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ORIGINAL ARTICLE

# Dose-adjusted EPOCH with or without rituximab for aggressive lymphoma patients: real world data

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## Abstract

CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) −/+ rituximab (R) is the standard chemotherapeutic regimen for aggressive lymphoma, but is insufficient for aggressive lymphoma with adverse prognostic factors. Dose-adjusted (DA)-EPOCH (etoposide, doxorubicin, cyclophosphamide, vincristine, and prednisolone) −/+ R demonstrates excellent efficacy against some aggressive lymphoma. Thus, we conducted a retrospective study to evaluate the feasibility and efficacy of this therapy in clinical practice. We enrolled 149 patients from 17 institutions diagnosed between 2007 and 2015. The median follow-up period for survivors was 27 months (range 0.2–123). The complete response (CR) rate of newly diagnosed patients was 79% (95% CI 68–87%). All patients were hospitalized to receive this therapy and 94% of patients also received granulocyte-colony-stimulating factor support. There were no treatment-related deaths. Febrile neutropenia (FN) and grade 3 or 4 infection occurred in 55% and 28% of patients, respectively. There were no significant differences in FN or infection between young (≤ 65 years) and elderly patients (> 65 years). In newly diagnosed diffuse large B-cell lymphoma-not otherwise specified patients ($n = 46$), the CR rate was 80% (95% CI 64–91%) and the 2-year OS rate was 81% (95% CI 66–90%). In the present study, DA-EPOCH −/+ R exhibited excellent efficacy and feasibility for aggressive lymphoma.

**Keywords** DA-EPOCH · Lymphoma · DLBCL

## Introduction

Aggressive lymphomas are heterogeneous, but potentially curative diseases. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) therapy had been the standard chemotherapeutic regimen for the majority of aggressive lymphomas [1]. A randomized clinical trial established CHOP with rituximab (R) therapy as the frontline standard of care for newly diagnosed diffuse large B-cell lymphoma (DLBCL) [2]. The international prognostic index (IPI) was established to predict the outcomes of aggressive lymphoma patients. Afterwards, the National Comprehensive Cancer

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Network (NCCN)-IPI was established for predicting survival for aggressive lymphoma patients in the R era. The 5-year overall survival rates of patients with DLBCL treated in the R era were previously reported to be 96, 82, 64, and 33% for patients with low, low-intermediate, high-intermediate, and high NCCN-IPI, respectively [3]. However, R-CHOP is not sufficient for DLBCL with high risk of IPI and is also not standard therapy for other types of aggressive lymphomas, such as intermediate (double hit) lymphoma.

EPOCH (etoposide, doxorubicin, cyclophosphamide, vincristine, and prednisolone) chemotherapy was developed as a salvage regimen for relapsed or refractory lymphoma [4]. EPOCH therapy is unique in that it is a continuous intravenous infusion of etoposide, doxorubicin, and vincristine for 96 h. Lymphoma cells exposed to prolonged low concentrations of anticancer drugs were less resistant than those exposed to brief high concentrations of anticancer drugs [5]. A pharmacokinetic analysis revealed that blood concentrations of etoposide and doxorubicin vary among patients [6]. Based on these findings and the maintenance of blood concentrations, dose-adjusted (DA)-EPOCH with adjusted dosages of etoposide, doxorubicin, and cyclophosphamide depending on neutrophil and blood platelet counts in the latest cycle was developed, and demonstrated high efficacy for previously untreated large-B-cell lymphoma in a phase II study [7].

DA-EPOCH −/+ R exhibited excellent efficacies for primary mediastinal large B-cell lymphoma (PMBCL) [8–11], BL [12], peripheral T-cell lymphoma (PTCL) [13], anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) and ALK-negative ALCL [14], DLBCL with the germinal center B-cell (GC) type [15], and HIV-associated B-cell lymphoma [16, 17]. Furthermore, a phase II study on DA-EPOCH-R combined with high-dose methotrexate for untreated stage II-IV CD5-positive DLBCL also reported promising efficacy [18, 19]. However, the efficacy of DA-EPOCH-R for DLBCL was not noted in a previous clinical study [20].

The feasibility and efficacy of DA-EPOCH −/+ R have been examined in clinical trials, but have not been fully evaluated in clinical practice. Therefore, we herein conducted a retrospective study to evaluate the feasibility and efficacy of DA-EPOCH −/+ R for aggressive lymphoma in clinical practice in Japan.

## Materials and methods

### Study design

This is a multicenter retrospective study. Patients who met the following criteria were enrolled in the present study: (1) patients who received DA-EPOCH −/+ R as first- or second-line therapy or higher, (2) patients who were diagnosed with either of the following types of aggressive malignant lymphoma according to the 2008 WHO classification of hematopoietic tumors: DLBCL-not otherwise specified (NOS), T-cell histiocyte-rich large B-cell lymphoma, primary cutaneous DLBCL, leg type, EBV-positive DLBCL of the elderly, DLBCL with associated chronic inflammation, PMBCL, intravascular large B-cell lymphoma, ALK-positive large B-cell lymphoma, plasmablastic lymphoma, large B-cell lymphoma arising in HHV-8-associated multicentric Castleman disease, primary effusion lymphoma, BL, any type of B-cell lymphoma, such as unclassifiable, with features intermediate between DLBCL and BL, or transformation from indolent B-cell lymphoma, or any type of PTCL, (3) approval from the local Ethics Committee, (4) patients who were older than 15 years when they received DA-EPOCH −/+ R, and (5) patients who received DA-EPOCH −/+ R between 2007 and 2015. Primary central nervous system lymphoma patients were excluded. Dose modifications to DA-EPOCH were performed according to previous studies (14, 20).

