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Burkitt lymphoma in adults: a prospective study of 72 patients treated with an adapted pediatric LMB protocol

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On behalf of GELA and GOELAMS

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Background: We conducted a phase II study to evaluate in 72 adult patients the efficacy of the intensive LMB chemotherapy regimen, previously reported by the Société Française d'Oncologie Pédiatrique for children with Burkitt lymphoma and L3 acute lymphoblastic leukemia.

Patients and methods: Treatment began with a prephase (low-dose steroids, vincristine and cyclophosphamide), except in patients with low tumor burden. Group A (resected stage I and abdominal stage II disease) received three courses of vincristine, cyclophosphamide, doxorubicin and prednisone. Group B (not eligible for groups A or C) received five courses of chemotherapy comprising high-dose methotrexate, infusional cytarabine and intrathecal (IT) methotrexate. Group C (patients with central nervous system and/or bone marrow involvement with <30% of blast cells) received eight courses containing intensified high-dose methotrexate, high-dose cytarabine, etoposide and triple IT injections.

Results: The 2 year event-free survival and overall survival rates for the 72 patients were 65% and 70%, respectively. Age ≥33 years and high lactate dehydrogenase value were associated with a shorter survival. No response to COP was also associated with a poor outcome in group B.

Conclusion: Patients with advanced-stage Burkitt lymphoma, including those with bone marrow and/or central nervous system involvement, can be cured with a short-term intensive chemotherapy regime tailored to the tumor burden.

Key words: adult patients, Burkitt lymphoma, chemotherapy, prognostic factors

Introduction

Although Burkitt lymphoma accounts for ∼40% of all childhood non-Hodgkin lymphoma, it represents <5% of lymphoma cases in adults [1]. Therefore there are fewer reports on the outcome of Burkitt patients in adult than in pediatric series. When Burkitt lymphoma is treated with standard CHOP-based combination therapies, the outlook for survival is usually considered to be poor, with 2 and 5 year overall survival rates ranging from 50% to 65% and decreasing to <30% in case of bone marrow (BM) or central nervous system (CNS) involvement [2–4]. We found an 5 year overall survival rate of 53% with a median follow-up of 53 months in a series of 52 adult HIV-negative Burkitt lymphoma patients without BM or CNS involvement who were treated with a reinforced CHOP regimen called ACVBP used by the GELA Group [2]. The probability of survival does not seem to differ when adults with Burkitt lymphoma are treated with protocols designed for ALL [5,6].

In stark contrast, the results of treatment of children with Burkitt lymphoma have dramatically improved during recent decades. In the 1980s, the Société Française d'Oncologie Pédiatrique (SFOP) conducted successive LMB therapeutic trials for Burkitt lymphoma and FAB L3 leukemia (L3ALL). These LMB protocols have improved the outcome of children with Burkitt lymphoma, with survival rates exceeding 90% even in patients with CNS lymphoma or L3ALL [7–10]. The mainstay of these protocols is brief-duration high-intensity chemotherapy regimens containing systemic high-dose methotrexate, with the adjunction of high-dose cytarabine in patients with CNS disease. The first courses of chemotherapy are adapted according to early tumor response. Patients who fail to respond to initial debulking chemotherapy are treated with higher-intensity cytarabine–VP16-based consolidation chemotherapy.

Administering the brief-duration high-intensity chemotherapy programs used in children and adolescents to adults appears to yield better results. In a retrospective analysis, a 3 year survival rate of 74% was achieved in a series of 65 adult patients who were

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treated with the LMB pediatric protocols [11]. Other authors have published similar findings [12–16]. In this report we summarize the results obtained for 72 adult patients treated in a multicenter prospective study using the SFOP LMB89 protocol [10].

Patients and methods

Patients

In 1996 we initiated a prospective multicenter trial, designated LMB95, for patients with newly diagnosed Burkitt lymphoma with <30% of tumor cell infiltration of bone marrow. The patients were aged >18 years and had no history of immunodeficiency (HIV-negative patients). They were enrolled between July 1996 and March 2001 at 36 participating centers. All patients gave their written informed consent before entering the study, which was performed in accordance with the Helsinki Declaration. Our Institutional Review Board approved the study.

