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REVIEW ARTICLE

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Current progress and future perspectives of research on intravascular large B-cell lymphoma

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Abstract

Intravascular large B-cell lymphoma is a rare disease of the large B cells characterized by selective growth in the lumina of small vessels in systemic organs. Since first reported in 1959, the difficulty of obtaining sufficient tumor cells from biopsy specimens has hampered the elucidation of its underlying biology. Recent progress using xenograft models and plasma cell-free DNA has uncovered genetic features that are similar to those of activated B-cell type diffuse large B-cell lymphoma, including *MYD88* and *CD79B* mutations and frequent alterations in immune check point-related genes such as *PD-L1* and *PD-L2*. Given the improvement in clinical outcomes and a higher risk of secondary central nervous system (CNS) involvement in the rituximab era, a phase 2 trial of R-CHOP combined with high-dose methotrexate and intrathecal chemotherapy as a CNS-oriented therapy has been conducted. This trial, the PRIMEUR-IVL study, has displayed good progression-free survival and a low cumulative incidence of secondary CNS involvement. Long-term follow-up within this trial is still ongoing. Further understanding of the pathophysiology of the disease and improvements in clinical outcomes are still needed.

KEYWORDS

central nervous system involvement, genetic alterations, intravascular large B-cell lymphoma, PD-L1, R-CHOP therapy

1 | INTRODUCTION

Intravascular large B-cell lymphoma (IVLBCL) is a rare type of extranodal large B-cell lymphoma characterized by the selective growth of tumor cells in the lumina of systemic organ small vessels (Figure 1).[1] The disease mainly affects middle-aged and elderly adults, similar to other types of malignant lymphoma. A peculiar characteristic of the disease is the lack of lymphadenopathy, which is a general characteristic of malignant lymphoma, and the disease develops with nonspecific symptoms such as fever, general fatigue, and respiratory symptoms, which hamper timely and precise diagnosis. The existence of the disease is suspected only after the appearance of systemic symptoms mentioned above, and the delay in diagnosis directly leads to deteriorating general conditions due to progression. Since being listed in the 4th edition of the World Health Organization (WHO) classification as a distinct disease entity,[2] awareness of the disease has improved, leading to increased timely diagnosis. In this review, we will discuss recent progress in research and treatment of the disease and future perspectives.

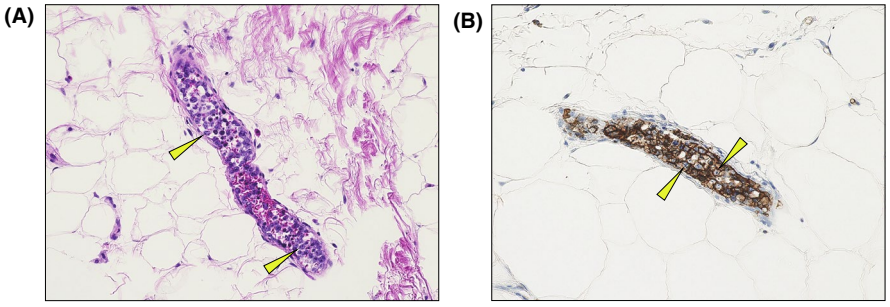

FIGURE 1 Pathological specimen from a patient diagnosed with IVLBCL. Pathological specimen of a random skin biopsy from a patient with IVLBCL are shown. Yellow arrowheads show IVLBCL tumor cells. Tumor cells lodge in the lamina of vessels in the adipose tissue of the skin. Hematoxylin and eosin staining (A) and CD20 staining (B) are shown. (original magnification ×200)

2 | EPIDEMIOLOGY

The incidence of IVLBCL from the Japanese Society of Hematology registry data is shown in Figure 2. IVLBCL accounts for 1% of B-cell lymphomas. In Japan, the number of patients with malignant lymphoma is estimated to be 35 700 per y (http://gdb.ganjoho.jp/), and therefore an estimated 300-400 patients annually develop IVLBCL. The slight increase of IVLBCL is inferred to be due to more precise diagnosis. From the Surveillance, Epidemiology, and End Results (SEER) registry data in the USA, the incidence of IVLBCL is estimated to be 0.095 per 1 000 000 per year, which is lower than that in Japan.[3] However, the incidence of IVLBCL in the USA has increased markedly compared with nodal diffuse large B-cell lymphoma (DLBCL) (annual percentage change [APC] from 2000 to 2013 of 9.84 in IVLBCL vs 0.39 in DLBCL), which implies that diagnosis of IVLBCL has increased due to improved awareness of the disease. The disease has a male-female ratio of 1.1:1 according to a previous retrospective analysis in Japan.[4]

