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Outcomes of adults and children with primary mediastinal B-cell lymphoma treated with dose-adjusted EPOCH-R

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Summary

Treatment with dose-adjusted EPOCH (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone) chemotherapy and rituximab (DA-EPOCH-R) has become the standard of care for primary mediastinal B-cell lymphoma (PMBCL) at many institutions despite limited data in the multi-centre setting. We report a large, multi-centre retrospective analysis of children and adults with PMBCL treated with DA-EPOCH-R to characterize outcomes and evaluate prognostic factors. We assessed 156 patients with PMBCL treated with DA-EPOCH-R across 24 academic centres, including 38 children and 118 adults. All patients received at least one cycle of DA-EPOCH-R. Radiation therapy was administered in 14·9% of patients. With median follow-up of 22·6 months, the estimated 3-year event-free survival (EFS) was 85·9% [95% confidence interval (CI) 80·3–91·5] and overall survival was 95·4% (95% CI 91·8–99·0). Outcomes were not statistically different between paediatric and adult patients. Thrombotic complications were reported in 28·2% of patients and were more common in paediatric patients (45·9% vs. 22·9%, $P = 0{\cdot}011$). Seventy-five per cent of patients had a negative fluorodeoxyglucose positron emission tomography (FDG-PET) scan at the completion of DA-EPOCH-R, defined as Deauville score 1–3. Negative FDG-PET at end-of-therapy was associated with improved EFS (95·4% vs. 54·9%, $P < 0{\cdot}001$). Our data support the use of DA-EPOCH-R for the treatment of PMBCL in children and adults. Patients with a positive end-of-therapy FDG-PET scan have an inferior outcome.

Keywords: primary mediastinal B-cell lymphoma, DA-EPOCH-R, non-Hodgkin lymphoma, paediatric oncology.

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Primary mediastinal B-cell lymphoma (PMBCL) is a rare subtype of non-Hodgkin lymphoma (NHL) with unique clinical and molecular characteristics (Savage *et al*, 2003; Swerdlow *et al*, 2008). The disease classically occurs in adolescent and young adult women and presents with bulky mediastinal adenopathy. From a molecular standpoint, PMBCL is distinct from diffuse large B-cell lymphoma (DLBCL) and shares many biologic similarities with classical Hodgkin lymphoma, including dysregulation of JAK-STAT and NF-κB signalling and overexpression of PD1 (also termed PDCD1) ligands (Moller *et al*, 1986; Rosenwald *et al*, 2003; Guiter *et al*, 2004; Feuerhake *et al*, 2005).

As PMBCL is rare, there are few prospective studies evaluating therapy, resulting in no uniform standard of care. Both paediatric and adult clinical trials historically included patients with PMBCL on DLBCL protocols, however outcomes in the PMBCL subset differ. Adults with PMBCL have been treated with rituximab and anthracycline-containing chemotherapy regimens such as R-CHOP(rituximab + cyclophosphamide, doxorubicin, vincristine, prednisolone), R-HCVAD (rituximab + hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone + methotrexate and cytarabine), R-VACOP-B (rituximab + etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, bleomycin), or R-MACOP-B (rituximab + methotrexate/leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin), followed by radiation therapy (Rieger *et al*, 2011; Martelli *et al*, 2014; Soumerai *et al*, 2014; Pinnix *et al*, 2015; Binkley *et al*, 2016; Goldschmidt *et al*, 2016). Children with PMBCL have been treated on mature B-NHL protocols, which contain dose-intensive multi-agent chemotherapy without consolidative radiation (Seidemann *et al*, 2003; Pillon *et al*, 2004; Gerrard *et al*, 2013).

Excellent outcomes have recently been reported using infusional dose-adjusted etoposide, doxorubicin and cyclophosphamide with vincristine, prednisone and rituximab (DA-EPOCH-R) without radiotherapy. A single centre phase II study of this regimen in adults reported a 5-year event-free survival (EFS) of 93% (Dunleavy *et al*, 2013). Other single-centre retrospective analyses, including one reported with the prospective phase II trial, describe similar outcomes, however with small numbers of patients (Dunleavy *et al*, 2013; Pinnix *et al*, 2015; Binkley *et al*, 2016). The Cancer and Leukemia Group B/Alliance group recently reported preliminary results from a randomized phase III trial of R-CHOP *versus* DA-EPOCH-R in adults with DLBCL (Wilson *et al*, 2016). The number of patients with PMBCL enrolled on this trial was small ($n = 28$) and will probably be insufficient to draw definitive conclusions.

The experience in paediatrics with DA-EPOCH-R is also limited. The Berlin-Frankfurt-Münster (BFM) NHL group preliminarily reported an ongoing case series of 15 paediatric patients with PMBCL treated with DA-EPOCH-R with a 2-year EFS and overall survival (OS) of 92% (Woessmann *et al*, 2013). An international phase II trial is prospectively studying this regimen in children with PMBCL [Children's Oncology Group (COG) ANHL1131, NCT01516580]. This study recently completed accrual with outcomes not yet reported. In total, the published experience to date of DA-EPOCH-R for the treatment of PMBCL in children and adults is less than 100 patients including prospective and retrospective studies. Despite the limited experience, enthusiasm for this regimen has resulted in the adoption of DA-EPOCH-R as standard of care in many academic medical centres for the treatment of both children and adults with PMBCL.

Given the lack of data from large multi-centre studies evaluating DA-EPOCH-R in PMBCL, we performed a retrospective analysis of 156 paediatric and adult patients with PMBCL treated with DA-EPOCH-R to: (i) determine outcomes, (ii) investigate potential differences between children and adults, and (iii) evaluate the prognostic relevance of end-of-therapy fluorodeoxyglucose positron emission tomography (FDG-PET) imaging.

