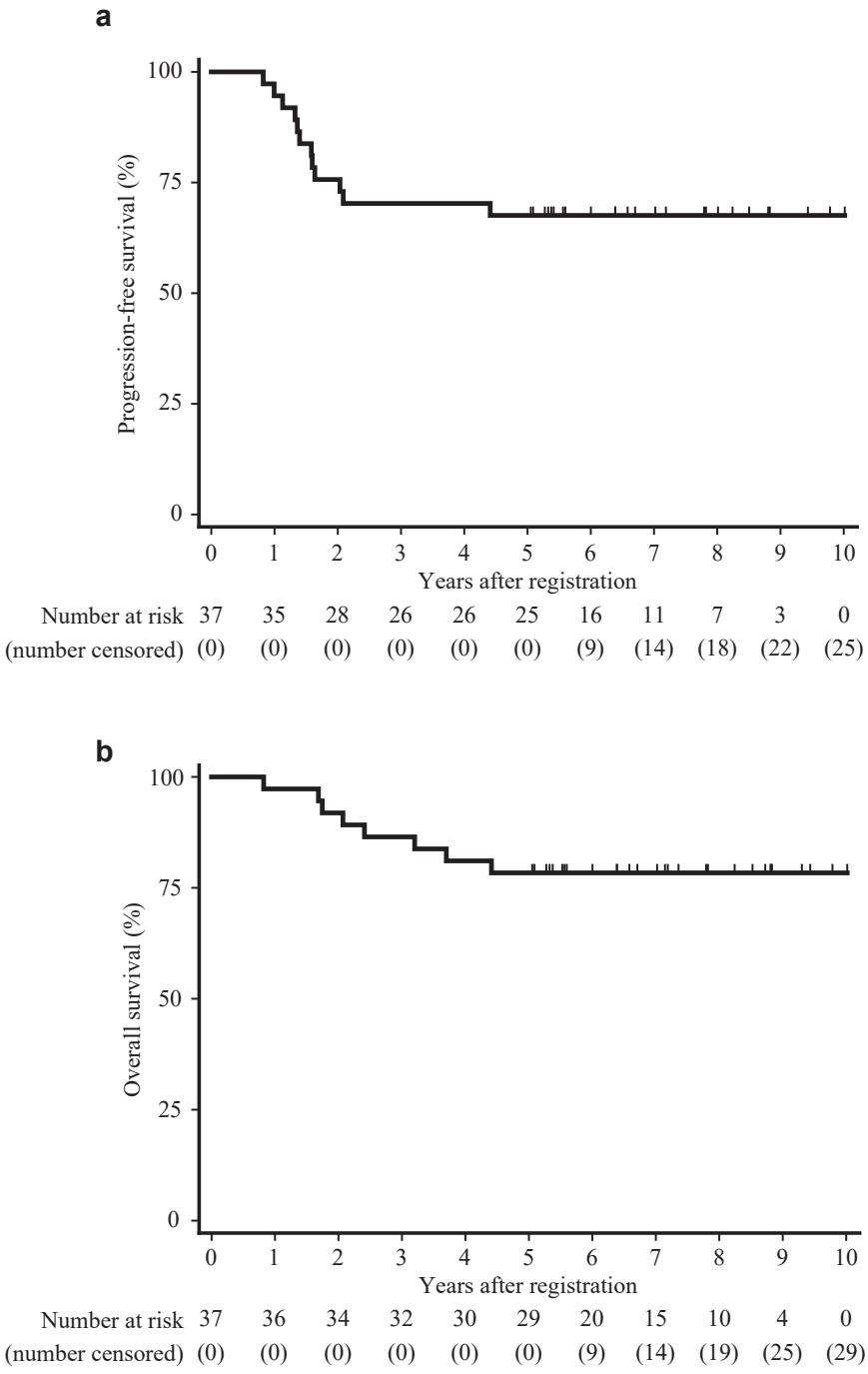

Fig. 2: **Progression-free survival and overall survival**. Progression-free survival (a) and overall survival (b) in all patients at the final analysis were shown.

myelodysplastic syndrome but died of an unknown cause. SCNSi occurred in a patient who developed the disease before the primary analysis. Collectively, the data suggest that the PRIMEUR-IVL protocol treatment resulted in a durable response in patients with untreated IVLBCL and without apparent CNS involvement at diagnosis. Therefore, standard chemotherapy combined with CNS-directed therapy is an effective treatment even in patients who have a disease type considered to have high risk of CNS recurrence.

