Dose-adjusted EPOCH-rituximab or intensified B-non-Hodgkin lymphoma therapy for pediatric primary mediastinal large B-cell lymphoma. Results from the study B-NHL-BFM-04 and the NHL-BFM registry 2012

Treatment outcomes for children and adolescents with primary mediastinal large B-cell lymphoma (PMBCL) with chemotherapy designed for childhood mature B-non-Hodgkin lymphoma (B-NHL) are inferior to those of children with other B-NHL-subtypes.[1-3] Consequently, B-NHL-type chemotherapy was first intensified and subsequently replaced by dose-adjusted chemo-immunotherapy with etoposide, prednisone, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) in the NHL-Berlin-Frankfurt-Münster (BFM)-study group. DA-EPOCH-R resulted in superior event-free (EFS) and overall survival (OS) compared to the previous B-NHL chemotherapy, however, in four patients central nervous system (CNS)-relapses occurred.

Treatment of children with PMBCL by chemotherapy protocols without rituximab including high-dose methotrexate, etoposide, ifosfamide, cyclophosphamide, cytarabine, vincristine, and corticosteroids, combined with intrathecal chemotherapy resulted in EFS rates at 5 years of 53–70%.[1-3] In order to improve outcome, treatment was intensified for patients with PMBCL in the trial B-NHL-BFM-04 (B04) by adding two courses of chemotherapy and prolonging the infusion time of high-dose methotrexate. In 2010, a modified DA-EPOCH-R regimen was recommended for PMBCL by the NHL-BFM study committee on the basis of a 5-year EFS of 93% in adults with PMBCL in a phase II study.[4] The modifications included the addition of a least one dose of intrathecal triple therapy (ITT), and a cumulative doxorubicin

Table 1. Clinical characteristics of the children and adolescents with primary mediastinal large B cell lymphoma.

	All eligible Patients (N=116)	Treatment		
		N95 (N=20)	B04 (N=29)	DA EPOCH R (N=67)
Study				
B04	45	–	29	16
N95	19	19	–	–
REG12	52	1	–	51
Sex				
f	62	7	17	38
m	54	13	12	29
Stage**				
III	94	20	19	55
IV	1	–	1	–
not evaluable*	19	–	9	10
unknown	2	–	–	2
CNS involvement				
not analyzed	16	–	8	8
no	100	20	21	59
Bone marrow involvement				
not analyzed	11	–	4	7
no	104	20	24	6
yes	1	–	1	–
Age at diagnosis (years)				
mean	15.8	14.7	15.7	16.2
range	1.4–21.7	1.4–17.9	10.3–18.6	8.4–21.7
LDH at diagnosis (U/L)				
mean	562	445	608	578
range	187–1,698	187–1,267	252–1,322	188–1,698
above normal range	89/96	unknown***	25/29 (86%)	64/67 (96%)
< 500	56	14	13	29
500 – <1,000	47	5	12	30
≥ 1,000	13	1	4	8
Duration of follow-up (months)				
mean	59	77	73	48
range	2–211.8	2–211.8	12.5–144.2	7.6–123.2

*no initial assessment of central nervous system (CNS) or bone marrow involvement; **St. Jude staging system;[15] ***upper limit of normal not reported in the study N95.NHL: N95: study NHL-BFM 95; B04: study B-NHL BFM 04; REG12: NHL-BFM Registry 2012; f: female; m: male; LDH: lactate dehydrogenase; DA-EPOCH-R: dose-adjusted etoposide, prednisone, cyclophosphamide, doxorubicin, and rituximab.