Methods

Study design

We conducted a multicentre retrospective analysis of patients with PMBCL diagnosed between 2005 and 2015 across 24 academic medical centres in the US and Canada. Centres queried their institutional databases to identify eligible subjects. Patients of any age were included if they had biopsy-proven PMBCL and received at least one cycle of DA-EPOCH-R. The diagnosis of PMBCL was made at the local institution based on World Health Organisation criteria (Swerdlow *et al*, 2008). Patients were excluded if they were known human immunodeficiency virus-positive or if they received chemotherapy prior to DA-EPOCH-R with the exception of corticosteroids or one cycle of reduction-phase chemotherapy with low dose cyclophosphamide, vincristine and prednisone. Paediatric patients treated on the prospective clinical trial COG ANHL1131 were also excluded as they will be reported separately. The Institutional Review Boards of all participating centres approved the study.

Data on diagnosis, treatment, and outcome were collected at the local sites and submitted for central analysis. The local radiologists assigned an FDG-PET Deauville score for end-of-therapy imaging. Participating sites submitted data on a total of 162 patients. Six patients were excluded: four for not meeting eligibility criteria and two for having inadequate data, leaving 156 patients for analysis. Among these 156 patients, 35 were treated by a paediatric oncologist and 121 were treated by a medical oncologist. Given that many patients aged 18–20 years were treated by a paediatric oncologist, we defined paediatric patients by age <21 years ($n = 38$) and adult patients by age ≥21 years ($n = 118$).

Statistical analysis

Baseline characteristics between groups were compared using the Wilcoxon Rank-Sum test for continuous variables and the Fisher's exact test for categorical variables. The probabilities of EFS and OS were calculated from the time of diagnosis using Kaplan–Meier estimates. Event-free survival was defined as the time from diagnosis to relapse, progression, second malignancy, death from any cause, or date of last follow-up. The administration of radiation therapy was not considered an event. Overall survival was defined as time from diagnosis to death from any cause or date of last follow-up. Survival differences between groups were compared by log-rank test. All statistical tests were two-sided with a significance level of 0·05. Analyses were performed using statistical software SAS Version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The baseline patient characteristics are presented in Table I. The median age was 31 years (range 9–70). The median age of patients treated by a paediatric oncologist was 16 years (range 9–21) and the median age of patients treated by a medical oncologist was 34 years (range 18–70). Sixty-four per cent of patients were female. Eastern Cooperative Oncology Group performance status among patients aged ≥18 years was 0 or 1 in 81% of patients. The median diameter of the largest tumour was 11·5 cm (range 5·2–18·6 cm). Paediatric patients were more likely to present with a bulky tumour >10 cm (78·4% vs. 57·9%, $P = 0·031$). Other baseline characteristics did not differ between paediatric and adult patients including: B symptoms

Table I. Patient characteristics*.

	Total cohort $n = 156$	Paediatrics (age <21 years) $n = 38$	Adults (age ≥21 years) $n = 118$	*P* value Paediatric *versus* adult
Age, years: median (range)	31 (9–70)	16 (9–20)	34 (21–70)	**<0·01**
Female sex: *n* (%)	100 (64·1)	21 (55·3)	79 (66·9)	0·243
ECOG performance status: median (range)	1 (0–4)	N/A	1 (0–4)	N/A
Stage: *n* (%)				
I	26 (16·8)	1 (2·6)	25 (21·4)	N/A†
II	68 (43·9)	9 (23·7)	59 (50·4)	
III	30 (19·4)	23 (60·5)	7 (6·0)	
IV	31 (20·0)	5 (13·2)	26 (22·2)	
Staging system used: *n* (%)				
Ann Arbor	128 (82·6)	13 (34·2)	115 (98·3)	**<0·001**
Murphy	27 (17·4)	25 (65·8)	2 (1·7)	
B symptoms: *n* (%)	61 (39·9)	11 (30·6)	50 (tumour)	0·244
Bulky tumour >10 cm: *n* (%)	95 (62·9)	29 (78·4)	66 (57·9)	**0·031**
LDH > ULN: *n* (%)	125 (82·8)	30 (85·7)	95 (81·9)	0·799
Extranodal disease‡: *n* (%)	51 (32·9)	15 (39·5)	36 (30·8)	0·328
Pleural effusion: *n* (%)	73 (48·0)	20 (58·8)	53 (44·9)	0·176
Pericardial effusion: *n* (%)	82 (53·9)	19 (55·9)	63 (53·4)	0·847
$CD20^+$ malignant cells: *n* (%)	146 (98·6)	30 (100)	116 (98·3)	1·000

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; *n*, number; N/A, not available; ULN, upper limit of normal.
*The percentage of patients among those for whom that variable was reported.
†Disease stage cannot be compared between paediatric and adult patients due to different staging systems used in paediatric (Murphy Classification) and adult (Ann Arbor) practice.
‡Sites of extranodal disease include: lung ($n = 12$), bone/bone marrow ($n = 6$), chest wall ($n = 3$), adrenal gland ($n = 2$), pancreas ($n = 2$), muscle ($n = 2$), kidney ($n = 1$), spinal canal ($n = 1$), parotid ($n = 1$), pericardium ($n = 1$), atrium ($n = 1$), bowel ($n = 1$), multiple sites ($n = 18$).
Bold: $P<0·5$.