Biopsies, imprints and fine-needle aspirations from patients enrolled in the clinical trial were reviewed by two expert hematopathologists (JB and MR). Conventional morphology was performed on paraffin-embedded sections stained with hematoxylin–eosin and May–Grunwald–Giemsa stained imprints and fine-needle aspiration. Morphological analysis was completed by either immunohistochemistry on paraffin sections to detect B-cell markers (CD20, CD79a and CD10), BCL2 protein and ki67 expression using immunoperoxidase technique, and/or when cell suspension was available flow cytometry was also performed to analyze the expression of B-cell markers (CD10, CD19, CD20, CD22, CD24 and the light-chain κ or λ surface immunoglobulin). Cases were classified according to the World Health Organization (WHO) criteria identifying classical Burkitt lymphoma and two morphological variants: with plasmacytoid differentiation, and atypical Burkitt/Burkitt-like lymphoma where the lymphomatous proliferation has the features of Burkitt lymphoma with a very high growth fraction with more pleomorphic lymphomatous cells than in the classical form [17].

Staging procedures included blood counts and chemistries, chest radiography, CT of the chest, abdomen and pelvis, bone marrow aspirate and biopsy, and a lumbar puncture. The number of extranodal sites and the diameter of the largest tumor mass were determined. The serum lactate dehydrogenase (LDH) level was expressed as a percentage of the maximal normal value. Disease staging was according to the Ann Arbor and St Jude systems [18]. In the present study, 'abdominal stage II' disease is specifically defined as localized gut tumors having undergone complete resection without extensive surgery. Involvement of a node immediately adjacent to the tumor was accepted, provided that the adjacent nodes were proven tumor free at histological analysis. Otherwise, involvement of several nodes or of a distant mesenteric node or other signs of abdominal spread, such as ascites or hemoperitoneum, led to the classification of the tumor as stage III disease. CNS disease was defined as the presence of blasts in the cerebrospinal fluid (CSF), whatever the number, cranial nerve palsy unrelated to a facial tumor, clinical signs of spinal cord compression and/or an intracranial mass.

Chemotherapy regimen (Fig. 1 and Table 1)

Patients were allocated to three groups, A, B and C, according to the modified St Jude system [8], with escalation of treatment intensity but with adaptation according to age for patients included in group C. Patients with completely resected stage I and abdominal stage II disease were assigned to group A. This selected group of patients, who were expected to have a very good prognosis, received only three COPAD courses and no intrathecal (IT) injections. Patients with unresected stage I, non-abdominal stage II and any stage III or IV disease without CNS or BM involvement were assigned to group B. Treatment was adapted to that of the short arm of the pediatric LMB84 protocol [8]. If disease failed to respond after the prephase COP regimen, group B patients were switched to group C therapy (but were nonetheless analyzed with group B patients). Patients in group C had CNS involvement (CNS+) or BM involvement (BM+). Treatment was derived from the LMB89 protocol with a higher dose of MTX (8 g/m^2), triple IT injections and more intensive consolidation with high-dose cytarabine (HDAra-C) and VP16 [10]. Group B patients were evaluated at day 7 following the initial debulking prephase with COP. Patients were considered as responders if tumor shrinkage attained at least 20%. Cranial irradiation (24 Gy) was delivered only to patients with CNS involvement. Doses of methotrexate (MTX) (in g/m^2) and HDAra-C (Ara-C) (in g/m^2) were suited to age and the presence of CNS involvement (Table 2). If complete remission was not obtained after the first CYM course in group B and the second CYVE course in group C, treatment was intensified with high-dose chemotherapy (HDCT) followed by autologous stem cell transplantation. The preparative regimen was the previously described BEAM regimen (BCNU, VP16, ara-C and melphalan). HSC collection was performed after CYVE therapy when less than complete remission was documented after the third or fourth induction–consolidation course. No local irradiation therapy was planned in the protocol in cases of residual disease. Intervals between induction and consolidation courses were as short as possible in all groups, and chemotherapy was to be started as soon as the absolute neutrophil count was >1.5 × 10^9/liter and platelet count was >100 × 10^9/litre. G-CSF was not systematically recommended. At diagnosis, vigorous alkaline diuresis was obtained, with furosemide if necessary, and a uricolytic (urate-oxydase) was instituted before the initiation of treatment.