### Dosage selection

Dose modifications to DA-EPOCH were performed according to previous studies [14, 20]. The doses of cyclophosphamide, etoposide, and doxorubicin were adjusted based on the minimum neutrophil or platelet count during the latest treatment cycle. If the minimum neutrophil count was more than $0.5\times10^9$ /L, we increased the dosage by 20%. If the minimum neutrophil count was less than $0.5\times10^9$ /L on more than two occasions or the minimum platelet count was less than $25\times10^9$ /L once, the dosage was reduced by 20%. Otherwise, patients received the same dosages.

### Statistical analysis

Clinical characteristics were compared using the *t*-test and Mann–Whitney test. OS was defined from the date of receiving DA-EPOCH −/+ R to death or lost to the follow-up. Survival was evaluated using Kaplan–Meier and multivariate proportional hazard (Cox) analyses. All statistical tests were two-sided with a significance level of 0.05. Statistical analyses were performed using the software Stata SE version 14.2.

## Results

### Patient characteristics

A total of 149 patients with aggressive lymphoma who received DA-EPOCH −/+ R between 2007 and 2015 were

enrolled in the present study from 17 institutes in Japan. The median follow-up durations for all surviving patients and surviving patients with no prior treatment were 27 months (range 0.2–123) and 26 months (range 0.2–123), respectively. Patient characteristics at diagnosis were as follows: male, 55%; median age, 62 years (range 17–87); ≥ 60 years, 56% (Table 1). Table 2 shows the number of patients according to the subtypes of lymphoma: 64 patients with DLBCL-NOS, 17 BL, 16 PMBCL, 14 follicular lymphoma (FL) with transformation, 13 adult T-cell leukemia/lymphoma (ATL), and other types of lymphoma.

All patients were hospitalized to receive this therapy, and a central venous (CV) catheter and fully implantable CV access port were used in 86 and 10% of patients, respectively. In total, 94% of patients received granulocyte-colony-stimulating factor (G-CSF) support including pegfilgrastim (17%) (Table 3). Among 149 patients, we have no outcome data of 11 patients, because they had regimen changed ($n = 10$) or were transferred to other hospital ($n = 1$) before evaluation. Computed tomography (CT) and positron emission tomography (PET)-CT were used to evaluate the efficacy of treatment in 58/138 (42%) and 68 (49%) patients, respectively. Seven (5%) patients showed disease progression, which was recognized by symptoms. Five (4%) patients were evaluated as CR ($n = 2$), PR ($n = 2$), and SD ($n = 1$), but we have no data how they were evaluated.

**Table 1** Characteristics of all patients ($n = 149$) and patients with newly diagnosed DLBCL-not otherwise specified ($n = 46$)

| | | All patients | Newly diagnosed DLBCL patients |
|---|---|---|---|
| Characteristic | | No. (%) | No. (%) |
| Sex | Male | 82 (55) | 23(50) |
| | Female | 67 (45) | 23(50) |
| Age | Median (range) | 62 (17–87) | 65 (28–87) |
| | < 60 | 65 (44) | 16 (35) |
| | ≥ 60 | 84 (56) | 30 (65) |
| ECOG-PS* | < 2 | 92 (65) | 25 (54) |
| | ≥ 2 | 49 (35) | 21 (46) |
| Stage | I, II | 32 (22) | 8 (17) |
| | III, IV | 116 (78) | 38 (83) |
| Extranodal involvement | Positive | 121 (82) | 42 (91) |
| | Negative | 26 (18) | 4 (9) |
| Prior treatment | 0 | 89 (60.5) | |
| | 1 | 47 (32) | |
| | > 1 | 11 (7.5) | |
| Ki67 | < 90% | 45 (64) | 20 (77) |
| | ≥ 90% | 25 (36) | 6 (23) |
| CD5 | Positive | | 18 (49) |
| | Negative | | 19 (51) |
| BCL2 | Positive | | 28 (88) |
| | Negative | | 4 (12) |
| MYC | Positive | | 9 (53) |
| | Negative | | 8 (47) |
| BCL6 | Positive | | 20 (77) |
| | Negative | | 6 (23) |
| EBER* | Positive | | 0 |
| | Negative | | 16 (100) |
| B symptoms | Positive | | 15 (34) |
| | Negative | | 29 (66) |
| IPI* | L*, LI* | | 12 (27) |
| | HI*, H* | | 33 (73) |

*ECOG-PS* Eastern Cooperative Oncology Group (ECOG) Performance Status, *EBER* Epstein–Barr virus-encoded small RNA, *IPI* International prognosis index, *L* low, *LI* low-intermediate, *HI* high-intermediate, *H* high

