

## Cyclophosphamide Monotherapy in Children With Burkitt Lymphoma: A Study From the French–African Pediatric Oncology Group (GFAOP)

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**Background.** The French African Group of Pediatric Oncology was set-up to improve quality of care for children with cancer. Preliminary observations on the efficacy in Burkitt lymphoma (BL) of a cyclophosphamide monotherapy (CPM) have been published. We report the results of a multicentric prospective study combining first-line CPM and a multidrug second-line chemotherapy (SC) for refractory/relapsed patients. **Procedure.** Patients  $\leq 18$  years with Burkitt or Burkitt-like lymphoma, were included in six countries (Burkina-Faso, Cameroon, Ivory Coast, Madagascar, Mali, and Senegal). All patients received three weekly CPM courses (1.2 g/m<sup>2</sup> IV with intrathecal methotrexate and hydrocortisone), stage 3/4 patients received three further courses. SC added methotrexate, vincristine, cytarabine, and prednisone. **Results.** There were 178 patients included (42 stage 1/2, 134 stage 3/4, and 2 unknown). Isolated facial

localization was found in 41 patients, diffuse abdominal involvement in 120 patients including 65 with both. Nine early deaths were reported, toxicity occurred in 136/743 courses (83 patients) and was predominantly hematological. After CPM, complete remission (CR) rate was 47% with a 33% EFS. Because of rapid progression 76/108 eligible patients (85 primary refractory and 23 relapses) received SC resulting in 35.7% CR but a 21% toxic death rate. The OS of the whole strategy was 50.5% and correlated to stage. **Conclusion.** A prospective multicentric study on BL was feasible in very low-income countries. CPM can be recommended in stage 1–2 because of optimal cost/benefit ratio. However, more intensive strategies, still adapted to socio-economic conditions, are required for advanced stages 3 and 4. *Pediatr Blood Cancer* 2011;56:70–76. © 2010 Wiley-Liss, Inc.

**Key words:** Burkitt lymphoma; chemotherapy; children; cyclophosphamide; monotherapy; non-Hodgkin lymphoma; sub-saharan Africa

### INTRODUCTION

Burkitt lymphoma (BL) a mature B-cell neoplasm, initially described in 1957 by Denis Burkitt, is the most common pediatric cancer in Africa [1–3]. The endemic form, classically presents as a jawbone tumor. Its incidence is high, 50–100 cases per million during the first 15 years of life. Environmental factors play a major role in BL: geographical distribution coincides with endemic area of Malaria, moreover, BL is the first human malignant pathology in which the role of Epstein–Bar Virus (EBV) was demonstrated [4]. The sporadic form, characterized by massive abdominal involvement, is mainly described in Europe and America with a low incidence (1.9 per million in Europe and 4.6 per million in France) [5,6]. Finally, BL as well as other lymphoproliferative disorders can also develop as a complication of inherited or acquired severe immune deficiencies; during the last decades, an association with HIV has been largely described [7].

Despite the high prevalence of BL, reports on its optimal management and long-term outcome in Africa are scarce. In this continent, especially in sub-Saharan countries, socio-economic constraints significantly affect access to care causing diagnostic delay, as well as treatment and/or follow-up abandonment. Survival rates above 90% are obtained in industrialized countries with very intensive chemotherapy regimen such as the French LMB or German BFM protocols [8,9]. These regimens are based on intensive short-pulse chemotherapy in order to achieve maximum cell kill and therefore require a very high level of supportive care and trained multidisciplinary team.

In October 2000, doctors from France and French speaking African countries, created an international association named “Groupe Franco-Africain d’Oncologie Pédiatrique” (GFAOP). The main objective of this group is to improve the quality of care of

African children suffering from cancer through the development of adapted clinical research programs [10]. BL has been selected, according to its high incidence and hope for cure. The first GFAOP prospective study on B-cell lymphoma using a modified LMB protocol in North African countries has been recently published with encouraging results [11]. The second GFAOP study on BL was designed for sub-Saharan countries (Burkina-Faso, Cameroon, Ivory Coast, Mali, Madagascar, and Senegal). The primary objective of this study was to reproduce the results reported by Hesselting et al. [12] showing a 50% EFS with cyclophosphamide monotherapy (CPM) associated with intrathecal methotrexate. The secondary objectives were to evaluate the feasibility of the whole strategy in a multicenteric settings both for first-line CPM monotherapy and for relapse/refractory patients requiring chemotherapy with a

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Conflict of interest: Nothing to declare.