3 | PATHOGENESIS OF IVLBCL

A fundamental question about IVLBCL is why tumor cells lodge into and proliferate in vessels instead of forming a mass, despite the disease being a biological subtype of DLBCL. In addition, the biological differences between the "classic form" and "hemophagocytic form" have not been resolved.[1] In a previous report, the lack of adhesion molecules such as CD29 and CD54 was associated with this specific phenotype based on speculation that leucocyte migration is inhibited in IVLBCL.[5] However, these findings have not been confirmed by subsequent studies. We previously reported that there was no loss in the expression of specific adhesion molecules using patient-derived xenograft (PDX) models.[6] The association between IVLBCL pathogenesis and the inhibition of leucocyte migration is still unanswered.

DLBCL is classified into germinal center B-cell (GCB) and activated B-cell (ABC) types according to the cell of origin.[7,8] IVLBCL has been assumed to be mainly classified into the ABC type because it is an extranodal large B-cell lymphoma. A previous analysis of 96 patients with IVLBCL revealed that CD10, BCL6, and MUM1 expression levels were 13%, 26%, and 95% of controls, respectively, and most IVLBCL patients were of non-GCB type according to the Hans classifier.[9,10] Precise diagnosis of IVLBCL is made by the presence of a small number of lymphoma cells in the blood vessels in pathological specimens, but difficulty in obtaining sufficient tumor materials from pathological specimens has hindered gene expression profiling analysis using microarrays.

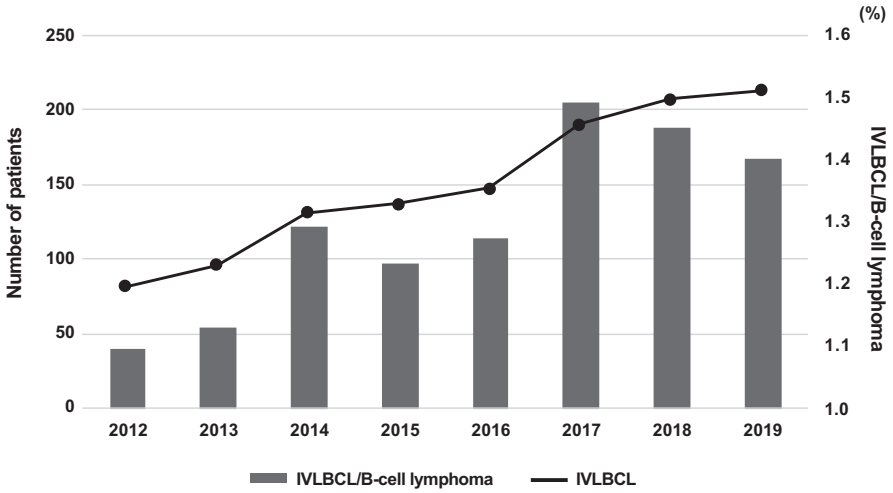

FIGURE 2 Annual trends in the number of patients with IVLBCL and the proportion of diffuse large B-cell lymphoma. Annual trends in the number of patients with IVLBCL (circles) and the proportion of diffuse large B-cell lymphoma (gray bars) are shown. This graph was created from registry data from, the Japanese Society of Hematology (http://www.jshem.or.jp)

Comprehensive genomic copy number analyses have been performed since the 2000s, and a difference in genomic copy number between GCB type DLBCL and ABC type DLBCL has been reported.[11] In addition, comprehensive gene mutation analysis using next generation sequencing technology, which has rapidly improved, has allowed us to analyze the genomic abnormalities in DLBCL.[12,13] These analyses have demonstrated both differential and common genetic mutations in each subtype of DLBCL. In the GCB type, genetic alterations in *EZH2*, *SGK1*, *GNA13*, *IRF8*, *B2M*, *CREBBP*, *TNFRSF14*, and *BCL2* are found. In the ABC type, genetic alterations in *ETV6*, *CD79B*, *MYD88*, *TBL1XR1*, *PIM1*, and *CDKN2A* are found. Common alterations in both subtypes include mutations in *ATM*, *SETD1B*, *NOTCH2*, *TP53*, *MLL2*, *EP300*, and *SETD2*.[14]