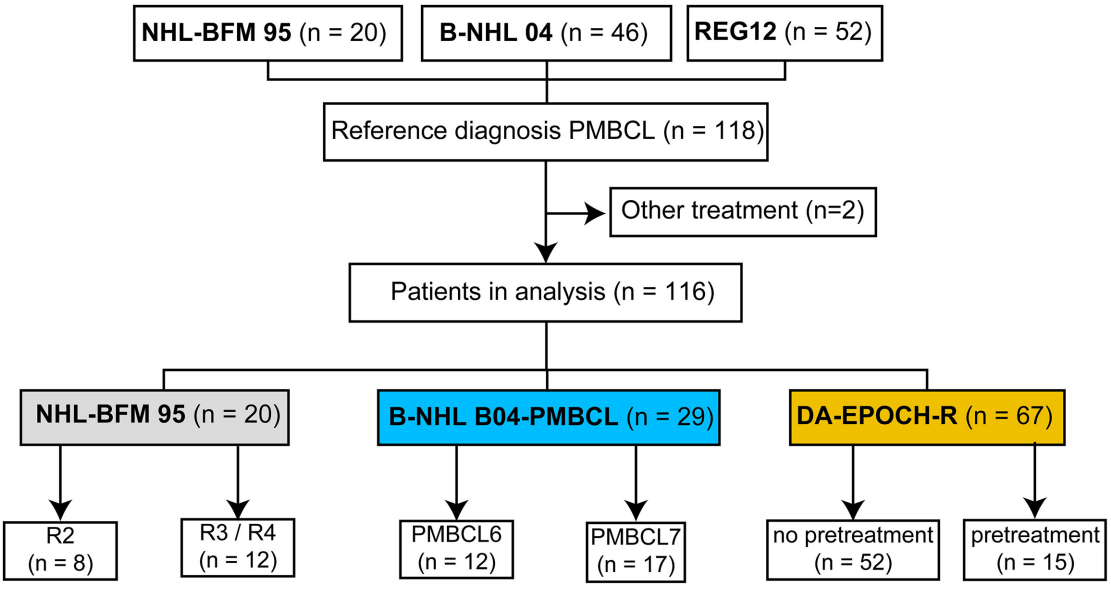

Figure 1. Patient allocation and treatment assignment. Patients with diagnosis of primary mediastinal large B-cell lymphoma (PMBCL) were identified from 3 trials. Two patients received treatment not according to protocol and were excluded from the analysis. One patient from the non-Hodgkin lymphoma Berlin-Frankfurt-Münster (NHL-BFM) Registry 2012 (REG12) received treatment according to the NHL-BFM 95 treatment strategy (R2).

dose limit at 360 mg/m^2 of body-surface area (BSA). A first analysis by our group of 15 patients treated with DA-EPOCH-R showed an EFS and OS of 92±8% after 2 years.[5] A retrospective analysis of 156 adults and children with PMBCL treated with DA-EPOCH-R reports an EFS of 86% at 3 years.[6] However, in the prospective Intergroup trial testing DA-EPOCH-R, the 2-year EFS of children and adolescents with PMBCL was 72%, not different from the historical control.[7]

We analyzed children and adolescents with PMBCL confirmed by central histopathological review, excluding mediastinal grey zone lymphoma, enrolled in the B04 trial (German clinical trial registry: DRKS00009436) or the NHL-BFM Registry 2012 between 2004 and 2019 to i) assess the efficacy of intensified B-NHL-BFM chemotherapy (n=29 patients) and modified DA-EPOCH-R (n=67 patients), ii) compare it retrospectively to the treatment regimen in the NHL-BFM 95 trial (N95, n=20 patients) and iii) identify risk factors for treatment failure with DA-EPOCH-R.

Treatment details for N95, B04 and DA-EPOCH-R are summarized in the *Online Supplementary Table S1*. N95 treatment was stratified by lactate dehydrogenase (LDH) and stage to risk groups R2–R4, as previously reported.[8] In B04, treatment was intensified by adding two courses: patients with LDH <500 U/L received six (PMBCL6), those with LDH ≥500 U/L seven (PMBCL7) 5-day courses of chemotherapy including high-dose methotrexate infused over 24 hours (h) and ITT. Outside the protocol, three patients received one or two doses of rituximab and one patient received initial emergency-mediastinal radiotherapy. One patient each after B04 and DA-EPOCH-R received radiotherapy for a persisting mediastinal mass. From September 2010, DA-EPOCH-R was recommended with the described modifications. Erroneously, 60 mg/m^2 prednisone was used instead of 120 mg/m^2 as protocol-specified for 26 patients.

The primary endpoint was the EFS at 5 years, defined as time from diagnosis to death, relapse, progressive disease, or secondary malignancy, estimated using the Kaplan-Meier method. OS was defined as time from diagnosis to death. Survival and competing risk comparisons were performed by log-rank analysis and Gray´s test.[9] Data were updated as of January 3, 2021.

For this analysis, 116 of 118 registered patients were included (Figure 1). Their median age was 16.2 years, 53% were female. Patient characteristics are summarized in Table 1.

Fifteen patients in the trial N95 and 15 patients treated by DA-EPOCH-R enrolled in B04 have been reported previously.[2,5,8]

Of 20 patients treated according to N95, six patients with LDH levels at diagnosis ≥500 U/L received the intended treatment (R3/R4). Of 14 patients with LDH <500 U/L, eight received the protocol-intended treatment with four courses (R2) and six were treated more intensively (R3/R4). B04 therapy was used for 29 patients, of whom 12 with LDH <500 U/L were scheduled for six courses, one for seven. All 16 patients with LDH ≥500 U/L received the intended treatment with seven courses.

