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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

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ABSTRACT

CD5-positive diffuse large B-cell lymphoma (CD5⁺ DLBCL) is characterized by poor prognosis and a high frequency of central nervous system relapse after standard immunochemotherapy. We conducted a phase II study to investigate the efficacy and safety of dose-adjusted (DA)-EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) combined with high-dose methotrexate (HD-MTX) in newly diagnosed patients with CD5⁺ DLBCL. Previously untreated patients with stage II to IV CD5⁺ DLBCL according to the 2008 World Health Organization classification were eligible. Four cycles of DA-EPOCH-R followed by two cycles of HD-MTX and four additional cycles of DA-EPOCH-R (DA-EPOCH-R/HD-MTX) were planned as the protocol treatment. The primary end point was 2-year progression-free survival (PFS). Between September 25, 2012, and November 11, 2015, we enrolled 47 evaluable patients. Forty-five (96%) patients completed the protocol treatment. There were no deviations or violations in the DA-EPOCH-R dose levels. The complete response rate was 91%, and the overall response rate was 94%. At a median follow up of 3.1 years (range, 2.0-4.9 years), the 2-year PFS was 79% [95% confidence interval (CI): 64-88]. The 2-year overall survival was 89% (95%CI: 76-95). Toxicity included grade 4 neutropenia in 46 (98%) patients, grade 4 thrombocytopenia 12 (26%) patients, and febrile neutropenia in 31 (66%) patients. No treatment-related death was noted during the study. DA-EPOCH-R/HD-MTX might be a first-line therapy option for stage II-IV CD5⁺DLBCL and warrants further investigation. (Trial registered at: UMIN-CTR: UMIN000008507.)

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Introduction

Diffuse large B-cell lymphoma (DLBCL) includes a heterogeneous group of lymphomas with various clinicopathological and genetic features.^{1,2} The current standard first-line therapy of DLBCL is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Gene expression profiling (GEP) has identified activated B-cell-like (ABC), germinal center B-cell-like (GCB), and unclassified DLBCL.³ ABC DLBCL exhibits worse prognosis than GCB DLBCL after R-CHOP.⁴

CD5-positive (CD5⁺) DLBCL is an immunohistochemical subgroup of DLBCL, not otherwise specified (NOS) in the 2008 World Health Organization (WHO) classification and accounts for 5-10% of DLBCL.¹ It is associated with various clinical characteristics, such as elderly onset, advanced stage at diagnosis, elevated lactate dehydrogenase (LDH) level, and frequent involvement of extranodal sites.⁵⁻¹⁰ Ninety percent of CD5⁺ DLBCL cases are positive for BCL2,^{6,9} which has been reported as a risk factor for short survival in DLBCL. The patients with CD5⁺ DLBCL show significantly worse survival than those with CD5⁻ negative (CD5⁻) DLBCL after R-CHOP,^{7,9-14} and is also characterized by a high incidence of central nervous system (CNS) relapse (8-13%), mainly brain parenchymal relapse.^{8,10} CNS relapse strongly affects the prognosis of CD5⁺ DLBCL.⁸ Up to 80% of CD5⁺ DLBCL are classified as ABC DLBCL by GEP,^{9,15,16} and CD5 expression is significantly associated with the poor prognosis of patients with ABC DLBCL.^{9,15}

Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) is an infusional regimen that incorporates a dynamic dose adjustment and has shown excellent efficacy in BCL2⁺ DLBCL.^{17,18} High-dose methotrexate (HD-MTX) is commonly used in the treatment of primary DLBCL of the CNS.¹⁹ To explore a more effective first-line chemotherapy for CD5⁺ DLBCL, we have been investigating DA-EPOCH-R combined with high-dose methotrexate (HD-MTX) therapy (DA-EPOCH-R/HD-MTX) since 2009.²⁰ In 2009, when we were planning this study, eight cycles of R-CHOP was used as the standard treatment for the patients with advanced DLBCL.²¹ In previous phase II trials using DA-EPOCH-R, patients received two cycles beyond complete response (CR) or stable changes after six cycles of DA-EPOCH-R.^{17,18} Considering the aggressiveness of CD5⁺ DLBCL, we selected eight cycles of DA-EPOCH-R based on the maximum number of cycles in original studies of DA-EPOCH-R.^{17,18,22} Because most CNS relapse events in patients with CD5⁺ DLBCL during R-CHOP have been documented within 6 months after diagnosis,⁸ we added two cycles of HD-MTX between the fourth and the fifth cycles of DA-EPOCH-R. In our retrospective analysis of five patients with untreated stage IV CD5⁺ DLBCL who received DA-EPOCH-R/HD-MTX, the overall response rate (ORR) was 100%, and all toxicities were manageable.²⁰ Of note, all of the patients belonged to the high-risk group of the International Prognostic Index (IPI),²³ and three patients had CNS involvement at diagnosis. To further evaluate the efficacy of DA-EPOCH-R/HD-MTX for newly diagnosed CD5⁺ DLBCL, we have been conducting a prospective, multicenter, single-arm, open-label, phase II trial in 31 hospitals in Japan since 2015 (*registered at: UMIN000008507*). Here, we report the primary analysis results of that trial.

Methods

Study design and participants

In this multicenter phase II trial, eligible patients were 20-75 years of age and had newly diagnosed CD5⁺ CD20⁺ DLBCL with Ann Arbor stage II-IV disease (see *Online Supplementary Methods*). The diagnosis of CD5⁺ DLBCL was made according to the 2008 WHO criteria¹ as DLBCL, NOS with CD5 and CD20 expression in tumor cells based on immunohistochemistry and/or flow cytometry. A complete list of inclusion and exclusion criteria is shown in *Online Supplementary Table S1*. The study was approved by the protocol review committee of the study as well as the institutional review board of each institution in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before enrollment.

Treatment

The protocol treatment comprised four cycles of DA-EPOCH-R followed by two cycles of HD-MTX and four additional cycles of DA-EPOCH-R. DA-EPOCH-R was administered according to original reports.^{17,18,22} The treatment details are described in the *Online Supplementary Methods*. The fourth and fifth cycles of DA-EPOCH-R were administered at the same dose level. MTX was administered intravenously at a dose of 3.5 g/m² on a 14-day cycle with leucovorin rescue. The patients did not receive intrathecal chemotherapy. Acyclovir and trimethoprim-sulfamethoxazole were administered prophylactically. Radiation therapy was not permitted during the protocol treatment.

Diffuse large B-cell lymphoma subtyping

Following patient enrollment, formalin-fixed paraffin-embedded (FFPE) sections were histologically reviewed according to both the 2008 WHO criteria and the 2017 WHO criteria by the central pathology review board because the WHO classification was updated during the study period.^{1,2} DLBCL cell-of-origin (COO) subtypes were determined based on an immunohistochemical method developed by Hans *et al.*²⁴ and gene-expression-based Lymph2Cx assay.²⁵ The details of immunohistochemistry and the methods of Lymph2Cx assay are given in the *Online Supplementary Methods*.

End points

The primary end point was 2-year progression-free survival (PFS) (see the *Online Supplementary Methods*). Secondary end points were CR rate, ORR, 2-year overall survival (OS), 2-year CNS relapse rate, and toxicity. As a preplanned exploratory analysis, we assessed survival in each subgroup of COO, IPI, and CNS-IPI categories.²⁶ Treatment responses were assessed at each participating institute using positron emission tomography-computed tomography within 6-8 weeks after the beginning of the eighth cycle of DA-EPOCH-R according to the revised International Working Group Criteria.²⁷ Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