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**TABLE I. Reasons for Ineligibility of 79 Patients**

Reasons	Number of patients (%)
Disease extension <sup>a</sup>	28 (35.4)
Very bad clinical condition	17 (21.5)
Socio-economic reasons	13 (16.4)
Other treatment protocol	9 (11.4)
HIV infection	3 (3.8)
Parental refusal	2 (2.5)
No documentation <sup>b</sup>	1 (1.3)
Unknown	6 (7.6)

<sup>a</sup>Patients with massive bone marrow infiltration >70% (5 patients) and/or CNS disease (22 patients) and/or clinical spinal cord compression (1 patient) were ineligible; <sup>b</sup>One patient had no histological or cytological documentation.

more intensive multidrug regimen. We report here the results of this approach on a series of 178 consecutive patients treated during a 3-year period.

## METHODS

### Eligibility

Untreated patients  $\leq 18$  years of age with proven non-Hodgkin lymphoma either Burkitt or Burkitt-like appearance was eligible. Diagnosis relied on cytology and/or histology and immunology if available. All disease sites and stages according to Murphy's classification were eligible except patients with massive bone marrow infiltration >70% and/or CNS disease and/or clinical spinal cord compression [13]. Patients with major pathology, in particular HIV or terminal disease were excluded. Parents had to be informed and to agree with the therapeutic program, according to each country regulations.

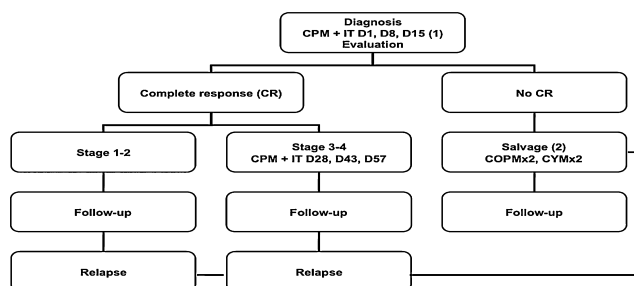
From April 2005 to March 2008, 257 consecutive patients with BL have been registered in the central database by six centers (Antananarive, Abidjan, Bamako, Dakar, Ouagadougou, and Yaoundé). As shown in Table I, 79 patients were excluded because of ineligibility criteria: therefore 178 patients were available for analysis.

### Diagnosis and Staging

Diagnostic procedures consisted in cytology using fine-needle aspiration (FNA) of the tumor or histopathologic confirmation of B-cell lymphoma (Burkitt or Burkitt like lymphoma). All patients underwent clinical examination including nutritional status, imaging investigations, including chest X-ray and abdominal ultrasound, bone marrow aspiration in two sites, blood counts, serum chemistry, cerebrospinal fluid (CSF) analysis, and screening for Hepatitis B, C, and HIV infection.

### Chemotherapy Regimen

The treatment consisted in three weekly CPM courses (1.2 g/m<sup>2</sup> IV bolus) associated with intrathecal methotrexate together with hydrocortisone (15 mg of each). The whole treatment strategy was stratified on initial stage and early response. Tumor evaluation had to be performed on day 21 as illustrated in Figure 1. A more intensive second-line multidrug regimen (Table II) was designed for patients



**Fig. 1.** Protocol strategy. (1) First-line chemotherapy using CPM 1.2 g/m<sup>2</sup> IV bolus (associated with intrathecal methotrexate 15 mg and hydrocortisone 15 mg) was delivered weekly for cycles 1–3 and every 2 weeks for cycles 4–6. (2) Details on second-line chemotherapy for refractory/relapsed patients are shown in Table II.

with insufficient response during or at the end of CPM monotherapy or relapsing during follow-up.

