original reports

# Dose-Adjusted Etoposide, Doxorubicin, and Cyclophosphamide With Vincristine and Prednisone Plus Rituximab Therapy in Children and Adolescents With Primary Mediastinal B-Cell Lymphoma: A Multicenter Phase II Trial

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abstract

**PURPOSE** A dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone plus rituximab (DA-EPOCH-R) regimen has been shown to deliver excellent survival for adults with primary mediastinal large B-cell lymphoma (PMLBL) without the use of radiotherapy. No international prospective evaluation of this regimen has previously been reported in children and adolescents.

**PATIENTS AND METHODS** We conducted an international single-arm phase II trial involving patients younger than age 18 years with PMLBL who were to receive six courses of DA-EPOCH-R. The primary end point was event-free survival (EFS). Overall survival and toxicity were also assessed. This trial was registered (ClinicalTrials.gov identifier: NCT01516567).

**RESULTS** Analyses were based on 46 patients. The median age was 15.4 years (interquartile range: 14-16 years). The median follow-up was 59.0 months (interquartile range: 52.6-69.2 months). Fourteen events were observed (eight relapses or progressions (including three parenchymal CNS relapses), four residual lymphoma, and two second malignancies). The 4-year EFS was 69.6% (95% CI, 55.2 to 80.9), which did not differ from the rate observed historically ($P = .59$). Seven deaths occurred (six disease-related and one second malignancy). The overall survival was 84.8% (95% CI, 71.8 to 92.4). Twenty-two patients (48%) reached dose levels $\geq 4$. Nonhematologic adverse events grade $\geq 3$ or cardiac adverse events grade $\geq 2$ occurred in 47 of 276 (17%) courses and 30 of 46 patients (65%).

**CONCLUSION** DA-EPOCH-R did not improve the EFS compared with a historical control in this first prospective multisite international study of children and adolescents with PMLBL. Further studies are required to determine the optimum therapy for children and adolescents with this lymphoma.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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## INTRODUCTION

Primary mediastinal large B-cell lymphoma (PMLBL) is a distinct pathologic entity characterized by an anterior mediastinal mass thought to arise from a thymic medullary B cell, accounting for approximately 2% of pediatric mature B-cell lymphoma. Pathologically, the disease is indistinguishable from that seen in adult patients.[1] Children with PMLBL are older than children with other Non-Hodgkin Lymphoma (NHL), and there is a female predominance.[2] Historically, PMLBL has had a poorer outcome in pediatric patients compared with other mature B-NHL with a 5-year event-free survival (EFS) of 65%-75% using a chemotherapy-only approach in several international series.[2-5]

More recently, outstanding survival for adult patients with PMLBL has been reported without the need for routine irradiation through the use of the chemo-immunotherapy regimen, dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone plus rituximab (DA-EPOCH-R). The single-institution, uncontrolled phase II report of 51 adult patients from the US National Cancer Institute (NCI) showed a 5-year EFS of 93% with an overall survival (OS) of 97%, and 16 adult patients treated at Stanford had an EFS and OS of 100%.[6]

## CONTEXT

**Key Objective**

Primary Mediastinal Large B-cell Lymphoma (PMLBL) in children and adolescents has a poorer outcome than other mature B-cell non-Hodgkin lymphomas when treated with the similar regimens. A dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone plus rituximab (DA-EPOCH-R) regimen has been reported to give outstanding survival in adults with PMLBL. This prospective and multicenter study evaluated the efficacy of DA-EPOCH-R in children and adolescents.

**Knowledge Generated**

DA-EPOCH-R was not shown to be superior to historical chemotherapy regimens in children and adolescents with PMLBL. However, the emergence of CNS relapses and acute cardiac toxicity were observed—events unseen and only rarely seen with other pediatric regimens.

**Relevance**

DA-EPOCH-R has been adopted widely in many countries to treat PMLBL in children and adolescents. However, it should not be considered the optimum therapy for children and adolescents with this disease and further prospective trials of other regimens and new agents are required.

Given the outstanding published reports of the efficacy of DA-EPOCH-R, a randomized trial was not considered feasible. We thus conducted an international, prospective single-arm phase II trial (Inter-B-NHL ritux 2010) to establish whether DA-EPOCH-R could improve EFS compared with historical control in children and adolescents with PMLBL.

