RESEARCH LETTER

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TO THE EDITOR:

Risk factor analysis of 115 children and adolescents with primary mediastinal B-cell lymphoma treated with DA-EPOCH-R

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Primary mediastinal large B-cell lymphoma (PMBCL) is an aggressive B-cell non-Hodgkin lymphoma (B-NHL) recognized by the World Health Organization classification as a separate entity with molecular similarities to diffuse large B-cell and classical Hodgkin lymphoma.[1,2] In adult patients, event-free survival (EFS) rates improved to 93% with the addition of rituximab to dose-adjusted regimens such as DA-EPOCH-R (dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and rituximab).[3] However, in children (<18 years) DA-EPOCH-R treatment resulted in EFS between 70% and 85%.[4-7] Strikingly, central nervous system (CNS) relapses accounted for 5% to 8% of the events in pediatric patients treated with DA-EPOCH-R,[4,6,7] compared to none in those treated with pediatric block-like B-lNHL–type therapies.[8,9] An additional concern in the use of DA-EPOCH-R in pediatrics is that the cumulative doxorubicin dose exceeds 300 mg/m^2 in most patients, which is associated with a significant risk of late cardiotoxicity.[10] Therapy should be optimized by risk-based stratification allowing treatment intensity reduction in low-risk and further intensification, including CNS-targeting therapies, in high-risk patients. In adult patients with PMBCL, both clinical and molecular risk factors, such as extranodal involvement, bulky disease, and lactate dehydrogenase (LDH) levels and *DUSP2* and *CD58* mutational status have been described.[11,12]

To identify risk factors for relapse in pediatric and young adult patients with PMBCL, we performed a prognostic factor analysis combining 2 large series of pediatric patients with PMBCL treated with DA-EPOCH-R without additional radiotherapy. This analysis encompasses 115 pediatric patients with PMBCL (<22 years; median age, 15.9 years): 45 patients included in the Inter-B-NHL-Ritux 2010 phase 2 study (2012-2016)[4] and 70 patients prospectively registered in the NHL-BFM registry (2010-2022).[7] Data from additional 16 patients from the NHL-BFM registry, who received pretreatment with at least 1 chemotherapy course before DA-EPOCH-R, were added to the cohort for sensitivity analysis.

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Data will be available from the corresponding author, Friederike Meyer-Wentrup (f.meyer-wentrup@prinsesmaximacentrum.nl), upon reasonable request.

The full-text version of this article contains a data supplement.

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Table 1. Characteristics of the 115 patients with PMBCL included in the analysis