Because this was the first clinical trial for untreated CD5⁺ DLBCL, we obtained historical controls of 2-year PFS (51%) from the data set of our previous retrospective study of CD5⁺ DLBCL.⁸ (See the *Online Supplementary Methods* and *Online Supplementary Figure S1* for details) We anticipated that 41 evaluable patients were needed to achieve 80% power to detect a 20% difference in 2-year PFS from the historical control (51%) with a one-sided type I error of 0.05. The planned sample size was 45 patients with the expectation that 10% would be ineligible. Survival estimates were calculated using the Kaplan-Meier method, and 95% confidence

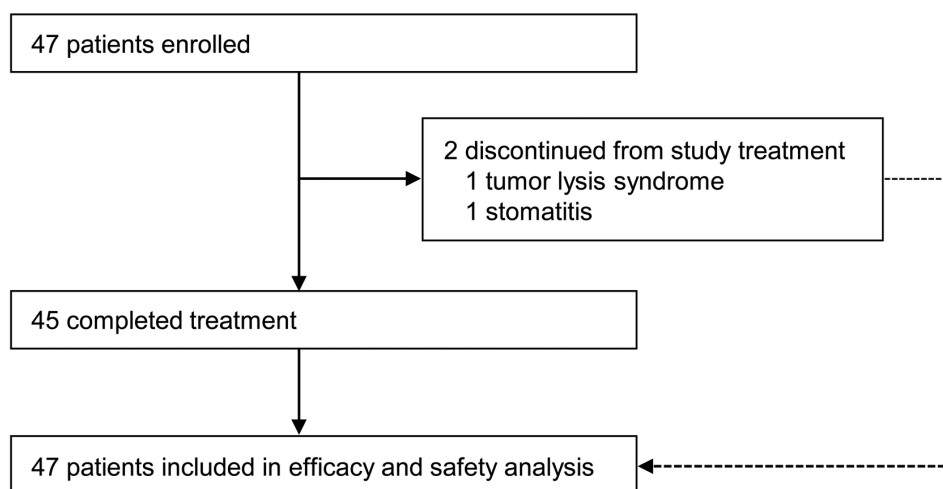


Figure 1. Trial profile.

intervals (CI) were estimated using Greenwood's formula. All analyses were performed using SAS v9.4 (Cary, NC, USA) statistical package.

Results

Patients' characteristics

A total of 47 patients from 24 participating institutions were enrolled in the study between July 2012 and November 2015 (Figure 1). The central pathology review confirmed the diagnosis of all patients as CD5⁺ DLBCL based on the 2008 WHO criteria. The review also revealed that two patients had high-grade B-cell lymphoma, NOS based on the 2017 WHO classification. The baseline clinical features and disease characteristics are listed in Table 1. Thirty-six percent of the patients were over 65 years of age. Skin/subcutaneous tissue was the most frequent site of extranodal involvement (15%). One patient had primary testicular DLBCL.

For one case, the quality of the RNA extracted from the FFPE tissue sample was inadequate, but the remaining 46 cases were analyzed using GEP. Thirty-nine (85%) of 46 cases were classified as ABC DLBCL, four (9%) were classified as GCB DLBCL, and three (7%) were unclassified. The morphological and immunophenotypical features are summarized in Table 2. Based on Hans' criteria, 72% of the 46 patients examined were classified as non-GCB DLBCL.

Treatment and response

Forty-five (96%) patients completed the protocol treatment. In the remaining two patients, treatment was discontinued because of tumor lysis syndrome (TLS) with hyperkalemia after the first administration of rituximab and grade 3 stomatitis during the sixth cycle of DA-EPOCH-R. The dose-adjustment map of DA-EPOCH-R is shown in *Online Supplementary Figure S2*. The range of the dose level of DA-EPOCH-R was 1-4; median dose level of DA-EPOCH-R was two. The maximum dose level of DA-EPOCH-R was 1 in 26.1%, 2 in 32.6%, 3 in 26.1%, 4 in 15.2%, and >4 in 0%. There were no deviations or viola-

tions in determining the dose levels of DA-EPOCH-R. All patients were administered with DA-EPOCH-R/HD-MTX entirely in the hospital. Of the 47 patients evaluable for response, 43 patients achieved a CR (91%; 95%CI: 80-98%), one patient achieved a partial response, and two patients experienced progressive disease. The ORR was 94% (95%CI: 82-99%).