**Table 2** Subtypes of all patients ($n=149$)

| Subtype (new) | No |
|---|---|
| DLBCL-NOS | 64 (46) |
| PMBCL | 16 (15) |
| Double-hit lymphoma | 4 (3) |
| BL | 17 (9) |
| FL with transformation | 14 (4) |
| IVL | 1 (1) |
| MCL | 1 (1) |
| PBL | 2 (2) |
| PTCL-NOS | 5 (2) |
| AITL | 2 (0) |
| ALCL | 4 (3) |
| ATL | 13 (2) |
| ALL | 2 (0) |
| Aggressive-NOS | 4 (1) |

*DLBCL-NOS* diffuse large B-cell lymphoma-not otherwise specified, *PMBCL* primary mediastinal large B-cell lymphoma, *BL* Burkitt lymphoma, *FL* follicular lymphoma, *IVL* intravascular lymphoma, *MCL* mantle cell lymphoma, *PBL* plasmablastic lymphoma, *PTCL-NOS* peripheral T cell lymphoma-not otherwise specified, *AITL* angioimmunoblastic T-cell lymphoma, *ALCL* anaplastic large cell lymphoma, *ATL* adult T-cell leukemia/lymphoma, *ALL* acute lymphoblastic leukemia, *NOS* not otherwise specified

**Table 3** Number of patients who received G-CSF support and the administration route of chemotherapy in the present study ($n=149$)

| | | No. (%) |
|---|---|---|
| G-CSF* support | Positive | 140 (94) |
| | (PEG-GCSF*) | (25 (17)) |
| | None | 9 (6) |
| Access | CVC* | 127 (86) |
| | Port* | 15 (10) |
| | Peripheral | 6 (4) |

*G-CSF* granulocyte-colony-stimulating factor, *PEG-GCSF* pegfilgrastim, *CVC* central venous catheter, *Port* central venous access port

## Treatment response and outcome

The complete response (CR) rate of patients with no prior treatment was 79% (95% CI 68–87%) (Table 4). The overall response rate (ORR) was 91% (95% CI 83–96%). The 2-year OS was 85% (95% CI 75–91%) (Table 4, Fig. 1). The responses and 2-year OS of newly diagnosed other aggressive lymphoma typed patients are shown in Table 4. The CR rates of newly diagnosed PMBCL patients ($n=15$) and BL patients ($n=9$) were 86% (95% CI 57–98%) and 88% (95% CI 47–100), respectively.

The maximum dose level of DA-EPOCH was < level 1 in 13% of patients, level 1 in 57%, level 2 in 11%, level 3 in 13%, and > level 3 in 7%. The median maximum dose level of DA-EPOCH was level 1 (Table 5). No significant difference was observed in the maximum dose level of DA-EPOCH between young patients (≤ 65 years) and elderly patients (> 65 years) ($P=0.24$). The median number of cycles was 4 (range 1–8). Ninety-four patients (63%) discontinued this regimen. The reasons for discontinuation were as follows: progressive disease (PD) ($n=19$), changing the regimen due to a poor response ($n=19$), receiving autologous or allogeneic hematopoietic stem cell transplantation (HSCT) ($n=23$), toxicity ($n=6$), and unknown ($n=27$). Fifty-five patients (37%) received 6 or more cycles. Ninety percent (55/61) of patients received 6 or more cycles, excluding those who finished treatment in less than 6 cycles because of PD, changing the regimen or receiving autologous or allogeneic HSCT, or an unknown reason. A significant difference was not observed in the percentage of patients receiving 6 or more cycles between young patients (≤ 65 years) and elderly patients (> 65 years) ($P=0.13$).

## Newly diagnosed DLBCL-NOS patients

Patients with newly diagnosed DLBCL-NOS ($n=46$) exhibited the following clinical features: median age: 65 years (range 28–87 years); ≥ 60 years, 65% (Table 1). The median follow-up duration for the survival of newly diagnosed DLBCL-NOS patients was 25 months (range 3–80 months). ORR was 88% (95% CI 73–96%) and the CR rate was 80% (95% CI 64–91%) (Table 4). The 2-year OS of newly diagnosed DLBCL-NOS patients was 81% (95% CI 66–90%) (Fig. 2). The 2-year OS of CD5-positive DLBCL patients ($n=18$) and MYC-positive DLBCL patients ($n=7$) was 88% (95% CI 61–97%) and 88% (95% CI 39–98%), respectively. No significant differences were observed in OS according to the maximum dose level of DA-EPOCH-R (less than level 2 vs. level 2 and higher, $P=0.26$; less than level 3 vs. level 3 and higher, $P=0.75$) or the CD5 expression ($P=0.36$). The numbers of patients 70 years or older and 80 years or older were 15 (33%) and 5 (11%), respectively. The CR rate of patients aged 70 years or older was 92% (95% CI 64–100%), while that of those aged 80 years or older was 100% (95% CI 40–100%). The estimated 2-year OS rate of patients aged 70 years or older was 87% (95% CI 56–97%), and that of those aged 80 years or older was 80% (95% CI 20–97%).