### Supportive Care

Three days before the start of chemotherapy, treatment for intestinal parasites was to be given (mebendazole or other available antiparasitic drugs). Twelve hours before the first dose of chemotherapy, alkaline hydration was started in association with allopurinol to prevent lysis syndrome. Transfusions were recommended when hemoglobin level fell under 70 g/L and platelet counts under  $20 \times 10^9/L$ . In case of febrile neutropenia instructions were to hospitalize the patient and immediately start broad-spectrum IV antibiotics after blood cultures if available (provided antibiotics were cefotaxime and amikacin; vancomycin, or teicoplanin were added if suspected staphylococcal infection). Amphotericin B and fluconazole were the proposed drugs in case of suspected fungal infections. The diagnosis of malaria by small blood smears was systematically done in case of fever whatever the hematological status.

**TABLE II. Second-Line Chemotherapy Regimen**

COPM (course 1 and 2)
Vincristine 2 mg/m <sup>2</sup> IV (max. 2 mg) on day 1
Prednisone 60 mg/m <sup>2</sup> PO or IV, day 1–5 then stop over 3 days
Cyclophosphamide 500 mg/m <sup>2</sup> /day IV divided in two injections, days 2–4, with IV hydration
Methotrexate 3 g/m <sup>2</sup> IV in 2 hr, on day 1 with folic acid rescue and alkalization
Methotrexate + hydrocortisone 15 mg of each given intrathecally on days 2 and 6
CYM (course 3 and 4)
Methotrexate 3 g/m <sup>2</sup> IV in 2 hr, on day 1 with folic acid rescue and alkalization
Cytarabine 100 mg/m <sup>2</sup> /day SC, day 2–6 divided in two injections
Methotrexate + hydrocortisone 15 mg of each given intrathecally on day 2
Cytarabine 30 mg + hydrocortisone 15 mg intrathecally on day 7

Courses were started as soon as possible depending on hematological recovery (neutrophils  $\geq 1 \times 10^9/L$  and platelets  $\geq 100 \times 10^9/L$  usually with an interval of 18 days).

## Response Criteria

Complete remission (CR) was defined as disappearance of all tumor confirmed at clinical examination X-rays and ultrasound examination of abdomen; patients in CR underwent bone marrow smear and CSF analysis to confirm complete remission. Patients with stable small residual mass on imaging at any evaluation were considered in CR.

## Statistical Methods

Overall survival (OS) and event free survival (EFS) were calculated according to Kaplan–Meier [14]. EFS was defined from the onset of treatment until the occurrence of any of the following events: relapse, death from any cause, or disease progression. OS was defined from the first day of chemotherapy to death or loss to follow-up.

## RESULTS

### Characteristics of the Population (178 Patients)

Median age at diagnosis was 7 years (8 months to 15 years 8 months) with a sex ratio of 2:1, registration by each center varied from 7 to 68 patients with a median of 26 patients.

Diagnosis relied on cytology only in 138 patients (75%), biopsy only in four patients, and both in 35 patients (unknown for 1 patient). Burkitt or Burkitt-like lymphoma was diagnosed in 150 patients, for the remaining 28 patients the sub-type of lymphoma was not available.

Median duration of symptoms before diagnosis was 68 days. At initial presentation malnutrition was reported for 63 patients (35.4%), infection for 32 patients, cardiorespiratory complications for 16 patients. HIV testing was performed and negative in 158 patients (91%), viral hepatitis was present in 7 out of 91 tested patients.

Median hemoglobin level was 99 g/L (35–150 g/L). Twenty-eight parasitic infestations were found in 20 out of 79 patients tested (*Ascaris* three patients, *Schistosoma* five patients, *Entamoeba* six patients, *Trichocephales* nine patients, *Ancylostoma* three patients, *Microfilaria Loa Loa* two patients). Twenty out of 171 patients tested at diagnosis showed elevated creatinine dosage  $>1.5\times$  the age-specific reference level.

Main socio-economic characteristics of the patients and their families are described in Table III. Both anticancer drugs and broad-spectrum antibiotics were provided through private funding with an average cost of 685\$ per patient.

The stage was reported in 176 patients: 19 stage 1 (10.8%), 23 stage 2 (13.1%), 128 stage 3 (72.7%), and 6 stage 4 (3.4%). Bone marrow aspiration was performed in 142 patients (79.8%) with 6 being positive; all patients with missing marrow evaluation (29 patients) were treated and analyzed according to reported stage.