Among 67 patients treated by DA-EPOCH-R, 15 received pretreatment other than one dose of rituximab or a BFM-type prephase (B04 chemotherapy in 13 patients - 1 course A24 in 2, 1 course AA24 in 10 patients, 2 courses AA24 and BB24 in 1 patient, 2 courses of OEPA and one course of R-CHOEP in 1 patient each). Fifty-two patients without pretreatment received six (n=50) or eight (n=2) courses of DA-EPOCH-R. The mean cumulative doxorubicin dose was 310 mg/m^2 of BSA (range, 200–415 mg/m^2). The median number of ITT was 2.5 (range, 0–8) in 50 patients with available data. The maximal dose levels reached were 1, 2, 3, 4, and 5 in 5 (10%), 6 (12%), 17 (34%), 17 (34%) and 5 (10%) patients, respectively, and unknown in two patients.

The levels reached were slightly lower than reported by Dunleavy and colleagues.[4] Dose decisions were at the discretion of the treating physicians, and reasons for non-escalation might include concerns for sequelae, overestimation of hematological toxicity due to frequent blood counts for dose decisions, or the fact that G-CSF was not

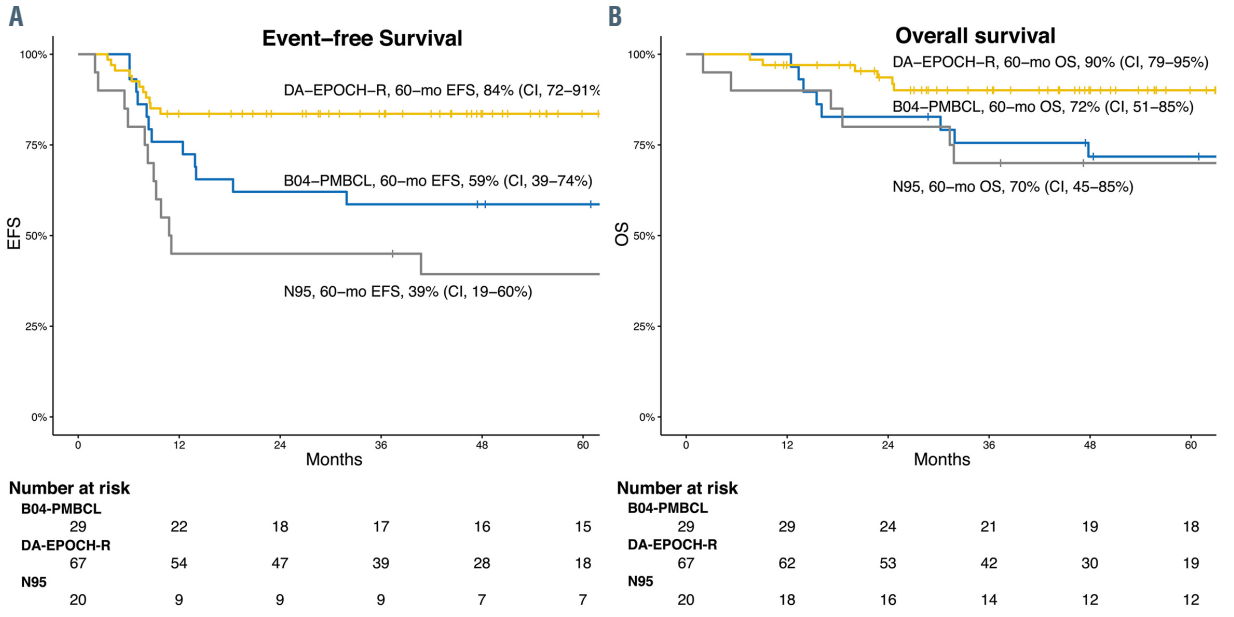

Figure 2. Event-free survival and overall survival at 5 years for patients with primary mediastinal large B-cell lymphoma treated with the treatment regimen NHL-BFM 95, B-NHL-BFM 04 or DA-EPOCH-R. (A) Event-free survival (EFS) and (B) overall survival for patients with primary mediastinal large B-cell lymphoma (PMBCL) according to the type of treatment. EFS was significantly different between DA-EPOCH-R and B-non-Hodgkin lymphoma Berlin-Frankfurt-Münster (B-NHL-BFM) B04 (P=0.024) and DA-EPOCH-R and NHL-BFM 95 (N95) (P<0.001). The difference between 04 and N95 was not significant (P=0.142). DA-EPOCH-R: dose-adjusted chemo-immunotherapy etoposide, prednisone, cyclophosphamide, doxorubicin, and rituximab.

administered to all patients (only 39 of 46 (85%) of patients with available data).