As mentioned above, the difficulty in obtaining a sufficient number of lymphoma cells has hampered comprehensive genetic analyses of IVLBCL. One solution is the development of PDX models. Tumor cells from PDX models retain the characteristics of their original patient tumors despite potential clonal selection during development of the model. We previously reported the development of PDX models established from IVLBCL patients,[6] and we analyzed the genetic characteristics of IVLBCL tumor cells that were amplified in the models. Genomic copy number analyses using array comparative genomic hybridization (CGH) demonstrated the deletion of 6q and 9p, which is similar to ABC type DLBCL. Moreover, IVLBCL was clustered into the ABC type according to gene expression profiling.

For genetic mutation analysis in IVLBCL, 2 groups in Japan and the Netherlands performed targeted sequencing of formalin-fixed paraffin-embedded specimens or peripheral blood cell-free DNA (cfDNA); both groups revealed a high frequency of changes in *MYD88* and *CD79B* accumulated in ABC type DLBCL.[15,16] We recently reported a comprehensive genetic analysis of 21 IVLBCL patients by whole exome sequencing using 18 cfDNA, 4 PDX models, and 2 bone marrow nuclear cell samples.[17] In our analysis, we demonstrated a higher frequency of mutations in *MYD88* (57%), *CD79B* (67%), *SETD1B* (57%), *HLA-B* (57%), *HLA-A* (33%), *HLA-C* (33%), and *CD58* (29%), similar to ABC type DLBCL, and the loss of *CDKN2A/2B* in 86% of patients. Applied to the recently proposed molecular genetic classification,[18,19] 17 of 21 patients were classified into the MCD type (n = 15) or as a composite type with features of MCD type (n = 2), suggesting genetic similarity between the MCD-type DLBCL and IVLBCL. As described below, there is a geographical difference in clinical presentation between European and Asian countries, such as the disease being restricted to skin involvement.[20,21] In fact, data from the Netherlands showed that 25% of patients had limited skin disease.[16] Different frequencies of CD79B Y176 mutations between the Netherlands (26%; 6 of 23 patients) and our recent cohort (62%; 13 of 21 patients) might contribute to the different clinical presentation, however further investigation is warranted to draw firm conclusions as the source of DNA differed between these investigations.[17]

In addition, recent immunohistochemical staining analyses have revealed that a substantial proportion of patients with IVLBCL have PD-L1-positive expression, which implies an association between PD-L1 expression and IVLBCL pathogenesis.[22-24] Regarding PD-L1 genomic alterations, a structural variant of PD-L1 including the 3′-untranslated region results in higher PD-L1 expression in adult T-cell leukemia/lymphoma.[25] Intriguingly, our analysis also revealed that 8 of 21 (38%) patients had accompanying *PD-L1*/*PD-L2* changes, which is a higher frequency than that in DLBCL.[17] Furthermore, our analysis also revealed a correlation between structural variants of *PD-L1* and expression, as confirmed by immunohistochemical staining using PD-L1 antibodies recognizing 3 different epitopes: clone 28-8 recognizing full-size PD-L1, clone E1J2J recognizing the extracellular domain, and clone SP142 recognizing the 3′ terminal region of the gene. Considering that PD-L1 expression varies in each organ in individual IVLBCL patients,[26] the potential association of PD-L1 expression with particular characteristics is interesting and warrants future investigation.

