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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=0.011). 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<0.001). 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

Introduction:


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 (Binkley, et al 2016, Dunleavy, et al 2013, Pinnix, et al 2015). The Cancer and Leukemia Group B/Alliance group recently reported preliminary results from a randomized phase III trial of R-CHOP vs. 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.

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(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, ). 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: (1) determine outcomes, (2) investigate potential differences between children and adults, and (3) 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).

**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 >10cm (78.4% vs. 57.9%, p=0.031). Other baseline characteristics did not differ between paediatric and adult patients including: B symptoms (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 non-Hodgkin lymphoma, 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 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<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) (Figure 1). Patients who were escalated to dose level 4 or higher did not have different 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 to 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) (Figure 2A). Overall survival was not statistically different in patients with a negative vs. 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) (Figure 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 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=0.031). Paediatric patients were also more likely to be escalated to dose level 4 or higher (54.1% vs. 32.7%, p=0.031). 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 vs. an implanted port (12.5% vs. 9.2%, p=0.565). Paediatric patients had an increased incidence of thrombosis (45.9% vs. 22.9%, p=0.001) and a trend toward increased incidence of catheter-associated thrombosis (18.4% vs. 6.8%, p=0.053). 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<0.001) and OS (100% vs. 83%, p<0.001) (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%,...
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<0.001). 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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Disclosure of Conflicts of Interest: NLB has served as a consultant for Seattle Genetics, Forty Seven and KITE, and has received research funding from Seattle Genetics, Janssen, Pharmacyclics, Genentech, Pfizer, Celgene, Millennium, KITE, Merck, Bristol-Myers Squibb, Forty Seven and Affimed Therapeutics. BC has received research funding from Seattle Genetics, Immunomedics, Celgene, Genentech/Roche, Merck, Acerta Pharma, Pharmacyclics, Janssen and Bristol-Myers Squibb. CC has served as a consultant for Infinity Pharmaceuticals and received research funding from Celgene. SMS has served as a consultant for Genentech/Roche, TG Therapeutics, Gilead Sciences, Pharmacyclics, NanoString Technologies, Genmab, Pharmacyclics, Forty Seven and Juno Therapeutics. JS has served as a consultant for Seattle Genetics and received research funding from Celgene, Seattle Genetics, MedImmune and Pharmacyclics. RG has served as a consultant for Amgen. JPL has served as a consultant for Gilead, June, KITE, Genmab, NanoString, Regeneron, Abbvie, Sutro, Sunesis, Bristol-Myers Squibb and Genentech. All other authors have no Conflicts of Interest to report.

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Figure 1:
Kaplan-Meier estimate of (A) event-free survival (EFS); (B) overall survival (OS) for paediatric and adult patients.
**Figure 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 I: Patient Characteristics*

<table>
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<tr>
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<th>Total Cohort n=156</th>
<th>Paediatrics (age &lt;21 years) n=38</th>
<th>Adults (age ≥21 years) n=118</th>
<th>p value paediatric vs. adult</th>
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<tr>
<td>Age, years: median (range)</td>
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<td>16 (9–20)</td>
<td>34 (21–70)</td>
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<td>Stage: n (%)</td>
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<td>115 (98.3)</td>
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<td>27 (17.4)</td>
<td>25 (65.8)</td>
<td>2 (1.7)</td>
<td></td>
</tr>
<tr>
<td>B symptoms: n (%)</td>
<td>61 (39.9)</td>
<td>11 (30.6)</td>
<td>50 (tumour)</td>
<td>0.244</td>
</tr>
<tr>
<td>Bulky tumour &gt;10 cm: n (%)</td>
<td>95 (62.9)</td>
<td>29 (78.4)</td>
<td>66 (57.9)</td>
<td>0.031</td>
</tr>
<tr>
<td>LDH &gt; ULN: n (%)</td>
<td>125 (82.8)</td>
<td>30 (85.7)</td>
<td>95 (81.9)</td>
<td>0.799</td>
</tr>
<tr>
<td>Extranodal disease*: n (%)</td>
<td>51 (32.9)</td>
<td>15 (39.5)</td>
<td>36 (30.8)</td>
<td>0.328</td>
</tr>
<tr>
<td>Pleural effusion: n (%)</td>
<td>73 (48.0)</td>
<td>20 (58.8)</td>
<td>53 (44.9)</td>
<td>0.176</td>
</tr>
<tr>
<td>Pericardial effusion: n (%)</td>
<td>82 (53.9)</td>
<td>19 (55.9)</td>
<td>63 (53.4)</td>
<td>0.847</td>
</tr>
<tr>
<td>CD20+ malignant cells: n (%)</td>
<td>146 (98.6)</td>
<td>30 (100)</td>
<td>116 (98.3)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*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).

ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; n: number; N/A: not available; ULN: upper limit of normal.
Table II:

Treatment Characteristics:

<table>
<thead>
<tr>
<th></th>
<th>Total Cohort n=156</th>
<th>Paediatrics (age &lt;21 years) n=38</th>
<th>Adults (age ≥21 years) n=118</th>
<th>p value paediatric vs. adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of cycles of DA-EPOCH-R: median (range)</td>
<td>6 (1–8)</td>
<td>6 (6–8)</td>
<td>6 (1–8)</td>
<td>0.148</td>
</tr>
<tr>
<td>Patients escalated to at least dose level 4: n (%)</td>
<td>57/150 (38.0)</td>
<td>20/37 (54.1)</td>
<td>37/113 (32.7)</td>
<td><strong>0.031</strong></td>
</tr>
<tr>
<td>Patients not escalated beyond dose level 1: n (%)</td>
<td>15/150 (10.0)</td>
<td>2/37 (5.4)</td>
<td>13/113 (11.5)</td>
<td>0.360</td>
</tr>
<tr>
<td>Patients receiving RT: n (%)</td>
<td>23/154 (14.9)</td>
<td>4/36 (11.1)</td>
<td>19/118 (16.1)</td>
<td>0.598</td>
</tr>
<tr>
<td>Radiation dose, Gy: median (range)</td>
<td>36.4 (28.0–50.4)</td>
<td>30.6 (30.0–50.4)</td>
<td>36.4 (28.0–50.4)</td>
<td>0.887</td>
</tr>
<tr>
<td>Patients receiving growth factor support: n (%)</td>
<td>148/150 (98.7)</td>
<td>33/34 (97.1)</td>
<td>115/116 (99.1)</td>
<td>0.403</td>
</tr>
<tr>
<td>Type of growth factor: n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCSF alone</td>
<td>55/148 (37.2)</td>
<td>19/32 (59.4)</td>
<td>36/116 (31.0)</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>PEG-GCSF alone</td>
<td>87/148 (58.8)</td>
<td>11/32 (34.4)</td>
<td>76/116 (65.5)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>6/148 (4.1)</td>
<td>2/32 (6.3)</td>
<td>4/116 (3.4)</td>
<td></td>
</tr>
</tbody>
</table>

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;
Table III:

Evaluation of End-of-therapy FDG-PET

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>Relapsed (n)</th>
<th>Not relapsed (n)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET + (Deauville 4–5)</td>
<td>13</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>PET – (Deauville 1–3)</td>
<td>4</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>108</td>
<td></td>
</tr>
</tbody>
</table>

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).