**Table 4** Treatment response rate and 2-year overall survival rate of patients

| | All patients ($n=149$) | No prior treatment patients ($n=89$) | Newly diagnosed DLBCL* patients ($n=46$) |
|---|---|---|---|
| | % (95% CI) | % (95% CI) | % (95% CI) |
| Response | | | |
| CR* | 59% (50–67) | 79% (68–87) | 80% (64–91) |
| PR* | 17% (11–24) | 12% (6–22) | 7% (2–20) |
| SD* | 7% (3–12) | 1% (0–7) | 3% (0.1–13) |
| PD* | 18% (12–26) | 8% (3–16) | 10% (3–24) |
| 2-year OS rate | 69% (60–76) | 85% (75–91) | 81% (66–90) |

| | Newly diagnosed CD5-positive DLBCL* patients ($n=18$) | Newly diagnosed MYC-positive DLBCL* patients ($n=7$) | Newly diagnosed PMBCL* patients ($n=15$) |
|---|---|---|---|
| | % (95% CI) | % (95% CI) | % (95% CI) |
| Response | | | |
| CR* | 88% (65–99) | 86% (42–100) | 86% (57–98) |
| PR* | 6% (0.1–27) | 0% (0–41) | 14% (2–43) |
| SD* | 0% (0–19) | 0% (0–41) | 0% (0–23) |
| PD* | 6% (0.1–27) | 14% (0.4–58) | 0% (0–23) |
| 2-year OS rate | 88% (61–97) | 88% (39–98) | 100% (-) |

| | Newly diagnosed BL* patients ($n=9$) | Newly diagnosed FL with transformation patients ($n=4$) |
|---|---|---|
| | % (95% CI) | % (95% CI) |
| Response | | |
| CR* | 88% (47–100) | 75% (19–99) |
| PR* | 0% (0–37) | 25% (0.6–81) |
| SD* | 0% (0–37) | 0% (0–60) |
| PD* | 12% (0.3–523) | 0% (0–60) |
| 2-year OS rate | 89% (43–98) | 75% (13–96) |

*DLBCL* diffuse large B-cell lymphoma-not otherwise specified, *BL* Burkitt lymphoma, *FL* follicular lymphoma, *ATL* adult T-cell leukemia/lymphoma, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

## Adverse events

There were no treatment-related deaths in the present study. Febrile neutropenia (FN) was observed in 55% of patients and infection of higher than grade 3 or 4 in 28% (Table 6). In elderly patients (> 65 years), FN was noted in 61% and infection of higher than grade 3 or 4 in 32%. There were no significant differences in FN or infection between young and elderly patients. Hematological toxicities of higher than grade 3 or 4 were common and as follows: leukocytopenia 93%, neutropenia 93%, anemia 74%, and thrombocytopenia 58%. Significant differences were observed in leukocytopenia and neutropenia between young and elderly patients. Other non-hematological adverse events of grade 3 or 4 were as follows: constipation 6%, ileus 3%, tumor lysis syndrome 3%, peripheral motor neuropathy 1%, peripheral sensory neuropathy 1%, cardiac events 1%, and thrombosis 1%. There were no significant differences in the incidence of grade 3–4 non-hematological adverse events between elderly and younger patients, except for constipation ($P<0.01$).

## Discussion

Phase 2 studies on DA-EPOCH-R previously revealed excellent efficacies for some aggressive lymphomas, such as DLBCL, PMBCL, and DLBCL with MYC rearrangement. However, the DA-EPOCH-R regimen did not become a standard therapy for newly diagnosed DLBCL patients because it was shown to be more toxic and did not improve PFS or OS compared with R-CHOP in a recent randomized phase 3 study on newly diagnosed DLBCL patients [20]. We conducted a prospective phase 2 study for newly diagnosed CD5-positive DLBCL with 4 cycles of DA-EPOCH-R

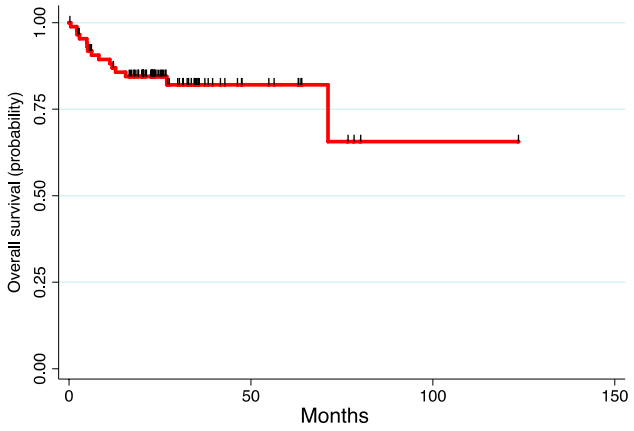


**Fig. 1** Kaplan–Meier estimates of overall survival for patients with no prior treatment ($n=89$) receiving dose-adjusted EPOCH (etoposide, doxorubicin, cyclophosphamide, vincristine, and prednisolone) −/+ R (rituximab) therapy (DA-EPOCH −/+ R). Analysis of overall survival for patients with no prior treatment in the present study ($n=89$)