Variable	NHL-BFM (n = 70)	Inter-B-NHL-Ritux (n = 45)	Overall (N = 115)
Inclusion period, date of diagnosis (min-max)	March 2010-October 2022	March 2012-April 2016	March 2010-October 2022
Demographics			
Female, n (%)	40 (57.1)	25 (55.6)	65 (56.5)
Age, median (range), y	16.6 (8.4-21.6)	15.3 (7.6-17.9)	15.9 (7.6-21.6)
5-15 y, n (%)	14 (20)	20 (44.4)	34 (29.6)
≥16 y, n (%)	56 (80)	25 (55.6)	81 (70.4)
Performance status at diagnosis, n (%)			
ECOG 0	8 (12.1)	24 (54.5)	32 (29.1)
ECOG 1	36 (54.5)	11 (25)	47 (42.7)
ECOG 2	15 (22.7)	4 (9.1)	19 (17.3)
ECOG 3	3 (4.5)	3 (6.8)	6 (5.5)
ECOG 4	4 (6.1)	2 (4.5)	6 (5.5)
LDH			
LDH × UNL, median (range)	2.0 (0.8-6.8)	1.5 (0.6-5.1)	1.8 (0.6-6.8)
LDH ≥1 × UNL, n (%)	63 (94)	36 (80)	99 (88.4)
LDH ≥2 × UNL, n (%)	34 (50.7)	15 (33.3)	49 (43.8)
Tumor size, stage, and sites, n (%)			
Tumor >10 cm	–	30 (66.7)	–
Tumor 5-10 cm	–	15 (33.3)	–
Ann Arbor stage II	46 (69.7)	31 (68.9)	77 (69.4)
Ann Arbor stage III	6 (9.1)	1 (2.2)	7 (6.3)
Ann Arbor stage IV	14 (21.2)	13 (28.9)	27 (24.3)
Lung involvement	11 (16.4)	13 (28.9)	24 (21.4)
Extrathoracic involvement	36 (51.4)	29 (64.4)	65 (56.5)
Subdiaphragmatic involvement	20 (28.6)	14 (31.1)	34 (29.6)
Renal involvement	10 (14.3)	11 (24.4)	21 (18.3)
Bone marrow involvement	1 (1.5)	1 (2.2)	2 (1.8)
Extranodal sites, mean (SD)	1.5 (1.5)	2.1 (2.0)	1.7 (1.7)
Extranodal sites, median (Q1-Q3)	1 (0-2)	2 (1-3)	1 (0-3)
0 extranodal	23 (32.9)	11 (24.4)	34 (29.6)
1 extranodal	16 (22.9)	9 (20)	25 (21.7)
2 extranodal	14 (20)	11 (24.4)	25 (21.7)
≥3 extranodal	17 (24.3)	14 (31.1)	31 (27)
Immunohistological characteristics			
KI67, mean (SD)	–	72.9 (18.3)	–
KI67, median (Q1-Q3)	–	80 (60-90)	–
KI67, min-max	–	40-100	–
MUM 0%, n (%)	0	3 (11.1)	3 (6.8)
MUM 0%-25%, n (%)	8 (47.1)	8 (29.6)	16 (36.4)
MUM 26%-50%, n (%)	3 (17.6)	3 (11.1)	6 (13.6)
MUM 51%-75%, n (%)	5 (29.4)	7 (25.9)	12 (27.3)
MUM >75%, n (%)	1 (5.9)	6 (22.2)	7 (15.9)
Max dose level reached, n (%)			
Max dose level 1	7 (10.3)	4 (8.9)	11 (9.7)
Max dose level 2	5 (7.4)	6 (13.3)	11 (9.7)
Max dose level 3	24 (35.3)	14 (31.1)	38 (33.6)
Max dose level 4	21 (30.9)	12 (26.7)	33 (29.2)

ECOG, Eastern Cooperative Oncology Group; max, maximum; min, minimum; Q1, first quartile; SD, standard deviation; UNL, upper normal limit.

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Table 1 (continued)

Variable	NHL-BFM (n = 70)	Inter-B-NHL-Ritux (n = 45)	Overall (N = 115)
Max dose level 5	7 (10.3)	5 (11.1)	12 (10.6)
Max dose level 6	4 (5.9)	4 (8.9)	8 (7.1)
Follow-up time			
Median (Q1-Q3), y	3.3 (2.1-5.1)	4.9 (4.4-5.8)	4.4 (3.0-5.3)
Min-max, y	0.5-8.8	1.0-6.4	0.5-8.8
Minimal follow-up living, y	0.5	2.9	0.5

ECOG, Eastern Cooperative Oncology Group; max, maximum; min, minimum; Q1, first quartile; SD, standard deviation; UNL, upper normal limit.