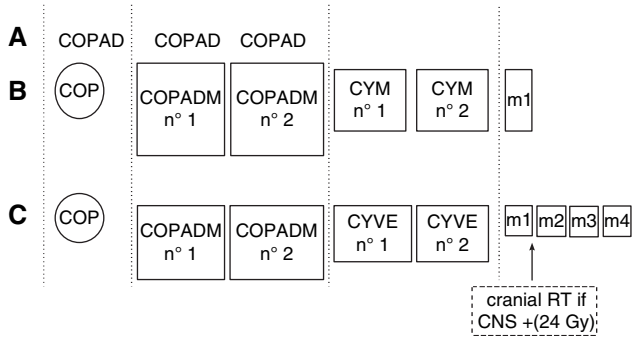

Figure 1. LMBA 95 protocol schedule. Patients were stratified into three risk groups (A, B and C) depending on stage, resection status, presence of blasts in BM and CNS involvement. The treatment courses are listed in Table 1 (m, maintenance chemotherapy). Duration of therapy was 7 weeks in group A, 14 weeks in group B and 26 weeks in group C.

Response criteria

Complete remission (CR) was defined as the disappearance of all clinical evidence of disease and the normalization of all laboratory and radiographic results which were abnormal before treatment. Partial response (PR) was defined as a >50% reduction in tumor mass. Progressive disease was considered a treatment failure.

Statistical methods

Study endpoints were response to induction, event-free survival (EFS) and overall survival. EFS was calculated from the start of chemotherapy to the date of progression, relapse or death from any cause.

Overall survival rates were measured from the date of the initiation of treatment to death from any cause, or to the last follow-up. Survival curves were estimated using the Kaplan–Meier method. The clinical features that were evaluated for potential prognostic significance included the Ann. Arbor and St Jude stages, the performance status (PS), extranodal disease, size of

Table 1. LMBA 95: treatment courses

Regimen	Dose	Administration	Days
Prephase			
COP			
CPM	0.3 g/m^2	IV	1
VCR	1 mg/m^2 (max 2 mg)	IV	1
Pred	60 mg/m^2	IV or orally	1–7
MTX + HC (*C:+Ara-C*)	15 mg (*C: +40 mg*)	IT	1 (*C: +3 +5*)
Induction phase			
COPADM no. 1, started 1 week after first day of reduction phase			
VCR	1.4 mg/m^2 (max 2 mg)	IV	1
HD MTX	B: 3 mg/m^2	IV 3h	1
CFR	15 mg/m^2 × 4/day		2, 3, 4
MTX + HC (*C:+Ara-C*)	15 mg (*C: +40 mg*)	IT	2, 6 (*C: +4*)
ADR	60 mg/m^2	IV	2
CPM	0.5 g/m^2	IV (in 2 fractions)	2, 3, 4
Pred	60 mg/m^2	IV or orally	1–6
COPADM no. 2: similar to COPADM no. 1 except for			
Second dose VCR	1.4 mg/m^2 (max 2 mg)	IV	6
CPM	1 g/m^2	IV (in 2 fractions)	2, 3, 4
COPAD (g A): similar to COPADM no. 1, but without HD MTX and IT and additional dose of VCR			
VCR	1.4 mg/m^2 (max 2 mg)	IV	6
Consolidation phase			
GB:CYM nos 1 and 2			
HD MTX	3 g/m^2	IV (3 h)	1
CFR	15 mg/m^2 × 4/day		2, 3, 4
MTX + HC	15 mg	IT	2
Ara-C	100 mg/m^2	CI	2–6
Ara-C + HC	30 mg + 15 mg	IT	6
C:CYVE nos 1 and 2			
Ara-C	*50 mg/m^2*	*CI*	*1–5 over 12 h*
HD Ara-C	*3 g/m^2*	*IV (3 h)*	*2–5*
VP16	*200 mg/m^2*	*IV*	*2–5*
Maintenance (monthly alternated courses)			
m1			
VCR	1.4 mg/m^2 (max 2 mg)	IV	1
HD MTX	B: 3 g/m^2	IV (3 h)	1
CFR	15 mg/m^2 × 4/day		2–4
Pred	60 mg/m^2	Orally	1–5
MTX + HC (*C: +Ara-C*)	15 mg (*C: +40 mg*)	IT	2
CPM	0.5 g/m^2	IV	1,2
ADR	60 mg/m^2	IV	2
m3: similar to m1 but without HD MTX and IT			
m2 or m4			
VP16	*150 mg/m^2*	*IV*	*28–30*
Ara-C	*100 mg/m^2*	*SC (in 2 fractions)*	*28–32*

Italic type: specific to group C.