An isolated facial tumor was found in 41 patients (23%) accounting for all stage 1 and all but one stage 2. The remaining stage 2 patient presented with testicular localization. Diffuse abdominal involvement (stage 3) was reported in 120 patients, including 65 patients presenting also with facial localization. Palpable abdominal mass was found at clinical examination in 93 patients and initial gastrointestinal complications in 30 patients. Tumor size was  $>15$  cm in 52 patients, ascitis was reported in 36 patients. Other organs involved were liver (34 patients), kidneys (34 patients),

**TABLE III. Patients and Families Socio-Economic Characteristics**

Habitation	
City	36.6%
City suburbs	13.7%
Village or rural area	49.7%
Absence of school education	
Patients	52%
Parents (father/mother)	50%/58%
Parents income/insurance	
Low income	79.5%
Health insurance	0%
Proximity of the unit	
Median distance	156 km (1–1,200 km)
Median time to reach the unit	3 hr (15 min–3 days)
Possibility of housing near hospital	66%

pleura (8 patients), ovary (3 patients), testis (2 patients), and bone (4 patients).

Eight patients had non-abdominal stage 3 (lymph nodes on both sides of diaphragm five patients, thoracic involvement two patients, bone lesions one patient); seven of them had also head and neck localization as well as four out of the six remaining patients with stage 4. Finally 117 patients (65.7%), whatever their stage, had facial localization isolated or associated to other sites of disease.

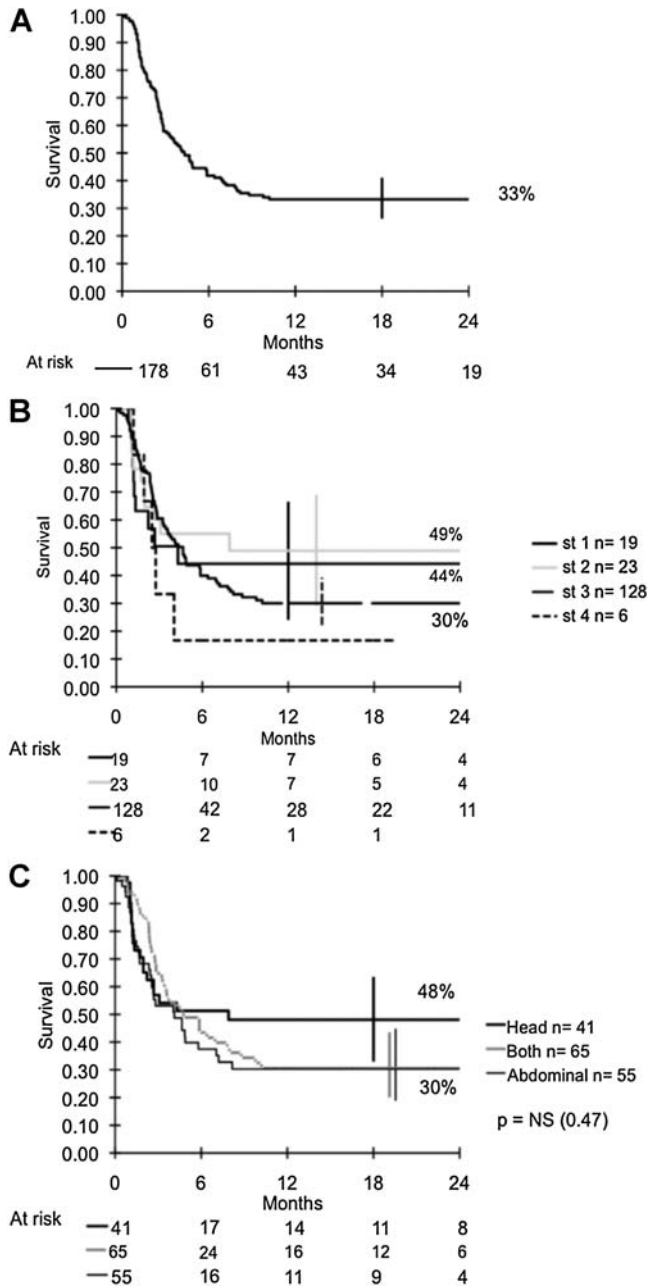
### Toxicity and Response After CPM Monotherapy

One hundred fifty-four patients received three courses and 73 patients six courses, data on 743 CPM courses could be analyzed. Treatment intervals followed protocol recommendations in 85% of courses 1–3 ( $7 \pm 3$  days), and 89.2% of courses 4–6 ( $14 \pm 3$  days).