The primary outcome was EFS. Secondary outcomes included time to treatment failure (TTF) and overall survival (OS). Events considered for EFS were progression/relapse, residual tumor with histologically proven vital cells, secondary malignancy, or death from any cause; for TTF, progression/relapse and residual tumor with histologically proven vital cells; and for OS, death from any cause. Survival distributions were estimated using the Kaplan-Meier method. The prognostic value of age, LDH level, subdiaphragmatic/renal involvement, extranodal disease, and performance status (Eastern Cooperative Oncology Group [ECOG]) was assessed using multivariable Cox proportional hazards models stratified on the study, with hazard ratios (HRs) and 95% confidence intervals (CIs) reported for each covariate. Model robustness was investigated by backward stepwise selection with the Akaike information criterion as the stopping rule, and by nonparametric bootstrap resampling with 5000 iterations. In addition, a Fine-Gray competing risks model was fitted, with CNS relapse as event of interest and non-CNS relapse and death defined as competing risks. For this model subdiaphragmatic/renal involvement was analyzed as a binary covariate (renal involvement vs none) due to the absence of CNS relapses in patients with subdiaphragmatic nonrenal involvement. One-year and 3-year cumulative incidences with 95% CIs were estimated using Aalen-Johansen curves. Multilevel multiple imputation was used to handle missing data (ECOG status, LDH levels).

Patient characteristics were similar between both cohorts (Table 1). The median age was 15.9 years (range, 7.6-21.6), 57% were female. Ann Arbor stage II was observed in 70%, III in 6%, and IV in 24% of patients. Lung, extrathoracic, subdiaphragmatic, renal, and bone marrow involvement occurred in 21%, 57%, 30%, 18%, and 2% of patients, respectively. The median follow-up was 53 months (interquartile range, 36-63).

Twenty-four events were observed, including 6 parenchymal CNS relapses and 11 deaths. The 3-year EFS and OS rates were 79% (95% CI, 73-85) and 89% (95% CI, 85-94), respectively. In the multivariable Cox model for EFS, subdiaphragmatic (excluding renal) and renal vs no subdiaphragmatic involvement were associated with HRs of 2.3 (95% CI, 0.6-9.2; $P = .2$) and 4.3 (95% CI, 1.1-16.8; $P = .04$), respectively (Table 2; supplemental Figure 1). Backward selection retained this variable with similar coefficient estimation. In bootstrap resampling, this factor was retained in 59% of replications. Performance status and number of extranodal sites were selected in 34% and 32% of replications, respectively. Similar results were found for the TTF end point. For the OS end point, the low number of events led to the selection of an empty model after backward selection.

Table 2. Results of the prognostic factor analysis for the end points EFS and TTF

	EFS		TTF	
Variable	**HR (95% CI); *P* value**	**Bootstrap inclusion frequency, %**	**HR (95% CI); *P* value**	**Bootstrap inclusion frequency, %**
Age at diagnosis	1.0 (0.8-1.2); $P = .86$	25.0	1.0 (0.8-1.2); $P = .82$	28.2
Performance status		33.7		41.4
ECOG 1 vs 0	1.9 (0.6-5.9); $P = .29$		2.5 (0.7-9.1); $P = .17$	
ECOG 2-4 vs 0	0.9 (0.2-3.6); $P = .82$		1.1 (0.2-4.9); $P = .93$	
LDH level		8.8		8.0
LDH >2 vs <2 UNL	0.7 (0.3-1.9); $P = .50$		0.8 (0.3-2.0); $P = .59$	
Involved sites	Variable selected	58.8	Variable selected	59.5
Subdiaphragmatic involvement without renal involvement vs no subdiaphragmatic involvement	2.3 (0.6-9.2); $P = .22$		2.9 (0.7-11.6); $P = .14$	
Renal involvement vs no subdiaphragmatic involvement	4.3 (1.1-16.8); $P = .04$		4.7 (1.1-20.0); $P = .04$	
No. of extranodal sites	1.0 (0.8-1.4); $P = .84$	31.6	1.1 (0.8-1.5); $P = .69$	35.1

UNL, upper normal limit.

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In the Fine-Gray competing risks model for CNS relapse, renal involvement was associated with a subdistribution HR of 15.9 (95% CI, 2.5-100; $P = .003$) and 1- and 3-year cumulative incidences of 24% (95% CI, 8.3-44) compared with 0% and 1.2% (95% CI, 0.10-6.0), respectively, in patients without renal involvement.