## PATIENTS AND METHODS

### Trial Oversight and Design

This phase II trial was an academic international study of two cooperative groups—the European Intergroup for Childhood Non-Hodgkin Lymphoma and the Children's Oncology Group (COG)—involving nine countries, sponsored by Gustave Roussy (for countries of the European Intergroup for Childhood Non-Hodgkin Lymphoma) and COG (for Australia, Canada, and the United States). F. Hoffmann-La Roche-Genentech provided partial funding and rituximab at no cost but had no part in the trial design, conduct of the study, or in the preparation of the manuscript.

Parents or patients (if appropriate) signed the informed consent and assent forms before enrollment in the trial. In each country, the Protocol (online only) was approved by the relevant ethics and regulatory bodies. An independent data and safety monitoring committee monitored trial progress.

### Patients

Eligible patients were age 6 months to 18 years with newly diagnosed PMLBL. Pathology slides were reviewed at national level in each country in Europe or centrally within COG, but this was not mandatory before enrollment. CSF cytology was mandatory at initial workup, and patients with CNS disease were excluded. Other main exclusion criteria were congenital immunodeficiency, prior organ transplantation, previous malignancy, known positive HIV serology, and prior exposure to rituximab. Because of potential rituximab-induced immunodeficiency, patients with severe active viral infection, especially hepatitis B virus (HBV) or HBV carrier history and/or positive HBV serology (except immunized status), were not eligible. There were no exclusion criteria on the basis of organ function with recommended dose guidelines for organ dysfunction provided in the Protocol.

Initial workup within 8 days before registration was performed for staging including clinical examination, chest and abdominal computed tomography (CT), or magnetic resonance imaging according to tumor site, bilateral bone marrow aspirates and biopsy, CSF cytology, and lactate dehydrogenase level. $^{18}$F-fluorodeoxyglucose positron emission tomography-CT (PET-CT) was recommended, but staging was not based on its result.

### Treatment

All patients received six courses of DA-EPOCH-R with granulocyte colony-stimulating factor (G-CSF), and dose escalation of doxorubicin, etoposide, and cyclophosphamide followed previously reported schedule (Data Supplement, online only).[6,7] A prephase of low-dose cyclophosphamide, vincristine, and prednisone was allowed 1 week before commencement of DA-EPOCH-R for patients requiring urgent treatment while awaiting histologic confirmation. $^{18}$F-fluorodeoxyglucose PET-CT was recommended at diagnosis, after two courses, and for complete remission assessment after the sixth course of DA-EPOCH-R. No treatment decisions were to be based on the PET-CT results. However, at the end of therapy, if PET-CT was positive, or a large residual tumor remained, then biopsy or removal of the residual mass was recommended.

### End Points

The primary end point was EFS defined as the interval from registration in the trial to the presence of viable cells in any

residual mass after the sixth DA-EPOCH-R course, relapse, progressive disease, second malignancy, or death from any cause. All events were validated by the Steering Committee.

### Secondary End Points

Secondary end points were OS (defined as the time between random assignment and death from any cause or the last follow-up contact for patients who were alive), complete remission rate at the assessment time, acute and long-term toxicity, adverse events (AEs) graded according to NCI-CTC V4: nonhematologic AE grade ≥ 3 and cardiac AE grade 2-5, abnormal left ventricular ejection fraction or abnormal left ventricular shortening fraction, rituximab infusion reactions, and immune reconstitution assessed by immunoglobulin (G, A, and M) levels and lymphocyte counts at 1 year and every year during follow-up until normal level, postvaccination antibody levels, and need for immunoglobulin infusion.

### Statistical Analysis

Historically, a long-term (≥ 4 years) EFS of 67% was established (on the basis of analysis of a merged data set of 114 pediatric patients with PMLBL, treated with chemotherapy used for other pediatric B-NHL, in published series from European and American studies[8]), with most events occurring in the first 2 years (a 1-year rate of 75% and a 2-year rate of 69%). As no disease relapses occurred after 4 years, EFS at this point represents a cure fraction. The efficacy of DA-EPOCH-R therapy was assessed by comparing the EFS for the sample of children and adolescents included in the trial with a fixed outcome, reflecting the historical survival. The null hypothesis was that the EFS for these patients is $EFS(t) = 0.67 + 0.33\{\exp(-1.5t)\}$ versus the alternative with $EFS(t) = [0.67 + 0.33\{\exp(-1.5t)\}]^R$, where R is $< 1.0$. A one-sample log-rank test[9] was used to compare the EFS experience with the fixed null outcome. Testing was performed at the 0.10 level of statistical significance (one-sided). A sample size of 40 patients would provide 90% power to detect a true long-term EFS of 84.6% and 80% power to detect a true long-term EFS of 82.4%. Further details are given in the Data Supplement.