(in 39·9% of all patients), elevated lactate dehydrogenase (in 82·8%), extranodal disease (in 32·9%), pleural effusion (in 48·0%) and pericardial effusion (in 53·9%). Twenty-two per cent of adult patients and 13% of paediatric patients had stage IV disease. Comparisons between paediatric and adult patients with regard to stage could not be made due to different staging systems for paediatric and adult NHL, specifically the Murphy Staging System in paediatrics and the Ann Arbor System in adults (Lister *et al*, 1989; Murphy *et al*, 1989). In the Murphy Staging System, mediastinal disease is considered stage III.

Treatment characteristics

Treatment characteristics are presented in Table II. All patients received at least one cycle of DA-EPOCH-R. Ninety-four per cent of patients completed 6 cycles ($n = 143$) or 8 cycles ($n = 4$). Among patients who received less than 6 cycles the reasons for discontinuation were progressive disease ($n = 2$), toxicity ($n = 4$) or not reported/available ($n = 3$). Ninety-nine per cent of patients received growth factor support during treatment. Paediatric patients were more likely to receive filgrastim (used in 59·4% of children and 34·4% of adults). Adult patients were more likely to receive pegfilgrastim (used in 65·5% of adults and 31·0% of children). Dose escalation beyond dose level 1 occurred in 91% of patients and was independent of the type of growth factor received. The maximum dose level reached was: level 1 in 9·3% of patients, level 2 in 24·0%, level 3 in 27·3%, level 4 in 28·0% and level 5 in 11·3%. Paediatric patients were more likely to be escalated to dose level 4 or higher (54·1% vs. 32·7%, $P = 0·031$).

Radiation therapy (RT) after DA-EPOCH-R was administered in 23 of 154 patients (14·9%) at the discretion of the treating physician. The proportion of patients receiving RT did not differ in paediatric and adult patients. The median radiation dose was 36 Gy (range 28–50·4 Gy).

Thrombotic complications

Patients with PMBCL may have multiple risk factors for venous thrombosis, including vascular compression from a bulky mediastinal tumour, an inflammatory state from underlying malignancy and an indwelling central venous catheter. In our cohort, 28·2% of patients experienced a thrombosis during treatment. The sites of thromboses included: upper extremity ($n = 22$), internal jugular vein or superior vena cava ($n = 10$), intracardiac ($n = 5$), pulmonary embolism ($n = 5$) and lower extremity ($n = 2$). Thirty-four per cent of thrombosis cases were considered related to a central venous catheter. The rates of catheter-associated

Table II. Treatment characteristics.

	Total cohort $n = 156$	Paediatrics (age <21 years) $n = 38$	Adults (age ≥21 years) $n = 118$	*P* value Paediatric *versus* adult
Total number of cycles of DA-EPOCH-R: median (range)	6 (1–8)	6 (6–8)	6 (1–8)	0·148
Patients escalated to at least dose level 4: *n* (%)	57/150 (38·0)	20/37 (54·1)	37/113 (32·7)	**0·031**
Patients not escalated beyond dose level 1: *n* (%)	15/150 (10·0)	2/37 (5·4)	13/113 (11·5)	0·360
Patients receiving RT: *n* (%)	23/154 (14·9)	4/36 (11·1)	19/118 (16·1)	0·598
Radiation dose, Gy: median (range)	36·4 (28·0–50·4)	30·6 (30·0–50·4)	36·4 (28·0–50·4)	0·887
Patients receiving growth factor support: *n* (%)	148/150 (98·7)	33/34 (97·1)	115/116 (99·1)	0·403
Type of growth factor: *n* (%)				
GCSF alone	55/148 (37·2)	19/32 (59·4)	36/116 (31·0)	**0·005**
PEG-GCSF alone	87/148 (58·8)	11/32 (34·4)	76/116 (65·5)	
Both	6/148 (4·1)	2/32 (6·3)	4/116 (3·4)	

DA-EPOCH-R, dose-adjusted etoposide, doxorubicin and cyclophosphamide with vincristine, prednisone and rituximab; GCSF, granulocyte colony-stimulating factor; *n*, number; PEG-GCSF, pegylated granulocyte colony-stimulating factor; RT, radiotherapy.
Bold: $P<0·5$.

thrombosis were similar among patients with a peripherally inserted central catheter (PICC) and those with an implanted port (12·5% vs. 9·2%, $P = 0·565$). Paediatric patients had a higher rate of thrombosis overall compared to adults (45·9% vs. 22·9%, $P = 0·011$). There was also a trend toward increased catheter-associated thrombosis in paediatric patients but this was not statistically significant (18·4% vs. 6·8%, $P = 0·053$).

Monitoring for cardiac toxicity

Long-term cardiac toxicity is a concern in patients exposed to anthracycline chemotherapy and/or mediastinal radiation. Although the follow-up of this study is too short to comprehensively evaluate for cardiac toxicity, we collected data on monitoring patterns and any reports of early cardiac abnormalities. Ninety-two of 156 patients (59%) underwent echocardiogram monitoring after the initiation of treatment. Paediatric patients were more likely to undergo screening echocardiograms (94·7% vs. 47·5%, $P \leq 0·001$). Cardiac abnormalities were reported in 15·6% and 13·1% of paediatric and adult patients respectively. Abnormalities included left ventricular dysfunction ($n = 6$), unspecified cardiomyopathy ($n = 3$), septal wall dyskinesis ($n = 2$), pericarditis ($n = 1$) and arrhythmia ($n = 1$).