The sensitivity analysis included 16 additional patients from the NHL-BFM cohort who had received pretreatment with other chemotherapy courses (AA24, A4, CHOEP (cyclophosphamide, hydroxydaunorubicin [also known as doxorubicin or adriamycin], oncovin [also known as vincristine], etoposide, and prednisone [or prednisolone]), and OEPA (oncovin [also known as vincristine], etoposide, prednisone, and adriamycin [also known as doxorubicin]) before DA-EPOCH-R. A total of 29 events occurred in 131 patients. Thirteen patients died. In this analysis, the subdiaphragmatic/renal involvement variable had the highest bootstrap inclusion frequencies (>50% for EFS and TTF end points, 46% for OS) and was selected in the backward selection of the OS and EFS end points. The number of extranodal sites was selected in the backward selection of the TTF end point. Results from the sensitivity analysis were similar to those of the main analysis for the effect of renal involvement on CNS relapses.

Our findings consistently point to renal and subdiaphragmatic involvement as key prognostic factors, as these variables were repeatedly selected in multivariable models and retained in a large proportion of bootstrap replications. Other baseline covariates such as age, performance status, and LDH levels showed low inclusion frequencies, suggesting a limited and unstable prognostic contribution in this setting. Of particular interest, renal involvement emerged as the only strong predictor of CNS relapse. Although the associated HR was high, this might reflect sparse data bias due to the near absence of CNS events in the patients without renal disease. The limited number of CNS events, together with the relatively small size of the subgroup wit renal involvement, warrants caution in the interpretation of these findings.

Our data partially correspond to findings in older patients with PMBCL treated with DA-EPOCH-R or R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin [also known as doxorubicin or adriamycin], oncovin [also known as vincristine], and prednisone [or prednisolone]), in whom extranodal manifestations also predict adverse outcome.[11] The CNS relapse incidence of 5.2% in our cohort was higher than reported previously in older patients (1.5%-2%).[13] Renal involvement appears to be more frequent in our cohort of younger patients with PMBCL than reported previously in a cohort with a median age of 32 years (21/115 [18%] vs 23/564 [4%] in the study by Vassilakopoulos et al,[13] $P_{Fisher} < .001$),[9] in which it has also been associated with the risk of CNS relapse.[13,14]

In conclusion, subdiaphragmatic involvement was observed in 30% of patients and was the most robust prognostic factor for inferior EFS in this large cohort of 115 children/adolescents with PMBCL treated with DA-EPOCH-R. Renal involvement was associated with an increased relapse risk and especially parenchymal CNS relapse. All but 1 CNS relapse (5/6) occurred among the 21 children with renal involvement. Together with the observation of absent CNS relapses with pediatric block-like B-NHL therapy, this finding supports the introduction of CNS prophylaxis with systemic (eg, dexamethasone, high-dose cytarabine, or methotrexate) or intrathecal therapy in children with renal involvement treated with DA-EPOCH-R. Staging at diagnosis should include analysis of cerebrospinal fluid and if clinically indicated imaging of the CNS. Risk stratification based on subdiaphragmatic involvement and prospective evaluation of further predictive biomarkers already described in adults, such as molecular aberrations,[11] cytokine levels, and early positron emission tomography (PET) response[15] will be investigated in the upcoming European InterGroup for Childhood Non-Hodgkin Lymphoma (EICNHL) PMBCL treatment study.

The Inter-B-NHL-Ritux 2010 phase 2 study and the NHL-BFM registry (2010-2022) were both approved by institutional review board and was conducted in accordance with the Declaration of Helsinki.

Contribution: F.M.-W., S.F.J., F.K., A. Auperin, V.M.-C., and W.W. designed the research, analyzed and interpreted the data, and wrote the manuscript; S.F.J. and A. Auperin performed statistical analyses; and S.A., M.A., A. Attarbaschi, G.A.A.B., B.B., F.C., T.G., E.K., W.K., R.R.M., M.T., and M.Z. discussed and reviewed the data and wrote the manuscript.

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