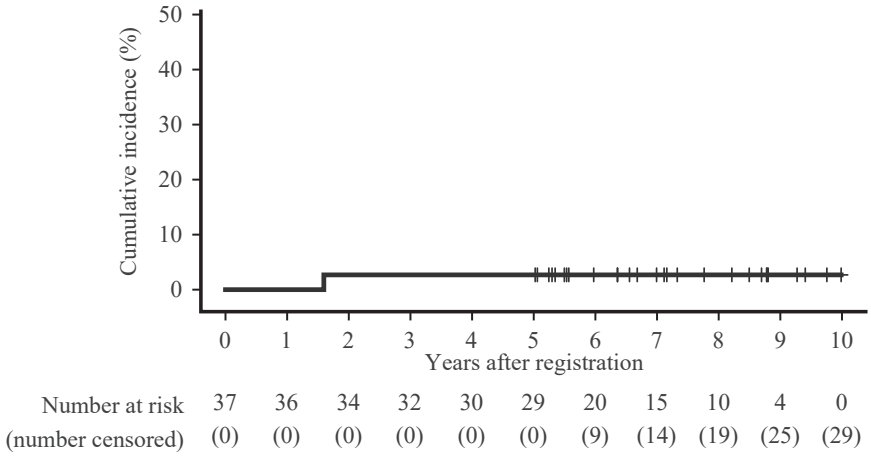

***Fig. 3:* Cumulative incidence of secondary central nervous system involvement**. Cumulative incidence of secondary central nervous system involvement in all patients at the final analysis was shown.

The primary analysis of this study demonstrated the efficacy of the protocol treatment assuming a threshold PFS of 35% and an expected PFS of 60% based on a retrospective analysis.[8] An interesting point of the present study is whether the addition of CNS-directed therapy to standard chemotherapy contributes to improving clinical outcomes. We thus attempted to compare the present outcomes with those of patients who received R-CHOP or R-CHOP-like chemotherapy without any CNS-directed therapy in the previous retrospective cohort as an ad-hoc analysis. As shown in Table S2, the baseline characteristics in the present study was more favourable than those in the previous cohort in terms of performance status (PS), the presence of B symptoms, and the proportion of patients with remarkably elevated soluble IL-2 receptor levels, and so on. Although we compared PFS, OS and sCNSi in the present study with those in the previous cohort (Figure S1a, b, and c), the results of this ad-hoc analysis were not conclusive, as the background information of the present and previous cohorts differed despite the IPTW adjustment. However, given that the cumulative incidence of sCNSi in the present study was low and that the prognosis of patients with sCNSi in the previous cohort was poor,[9] the addition of CNS-directed therapy might have contributed to the outcomes in the present study.

During the study period, only one patient developed sCNSi. Whether CNS-directed therapy of stand-alone HDMTX or IT decreases sCNSi in DLBCL remains controversial; however, negative results regarding HDMTX and IT have been reported.[16–22] In contrast, the efficacy of combined HDMTX and IT has been also reported.[20,23] In the present study, we planned to use CNS-directed treatment in combination therapy because our retrospective cohort demonstrated sCNSi of leptomeningeal disease and parenchymal disease in patients with IVLBCL. Importantly, as none of the previous evaluations of the efficacy of CNS-directed therapy for DLBCL included IVLBCL, it would be hard to adapt those conclusions to the present study. However, treatments of HDMTX for parenchymal disease and IT for leptomeningeal disease might have contributed efficiently to this result. Considering the possibility that efficacy of the same treatment may differ between DLBCL and IVLBCL, further investigations are required to determine whether CNS-directed therapy is effective in IVLBCL.

R-CHOP chemotherapy is a longstanding standard chemotherapy in DLBCL.[24,25] In recent genetic analyses of IVLBCL, most cases were classified as activated B-cell type.[26,27] Given that polatuzumab vedotin combined with R-CHP (pola-R-CHP) exhibits superior efficacy to R-CHOP in ABC type DLBCL, the pola-R-CHP regimen might be superior to R-CHOP as the baseline chemotherapy for IVLBCL.[28,29] In the present study, three patients exhibited durable response after HDT with ASCT for relapsed IVLBCL, which indicates that the disease is potentially curable in these three patients. The change of the primary treatment from R-CHOP to pola-R-CHP might lead to improved survival without recurrence in these potentially curable patients. In addition, it would be interesting to know whether the replacement of R-CHOP with pola-R-CHP could attenuate the need for CNS-directed therapy. In the POLARIX study, 86 patients (19.6%) in the R-CHOP group and 72 patients (16.4%) in the pola-R-CHP group received some kind of CNS-directed therapy, after which sCNSi occurred in 12 patients (2.7%) in the R-CHOP group and 13 patients (3.0%) in the pola-R-CHP group.[28] Given that there was no difference of the incidence of sCNSi, it can be inferred that the reduction in PFS events in the pola-R-CHP group was due to systemic relapse but not sCNSi. Therefore, even in the era of pola-R-CHP, it is possible

that CNS-directed therapy may still be required, at least for IVLBCL. Although the reduction in PFS events may reduce late sCNSi, it seems difficult to immediately omit CNS-directed therapy for IVLBCL by switching to pola-R-CHP therapy.

