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Prospective therapeutic studies of disseminated extranodal large B-cell lymphoma including intravascular large B-cell lymphoma

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Abstract: This study aimed to establish a standard treatment for disseminated extranodal large B-cell lymphoma, including intravascular large B-cell lymphoma (DEN-LBCL/IVL), and to validate the clinical diagnostic criteria we proposed. Between 2006 and 2016, 22 patients were enrolled in a clinical trial conducted by the Hokuriku Hematology Oncology Study Group. The first cycle of chemotherapy consisted of dose-reduced cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) with delayed administration of rituximab. From the second to the sixth cycle, patients received conventional rituximab and CHOP therapy. The primary endpoint was overall survival (OS), while the secondary endpoints included the complete response (CR) rate and time to treatment failure (TTF). The results showed a CR rate of 73%, a median OS of 65 months, and a median TTF of 45 months. These findings indicate that patients with DEN-LBCL/IVL were effectively treated with our new chemoimmunotherapy regimen. Our clinical diagnostic criteria are useful for identifying patients who require early intervention.

***Keywords*:** intravascular large B-cell lymphoma, random skin biopsy, R-CHOP, clinical diagnostic criteria

Introduction

Intravascular large B-cell lymphoma (IVL) was first documented by Pfleger and Tappeiner in 1959 (*1*). IVL is defined as a subtype of diffuse large B-cell lymphoma (DLBCL) and recognized in the 2017 WHO classification (*2*). An Asian variant characterized by hemophagocytic syndrome was established by Murase *et al.* (*3*). Most IVL studies involve small, retrospective case analyses. A large-scale prospective study is needed to evaluate treatment protocols. IVL diagnosis is limited to cases with confirmed occlusion of vascular lumens by neoplastic B-cells. However, some cases with diffuse large lymphoid cell proliferation in the bone marrow (BM) without clear masses might still originate from IVL. These include primary BM DLBCL or disseminated extranodal DLBCL (DEN-LBCL) without masses. Patients with pathologically confirmed IVL and those with clinically suspected IVL would experience similar rapidly deteriorating clinical courses, which could lead to death. Recently, Suzuki *et al.* (*4*) reported no significant differences in characteristics and prognosis between IVL expressing PD-L1 and extranodal lymphomas. Early clinical diagnostic criteria for DEN-LBCL/IVL have been reported to be useful for diagnosis (*5*), and random skin biopsy (RSB) and BM biopsies are recommended (*6*). Most IVL patients present with multiple organ involvement and are classified as Stage IV according

to the Ann Arbor classification. They also have high-risk scores on the International Prognostic Index (IPI) (*7*). Standard treatment for DLBCL, such as CHOP chemotherapy (*8*), is considered for IVL. Anthracycline-based chemotherapy has shown effectiveness (*9*). Murase *et al.* (*10*) reported that patients treated with non-anthracycline-based chemotherapy had a poor prognosis. Rituximab-containing chemotherapy significantly improved outcomes in Japanese patients (*11*). To reduce the risk of infusion reactions, rituximab should be administered after debulking with CHOP. For patients expected to have severe bone marrow suppression due to BM infiltration, a reduced CHOP dose is recommended initially. We developed a new protocol with reduced-dose CHOP followed by rituximab and evaluated its efficacy. Additionally, we assessed early clinical diagnostic criteria and pathological diagnostic rates, and report these findings.

Study methods and analysis

In this study, patients aged 20 years or older with primary DEN-LBCL/IVL were enrolled, confirmed pathologically or meeting clinical diagnostic criteria (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=85*). Rapidly progressive cases began treatment based on clinical diagnosis. Exclusion criteria included suspected connective tissue disease/vasculitis, severe infections, prior chemotherapy, human immunodeficiency virus (HIV), human T-cell leukemia virus type 1 (HTLV-1), and hepatitis B virus (HBV) antigen positivity, among others. Written informed consent was obtained, the trial was approved by institutional review boards, registered in the UMIN Clinical Trials Registry (ID: 000001309), and conducted in accordance with the Declaration of Helsinki.

