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Original Research Article

Treatment of paediatric lymphoblastic lymphoma in sub-Saharan Africa: experience of the pediatric oncology unit of Gabriel Touré Hospital.

Background:

Lymphoblastic lymphomas (LBL) are malignant proliferations of the lymphoid precursors of B or T cells. LBL accounts for approximately 2% of all non-Hodgkin's lymphomas in the developed countries. Until the 1970s, diffuse lymphoblastic lymphoma was considered incurable. With intensive multidrug regimens, the majority of patients can now be cured. Event-free survival (EFS) is 70 to 80% in developed countries.

In Africa, and particularly in Mali, there are few published studies on the management of this type of cancer in children.

Abstract:

The aim of this retrospective study was to evaluate the treatment and outcomes of children with LBL according to the modified EURO-LB 08 protocol at the Pediatric Oncology Unit of the CHU Gabriel Touré of Bamako, Mali. All patients less than 15 years old, with histologic proven LBL treated between October 23, 2009 and April 30, 2016 were included in the study. Ten patients with LBL met the inclusion criteria. LBL accounted for 0.8% of admissions during this period. The age group of 6-11 years represented the majority (n = 7; 70%). The sex ratio was 2.3:1 for girls and boys respectively. Eighty percent of patients had good nutritional status on admission. Polyadenopathy was found in 7 patients (70%). One patient presented with mediastinal mass. Pleural effusion was associated with polyadenopathy in one patient. Stage 3 was predominant (n = 7; 70%). The diagnosis was made by cytology in 80% of patient and histology and immunohistochemistry in 2 patients. Eight patients completed treatment. Grade III neutropenia and anemia was observed in 5 patients. Three patients died from tumor progression during treatment and two patients died from treatment-related toxicity. Three patients were in complete remission at the end of treatment.

Early diagnosis and better availability of anticancer drugs may improve the overall survival rate of patients with LBL in Mali.

Introduction:

Lymphoblastic lymphomas (LBL) are malignant proliferations of the lymphoid precursors of

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B or T cells. For decades, LBL and acute lymphoblastic leukemias were considered to be the same disease. The two diseases are very similar, epidemiologically, clinically and immuno-phenotypically. Hepato-splenomegaly is more common in ALL than LBL. By definition ALL has bone marrow involvement whereas LBL has marrow infiltration in 20-25% [1]. Small molecular profiling and genomic studies have demonstrated differential gene expression profiles and loss of heterozygosity at the 6q locus, suggesting the presence of underlying biologic differences [2]. LBL accounts for approximately 2% of all non-Hodgkin's lymphomas in the developed countries [3]. Event-free survival (EFS) is 70 to 80% in developed countries [4]. In Africa, and particularly in Mali, there are few published studies on the management of this type of cancer in children. The objective of this study was to determine the clinical feature and outcomes of patients with LBL treated according to a modified EURO-LB 08 protocol, in the pediatric oncology unit of CHU Gabriel Touré of Bamako, Mali.

Patients and methods:

In this retrospective study, all children under the age of 15 years with histologic proven LBL treated at the pediatric oncology unit at the CHU Gabriel Touré in Bamako, Mali between October 23, 2009 and April 30, 2016, were included. Exclusion criteria were: age over 15 years, HIV positive patients and severe malnutrition on initial admission. Initial evaluation included routine blood testing, chest x-ray, abdominal ultrasound, bone marrow aspiration and biopsy, diagnostic lumbar puncture, tissue cytology and/or histology. The stage of the disease was determined according to the St. Jude staging system [5]. The chemotherapy regimen is detailed in tables 1, 2, 3. Patients were treated continuously for 6 months. Tumor response was evaluated after each cycle of treatment.

Definition of Response Criteria:

Complete remission is defined as the disappearance of any clinical and biological signs with imaging and evaluation of normal marrow and CSF.

Early response to treatment is defined for patients who are in CR at the end of the induction treatment.

Partial remission is defined as a 30% or more decrease in size of the primary lesions.

Relapse is defined as the reappearance of the tumor in any site.

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Progressive disease:

A >25% increase in tumor volume in any site of residual disease compared to immediate pre-study volume or compared to volume of best prior response at that site, or

The reappearance of tumor site of involvement (including marrow and CNS) which had responded completely to therapy (including surgery), or

The appearance of tumor in previously uninvolved sites.

Statistical analysis:

The follow-up time for each patient was counted from inclusion in the study to the latest information. For overall survival (OS), all deaths were included regardless of cause and survival times of living patients were censored at the closing date. For EFS, the first progression on any site or death without progression was noted as an event, and the times were censored to date for the patient, who was living on the date without progression of the disease. The data obtained from the medical records of patients were analyzed on IBM SPSS version 20 (SPSS Inc., Chicago, IT).

Results:

Ten patients with LBL were included in the study. LBL accounted for 2.15% of the non-Hodgkin lymphomas (n = 463) during this period. The age group of 6-11 years represented 70% (n = 7); The median age was 8 years. The sex ratio was 2.3:1 in favor of girls. Eighty per cent of patients had good nutritional status at admission. Polyadenopathy was found in 7 patients (70%). Two patients had mediastinal mass.

The pleural involvement associated with polyadenopathy was found in one patient. Stage 3 was predominant (n = 7; 70%). Bone marrow infiltration was found in two patients (20%). The diagnosis was made by cytology in 80% of the patients; Histology plus immunohistochemistry was performed in 2 patients. Cellular phenotype was unknown in 80% of cases. Stage III was predominant (70%, n = 7). Eight patients received full treatment. Grade III anemia and neutropenia was observed in 5 patients. Three patients died from tumor progression during treatment. Two patients died from treatment related toxicity. Two patients discontinued treatment. Three patients were in complete remission at the end of treatment (30%). The characteristics of the patients included are detailed in Table 4.

