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Treatments and Outcomes of Newly Diagnosed CD5-Positive Diffuse Large B-Cell Lymphoma: A Multi-Institutional Observational Study

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ABSTRACT

CD5-positive diffuse large B-cell lymphoma (CD5+ DLBCL) is characterized by a poor prognosis and frequent central nervous system (CNS) relapse. Sandwich therapy comprising dose-adjusted (DA)-EPOCH-R (etoposide, prednisolone, vincristine,

cyclophosphamide, doxorubicin, and rituximab) and high-dose methotrexate (HD-MTX) (DA-EPOCH-R/HD-MTX) showed excellent efficacy and manageable safety in a phase II study of patients diagnosed with stage II–IV CD5+ DLBCL. To validate the results of that study and elucidate the current state of treatment for CD5+ DLBCL, we retrospectively analyzed the outcomes of patients with CD5+ DLBCL diagnosed between 2016 and 2021 who received anthracycline-containing chemotherapy with rituximab. Among the 346 patients evaluated, 62 (18%) received DA-EPOCH-R/HD-MTX. The median follow-up time was 43 months. In 55 patients with stage II–IV disease treated with DA-EPOCH-R/HD-MTX, the 2-year overall survival (OS), progression-free survival, and cumulative incidence of CNS relapse were 87% (95% CI, 73%–94%), 76% (95% CI, 61%–86%), and 7.3% (95% CI, 2.4%–16%), respectively. There were no treatment-related deaths. Febrile neutropenia occurred in 18 (33%) patients. Multivariate analysis of the 346 patients identified elevated serum lactate dehydrogenase levels, multiple extranodal involvement, no intrathecal MTX (IT-MTX), and no DA-EPOCH-R/HD-MTX as independent risk factors for OS. Only one CNS relapse event was observed in 28 patients who received both HD-MTX and IT-MTX. Our study provides real-world data on the treatments and outcomes of a large number of patients. The favorable survival and manageable toxicity of DA-EPOCH-R/HD-MTX have been validated in clinical settings. The use of HD-MTX and IT-MTX might be effective for preventing CNS relapse in patients with CD5+ DLBCL.

1 | Introduction

CD5-positive diffuse large B-cell lymphoma (CD5+ DLBCL) comprises 5%–10% of DLBCL-not otherwise specified (NOS) and is associated with elderly onset, advanced stage at diagnosis, elevated serum lactate dehydrogenase (LDH) levels, and frequent involvement of extranodal sites [1–5]. Ninety percent of CD5+ DLBCL cases are positive for BCL2 according to immunohistochemistry, and up to 80% of CD5+ DLBCL cases are classified as the activated B-cell (ABC) type by gene expression profiling [5–7]. Direct sequencing and next-generation sequencing revealed that myeloid differentiation primary response 88 (*MYD88*) (L265P) and *CD79B* mutations are detected in 33%–52% and 38% of patients with CD5+ DLBCL, respectively [8, 9].

Patients with CD5+ DLBCL exhibit significantly worse survival than those with CD5-negative DLBCL after treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) [10–15]. The dose-adjusted (DA)-EPOCH-R (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab) regimen is known to have excellent efficacy in treating BCL2-positive DLBCL [16, 17]. CD5+ DLBCL is also characterized by a high incidence of central nervous system (CNS) relapse (13%), involving mainly the brain parenchyma [2, 4]. High-dose methotrexate (HD-MTX), which penetrates the blood–brain barrier, has been used as prophylaxis for CNS relapse in high-risk patients with DLBCL [18, 19]. To explore a more effective first-line chemotherapy for CD5+ DLBCL, we conducted a phase II study of a sandwich therapy of DA-EPOCH-R combined with HD-MTX (DA-EPOCH-R/HD-MTX) for newly diagnosed stage II–IV CD5+ DLBCL patients (UMIN000008507). Two cycles of HD-MTX were added between the fourth and fifth cycles of DA-EPOCH-R because CNS relapse events in CD5+ DLBCL patients treated with (R)-chemotherapy are often documented during first-line treatment [2, 4]. That study enrolled 47 eligible patients and showed excellent efficacy, as follows: 2-year overall survival (OS), 89%; progression-free survival (PFS), 79%; and cumulative incidence of CNS relapse, 9% [20]. Major toxicity included grade 4 neutropenia in 46 (98%) patients, grade 4 thrombocytopenia in 12 (26%) patients, and febrile neutropenia in 31 (66%) patients.

Since the first publication of these results, DA-EPOCH-R/HD-MTX has been introduced in practice in Japan. The establishment of a standard therapy for rare diseases will require outcome studies investigating the relevance of new treatments in a real-world setting. To validate the results from the clinical trial of DA-EPOCH-R/HD-MTX and elucidate the current status and prognostic factors of CD5+ DLBCL, we conducted a large retrospective cooperative study of patients with CD5+ DLBCL diagnosed between 2016 and 2021 in Japan.

2 | Material and Methods

2.1 | Study Design

This was a multicenter retrospective study of patients with CD5+ DLBCL in Japan. The diagnosis of CD5+ DLBCL was made at each participating hospital according to the revised 4th edition WHO criteria as DLBCL, NOS with CD5 expression in tumor cells based on immunohistochemistry and/or flow cytometry. The data of consecutive patients diagnosed with CD5+ DLBCL from January 2016 to December 2021 were retrospectively collected from 30 hospitals. Subtyping of DLBCL cell-of-origin was determined based on Hans' criteria [21]. G-banding and fluorescence in situ hybridization studies for *MYC* were performed at the physician's discretion. In this study, we defined the retrospective validation DA-EPOCH-R/HD-MTX cohort as the cohort of patients who received DA-EPOCH-R followed by HD-MTX and additional cycle(s) of DA-EPOCH-R.

The purpose of this study was to validate the results from the clinical trial of DA-EPOCH-R/HD-MTX and elucidate the current status and prognostic factors of CD5+ DLBCL. Patients who had CNS involvement at diagnosis and those who had not received any anthracycline-containing chemotherapy with rituximab were excluded.

2.2 | Statistical Analysis

For validation analysis, the outcomes of stage II–IV patients who received DA-EPOCH-R/HD-MTX in our cohort were

compared with those of patients in the previous phase II study [20]. For analyses of clinical features, treatment choices, and prognostic factors, all eligible patients with CD5+ DLBCL were included.

The primary endpoint in this study was OS. The secondary endpoints were PFS, the cumulative incidence of CNS relapse, and toxicity. OS was defined as the time from the date of diagnosis to the date of death from any cause. PFS was defined as the time from the date of diagnosis to the earliest date of progression, relapse, or death from any cause. Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 5.0. The distributions of variables between the two groups were assessed using Fisher's exact test. Survival estimates were calculated using the Kaplan–Meier method. The cumulative incidence of CNS relapse was analyzed using Gray's test, with CNS relapse and death without CNS involvement as competing events. The 95% confidence intervals (CIs) were estimated using Greenwood's formula. The details of the univariate analysis, multivariate analysis, and propensity score-matched analysis are given in the Supporting Information S2: Methods. All p values were two-sided and had an overall significance level of 0.05. Statistical analyses were performed using the SPSS version 29 (IBM, NY, USA) package and EZR version 1.64 [22].