The first chemotherapy cycle involved two-thirds of the conventional dose of each CHOP drug, except for prednisolone. Rituximab was administered on day 7 if CD20 expression was confirmed. Dosage adjustments were permitted for patients with BM suppression, poor performance status (PS), or advanced age. From the second to sixth cycles, conventional R-CHOP therapy was given. Criteria for continuing to the second cycle included fever reduction, PS improvement, LDH normalization, and neutrophil count recovery. Treatment was discontinued if criteria were not met by day 28. After six R-CHOP cycles, peripheral blood stem cell (PBSC) harvesting was performed for younger patients (< 70 years) or those with improved PS. High-dose chemotherapy with autologous PBSC transplantation (autoPBSCT) followed PBSC harvesting. In older patients (≥ 70 years) or those with poor PS, additional chemotherapy with high-dose methotrexate (MTX) and rituximab was administered to prevent central nervous system (CNS) recurrence and improve prognosis. The protocols for PBSC harvesting and high-dose chemotherapy combined with autoPBSCT were not specified in this study. Preventative measures included sulfamethoxazole/trimethoprim to prevent Pneumocystis infection and additional antifungal agents. Patients positive for hepatitis B core or surface antibodies were monitored monthly for HBV-DNA and treated with antiviral agents if needed.

IVL rarely forms masses, so we created our own response evaluation criteria (Supplemental Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=85*). The primary endpoint was overall survival (OS), with secondary endpoints including complete remission (CR) rate, concordance rate between clinical diagnosis and pathologically confirmed diagnosis in clinically diagnosed patients, diagnostic yields of BM and RSB, and time to treatment failure (TTF). TTF was the interval from enrollment to disease progression or death. OS and TTF were analyzed using the Kaplan-Meier method.

Clinical trial outcomes and diagnostic evaluations

Patient characteristics

A total of 22 patients were recruited from six medical institutions between March 2006 and March 2016. There were 12 men and 10 women, with a median age of 74 years (range 52–89 years) (Supplemental Table S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=85*). The median follow-up for survivors was 35 months.

Survival and treatment outcomes

Six patients (38%) experienced recurrence, two of whom received salvage treatment and survived (117 and 124 months). Eleven patients died; five died during treatment before CR confirmation. Causes of death included pneumonia (n = 1), sepsis (n = 1), multiple organ failure (n = 2), and disease progression (n = 1). Four died after recurrence, and two in remission from complications. Median OS and TTF were 65 and 46 months, respectively (Figure 1A.1B).

Of 22 patients, 16 (73%) achieved CR/ CR unconfirmed (CRu), three had progressive Disease (PD), and three were not Evaluable (NE) (Table 1). The first patient died of organ failure after the first chemotherapy cycle, the second of pneumonia after the third cycle, and the last was removed after the first cycle due to bronchial pneumonia.

Diagnostic accuracy and effectiveness

Ten patients started treatment based on clinical criteria alone; eight were later confirmed with IVL by pathological examination, giving an 80% concordance rate. The remaining two were diagnosed with DEN-