## RESULTS

### Patients

Between April 2012 and April 2016, 48 patients were registered in the study: There was a suspension of enrollment between March 19 and June 16, 2015 because of pending approval of an amendment to increase the total number of patients from 40 to 47 because of a protocol error that resulted in the first seven patients receiving only 50% of the intended dose of prednisolone (60 mg/m$^2$/d in two divided doses on days 1-5 instead of 120 mg/m$^2$/d in two divided doses on days 1-5; Data Supplement). Two patients were deemed ineligible and excluded: one with a diagnosis of Burkitt leukemia who did not receive any trial therapy as the error was noted quickly and another patient whose diagnosis was Hodgkin Lymphoma on national pathologic review. The patient was treated with DA-EPOCH-R and relapsed at 2.8 years from diagnosis. As patients who received full dose of prednisolone did not have better outcome than the patients who received half dose (Data Supplement), the analyses were based on the 46 eligible patients registered with a diagnosis of PMLBL.

Patient characteristics (Table 1) revealed a predominance (57%) of female patients. The median age was 15.4 years (interquartile range [IQR]: 14-16 years). Thirty-one (67%) patients had large (> 10 cm) mediastinal masses. Initial staging confirmed Ann Arbor stage II disease in 31 patients, stage III in one patient, and stage IV in 12; data were missing for two patients.

National pathologic review was performed for 43 patients, and PMLBL was confirmed for 41 patients. Diffuse large B-cell lymphoma, centroblastic variant, was diagnosed in one patient (no event), and Gray zone NHL was diagnosed in one patient (event at 7 months and died at 21.5 months). The remaining three patients had a local pathologic diagnosis of PMLBL.

### Treatment

All patients received six courses of DA-EPOCH-R. In addition, 19 (41%) received a cyclophosphamide, vincristine, and prednisone course before the first DA-EPOCH-R course. Twenty-two of 46 patients (48%) reached at least dose level 4. Data were available to assess the adherence to the dose escalation rules for DA-EPOCH-R in 42 of 46 (91%) patients. Twelve of 42 (29%) patients should have received a dose escalation in at least one course of DA-EPOCH-R, and 4 of 42 (10%) patients should have had a dose reduction in at least one course of DA-EPOCH-R. Thirty-three (72%) and 11 (24%) patients received ≥ 300 mg/m$^2$ and ≥ 350 mg/m$^2$ of total cumulative dose of doxorubicin, respectively.

### Efficacy

The median follow-up was 59.0 months (IQR 52.6-69.2 months). There were a total of 14 events (Table 2). There were four inadequate response with viable cells in the residual mass, eight progressions or relapses, and two second malignancies (Hodgkin Lymphoma and acute promyelocytic leukemia). Among the progression or relapses, three involved the CNS parenchyma (two isolated including one with blasts in CSF and one combined with thoracic progression; all three patients had correct DA-EPOCH-R dose escalation). The EFS at 4 years was 69.6% (95% CI, 55.2 to 80.9; Fig 1A). The comparison of the observed EFS with historical $EFS = [0.67 + 0.33\{\exp(-1.5t)\}]$ was not significant ($P$ value = .59). DA-EPOCH-R did not, therefore, significantly improve EFS as compared with the historical rate. The 4-year EFS of the 12 patients who should have received a dose escalation in at least one course of DA-EPOCH-R was 58.3% (95% CI, 32.0 to 80.7), and it was 76.7% (95% CI, 59.1 to 88.2) for the 30 other patients

**TABLE 1.** Baseline Characteristics

| Characteristic | No. (%) |
|---|---|
| All | 46 (100) |
| Female sex | 26 (57) |
| Age, years | |
| Median (range) | 15.4 (7-17) |
| Interquartile range | 14-16 |
| Distribution, years | |
| 7 to < 12 | 4 (8) |
| 12 to < 15 | 15 (33) |
| 15 to < 18 | 27 (59) |
| National pathologic review | |
| PMLBL | 41 (89) |
| DLBCL | 1 (2) |
| Gray zone lymphoma | 1 (2) |
| Not done[a] | 3 (7) |
| Ann Arbor stage | |
| I | 0 |
| II | 31 (67) |
| III | 1 (2) |
| IV | 12 (26) |
| Not available | 2 (4) |
| Lactate dehydrogenase | |
| < 2 × ULN | 31 (67) |
| ≥ 2 × ULN | 15 (33) |
| Sites of involvement | |
| Mediastinum | |
| Tumor ≤ 10 cm diameter | 15 (33) |
| Tumor > 10 cm diameter | 31 (67) |
| Subdiaphragmatic involvement | 14 (30) |
| Bone marrow involvement | 1 (2) |

Abbreviations: DLBCL, diffuse large B-cell lymphoma; PMLBL, primary mediastinal large B-cell lymphoma; ULN, upper limit of normal.