Event-free survival and overall survival

With a median follow-up of 22·6 months (range 2·7–101·0 months), 135 of 156 patients are alive and disease-free. The estimated 3-year EFS was 85·9% (95% CI 80·3–91·5) and OS was 95·4% (95% CI 91·8–99·0). Outcomes were not statistically different between paediatric and adult patients with regard to both EFS (81·0% vs. 87·4%, $P = 0·338$) and OS (90·7% vs. 97·1%, $P = 0·170$) (Fig 1). Patients who were escalated to dose level 4 or higher did not have different

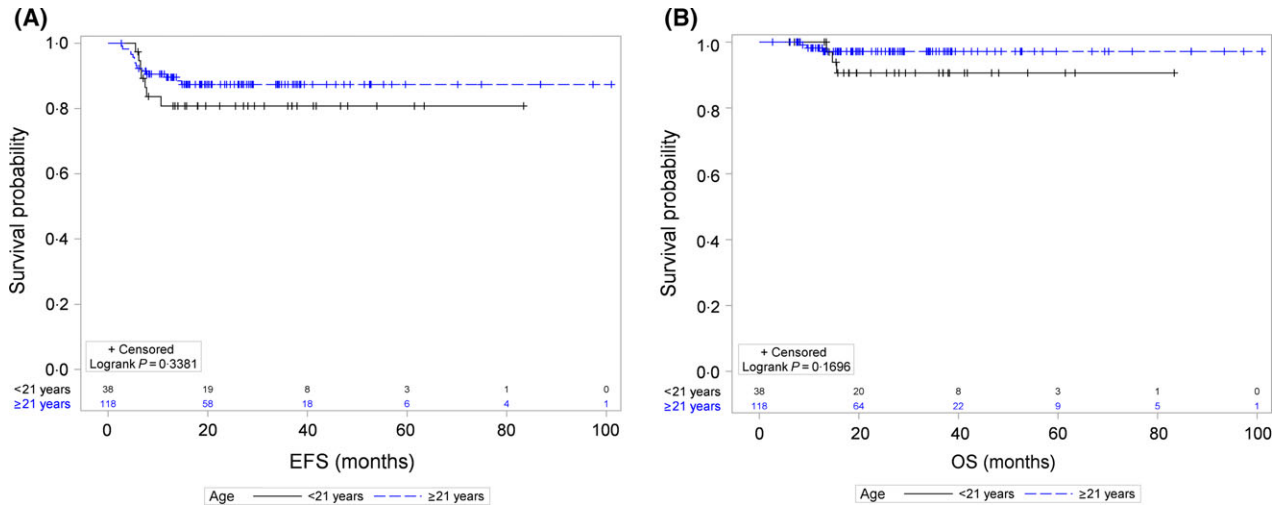

Fig 1. Kaplan–Meier estimate of (A) event-free survival (EFS); (B) overall survival (OS) for paediatric and adult patients.

outcomes compared to others (EFS 88·7% vs. 86·6%, $P = 0·651$; OS 95·6% vs. 96·2%, $P = 0·984$).

Relapsed or refractory disease occurred in 21 of 156 patients (13·5%) including 2 patients with progression on therapy. The median time from diagnosis to relapse was 6·0 months (range 2·8–14·8). The sites of relapse included: mediastinum ($n = 9$), central nervous system ($n = 4$), non-mediastinal nodal sites ($n = 2$), mediastinum and lung ($n = 2$), isolated lung ($n = 1$) and multiple nodal/extranodal sites ($n = 3$). Of the 19 patients who had an end-of-therapy FDG-PET and then subsequently relapsed, 12 had a positive end-of-therapy FDG-PET (nine with a Deauville score of 5 and three with a score of 4); four had a negative end-of therapy FDG-PET and two patients did not have a reported Deauville score. Among the 21 patients with relapsed/refractory disease, 10 received additional therapy and are disease-free at the time of publication, six are alive with evidence of disease, and five have died of PMBCL. In addition, there was one death due to a complication from a tracheoesophageal repair in a patient in remission. Among the 10 patients with relapsed/refractory disease who are currently disease-free, six achieved a sustained remission after chemotherapy followed by autologous stem cell transplant (ASCT); two patients relapsed after ASCT and achieved remission after allogeneic SCT and RT respectively; one patient achieved remission with RT alone, and one patient achieved remission with nivolumab after an incomplete response to six prior therapies.

End-of-therapy FDG-PET

To evaluate the predictive value of FDG-PET imaging at the completion of DA-EPOCH-R, we collected data on end-of-therapy imaging and FDG-PET score according to Deauville criteria (Barrington *et al*, 2014). 'End-of-therapy' was defined as the completion of DA-EPOCH-R chemotherapy. One hundred and fifty-one of 156 patients (97%) had an end-of-therapy FDG-PET scan and the Deauville score was reported in 125 of 151 (83%) patients. A Deauville score of 1–3 was considered negative. Seventy five per cent of patients had a negative FDG-PET scan. Positive Deauville scores of 4 and 5 were reported in 14% and 11% of patients respectively. The rate of a negative FDG-PET scan did not differ between paediatric and adult patients (76·7% vs. 74·7%, $P = 1·00$). Patients with a positive FDG-PET scan were more likely to receive RT than those with a negative FDG-PET scan (38·7% vs. 6·5%, $P < 0·001$).

Patients with a negative end-of-therapy FDG-PET scan had an improved 3-year EFS compared to those with a positive FDG-PET (95·4% vs. 54·9%, $P < 0·001$) (Fig 2A). Overall survival was not statistically different in patients with a negative *versus* positive FDG-PET (96·2% vs. 87·1%, $P = 0·095$) but survival was inferior among those with a Deauville score of 5 when compared to all others (74·1% vs. 96·7%, $P = 0·001$) (Fig 2B). The sensitivity and specificity of end-of-therapy PET to predict relapse in this cohort was 76·5% and 83·3% respectively. End-of-therapy PET had a positive predictive value of 41·9% and a negative predictive value of 95·7% (Table III).