Survival

With a median follow up of 3.1 years (range, 2.0-4.9), the 2-year PFS was 79% (90%CI: 67-87%; 95%CI: 64-88%) (Figure 2A). This finding compared favorably with that of the historical control (51%). The 2-year OS was 89% (90%CI: 79-95%; 95%CI: 76-95%) (Figure 2B). One patient with CR died in a traffic accident 0.8 years after enrollment.

In a preplanned exploratory subgroup analysis, there was no significant difference in PFS (*Online Supplementary Figure S3A*) or OS (*Online Supplementary Figure S3B*) according to COO categories. The 2-year PFS and OS for CD5⁺ ABC DLBCL (n=39) were 77% and 87%, respectively. There was no significant difference in PFS according to gender and each risk factor for IPI (*data not shown*).

Central nervous system relapse

The 2-year CNS relapse rate was 9% (n=4; 90%CI: 4-19%, 95%CI: 3-21%) (Figure 3A). During the follow-up period, no patient experienced CNS relapse more than 2 years from enrollment. There was no significant difference in PFS among the CNS-IPI categories ($P=0.58$) (Figure 3B). Ten patients in the CNS IPI high-risk group were classified as ABC (n=8), GCB (n=1), and unclassified DLBCL (n=1).

The clinical characteristics of four patients who experienced CNS relapse are summarized in *Online Supplementary Table S2*. Among them, one patient had primary testicular DLBCL. Two patients were diagnosed as having high-grade B-cell lymphoma, NOS with *MYC* rearrangement based on the 2017 WHO criteria. Neither of these patients had the *BCL2* translocation, and both were positive for CD10 and *BCL2* by immunohistochemistry. For the remaining one patient, the protocol treat-

Table 1. Baseline clinical features and disease characteristics.

Characteristic	All patients (n=47)
Age, years	
Median	62
Range	37-74
>60 years	28 (60%)
Sex	
Male	18 (38%)
Female	29 (62%)
Stage	
II	20 (43%)
III-IV	27 (57%)
ECOG PS	
0 or 1	45 (96%)
>1	2 (4%)
Serum LDH level	
Normal	16 (34%)
Elevated	31 (66%)
Extranodal sites	
0 or 1	31 (66%)
>1	16 (34%)
IPI risk category	
Low/Low-intermediate	25 (53%)
High-intermediate/High	22 (47%)
CNS-IPI risk category	
Low	14 (30%)
Intermediate	23 (49%)
High	10 (21%)
Cell-of-origin*	
ABC	39 (85%)
GCB	4 (9%)
Unclassified	3 (7%)

ABC: activated B-cell-like; CNS: central nervous system; EBV: Epstein-Barr virus-encoded RNA-1; GCB: germinal center-B-cell-like; IPI: International Prognostic Index; PS: performance status. *Examined by Lymph2Cx using formalin-fixed and paraffin-embedded tissues (n=46).

ment was discontinued after the first drug administration due to grade 4 TLS. CNS relapses occurred in two patients (one patient had leptomeningeal disease with tumor of ethmoid sinus, and the other patient had brain parenchymal disease alone) before HD-MTX of the protocol treatment.

Toxicity

Toxicity was assessed in all 445 cycles of DA-EPOCH-R/HD-MTX with 357 cycles of DA-EPOCH-R in all 47 patients. Table 3 lists adverse events in all 445 cycles of DA-EPOCH-R/HD-MTX, and *Online Supplementary Table S3* lists adverse events in 357 cycles of DA-EPOCH-R. There were no treatment-related deaths. The most common grade 3 non-hematologic toxicity was elevated ALT (28%). Four patients experienced grade 3 infection, including catheter-related infection, cellulitis, endocarditis, and urinary tract infection. Grade 3 peripheral motor neuropathy and peripheral sensory neuropathy occurred in 4% of patients, separately. There was no grade 3 cardiac toxicity. Grade 4 neutropenia and thrombocytopenia were present in 98% and 26% of patients, respectively.