[a]These cases received a diagnosis of PMLBL on local pathologic review.

(log-rank test *P* value = .15). There were seven deaths, six because of progression or relapse and one because of second malignancy (acute promyelocytic leukemia). The OS was 84.8% (95% CI, 71.8% to 92.4%) at 4 years (Fig 1B; Sensitivity analyses are given in the Data Supplement).

### Response to Treatment and PET Imaging

After the completion of the sixth course of DA-EPOCH-R, 33 of 46 (72%) patients had a residual mass. In total, 19 of 33 had biopsies or excisions or partial excisions: six had viable tumor cells (median residual mass size: 52 mm, range, 11-86) and for 13 patients, the histology revealed complete necrosis (median residual mass size: 56 mm, range, 15-104). Thirty-nine patients (85%) were considered to have achieved complete remission. Of the remaining patients, four (9%) had persistent disease histologically proven, two had disease progression histologically proven, and one had persistent disease not histologically proven (residual mass of 100 mm followed by early progression).

Forty-two patients (91%) had PET-CT after the end of therapy (Table 3). The negative predictive value of PET-CT was found to be 23/26 = 88.5% (95% CI, 69.9 to 97.6), whereas the positive predictive value was 7/11 = 63.6% (95% CI, 30.8 to 89.1). Of note, among the three patients with negative end-of-therapy PET-CT and subsequent relapse, two had isolated CNS relapse 4 and 18 months after PET-CT (8 and 22 months after enrollment).

### Safety

Acute AEs were assessed in all patients and all 276 courses except neutropenia and thrombopenia that were assessed in 42 patients (91%) and 252 courses. No toxic deaths were reported. Grade 4 neutropenia occurred in 106 of 251 courses (42%), and grade 4 thrombocytopenia occurred in eight of 252 courses (3%). Nonhematologic toxicities of grade ≥ 3 or cardiac toxicity grade ≥ 2 occurred in 47 of 276 courses (17%) among 30 of 46 patients (65%; Table 4). The most frequent AE was febrile neutropenia with 29 episodes among 276 courses (10.5%) in 21 patients (46%). Ten infections (3.6%) of grade ≥ 3 were observed in eight patients (17%).

### Cardiac Toxicity

There were four adverse cardiac events (grade ≥ 2) in four (8.7%) patients reported during treatment. Two patients had had a pericardial effusion (grade 2) likely disease-related. A further patient developed atrial fibrillation (grade 3) after the third course of chemotherapy, and the final patient had left ventricular systolic dysfunction (grade 2) after the fifth cycle of therapy. Twenty-six of 36 patients with continuous first complete remission (72%) have had echocardiographic evaluation at 1 year following the last chemotherapy; of these, one (3.8%) patient met cardiac toxicity criteria with a Shortening Fraction of 26%. Long-term cardiac outcome requires further follow-up. One last patient had severe idiopathic pleuroparenchymal fibroelastosis that occurred 3 years after enrollment and 2 years after relapse and required lung transplantation but had normal cardiac function.

### Immunity Status

At the end of treatment, 19 of 30 (63%) evaluable patients had low immunoglobulin G (IgG; less than the lower limit of the normal range), whereas at 1 year after inclusion in the study, 11 of 22 (50%) evaluable patients had low IgG. Six patients received immunoglobulin infusions, all of them for low IgG levels without infection, and, for four patients, immunoglobulin infusions started after treatment failure (relapse or progression or persistent disease). The