There are some limitations of the present study. The trial was a single-arm, multicentre, phase 2 study, and contains patient selection bias inherent to the prospective trial setting. In addition, background information between the present study and previous cohort in the historical comparison could not be completely adjusted even with the IPTW adjustment. In addition to the inherent weakness of historical control considered to be major limitation,[30] the historical comparison was not apparently conclusive. Moreover, the timely diagnosis before disease progression derived from the improved awareness of the disease and the improvement of the quality of the care derived from the accumulated experiences of physicians might lead to favourable outcomes. As a result, it might lead to overestimate the study result. It will be necessary to further clarify the real-world data of this treatment through future studies. Nonetheless, the findings of this study, obtained from the only such prospective trial internationally, are clearly important with respect to selecting the optimal treatment for patients with IVLBCL. The present results indicate that further investigation is warranted regarding optimal initial treatments using novel agents and/or antibodies, initial treatment for IVLBCL in patients with CNS involvement at diagnosis, and treatments for relapsed/refractory IVLBCL including immune cell therapy.

Contributors

K. Shimada, M. Yamaguchi, K.M., M.O., Y. Masaki, R.S., S.N., and T.K. designed the study and wrote the protocol; K. Shimada, M. Yamaguchi, K.M., K. Sato, S.K., H.N., J.T., N.F., K.N., K.M., E.O., A.O., Y.S., T.U., S.K., A.W., D.E., Y. Kondo, A.M., Y. Kin, Y. Minami, D.H., and T.N. treated patients and/or collected the data and samples; K. Shimada, M. Yamaguchi, Y. Kuwatsuka, Y.A., and T.K. analysed and interpreted the data; Y. Kuwatsuka and Y.A. verified the underlying data; M. Yamaguchi and T.K. provided financial support; K. Shimada, Y. Kuwatsuka, and Y.A. performed the statistical analysis; S.S. and S.N. prepared and diagnosed pathological specimens for central pathological review; H.K. and S.N. supervised research and K. Shimada, M. Yamaguchi, Y. Kuwatsuka, and T.K. wrote the manuscript. All authors read and approved the final version of the manuscript.

Data sharing statement

Qualified researchers may contact the corresponding author (K. Shimada) to request individual-level patient clinical data. Requests will be reviewed based on their scientific merit. In compliance with the domestic ethical guideline and the relevant act, individual de-identified patient data that are the basis for the results reported in this article can be shared under the approval of each institutional review board until 5 years after the end of this study. The study protocol and statistical analysis plan will be available in the appendix of this article immediately after publication to anyone who wishes to access them.