Twelve of the 31 patients with a positive FDG-PET received RT. Outcomes among patients with a positive FDG-PET scan who received RT were inferior compared to those who did not (2-year EFS 33·3% vs. 68·6%, $P = 0·011$), however this is probably influenced by selection bias (in the decision to add RT). Of note, among the 19 patients with a positive end-of-therapy FDG-PET who received no further therapy, 13 are alive without recurrent disease with a median follow up of 17·0 months (range 6·0–61·5).

Discussion

This report is the largest analysis of DA-EPOCH-R for the treatment of PMBCL and the first study on the use of this regimen in children. Although the analysis is retrospective

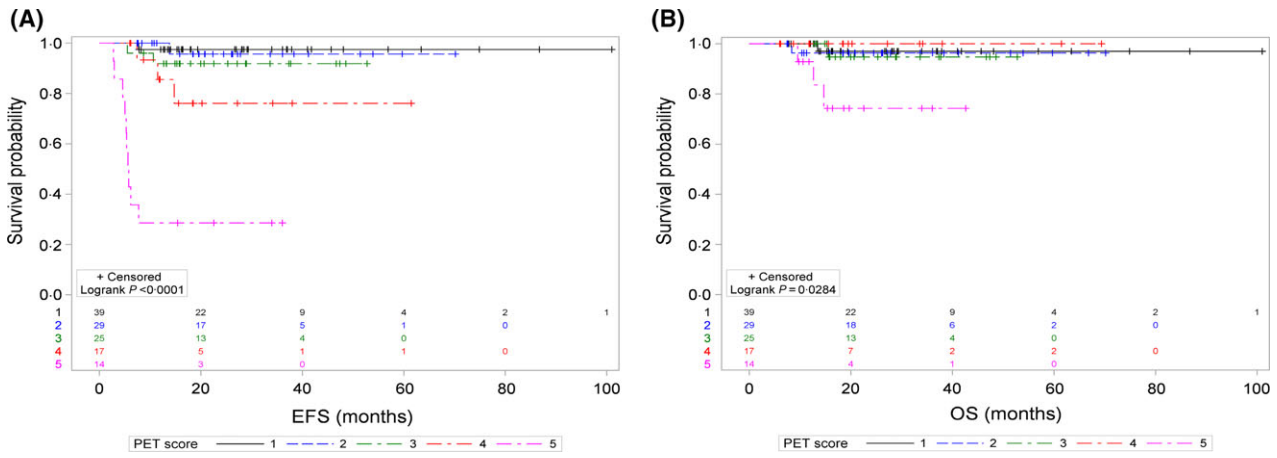

Fig 2. Kaplan–Meier estimate of (A) event-free survival (EFS); (B) overall survival (OS) by end-of-therapy fluorodeoxyglucose positron emission tomography (PET) Deauville Score.

Table III. Evaluation of end-of-therapy FDG-PET.

	Disease status		
	Relapsed (*n*)	Not relapsed (*n*)	Percentage
PET+ (Deauville 4–5)	13	18	
PET− (Deauville 1–3)	4	90	
Total	17	108	
Sensitivity			76·5
Specificity			83·3
Positive predictive value			41·9
Negative predictive value			95·7

Calculations are based on data from 125 patients with available Deauville scoring for end-of-therapy fluorodeoxyglucose positron emission tomography (FDG-PET).

with inherent limitations, the large number of patients across 24 academic medical centres, enables us to describe the real-world experience of this treatment approach. With an estimated 3-year EFS of 85·9% and OS of 95·4%, our study supports the use of DA-EPOCH-R for the treatment of children and adults with PMBCL.

We included both paediatric and adult patients in our analysis as PMBCL predominantly affects patients in the adolescent and young adult age (AYA) range. Most baseline characteristics of disease did not differ between paediatric patients (defined here as age <21 years) and adults (age ≥21 years) with the exception of bulky mediastinal adenopathy (>10 cm), which was more common in paediatric patients (78·4% vs. 57·9%, $P = 0{\cdot}031$). Paediatric patients were also more likely to be escalated to dose level 4 or higher (54·1% vs. 32·7%, $P = 0{\cdot}031$). This difference will be important to consider when interpreting long-term toxicity, as it is likely that children received a higher total anthracycline and alkylator dose. Outcomes including EFS and OS were similar between paediatric and adult patients. Given that we also did not observe a difference in outcome based on final dose level achieved, it would be reasonable to consider setting a limitation to the total anthracycline dose in children, as has been adopted by the NHL-BFM Study Group where the maximum cumulative dose of doxorubicin is 360 mg/m^2 (Woessmann *et al*, 2013).

Venous thromboembolism (VTE) is a common cause of adverse outcome among patients with cancer and is particularly relevant in PMBCL where patients may have additional risk factors for VTE including female sex, large burden of disease and an indwelling central venous catheter (Lee *et al*, 2006; Streiff, 2016). In our cohort, the incidences of any thrombosis and of catheter-associated thrombosis were 28·2% and 9·6%, respectively. A recent meta-analysis of VTE among patients with cancer demonstrated that PICCs were associated with a higher rate of thrombosis than implanted ports (Saber *et al*, 2011). In our cohort, we did not observe differences in the rate of thrombosis among patients with a PICC *versus* an implanted port (12·5% vs. 9·2%, $P = 0{\cdot}565$). Paediatric patients had an increased incidence of thrombosis (45·9% vs. 22·9%, $P = 0{\cdot}001$) and a trend toward increased incidence of catheter-associated thrombosis (18·4% vs. 6·8%, $P = 0{\cdot}053$). As we did not have information on the clinical presentation of thrombosis, we do not know how many of these events were asymptomatic. It is possible that paediatric patients were more likely to be diagnosed with asymptomatic VTE identified through screening echocardiograms (performed in 94·7% of children and 47·5% of adults). Paediatric patients may also be at higher risk for thrombosis due a higher incidence of a bulky mediastinal mass. Given the high rate of thrombosis in both children and adults, prophylactic anticoagulation should be considered.