CPM, cyclophosphamide; VCR, vincristine (maximum dose, 2 mg by injection); Pred, prednisone; MTX, methotrexate; HC, hydrocortisone; HD, high dose; CFR, citrovorum factor rescue (leucovorin); ADR, adriamycin (doxorubicin), Ara-C, cytarabine; VP16, etoposide; IV, intravenous; IT, intrathecal; CI, continuous infusion; SC, subcutaneously.

Table 2. Dose adaptation in patients treated in group C according to age and CNS involvement

Age (years)	CNS+, BM±			
	MTX (g/m^2)	Ara-C (g/m^2)	MTX (g/m^2)	Ara-C (g/m^2)
≤40	8	3	3	2
40–60	3	2	2	2
>60	2	1	1	1

the largest tumor and the serum LDH level. Univariate analyses were performed using Fisher's exact test and log rank tests. Features independently associated with overall survival were identified in the multivariate analysis by Cox regression analysis.

Results

Patients

Eighty-nine patients were enrolled. One patient with liver failure unrelated to lymphoma and 16 cases that did not satisfy the Burkitt lymphoma diagnosis criteria were excluded (eight DLBCL, one mantle cell lymphoma, one transformed lymphoma, five ALL3 and one proB-ALL). Fifty-eight cases were classified as classical Burkitt lymphoma, and nine cases with pleomorphic lymphomatous cells were classified as atypical/Burkitt like lymphoma. Five cases with insufficient material could not be subclassified.

A cytogenetic analysis was performed in 25 cases (33%) and clonal chromosome aberrations were evidenced in 22 cases; no metaphases could be obtained in the three remaining cases. Seventeen patients had a t(8;14), one had a t(2;8) and one had a t(8;22). In the other three cases a very complex karyotype was observed with a t(14;18) in one case and a t(3;22) in another.

The clinical characteristics of the 72 patients are listed in Table 3. Forty-seven patients (65%) had abdominal stage II or III disease according to the St Jude classification, including eight cases with a gastric tumor. Several extranodal sites were involved in 55 patients: stomach (eight cases), ileo-cecum (35 cases), CNS (11 cases), bone marrow (10 cases), liver (five cases), bone (four cases), skin (two cases), lung (one case), breast (one case) and uterus (one case). Ten patients had BM involvement, with <30% of blasts according to the inclusion criteria. Eleven patients had CNS involvement with blasts in CSF (11 cases) and cranial nerve palsies (five cases). Neither an intracranial mass nor cord compression was observed. Tumor sizes ranged from 2 to 20 cm and 22 patients (31%) had bulky disease of diameter >10 cm. Twenty-one patients (29%) had a PS >1. Forty-three patients (58%) had an LDH level elevated above the normal.

Therapy results

Six patients (8%) were treated in group A, 50 (70%) in group B and 16 (22%) in group C.

Table 3. Patient characteristics (n = 72) and univariate analysis of overall survival

	Number (%)	2-year overall survival (%)	P-value
Age			
Median (range): 33 (18–76) years			
<33 years	37 (51)	84	0.01
≥33 years	35 (49)	60	
Male/female	59/13		
Ann Arbor stage			
I–II	24 (33)	71	0.96
III–IV	48 (67)	73	
St Jude Stage			
I–II	26 (36)	77	0.45
III–IV	46 (64)	69	
Tumor mass			
<10 cm	50 (69)	76	0.41
≥10 cm	22 (31)	63	
Extranodal site			
0–1	42 (58)	78	0.07
≥2	30 (42)	63	
Performance status			
0–1	50 (70)	72	0.79
≥2	21 (30)	71	
Serum LDH level			
Normal	29 (40)	86	0.02
Elevated	43 (60)	63	
IPI			
0–1	33 (46)	79	0.22
≥2	39 (54)	66	

LDH, lactate dehydrogenase; IPI, International Prognostic Index.

Response to prephase COP chemotherapy. Among the 50 patients treated in group B, 34 (68%) were considered to be responders to COP.