Early deaths were reported in nine cases during CPM treatment: one patient died during hydration phase before chemotherapy, five additional patients during the first course mainly due to infection and/or hematologic complications (three patients), one patient had fatal lysis syndrome and the last patient asphyxia due to bulky facial extension at day 1; other early toxic deaths were due to infections and occurred during course 2 (two patients) or 4 (one patient). Two additional patients died after course 5 from infection associated with tumor progression.

Toxicity was reported for 136 courses (18%) in 83 patients and was predominantly hematological as expected: hemoglobin level  $<70$  g/L in 35 courses, neutropenia  $<0.5 \times 10^9/L$  in 37, and thrombopenia  $<20 \times 10^9/L$  in 3. Fever of unknown origin was reported in 77 cases and documented infections in 15; broad-spectrum antibiotics were given in 85 courses. Grade 3/4 gastrointestinal toxicity included diarrhea (13 cases), vomiting (14 cases), and mucositis was found in six cases.

Complete remission after CPM monotherapy alone was observed in 83 out of 176 evaluable patients (11 stage 1, 9 stage 2, 61 stage 3, and 2 stage 4). During follow-up 58 patients remained alive in first CR, 1 patient died in CR of malaria, and 1 patient of unknown reason. Outcome of the entire cohort (global EFS: Fig. 2A, EFS according to stage (2B) or tumor localization (2C)) are shown in Figure 2. For this analysis, the need for second-line chemotherapy (SC) being considered as a failure.

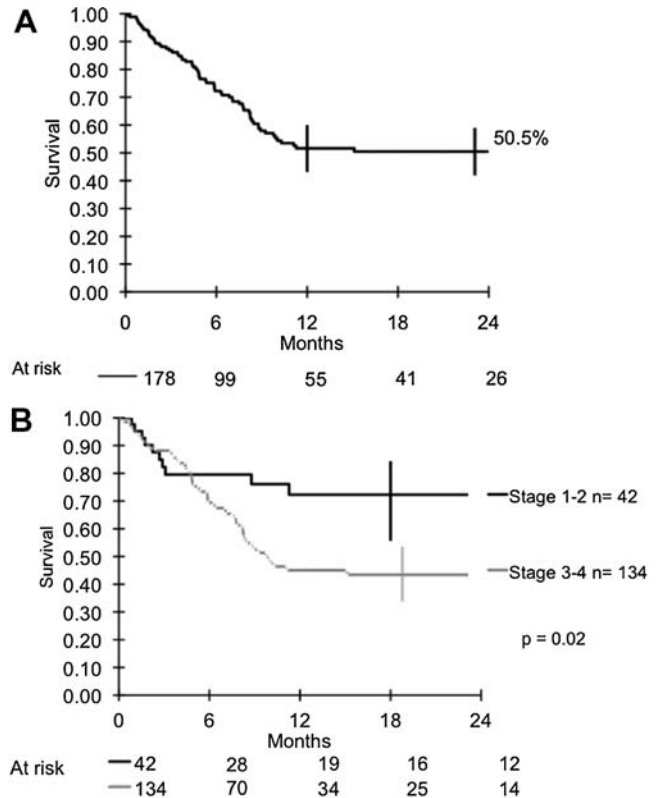


**Fig. 2.** Outcome after cyclophosphamide monotherapy: Global EFS (A) and EFS according to stage (B) or localization (C) (patients requiring second-line chemotherapy were considered as failures).

### Second-Line Chemotherapy and Global Outcome

According to protocol recommendations, 108 patients (primary refractory 85 patients and relapses 23 patients) were eligible. However, 32 patients (29.6%) could not receive the second-line chemotherapy the majority of which because of rapid progression and death.

Therefore, second-line treatment was given to 76 patients for either initial failure (59 patients) or relapse (17 patients). Within refractory patients 14 patients were stage 1/2, 42 stage 3 (27 patients during CPM monotherapy and 15 patients after 6 courses) and 3



**Fig. 3.** Survival of the whole cohort (A) and survival according to stage (B).

stage 4. Relapse was diagnosed after a median duration of CR of 68 days (17–220 days); 15/17 relapsed patients were initially stage 3.