3 | Results

3.1 | Patient Characteristics

A total of 413 patients diagnosed with CD5+ DLBCL between January 2016 and December 2021 in 30 hospitals were retrospectively registered. Among the 413 patients, 22 were excluded because of an ineligible diagnosis or insufficient clinical information, 18 had CNS involvement at diagnosis, and 27 did not receive any anthracycline-containing chemotherapy with rituximab. Overall, 346 patients were deemed eligible (Figure S1). No patient had a past medical history of lymphoproliferative disorders, including chronic lymphocytic leukemia or small lymphocytic lymphoma.

The baseline clinical features and disease characteristics of all 346 patients are listed in Table 1. The median age at diagnosis was 71 (range, 23–92) years. Among them, 266 patients (77%) were older than 60 years, and 252 (73%) had stage III or IV disease. According to Hans' criteria, the non-germinal center B-cell (GCB) type accounted for 67% of the 274 patients examined. According to the CNS-International Prognostic Index (CNS-IPI), 144 (42%) patients were in the high-risk group.

MYC rearrangements were assessed by fluorescence in situ hybridization (n = 35) and G-banding (n = 159) in the entire retrospective cohort. G-banding results were obtained for 77 cases, and no results were obtained for 82 cases due to poor proliferation. There were no patients with double/triple-hit lymphoma according to the institutional diagnosis. *MYC* rearrangement was documented in 5 cases: two by fluorescence in situ hybridization, two by t(8;14) via G-banding, and one by adding 8(q24) via G-banding.

3.2 | First-Line Treatment

Among the 346 patients, 62 (18%) received DA-EPOCH-R/HD-MTX, and 284 (82%) were treated with the other R-chemo group (Supporting Information S2: Table S1). The regimens of the other R-chemo group were R-CHOP (n = 228, 66%), DA-EPOCH-R (n = 29), and R-pirarubicin (THP)-COP (n = 27). The median age was 67 years (range, 29–75) in the DA-EPOCH-R/HD-MTX group and 72 years (range, 23–92) in the other R-chemo group (Table 1). Although the DA-EPOCH-R/HD-MTX group tended to have more patients with Eastern Cooperative Oncology Group performance status (ECOG PS) > 1 than the other R-chemo group did (p = 0.09), the DA-EPOCH-R/HD-MTX group included significantly fewer patients aged > 60 years (p < 0.01).

For CNS prophylaxis, HD-MTX alone was used in 84 patients (24%), intrathecal (IT)-MTX alone was used in 69 (20%), and both HD-MTX and IT-MTX were used in 28 (8%) (Supporting Information S2: Table S2). The other 165 (48%) patients did not receive any CNS prophylaxis. Among the 144 patients in the high-risk group of the CNS-IPI, 68 (41%) received no CNS prophylaxis, 35 (42%) received HD-MTX, 27 (39%) received IT-MTX, and 14 (50%) received both HD-MTX and IT-MTX. Among the 28 patients who received both HD-MTX and IT-MTX, 5 (18%) and 6 (21%) patients had testis and paranasal sinus involvement, respectively.

3.3 | Validation Analysis of the Phase II Study of DA-EPOCH-R/HD-MTX in the Retrospective Validation Cohort

The baseline clinical features of 310 patients with stage II to IV CD5+ DLBCL are shown in Supporting Information S2: Table S3. DA-EPOCH-R/HD-MTX was selected for 55 (18%) patients with stage II–IV disease (Figure 1A). Eight cycles of DA-EPOCH-R were given in 31 patients, 7 in 13 patients, 6 in 8 patients, 5 in 2 patients, and 4 in 1 patient.

The median follow-up time was 43 months. The 2-year OS and PFS in the retrospective validation DA-EPOCH-R/HD-MTX cohort were 87% (95% CI, 73%–94%; Figure 1B) and 76% (95% CI, 61%–86%; Figure 1C), respectively. The 2-year cumulative incidence of CNS relapse was 7.3% (95% CI, 2.4%–16%; Figure 1D). Comparing the retrospective validation DA-EPOCH-R/HD-MTX cohort (n = 32) with the phase II DA-EPOCH-R/HD-MTX cohort (n = 32), there was no significant difference in the OS (p = 0.32, Figure 2A) or PFS (p = 0.93, Figure 2B) between the two groups in the propensity score-matched analysis. Survival analysis comparing stage II to IV patients who received DA-EPOCH-R/HD-MTX and those treated with other R-chemo in the entire retrospective cohort is summarized in the Supplementary Results (Figure S4).

The incidences of grade 3 to 4 adverse events observed during DA-EPOCH-R/HD-MTX are listed in Table 2. The grade 4 non-hematologic toxicities included infection (4%), tumor lysis syndrome (2%), and thrombosis (2%). The most common grade 3 non-hematologic adverse event was infection (11%). Febrile

TABLE 1 | Patient demographics and baseline clinical characteristics in the entire retrospective cohort (n = 346).

Characteristic	All patients (n = 346) n (%)	DA-EPOCH-R/HD-MTX (n = 62) n (%)	The other R-chemo (n = 284) n (%)	p[a]
Age (years)				
Median (range)	71 (23–92)	67 (29–75)	72 (23–92)	<0.01
≤ 60 years	80 (23)	26 (42)	54 (19)	
> 60 years	266 (77)	36 (58)	230 (81)	
Sex				
Male	187 (54)	32 (52)	155 (55)	0.68
Female	159 (46)	30 (48)	129 (45)	
Stage				
I-II	94 (27)	18 (29)	76 (27)	0.75
III-IV	252 (73)	44 (71)	208 (73)	
ECOG PS				
0 or 1	240 (69)	37 (60)	203 (72)	0.09
> 1	106 (31)	25 (40)	81 (29)	
Extranodal site(s)				
0 or 1	201 (58)	31 (50)	170 (60)	0.16
> 1	145 (42)	31 (50)	114 (40)	
Serum LDH				
Normal	100 (29)	13 (21)	87 (31)	0.16
Elevated	246 (71)	49 (79)	197 (69)	
IPI				
Low/low-int	128 (37)	23 (37)	105 (37)	1.00
High-int/high	218 (63)	39 (63)	179 (63)	
B symptoms				
Absent	242 (71)	40 (66)	202 (72)	0.35
Present	100 (29)	21 (34)	79 (28)	
Unknown	4	1	3	
COO (Hans)				
GCB	92 (34)	13 (27)	79 (35)	0.32
Non-GCB	182 (66)	36 (74)	146 (65)	
Unknown	72	13	59	
CNS-IPI				
Low	59 (17)	13 (21)	46 (16)	—
Intermediate	143 (41)	22 (36)	121 (43)	
High	144 (42)	27 (44)	117 (41)	

Abbreviations: CNS, central nervous system; COO, cell-of-origin; DA-EPOCH-R, dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin and rituximab; ECOG PS, Eastern Cooperative Group Performance Status; GCB, germinal center B; HD-MTX, high-dose methotrexate; int, intermediate; IPI, International Prognostic Index; LDH, lactate dehydrogenase; R-chemo, rituximab-containing chemotherapy.
[a]DA-EPOCH-R/HD-MTX versus the other R-chemo.

neutropenia was reported in 18 (33%) patients. There were no severe renal adverse events or treatment-related deaths. There was no obvious increase in severe toxicity between the patients treated with 8 cycles of DA-EPOCH-R and those who received fewer than 8 cycles of DA-EPOCH-R in the retrospective validation DA-EPOCH-R/HD-MTX cohort (Supporting Information S2: Table S4).