Response to therapy. Fifty-three patients (72%) achieved a CR at the end of treatment. Of these 53 patients, 47 (65%) achieved a CR with the planned program, one after a modified protocol (one toxicity-related problem), one after additional cervical radiotherapy and four after HDCT followed by autologous stem cell transplantation because of partial response at evaluation after the third (two patients in group B) or fourth (two patients in group C) induction–consolidation courses. Nineteen patients failed to respond and died, three due to early toxicity before the evaluation of response and 16 because of failure to respond to initial treatment (less than a partial response) even though five had received HDCT with reinjection of stem cells (including allogeneic stem cells in two patients). Four patients aged >60

years were included in this trial. Two of them were alive in complete remission 19 and 61 months after starting therapy; the other two patients died on therapy 4 and 6 months after starting therapy.

Relapses. Four patients relapsed. Three relapses occurred in patients treated in group B and all three patients died. One patient in group A relapsed with CNS involvement and was successfully salvaged with cytarabine–VP16-based combination therapy and HDCT. No relapse was observed in group C once a CR had been obtained.

Toxicity-related deaths. Three patients, all in group B, died of infectious disease, two after the 2 second COPADM induction course and one after the final consolidation course.

Treatment-related toxicity and morbidity. A full assessment for toxicity was performed on 433 courses of chemotherapy (Table 4). With the prephase treatment (COP chemotherapy) and the associated supportive care protocol, none of the patients required dialysis for tumor lysis syndrome. The course following a COPADM cycle was generally started at a median of 18 days later. Myelosuppression was the main treatment complication, especially during the COPADM and CYVE courses. More than 40% of the patients experienced febrile neutropenia requiring intravenous antibiotics, and more than 50% required transfusions. Mucositis (grade III–IV), was observed in 14% and 12% during the COPADM and CYVE courses, respectively, and in <7% during the other chemotherapy cycles. Grade II–IV mucositis was no more frequent in group C (including high-dose methotrexate at 8 g/m^2 during the COPADM courses) than in other therapy groups (P = 0.23). Three patients developed transient grade III (two cases) or grade II (one case) renal toxicity during the COPADM course, which was led to subsequent reduction of the methotrexate dose in two cases. No central neurological toxicity was observed, and only two patients experienced grade II peripheral neurological toxicity. No other major therapy-related toxicity was observed.

Table 4. Main toxicities of induction/consolidation courses

	COPAD	COPADM	CYM	CYVE
No. of courses	18	130	89	25
Red cell transfusion (%)	0	48	45	72
Platelet transfusion (%)	0	17	27	56
Mucositis				
Grade 3 (%)	0	9	2	12
Grade 4 (%)	0	5	2	0
Febrile neutropenia (%)	6	42	26	32
Severe infection[a] (%)	0	18	8	20
Life threatening (%)	0	3	0	0
Toxicity-related deaths	0	2	0	0

[a]Sepsis, urine infection, extensive skin infection, pneumonitis, 'shock' without bacteriological documentation.

Event-free and overall survival. The median follow-up was 32 (range 12–64) months. EFS and overall survival rates estimated for the 72 patients at 2 years were 65% [95% confidence interval (CI), 54–77%) and 70% (95% CI, 59–81%), respectively (Figs 2 and 3). The 2year EFS and overall survival estimates for the three groups of patients were 67% (95% CI, 23–99%) and 83% (95% CI, 53–99%), respectively, for group A, 66% (95% CI, 52–79%) and 70% (95% CI, 57–83%) for group B, and 62% (95% CI, 35–89%) and 67% (95% CI, 43–92%) for group C.

The 2 year survival estimates according to the St Jude classification were 77% (95% CI 54–90%) for patients with stage I–II disease, and 66% (95% CI, 55–83%) for those with stage III–IV disease. Ten of the 16 patients treated in group C and eight of them remained alive in CR. In the univariate analysis of EFS performed for the 72 patients, 2 year EFS was significantly

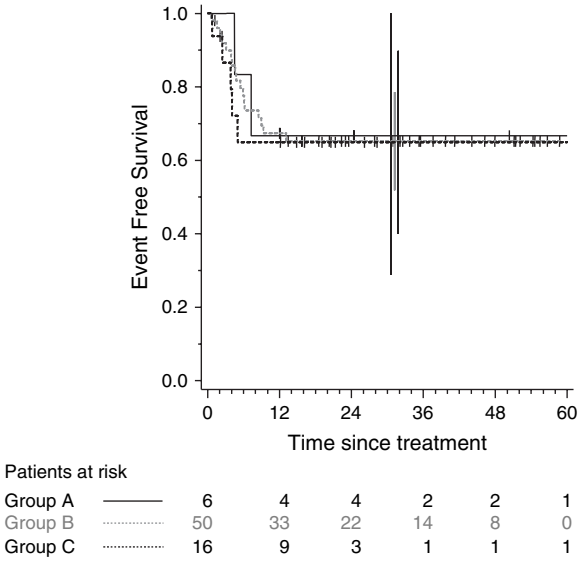

Figure 2. EFS curve of the 72 patients according to the treatment groups (A, B and C).