The targeted ANC ($<0.5 \times 10^9/L$) occurred in 77% of

Table 2. Morphological and immunophenotypical features.

	All patients (n=47)
Morphology	
Common variant	31 (66%)
Giant cell rich variant	3 (6%)
Polymorphic variant	12 (26%)
Immunoblastic variant	1 (2%)
Immunohistochemistry	
CD5*	47 (100%)
CD20	47 (100%)
CyclinD1	0 (0%)
CD10†	13 (28%)
BCL6‡	39 (85%)
MUM1‡	44 (96%)
MYC‡	26 (57%)
BCL2‡	45 (98%)
MYC positive/BCL2 positive‡	26 (57%)
COO subtype by Hans' criteria	
GCB‡	13 (28%)
Non-GCB‡	33 (72%)
EBER <i>in situ</i> ‡	0 (0%)

COO: cell-of-origin; EBV: Epstein-Barr virus-encoded RNA-1; GCB: germinal center-B-cell-like. *Assessed by flow cytometry in 4 patients. †Examined in 46 patients.

cycles. Thrombocytopenia of $<25 \times 10^9/L$ occurred in 8% of cycles. Febrile neutropenia (FN) occurred in 66% of patients and 23% per cycle of DA-EPOCH-R (Table 3 and *Online Supplementary Table S3*). All patients who experienced FN recovered from the toxicity soon after initial antibiotics therapy. Possible second malignancies were documented in three patients (age, 64-74 years; acute myeloid leukemia, n=1; glioblastoma, n=1; and colon cancer in adenoma, n=1). In two of these patients, the second malignancy was diagnosed after salvage chemotherapy for relapsed CD5+ DLBCL.

Discussion

To the best of our knowledge, this is the first clinical trial for CD5+ DLBCL. At the beginning of this trial in 2015, we calculated the threshold 2-year PFS using our previous retrospective study including 337 patients with CD5+ DLBCL. In 149 patients with newly diagnosed stage II-IV CD5+ DLBCL who received rituximab-containing chemotherapy (R-chemo) and had available follow-up data, the 2-year PFS was 51%. Recently, the results of several retrospective studies of CD5+ DLBCL in the rituximab-era (R-era) were reported. In both cohorts of 102 patients with all stage CD5+ DLBCL who received R-chemo at nine institutes in the United States¹⁰ and 31 patients with all stage CD5+ DLBCL who received R-CHOP in other Western countries,⁹ the 2-year OS was less than 50%. Therefore, we consider that our threshold setting was reasonable and that the 2-year PFS (79%) by the protocol treatment in our present study was superior to the historical control.

Few reports have described the use of DA-EPOCH-R for CD5+ DLBCL. For all DLBCL subtypes, there was no sig-

nificant difference in survival between patients who received R-CHOP and patients who received DA-EPOCH-R in a large randomized controlled trial.²⁸ In that trial, the prognosis stratified by CD5 was not shown. In the largest study including 130 DLBCL patients who were examined for CD5 expression and received DA-EPOCH-R, 16 (12.3%) patients had CD5⁺ DLBCL.²⁹ At a median follow up of 28.5 months, 37.5% of patients in the CD5⁺ DLBCL group had died, which showed a significantly worse survival than those in the CD5⁻ DLBCL. The 2-year OS was 89% (90%CI: 79-95%; 95%CI: 76-95%) for DA-EPOCH-R/HD-MTX in our present trial.