The use of end-of-therapy FDG-PET imaging to predict outcome is of considerable interest in PMBCL. In the prospective International Extranodal Lymphoma Study Group (IELSG)-26 trial, 125 adult patients with PMBCL were treated with rituximab combined with MACOP-B, VACOP-B, or CHOP after which they underwent FDG-PET imaging. Radiation therapy was administered at the discretion of the physician in 89·6% of patients. Patients with FDG-PET uptake at or above the level of the liver had an inferior 5-year progression-free survival (99% vs. 68%, $P < 0{\cdot}001$) and OS (100% vs. 83%, $P < 0{\cdot}001$) (Martelli *et al*, 2014). Similar outcomes have been reported in retrospective series evaluating patients who received various treatment regimens (Filippi *et al*, 2013; Nagle *et al*, 2015; Pinnix *et al*, 2015). The utility of end-of-therapy FDG-PET in the context of DA-EPOCH-R therapy was evaluated in the National Cancer Institute (NCI) phase II trial with recently presented preliminary data (Melani *et al*, 2016). In that series, a positive FDG-PET, defined as a Deauville score of 4 or 5, was associated with inferior 5-year EFS (92% vs. 80%, $P = 0{\cdot}043$). In paediatric NHL, there is very limited data on the prognostic value of FDG-PET and no data specifically in PMBCL (Sandlund *et al*, 2015). In our study the impact of FDG-PET after DA-EPOCH-R was more pronounced than that reported from the NCI data with a 3-year EFS of 95·4% in PET-negative patients and 54·9% in PET-positive patients ($P < 0{\cdot}001$). Our data support the use of end-of-therapy FDG-PET to predict outcome after DA-EPOCH-R and validate the use of Deauville score ≥4 as an appropriate cut-off for PET positivity. It is important to note, however, that the positive predictive value of PET in this cohort was relatively low (42%) and a portion of patients with a positive PET were observed without further therapy and did not experience relapse.

The role of radiation therapy in the context of DA-EPOCH-R treatment is not well defined. This question is of particular interest in those patients with a positive end-of-therapy FDG-PET for whom outcomes are inferior. The IELSG is conducting a randomized trial evaluating the role of radiation after immunochemotherapy in patients with PMBCL, however this will include patients treated with a variety of regimens and those with a negative FDG-PET (Cavalli *et al*, 2016). In our cohort 14·9% of patients

received RT. The retrospective nature of our data limits our ability to draw definitive conclusions about the role of RT. Among the 31 patients with a positive FDG-PET, 19 received no further therapy and 13/19 are alive without recurrent disease. This suggests that a subset of patients with positive FDG-PET may not require RT.

This retrospective trial has several limitations, which are important to consider. Given that many centres did not uniformly adopt this therapeutic approach until the phase II trial was published in 2013, the median follow-up is currently 22·6 months. Longer follow-up will be needed to capture late relapses as well as long-term toxicity. The diagnosis of PMBCL was made at local institutions and was not subject to central pathology review. This introduces the possibility of inclusion of other lymphoma subtypes, such as DLBCL or grey zone lymphoma, which can be mistaken for PMBCL. The comparisons between paediatric and adult patients are also limited by the retrospective nature of this study and may be influenced by factors other than patient age, including differences in treatment practice between paediatric and adult practitioners and potential selection bias. Lastly, the scoring of end-of-therapy FDG-PET imaging was performed by local radiology rather than central radiology review. Despite these limitations, our study reflects the real-world experience of this treatment regimen and has the strengths of a large number of patients, the contribution of many academic centres, and the inclusion of paediatric patients.

In conclusion, this large retrospective analysis demonstrates that DA-EPOCH-R is a reasonable treatment approach for both children and adults with PMBCL. Our data indicate that end-of-therapy FDG-PET imaging can be used to identify a group of patients with a higher risk of relapse for whom additional or novel therapy may be warranted. As PMBCL predominantly affects the AYA population, joint collaborations between paediatric and adult oncologists may help to accelerate future clinical trials in this rare lymphoma subtype.

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Authorship contributions

LGR, CMB, and JPL designed the research; TO, NLB, AL, WMD, MJB, KD, KAM, BC, CC, SMS, JG, AT, MJO, SA, SW, BA, BM, JS, ZA, MP, HD, RG, DMS, WAZ, CF, JL, MEW, and JLS contributed data; LGR, TO, ZC, CMB, and JPL analysed the data; LGR and JL wrote the manuscript; all authors reviewed/edited the manuscript.

Disclosure of conflicts of interest

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References

Barrington, S.F., Mikhaeel, N.G., Kostakoglu, L., Meignan, M., Hutchings, M., Mueller, S.P., Schwartz, L.H., Zucca, E., Fisher, R.I., Trotman, J., Hoekstra, O.S., Hicks, R.J., O'Doherty, M.J., Hustinx, R., Biggi, A. & Cheson, B.D. (2014) Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *Journal of Clinical Oncology*, **32**, 3048–3058.

