Rituximab in addition to LMB-based chemotherapy regimen in children and adolescents with primary mediastinal large B-cell lymphoma: results of the French LMB2001 prospective study

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Abstract

Primary mediastinal large B-cell lymphoma (PMLBL) is a rare entity predominantly affecting adolescents and young adults. Recently, an international phase II trial in pediatric patients using dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone plus rituximab (DA-EPOCH-R) failed to reproduce excellent survival reported in some adult studies. The optimal therapy regimen needs to be determined in this disease. The French prospective LMB2001 trial included all patients ≤18 years with mature B-cell lymphoma treated in French centers. For patients with PMLBL, treatment included four to eight courses of Lymphomes Malins B (LMB)-based chemotherapy without radiotherapy. From 2008, rituximab was added before each chemotherapy course. From 09/2001 to 03/2012, 42 patients with PMLBL were registered. The median age was 15 years (range, 8-18). Twenty-one patients were treated with chemotherapy plus rituximab. The median follow-up was 7.1 years (interquartile range, 5.8-11.1). Five-year event-free and overall survival were 88.1% (95% confidence interval (CI): 75.0-94.8) and 95.2% (95% CI: 84.0-98.7) for the whole population. The 5-year EFS was 81.0% (95% CI: 60.0-92.3) and 95.2% (95% CI: 77.3-99.2) (hazard ratio =0.24; 95% CI: 0.03-2.2) and 5-year overall survival was 90.5% (95% CI: 71.1-97.3) and 100% for patients treated without and with rituximab, respectively. Only one of 21 patients treated with rituximab and LMB-based chemotherapy had local early treatment failure but achieved prolonged complete remission with second-line chemotherapy and radiotherapy. Intensive LMB-based chemotherapy with rituximab achieved excellent survival in children/adolescents with PMLBL. Further international prospective studies are required to confirm these results in this population.

Introduction

Primary mediastinal (thymic) large B-cell lymphoma (PMLBL) is a distinct pathogenetic subtype of mature B-cell neoplasms.[1] It is a rare entity representing 2-4% of adult and pediatric non-Hodgkin lymphoma.[2,3] PMLBL

most commonly presents in female adolescents and young adults with signs and symptoms of bulky mediastinal disease. It is biologically related to nodular sclerosis Hodgkin lymphoma on pathology and gene expression profiling although some phenotype markers (MUM1, MAL),[4] as well as lactate dehydrogenase (LDH) levels and 18fluorodeoxyglucose-positron emission tomography/ computed tomography (18F-FDG PET/CT) findings help discriminate mediastinal Hodgkin lymphoma from PMLBL.[5] In adults with PMLBL, although there is a lack of consensus about the optimal therapeutic strategy for newly diagnosed patients, highly curative strategies, including rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) and dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone plus rituximab (DA-EPOCH-R) are mainly recommended.[6] However, significant cumulative doses of chemotherapy are achieved with both chemotherapy regimens and a substantial rate of patients still need radiation therapy (RT), especially with R-CHOP.

In children and adolescents, the first prospective international phase II study of DA-EPOCH-R regimen[7] failed to reproduce the outstanding survival reported with this regimen in some adults studies. Treatment strategies originally designed for Burkitt lymphoma are successfully used for children with diffuse large B-cell lymphoma (DLBCL)[8,9] but patients with PMLBL presented more aggressive disease and specific approaches were needed.[10,11] Herein, we reported the experience of the prospective French LMB 2001 study with 42 PMLBL patients treated with intensive LMB-based chemotherapy between 09/2001 and 03/2012, with the addition of rituximab from 2008.

Methods

Diagnosis, classification and staging

The French LMB 2001 prospective study included patients less or equal to 18 years old, with mature B-cell lymphoma including PMLBL. Patients with known pre-existing immunodeficiency were not included. For the purpose of this analysis, pathology was planned to be reviewed by national experts for diagnosis as PMLBL. The LMB2001 study has been approved by the SFCE Scientific Committee and National Ethics Committee. Parents/legal guardians provided written informed consent for the inclusion of their children in the studies in accordance with the Declaration of Helsinki. Minimal work-up included clinical examination, chest x-ray, abdominal ultrasound or CT, two bone marrow (BM) aspirates and biopsies, cerebrospinal fluid (CSF) cytology, and standard blood analysis including LDH level (≤ or >2N the upper limit of the institution's normal range). PET/CT was recommended but staging was not based on its result only. Other imaging was performed as clinically indicated. Staging was based according to the St Jude's/Murphy's and Ann Arbor classifications.

