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# Excellent outcome of children/adolescents with primary mediastinal large B-cell lymphoma treated with a FAB/LMB-based chemotherapy regimen with rituximab

Primary mediastinal (thymic) large B-cell lymphoma (PMLBL) is a distinct pathogenic subtype of mature B-cell neoplasms related to the nodular sclerosis subtype of Hodgkin lymphoma.<sup>1</sup> It is a rare entity accounting for 2-4% of adult and pediatric non-Hodgkin lymphomas (NHL).<sup>2,3</sup>

Treatment strategies originally designed for Burkitt lymphoma have been successfully used for children with diffuse large B-cell lymphoma,<sup>4,5</sup> but patients with PMLBL have a more aggressive disease and a specific approach was needed.<sup>6,7</sup> In fact, the first prospective international phase II study of the DA-EPOCH-R regimen<sup>8</sup> (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab) in children and adolescents failed to replicate the exceptional survival outcomes reported in some adult studies.<sup>9,10</sup> Specifically, 12 out of the 46 enrolled patients experienced relapse with three parenchymal central nervous system (CNS) events. We previously reported excellent results, in a small cohort of 21 patients, of French-American-British/Lymphomes Malins B

(FAB/LMB)-based chemotherapy combined with rituximab. Here we expand our analysis to include a second cohort of 23 patients treated after the DA-EPOCH phase II trial, reaching a total of 44 patients treated with FAB/LMB-based chemotherapy and rituximab for PMLBL between January 2008 and December 2021.

All patients under 21 years old with a confirmed diagnosis of PMLBL treated at Société Française des Cancers de l'Enfant et de l'Adolescent (SFCE) centers were included if they received FAB/LMB-based chemotherapy with rituximab. All 44 patients are registered in The French National Registry of Childhood Cancers (RNCE) and provided informed consent. This retrospective analysis was approved by the local institutional review board (CLEA-2024 N 374).

The planned PMLBL treatment regimen consisted of six courses of rituximab combined with chemotherapy: two courses of R-COPADM group B (rituximab plus cyclophosphamide, vincristine, prednisone, adriamycin, high-dose methotrexate and 1 intrathecal treatment) followed by two

**Table 1.** French-American-British/Lymphomes Malins B-based regimen for the treatment of primary mediastinal large B-cell lymphoma.

	Chemotherapy	Rituximab
Prephase COP*	Cy 300 mg/m <sup>2</sup> D1 Vincristine 2 mg/m <sup>2</sup> D1 IT <sup>‡</sup> (MTX HSHC) D1 Prednisone 60 mg/m <sup>2</sup> /day D1-7	-
Courses 1 and 2 COPADM	Vincristine 2 mg/m <sup>2</sup> D1 MTX 3 g/m <sup>2</sup> D1 Cy 250 mg/m <sup>2</sup> /12 h D2-4 Adriamycin 60 mg/m <sup>2</sup> D2 IT (MTX HSHC) D2 Prednisone 60 mg/m <sup>2</sup> D1-5	375 mg/m <sup>2</sup> D1
Courses 3 and 4 CYVE	Cytarabine 50 mg/m <sup>2</sup> IV 12 h D1-5 Cytarabine 3 g/m <sup>2</sup> D2-5 VP16 200 mg/m <sup>2</sup> D2-5	375 mg/m <sup>2</sup> D1
Courses 5 and 6 Seq3	Vincristine 2 mg/m <sup>2</sup> D1 Cy 500 mg/m <sup>2</sup> /day D1-2 Adriamycin 60 mg/m <sup>2</sup> D1 Prednisone 60 mg/m <sup>2</sup> D1-5	375 mg/m <sup>2</sup> D1
Cumulative doses	Cy: 5,300 mg/m <sup>2</sup> Adriamycin: 240 mg/m <sup>2</sup> IT: 2 to 3	6 doses of 375 mg/m <sup>2</sup>

\*A COP prephase is not mandatory but may be useful 1 week prior to commencement of course 1 for patients requiring urgent treatment while awaiting histological confirmation. <sup>‡</sup>Intrathecal therapy is optional during COP prephase treatment. Cy: cyclophosphamide; D: day; IT: intrathecal; MTX: methotrexate; HSHC: hydrocortisone hemissuccinate; VP16: etoposide; IV: intravenous.

courses of R-CYVE group C (rituximab plus high-dose cytarabine and etoposide) and two courses of maintenance therapy with rituximab without radiotherapy<sup>11</sup> (Table 1).