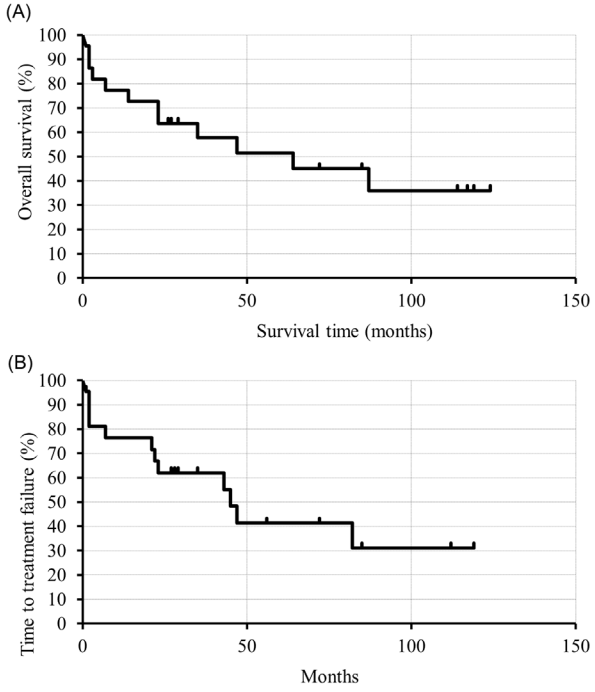

Figure 1. (A) Overall survival. The median overall survival (OS) was 65 months (11 deaths). Of these, five died during treatment without achieving complete response (CR). The causes of death included pneumonia (1), sepsis (1), multiple organ failure (2), and disease progression (1). Four patients died after recurrence, and two died while in remission of complications (one from cerebral infarction and the other from pneumonia). **(B) Time to treatment failure.** The median time to treatment failure (TTF) was 46 months, with six patients having recurrence. Of these, two patients received salvage treatment and were alive at the time of the last follow-up.

Table 1. Response

	All *n* = 22	R-CHOP *n* = 15	PBSCT+ *n* = 4	MTX+ *n* = 3
CR/Cru	16	9	4	3
PD	3	3	-	-
NE	3	3	-	-
Relapse	6	4	1	1

R-CHOP: R-CHOP therapy only. PBSCT+: Six cycles of R-CHOP, followed by PBSCT. MTX+: Six cycles of R-CHOP, followed by two cycles of high-dose MTX (2 g/m^2 as a single dose) and R-CHOP. CR: complete response, CRu: unconfirmed, PD: progressive disease, NE: not evaluable.

LBCL/IVL by BM smears, with monoclonal B-cell populations detected by flow cytometry.

BM examination diagnosed 14 (64%) of 22 patients with DEN-LBCL/IVL. RSB biopsy confirmed six (35%) of 17 patients. Three patients showed no lymphoma cells in BM or skin (Supplemental Table S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=85*).

Discussion

Most studies on IVL have examined a limited number of cases, often retrospectively, focusing on preexisting patient data. The standard treatment for IVL remains unestablished, with R-CHOP chemotherapy being the most administered regimen. A Japanese retrospective study (*11*) on 49 IVL patients treated with rituximab-containing chemotherapy reported an 82% CR rate, with progression-free survival (PFS) and OS rates at 2 years of 56% and 66%, respectively, aligning with outcomes in high-risk DLBCL patients classified by the IPI. In North America, a study (*12*) of 29 IVL patients revealed that 18 underwent first-line chemotherapy, with 15 completing it. Of those, 53% achieved CR, and the overall three-year survival rate was 42.7%, with a 64.2% event-free survival rate. In a retrospective study (*13*) of 12 patients with IVL conducted in China, 11 received R-CHOP therapy, and the overall response rate (ORR) and CR rate were 90.1% and 66.7%, respectively.

In the present study, the CR/CRu rate was 73%, with median OS and TTF of 65 and 46 months, respectively. To mitigate infusion reactions and severe BM suppression during the first chemotherapy cycle, a new regimen of dose-reduced CHOP (two-thirds of the normal dose) with delayed rituximab administration was used. The CR rate, OS, and TTF achieved were similar to those reported in previous studies (Supplemental Table S4, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=85*). Evaluations of high-dose chemotherapy combined with autoPBSCT in IVL patients are also limited to retrospective analyses. Meissner *et al.* (*14*) conducted a study on 11 IVL patients registered in the European Society for Blood and Marrow Transplantation database, treated with autoPBSCT. They reported two-year PFS and OS rates of 81% and 91%, respectively. Similarly, Kato *et al.* (*16*) retrospectively analyzed 61 IVL patients treated with autoPBSCT, reporting three-year OS and PFS rates of 89.1% and 82.8%, respectively.

In our study, four patients underwent high-dose chemotherapy with autoPBSCT. One patient experienced recurrence, but the others remained alive without recurrence at the time of analysis, with TTFs of 35, 43, 112, and 119 months, respectively. Three elderly patients ineligible for autoPBSCT received additional chemotherapy, including high-dose MTX. One had a recurrence in the BM, one died in remission from cerebral infarction, and the third was alive without recurrence at analysis.