**TABLE 2.** Events

| Patient No. | Description (site) | Time From Inclusion (months) | Maximum Dose Level | Dose Adjustment[a] | Further Therapy | Patient Status (follow-up in months) |
|---|---|---|---|---|---|---|
| 120 | Persistent disease | 4 | 1 | No data | NA | DoD (21) |
| 124 | Persistent disease (followed by rapid progression including CNS) | 4 | 1 | Incorrect | NA | DoD (12) |
| 23 | Persistent disease | 5 | 3 | Incorrect | R-DHAP and DXT | DoD (11) |
| 8 | Persistent disease | 5 | 2 | Correct | R-ICE ×3 and BEAM autograft | Alive (61) |
| 5 | Progression (local) | 4 | 4 | Incorrect | R-DHAP ×2, R-ICE ×3, autograft, and DXT | Alive (73) |
| 99 | Progression (local)[b] | 7 | 5 | Correct | NA | DoD (21) |
| 69 | Progression (local) | 7 | 3 | Incorrect | NA | DoD (15) |
| 19 | Relapse (CNS) | 8 | 4 | Correct | HDMTX, RCYVE, autograft, and brain EBRT | Alive (72) |
| 81 | Relapse (local) | 10 | 2 | No data | NA | DoD (17) |
| 103 | Relapse (local) | 11 | 5 | Incorrect (undue increase) | NA | Alive (52) |
| 24 | Relapse (CNS) | 22 | 3 | Correct | FAB/LMB Group C3, autograft, and brain EBRT | Alive (58) |
| 90 | Relapse (local) | 33 | 1 | Incorrect | NA | Alive (59) |
| 29 | Second malignancy (AML) | 22 | 4 | Correct | None | DoD (22) |
| 1 | Second malignancy (HL) | 33 | 2 | Correct | NA | Alive (63) |

Abbreviations: AML, acute promyelocytic leukemia; BEAM, carmustine, etoposide, cytarabine, melphalan; DoD, died of disease; DXT, radiotherapy; EBRT, external beam radiotherapy; FAB/LMB, French-American-British/Lymphomes malins B; HDMTX, high-dose methotrexate; HL, Hodgkin lymphoma; NA, details not available; RCYVE, rituximab, high-dose cytarabine, etoposide; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide.

[a]Except when otherwise specified, Incorrect means should have been increased more.

[b]Two months before progression, patient had persistent disease not histologically proven at time of assessment.

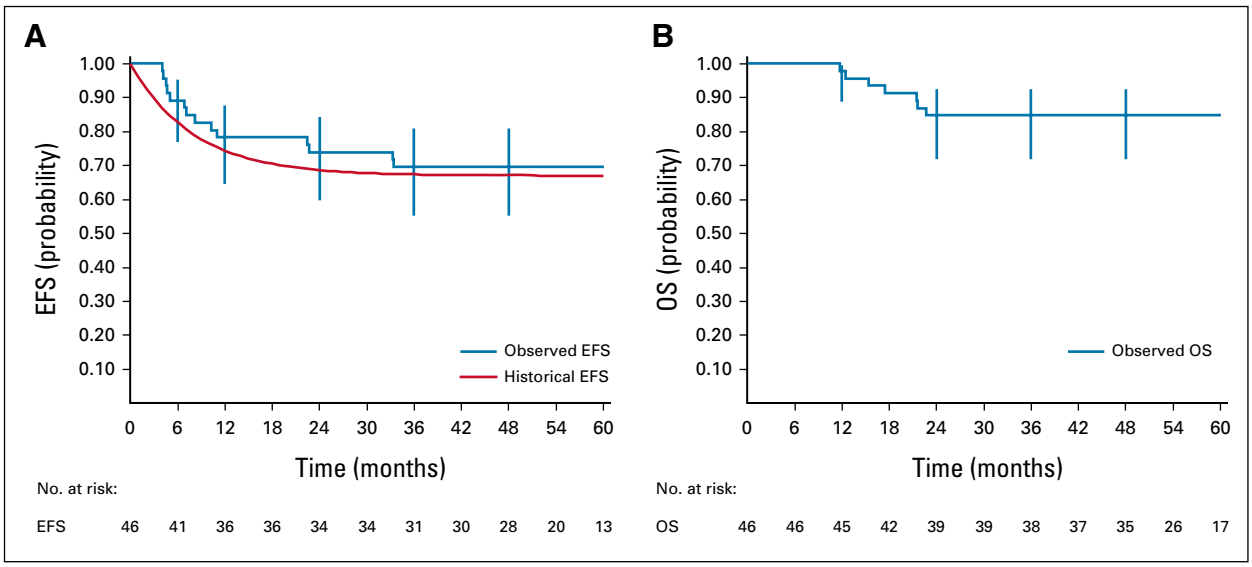


**FIG 1.** Kaplan-Meier estimates of (A) EFS and (B) OS in PMLBL. Vertical lines represent the Rothman 95% CIs; point estimates of 12-, 24-, 36-, and 48-month EFS and OS with 95% CIs are shown. EFS, event-free survival; OS, overall survival; PMLBL, primary mediastinal large B-cell lymphoma.

**TABLE 3.** PET Evaluation After the Sixth DA-EPOCH-R and Histologic Exploration and/or Follow-up

| PET Evaluation | Histology-Negative and No Relapse or Progression at 24 Months | Histology-Positive or Relapse or Progression Within the First 24 Months | Total |
|---|---|---|---|
| PET-negative[a] | 23 | 3 | 26 |
| PET-positive | 4 | 7 | 11 |
| PET equivocal | 5 | 0 | 5 |
| Total | 32 | 10 | 42 |

Abbreviations: DA-EPOCH-R, dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone plus rituximab; PET, positron emission tomography.