4 | CLINICAL CHARACTERISTICS OF IVLBCL

IVLBCL differs clinically from other types of malignant lymphoma in that it develops with nonspecific symptoms such as fever, general malaise, and dyspnea, but not lymphadenopathy or tumor mass formation. These symptoms can occur in nonmalignant diseases such as collagen disease and infectious disease, leading to difficulty in diagnosis. In a previous retrospective cohort in Japan, the most common clinical symptoms in IVLBCL were fever, general malaise, neurological symptoms, and dyspnea, which were observed in 73%, 25%, 25%, and 19% of patients, respectively.[4] In the Japanese cohort, skin eruption was observed in only 6% of patients. However, while fever was the most observed symptom in a European cohort, similar to that in Japan, neurological symptoms and skin eruptions were found in 35% and 40%, respectively, of patients in the European cohort.[21] Notably, IVLBCL restricted to the skin is described as the "cutaneous variant."[21]

Before being listed in the WHO classification, IVLBCL reports from the USA were extremely limited, but a retrospective study from academic centers in the USA has been recently reported.[27] In 54 patients with IVLBCL, characteristics were as follows: 23 males and 30 females, a median age at diagnosis of 63 y, median Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2, and 62% of PS more than 1. Nonspecific "B" symptoms defined as fever, night sweats, and body weight loss were observed in 29 (66%) of 44 evaluable patients. Neurological symptoms were also common and observed in 18 (41%) of 43 patients, and rash, cutaneous nodules, and hemangiomas were observed in 9 (21%) patients each. In 17 patients with PS of 0-1, 7 patients had skin symptoms, which implied that those patients were considered to have the cutaneous variant. In terms of diagnostic sites, bone marrow, skin, and CNS were the main sites for organ biopsies. Hemophagocytosis was observed in 5 (12%) patients. Lactate dehydrogenase (LDH) elevation was common with a median of 576 U/L, and 60% of patients were categorized at high risk of International Prognostic Index (IPI). In total, 69% and 48% of patients had accompanying anemia and thrombocytopenia,

respectively.[27] Although skin eruption and neurological symptoms were more common in the USA than in Japan, the clinical aggressiveness of IVLBCL did not differ much (Table 1).

5 | IMAGING STUDIES

Despite the lack of lymphadenopathy, organ enlargements such as those of the liver, spleen, kidney, and adrenal gland, as observed in imaging studies are common abnormalities in IVLBCL. Hepatosplenomegaly is observed in 50%-80% of patients,[28] and ground-glass opacity is frequently observed as lung lesions. Although organomegaly in computed tomography (CT) images may indicate IVLBCL, it often persists even after remission. Given the difficulty of base-line assessments of organ enlargement, response evaluations of CT images are not sufficient in IVLBCL. For fluorodeoxyglucose (FDG)-positron emission tomography (PET)(/CT), it is presumed that FDG uptake is enhanced in IVLBCL because of its aggressive clinical behavior and biological similarity to ABC type DLBCL. In fact, many previous reports have revealed the usefulness of FDG-PET(/CT)-positive findings at particular biopsy sites for the diagnosis of IVLBCL.[29-31] However, as previously reported, tumor invasion false negatives in FDG-PET can occur when the tumor cell density of the organ is not sufficiently high.[32] Recently, Shi et al reported a retrospective analysis of FDG-PET/CT findings in 16 patients with IVLBCL. In that report, a positive finding in bone marrow was observed in 13 (81%) patients, in liver in 12 (75%) patients, in spleen in 10 (63%) patients, in lung in 14 (88%) patients, and in kidney in 8 (59%) patients.[33] There is no doubt that FDG-PET(/CT) plays a useful role in diagnosing IVLBCL, especially for observing biopsy sites; however, further investigations are required regarding its usefulness for response evaluation. For MRI, ischemic change is a common finding in brain imaging studies.[34] Abe et al analyzed MRI findings in IVLBCL patients and reported high intensity signals in the pons in T2 weighted images that were not associated with impaired consciousness.[35] In our institute, a IVLBCL patient with a similar MRI finding has been observed, but the clinical significance warrants further study.