Study therapy

LMB2001 was a FAB (French-American-British)/LMB 96-based protocol. Treatment was based on St Jude's/Murphy's stage. Therapeutic groups were defined as in previous LMB studies.[9] All patients received a prephase of low-dose cyclophosphamide, vincristine, and prednisone (COP). Group B patients (stage III and non-CNS stage IV with marrow involvement <25%) received therapy similar to Group B on FAB/LMB96 with four cycles of chemotherapy. For all Group C patients, Group C1 patients (stage IV disease with marrow involvement ≥25% without CNS-positive disease) received high-dose methotrexate (HD MTX) (8 g/m^2) as previously given over 4 hours, whereas Group C3 patients (central nervous system [CNS]-positive) received HD MTX (8 g/m^2) over 24 hours.[12] Consecutive courses were given as soon as blood counts recovered and the patient's condition allowed, except for the maintenance courses, which were given at 28-day intervals.

From 2008, it was recommended to add rituximab (R) as an intravenous (IV) infusion (375 mg/m^2) on day 1 of each chemotherapy course. Additionally, based on an unpublished prognostic analysis, patients with bulky mediastinal mass (>10 cm) and/or high LDH serum level (> 2N on the Institution upper limit value), and/or lombo-aortic nodes were assigned to Group C1 regimen. Lastly, in 2010, the LMB-modified B/C chemotherapy with rituximab (total 6 doses) was recommended for all patients, consisting of two courses of RCOPADM Group B (cyclophosphamide, vincristine, prednisone, adriamycin, HD MTX 3 g/m^2) followed by two courses of RCYVE Group C (with high-dose cytarabine, and etoposide) and two courses of maintenance therapy with rituximab. Patients received two double intrathecal (DIT) only at day 2 of each COPADM course (Table 1).

Remission assessment was performed after the first consolidation course for Group B and after the second consolidation course for Group C and B/C. In patients with a residual mass by radiographic evaluation, an excision or biopsy for pathology review was recommended. However, as residual mass is frequent in PMLBL, if the therapy response was adequate and a biopsy was not performed, the patients were to remain on assigned treatment, and remission re-evaluated at the end of therapy. For Group B patients, if viable tumor cells were identified, the therapy was switched to the more intensive Group C1 regimen. Patients with biopsy-proven viable tumor cells after the second consolidation course ((R)CYVE2) were considered to have primary refractory disease and evaluated as an event. No-treatment decisions were based on 18F-FDG PET/CT results only, and 18F-FDG PET/CT were not reviewed for the purpose of this analysis. Patients with per-

Table 1. Outline of the LMB 2001 protocol for PMLBL patients

	Prephase	Course 1	Course 2	Course 3	Course 4	Course 5	Course 6	Course 7	Course 8	Cumulative dose
B	COP* Cy 300 mg/m² D1 VCR 2 mg/m² D1 IT (MTX HSHC) D1 pred 60 mg/m²/D D1-7	COPADM VCR 2 mg/m² D1 MTX 3 g/m² D1 Cy 250 mg/m²/ 12 h D2-4 Adriamycin 60 mg/m² D2 IT (MTX HSHC) D2;6 pred 60 mg/m² D1-5	COPADM VCR 2 mg/m² D1 MTX 3 g/m² D1 Cy 250 mg/m²/ 12 h D2-4 Adriamycin 60 mg/m² D2 IT (MTX HSHC) D2;6 pred 60 mg/m² D1-5	CYM MTX 3 g/m² D1 cytarabine 100 mg/m² D2-6 IVC 24h IT (MTX HSHC D2; HSHC araC D7)	CYM MTX 3 g/m² D1 cytarabine 100 mg/m² D2-6 IVC 24 h IT (MTX HSHC D2; HSHC araC D7)					Cyclophospha- mide 3,300 mg/m² Adriamycin 120 mg/m² IT=8*
C1	COP* Cy 300 mg/m² D1 VCR 2 mg/m² D1 IT (MTX HSHC araC) D1, D3, D5 pred 60 mg/m² D1-7	COPADM VCR 2 mg/m² D1 MTX 8 g/m² D1 Cy 250 mg/m²/ 12 h D2-4 Adriamycin 60 mg/m² D2 IT (MTX HSHC AraC) D2, 4, 6 pred 60 mg/m² D1-5	COPADM VCR 2 mg/m² D1 MTX 8 g/m² D1 Cy 500 mg/m²/ 12 h D2-4 Adriamycin 60 mg/m² D2 IT (MTX HSHC AraC) D2, 4, 6 pred 60 mg/m² D1-5	CYVE cytarabine 50 mg/m² IVC 12 h D1-5 Cytarabine 3 g/m² D2-5 VP16 200 mg/m² D2-5	CYVE cytarabine 50 mg/m² IVC 12 h D1-5 Cytarabine 3 g/m² D2-5 VP16 200 mg/m² D2-5	Seq1 VCR 2 mg/m² D1 MTX 8 g/m² D1 Cy 500 mg/m² D2-3 Adriamycin 60 mg/m² D2 IT (MTX HSHC AraC) D2 pred 60 mg/m² D1-5	Seq2 Cytarabine 50 mg/m²/12 h D1-5 VP16 150 mg/m² D1-3	Seq3 VCR 2 mg/m² D1 Cy 500 mg/m² D1-2 Adriamycin 60 mg/m² D1 pred 60 mg/m² D1-5	Seq4 Cytarabine 50 mg/m²/12 h D1-5 VP16 150 mg/m² D1-3	Cyclophospha- mide 6,800 mg/m² Adriamycin 240 mg/m² IT=7*