Between January 2008 and December 2021, a total of 44 patients were identified with newly diagnosed B-cell NHL confirmed as PMLBL either through central review in the LMB2001 prospective study (N=21) or by assessment by a pathologist of the French Lymphoma Study Association (N=23). Table 2 summarizes the baseline characteristics of the patients and their responses to treatment. The median age at diagnosis was 15.9 years (interquartile range, 15.0-16.9 years). Twenty-seven of the patients were female (61%). Thirty-five patients (80%) presented with large mediastinal masses of 10 cm or more, while 18 patients (41%) had high lactate dehydrogenase levels (more than twice the institutional upper limit of normal for adults). One patient had bone marrow involvement and two patients were considered to have CNS disease (one experienced facial paresthesia with normal magnetic resonance imaging, but examination of the cerebrospinal fluid was not feasible; the other had an asymptomatic epidural mass). Overall, no patient had positive cerebrospinal fluid. According to the Ann Arbor classification, 20 patients (45.5%) had stage II disease, four patients (9%) had stage III and 20 patients (45.5%) had stage IV.

All patients received FAB/LMB-based chemotherapy, with three patients treated in group B, 13 in group C1 (*Online Supplementary Table S1*) and 28 in group B/C, named the "FAB/LMB-based PMLBL regimen" with two courses of R-COPADM group B followed by two courses of R-CYVE group C and two courses of maintenance therapy (Table 1). Each patient received six doses of rituximab in combination with the chemotherapy regimen.

One patient experienced disease progression shortly after the first cycle of R-COPADM. Among the remaining 43 patients, nine achieved complete response by the end of treatment while 34 (79.1%) still had a residual mass on imaging. Of these 34 patients, 18 underwent biopsies revealing only one case with viable tumor cells while histological examination indicated complete necrosis in the other 17 patients. According to international pediatric non-Hodgkin lymphoma response criteria, treatment responses were as followed: nine complete responses, 17 biopsy-negative complete responses, ten unconfirmed complete responses, six partial responses, one no response and one case of progressive disease (Table 2).<sup>12</sup> Ultimately, 42 patients (95%) were deemed to have achieved complete remission by the end of first-line treatment, with nine showing a complete response on imaging, 17 with complete necrosis on histology, and 16 with unexplored residual masses.

Thirty-six patients (82%) underwent <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (<sup>18</sup>F-FDG PET)/computed tomography (CT) (combined with morphological assessment via CT for all) after a median of four chemotherapy courses (range, 3-6). Among them 14 (40%) were deemed positive

according to current Cheson criteria (N=8) or a Deauville score >3 (N=6) (*Online Supplementary Figure S1*). Of these 14 patients, nine underwent biopsy with only one showing histologically positive residual disease. None of these patients experienced further progression after a follow-up period of at least 1.4 years from the initial diagnosis, giving a positive predictive value of 1/14 (7%), with an exact 95% confidence interval (95% CI) of 2%-34%. Among the 22 patients with negative <sup>18</sup>F-FDG PET/CT results according to the Cheson criteria (N=12) or with a Deauville score <4 (N=10), none experienced treatment failure (negative predictive value=100%, exact 95% CI: 85%-100%) (*Online Supplementary Figure S1*).

The median follow-up was 4.3 years (interquartile range, 2.7-6.5 years). A total of three events were observed, all of which were local failures (*Online Supplementary Table S2*). There was one case of early progression during treatment (after the first course of R-COPADM), one insufficient response with viable cells in the residual mass (after the

**Table 2.** Baseline characteristics of the patients and response to therapy.

Clinical and biological characteristics	All patients, N=44
Female, N (%)	27 (61)
Age in years, median (interquartile range) [range]	15.9 (15.0-16.9) [10.1-18.1]
Aged 10-15 years, N (%)	11 (25)
Aged 15-21 years, N (%)	33 (75)
Ann Arbor stage, N (%)	
II	20 (45.5)
III	4 (9)
IV	20 (45.5)
Mediastinal tumor >10 cm, N (%)	35 (80)
Sites of involvement, N (%)	
Sub-diaphragmatic	16 (36)
Bone marrow	1 (2)
Central nervous system*	2 (5)
LDH >2xULN range,** N (%)	18 (41)
Initial therapeutic group, N (%)	
Group B	3 (7)
Group B/C or C	41 (93)
Tumor response, N (%)	
Complete response	9 (21)
Complete response, biopsy negative	17 (39)
Complete response, unconfirmed	10 (23)
Partial response	6 (13)
No response***	1 (2)
Progressive disease	1 (2)

\*Central nervous system involvement consisted in one case of facial paresthesia with normal magnetic resonance imaging but cerebrospinal fluid could not be examined, and one case of an asymptomatic epidural mass. \*\*Data missing for two patients. \*\*\*According to international pediatric non-Hodgkin lymphoma response criteria.