In a large retrospective study including 102 patients with CD5⁺ DLBCL, 6 of 7 patients with untreated CD5⁺ DLBCL who received DA-EPOCH-R achieved a CR and

were disease-free with a median follow up of 30 months.¹⁰ In another study, CD5 expression in DLBCL was identified as a risk factor for short OS in a cohort of patients who received R-EPOCH,²⁹ which indicated that R-EPOCH alone may be insufficient to cure this disease. In the present study of stage II-IV CD5⁺ DLBCL, HD-MTX therapy was added between the fourth and fifth cycles of DA-EPOCH-R. In our trial, the completion rate of the protocol treatment was high. Moreover, there were no deviations or violations in the dose-adjustment of DA-EPOCH-R. All patients received DA-EPOCH-R/HD-MTX only in the hospital. These features may have contributed to the excellent efficacy of DA-EPOCH-R/HD-MTX in our trial. However, a considerable number of female patients (62%), patients with PS <2 (96%), and those with

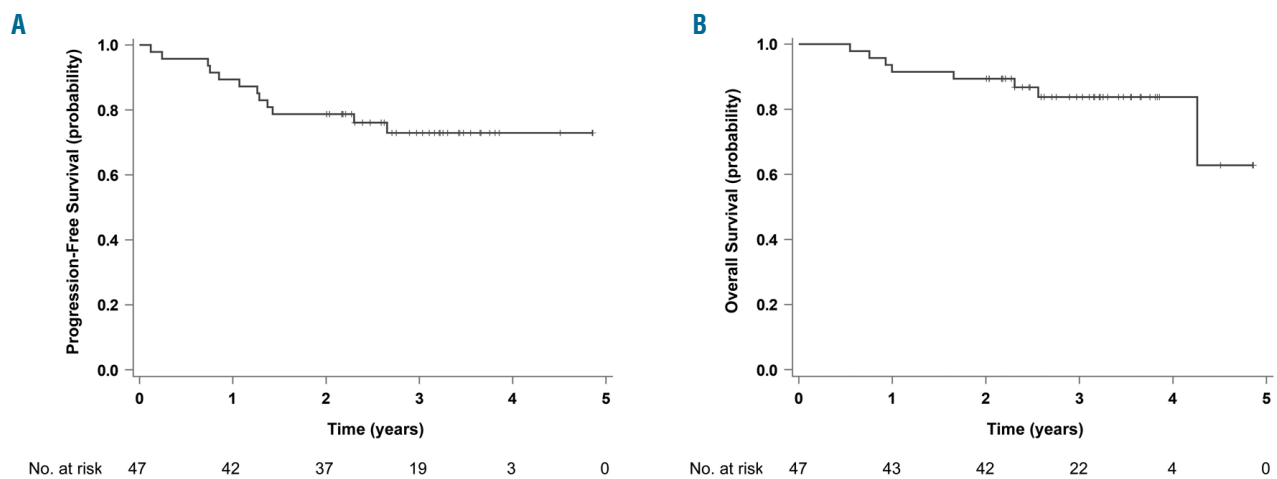


Figure 2. Survival curves for patients with CD5-positive diffuse large B-cell lymphoma. (A) Progression-free survival and (B) overall survival for all patients (n=47).