3.4 | Survival Analysis of the Entire Retrospective Cohort

In all 346 patients, OS and PFS at 2 years were 80% and 67%, respectively (Figure S2A,B). Univariate analysis for OS identified five risk factors, namely, IPI, serum hypoalbuminemia, elevated soluble interleukin-2 receptor levels, no use of IT-MTX,

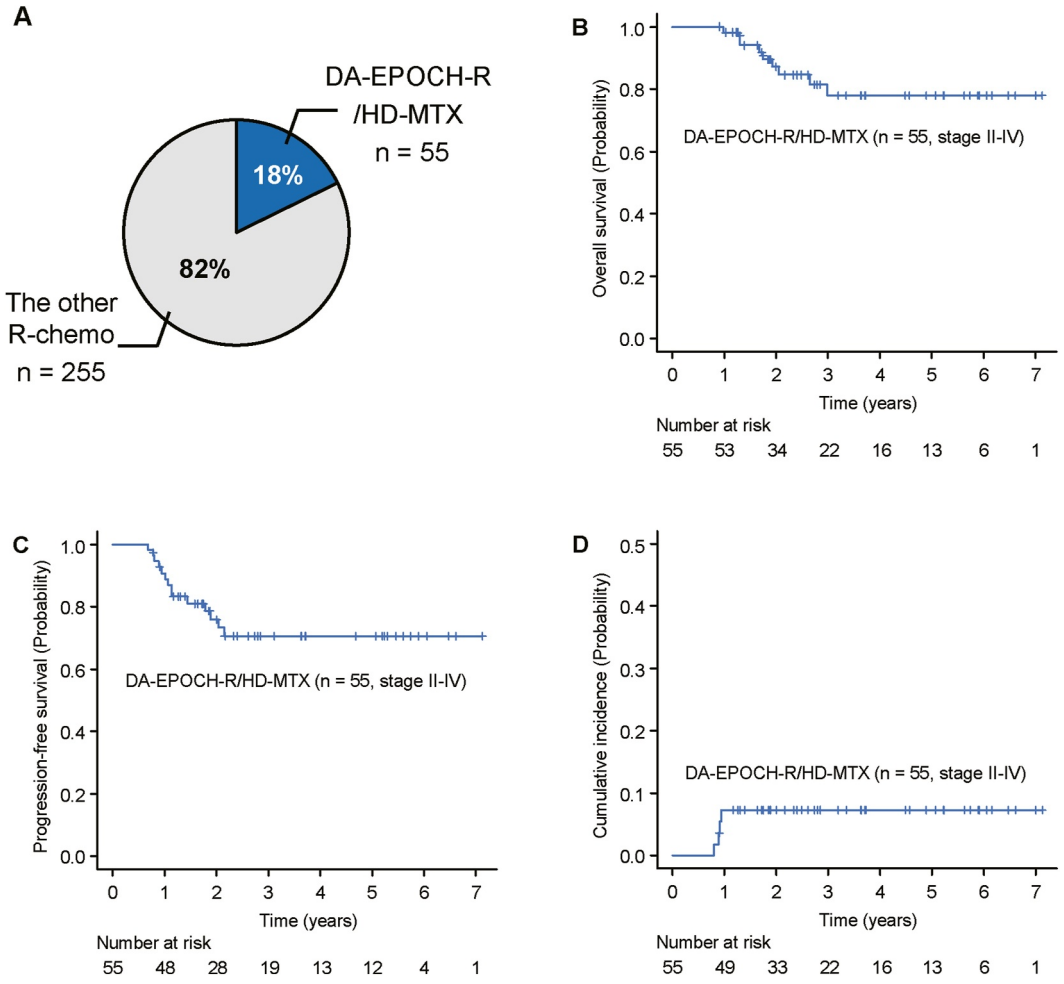

FIGURE 1 | Proportion of first-line treatment regimen (A). Overall survival (B), progression-free survival (C), and cumulative incidence of CNS relapse (D) in the retrospective validation DA-EPOCH-R/HD-MTX cohort. CNS, central nervous system; DA-EPOCH-R, dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab; HD-MTX, high-dose methotrexate; R-chemo, rituximab-containing chemotherapy.

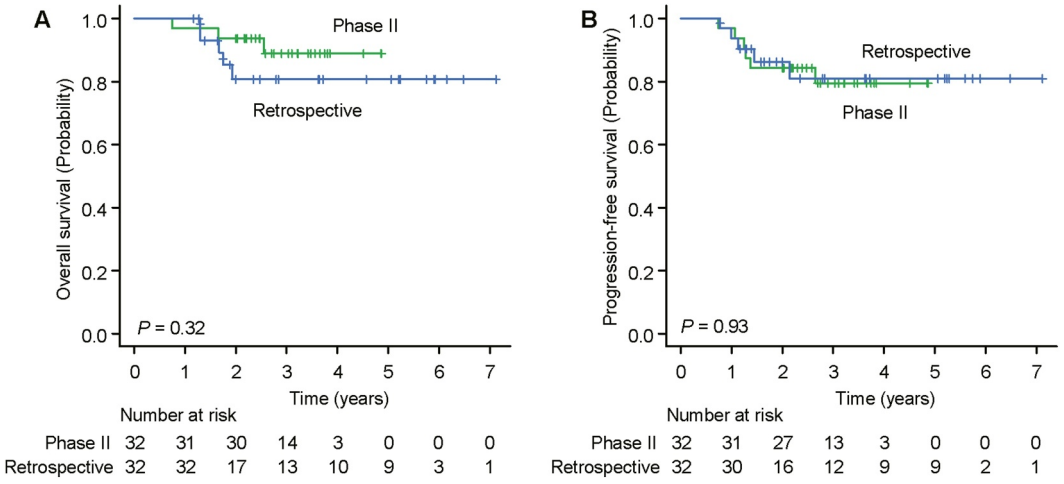

FIGURE 2 | Overall survival (A) and progression-free survival (B) in the retrospective validation DA-EPOCH-R/HD-MTX cohort compared with those of the phase II DA-EPOCH-R/HD-MTX cohort using propensity score-matched analysis. DA-EPOCH-R, dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab; HD-MTX, high-dose methotrexate; R-chemo, rituximab-containing chemotherapy.

and no use of DA-EPOCH-R/HD-MTX. Multivariate analysis of OS identified elevated serum LDH (hazard ratio [HR], 2.75; 95% CI, 1.35–5.58; $p = 0.005$), > 1 extranodal involvement (HR, 2.73; 95% CI, 1.63–4.56; $p < 0.001$), IT-MTX (HR, 0.47; 95% CI, 0.28–0.79; $p = 0.004$), and DA-EPOCH-R/HD-MTX (HR, 0.36; 95% CI, 0.18–0.73; $p = 0.005$) as independent prognostic factors (Table 3).