In 15 pretreated patients, the median number of DA-EPOCH-R-courses was five, the median number of ITT was five, and the mean cumulative dose of doxorubicin was 260 mg/m^2 BSA.

For treatment by DA-EPOCH-R, B04 and N95, estimates for EFS at 5 years were 84% (95% confidence interval [CI]: 72–91), 59% (95% CI: 39–74), and 39% (95% CI: 19–60), respectively (Figure 2). OS 90% (95% CI: 79–95), 72% (95% CI: 51–85) and 70% (95% CI: 45–85), respectively (Figure 2). EFS and OS with DA-EPOCH-R were significant superior to treatment with B04 (P=0.016 for EFS, P=0.039 for OS) and N95 P<0.001 for EFS and P=0.026 for OS).

The observed EFS with DA-EPOCH-R was comparable to that of other trials ranging from 72% to 93%.[4,6,7,10,11] To what extent rituximab alone contributed to the superior outcome cannot be answered by our data. The addition of rituximab to CHOP improved outcomes in adult patients with PMBCL.[12] Recent preliminary data from the non-randomized, prospective IELSG37 trial suggest similar efficacy for DA-EPOCH-R and R-CHOP14.[13] The AEIOP reported 13 pediatric PMBCL patients treated with a modified MTX-based BFM-type backbone combined with rituximab resulting in an EFS of 84%.[14] These data indicate that addition of rituximab contributed substantially to the improved outcome.

Estimated EFS at 5 years for patients with LDH <500 U/L receiving PMBCL6, R3/R4, and R2 in B04/N95 were 67% (95% CI: 34–86), 67% (95% CI: 19–90), and 19% (95% CI: 1–54), respectively (*Online Supplementary Figure S1A*), with a significant difference between PMBCL6 and R2 (P=0.047). PMBCL7 was given to 16 patients with LDH ≥500 U/L in B04, R3/R4 in N95 to eight patients. The estimated EFS was 50% (95% CI: 25–71) and 33% (95% CI: 5–68), respectively (P=0.45, *Online Supplementary Figure S1B*). The improvement with intensified B-NHL therapy in patients with LDH levels <500 U/L but not among those with LDH levels ≥500 U/L indicates a possible limit for further improvements by modifying standard B-NHL chemotherapy for PMBCL.

In patients treated by DA-EPOCH-R without pretreatment, EFS and OS at 5 years were 87% (95% CI: 74–93) and 91% (95% CI: 78–97), not significantly different from the outcome for 15 patients receiving DA-EPOCH-R after pretreatment (with an EFS and OS of 73% (95% CI: 44–89) and 86% (95% CI: 55–96), respectively (P=0.2 for EFS, P=0.54 for OS, *Online Supplementary Figure S2*). The heterogeneity in treatment with pretreatment in about 20% of patients is a limitation of our analysis, but likely reflects real-world diagnostic uncertainties, with a final diagnosis of PMBCL only made by central histopathological review in conjunction with the typical location.

There was no significant difference in EFS according to sex, initial LDH, extra-thoracic involvement, prednisone dose or the maximal dose-level reached in DA-EPOCH-R. Mean age was lower in patients experiencing relapse (hazard ratio [HR]: 0.74, P=0.012), resulting in an EFS of 90% (95% CI: 76–96) for 41 patients ≥16 years, compared with 73% (95% CI: 52–86) for 26 patients <16 years (P=0.07). The limited number of patients might explain that we could not identify risk factors for treatment failure with DA-EPOCH-R except for younger age.

At relapse four of 11 (37%) patients treated by DA-EPOCH-R had parenchymal CNS involvement compared to zero of 22 after B04 chemotherapy (Gray´s test, P=0.08). Three of these patients had received only 60 mg/m^2 prednisolone, two reached only dose level 1 or 2 and one received only one ITT for CNS prophylaxis. Further explanations for a possibly higher risk of CNS-relapse after DA-EPOCH-R include the use of prednisone

instead of dexamethasone and the omission of high-dose methotrexate, both part of the B-NHL therapy.

In conclusion, our prospective data confirmed DA-EPOCH-R as effective treatment for children and adolescents with PMBCL with only one patient receiving consolidation radiotherapy. Further trials on PMBCL should address the risk of CNS relapse and identify prognostic markers. Low patient numbers in this orphan disease call for collaborative, international trials including patients of the whole age spectrum.

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