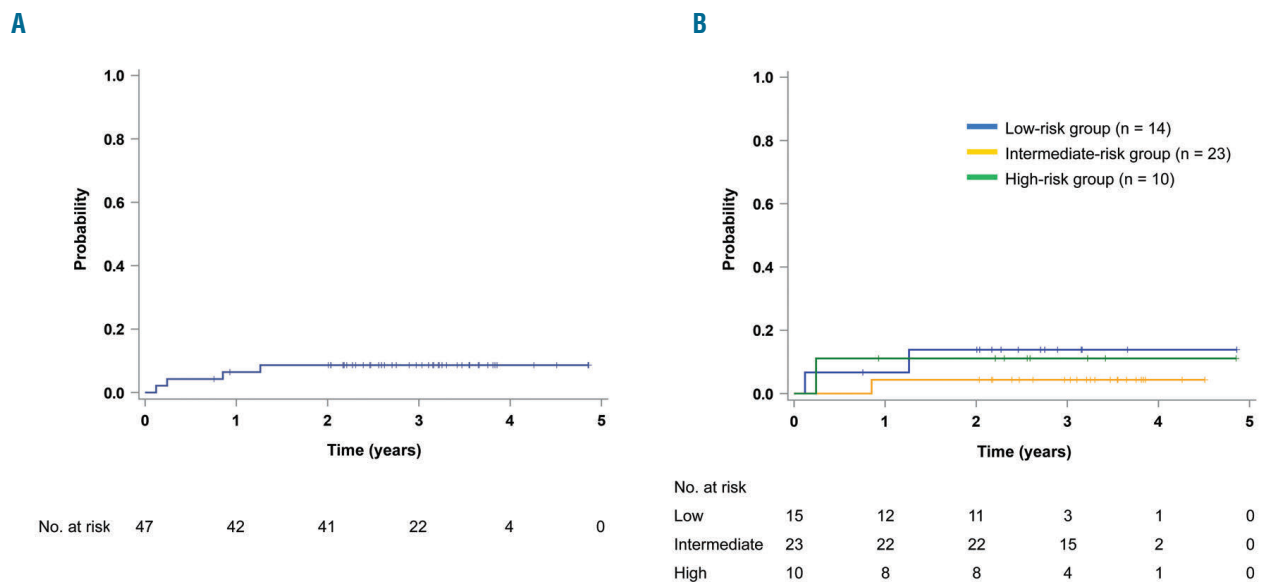


Figure 3. Central nervous system (CNS) relapse in CD5-positive diffuse large B-cell lymphoma patients (n=47). (A) Probability of CNS relapse. (B) Probability of CNS relapse according to the CNS-International Prognostic Index.

low/low-intermediate IPI risk (53%) were enrolled in the present study. In the subgroup analysis of PFS, there was no significant difference between those with and those without risk factors for gender, PS, and IPI group, although the sample size was small. Considering these results, further studies are needed to establish DA-EPOCH-R/HD-MTX as a standard therapy for newly diagnosed stage II-IV CD5+ DLBCL. Nevertheless, we consider that this regimen might be regarded as a treatment option, because CD5 expression can be easily examined in clinical practice.

The incidence of CNS relapse for all patients with DLBCL treated with R-CHOP has been reported to be 1.9-6.4%,³⁰⁻³² whereas the incidence of CNS relapse for CD5+ DLBCL in the R-era were reported as 13% in our retrospective study,⁸ 8% in a study in Western countries,⁹ and 33% in ten patients treated with DA-EPOCH-R in a retrospective study.²⁹ Although our present trial does not have a sufficient statistical power to assess the reduction in CNS relapse, the incidence of CNS relapse in the present study (9%; 95%CI: 3-21%) seems to be lower than that for DA-EPOCH-R alone. To further reduce the incidence of CNS relapse, development of systemic chemotherapy in combination with one or more newer agents that cross

the blood-brain barrier, including ibrutinib,^{33,34} lenalidomide³⁵ and tumor necrosis factor- α coupled with NGR,³⁶ is warranted. Combining a high CNS-IPI score and ABC/classified COO were reported to identify a patient subgroup at high risk for developing CNS relapse.³⁷ Of note, in the present trial, 90% of patients in the CNS-IPI high-risk group were ABC/unclassified DLBCL. However, in four patients with CNS relapse, one patient had primary testicular lymphoma, which should be treated with a specific treatment strategy including local radiotherapy.³⁸ Moreover, 2 of the 4 patients with CNS relapse had high-grade B-cell lymphoma, NOS with *MYC* translocation, which is known to result in a relatively high incidence of CNS relapse.³⁹ These results suggest that CD5+ DLBCL diagnosed according to the 2008 WHO criteria was a heterogeneous lymphoma and that DA-EPOCH-R/HD-MTX might be beneficial for patients with CD5+ DLBCL in the WHO 2017 era.