TABLE 2 | Adverse events in the retrospective validation DA-EPOCH-R/HD-MTX cohort (stage II–IV, $n = 55$).

	Grade 3 *n* (%)	Grade 4 *n* (%)
Hematologic adverse events		
Neutropenia	2 (4)	48 (87)
Leukopenia	3 (5)	43 (78)
Thrombocytopenia	15 (27)	16 (29)
Anemia	29 (53)	2 (4)
Febrile neutropenia	18 (33)	0
Non-hematologic adverse events		
AST increased	2 (4)	0
ALT increased	3 (5)	0
Hyponatremia	1 (2)	0
Constipation	2 (4)	0
Nausea	2 (4)	0
Infection	6 (11)	2 (4)
Allergic reaction	1 (2)	0
Tumor lysis syndrome	1 (2)	1 (2)
Peripheral sensory neuropathy	2 (4)	0
Pneumonitis	1 (2)	0
Thrombosis	0	1 (2)
Others	3 (5)	0

Note: Grade 3 Gastrointestinal disorders - Other, specific (intestinal emphysema) ($n = 1$), mucositis ($n = 1$), and fatigue ($n = 1$) were observed.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DA-EPOCH-R, dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab; HD-MTX, high-dose methotrexate.

TABLE 3 | Univariate and multivariate analyses for factors affecting the OS in the entire retrospective cohort ($n = 346$).

	Univariate			Multivariate		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age > 60 years	2.04	1.14–3.60	0.01	1.39	0.78–2.49	0.27
Elevated serum LDH	3.63	1.94–6.81	< 0.001	2.75	1.35–5.58	0.005
ECOG PS > 1	1.94	1.29–2.93	0.002	1.31	0.82–2.10	0.26
Stage III or IV	1.75	1.04–2.96	0.04	0.64	0.33–1.25	0.19
Extranodal sites > 1	2.29	1.52–3.46	< 0.001	2.73	1.63–4.56	<0.001
Hypoalbuminemia	2.29	1.40–3.73	< 0.001	1.16	0.68–2.00	0.58
Elevated sIL-2R	3.31	1.22–9.01	0.02	1.23	0.35–4.30	0.75
Male sex	1.20	0.79–1.80	0.39	—	—	—
Non-GCB (Hans)	1.22	0.73–2.02	0.45	—	—	—
HD-MTX	0.75	0.48–1.17	0.20	—	—	—
IT-MTX	0.57	0.35–0.93	0.03	0.47	0.28–0.79	0.004
Both HD-MTX and IT-MTX	0.74	0.34–1.60	0.45	—	—	—
DA-EPOCH-R/HD-MTX	0.51	0.27–0.99	0.046	0.36	0.18–0.73	0.005

Abbreviations: CD5+ DLBCL, CD5-positive diffuse large B-cell lymphoma; CI, confidence interval; DA-EPOCH-R, dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab; ECOG PS, Eastern Cooperative Group Performance Status; GCB, germinal center B; HD-MTX, high-dose methotrexate; HR, hazard ratio; IT-MTX, intrathecal methotrexate; LDH, lactate dehydrogenase; OS, overall survival; sIL-2R, soluble interleukin-2 receptor.

3.5 | Analysis of CNS Relapse in the Entire Retrospective Cohort

Among all 346 patients, the cumulative incidence of CNS relapse at 2 years was 8.5% (Figure S2C). Univariate analysis revealed that a high CNS-IPI was a risk factor for CNS relapse (HR, 2.20; 95% CI, 1.09–4.43; $p = 0.03$), and patients with > 1 extranodal involvement (HR, 1.83; 95% CI, 0.91–3.67; $p = 0.09$), bone marrow involvement (HR, 1.98; 95% CI, 0.97–4.04; $p = 0.06$), and paranasal sinus involvement (HR, 2.41; 95% CI, 0.96–6.09; $p = 0.06$) tended toward CNS relapse (Supporting Information S2: Table S5). Among the 5 cases with *MYC* rearrangement, CNS relapse was not observed.

The cumulative incidence of CNS relapse at 2 years in patients who received HD-MTX ($n = 112$) and those who did not ($n = 234$) was 8.1% and 8.6%, respectively. There were no significant differences in the cumulative incidence of CNS relapse between the two groups ($p = 0.89$) (Figure 3B). The cumulative incidence of CNS relapse at 2 years in patients who were treated with IT-MTX ($n = 97$) was 7.5%, whereas that in patients who did not receive IT-MTX ($n = 249$) was 8.9% (Figure 3C). There were no significant differences in the cumulative incidence of CNS relapse between the two groups ($p = 0.61$). The cumulative incidence of CNS relapse at 2 years was 9.6%, 9.0%, 3.7% ($n = 1$), and 8.5% for the HD-MTX alone, IT-MTX alone, both HD-MTX and IT-MTX, and no prophylaxis groups, respectively (Figure 3D). There were no significant differences in the cumulative incidence of CNS relapse among the four groups.

3.6 | Patterns of Progression and Salvage Therapy

During the follow-up period, 123 patients experienced disease progression. The 1-year OS after disease progression in patients who experienced disease progression was 47% (Figure S3).

Among the 123 patients, 32 patients (26%) experienced disease progression with CNS involvement, and 91 patients (74%) experienced systemic progression without CNS involvement. Among the 32 patients, 27 experienced isolated relapse in the CNS, and 5 experienced concurrent systemic relapse