Next, we assessed the concordance rate between clinical and pathological diagnoses in patients diagnosed using clinical criteria alone (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=85*). Of the 22 patients in the clinical trial, 10 started treatment based solely on these criteria. Eight were later definitively diagnosed with IVL *via* pathological examination, resulting in an 80% diagnostic concordance rate, which is satisfactorily high. Given the rapid progression of DEN-LBCL/IVL, patients often become too advanced for successful

treatment while awaiting a pathological diagnosis. The clinical diagnostic criteria used in this study are thus highly beneficial but do not always ensure an accurate diagnosis. Close monitoring and assessment are crucial when initiating treatment without a pathological diagnosis. Patients should be well-informed about their diagnosis and treatment. Ideally, treatment should commence after a definitive pathological diagnosis.

The diagnostic yields of BM examination and RSB were also evaluated. BM examination identified 14 patients with DEN-LBCL/IVL (64%). RSB were performed on 17 patients, detecting IVL in six (35%). Only three patients showed no infiltration in the BM or skin. Two of these were definitively diagnosed with IVL in other organs (spleen and brain). The last patient only had a clinical diagnosis of DEN-LBCL/IVL. RSB should be performed on all eligible patients as it is minimally invasive. Matsue *et al.* (*6*) reported a 71% positivity rate in RSB. In a study conducted by Maekawa *et al.* (*17*) in nine patients with IVL, they found significant detection rates of tumor cells in various skin layers, suggesting random skin biopsy using a 4-mm punch is effective for patients with thrombocytopenia and coagulation abnormalities. In the present study, only two patients were diagnosed with IVL by skin biopsy alone. However, because this procedure is minimally invasive, it should be performed on all eligible patients.

Shimada *et al.* (*18*) conducted a multicenter, prospective study on a chemoimmunotherapy regimen of R-CHOP followed by rituximab with high-dose MTX and additional R-CHOP cycles. The study showed this regimen's effectiveness in treating IVL patients. However, the included cases had relatively favorable conditions, with better PS and organ function. In practice, many IVL cases are severe and life-threatening; thus, after rapid BM and skin biopsy examination, chemotherapy may need to start before a definitive pathological diagnosis if the patient's PS deteriorates. Respecting Shimada's data, we conducted this trial for more severe cases. Early treatment based on clinical diagnostic criteria could save many DEN-LBCL/IVL patients, especially those of advanced age or with multiple organ failure.

Our study had several limitations. First, the case enrollment period was very long, spanning 10 years, with only 22 patients registered, averaging just 2.2 cases per year. Second, due to the long enrollment period, the observation period varied greatly according to the date of registration; however, the survival curves did not reach the plateau phase in both OS and TTF.

In conclusion, patients with DEN-LBCL, including IVL, were effectively treated with a new chemoimmunotherapy regimen starting with dose-reduced CHOP and delayed rituximab, followed by conventional R-CHOP. The clinical diagnostic criteria were helpful for early intervention. Larger studies are needed to confirm these findings.