Continued on following page.

C3	COP* Cy 300 mg/m² VCR 2 mg/m² IT (MTX HSHC araC) D1, D3, D5 pred 60 mg/m²/D D1-7	COPADM VCR 2 mg/m² D1 MTX 8 g/m² D1 Cy 250 mg/m²/12 h D2-4 Adriamycin 60 mg/m² D2 IT (MTX HSHC AraC) D2, 4, 6 pred 60 mg/m² D1-5	COPADM VCR 2 mg/m² D1 MTX 8 g/m² D1 Cy 500 mg/m²/12 h D2-4 Adriamycin 60 mg/m² D2 IT (MTX HSHC AraC) D2, 4, 6 pred 60 mg/m² D1-5	CYVE IT (MTX +HSHC) D1 cytarabine 50 mg/m² IVC 12 h D1-5 Cytarabine 3 g/m² D2-5 VP16 200 mg/m² D2-5 MTX 8 g/m² D18 IT (MTX HSHC AraC) D2	CYVE IT (MTX +HSHC) D1 cytarabine 50 mg/m² IVC 12 h D1-5 Cytarabine 3 g/m² D2-5 VP16 200 mg/m² D2-5	Seq1 VCR 2 mg/m² D1 MTX 8 g/m² D1 Cy 500 mg/m² D2-3 Adriamycin 60 mg/m² D2 IT (MTX HSHC AraC) D2 pred 60 mg/m²/D D1-5	Seq2 Cytarabine 50 mg/m²/12 h VP16 150 mg/m² D1-3 D1-5	Seq3 VCR 2 mg/m² D1 Cy 500 mg/m² D1-5 Adriamycin 60 mg/m² D1 pred 60 mg/m²	Seq4 Cytarabine 50 mg/m²/12 h D1-5 VP16 150 mg/m² D1-3	Cyclophospha-mide 6,800 mg/m² Adriamycin 240mg/m² IT=10*
B-C (after 2010)	COP* Cy 300 mg/m² D1 VCR 2 mg/m² D1 IT (MTX HSHC) D1, pred 60 mg/m² D1-7	COPADM VCR 2 mg/m² D1 MTX 3 g/m² D1 Cy 250 mg/m²/12 h D2-4 Adriamycin 60 mg/m² D2 IT (MTX HSHC) D2 pred 60 mg/m² D1-5	COPADM VCR 2 mg/m² D1 MTX 3 g/m² D1 Cy 250 mg/m²/12 h D2-4 Adriamycin 60 mg/m² D2 IT (MTX HSHC) D2 pred 60 mg/m² D1-5	CYVE cytarabine 50 mg/m² IVC 12 h D1-5 Cytarabine 3 g/m² D2-5 VP16 200 mg/m² D2-5	CYVE cytarabine 50 mg/m² IVC 12 h D1-5 Cytarabine 3 g/m² D2-5 VP16 200 mg/m² D2-5	Seq3 VCR 2 mg/m² D1 Cy 500 mg/m² D1-2 Adriamycin 60 mg/m² D1 pred 60 mg/m² D1-5	Seq3 VCR 2 mg/m² D1 Cy 500 mg/m² D1-2 Adriamycin 60 mg/m² D1 pred 60 mg/m² D1-5			Cyclophospha-mide 5,300 mg/² Adriamycin 240 mg/m² IT= 2*
Rituximab (after 2008)		375 mg/m² D1	375 mg/m² D1	375 mg/m² D1	375 mg/m² D1	375 mg/m² D1	375 mg/m² D1			