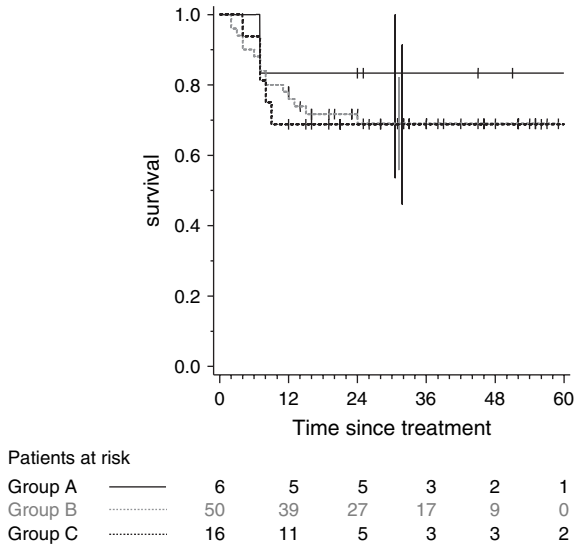

Figure 3. Overall survival curve of the 72 patients according to treatment group (A, B, C).

better among patients with a low serum LDH level ($P = 0.02$) and patients aged <33 years (less than the median age value) ($P = 0.006$).The treatment group (A, B and C), sex, PS, histologic subclassification into Burkitt and atypical Burkitt/Burkitt-likelymphoma, International Prognostic Index (IPI), Ann Arbor and Murphy stages, and the presence of bulky disease (>10 cm) were also evaluated but were not predictive for EFS. In the multivariate analysis, both the serum LDH level and age remained predictive of outcome ($P = 0.01$). With regard to the patients in group B (50 patients), the serum LDH level, age and failure to respond after prephase COP chemotherapy were prognostic factors for EFS (P-values of 0.02, 0.004 and 0.02, respectively). In the mutivariate analysis of EFS performed in group B, the serum LDH level, age and response to COP remained predictive of outcome (P-values of 0.006, 0.002 and 0.004, respectively).

Table 3 lists the factors that adversely affected the outcome of the 72 patients. As shown by univariate analysis, age ≥33 years ($P = 0.01$) (Fig. 4) and a high LDH level ($P = 0.02$) were found to be significantly associated with poor overall survival. Ann Arbor or St Jude stages III–IV, bulky disease, PS > 1, histologic subclassification into Burkitt and atypical Burkitt/Burkitt-like lymphoma and the presence of at least two extranodal sites was not predictive of outcome. In the multivariate analysis, only a high LDH level ($P = 0.03$, RR 3.3, range 1.1–9.7) and age ≥33 years ($P = 0.02$, RR 3.1, range 1.1–7.5) appeared independent. In both univariate and multivariate analyses of the 50 patients treated in group B, failure to respond to COP was also identified as a poor prognostic factor for overall survival (Fig. 5). Two year overall survival was 48% (95% CI, 23–74%) for the 16 patients who failed to respond to COP compared with 82% (95% CI, 69–95%) for the 34 patients who responded ($P = 0.01$, RR 3.7, range 1.3–10.4).

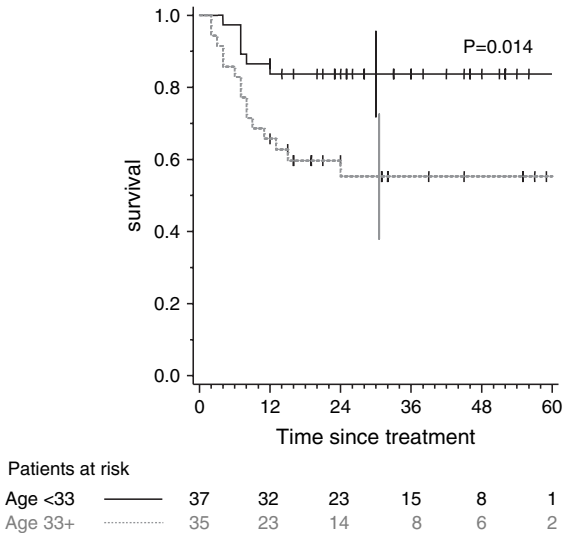

Figure 4. Overall survival curve of the 72 patients according to age.