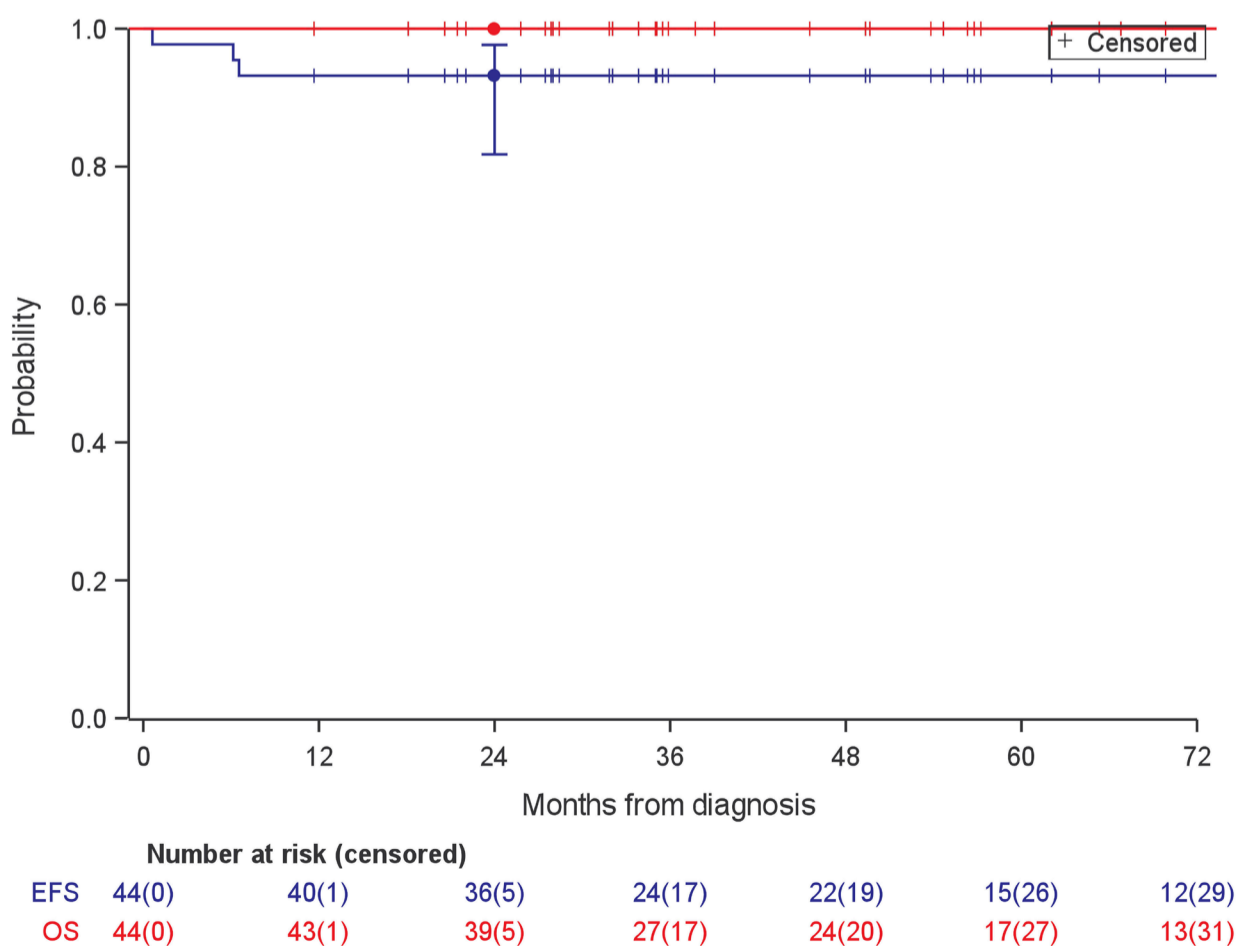
second course of R-CYVE), and one relapse. The patient who experienced progression after the first course of R-COPADM achieved a complete response after three courses of R-ICE (rituximab plus ifosfamide, carboplatin and etoposide). The patient with viable cells in a residual mass had progression after R-ICE (2 courses) but achieved a complete response after receiving a combination of brentuximab-nivolumab (4 cycles). The remaining patient, who relapsed 6.6 months after diagnosis, had a residual mass at the end of therapy but necrosis was observed upon histological analysis of a large biopsy. A diagnosis of high-grade B-cell lymphoma, not otherwise specified, was made at relapse and treatment involved R-ICE combined with ibrutinib in the SPARKLE trial.<sup>13</sup> All three patients achieved a complete response and underwent consolidation with high-dose BEAM chemotherapy (carmustine, etoposide, cytarabine and melphalan) and autologous hematopoietic stem cell transplantation followed by local radiation therapy. They are currently alive without disease 2.7, 5 and 11 years after the initial treatment failure. The 5-year event-free and overall survival rates for the entire cohort were 93.2% (95% CI: 81.8%-97.7%) and 100%, respectively (Figure 1).