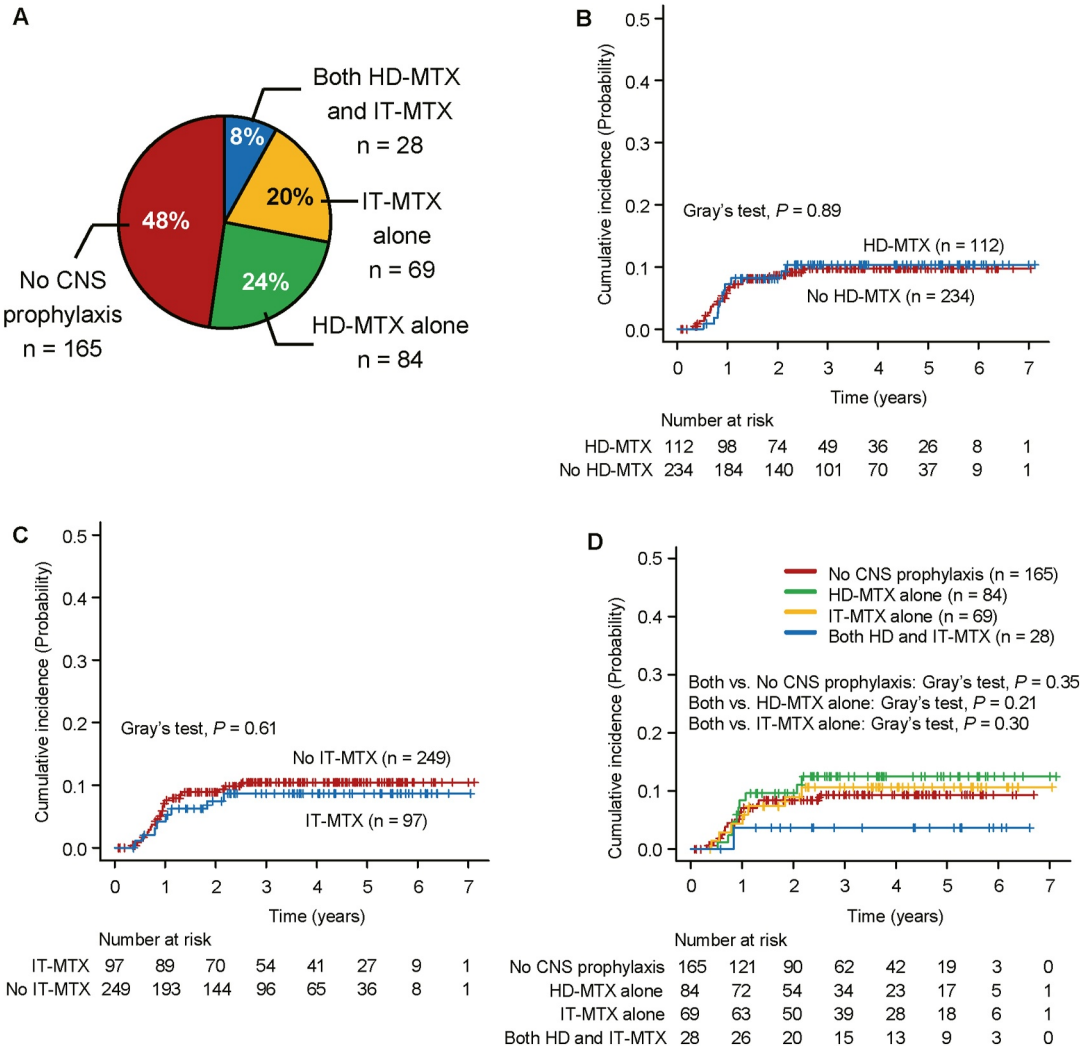

FIGURE 3 | Proportion of CNS prophylaxis (A). The cumulative incidence of CNS relapse in patients with CD5+ DLBCL treated with HD-MTX (B), IT-MTX (C), or a CNS prophylaxis strategy (D) among the entire retrospective cohort. CD5+ DLBCL, CD5-positive diffuse large B-cell lymphoma; CNS, central nervous system; HD-IT-MTX, intrathecal methotrexate; MTX, high-dose methotrexate.

(Supporting Information S2: Table S2). The brain parenchyma was the most common site of CNS relapse (n = 23, 72%).

Among the patients with disease progression after first-line treatment, 15 and 3 patients underwent autologous and allogenic hematopoietic stem cell transplantation, respectively. Chimeric antigen receptor T-cell therapy was performed for 5 patients.

4 | Discussion

To our knowledge, this is the largest study on the treatments and outcomes of patients with CD5+ DLBCL in a real-world setting. Our results confirmed the favorable survival and manageable toxicity of DA-EPOCH-R/HD-MTX in clinical practice. Our study provides additional information on CNS prophylaxis during first-line treatment of CD5+ DLBCL.

Compared with patients in the phase II DA-EPOCH-R/HD-MTX cohort [20], DA-EPOCH-R/HD-MTX was selected for more patients with ECOG PS > 1 at initial diagnosis in the retrospective validation DA-EPOCH-R/HD-MTX cohort (46% vs. 4%). According to the propensity score-matched analysis, there was no significant difference in OS or PFS between the retrospective validation DA-EPOCH-R/HD-MTX cohort and the phase II DA-EPOCH-R/HD-MTX cohort. The favorable efficacy of DA-EPOCH-R/HD-MTX for patients with stage II to IV CD5+ DLBCL was validated in practice. The OS of the DA-EPOCH-R/HD-MTX group tended to be better than that of the other R-chemo group in the propensity score-matched analysis. It should be noted that the survival benefit of DA-EPOCH-R/HD-MTX in this study was not clear, considering immortal time biases until the patients received DA-EPOCH-R followed by HD-MTX and additional cycle(s) of DA-EPOCH-R. The manageable toxicity of DA-EPOCH-R/HD-MTX in a clinical trial was confirmed in the retrospective validation DA-EPOCH-R/HD-MTX cohort. The incidence of cardiac events, peripheral neuropathy, and thrombosis was low and comparable to the incidence reported in the phase II DA-EPOCH-R/HD-MTX cohort. Febrile neutropenia occurred at a high rate (65%) in the phase II DA-EPOCH-R/HD-MTX cohort [20], and the incidence was reduced to 33% in the retrospective validation DA-EPOCH-R/HD-MTX cohort. There was no treatment-related death. The grade 3 or higher adverse events that were not observed in the phase II DA-EPOCH-R/HD-MTX cohort were grade 3 intestinal emphysema (n = 1) and grade 3 fatigue (n = 1). These adverse events were manageable. To exclude patients who received DA-EPOCH-R/HD-MTX in the phase II DA-EPOCH-R/HD-MTX cohort [20], we collected data from patients diagnosed with CD5+ DLBCL from 2016 to 2021. DA-EPOCH-R/HD-MTX requires hospitalization and is more complicated than R-CHOP. These factors may explain why only 18% of patients with stage II to IV disease received DA-EPOCH-R/HD-MTX as first-line treatment in practice.

DA-EPOCH-R/HD-MTX was identified as an independent favorable prognostic factor for OS in the entire retrospective cohort by multivariate analysis. However, a single-institution retrospective analysis reported that DA-EPOCH-R therapy alone did not improve the prognosis of patients with CD5+ DLBCL [23]. A possible reason for this difference is that many patients with CD5+ DLBCL are divided into a high-risk CNS-IPI group or a non-GCB group, both of which are associated with a high incidence of CNS relapse [24]. In the entire retrospective cohort, 42% of the patients were in the high-risk group for CNS-IPI, and 67% were in the non-GCB group. A subgroup analysis of an international observational study of HD-MTX as CNS prophylaxis in high-risk aggressive B-cell lymphoma patients showed that no patient experienced CNS progression after achieving a complete response with DA-EPOCH-R-like therapy and HD-MTX [25]. Therefore, the addition of HD-MTX to DA-EPOCH-R might confer benefits in the first-line treatment of CD5+ DLBCL.