TABLE 1 Comparison of symptoms and laboratory findings of IVLBCL patients among geographical areas

Symptoms and laboratory findings	Japanese cohort[4]	European cohort[21]	US cohort[27]
Symptoms			
Fever	73%	44%	66% as B symptoms
Neurological symptoms	25%	35%	41%
General fatigue	25%	16%	18%
Gastrointestinal symptoms	19%	5%	9%
Dyspnea	19%	3%	21%
Edema	10%	5%	–
Urinary tract symptoms	2%	8%	–
Skin eruptions	6%	40%	21%
Laboratory findings			
Anemia	68%	63%	69%
Thrombocytopenia	58%	29%	48%
Leukocytopenia	27%	24%	–
Elevated LDH	98%	86%	–

6 | DIAGNOSIS OF IVLBCL

The current gold standard for the diagnosis of IVLBCL is confirmation of tumor cells in pathological specimens when the disease is suspected from progressive illness with fever and elevated serum LDH, not only in middle-aged or elderly adults but also in young adults. When appropriate biopsy samples are obtained, it is not always difficult for pathologists to make a precise diagnosis as large tumor cells are found in the lumen of small vessels or along the sinusoids of organs. Immunohistochemical staining for CD20 and CD34 is particularly useful for diagnosis, as the staining facilitates confirmation of tumor cells in blood vessels or along the sinusoids. However, precise diagnosis by bone marrow clot is often difficult because of the paucity of tumor cells on the specimens. It is therefore desirable to perform both bone marrow aspiration and biopsy with bone marrow examination. The detection of tumor cells by flow cytometry is often difficult. Combining random skin biopsies widely used since the late 2000s with bone marrow examination, diagnosis can be made for most IVLBCL.[36,37] Immediate work-up by both methods is recommended when the disease is suspected. Enzan et al retrospectively analyzed 82 random skin biopsy specimens from 25 IVLBCL patients; tumor cells were only detected in subcutaneous adipose tissue in 38 (46%) specimens. The median minimum depth from the skin surface to tumor cells was 3.64 mm, and minimum depths of more than 4 and 5 mm were found in 47% and 37% of specimens, respectively.[38] In addition, Matsue et al retrospectively analyzed 114 random skin biopsies from 111 patients in a single institute; in 33 IVLBCL patients, tumor cells were successfully found in 26 (79%) patients from the first random skin biopsy.[39] Considering the above findings, when random skin biopsies are performed, tumor cells are often found in vessels in the subcutaneous adipose tissue, and repetitive biopsies are occasionally required for accurate diagnosis of IVLBCL. However, we should pay attention to patient coagulation status when incisional biopsies are performed, as untreated IVLBCL patients may have disseminated coagulation syndrome (DIC) leading to critical bleeding events after random skin biopsy.[40] In line with these findings, the diagnostic sites have been changed in Japan. In an older retrospective analysis, 81% of patients were diagnosed by bone marrow findings, and only 15% were diagnosed by skin biopsies.[41] However, in a recent prospective trial, tumor cells in bone marrow and skin were found in 62% of participating patients each.[28] These findings indicate that most patients with IVLBCL are diagnosed by bone marrow aspiration/biopsy and/or skin biopsy.

As mentioned above, we reported comprehensive genetic analysis with whole exome sequencing using cfDNA of IVLBCL patients. cfDNA from tumor cells is enriched in the untreated plasma of IVLBCL patients.[17] It is therefore expected that cfDNA will assist in the accurate diagnosis of IVLBCL, particularly in patients for whom the disease is suspected but whose tumor cells cannot be confirmed by organ biopsies. In the same context, accurate diagnosis of CNS involvement in IVLBCL patients is also difficult. Considering recent findings of cerebrospinal fluid (CSF) in CNS lymphoma and IVLBCL, cfDNA in CSF in addition to flow cytometry might be a promising way to accurately evaluate CNS involvement.[42-44]

7 | TREATMENT OF IVLBCL

Clinical outcomes of IVLBCL in the pre-rituximab era were dismal,[45] with an overall survival at 3 y according to the International Extranodal Lymphoma Study Group (IELSG) of 33% in patients receiving anthracycline-containing chemotherapies.[46] In September 2003, the use of rituximab was approved in patients with DLBCL in Japan, and rituximab-containing chemotherapies have since been applied to patients with IVLBCL.[47] A Japanese retrospective study suggested that clinical outcomes of IVLBCL patients receiving rituximab-containing chemotherapies were significantly better than those receiving other chemotherapies; the 2-y progression-free survival (PFS) and overall survival (OS) were 56% and 66% in patients in the rituximab-containing chemotherapy group, respectively, while the 2-y PFS and OS were 27% and 41% in the other chemotherapy group, respectively.[4,9] A European cohort study has also shown improved clinical outcomes in patients receiving rituximab-containing chemotherapies,[48,49] indicating a new era for IVLBCL patients. A subsequent analysis regarding the cause of progression in the Japanese cohort revealed a high risk of CNS recurrence even in patients with no neurological symptoms at diagnosis. The risks of CNS recurrence at 1 and 3 y were 17% and 22% respectively in patients without CNS involvement at diagnosis who received rituximab-containing chemotherapies.[50] In particular, among patients without CNS involvement at diagnosis, 7 of 17 with CNS recurrence developed disease within 6 mo after diagnosis, while CNS recurrence developed with parenchymal disease in 10 of 17 patients, with leptomeningeal disease in 5 of 17 patients, and with both in 1 patient.[50]