This analysis, conducted on a larger cohort of patients with PMLBL treated in France with FAB/LMB-based chemotherapy combined with rituximab, confirmed the outstanding outcomes previously described. The good results of the combination of immunotherapy with chemotherapy are in stark contrast to those of chemotherapy alone.<sup>6,11</sup> These favorable outcomes also stand in contrast to the results observed with DA-EPOCH-R in 46 children and adolescents enrolled in the international Inter B-NHL Ritux 2010 phase II

study.<sup>8</sup> Despite the patients' characteristics being similar in the two studies, the phase II study recorded a significantly higher number of events, including 12 disease-related events with three (6.5%) parenchymal CNS relapses.

This highlights the need to refine risk factors for CNS relapse, and identify patients who may benefit from CNS prophylaxis.<sup>8,14</sup> The phase II, 4-year event-free and overall survival rates were 69.6% (95% CI: 55.2%-80.9%) and 84.8% (95% CI: 71.8%-92.4%), respectively.

The BFM NHL group presented their multicenter experience, spanning from 2004 to 2019: 67 patients were treated with modified DA-EPOCH-R (including the addition of at least one intrathecal triple therapy and capping the cumulative doxorubicin dose at 360 mg/m<sup>2</sup>) and 29 received B-NHL BMF04 intensified chemotherapy.<sup>15</sup> Among patients treated with DA-EPOCH-R, the 5-year event-free and overall survival rates were 84% (95% CI: 72%-91%) and 90% (95% CI: 79%-95%), respectively. Despite incorporation of triple intrathecal therapy, four out of 11 patients experiencing progression or relapse had parenchymal CNS disease, underscoring the importance of CNS-directed therapy in PMLBL. Since 2008 the French recommendation, described as a FAB/LMB-based PMLBL regimen with rituximab, has included two intrathecal therapies alongside high-dose methotrexate and high-dose cytarabine. This strategy has demonstrated good CNS control and efficacy, with only three local failures and a 5-year overall survival rate of 100%. The limited number of events precludes definitive conclusions regarding the role of the different chemotherapy arms. While the acute toxicity of FAB/LMB chemotherapy was significant,<sup>16</sup> overall treatment burden remained manageable, with a cumulative dose of



**Figure 1. Kaplan-Meier estimates of event-free survival and overall survival in the entire cohort.** EFS: event-free survival; OS: overall survival.

cyclophosphamide of 5,300 mg/m<sup>2</sup> and a cumulative dose of adriamycin of 240 mg/m<sup>2</sup>. Additionally, only three patients received local radiation therapy after relapse.

Regarding novel agents for PMLBL, while phase II results of brentuximab-vedotin were disappointing, with an overall response rate of only 13.3%, targeted therapy, such as brentuximab-vedotin combined with PD1 inhibitors, could offer opportunities as a second-line therapy.<sup>17-20</sup> One patient in our cohort benefited from this combination.

In first-line treatment, the outcome achieved with an FAB/LMB-based PMLBL intensive regimen with rituximab is excellent, with an overall survival rate of 100%. Nevertheless, new prospective studies are necessary to explore the potential for de-escalating frontline treatment through the addition of upfront immunotherapy such as an anti-PD1 monoclonal antibody. This will also require identification of sensitive clinical and biological predictors to allow safe treatment de-escalation and define risk factors for CNS relapse. Conversely, for those rare patients resistant to this initial line of treatment, a novel therapy such as an anti-PD1 monoclonal antibody or other targeted therapies based on molecular alterations identified in tumor cells could prove beneficial in combination with chemotherapy. Moving forward, future clinical trials should ideally incorporate clinical, biological or imaging prognostic factors identified through collaborative inter-group studies.

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### Disclosures

No conflicts of interest to disclose.

### Contributions

CP, AA, MED and VM-C conceived the study and oversaw the project. AP, M-LG, PG, SD, SH, TL, MB, BJ, AL, AJ, AS, CR, MS, JB, AV, GP, MP, NB, FM, JL-P, CP and VM-C provided patients. AP, VM-C, AA, CP and MED collected and assembled data. AA performed the statistical analysis. MED, AP, AA, CP and VM-C analyzed and interpreted data. MED, AP and VM-C wrote the manuscript. All authors approved the manuscript.

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### Data-sharing statement

Data can be made available upon reasonable request.

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