Declaration of interests

K. Shimada reports grants from the Japan Agency for Medical Research and Development (AMED), during the conduct of the study; grants from Otsuka and Kyowa Kirin, outside of the submitted work; consulting fees from Chugai, Eli Lilly, AbbVie, Kyowa Kirin, BeiGene, and Ohara, outside of the submitted work; payment or honoraria from Takeda, Kyowa Kirin, CSL Behring, Eisai, Chugai, Daiichi Sankyo, AstraZeneca, Janssen, Bristol-Myers Squibb, Nippon Shinyaku, Ono, Gilead, AbbVie, Genmab, Novartis, Incyte, Meiji Seika Pharma, Mundi Pharma, SymBio, Sanofi, and Asahi Kasei, outside of the submitted work. M. Yamaguchi reports grants from AMED during the conduct of the study; grants from AstraZeneca, Chugai, Genmab, Incyte, and AbbVie, outside of the submitted work; consulting fees from Genmab, BeiGene, and Nihon Servier, outside of the submitted work; payment or honoraria from Chugai, Kyowa Kirin, AbbVie, Bristol-Myers Squibb, Janssen, Meiji Seika Pharma, MSD, Nippon Shinyaku, SymBio, Takeda, and Eisai, outside of the submitted work. K. Matsue reports grants from AMED during the conduct of the study and grants from AstraZeneca, outside of the submitted work. S. Kusumoto reports grants from Chugai, Kyowa Kirin, Janssen, and Daiichi Sankyo, outside of the submitted work; and payment or honoraria from Chugai, Kyowa Kirin, Janssen, and Daiichi Sankyo, outside of the submitted work. H. Nagai reports grants from Takeda, Kyowa Kirin, and Chugai, outside of the submitted work; and payment or honoraria from Takeda, Kyowa Kirin, Chugai, and Nippon Kayaku, outside of the submitted work. J. Takizawa reports grants from Janssen, AstraZeneca, AbbVie, Novartis, Kyowa Kirin, Chugai, Nippon Kayaku, Mitsubishi Tanabe, Eli Lilly, and Asahi Kasei, outside of the submitted work and payment or honoraria from Janssen, AstraZeneca, AbbVie, Novartis, Kyowa Kirin, Chugai, and Nippon Kayaku, outside of the submitted work. N. Fukuhara reports grants from AbbVie, Chugai, Chordia therapeutics, Genmab, Incyte, Kyowa Kirin, Loxo Oncology, and Takeda, outside of the submitted work; payment or honoraria from AbbVie, AstraZeneca, Bristol-Myers Squibb, Chugai, CSL Behring, Eisai, Eli Lilly, Genmab, Janssen, Kyowa Kirin, Nippon Shinyaku, Novartis, Ono, Sanofi, SymBio, and Takeda, outside of the submitted work. K. Nagafuji report grants from Kyowa Kirin, Chugai, and Ono, outside of the submitted work. K. Miyazaki reports grants from Eisai, Takeda, Nippon Shinyaku, Otsuka, Chugai, Asahi Kasei, Sumitomo, and Zenyaku Kogyo, outside of the submitted work; payment or honoraria from Chugai, SymBio, Janssen, Eisai, Nippon Shinyaku, AstraZeneca, Bristol-Myers Squibb, Meiji Seika Pharma, AbbVie, Genmab, Novartis, Incyte, Asahi Kasei, and Ono, outside of the submitted work. T. Uchida reports payment or honoraria from Novartis, Janssen, AbbVie, Nippon Shinyaku, Kyowa Kirin, Nippon Kayaku, Takeda, Kissei, Meiji Seika Pharma, Bristol-Myers Squibb, Sanofi, Chugai, Asahi Kasei and Eisai, outside of the submitted work. D. Ennishi reports grants from Nippon Shinyaku, Chugai, and Eisai, outside of the submitted work; payment or honoraria from Eisai, Chugai, SymBio, Bristol-Myers Squibb, Kyowa Kirin, and Nippon Shinyaku, outside of the submitted work. Y. Minami reports consulting fees from Takeda and CMIC, outside of the submitted work and payment or honoraria from Novartis, Astellas, Pfizer, Daiichi Sankyo, and Otsuka, outside of the submitted work. Y. Masaki reports grants from Astellas, Eisai, Pfizer, Taisho, Taiho, Chugai, Nippon Kayaku, MSD, Kyowa Kirin, Ono, Asahi Kasei, Daiichi Sankyo, Takeda, Teijin, and Mochida, outside of the submitted work. M. Okamoto reports grants from Chugai, outside of the submitted work; and payment or honoraria from AbbVie, Janssen, Sanofi, Shinnihonseiyaku, and Kyowa Kirin, outside of the submitted work. Y. Atsuta reports consulting fees from JCR Pharmaceuticals and Kyowa Kirin, outside of the submitted work; and payment or honoraria from Otsuka, Chugai, Novartis, AbbVie, Janssen, and Meiji Seika Pharma, outside of the submitted work. H. Kiyoi reports grants from Chugai, Kyowa Kirin, Zenyaku Kogyo, Sumitomo, Eisai, Daiichi Sankyo, Otsuka, Perseus, CURED, Astellas, Asahi Kasei, AbbVie, Nippon Kayaku, Nippon Shinyaku, JCR Pharmaceuticals, and Takeda, outside of the submitted work; payment of honoraria from Chugai, Eisai, Daiichi Sankyo, Astellas, AbbVie, AstraZeneca, Novartis, SymBio, Bristol-Myers Squibb, Amgen, Meiji Seika Pharma, Pfizer, Nippon Kayaku, Towa, Ono, MSD, Pharma Essentia Japan, Asahi Kasei, and Kissei, outside of the submitted work. R. Suzuki reports grants from Chugai, Kyowa Kirin, Shionogi, Taiho, Eisai, and Otsuka, outside of the submitted work; and payment or honoraria from Chugai, Kyowa Kirin, AbbVie, Bristol-Myers Squibb, Eisai,

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103078.

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