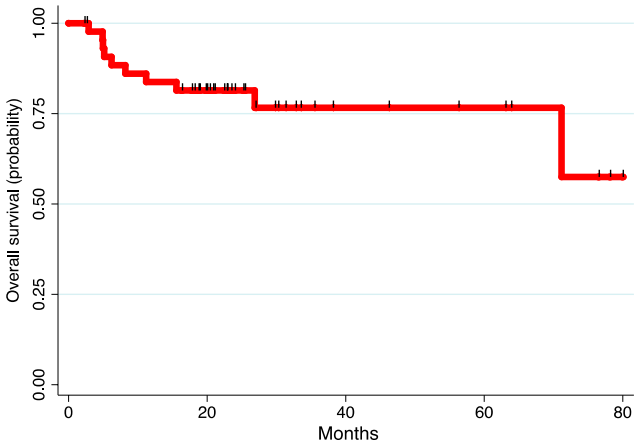


**Fig. 2** Kaplan–Meier estimates of overall survival for patients with newly diagnosed DLBCL-not otherwise specified ($n=46$) receiving dose-adjusted EPOCH (etoposide, doxorubicin, cyclophosphamide, vincristine, and prednisolone)—R (rituximab) therapy (DA-EPOCH-R). Analysis of overall survival for patients with newly diagnosed DLBCL-not otherwise specified in the present study ($n=46$)

**Table 5** The maximum dose level of DA*-EPOCH*

| | All patients ($n=149$) | Young patients ($\leq 65$) ($n=84$) | Elderly patients ($>65$) ($n=65$) |
|---|---|---|---|
| Maximum dose level | No. (%) | No. (%) | No. (%) |
| $<1$ | 19 (13) | 8 (10) | 11 (17) |
| 1 | 85 (57) | 51 (61) | 34 (52) |
| 2 | 16 (11) | 7 (8) | 9 (14) |
| 3 | 19 (13) | 12 (14) | 7 (11) |
| $>3$ | 10 (6) | 6 (7) | 4 (6) |
| | | | $P^{**}=0.24$ |

*DA* dose-adjusted, *EPOCH* etoposide, doxorubicin, cyclophosphamide, vincristine, and prednisolone

**Mann–Whitney analysis

followed by 2 cycles of HD-MTX and 4 additional cycles of DA-EPOCH-R [18, 19]. CD5-positive DLBCL has a poor prognosis [21, 22]; however, this phase 2 study showed manageable safety profile and excellent efficacies as 2-year PFS of 79%. A recent randomized phase 3 study [20] showed that DLBCL patients with a high IPI score achieved a slightly better outcome with DA-EPOCH-R than with R-CHOP. A retrospective study recently reported that DA-EPOCH-R resulted in better patient outcomes than the R-CHOP regimen for DLBCL patients younger than 60 years, with the GCB phenotype, and those with high-risk IPI [23]. In addition, a phase 2 study showed efficacy of DA-EPOCH-R for untreated DLBCL with MYC rearrangement [24]. The present study showed that the CR rate of patients with no prior treatment was 79%, ORR was 91%, and the 2-year OS as 85% by DA-EPOCH therapy. Among newly diagnosed DLBCL-NOS patients, ORR was 88% (95%CI: 73–96%), the CR rate was 80% (95%CI: 64–91%), and the 2-year OS was 81% (95%CI: 66–90%). Furthermore, some phase 2 clinical trials showed that DA-EPOCH had excellent efficacy for PMBCL patients [8–11, 25, 26]. A phase 2 study on DA-EPOCH-R in PMBCL showed an EFS of 93% [8]. A retrospective, multicenter study reported a 3-year EFS of 86% in 156 patients with PMBCL receiving DA-EPOCH-R [11] and another retrospective study showed that 76 PMBCL patients with DA-EPOCH-R and 56 patients with R-CHOP had 2-year PFS of 85 and 76%, respectively ($P=0.28$) [25]. In the present study, DA-EPOCH-R therapy resulted in ORR of 100%, a CR rate of 85.7%, and 2-year OS of 100%. We cannot show PFS because we did not collect the data. The present study has limitations in this regard. However, outcomes except for PFS were as good as in the past study. Therefore, DA-EPOCH-R may become to be a candidate of standard therapy for PMBCL and CD5-positive DLBCL or DLBCL with high IPI or DLBCL with MYC rearrangement.

R-CHOP has unsatisfactory efficacy for elderly DLBCL patients [27]. The standard dose of R-CHOP for elderly DLBCL patients was previously shown to result in severe adverse events and treatment-related death [28]. Therefore, reduced-dose R-CHOP was developed and showed a favorable CR rate and OS in elderly DLBCL patients. However, these benefits were limited to elderly DLBCL patients with high IPI [29]. A previous study reported that reduced-dose EPOCH-R was effective for elderly DLBCL patients with advanced-stage disease and high IPI (3-year OS of 63%) [30]. However, the efficacy of DA-EPOCH-R for elderly DLBCL patients currently remains unknown. In