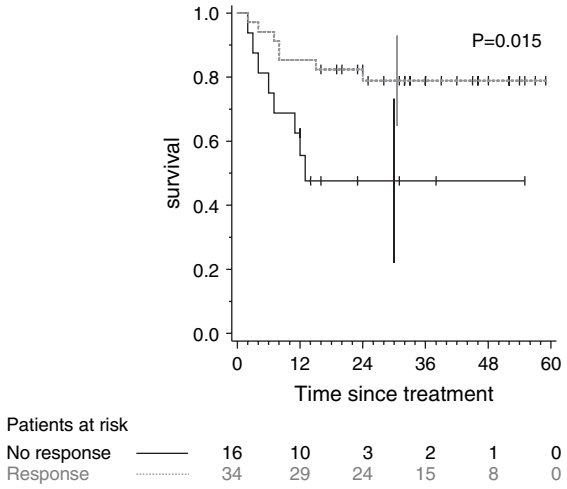

Figure 5. Overall survival curve of the 50 patients treated in group B according to response at day 7 of therapy (COP).

Discussion

We observed a 2 year survival rate of 70% with a median follow-up of 32 months in a large prospective series of 72 adult Burkitt lymphoma patients treated with the French pediatric LMB protocol based on more intensive CNS prophylaxis, including systemic HDMTX, high-dose ara-C with or without VP16 and several IT injections. Our results show that adult patients with advanced-stage Burkitt lymphoma, including those with BM and/or CNS involvement, can indeed be cured with a short-term intensive multi-agent chemotherapy regimen tailored to age, tumor burden, CNS disease and initial response to COP. In patients <33 years, survival can attain 84%, which compares favorably with the pediatric experience [10]. The results of this prospective trial corroborate the retrospective results of Soussain et al. [11]. They reviewed the files of 65 adult patients with Burkitt or L3ALL who were treated with the LMB protocol. With a median follow-up of 57 months, the 3 year survival rate was 74%. Our estimated 2 year survival rate of 70% is also comparable with that obtained by Mead et al. [16] on behalf of the UK Lymphoma Group. They used the alternating non-cross-resistant regimen (NCI 89-C-41), originally developed by Magrath et al. [14] at the National Cancer Institute in the USA. This regimen evolved from a long experience of treating childhood high-grade lymphoma and contained cyclophosphamide, vincristine, doxorubicin, HDMTX (CODOX-M)/ifosfamide, etoposide and high-dose cytarabine (IVAC). In the original series reported by Magrath et al. [14], adults and children with Burkitt lymphoma had a similar prognosis when they were treated with this multi-agent combination, and all the 20 young adults remained event free with a minimum of 1 year of follow-up. Using the same scheme, Mead et al. [16] achieved a 2 year survival rate of 73% in a larger series of 40 patients. These regimens, which were originally designed for the treatment of ALL, seem to yield better results than the standard regimens used for aggressive diffuse large B-cell lymphomas which achieve cure in ~50% of patients [2–4].

In our study, cytogenetic analysis was possible in 25/76 cases (33%) and revealed 8q24 abnormalities reminiscent of a c-*myc* rearrangement in 83% of cases. Genetic abnormalities have been

reported in up to 80% of adult patients with Burkitt lymphoma or L3ALL [12,13,15]. However, only 40% of these cases had cytogenetic findings indicative of a c-*myc* rearrangement, which is lower than we observed and suggests that other lymphoma subtypes were included in those series [12,13,15].