Binkley, M.S., Hiniker, S.M., Wu, S., Natkunam, Y., Mittra, E.S., Advani, R.H. & Hoppe, R.T. (2016) A single-institution retrospective analysis of outcomes for stage I–II primary mediastinal large B-cell lymphoma treated with immunochemotherapy with or without radiotherapy. *Leukaemia & Lymphoma*, **57**, 604–608.

Cavalli, F., Ceriani, L. & Zucca, E. (2016) Functional imaging using 18-fluorodeoxyglucose PET in the management of primary mediastinal large B-cell lymphoma: the contributions of the International Extranodal Lymphoma Study Group. *American Society of Clinical Oncology educational Book*, **35**, e368–e375.

Dunleavy, K., Pittaluga, S., Maeda, L.S., Advani, R., Chen, C.C., Hessler, J., Steinberg, S.M., Grant, C., Wright, G., Varma, G., Staudt, L.M., Jaffe, E.S. & Wilson, W.H. (2013) Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *New England Journal of Medicine*, **368**, 1408–1416.

Feuerhake, F., Kutok, J.L., Monti, S., Chen, W., LaCasce, A.S., Cattoretti, G., Kurtin, P., Pinkus, G.S., de Leval, L., Harris, N.L., Savage, K.J., Neuberg, D., Habermann, T.M., Dalla-Favera, R., Golub, T.R., Aster, J.C. & Shipp, M.A. (2005) NFkappaB activity, function, and target-gene signatures in primary mediastinal large B-cell lymphoma and diffuse large B-cell lymphoma subtypes. *Blood*, **106**, 1392–1399.

Filippi, A.R., Piva, C., Giunta, F., Bello, M., Chiappella, A., Caracciolo, D., Zotta, M., Douroukas, A., Ragona, R., Vitolo, U., Bisi, G. & Ricardi, U. (2013) Radiation therapy in primary mediastinal B-cell lymphoma with positron emission tomography positivity after rituximab chemotherapy. *International Journal of Radiation Oncology Biology Physics*, **87**, 311–316.

Gerrard, M., Waxman, I.M., Sposto, R., Auperin, A., Perkins, S.L., Goldman, S., Harrison, L., Pinkerton, R., McCarthy, K., Raphael, M., Patte, C. & Cairo, M.S.; French-American-British/Lymphome Malins de Burkitt 96 (FAB/LMB 96) International Study Committee. (2013) 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.

Goldschmidt, N., Kleinstern, G., Orevi, M., Paltiel, O., Ben-Yehuda, D., Gural, A., Libster, D., Lavie, D. & Gatt, M.E. (2016) Favorable outcome of primary mediastinal large B-cell lymphoma patients treated with sequential RCHOP-RICE regimen without radiotherapy. *Cancer Chemotherapy and Pharmacology*, **77**, 1053–1060.

Guiter, C., Dusanter-Fourt, I., Copie-Bergman, C., Boulland, M.L., Le Gouvello, S., Gaulard, P., Leroy, K. & Castellano, F. (2004) Constitutive STAT6 activation in primary mediastinal large B-cell lymphoma. *Blood*, **104**, 543–549.

Lee, A.Y., Levine, M.N., Butler, G., Webb, C., Costantini, L., Gu, C. & Julian, J.A. (2006) Incidence, risk factors, and outcomes of catheter-related thrombosis in adult patients with cancer. *Journal of Clinical Oncology*, **24**, 1404–1408.

Lister, T.A., Crowther, D., Sutcliffe, S.B., Glatstein, E., Canellos, G.P., Young, R.C., Rosenberg, S.A., Coltman, C.A. & Tubiana, M. (1989) Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *Journal of Clinical Oncology*, **7**, 1630–1636.

Martelli, M., Ceriani, L., Zucca, E., Zinzani, P.L., Ferreri, A.J., Vitolo, U., Stelitano, C., Brusamolino, E., Cabras, M.G., Rigacci, L., Balzarotti, M., Salvi, F., Montoto, S., Lopez-Guillermo, A., Finolezzi, E., Pileri, S.A., Davies, A., Cavalli, F., Giovanella, L. & Johnson, P.W. (2014) [18F]fluorodeoxyglucose positron emission tomography predicts survival after chemoimmunotherapy for primary mediastinal large B-cell lymphoma: results of the International Extranodal Lymphoma Study Group IELSG-26 Study. *Journal of Clinical Oncology*, **32**, 1769–1775.

Melani, C.J., Advani, R., Chen, C.C., Walters, K.M., Venzon, D., Steinberg, S.M., Shovlin, M., Jaffe, E.S., Pittaluga, S., Roschewski, M., Wilson, W.H. & Dunleavy, K. (2016) DA-EPOCH-R in primary mediastinal B-cell lymphoma; analysis of end of therapy FDG-PET and outcome. *Blood*, **128**, 1116–1116.

Moller, P., Lammler, B., Herrmann, B., Otto, H.F., Moldenhauer, G. & Momburg, F. (1986) The primary mediastinal clear cell lymphoma of B-cell type has variable defects in MHC antigen expression. *Immunology*, **59**, 411–417.

Murphy, S.B., Fairclough, D.L., Hutchison, R.E. & Berard, C.W. (1989) Non-Hodgkin's lymphomas of childhood: an analysis of the histology, staging, and response to treatment of 338 cases at a single institution. *Journal of Clinical Oncology*, **7**, 186–193.

Nagle, S.J., Chong, E.A., Chekol, S., Shah, N.N., Nasta, S.D., Glatstein, E., Plastaras, J.P., Torigian, D.A., Schuster, S.J. & Svoboda, J. (2015) The role of FDG-PET imaging as a prognostic marker of outcome in primary mediastinal B-cell lymphoma. *Cancer Medicine*, **4**, 7–15.