As mentioned above, most IVLBCL patients are classified as having a high or high-intermediate risk of IPI.[4] Considering each index parameter of CNS-IPI as reported in 2016, age (>60 y), ECOG PS (≥2), LDH (>ULN [upper limit of normal]), the number of extranodal involvements (≥2), and clinical stage (III or IV), and the existence of kidney or adrenal gland involvement, IVLBCL patients can be categorized as high risk for CNS-IPI.[51] Given that the incidence of secondary CNS involvement at 2 y is 10.2% in patients with a high risk of CNS-IPI,[51] the addition of CNS-oriented therapy for IVLBCL patients is quite reasonable. Overall, these retrospective studies revealed unresolved needs for IVLBCL in the post-anti-CD20 monoclonal antibody era, which are (a) to investigate clinical outcomes by prospective trials, and (b) to further improve clinical outcomes for those with a high risk of secondary CNS involvement.

7.1 | A prospective trial for IVLBCL

To improve clinical outcomes for untreated IVLBCL patients, a phase 2 study (the PRIMEUR-IVL study [C-SHOT1004 study], UMIN-CTR000005707, jRCTs041180165) has been conducted.[28] Considering that the standard regimen for DLBCL is R-CHOP (where R is rituximab, C is cyclophosphamide, H is doxorubicin [hydroxydaunomycin], O is vincristine [oncovin] and P is prednisolone) and that patients have CNS recurrence during the induction treatment and as both parenchymal and leptomeningeal diseases,[50,52-54] both high-dose methotrexate (HDMTX) and intrathecal chemotherapy (IT) were adopted as CNS-oriented therapies. A multicenter, single-arm, phase 2 trial was, therefore, conducted to test the safety and efficacy of a combined regimen of 6 cycles of R-CHOP with 2 cycles of rituximab plus HDMTX administered between the first and last of 3 cycles of R-CHOP, with 4 doses of IT for CNS treatment. The primary endpoint of this trial was 2-y PFS, and secondary endpoints were complete response rate, 2-y OS, 2-y cumulative incidence of secondary CNS involvement, a pattern of progression, and toxicity.[28]

In total, 38 patients were enrolled between June 2011 and July 2016. The safety profile was assessed in 38 patients and efficacy was assessed in 37 patients due to the exclusion of an ineligible patient after the completion of protocol treatment. Characteristics of eligible patients were 66 y of age (interquartile range [IQR] 59-74), 21 females, 7 (19%) with PS 3, and 33 (89%) who were at high-intermediate or high risk of IPI. "B" symptoms were observed in 30 (81%) patients (27 fever, 7 night sweats, and 7 bodyweight loss). Cytopenia was common; anemia, thrombocytopenia, or leukocytopenia were observed in 30 (81%), 17 (46%), and 11 (30%) patients, respectively. Hemophagocytosis was observed in 8 (22%) patients, and DIC was observed in only 1 (3%) patient.

With a median follow-up duration of surviving patients of 3.9 y, 2-y PFS was 76% (95% confidence interval [CI]: 58%-87%), which met the primary endpoint. The 2-y OS was 92% (95% CI: 77%-97%), and median PFS and OS were not reached. Complete response was achieved in 31 (84%) patients, and progressive disease during the protocol treatment was not observed. In total, 11 progression events occurred: 1 death by infection in remission after the protocol treatment, and the remaining 10 by progressive disease or relapsed disease. One of 4 patients with progressive disease developed CNS recurrence, and no patient with relapsed disease experienced secondary CNS involvement. The 2-y cumulative incidence of secondary CNS involvement was 3% (95% CI: 0.2%-12%). Intriguingly, 3 of 6 patients who developed relapsed disease survived the second remission after high-dose therapy (HDT) with autologous stem cell transplantation (ASCT).