**Table 6** Adverse events

| | All patients $n=149$ | | Young patients ($\leq 65$) $n=84$ | | Elderly patients ($>65$) $n=65$ | | P* |
|---|---|---|---|---|---|---|---|
| | ≥G1 | ≥G3 | ≥G1 | ≥G3 | ≥G1 | ≥G3 | |
| | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) | |
| Leukocytopenia | 145 (97) | 139 (93) | 82 (98) | 75 (89) | 64 (98) | 64 (98) | 0.03 |
| Neutropenia | 143 (96) | 139 (93) | 80 (95) | 76 (90) | 63 (97) | 63 (97) | 0.02 |
| Anemia | 147 (99) | 110 (74) | 82 (98) | 76 (90) | 65 (100) | 62 (95) | 0.06 |
| Thrombocytopenia | 123 (83) | 86 (58) | 67 (80) | 45 (54) | 56 (86) | 41 (63) | 0.07 |
| Febrile neutropenia | | 82(55) | | 42 (50) | | 40 (61) | 0.17 |
| Infection | 56 (38) | 42 (28) | 28 (33) | 21 (25) | 28 (43) | 21 (32) | 0.26 |
| Peripheral motor neuropathy | 5 (3) | 1 (1) | 3 (4) | 1 (1) | 2 (3) | 0 (0) | 0.86 |
| Peripheral sensory neuropathy | 29 (19) | 2 (1) | 16 (19) | 1 (1) | 13 (20) | 1 (2) | 0.88 |
| Cardiac events | 3 (2) | 2 (1) | 1 (1) | 0 (0) | 2 (3) | 2 (3) | 0.41 |
| Ileus | 6 (4) | 4 (3) | 3 (4) | 1 (1) | 3 (5) | 3 (5) | 0.72 |
| Stomatitis | 26 (17) | 2 (1) | 13 (15) | 1 (1) | 13 (20) | 1 (2) | 0.47 |
| Constipation | 79 (53) | 9 (6) | 37 (44) | 3 (4) | 42 (64) | 6 (9) | $<0.01$ |
| Tumor lysis syndrome | 7 (5) | 5 (3) | 4 (5) | 3 (4) | 3 (5) | 2 (3) | 0.95 |
| Hematuria | 2 (1) | 2 (1) | 1 (1) | 1 (1) | 1 (2) | 1 (2) | 0.86 |
| Thrombosis | 5 (3) | 1 (1) | 1 (1) | 0 (0) | 4 (6) | 1 (2) | 0.10 |

*Mann–Whitney analysis

the present study, we observed efficacy and feasibility for elderly DLBCL patients. DA-EPOCH-R may be a promising chemotherapeutic regimen for elderly DLBCL patients. Thus, further clinical trials are needed to confirm the efficacy of DA-EPOCH-R for elderly patients with DLBCL.

In the present study, the incidence rates of peripheral motor neuropathy, and peripheral sensory neuropathy of higher than grade 3 were markedly lower than those in previous studies [15, 20, 31]. A previous retrospective study [32] showed that thrombosis occurred in 35% of patients, in contrast to only 3% in the present study. In general, the incidence of thrombosis in the Japanese population is 1/8 or less than that of Western populations [33, 34]. This may explain why the incidence of thrombosis in the present study was lower than that in the previous study. However, thrombosis was detected in 5 patients (3%) and 4 out of 5 of these patients were elderly. Therefore, we need to consider the management of thrombosis when elderly patients are treated with DA-EPOCH therapy. On the other hand, the incidence rate of cardiac event was as low as that of previous studies [7, 15, 21, 31], and was lower than that treated by CHOP −/+ R. A systematic review and meta-analysis of cardiac event in patients treated by CHOP −/+ R showed that grade 3–4 cardiovascular adverse event was 2.35% [35]. A continuous intravenous infusion of doxorubicin may exert a favorable influence to reduce cardiac event. DA-EPOCH therapy may become a therapeutic option for patients with high cardiac event risk.

Although 94% of patients received G-CSF support, FN occurred in 82 patients (55%) and 40 elderly patients (60%). The incidence rates of leukocytopenia and neutropenia were higher in elderly patients than in young patients. However, no significant differences were observed in the incidence rates of FN and infection between elderly and young patients and there were no treatment-related deaths. The characteristic of this regimen, which is the dosage of anticancer drugs being adjusted according to hematological toxicities during the last cycle, may have had a favorable impact on these results. Previous clinical trials reported that the percentage of FN ranged between 35 and 37% [15, 20, 31], which was lower than that in the present study. This may have been because the present study included more severe patients than other studies. In the present study, the percentages of patients who were elderly (≥ 60 years) and had a worse Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (≥ 2) were higher than those in previous studies (56% vs 28–43%, 35% vs 13–26%, respectively). This may be attributed to the present study having a high incidence of FN. Regarding non-hematological toxicities, a significant difference was only observed in constipation between young and elderly patients. Therefore, DA-EPOCH-R may be feasible for elderly as well as young patients.

DA-EPOCH −/+ R requires the continuous intravenous infusion of anticancer drugs for 96 h. In general, DA-EPOCH therapy requires hospitalization. All patients in the present study were hospitalized to receive this therapy, as reported previously [36, 37]. Therefore, a new method or new devices for infusion regimens are needed to reduce hospital stays or enable its use in an outpatient setting.