Pillon, M., Di Tullio, M.T., Garaventa, A., Cesaro, S., Putti, M.C., Favre, C., Lippi, A., Surico, G., Di Cataldo, A., D'Amore, E., Zanesco, L. & Rosolen, A. (2004) 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.

Pinnix, C.C., Dabaja, B., Ahmed, M.A., Chuang, H.H., Costelloe, C., Wogan, C.F., Reed, V., Romaguera, J.E., Neelapu, S., Oki, Y., Rodriguez, M.A., Fayad, L., Hagemeister, F.B., Nastoupil, L., Turturro, F., Fowler, N., Fanale, M.A., Nieto, Y., Khouri, I.F., Ahmed, S., Medeiros, L.J., Davis, R.E. & Westin, J. (2015) 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. *International Journal of Radiation Oncology Biology Physics*, **92**, 113–121.

Rieger, M., Osterborg, A., Pettengell, R., White, D., Gill, D., Walewski, J., Kuhnt, E., Loeffler, M., Pfreundschuh, M. & Ho, A.D.; MabThera International Trial (MInT) Group. (2011) Primary mediastinal B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: results of the Mabthera International Trial Group study. *Annals of Oncology*, **22**, 664–670.

Rosenwald, A., Wright, G., Leroy, K., Yu, X., Gaulard, P., Gascoyne, R.D., Chan, W.C., Zhao, T., Haioun, C., Greiner, T.C., Weisenburger, D.D., Lynch, J.C., Vose, J., Armitage, J.O., Smeland, E.B., Kvaloy, S., Holte, H., Delabie, J., Campo, E., Montserrat, E., Lopez-Guillermo, A., Ott, G., Muller-Hermelink, H.K., Connors, J.M., Braziel, R., Grogan, T.M., Fisher, R.I., Miller, T.P., LeBlanc, M., Chiorazzi, M., Zhao, H., Yang, L., Powell, J., Wilson, W.H., Jaffe, E.S., Simon, R., Klausner, R.D. & Staudt, L.M. (2003) Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. *Journal of Experimental Medicine*, **198**, 851–862.

Saber, W., Moua, T., Williams, E.C., Verso, M., Agnelli, G., Couban, S., Young, A., De Cicco, M., Biffi, R., van Rooden, C.J., Huisman, M.V., Fagnani, D., Cimminiello, C., Moia, M., Magagnoli, M., Povoski, S.P., Malak, S.F. & Lee, A.Y. (2011) Risk factors for catheter-related thrombosis (CRT) in cancer patients: a patient-level data (IPD) meta-analysis of clinical trials and prospective studies. *Journal of Thrombosis and Haemostasis*, **9**, 312–319.

Sandlund, J.T., Guillerman, R.P., Perkins, S.L., Pinkerton, C.R., Rosolen, A., Patte, C., Reiter, A. & Cairo, M.S. (2015) International pediatric non-Hodgkin lymphoma response criteria. *Journal of Clinical Oncology*, **33**, 2106–2111.

Savage, K.J., Monti, S., Kutok, J.L., Cattoretti, G., Neuberg, D., De Leval, L., Kurtin, P., Dal Cin, P., Ladd, C., Feuerhake, F., Aguiar, R.C., Li, S., Salles, G., Berger, F., Jing, W., Pinkus, G.S., Habermann, T., Dalla-Favera, R., Harris, N.L., Aster, J.C., Golub, T.R. & Shipp, M.A. (2003) The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. *Blood*, **102**, 3871–3879.

Seidemann, K., Tiemann, M., Lauterbach, I., Mann, G., Simonitsch, I., Stankewitz, K., Schrappe, M., Zimmermann, M., Niemeyer, C., Parwaresch, R., Riehm, H. & Reiter, A.; NHL Berlin-Frankfurt-Münster Group. (2003) Primary mediastinal large B-cell lymphoma with sclerosis in pediatric and adolescent patients: treatment and results from three therapeutic studies of the Berlin-Frankfurt-Munster Group. *Journal of Clinical Oncology*, **21**, 1782–1789.

Soumerai, J.D., Hellmann, M.D., Feng, Y., Sohani, A.R., Toomey, C.E., Barnes, J.A., Takvorian, R.W., Neuberg, D., Hochberg, E.P. & Abramson, J.S. (2014) Treatment of primary mediastinal B-cell lymphoma with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone is associated with a high rate of primary refractory disease. *Leukaemia & Lymphoma*, **55**, 538–543.

Streiff, M.B. (2016) Thrombosis in the setting of cancer. *Hematology. American Society of Hematology. Education Program*, **2016**, 196–205.

Swerdlow, S.H., Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H., Thiele, J. & Vardiman, J.W. (2008) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press, Lyon.

Wilson, W.H., sin-Ho, J., Pitcher, B.N., Hsi, E.D., Friedberg, J., Cheson, B., Bartlett, N.L., Smith, S., Johnston, N.W., Kahl, B.S., Staudt, L.M., Blum, K., Abramson, J., Press, O.W., Fisher, R.I., Richards, K.L., Schoder, H., Chang, J.E., Zelenetz, A.D. & Leonard, J.P. (2016) Phase III randomized study of R-CHOP versus DA-EPOCH-R and molecular analysis of untreated diffuse large B-cell lymphoma: CALGB/Alliance 50303. *Blood*, **128**, 469–469.

Woessmann, W., Lisfeld, J. & Burkhardt, B. (2013) Therapy in primary mediastinal B-cell lymphoma. *New England Journal of Medicine*, **369**, 282.