ADM: adriamycin, doxorubicin; AraC: aracytine; VCR: vincristine; MTX: methotrexate; Cy: cyclophosphamide; pred: prednisolone; IT: intrathecal; RA: remission assessment. *A COP prephase is not mandatory but may be required one week prior to commencement of course 1 for patients requiring urgent treatment whilst awaiting histological confirmation. In case of COP prephase more intrathecal are administered. #remission assessment was required after 4 or 6 courses of chemotherapy. At the end of therapy, if PET-CT is positive, or a large residual tumor remains, then biopsy/removal of the residual mass is recommended. No treatment decisions were to be based on PET-CT results only.

sistent disease after the end of treatment received different therapies, including additional RT, second-line chemotherapy, and consolidation with high-dose chemotherapy and autologous stem cell transplantation.

Statistical analysis

The primary efficacy endpoint was event-free survival (EFS), defined as the time from the start of chemotherapy to the first of the following events: biopsy-positive residual disease following (R)CYVE number 2 or at the end of therapy, progressive disease, relapse, second malignant neoplasm, and death of any cause. Patients without any of these events were censored at the date of the last follow-up. The secondary efficacy endpoint was overall survival (OS), defined as the time from the start of chemotherapy to death from any cause, or to the date of the last follow-up for alive patients. EFS and overall survival (OS) were estimated with the Kaplan-Meier method.[13] The 95% confidence intervals (95% CI) of the survival rates were calculated with the Rothman method.[14]

Results

Baseline characteristics

Between 09/2001 and 03/2012, 42 of the 773 patients (5.4%) with newly diagnosed B-NHL were registered as LBL with mediastinum as primary site in the prospective French LMB2001 study. Baseline characteristics are summarized in Table 2. The median age at diagnosis was 15 years (range, 8.4-18). There were 24 females (57%). Thirty-three patients (79%) had large mediastinal masses of 10 cm or more, 18 patients (43%) had elevated LDH levels (> twice the institutional upper limit of the adult normal value), one patient had BM involvement and two patients were considered with CNS disease (one had facial paresthesia with normal magnetic resonance imaging but CSF could not be explored; one had asymptomatic epidural mass). No patient had positive CSF. In total, initial staging confirmed Ann Arbor stage II disease in 19 patients (45%), stage III in one patient (2%), and stage IV in 22 patients (52%).

Table 2. Baseline characteristics of the patients.

	All patients N=42	Patients treated without rituximab N=21	Patients treated with rituximab N=21
Female, N (%)	24 (57)	12 (57)	12 (57)
Age in years			
Median (range)	15 (8-18)	14 (8-17)	15 (10-18)
Distribution, N (%)			
≥ 8 - < 12 years	4 (10)	3 (14)	1 (5)
≥ 12 - < 15 years	17 (40)	9 (43)	8 (38)
≥ 15 - ≤ 18 years	21 (50)	9 (43)	12 (57)
Ann Arbor stage, N (%)			
II	19 (45)	10 (48)	9 (43)
III	1 (2)	0 (0)	1 (5)
IV	22 (52)	11 (52)	11 (52)
Mediastinal tumor ≥ 10 cm diameter, N (%)	33 (79)	17 (81)	16 (76)
Sites of involvement, N (%)			
Sub-diaphragmatic	11 (26)	4 (19)	7 (33)
Bone marrow involvement	1 (2)	0 (0)	1 (5)
Central nervous system	2* (5)	0 (0)	2 (10)
LDH >2, N (%)	18 (43)	10 (48)	8 (38)
Initial therapeutic group			
Group B	19	16	3
Group B/C or C	23	5	18

*Central nervous system involvement consisted in: facial paresthesia with normal magnetic resonance imaging but the cerebrospinal fluid (CSF) could not be explored=1; asymptomatic epidural mass=1. LDH: lactate dehydrogenase.

Figure 3. Events.