[a]Among the three patients with negative PET-CT and further relapse, two had isolated CNS relapse 4 and 18 months after PET-CT (8 and 22 months after enrollment).

occurrence of late infections after longer follow-up has not been evaluated.

## DISCUSSION

In this prospective, multisite international phase II study of DA-EPOCH-R in pediatric and adolescent patients with PMLBL, the 4-year EFS was 69.6% (95% CI, 55.2 to 80.9) and the long-term OS was 84.8% (95% CI, 71.8 to 92.4). No improvement in EFS over historical controls with pediatric chemotherapy-only regimens was observed with the use of the regimen DA-EPOCH-R. There have been few prospective trials of this regimen in the pediatric or adult populations, and comparison with monocentric or retrospective trials is difficult.

The characteristics of the patients included in this study differed from those included in the NCI phase II study[6] only with respect to age (median 15 *v* 30 years); in other respects, the patients were similar: sex distribution (57% *v* 59% female), large mediastinal masses (> 10 cm, 67% *v* 65%), and stage IV disease (27% *v* 29%). Similarly, with regard to treatment, more than 50% of patients in the NCI study achieved dose escalation ≥ 4% and 48% in the current study. Residual masses were observed in 36 of 51 (71%) in the NCI study and 33 of 46 (72%) in the current study. In the NCI study, viable tumor on biopsy of residual mass was not counted as an event for EFS analysis and neither was second malignancy. A reanalysis of our data using the NCI event criteria gives only a small increase of the 4-year EFS to 73.9% (95% CI, 59.7 to 84.4; Data Supplement). We examined the adherence to dose escalation rules and found that 29% of patients should have received a higher dose in at least one course of DA-EPOCH-R, but these data are not reported in other studies so it is not possible to assess whether this might have contributed to the outcome that we have observed. Among the 10 relapses that occurred locally (or were due to persistent disease), failure to escalate as per the Protocol was observed in five (one was due to gastric perforation and therefore clinically justified; Table 2). In the NCI study, five of 51(10%) patients who had evidence of continuous response between cycles 4 and 6 received eight cycles of DA-EPOCH-R. A major consideration for children is that eight cycles deliver a maximal possible cumulative anthracycline dose of approximately 600 mg/m$^2$, which is unacceptable because of high risk of long-term cardiac damage.[10]

The only prospective randomized trial of DA-EPOCH-R including patients with PMLBL was the Phase III Intergroup Trial Alliance/CALGB 50303 trial of DA-EPOCH-R versus R-CHOP for diffuse large B-cell lymphoma, 35 patients with PMLBL were included, and there was no difference in outcome between those treated in either arm.[11] Two retrospective studies of children and adolescents with PMLBL treated with DA-EPOCH-R have been reported.[12,13] The small number of patients (15) in the initial Berlin-Frankfurt-Munster report on DA-EPOCH-R makes further comment difficult; they observed a 2-year EFS of 92.8%. The maximum cumulative dose of doxorubicin was capped at 360 mg/m$^2$, and additional intrathecal therapy was given.[11] Of note was the inclusion of one isolated CNS relapse (6.7%) in the report consistent with the rate that we observed in the current study (6.5%). In the previous FAB/LMB experience with PMLBL,[3] using intrathecal therapy and other CNS-directed therapy such as high-dose methotrexate and aracytine, there were no CNS relapses at first relapse. Moreover, in the French LMB2001 prospective trial, among the 42 patients with PMLBL, none had CNS relapse, and among the 22 of 42 patients treated with rituximab in addition to LMB-based chemotherapy, only one relapsed (mediastinum).[14]

In the other retrospective series of children and adults with PMLBL treated with DA-EPOCH-R,[13] there were 38 children who experienced a 3-year EFS of 81%. The characteristics of the children included were somewhat different from what we observed (more large mediastinal masses, greater proportion with elevated lactate dehydrogenase, and fewer stage IV in our trial). When combined with the adults in the study, there was no prognostic significance found for dose level achieved and a positive PET-CT at the end of therapy was associated with a poor prognosis. The exploratory findings of our study cast doubt over their conclusion that the total cumulative dose of doxorubicin can be capped at 360 mg/m$^2$ as adopted by the Berlin-Frankfurt-Munster group, with no detriment to efficacy. Moreover, and as reported by others,[15] the positive predictive value of PET-CT at the end of therapy was low (64%) in our prospective trial. PET-CT was not used for clinical decision making in this study, and central review was not undertaken. It was not, therefore, possible to refine the level of PET-CT positivity for those without a complete metabolic response after six cycles of DA-EPOCH-R using Deauville score.