No treatment-related deaths occurred during the protocol treatment. Severe adverse events such as febrile neutropenia with septic shock, hypokalemia, and cerebral hemorrhage in 1 patient each were observed. Other frequent non-hematological toxicities were

febrile neutropenia (13 [34%]), hypokalemia (11 [29%]), hyponatremia (9 [24%]), hypoalbuminemia (8 [21%]), and hypophosphatemia (8 [21%]). Grade 3 tumor lysis syndrome was observed in 2 patients. Hematological toxicities were common: grade 3 or more leukocytopenia and neutropenia occurred in all patients. Adverse events leading to the discontinuation of protocol treatment were cerebral hemorrhage, septic shock in febrile neutropenia, the deterioration of PS due to nausea and anorexia, and the delay of commencement of rituximab plus HDMTX due to decreased creatinine clearance.[28]

These findings indicated the safety and efficacy of R-CHOP combined with CNS-oriented therapy for untreated IVLBCL patients without apparent CNS involvement at diagnosis. In addition, there was no apparent reduced efficacy even when HDMTX was inserted during R-CHOP, at least in patients with IVLBCL. Although a better ECOG PS score and lower incidence of hemophagocytosis in the PRIMEUR study compared with our previous retrospective study might affect better outcomes (Table 2), currently the combination of R-CHOP with HDMTX and IT is reasonable as a standard frontline treatment for untreated IVLBCL patients without apparent CNS involvement (Figure 3).

7.2 | Initial treatment in patients with CNS involvement at diagnosis

Although the PRIMEUR-IVL trial examined CNS-oriented therapy to prevent secondary CNS involvement, different treatment strategies should be established for IVLBCL patients with CNS involvement at diagnosis. Both systemic disease and CNS disease should be treated, and initial treatment for DLBCL with CNS involvement might be appropriate. However, the optimal treatment for DLBCL patients with CNS involvement has not been established.

TABLE 2 Patient characteristics of PRIMEUR-IVL study and previous retrospective analysis

	Previous retrospective study[50]	PRIMEUR-IVL study[28]
n	109	37
Age at diagnosis (y)		
Median	67	66
>60	78 (72%)	25 (68%)
Sex, male	60 (55%)	16 (43%)
Performance status >1	84 of 108 (78%)	15 (41%)
LDH > ULN	107 (98%)	36 (97%)
IPI		
Low or low-intermediate	4 (4%)	4 (11%)
High-intermediate or high	105 (96%)	33 (89%)
High	92 (84%)	21 (57%)
B symptoms present	91 (83%)	30 (81%)
Hemophagocytosis	65 (60%)	8 (22%)
sIL-2R level, ≥5000 U/mL	64 of 99 (65%)	16 (43%)

Abbreviations: IPI, international prognostic index; LDH, lactate dehydrogenase; n, number; sIL-2R, soluble interleukin-2 receptor; ULN, upper limit of normal.

According to the National Comprehensive Cancer Network guideline (https://www.nccn.org/guidelines/category_1) for DLBCL patients, treatment with R-CHOP combined with HDMTX administered on day 15 is recommended. However, the experience of this treatment for IVLBCL patients is extremely limited, and further investigation is required. Other regimens using HDMTX and/or high-dose cytarabine such as R-hyper-CVAD/MA (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate, and cytarabine) might be applicable for younger patients.[55] However, toxicities of intensified regimens are of concern in elderly patients, who account for more than half of the disease cases. Overall, initial care for IVLBCL patients with CNS involvement at diagnosis is an unmet clinical need, and further investigation and clinical experience are required.

7.3 | The role of HDT with autologous stem cell support

The role of HDT as initial treatment in IVLBCL has not been confirmed. Kato et al recently conducted a retrospective analysis of outcomes of 61 patients receiving HDT with ASCT as a consolidation therapy after initial treatment using registry data from the Japanese Society for Transplantation and Cellular Therapy. Their report revealed a good 5-y PFS of more than 80%.[56] HDT after salvage treatment resulted in long-term remission in 3 patients with relapsed disease in the PRIMEUR-IVL study, suggesting a meaningful role for HDT in treating IVLBCL.[28] It is however necessary to investigate the optimal timing of HDT to determine whether it is better as a consolidative therapy after initial treatment or as a salvage therapy at the relapsed phase.