Although HD-MTX and IT-MTX are often used for CNS prophylaxis in DLBCL patients [18, 19, 26], there is no optimal CNS prophylaxis strategy based on the results of randomized controlled trials. Thus, we analyzed CNS prophylaxis in CD5+ DLBCL patients using the largest number of patients. The cumulative incidence of CNS relapse at 2 years in both the HD-MTX and IT-MTX groups was low (3.7%), although not many patients were analyzed (n = 28). Large retrospective studies have shown that HD-MTX alone is not effective for CNS prophylaxis in patients with DLBCL [27–29]. Moreover, IT-MTX alone was not effective for CNS prophylaxis in patients with DLBCL whose CNS-IPI was high [24]. A systematic review showed that a lack of IT-MTX was not an independent factor for CNS relapse [30]. The possible efficacy of combination therapy with HD-MTX and IT-MTX for preventing CNS relapse warrants further investigation.

MYC rearrangements was present in 20% of cases with secondary CNS involvement with DLBCL (SCNSL) [31]. Among the entire retrospective cohort, 5 cases with *MYC* rearrangements did not have CNS involvement. Compared with those of systemic DLBCL, the similarities between SCNSL and primary CNS lymphoma (PCNSL) are in terms of antigen presentation and immune surveillance mechanism aberrations [31]. PCNSL is related to the MCD subtype, which is characterized by *MYD88*L265P and/or *CD79B* mutations [32, 33]. Similar to the 40% of cases with SCNSL [31], cases with CD5+ DLBCL harboring *MYD88*L265P and *CD79B* mutations account for 33%–52% and 38% respectively [8, 9]. Thus, patients with CD5+ DLBCL might develop CNS involvement via immune evasion from the tumor microenvironment.

Possible limitations of this retrospective study include the heterogeneity of the treatment selection and the sparse information from molecular analyses. Owing to the retrospective nature of this study, we have no data on COO molecular typing, CD5 gene expression, or *MYC* mutations. We could not perform additional studies of the tumor microenvironment because of the lack of sufficient clinical samples. A subgroup analysis of a phase III study for untreated DLBCL has shown that polatuzumab vedotin combined with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) was effective for ABC DLBCL [34]. Since CD5+ DLBCL is usually characterized as ABC DLBCL [5–7], pola-R-CHP or pola-R-CHP combined with HD-MTX might be effective for this disease, requiring further investigation. DA-EPOCH-R/HD-MTX may remain a reasonable treatment option, as supported by the results of the phase II

study [20] and this study focused on CD5+ DLBCL. Another study reported that the CD5 gene expression signature is a useful biomarker for identifying DLBCLs sensitive to Bruton's tyrosine kinase inhibition [35]. In conclusion, our present study reveals the current state of first-line treatment for CD5+ DLBCL, including CNS prophylaxis. Further investigations are warranted to establish an optimal treatment for CD5+ DLBCL in the era of precision medicine.

Author Contributions

K.M. and M.Y. designed the study, interpreted the data and wrote the manuscript; Y.N. interpreted the data, performed the statistical analysis and wrote the manuscript; N.A. confirmed the pathological diagnosis from case report forms; K.O., K.I., K.K. and R.S. interpreted the data; the other authors provided the clinical data; and all the authors critically reviewed and approved the manuscript.

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Ethics Statements

This study was approved by the institutional review board, performed in accordance with the Declaration of Helsinki, and conducted according to the national ethical guidelines [36]. This study was registered at the UMIN Clinical Trials Registry as #UMIN000049460.

Conflicts of Interest

Y.N. reports grants from AstraZeneca, Genmab, Incyte, AbbVie, Eisai, Takeda, Otsuka, Chugai, Asahi Kasei, Sumitomo Pharma and Kyowa Kirin and honoraria from Chugai and Nippon Shinyaku. K.M. reports grants from Eisai, Takeda, Nippon Shinyaku, Otsuka, Chugai, Asahi Kasei, Sumitomo Pharma, Kyowa Kirin and Zenyaku and honoraria from Chugai, SymBio, Janssen, Eisai, Nippon Shinyaku, AstraZeneca, Bristol Myers Squibb, Meiji Seika, AbbVie, Novartis, Incyte, Asahi Kasei, Ono, Kyowa Kirin and Genmab. D.M. reports grants from Amgen, Celgene, Kyowa Kirin, Novartis, Chugai, Ono, Takeda, Janssen, Sanofi, Otsuka, Bristol Myers Squibb, Astellas, Eisai, AbbVie, Taiho, MSD and Pfizer; consulting fees from Pfizer and honoraria from Ono, Celgene, Nippon Shinyaku, Janssen, Mundipharma, Eisai, Chugai, Kyowa Kirin, MSD, Zenyaku, Sanofi, SymBio, Takeda, AbbVie, Bristol Myers Squibb and AstraZeneca. H.T. reports honoraria from AstraZeneca, Bristol Meyers Squibb, Chugai, Janssen, Kyowa Kirin, Meiji Seika, Nippon Shinyaku, Mundipharma, Takeda, SymBio, Ono, Eisai and Sanofi. K.S. reports grants from AbbVie, Incyte, GSK, Sanofi, Novartis, Pfizer, Bristol Myers Squibb, Janssen, BeiGene, Kyowa Kirin, Ono, Otsuka and Chugai and honoraria from Bristol Myers Squibb, Sanofi and Janssen. E.N. reports honoraria from Chugai, Sumitomo Pharma, Kyowa Kirin, Janssen, Mundipharma, AstraZeneca, Ono, Takeda, Meiji Seika, Novartis, Bristol Myers Squibb and Nippon Kayaku. N. Takayama reports grants from Chugai, Takeda, Kyowa Kirin and Asahi Kasei and honoraria from AbbVie, Novartis, Janssen, Ono, Pfizer, Bristol Myers Squibb, Sanofi, Otsuka, Meiji Seika, Chugai, Takeda, Kyowa Kirin and Asahi Kasei. S. M. reports honoraria from Chugai, SymBio and Takeda. M. Yoshida reports honoraria from Takeda, Novartis and Astellas. M.N. reports grants from SymBio, Chugai and Kyowa Kirin and honoraria from Chugai, Kyowa Kirin, Eisai, Takeda, Nippon Shinyaku, Janssen, Sumitomo Pharma, AstraZeneca, AbbVie, SymBio, Bristol Myers Squibb, Genmab, Ono and Otsuka. I.T. reports grants from Asahi Kasei, Chugai, Eisai, Kyowa Kirin, Nippon Shinyaku, Otsuka, Sumitomo Pharma and Takeda and honoraria from AbbVie, Alexion, Asahi Kasei, Astellas, AstraZeneca, Bristol Myers Squibb, Chugai, CSL Behring, Eisai, Janssen, Kyowa Kirin, Nippon Shinyaku, Novartis, Novo Nordisk, Otsuka, Pfizer, Sanofi, Sumitomo Pharma, SymBio and Takeda. N.A. reports honoraria from Takeda and Eisai. K.I. reports grants from Chugai, Bristol Myers Squibb, Incyte, Genmab, LOXO Oncology, Daiichi Sankyo, Beigene, AbbVie, AstraZeneca, Regeneron, Yakult, Otsuka, Novartis, Pfizer, MSD, Bayer, Kyowa Kirin, Eisai, Janssen, Ono, Gilead and Amgen; consulting fees from AstraZeneca, Ono, Mitsubishi Tanabe, Eisai, Chugai, Bristol Myers Squibb, AbbVie, Takeda, Zenyaku, Genmab, Kyowa Kirin, MSD, Carna Biosciences, Novartis, Yakult, Nihon Shinyaku, Novartis and Beigene and honoraria from AstraZeneca, Ono, Eisai, Chugai, Janssen, Symbio, Bristol Myers Squibb, Daiichi Sankyo, Otsuka, AbbVie, Takeda, Eli Lilly, Genmab, Kyowa Kirin, MSD, Astellas, Pfizer, Meiji Seika, Novartis, Nihon Kayaku and Gilead. K.K. reports grants from AbbVie, MSD, Bristol Myers Squibb, Chugai, Daiichi Sankyo, Eisai, Janssen, Kyowa Kirin, Novartis and Ono; consulting fees from AbbVie, AstraZeneca, Chugai, Daiichi Sankyo, Eisai, Janssen and Novartis; and honoraria from Bristol Myers Squibb, Chugai, Dainippon Sumitomo, Janssen, Kyowa Kirin, MSD, Ono and Novartis. R.S. reports grants from Chugai, Kyowa Kirin, Shionogi, Taiho, Eisai and Ohtsuka and honoraria from Chugai, Kyowa Kirin, AbbVie, Bristol Meyers Squib, Eisai, Ohtsuka, MSD, Janssen, Takeda, Meiji Seika, Novartis and AstraZeneca. M. Yamaguchi reports grants from AstraZeneca, Chugai, Genmab, Incyte and AbbVie; consulting fees from Genmab, BeiGene and Nihon Servier; and honoraria from Chugai, Kyowa Kirin, AbbVie, Bristol Myers Squibb, Janssen, Meiji Seika, MSD, Nippon Shinyaku, SymBio, Takeda and Eisai.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/hon.70047.