Patient identification number	First line therapy	Site of progression/ relapse	Time from inclusion	2nd line chemo-therapy	Radiation therapy	High dose chemo-therapy	Patient status at last news
PMLBL1	Group B, R-	mediastinum	Progression after CYVE1 3.4 months*	R-DHAP (3): progression R-ICE (2): progression	No	No	DOD, 23 months
PMLBL2	Group B, R-	mediastinum	Progression after CYM 3.5 months1	R-ICE (2): progression R-EPOCH (2): progression	No	No	DOD, 9.3 months
PMLBL3	Group B, R-	mediastinum	Viable cells in residual mass after CYVE2 5.2 months	R-ICE (2)	Yes	BEAM and ASCT	CR, 6.9 years
PMLBL4	Group B, R-	mediastinum	Local relapse 9.9 months	CYVE (2) R (4)	No	No	CR2, 6.7 years
PMLBL5	Group B switched to C after COP, R+	mediastinum	Progression after R-COPADM1 0.6 months	R-ICE (3)	Yes	BEAM and ASCT	CR, 11 years

R: rituximab; BEAM: carmustine, etoposide, cytarabine, melphalan; DHAP: dexamethasone, high dose aracytin, cisplatinum; ICE: ifosfamide, etoposide, carboplatin; EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; ASCT: autologous stem cell transplantation; CR: complete remission; DOD: died of disease. *Candidemia after prolonged aplasia followed by disease progression.

Histological characteristics

The national pathological review was done for 36 of 42 patients (86%) and PMLBL diagnosis was confirmed for all except one case. For one case, a consensus diagnosis was not reached (differential diagnosis between PMLBL and grey zone lymphoma). The remaining six patients had a local pathological report compatible with the diagnosis of PMLBL.

All cases expressed B-cell marker CD20 and were negative for CD3. CD10, BCL6, MUM1, BCL2, CD23 expression were evaluated for 12 cases and showed staining in 21%, 73%, 55%, 42%, and 46% of cases, respectively. CD30 staining was weak and patchy found in 66% of cases. PDL1 expression was observed on tumor cells in 85% of cases. Finally, only one of 23 cases tested had EBER positivity by *in situ* hybridization.

Treatment and response

All patients received LMB-based chemotherapy: 19 patients were treated in Group B, 18 in Group C, and five with LMB-modified B/C. Twenty-one patients received rituximab (R+) (after 2008) while 21 did not (R-). Of the 40 (95%) patients who were received COP therapy, 33 had at least a 20% response. Two patients were transferred to Group C after COP therapy (1 R- ; 1 R+). Three patients had disease progression during therapy (2 R-, 1 R+). Among the 39 other patients, at remission assessment, two patients were in complete response (CR) while 37 had a residual mass on imaging, with a median size of 50 mm (range, 17-135; data available for 30 patients). In total, 26 of 37 had biopsies, excisions or partial excisions: one had viable tumor cells (R-; tumor size: 68 mm after CYM1 *vs*. 108 mm at baseline) and for all other patients, the histology revealed complete necrosis. Thirty-eight patients (90%, 95% CI: 77-97) were considered to have achieved CR (2 CR, 25 complete necrosis, and 11 residual mass not explored).

Thirty-seven patients (88%) had 18F-FDG PET/CT at remission assessment after a median of four chemotherapy courses (range, 3-6) of whom 26 (70%) were considered positive according to current Cheson criteria.[15] Among these 26 patients, four had further treatment failure, including one with histology positive residual disease, one with complete necrosis on biopsy, and two not biopsied (predictive positive value =15%; 95% CI: 4-35). Among the 11 patients with negative 18F-FDG PET/CT, none had treatment failure (predictive negative value =100%; 95% CI: 72-100).

Outcome

The median follow-up was 7.1 years (interquartile range, 5.8-11.1), 10.6 years for patients treated without rituximab, and 6.4 years for patients treated with rituximab. There

were a total of five events (all local failures) (Table 3) with one insufficient response and viable cells in the residual mass (R-, patient obtained and remained in CR after R-ICE and BEAM, ASCT and radiotherapy), three disease progressions during treatment (2 R-, 1 R+) and one relapse (R-, patient obtained and remained in CR2). There was no second malignancy. Two of the three patients who progressed during treatment died of disease despite second-line therapy. The third one (R+) was switched to Group C after COP because of insufficient response and had disease progression after RCOPADM1 but remained in continuous first CR after two courses of RICE, high-dose BEAM chemotherapy (carmustine, etoposide, cytarabine, and melphalan) and radiotherapy. In total, there were two deaths, the two following disease progression during therapy in R- patients. The probability of 5-year EFS was 88.1% (95% CI: 75.0-94.8) in the whole cohort and 81.0% (95% CI :60.0-92.3) in R- patients and 95.2% (95% CI: 77.3-99.2) in R+ patients corresponding to a hazard ratio of 0.24 (95% CI: 0.03-2.2) (Figures 1 and 2A). The probability of 5-year OS was 95.2% (95% CI: 84.0-98.7) in the whole cohort and 90.5% (95% CI: 71.1-97.3) in R- patients) and 100% in R+ patients (Figures 1 and 2B).