The data from our trial confirm that DA-EPOCH-R has a favorable acute toxicity profile compared with the combination of rituximab with chemotherapy for other pediatric B-NHL.[15] However, long-term evaluation of cardiac toxicity is required since 72% and 24% of patients

**TABLE 4.** Acute AEs Grade ≥ 3 or Cardiac AEs Grade ≥ 2

| | DA-EPOCH-R Cycle 1 | | DA-EPOCH-R Cycle 2 | | DA-EPOCH-R Cycle 3 | | DA-EPOCH-R Cycle 4 | | DA-EPOCH-R Cycle 5 | | DA-EPOCH-R Cycle 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Adverse Event** | **No.** | **%** | **No.** | **%** | **No.** | **%** | **No.** | **%** | **No.** | **%** | **No.** | **%** |
| At least one AE grade ≥ 3 or cardiac AE grade ≥ 2 | | | | | | | | | | | | |
| No | 34 | 74 | 41 | 89 | 44 | 96 | 41 | 89 | 36 | 78 | 33 | 72 |
| Yes | 12 | 26 | 5 | 11 | 2 | 4 | 5 | 11 | 10 | 22 | 13 | 28 |
| Febrile neutropenia | | | | | | | | | | | | |
| None | 44 | 96 | 44 | 96 | 45 | 98 | 42 | 91 | 38 | 83 | 34 | 74 |
| Grade 3 | 2 | 4 | 2 | 4 | 1 | 2 | 4 | 9 | 8 | 17 | 12 | 26 |
| Mucositis oral | | | | | | | | | | | | |
| None or grades 1 and 2 | 45 | 98 | 46 | 100 | 45 | 98 | 45 | 98 | 43 | 93 | 44 | 96 |
| Grade 3 | 1 | 2 | 0 | 0 | 1 | 2 | 1 | 2 | 3 | 7 | 2 | 4 |
| Infections | | | | | | | | | | | | |
| None or grades 1 and 2 | 42 | 91 | 45 | 98 | 46 | 100 | 46 | 100 | 45 | 98 | 42 | 91 |
| Grade 3 | 3 | 7 | 1 | 2 | 0 | 0 | 0 | 0 | 1 | 2 | 3 | 7 |
| Grade 4 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Sepsis | | | | | | | | | | | | |
| Grade 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| KT-related infection | | | | | | | | | | | | |
| Grade 4 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Upper respiratory infection | | | | | | | | | | | | |
| Grade 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 4 |
| Mediastinal infection | | | | | | | | | | | | |
| Grade 3 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Skin infection | | | | | | | | | | | | |
| Grade 3 (zona) | 2 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 |
| Dental cellulitis | | | | | | | | | | | | |
| Grade 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Wound infection | | | | | | | | | | | | |
| Grade 3 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cardiac adverse events grade ≥ 2 | | | | | | | | | | | | |
| Left ventricular systolic dysfunction (grade 2) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Atrial fibrillation (grade 3) | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pericardial effusion (grade 2) | 1 | 2 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other adverse events grade ≥ 3 | | | | | | | | | | | | |
| Hypophosphatemia (grade 3) | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypokalemia (grade 3) | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 |
| Hyperkalemia (grade 3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 |
| Dehydration (grade 3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 |
| Infusion reaction to rituximab (grade 3) | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Thromboembolic event (grade 4) | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 |
| Pleuritic pain (grade 3) | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gastric perforation (grade 4) | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vomiting (grade 3) | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Syncope (grade 3) | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

NOTE. Hematologic AEs, except febrile neutropenia, are not recorded in this table.

Abbreviations: AE, adverse event; DA-EPOCH-R, dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone plus rituximab.

received ≥ 300 mg/m$^2$ and ≥ 350 mg/m$^2$ of total cumulative dose of doxorubicin, respectively. The impact of rituximab on immunity is consistent with that seen in the trial for non-PMLBL patients.[16]

Although DA-EPOCH-R did not improve EFS in our study in comparison with historical controls treated with (LMB and other) chemotherapy only, it has been clearly demonstrated in adult patients with PMLBL that the addition of rituximab improves outcome.[17] It is possible that the failure to demonstrate an increase in survival with rituximab over historical control in the current study is related to the efficacy of the chemotherapy part of the regimen in children and adolescents; however, our study was not designed to assess the efficacy of adding rituximab to chemotherapy or the addition of rituximab to DA-EPOCH in children. Why we did not reproduce the outstanding NCI results is not clear although multisite evaluation of a regimen does not always replicate data generated by single institutions.