As experienced in children and adolescents, early-stage Burkitt lymphoma (patients with resected stage I and abdominal stage II tumors) does not require as intensive treatment as advanced stages. In the SFOP experience, children with such tumors were found to have a very good prognosis, with a 5 year EFS of 98% after two courses of COPAD without CNS-directed treatment [10]. Our results in adult patients did not seem to be as good as that observed in children. Among the six patients with completely resected Burkitt lymphoma who received three courses of COPAD according to the strategy defined in group A, one relapsed and another had disease progression during therapy. The patient who relapsed developed BM and CNS disease at relapse and was salvaged with HDCT. As the number of patients in group A was small in our series, a comparison with the results published in children would be limited. However, the 2 year EFS of 66% we observed suggests that this small subgroup of adult patients can no longer be singled out as a good-risk group.

We were able to identify the same prognostic factors in adults as those previously reported in children treated with the LMB regimen. As observed in children, a high serum LDH level and an older age were associated with a poor outcome. Response after 1 week of therapy was a strong prognostic factor for overall survival of patients in group B and suggests that rapid identification of patients who are unlikely to achieve a durable response to chemotherapy is possible. In the pediatric experience these poor responders to COP represent <5% of cases, but there were 28% in our series. Despite intensive ara-C and VP16-based consolidation therapy, the prognosis of these patients remained poor. Other early consolidation therapy such as HDCT could be tested in this group of patients. CNS involvement did not appear to be an adverse prognostic factor for group C patients. Furthermore, we did not observe any isolated CNS relapse in any of the 72 patients in this study. These data suggest that CNS-directed therapy in this regimen was effective without excessive neurological toxicity. In our protocol, radiotherapy was performed once chemotherapy was almost completed. We did not observe transverse myelitis or other severe neurologic changes such as those recently reported by the CALGB when cranial irradiation was performed earlier. However, radiotherapy was delivered to only seven of our patients with CNS involvement since the four other patients with CNS involvement failed therapy before the date of radiotherapy [15]. However, as stated in the report on the LMB89 trial [10], the role of cranial irradiation is still unclear since it is deferred until the fourth or fifth month of treatment and all failures occurred earlier.

Toxicity was high in group B where all the toxic deaths occurred. Toxicity-related mortality was 6% for this group and 4% for the entire series. Toxicity-related deaths were due to sepsis during neutropenia. No death was caused by tumor lysis syndrome. The prephase provides an opportunity to solve metabolic problems without having to deal with other toxicities such as aplasia and mucositis that arise in the induction phase. Patients who died from toxicity were aged 43, 50, 55 and 64 years and were among the older patients included in this study. Overall, tolerability of the trial was good, with only four toxic deaths among 76 patients, which was lower than reported in the first prospective multicenter pediatric trial with the same chemotherapies where 11/114 children died of toxicity [7]. For each patient, we calculated a relative dose equal to the dose really received divided by the planned dose. Patients aged <33 years received a mean relative dose of 1.01 and older patients received a relative dose of 0.92, which represents only 9% difference between these two groups. In group B, response rate to COP was the same in patients aged <33 years and ≥33 years, but outcome was poor in the older group (12/24 patients aged ≥33 years died compared with 3/26 aged <33 years; $P = 0.003$). Most of these deaths were due to disease progression. The four patients who died from toxicity were aged 43, 50, 55 and 64 years and are among the older patients included in this study. The difference in patient outcome according to age is explained by a poorer lymphoma control and more toxicity in older patients.

Very few patients could be salvaged after first-line chemotherapy. Only one group A patient could be salvaged with HDCT. All the other patients who progressed while on therapy (six in group B, six in group C and one in group A) or relapsed after therapy (three cases initially treated in group B) died of their disease. This very poor outcome for patients with recurrent or refractory disease treated with these short intensive regimens has also been reported by others, and suggests that few treatment options are available for these patients [13,16,19]. One way of improving therapeutic results could be to use rituximab combined with chemotherapy. This combination has shown its superiority over chemotherapy alone in diffuse large B-cell lymphomas, but few data are available for Burkitt lymphoma [20–23].

In conclusion, a survival rate of 70% was obtained in Burkitt lymphoma with multi-agent chemotherapy tailored to the tumor burden, the presence of CNS or BM involvement, and an early tumor response. Outcome needs to be improved in patients with a high LDH level or who fail to respond after the first week of therapy. New therapies have to be tested in patients with poor prognostic factors. Our current strategy is to stratify patients into two groups, according to the presence or absence of CNS and/or BM involvement, and to assess whether the adjunction of rituximab could improve EFS. We are also testing whether high-dose chemotherapy followed by HSC could improve outcome in patients who did not respond to initial COP chemotherapy.

Appendix

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