Discussion

In this prospective multicentric French LMB2001 study with intensive LMB chemotherapy in addition to rituximab since 2008, pediatric and adolescent patients with PMLBL achieved excellent survivals. Five-year EFS and OS were 88.1% (95% CI: 75.0-94.8) and 95.2% (95% CI: 84.0-98.7) for the whole population. The previous FAB/LMB 96 study in children and adolescents with PMLBL treated with Group B LMB chemotherapy reported a 5-year EFS and OS of 66 % (95% CI: 49-78) and 73% (95% CI: 56-84).[10] By comparison, in the current series, 21 patients with PMLBL were treated without rituximab (16 therapeutic Group B; 5 Group B/C or C) with 5-year EFS of 81.0% (95% CI: 60.0-92.3). Thus, these current results without rituximab compare favorably with previous FAB/LMB 96 (although not statistically different). Although there is no easy explanation, we cannot exclude that more intense chemotherapy may be more effective (all events except one in the current series occurred in patients treated in Group B and percentage of patients initially treated with Group C or B/C is higher in the current series). It has been distinctly demonstrated in adult patients with PMLBL that the addition of rituximab improves the outcome (HR for events 0.3; 95% CI: 0.1-0.8).[16] In the French LMB2001 study, the assessment of rituximab addition to LMB-based chemotherapy, which was not based on a randomized comparison but on a comparison of two periods, showed a similar HR (HR for events 0.24; 95% CI: 0.03-2.2) with 5-year EFS of 81.0% (95% CI: 60.0-92.3) without rituximab and 95.2% (95% CI: 77.3-99.2) with rituximab.

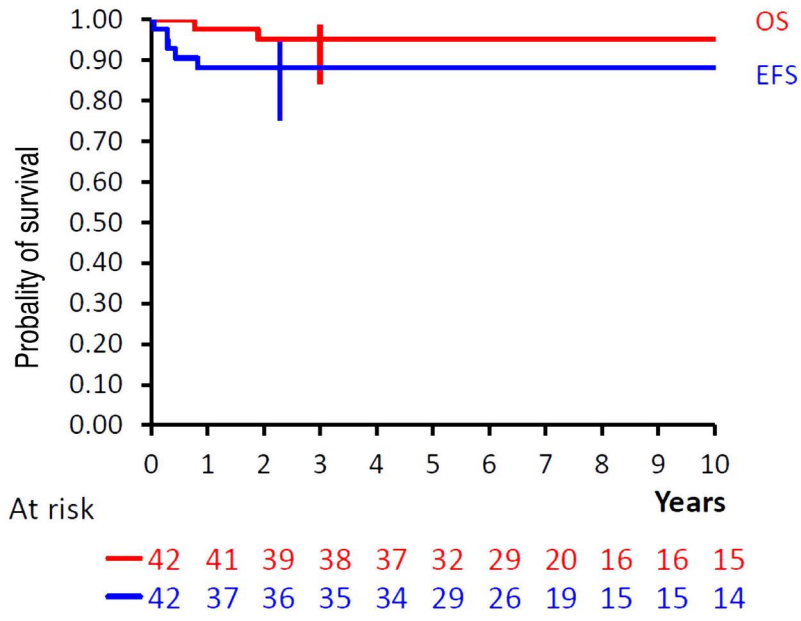

Figure 1. Kaplan Meier estimates of overall survival and event-free survival. Vertical lines represent the Rothman 95% confidence interval. EFS: event-free survival; OS: overall survival.