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Discussion:

This work presents a retrospective study of the management of LBL in the pediatric oncology unit of CHU Gabriel Touré from 23 October 2009 to 30 April 2016. Patients were treated according to the modified protocol EURO-LB 08. Modification of this protocol was driven by the relative unavailability of chemotherapy medications and supportive care. The prevalence of LBL at our center was 2.15% of non-Hodgkin lymphomas. This distribution is consistent with other reports [6]. However in Brazil, the prevalence is 25-36% [7, 8]. The median age at diagnosis was 8 years in our series, similar to those in other series [9]. Male predominance is also documented in similar publications [9, 10]. In our study, polyadenopathy was the most frequent mode of presentation. Compared to other studies, mediastinal mass was rare [10,11,12]. Murphy stage III disease was predominant in our study; this predominance was also found in the series published in Shanghai [12]. The diagnosis was made by cytology alone in 70% of cases in our series, which exemplifies difficulties in the practice of pediatric oncology in developing countries [13,14]. Immunohistochemistry remains the best tool for the diagnosis and characterization of LBL [15,16]. Bone marrow involvement is lower in our study compared to other similar studies [17]. Bone marrow or central nervous system involvement is not recognized as an independent prognostic factor for overall survival [18,19]. Eight patients received full treatment. Four patients (40%) were in complete remission at the end of the induction. Sandlung et al. reported end of induction complete remissions rate of 95% [20]. The modification of the EURO-LB 08 protocol and the low patient cohort would explain in part this low end-induction complete remission rate [20]. The duration of follow-up of our patients was 72 months. Three patients were in complete remission at the end of treatment (30%). This result is much lower than those reported by Sandlung et al. (90.2%) and Reiter et al (90%) [20]. The two toxic deaths are largely attributable to a lack of state of the art supportive care in our pediatric oncology center.

Treatment abandonment is common in pediatric oncology centers in developing countries, mainly due to unaffordability of healthcare.

Conclusion:

LBL remains unrepresentative of non-Hodgkin's malignant lymphomas in children and is a relatively rare cancer in sub-Saharan Africa. A large multicenter study will allow us to broadly evaluate the epidemiological and therapeutic aspects of this pathology in Africa.

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What is already known on this topic:

Lymphoblastic lymphomas (LBL) are malignant proliferations of the lymphoid precursors of B or T cells. LBL accounts for approximately 2% of all non-Hodgkin's lymphomas in the developed countries. With intensive multidrug regimens, the majority of patients can now be cured. Event-free survival (EFS) is 70 to 80% in developed countries.

What this study adds:

This study has shown that therapeutic de-escalation is an option to cure these children in developing countries, particularly in Mali, where we observe a problem of availability of anticancer drugs.

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Tab.1: Induction Protocol I (9 weeks)

- Prednisone : 60 mg/m²/day by mouth days 1 to day 38
- Vincristine: 1.5mg/m² /day iv, on d8, d15, d22 and d29.
- Doxorubicin: 30 mg/m² /day iv on d8; d15; d22; d29.
- L-Asparaginase: 10,000mg/m^2/day iv on d12; d18; d24; d30.
- Cyclophosphamide: 1000 mg/m²/day iv over 2h on days 36 and 64.
- Cytarabine: 75mg/m^2/day infuse over 1hr on days 38, 39, 40, 41, 45, 46, 47, 52, 53, 54, 55, 59, 60, 61, 62, 63 and 64.
- 6-Mercaptopurine: 60 mg/m2/d by mouth on days 36 and 64.

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Tab.2: Protocol M (8 weeks)

- 6-Mercantopurine (25mg/m^2/J) by mouth on days 1-56.
- Methotrexate (3g/m^2/day infusion over 10hrs on days 8, 22, 36 and 50.
- Folinic acid (15mg/m^2/d iv at hrs 42, 48 and 54 after infusion of MTX HD.
- Methotrexate 15mg +hydrocortisone 15mg IT on days 8, 22 and 36.

Tab.3: Re-induction: Protocol II (7 weeks)

- Dexamethasone: (10mg/m^2/d) by mouth from days 1-30.
- Vincristine (1.5mg/m^2/d) iv on day 8, 15, 22 and 29.
- Adriamycin: (30 mg/m^2/d) infused on days 8, 22 and 29.
- Asparaginase (10000 U/m^2/d) iv infusion over 1 hour on day 8 and 15.
- Cyclophosphamide (1000 mg/m^2/d) iv infusion over 2hrs on day 36
- Cytarabine (75mg/m^2/d) iv infusion over 1 hour on days 38-40, 45-49
- Methotrexate 15mg +hydrocortisone 15mg IT on days 38 and 45.

Tab.4: Patient characteristics

Characteristics	Number	Percentage (%)
sex		
Male	3	30
Female	7	70
Age (yrs)		
Range	3-11	100
Median	8	70
Clinical Presentation		
Mediastinal Mass	2	20
polyadenopathy	7	70
Pleural effusion	1	10
Diagnoses and Diagnostic Method		
Cytology	8	80
histology	2	20
Immunohistochemistry	2	20
T-cell LBL	1	10
Bcell -LBL	1	10

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Unknown	8	80
Stages		
I	1	10
III	7	70
IV	2	20
Bone marrow infiltration	2	20
Infiltration of spinal fluid	0	0
Treatment-related toxicity		
Toxic Death	2	20
Grade III Anemia	3	30
Grade III Neutropenia	4	40
Patient Outcome		
Complete Remission and completed treatment	3	30
Treatment Abandonment	2	20
Deaths	5	50

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