7.4 | Outcomes of other reports

A recent report from the USA mentioned above revealed that the median OS of 54 patients who mainly received R ± CHOP therapy was *c.* 5 y; however, the median OS was 1.1 y taking into account patients who could not receive treatments or ante-mortem diagnosis.[27] In addition, in a recent report of 29 patients from Canada, the median OS of 23 patients with ante-mortem diagnosis was *c.* 1 y, while that of 15 patients who received chemotherapies was not reached, and the 3-y OS was *c.* 60%.[57] Both reports suggested that timely and accurate diagnoses are vital for treating IVLBCL.

8 | FUTURE PERSPECTIVES

Although good clinical outcomes of initial treatments for IVLBCL patients without CNS involvement have been demonstrated, effective

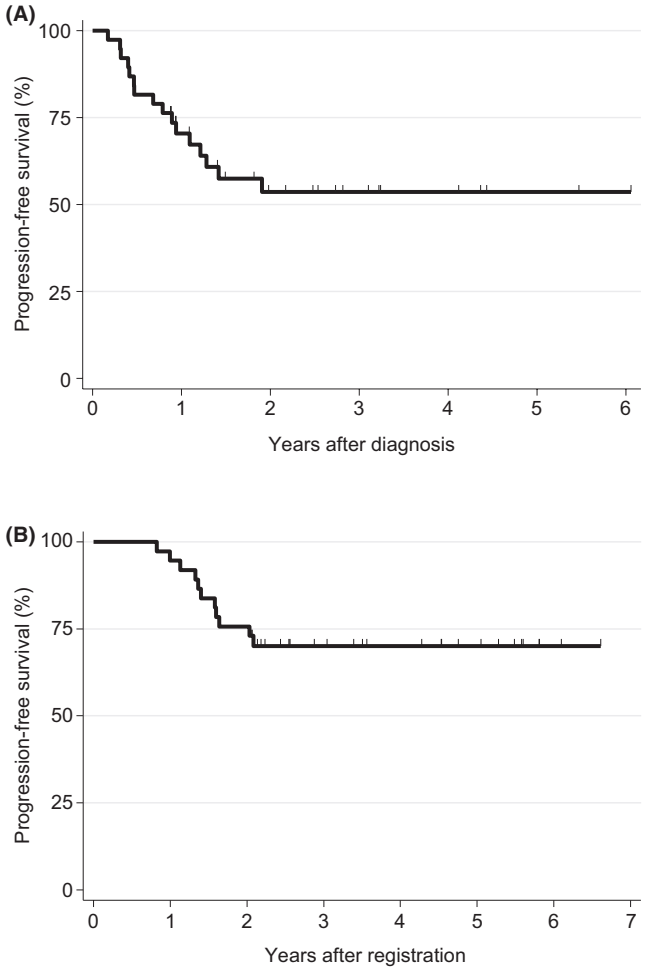

FIGURE 3 Change of progression-free survival in patients receiving rituximab-containing chemotherapies without apparent CNS involvement at diagnosis. Changes in progression-free survival of patients without apparent CNS involvement at diagnosis are shown. Outcomes of patients who received rituximab-containing chemotherapies in a previous Japanese retrospective cohort (n = 38) (A) (Ref.50) and outcomes of patients participating in the PRIMEUR-IVL study (n = 37) (B) (Ref.28) are shown

treatments for refractory disease remain an unsolved clinical issue. In addition, the fundamental pathogenesis of IVLBCL is also unresolved, despite the use of whole exome sequencing analysis. Future detailed investigations, using for example spatial transcriptomics and single cell analyses, might be required to understand the underlying biology. For treatment of refractory disease, the recent discovery of genetic abnormalities such as the high frequency of *MYD88* and *CD79B* mutations (MCD or C5 type) and the disruption of *PD-L1* might encourage novel treatment strategies.[18,19,58] Further and continuous investigations are warranted.

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