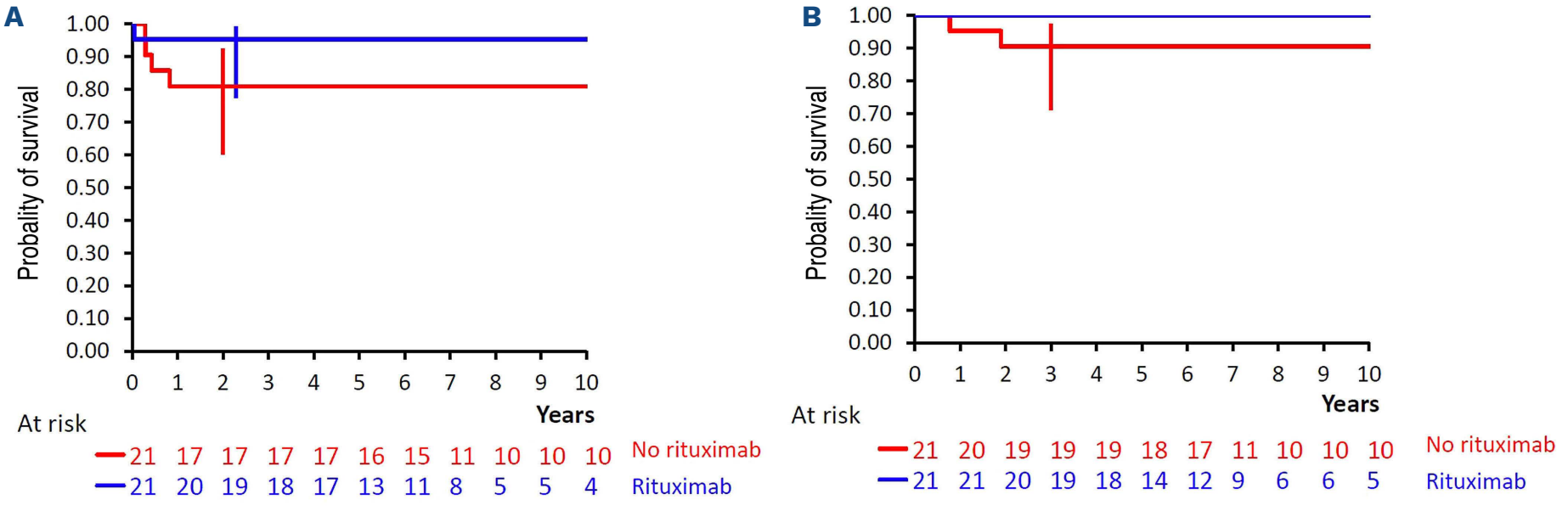

Figure 2. Kaplan Meier estimates of event-free survival and overall survival according to rituximab administration. (A) Event-free survival. (B) Overall survival. Vertical lines represent the Rothman 95% confidence interval.

These excellent results contrast with the results recently published with DA-EPOCH-R in 46 children and adolescents included in the international phase II Inter B-NHL-ritux 2010 study[7] (Table 4). Although the characteristics of the patients included in this study do not differ from those of the phase II Inter B-NHL-ritux 2010, 12 disease-related events were observed in the phase II, with 4-year EFS and OS of 69.6% (95% CI: 55.2-80.9) and 84.8% (95% CI: 71.8-92.4), respectively, and three (6.5%) parenchymal central nervous system relapses. All five disease-related events in the French LMB2001 study were local/mediastinal with no CNS relapses. Thus, CNS-directed therapy may be important in PMLBL and explains why we recommended since 2008 LMB B/C-modified regimen with rituximab, with some intrathecal therapy but also HD MTX and high-dose cytarabine (AraC). Recently, a real-world study from the French LYSA group also reinforces the benefit of dose intense immuno-chemotherapy regimens in PMLBL[17]: patients treated with R-ACVBP or R-CHOP14 achieved a better outcome than those treated with R-CHOP21 (progression-free survival of 89.4% *vs*. 74.7%). R-ACVBP also included some CNS-directed therapies such as HD MTX and intrathecal in the majority of patients and CNS relapse rate was low (2.9%) in this series.

By contrast with the pediatric phase II Inter-B-NHL ritux 2010 trial, outstanding survival for adult patients with PMLBL has been reported with DA-EPOCH-R in a single-institution, non-randomized phase II study, of 51 patients with EFS of 93% (95% CI: 81-98) and OS of 97% (95% CI: 81-99).[18] In the same way, a large multicenter retrospective analysis reported on the outcome of pediatric and adult patients treated with DA-EPOCH-R for PMLBL.[19] Survivals were not statistically different between pediatric and adult patients for both EFS (81.0% *vs.* 87.4%, *P*=0.338) and OS (90.7% *vs*. 97.1%, *P*=0.170).