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References

1. Pfleger L, Tappeiner J. On the recognition of systematized endotheliomatosis of the cutaneous blood vessels (reticuloendotheliosis?). Hautarzt. 1959; 10:359-363. (in Greman)
2. Nakamura S, Ponzoni M, Campo E. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. In: Swerdlow SH *et al.* (eds) Intravascular large B-cell lymphoma, rev 4th edition. IARC, Lyon, 2007; pp.317-318.
3. Murase T, Nakamura S, Kawauchi K, Matsuzaki H, Sakai C, Inaba T, Nasu K, Tashiro K, Suchi T, Saito H. An Asian variant of intravascular large B-cell lymphoma: Clinical, pathological and cytogenetic approaches to diffuse large B-cell lymphoma associated with haemophagocytic syndrome. Br J Haematol. 2000; 111:826-834.
4. Suzuki Y, Kohno K, Matsue K, Sakakibara A, Ishikawa E, Shimada S, Shimada K, Mabuchi S, Takahara T, Kato S, Nakamura S, Satou A. PD-L1 (SP142) expression in neoplastic cells predicts a poor prognosis for patients with intravascular large B-cell lymphoma treated with rituximab-based multi-agent chemotherapy. Cancer Med. 2000; 9:4768-4776.
5. Masaki Y, Dong L, Nakajima A, *et al*. Intravascular large B cell lymphoma: Proposed of the strategy for early diagnosis and treatment of patients with rapid deteriorating condition. Int J Hematol. 2009; 89:600-610.
6. Matsue K, Asada N, Odawara J, Aoki T, Kimura S, Iwama K, Fujiwara H, Yamakura M, Takeuchi M. Random skin biopsy and bone marrow biopsy for diagnosis of intravascular large B cell lymphoma. Ann Hematol. 2011; 90:417-421.
7. The international Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993; 329:987-994.
8. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, Glick JH, Coltman CA Jr, Miller TP. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med. 1993; 328:1002-1006.
9. Ferreri AJ, Campo E, Ambrosetti A, *et al*. Anthracycline-based chemotherapy as primary treatment for intravascular lymphoma. Ann Oncol. 2004; 15:1215-1221.
10. Murase T, Yamaguchi M, Suzuki R, Okamoto M, Sato Y, Tamaru J, Kojima M, Miura I, Mori N, Yoshino

T, Nakamura S. Intravascular large B-cell lymphoma (IVLBCL): A clinicopathologic study of 96 cases with special reference to the immunophenotypic heterogeneity of CD5. Blood. 2007; 109:478-485.
11. Shimada K, Matsue K, Yamamoto K, *et al*. Retrospective analysis of intravascular large B-cell lymphoma treated with rituximab-containing chemotherapy as reported by the IVL study group in Japan. J Clin Oncol. 2008; 26:3189-3195.
12. Brunet V, Marouan S, Routy JP, Hashem MA, Bernier V, Simard R, Petrella T, Lamarre L, Théorêt G, Carrier C, Knecht H, Fleury I, Pavic M. Retrospective study of intravascular large B-cell lymphoma cases diagnosed in Quebec: A retrospective study of 29 case reports. Medicine (Baltimore). 2017; 96:e5985.
13. Zhang Y, Zhu TN, Sun J, Zhong DR, Zhang W, Zhou DB. Clinical characteristics of intravascular large B cell lymphoma: A single-center retrospective study. Zhonghua Xue Ye Xue Za Zhi. 2018; 39:1004-1009.
14. Meissner J, Finel H, Dietrich S, *et al*. Autologous hematopoietic stem cell transplantation for intravascular large B-cell lymphoma: the European Society for Blood and Marrow Transplantation experience. Bone Marrow Transplant. 2017; 52:650-652.
15. Kato K, Ohno Y, Kamimura T, *et al*. Long-term remission after high-dose chemotherapy followed by auto-SCT as consolidation for intravascular large B-cell lymphoma. Bone Marrow Transplant. 2014; 49:1543-1544.
16. Kato K, Mori T, Kim SW, *et al*. Outcome of patients receiving consolidative autologous peripheral blood stem cell transplantation in the frontline treatment of intravascular large B-cell lymphoma: Adult Lymphoma Working Group of the Japan Society for Hematopoietic Cell Transplantation. Bone Marrow Transplant. 2019; 54:1515-1517.
17. Maekawa T, Komine M, Murata S, Fukushima N, Ohtsuki M. Random skin biopsy of patients with intravascular large B-cell lymphoma associated with thrombocytopenia and coagulation abnormalities: Proposal of a modified biopsy method. J Dermatol. 2015; 42:318-321.
18. Shimada K, Yamaguchi M, Atsuta Y, *et al*. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone combined with high-dose methotrexate plus intrathecal chemotherapy for newly diagnosed intravascular large B-cell lymphoma (PRIMEUR-IVL): A multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020; 21:593-602.

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