References

1. M. Yamaguchi, M. Seto, M. Okamoto, et al., "De Novo CD5+ Diffuse Large B-Cell Lymphoma: A Clinicopathologic Study of 109 Patients," *Blood* 99, no. 3 (2002): 815–821, https://doi.org/10.1182/blood.v99.3.815.

2. M. Yamaguchi, N. Nakamura, R. Suzuki, et al., "De Novo CD5+ Diffuse Large B-Cell Lymphoma: Results of a Detailed Clinicopathological Review in 120 Patients," *Haematologica* 93, no. 8 (2008): 1195–1202, https://doi.org/10.3324/haematol.12810.

3. S. H. Swerdlow, E. Campo, N. L. Harris, et al., *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Revised 4th ed. (Lyon: IARC Press, 2017).

4. K. Miyazaki, M. Yamaguchi, R. Suzuki, et al., "CD5-Positive Diffuse Large B-Cell Lymphoma: A Retrospective Study in 337 Patients Treated by Chemotherapy With or Without Rituximab," *Annals of Oncology* 22, no. 7 (2011): 1601–1607, https://doi.org/10.1093/annonc/mdq627.

5. Z. Y. Xu-Monette, M. Tu, K. J. Jabbar, et al., "Clinical and Biological Significance of De Novo CD5+ Diffuse Large B-Cell Lymphoma in Western Countries," *Oncotarget* 6, no. 8 (2015): 5615–5633, https://doi.org/10.18632/oncotarget.3479.

6. M. Suguro, H. Tagawa, Y. Kagami, et al., "Expression Profiling Analysis of the CD5+ Diffuse Large B-Cell Lymphoma Subgroup: Development of a CD5 Signature," *Cancer Science* 97, no. 9 (2006): 868–874, https://doi.org/10.1111/j.1349-7006.2006.00267.x.

7. K. Miyazaki, M. Yamaguchi, H. Imai, et al., "Gene Expression Profiling of Diffuse Large B-Cell Lymphomas Supervised by CD5 Expression," *International Journal of Hematology* 102, no. 2 (2015): 188–194, https://doi.org/10.1007/s12185-015-1812-2.

8. T. Takeuchi, M. Yamaguchi, K. Kobayashi, et al., "MYD88, CD79B, and CARD11 Gene Mutations in CD5-Positive Diffuse Large B-Cell Lymphoma," *Cancer* 123, no. 7 (2017): 1166–1173, https://doi.org/10.1002/cncr.30404.

9. T. Mishina, N. Oshima-Hasegawa, S. Tsukamoto, et al., "Genetic Subtype Classification Using a Simplified Algorithm and Mutational Characteristics of Diffuse Large B-Cell Lymphoma in a Japanese Cohort," *British Journal of Haematology* 195, no. 5 (2021): 731–742, https://doi.org/10.1111/bjh.17765.

10. L. Alinari, A. Gru, C. Quinion, et al., "De Novo CD5+ Diffuse Large B-Cell Lymphoma: Adverse Outcomes With and Without Stem Cell Transplantation in a Large, Multicenter, Rituximab Treated Cohort," *American Journal of Hematology* 91, no. 4 (2016): 395–399, https://doi.org/10.1002/ajh.24299.

11. D. Ennishi, K. Takeuchi, M. Yokoyama, et al., "CD5 Expression Is Potentially Predictive of Poor Outcome Among Biomarkers in Patients With Diffuse Large B-Cell Lymphoma Receiving Rituximab Plus CHOP Therapy," *Annals of Oncology* 19, no. 11 (2008): 1921–1926, https://doi.org/10.1093/annonc/mdn392.

12. N. A. Johnson, M. Boyle, A. Bashashati, et al., "Diffuse Large B-Cell Lymphoma: Reduced CD20 Expression Is Associated With an Inferior Survival," *Blood* 113, no. 16 (2009): 3773–3780, https://doi.org/10.1182/blood-2008-09-177469.

13. R. Hyo, N. Tomita, K. Takeuchi, et al., "The Therapeutic Effect of Rituximab on CD5-Positive and CD5-Negative Diffuse Large B-Cell Lymphoma," *Hematological Oncology* 28, no. 1 (2010): 27–32, https://doi.org/10.1002/hon.896.

14. G. Salles, D. de Jong, W. Xie, et al., "Prognostic Significance of Immunohistochemical Biomarkers in Diffuse Large B-Cell Lymphoma: A Study From the Lunenburg Lymphoma Biomarker Consortium," *Blood* 117, no. 26 (2011): 7070–7078, https://doi.org/10.1182/blood-2011-04-345256.

15. W. Y. Chuang, H. Chang, L. Y. Shih, et al., "CD5 Positivity Is an Independent Adverse Prognostic Factor in Elderly Patients With Diffuse Large B Cell Lymphoma," *Virchows Archiv* 467, no. 5 (2015): 571–582, https://doi.org/10.1007/s00428-015-1845-1.