Sixteen toxic deaths occurred during SC (21%): 7 patients at COPM1, 3 at COPM2, 3 at CYM1, and 3 at CYM2. The major cause of death in SC regimen was infection during neutropenia (11 patients). Median interval between all SC courses was 21 days as required by protocol with a minimum of 13 days and a maximum of 74 days.

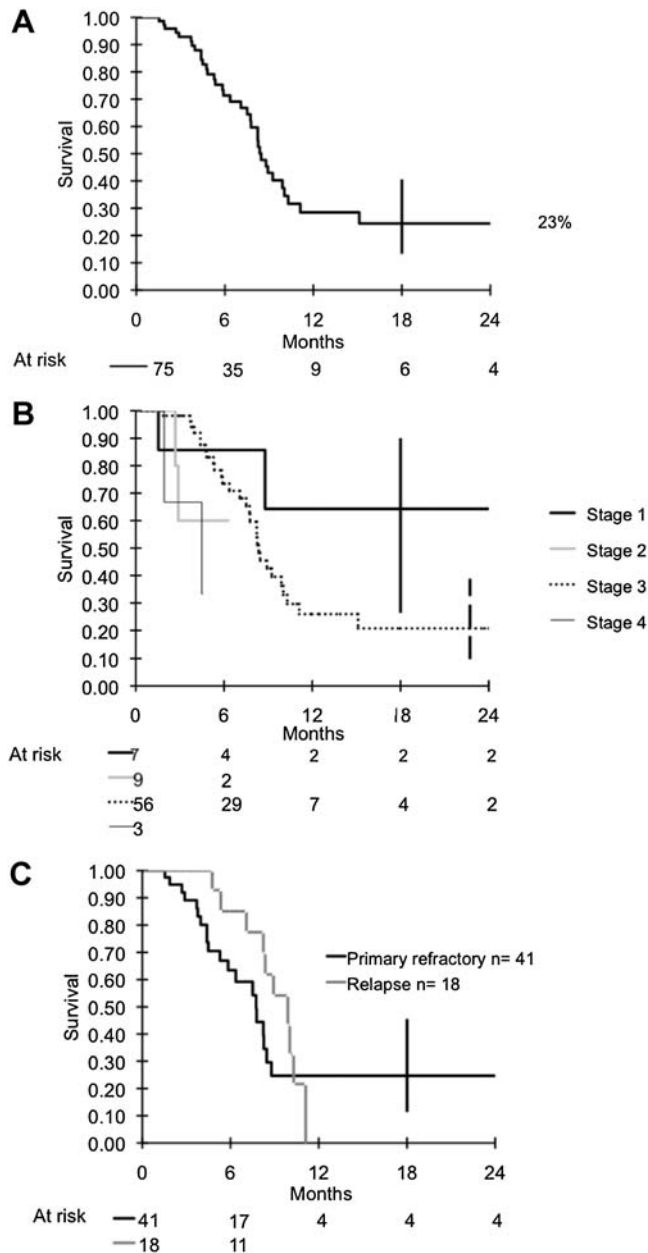
Overall 25 out of 70 evaluable patients (35.7%) achieved CR with second-line treatment: 5/7 stage 1, 3/7 stage 2, 16/53 stage 3, 1/3 stage 4. Three out of 15 patients treated for relapse obtained CR as well as 22 out of 55 primary refractory.

OS for the whole strategy including first- and second-line regimen was 50.5% as shown in Figure 3A and was statistically correlated with stage (Fig. 3B). OS was similar in patients with or without adequate marrow staging (46% vs. 44%, respectively,  $P = 0.79$ ).

Because of the high percentage of patients who did not receive SC, a separate analysis has been performed on patients really treated with second-line chemotherapy. OS, survival according to stage and indication for SC are shown in Figure 4.

### DISCUSSION

Preliminary observations in low-income countries on the efficacy of a monotherapy with an affordable drug such as CPM in endemic BL have been reported years ago [15]. However, the encouraging results of the first large cohort of 92 patients treated in Malawi with CPM alone (one to six courses every 2 weeks without intrathecal



**Fig. 4.** Outcome of patients receiving salvage chemotherapy (SC): overall survival (A) and survival according to stage (B) or reason for SC (C).

therapy) appeared only in 2003 [16]. Prolonged and more intensive weekly, oral or intravenous, CPM schemes together with intrathecal methotrexate have been reported by the same group in Malawi, Ghana, and Cameroon and results have been similar with EFS around 50% [12,17,18]. Based on the same approach, we report here the second-GFAOP study on B-cell lymphoma and the first launched in sub-Saharan countries, the countries with the lowest income in our group.