As expected, the incidence of grade 3 peripheral motor neuropathy, peripheral sensory neuropathy and cardiac events was low (4%, 4%, and 0%, respectively) and was comparable to that in previous studies including DA-EPOCH-R.^{17,18} Two-thirds (66%) of the patients in this study experienced FN, and the incidence was higher than

Table 3. Hematologic and non-hematologic toxicities.

	Grade 1-2	Grade 3	Grade 4	Grade 5
Hematologic adverse event				
Neutropenia	0	1 (2%)	46 (98%)	0
Leukopenia	1 (2%)	0	46 (98%)	0
Thrombocytopenia	13 (28%)	22 (47%)	12 (26%)	0
Anemia	11 (23%)	26 (55%)	10 (21%)	0
Febrile neutropenia	–	31 (66%)*	0	0
Non-hematologic adverse event				
Blood bilirubin increased	9 (19%)	2 (4%)	0	0
AST increased	36 (77%)	5 (11%)	0	0
ALT increased	30 (64%)	13 (28%)	0	0
Hyperglycemia	40 (85%)	1 (2%)	0	0
Hyponatremia	36 (77%)	7 (15%)	0	0
Hyperkalemia	20 (43%)	0	1 (2%)*	0
Hypokalemia	38 (81%)	8 (17%)	0	0
Hypocalcaemia	44 (94%)	1 (2%)	1 (2%)	0
Cardiac disorders	–	0	0	0
Constipation	31 (66%)	3 (6%)	0	0
Ileus	1 (2%)	2 (4%)	0	0
Nausea	33 (70%)	1 (2%)	0	0
Vomiting	9 (19%)	1 (2%)	0	0
Infection	–	4 (9%)*	0	0
Allergic reaction	11 (23%)	0	0	0
Tumor lysis syndrome	0	3 (6%)	1 (2%)	0
Peripheral motor neuropathy	11 (23%)	2 (4%)	0	0
Peripheral sensory neuropathy	29 (62%)	2 (4%)	0	0
Pneumonitis	2 (4%)	1 (2%)	0	0
Others	–	10 (21%)*	0	0

AST: aspartate aminotransferase; ALT: alanine aminotransferase. *Observed in 23% of all cycles of DA-EPOCH-R (Online Supplementary Table S3). †One patient experienced tumor lysis syndrome with hyperkalemia after the first administration of rituximab. ‡Catheter related infection (n=1), cellulitis (n=1), infective endocarditis (n=1), and urinary tract infection (n=1). §Oral mucositis (n=3), hypertension (n=2), pulmonary embolism (n=2), deep vein thrombosis (n=1), Palmar-Planter erythrodysesthesia syndrome (n=1), and anorexia (n=1).

that in previous reports (36-37%).^{17,18,28} However, the incidence of FN per cycle of DA-EPOCH in our study was 23%, which was comparable to that in previous reports for DA-EPOCH-R (19%).^{17,40} The long period (7 months) of this protocol treatment may have resulted in the high proportion of patients who experienced FN. All patients with FN promptly recovered after initial antibiotic therapy and had no serious events. Hence, the toxicity could be considered manageable. Although secondary malignancy was observed in three patients, all of them were older, and two of them were treated with salvage chemotherapy after relapse. A longer follow up is needed to adequately evaluate second malignancies.

Our study has several limitations. First, it is a non-randomized phase II study with a small number of patients. Second, 96% of the patients had good PS (< 2). Third, the follow-up period for the evaluation of secondary malignancy was short. Fourth, considering the rarity of the disease and the feasibility of the clinical trial, this study was not designed to assess 2-year CNS relapse rate as a primary end point. Nevertheless, our results showed promis-

ing efficacy and manageable toxicity of DA-EPOCH-R/HD-MTX for untreated stage II-IV CD5⁺ DLBCL, and this trial is an important initial step in developing a more effective treatment strategy. To assess long-term efficacy and toxicity including second malignancy, a 5-year follow up is scheduled in November 2020.

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