The lower acute toxicity of DA-EPOCH-R with similar EFS to historical pediatric regimens that did not include rituximab would commend it as a new standard; however, the observation of isolated and combined CNS relapse with its use sounds a note of caution as these are very rarely reported in historical pediatric series (but being recognized in protocols more commonly used in adults with a rate of 3%-4%[10]). Further prospective trials are required to define optimal treatment for pediatric and adolescent PMLBL, and it is likely that alternative regimens such as chemotherapy used for other pediatric B-NHL or novel agents (eg, NF-kB pathway inhibitors or anti-PD1 therapies) will be required to enable children and adolescents to realize the survival outcomes that have been observed in some adults treated with DA-EPOCH-R.


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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## REFERENCES

1. Oschlies I, Burkhardt B, Salaverria I, et al: Clinical, pathological and genetic features of primary mediastinal large B-cell lymphomas and mediastinal gray zone lymphomas in children. Haematologica 96:262-268, 2011
2. Burkhardt B, Zimmermann M, Oschlies I, et al: The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. Br J Haematol 131:39-49, 2005
3. Gerrard M, Waxman IM, Sposto R, et al: Outcome and pathologic classification of children and adolescents with mediastinal large B-cell lymphoma treated with FAB/LMB96 mature B-NHL therapy. Blood 121:278-285, 2013
4. Seidemann K, Tiemann M, Lauterbach I, et al: Primary mediastinal large B-cell lymphoma with sclerosis in pediatric and adolescent patients: Treatment and results from three therapeutic studies of the Berlin-Frankfurt-Münster Group. J Clin Oncol 21:1782-1789, 2003
5. Pillon M, Di Tullio MT, Garaventa A, et al: Long-term results of the first Italian Association of Pediatric Hematology and Oncology protocol for the treatment of pediatric B-cell non-Hodgkin lymphoma (AIEOP LNH92). Cancer 101:385-394, 2004
6. Dunleavy K, Pittaluga S, Maeda LS, et al: Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 368:1408-1416, 2013
7. Wilson WH, Grossbard ML, Pittaluga S, et al: Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: A pharmacodynamic approach with high efficacy. Blood 99:2685-2693, 2002
8. Patte C, Reiter A, Rosolen A, et al: Primary mediastinal large B-cell lymphoma (PMLBL) in chidren/adolescents. Data of European and American Groups. Ann Oncol 16:61-62, 2005
9. Finkelstein DM, Muzikansky A, Schoenfeld DA. Comparing survival of a sample to that of a standard population. J Natl Cancer Inst 95:1434-1439, 22003
10. van Dalen EC, van der Pal HJ, Kremer LC. Different dosage schedules for reducing cardiotoxicity in people with cancer receiving anthracycline chemotherapy. Cochrane Database Syst Rev 3:CD005008, 2016
11. Bartlett NL, Wilson WH, Jung SH, et al: Dose-adjusted EPOCH-R compared with R-CHOP as Frontline therapy for diffuse large B-cell lymphoma: Clinical outcomes of thePhase III Intergroup Trial Alliance/CALGB 50303. J Clin Oncol 37:1790-1799, 2019
12. Woessmann W, Lisfeld J, Burkhardt B, et al: Therapy in primary mediastinal B-cell lymphoma. N Engl J Med 369:282-284, 2013
13. Giulino-Roth L, O'Donohue T, Chen Z, et al: Outcomes of adults and children with primary mediastinal B-cell lymphoma treated with dose-adjusted EPOCH-R. Br J Haematol 179:739-747, 2017
14. Dourthe ME, Phulpin A, Auperin A, et al: Rituximab in addition to LMB-modified chemotherapy regimen in pediatric patients with primary mediastinal large B-cell lymphoma: Results of the French LMB2001 prospective study. Pediatr Blood Cancer 66:S38-S, 2019
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16. Minard-Colin V, Auperin A, Pillon M, et al: Rituximab for high-risk, mature B-cell non-Hodgkin's lymphoma in children. N Engl J Med 382:2207-2219, 2020
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**Dose-Adjusted Etoposide, Doxorubicin, and Cyclophosphamide With Vincristine and Prednisone Plus Rituximab Therapy in Children and Adolescents With Primary Mediastinal B-Cell Lymphoma: A Multicenter Phase II Trial**

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