Median age at diagnosis around 7 years and male predominance were similar to other studies in different countries [17–19]. As expected, a significant proportion of patients with BL registered in the database (30.7%) were not eligible for CPM monotherapy

mainly because advanced disease, very poor general conditions or endemic infections such as HIV. Moreover, even within the cohort of 178 eligible patients the above parameters have probably greatly influenced the overall results. Diagnosis delays, frequency of bulky disease and multiorgan involvement, high rates of severe denutrition and infections (35 and 18% respectively), low socio-economic conditions (Table III), loss for follow-up are the most representative examples of the difficulties encountered. The few other series of children treated for B-cell lymphoma in low-income countries reached similar conclusions. In a recent study including 100 children with all malignancies in Morocco, Tazi et al. [20] reported malnutrition in 37 patients. More specifically, Meremikwu et al. [21] found a 44% malnutrition rate in a series of 41 children treated for BL in Nigeria between 1997 and 2004. In the same study, 57.1% patients of the 22 properly discharged survivors did not keep any follow-up appointments. Similarly, Van Hasselt et al. [22] in a retrospective study of 160 patients treated in Malawi from 1988 to 1992 reported that only 25% of the patients completed the planned treatment. In most cases, the reasons for failing to keep appointments were not determined, but were likely to be related to the heavy costs of treatments and paraclinical exams but also transportation and housing contrasting with poverty of populations and absence of health insurance coverage.

The median duration between the first clinical signs and diagnosis was 68 days in our series. Together with economical reasons, the tendency for parents to consult traditional and other alternative providers of healthcare may have partly contributed to this delay. Insufficient training of physicians and nurses on the diagnosis and management of childhood cancers is also to be considered [10,23]. Community education on curability of childhood cancers, effective integration of alternative health practitioners into more efficient health care systems will require long-term public and private fundings as recently described [24]. In this study, the total per capita health care expenditure (including private and public funds) was evaluated in Tanzania or Senegal, respectively, at 12 and 29 US\$; this amount has to be compared to the average cost of treatment in our study of approximately 685\$ per patient.

Despite all pitfalls, a major objective of this study, the feasibility of a prospective and multicentric protocol in countries displaying the lowest-economic conditions within our group has been reached: unselected registration of patients, respect of shared standards of care for chemotherapy as well as supportive treatments, on time transmission of information to central database have followed protocol requirements.

Bulky abdominal involvement was prevalent in our series (120 patients, 67%), followed by facial localizations (117 patients, 65%), a high proportion of patients suffering from both (65 patients, 36%). This repartition contrasts with the initial report by Kazembe et al. [16] in Malawi showing 69% head localization and only 20% of abdominal forms; however, in this early study only clinical staging was available underestimating infraclinical abdominal disease. In further studies by the same group with a more adequate staging, either localization was found in around 70% of patients similarly to our results; however, the percentage of patients with isolated head localization is not available in these preliminary results [17,18]. Adequate comparison of stage repartition in our series with these reports is difficult because patients with overt marrow disease or CNS involvement were not eligible for our study as very low-survival rates around 10% were reported previously [17]. Therefore, whether or not differences in BL localizations reflect a more advanced disease in our cohort is questionable. The decreased inci-

dence of facial localizations during recent years, as described by other authors may also represent a true evolution of BL clinical presentation linked to environmental factors [25].

Nevertheless, this question remains of major importance as survival was significantly higher in the initial study in children with facial localizations only compared to all other sites (63.5% vs. 33.3%, respectively). Finally, understaging reported in 29 patients in our series was not responsible for poorer outcome of stage III patients as OS was similar in patients with or without adequate marrow staging (46% vs. 44%, respectively).

Toxicity of CPM monotherapy was high and mainly hematological (54.4% of courses) as expected from an intensive schedule of this agent. However, treatments could be delivered according to protocol recommendations in most cases (85% of courses 1–3 and 89.2% courses 4–6). Early deaths (before day 21 of CPM monotherapy) were high: 8 out of 178 patients but compare favorably with 10 out of 129 patients in the Hesseling et al. [17] study. Moreover, six of them occurred within the first week probably reflecting both the high-tumor load and associated conditions as described above.