16. W. H. Wilson, K. Dunleavy, S. Pittaluga, et al., "Phase II Study of Dose-Adjusted EPOCH and Rituximab in Untreated Diffuse Large B-Cell Lymphoma With Analysis of Germinal Center and Post-Germinal Center Biomarkers," *Journal of Clinical Oncology* 26, no. 16 (2008): 2717–2724, https://doi.org/10.1200/jco.2007.13.1391.

17. W. H. Wilson, S. H. Jung, P. Porcu, et al., "A Cancer and Leukemia Group B Multi-Center Study of DA-EPOCH-Rituximab in Untreated Diffuse Large B-Cell Lymphoma With Analysis of Outcome by Molecular Subtype," *Haematologica* 97, no. 5 (2012): 758–765, https://doi.org/10.3324/haematol.2011.056531.

18. J. S. Abramson, M. Hellmann, J. A. Barnes, et al., "Intravenous Methotrexate as Central Nervous System (CNS) Prophylaxis Is Associated With a Low Risk of CNS Recurrence in High-Risk Patients With Diffuse Large B-Cell Lymphoma," *Cancer* 116, no. 18 (2010): 4283–4290, https://doi.org/10.1002/cncr.25278.

19. H. Holte, S. Leppä, M. Björkholm, et al., "Dose-densified Chemoimmunotherapy Followed by Systemic Central Nervous System Prophylaxis for Younger High-Risk Diffuse Large B-Cell/Follicular Grade 3 Lymphoma Patients: Results of a Phase II Nordic Lymphoma Group Study," *Annals of Oncology* 24, no. 5 (2013): 1385–1392, https://doi.org/10.1093/annonc/mds621.

20. K. Miyazaki, N. Asano, T. Yamada, et al., "DA-EPOCH-R Combined With High-Dose Methotrexate in Patients With Newly Diagnosed Stage II–IV CD5-Positive Diffuse Large B-Cell Lymphoma: A Single-Arm, Open-Label, Phase II Study," *Haematologica* 105, no. 9 (2020): 2308–2315, https://doi.org/10.3324/haematol.2019.231076.

21. C. P. Hans, D. D. Weisenburger, T. C. Greiner, et al., "Confirmation of the Molecular Classification of Diffuse Large B-Cell Lymphoma by Immunohistochemistry Using a Tissue Microarray," *Blood* 103, no. 1 (2004): 275–282, https://doi.org/10.1182/blood-2003-05-1545.

22. Y. Kanda, "Investigation of the Freely Available Easy-To-Use Software 'EZR' for Medical Statistics," *Bone Marrow Transplantation* 48, no. 3 (2013): 452–458, https://doi.org/10.1038/bmt.2012.244.

23. B. Thakral, L. J. Medeiros, P. Desai, et al., "Prognostic Impact of CD5 Expression in Diffuse Large B-Cell Lymphoma in Patients Treated With Rituximab-EPOCH," *European Journal of Haematology* 98, no. 4 (2017): 415–421, https://doi.org/10.1111/ejh.12847.

24. M. Klanova, L. H. Sehn, I. Bence-Bruckler, et al., "Integration of Cell of Origin Into the Clinical CNS International Prognostic Index Improves CNS Relapse Prediction in DLBCL," *Blood* 133, no. 9 (2019): 919–926, https://doi.org/10.1182/blood-2018-07-862862.

25. K. L. Lewis, L. H. Jakobsen, D. Villa, et al., "High-Dose Methotrexate as CNS Prophylaxis in High-Risk Aggressive B-Cell Lymphoma," *Journal of Clinical Oncology* 41, no. 35 (2023): 5376–5387, https://doi.org/10.1200/jco.23.00365.

26. U. Vitolo, A. Chiappella, A. J. Ferreri, et al., "First-Line Treatment for Primary Testicular Diffuse Large B-Cell Lymphoma With Rituximab-CHOP, CNS Prophylaxis, and Contralateral Testis Irradiation: Final Results of an International Phase II Trial," *Journal of Clinical Oncology* 29, no. 20 (2011): 2766–2772, https://doi.org/10.1200/jco.2010.31.4187.

27. R. Puckrin, H. El Darsa, S. Ghosh, A. Peters, C. Owen, and D. Stewart, "Ineffectiveness of High-Dose Methotrexate for Prevention of CNS Relapse in Diffuse Large B-Cell Lymphoma," *American Journal of Hematology* 96, no. 7 (2021): 764–771, https://doi.org/10.1002/ajh.26181.

28. H. Jeong, H. Cho, H. Kim, et al., "Efficacy and Safety of Prophylactic High-Dose MTX in High-Risk DLBCL: A Treatment Intent-Based Analysis," *Blood Advances* 5, no. 8 (2021): 2142–2152, https://doi.org/10.1182/bloodadvances.2020003947.

29. S. Bobillo, E. Joffe, D. Sermer, et al., "Prophylaxis With Intrathecal or High-Dose Methotrexate in Diffuse Large B-Cell Lymphoma and High Risk of CNS Relapse," *Blood Cancer Journal* 11, no. 6 (2021): 113, https://doi.org/10.1038/s41408-021-00506-3.

30. T. A. Eyre, F. Djebbari, A. A. Kirkwood, and G. P. Collins, "Efficacy of Central Nervous System Prophylaxis With Stand-Alone Intrathecal Chemotherapy in Diffuse Large B-Cell Lymphoma Patients Treated With Anthracycline-Based Chemotherapy in the Rituximab Era: A Systematic Review," *Haematologica* 105, no. 7 (2020): 1914–1924, https://doi.org/10.3324/haematol.2019.229948.

31. J. Wight, P. Blombery, J. Lickiss, et al., "Systemic Diffuse Large B-Cell Lymphoma Involving the Central Nervous System Has High Rates of Defective Antigen Presentation and Immune Surveillance," *Haematologica* 109, no. 9 (2024): 3013–3018.

32. B. Chapuy, M. G. Roemer, C. Stewart, et al., "Targetable Genetic Features of Primary Testicular and Primary Central Nervous System Lymphomas," *Blood* 127, no. 7 (2016): 869–881, https://doi.org/10.1182/blood-2015-10-673236.

33. G. W. Wright, D. W. Huang, J. D. Phelan, et al., "A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma With Therapeutic Implications," *Cancer Cell* 37, no. 4 (2020): 551–568.e14, https://doi.org/10.1016/j.ccell.2020.03.015.

34. H. Tilly, F. Morschhauser, L. H. Sehn, et al., "Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma," *New England Journal of Medicine* 386, no. 4 (2022): 351–363, https://doi.org/10.1056/nejmoa2115304.

35. A. Cooper, S. Tumuluru, K. Kissick, et al., "CD5 Gene Signature Identifies Diffuse Large B-Cell Lymphomas Sensitive to Bruton's Tyrosine Kinase Inhibition," *Journal of Clinical Oncology* 42, no. 4 (2024): 467–480, https://doi.org/10.1200/jco.23.01574.

36. J. Eba and K. Nakamura, "Overview of the Ethical Guidelines for Medical and Biological Research Involving Human Subjects in Japan," *Japanese Journal of Clinical Oncology* 52, no. 6 (2022): 539–544, https://doi.org/10.1093/jjco/hyac034.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.