In conclusion, DA-EPOCH −/+ R is feasible in clinical practice setting including elderly patients, and is effective for aggressive lymphoma and has potential as a standard therapy for some types of aggressive lymphoma, such as PMBCL and CD5-positive DLBCL, DA-EPOCH −/+ R may be safe for previously untreated elderly DLBCL patients, although a randomized phase 3 study showed no superiority to R-CHOP therapy. A randomized phase 3 clinical trial for PMBCL or newly diagnosed DLBCL in elderly patients is warranted to estimate the efficacy and toxicity of DA-EPOCH −/+ R.

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## Compliance with ethical standards

**Conflict of interest** Dr. Matsuda has nothing to disclose. Dr. Suzuki reports personal fees from Bristol-Meyer Squib, personal fees from Novartis, personal fees from Kyowa-Hakko Kirin, personal fees from Chugai Pharmaceuticals, personal fees from Shionogi, personal fees from Takeda, personal fees from Meiji Seika Pharma, personal fees from MSD, personal fees from Ohtsuka, personal fees from Sawai, personal fees from Celgene, personal fees from Sumitomo Dainippon, personal fees from Eisai Pharmaceuticals, personal fees from Alexion Pharma, personal fees from Sanofi, personal fees from Gilead Sciences, personal fees from Abbvie, personal fees from Jazz Pharma, personal fees from Ono Pharma, personal fees from Janssen Pharmaceuticals, outside the submitted work; Dr. Takahashi reports personal fees from Kyowa Kirin Co., Ltd., personal fees from CELGENE CORPORATION, personal fees from Bristol-Myers Squibb Company, personal fees from Chugai Pharmaceutical Co., Ltd., outside the submitted work; Dr. Suehiro has nothing to disclose. 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## Appendix

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## References

1. McKelvey EM, Gottlieb JA, Wilson HE, Haut A, Talley RW, Stephens R, et al. Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. Cancer. 1976;38:1484–93.
2. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346:235–42.
3. Zhou Z, Sehn LH, Rademaker AW, Gordon LI, Lacasce AS, Crosby-Thompson A, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood. 2014;123:837–42.
4. Gutierrez M, Chabner BA, Pearson D, Steinberg SM, Jaffe ES, Cheson BD, et al. Role of a doxorubicin-containing regimen in relapsed and resistant lymphomas: an 8-year follow-up study of EPOCH. J Clin Oncol. 2000;18:3633–42.
5. Lai GM, Chen YN, Mickley LA, Fojo AT, Bates SE. P-glycoprotein expression and schedule dependence of adriamycin cytotoxicity in human colon carcinoma cell lines. Int J Cancer. 1991;49:696–703.
6. Wilson WH, Bates SE, Fojo A, Bryant G, Zhan Z, Regis J, et al. Controlled trial of dexverapamil, a modulator of multidrug resistance, in lymphomas refractory to EPOCH chemotherapy. J Clin Oncol. 1995;13:1995–2004.
7. Wilson WH, Grossbard ML, Pittaluga S, Cole D, Pearson D, Drbohlav N, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood. 2002;99:2685–93.
8. Dunleavy K, Pittaluga S, Maeda LS, Advani R, Chen CC, Hessler J, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med. 2013;368:1408–16.
9. Pinnix CC, Dabaja B, Ahmed MA, Chuang HH, Costelloe C, Wogan CF, et al. Single-institution experience in the treatment of primary mediastinal B cell lymphoma treated with immunochemotherapy in the setting of response assessment by 18fluorodeoxyglucose positron emission tomography. Int J Radiat Oncol Biol Phys. 2015;92:113–21.
10. Binkley MS, Hiniker SM, Wu S, Natkunam Y, Mittra ES, Advani RH, et al. A single-institution retrospective analysis of outcomes for stage I-II primary mediastinal large B-cell lymphoma treated with immunochemotherapy with or without radiotherapy. Leuk Lymphoma. 2016;57:604–8.
11. Giulino-Roth L, O'Donohue T, Chen Z, Bartlett NL, LaCasce A, Martin-Doyle W, et al. Outcomes of adults and children with primary mediastinal B-cell lymphoma treated with dose-adjusted EPOCH-R. Br J Haematol. 2017;179:739–47.
12. Dunleavy K, Pittaluga S, Shovlin M, Steinberg SM, Cole D, Grant C, et al. Low-intensity therapy in adults with Burkitt's lymphoma. N Engl J Med. 2013;369:1915–25.
13. Maeda Y, Nishimori H, Yoshida I, Hiramatsu Y, Uno M, Masaki Y, et al. Dose-adjusted EPOCH chemotherapy for untreated peripheral T-cell lymphomas: a multicenter phase II trial of West-JHOG PTCL0707. Haematologica. 2017;102:2097–103.
14. Dunleavy K, Pittaluga S, Shovlin M, Roschewski M, Lai C, Steinberg SM, et al. Phase II trial of dose-adjusted EPOCH in untreated systemic anaplastic large cell lymphoma. Haematologica. 2016;101:e27–e2929.
15. Wilson WH, Dunleavy K, Pittaluga S, Hegde U, Grant N, Steinberg SM, 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. J Clin Oncol. 2008;26:2717–24.
16. Dunleavy K, Little RF, Pittaluga S, Grant N, Wayne AS, Carrasquillo JA, et al. The role of tumor histogenesis, FDG-PET, and short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR) in HIV-associated diffuse large B-cell lymphoma. Blood. 2010;115:3017–24.
17. Sparano JA, Lee JY, Kaplan LD, Levine AM, Ramos JC, Ambinder RF, et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. Blood. 2010;115:3008–166.
18. Miyazaki K, Asano N, Yamada T, Takasaki H, Igarashi T, Nishikori M, et al. Dose-adjusted (DA)—EPOCH-R with high-dose methotrexate for newly diagnosed CD5-positive diffuse large B-cell lymphoma (CD5+DLBCL): interim results from a phase II study. Blood. 2016;128:2.
19. Miyazaki K, Asano N, Yamada T, Miyawaki K, Sakai R, Igarashi T, 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 2 study. Haematologica. 2019.
20. Bartlett NL, Wilson WH, Jung SH, Hsi ED, Maurer MJ, Pederson LD, et al. Dose-adjusted EPOCH-R compared with R-CHOP as frontline therapy for diffuse large B-cell lymphoma: clinical outcomes of the phase III intergroup trial alliance/CALGB 50303. J Clin Oncol. 2019:JCO1801994.
21. Yamaguchi M, Nakamura N, Suzuki R, Kagami Y, Okamoto M, Ichinohasama R, et al. De novo CD5+ diffuse large B-cell lymphoma: results of a detailed clinicopathological review in 120 patients. Haematologica. 2008;93:1195–202.
22. Ennishi D, Takeuchi K, Yokoyama M, Asai H, Mishima Y, Terui Y, 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. Ann Oncol. 2008;19:1921–6.
23. Zhang XY, Liang JH, Wang L, Zhu HY, Wu W, Cao L, et al. DA-EPOCH-R improves the outcome over that of R-CHOP regimen for DLBCL patients below 60 years, GCB phenotype, and those with high-risk IPI, but not for double expressor lymphoma. J Cancer Res Clin Oncol. 2019;145:117–27.
24. Dunleavy K, Fanale MA, Abramson JS, Noy A, Caimi PF, Pittaluga S, et al. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. Lancet Haematol. 2018;5:e609–e617617.
25. Shah NN, Szabo A, Huntington SF, Epperla N, Reddy N, Ganguly S, et al. R-CHOP versus dose-adjusted R-EPOCH in frontline management of primary mediastinal B-cell lymphoma: a multi-centre analysis. Br J Haematol. 2018;180:534–44.
26. Malenda A, Kolkowska-Lesniak A, Pula B, Dlugosz-Danecka M, Chelstowska M, Konska A, et al. Outcomes of treatment with dose-adjusted EPOCH-R or R-CHOP in primary mediastinal large B-cell lymphoma. Eur J Haematol. 2020;104:59–66.
27. Fields PA, Linch DC. Treatment of the elderly patient with diffuse large B cell lymphoma. Br J Haematol. 2012;157:159–70.