Complete remission rate after CPM monotherapy is 83/176 (47%) in our series, as imaging was required for response evaluation comparison with the clinical CR rate of 74.4% described in the Hesseling et al. [17] study is not possible. The resulting overall EFS in our series is 33% (considering requirement for SC as a failure) compared to the 50% 1 year EFS in stage 1–3 in the Hesseling et al. [17] study. The difference relies mainly on a lower EFS in stage 3 patients in our study (48% vs. 30%). Duration of follow-up cannot be responsible for this difference as the median time to relapse was 155 days versus 68 days in our study.

Using intensive multidrug chemotherapy as required by protocol for primary refractory (85 patients) or relapsing patients (23 patients) is a real challenge in our countries facing the lack of adequate supportive care. The impossibility to deliver second-line treatment in 29.6% of refractory/relapsed patient constitutes the first major demonstration.

Several studies in the literature have reported multidrug chemotherapy regimen for endemic BL either as first line of for relapsed/refractory patients. In a prospective study, Hesseling et al. [26] used a medium intensity rapid chemotherapy schedule (36 days) including steroids, high-dose methotrexate, vincristin, together with CPM, and intrathecal treatment for 42 consecutive newly diagnosed patients. The morbidity as well as early mortality (14 patients) of this approach were high. The projected EFS at 12 month (50% in stage 1, 50% in stage 2, 24% in stage 3, 25% in stage 4 with an overall EFS of 33%) were disappointing. The authors concluded that the low-dose intensity of CPM in this protocol may have contributed to this failure.

Interestingly in 28 patients with resistant disease (8 patients) or relapse (20 patients) after CPM monotherapy identical to our first-line treatment, a maintained complete remission was obtained in ten patients (36%) by increasing CPM dose intensity (60 mg/kg weekly) together with vincristine [27].

Our rescue protocol combined steroids, vincristine, cytarabine, and high-dose methotrexate together with a sustained-dose intensity of CPM (1.5 g/m<sup>2</sup>, for the first two courses). The resulting COPM and CYM sequences are derived from intermediate-risk group SFOP LMB protocols with anthracyclines removal to limit mucosal and hematologic toxicity [8]. In the first GFAOP study this approach in newly diagnosed patients led to a 55.6% EFS as recently published [11]. Those results are significantly worse compared to the 75.2%

EFS reported in North-African units with a higher intensity protocol very similar to the original LMB background. Similar results were reported by Davidson et al. [28] in two South African studies comparing a medium versus high-intensity schedule [29]. However, the high level of supportive care required for the feasibility of these regimen remains in 2009 out of reach for most units belonging to sub-Saharan countries.

In the present study of second-line chemotherapy, complete remission rate was 35.7% and OS 23% were similar to other studies with medium intensity schedules. As expected toxicity was mainly hematological and high as was the early death rate (21%). No significant prognosis factor could be found as survival was similar for early (three courses) or late (six courses) refractory patients or patients relapsing after CR.

Finally, the OS of the whole strategy, including second-line chemotherapy, was 50.5% in our series with initial stage being the only significant prognostic factor. Therefore, in our multicentric settings including six sub-saharan countries (Burkina-Faso, Cameroon, Ivory Coast, Mali, Madagascar, and Senegal) we could not reproduce Hesseling's et al. [12,17] results in Malawi using CPM monotherapy specially for advanced stage 3 patients. The reasons are probably multifactorial: more advanced disease, differences in tumor localizations, lower level of supportive care.

Because of those disappointing results in advanced stages 3 and 4, our group has decided to introduce more intensive multidrug LMB-derived strategies as first-line treatment. However, for patients with stage 1 or 2, the good results obtained with CPM monotherapy together with the optimal cost/benefit ratio lead us to recommend this strategy.

In conclusion, our data confirm the feasibility of prospective international studies in Sub-Saharan Africa and the possibility to improve childhood cancer cure through adapted therapeutic programs. However, continuous long-term support from both local and international public agencies and charity organizations as well as close collaborations with pediatric oncology societies are essential to maintain these results and bring hope for a better future.

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