Clinically and pathologically, PMLBL disease in the pediatric population is indistinguishable from that seen in adult patients. Thus, the difference in outcome between the two main DA-EPOCH-R studies is therefore hard to explain although the methodology of these studies is very different (i.e., international *vs*. single-institution). Other registry-based or retrospective studies of children and adolescents with PMLBL treated with DA-EPOCH-R have been also reported. The BFM NHL group reported their multicentric experience between 2004 and 2019 with modified DA-EPOCH-R (addition of at least one intrathecal triple therapy and a cumulative doxorubicin dose limit at 360 mg/m^2) (n=67 patients) or intensified chemotherapy B-NHL BMF04 (n=29 patients) and compared it retrospectively to the treatment regimen in the B-NHL BMF95 trial (n=20 patients), both without rituximab.[20] For patients treated with DA-EPOCH-R, the 5-year EFS and OS were 84% (95% CI: 72–91) and 90% (95% CI: 79–95), respectively. These results are intermediate between the outstanding results obtained in the phase II study in adult patients and the phase II Inter-B-NHL ritux 2010 in children (Table 4). However, despite the use of triple intrathecal, at relapse four of 11 patients treated with DA-EPOCH-R had parenchymal CNS disease, strengthening the fact that it is necessary to improve CNS disease control in this pathology.

Pediatric-type B-NHL regimens, such as LMB and others, have higher acute toxicity when compared with DA-EPOCH-R regimen. The DA-EPOCH-R phase II Inter-B-NHL ritux 2010 study in pediatric patients reported febrile neutropenia in 11% of courses and 46% of patients, infections grade ≥3 in 4% of courses and 17% of patients and stomatitis grade ≥3 in 3% of courses and 15% of patients. Although we did not register toxicity in the prospective French LMB2001 trial (but no toxic death occurred), other LMB-based chemotherapy trials with rituximab reported febrile neutropenia, infection grade ≥3 and stomatitis grade ≥3, in 92.6%, 58.6%, and 79.6% of patients, respectively.[21] However, management of long-term toxicity is also very important in this young population. The risks for significant long-term sequelae are relatively modest using

Table 4. Summary of R-DA-EPOCH studies and the LMB 2001 study.

Study	Regimen	Type of study	Population	N of patients	Median FU	N of events (CNS relapse)	EFS, % (95% CI)	OS, % (95% CI)
NCI[18]	DA-EPOCH-R	Phase 2, monocentric	Adults	51	5 years	3 (0)	93 (81-98)	97 (81-99)
BFM[19]	DA-EPOCH-R	Registry, multicentric	Child/ado	67	4 years	11 (4)	84 (72-91)	90 (79-95)
Inter B-NHL ritux 2010[7]	DA-EPOCH-R	Phase 2, multicentric	Child/ado	46	5 years	14 (3)	70 (55-81)	85 (72-92)
LMB 2001	R-LMB	Registry, multicentric	Child/ado	21	6 years	1 (0)	95 (77-99)	100
LMB 2001	LMB	Registry, multicentric	Child/ado	21	10 years	4 (0)	81 (60-92)	90 (71-97)

Child/ado: children/adolescents; CI: confidence interval; EFS: event-free survival; FU: follow-up; OS: overall survival; DA-EPOCH-R: dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone plus rituximab.

LMB chemotherapy backbone[22] and the total cumulative dose of doxorubicin is limited and of 240 mg/m^2 with the LMB B/C-modified combination (favorably compared with the DA-EPOCH-R in the Inter-B-NHL ritux 2010 study where 72% of patients received ≥300 mg/m^2 doxorubicin and 24% ≥350 mg/m^2)[7].

Although our study has some limitations, i.e., i) relative small series of 42 patients but it compares well with other published reports in this rare disease, ii) pathology review for only 85% of cases, iii) no randomized comparison between LMB chemotherapy only and LMB chemotherapy with rituximab, and iv) some differences during the study duration in terms of chemotherapy group recommendations, this was a prospective multicentric study, and we believe that these excellent results are important for the medical community of pediatric, adolescents, and young adults oncologists. Further prospective and international trials are required to confirm these results and define optimal treatment for patients with PMLBL (all ages included). Novel agents (e.g., NF-kB pathway inhibitors or anti-PD1 therapies combined or not with brentuximab-vedotin) may be required next to reduce chemotherapy intensity and improve outcome in this population.[23]

Disclosures

No conflicts of interest to disclose.

Contributions

CP, AA, MED, and VM-C conceived the study and oversaw the project; AP, NG, NA, JM, SH, CP, JL-P, TL, CS, CP and VM-C recruited patients; AP, VM-C, AA, CP, JB and MED collected and assembled data; AA performed statistical analysis; MED, AP, AA, JB, CP, 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

The data that support the findings of this study are available on request from the corresponding author.

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