28. Feugier P, Van Hoof A, Sebban C, Solal-Celigny P, Bouabdallah R, Ferme C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 2005;23:4117–266.
29. Peyrade F, Jardin F, Thieblemont C, Thyss A, Emile JF, Castaigne S, et al. Attenuated immunochemotherapy regimen (R-mini-iCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2011;12:460–8.
30. Zhang WH, Li GY, Ma YJ, Li ZC, Zhu Y, Chang J, et al. Reduced-dose EPOCH-R chemotherapy for elderly patients with advanced stage diffuse large B cell lymphoma. Ann Hematol. 2018.
31. Wilson WH, Jung SH, Porcu P, Hurd D, Johnson J, Martin SE, 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. 2012;97:758–65.
32. David RJ, Baran A, Loh KP, Casulo C, Barr PM, Friedberg JW, et al. Complications associated with dose-adjusted EPOCH-rituximab therapy for non-hodgkin lymphoma. Clin Lymphoma Myeloma Leuk. 2018;18:781–7.
33. Benotti JR, Dalen JE. The natural history of pulmonary embolism. Clin Chest Med. 1984;5:403–10.
34. Sakuma M, Nakamura M, Yamada N, Ota S, Shirato K, Nakano T, et al. Venous thromboembolism: deep vein thrombosis with pulmonary embolism, deep vein thrombosis alone, and pulmonary embolism alone. Circ J. 2009;73:305–9.
35. Linschoten M, Kamphuis JAM, van Rhenen A, Bosman LP, Cramer MJ, Doevendans PA, et al. Cardiovascular adverse events in patients with non-Hodgkin lymphoma treated with first-line cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP with rituximab (R-CHOP): a systematic review and meta-analysis. Lancet Haematol. 2020;7:e295–e308.
36. Lee YM. To reduce the average length of stay of patients who are admitted for DA-EPOCH-R chemotherapy regimen. BMJ Qual Improv Rep. 2015;4:2.
37. Pejsa V, Prka Z, Lucijanic M, Mitrovic Z, Pirsic M, Jaksic O, et al. Rituximab with dose-adjusted EPOCH as first-line treatment in patients with highly aggressive diffuse large B-cell lymphoma and autologous stem cell transplantation in selected patients. Croat Med J. 2017;58:40–8.