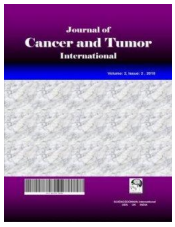

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Treatment of Paediatric Lymphoblastic Lymphoma in Sub-Saharan Africa: Experience of the Pediatric Oncology Unit of Gabriel Touré Hospital

Traoré Fousseyni[1*], Togo Boubacar[1], Diakité Abdoul Aziz[1], Issa Amadou[2], Diabaté Konimba[3] and Francis Eshun[4]

[1]Department of Paediatric Oncology, Gabriel-Toure Hospital, Bamako, Mali.
[2]Pediatric Surgery Service, Gabriel-Touré, Bamako, Mali.
[3]Radiation Therapy Service, Hospital of Mali, Bamako, Mali.
[4]Phoenix Children's Hospital, Phoenix, AZ, USA.

Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Lymphoblastic lymphomas (LBL) are malignant proliferations of the lymphoid precursors of T cells mainly. 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.

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

**Corresponding author: Email: drfousseynitraore@gmail.com;*

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 were 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.

Keywords: Lymphoblastic lymphomas; children; Mali.

1. INTRODUCTION

Lymphoblastic lymphomas (LBL) are malignant proliferations of the lymphoid precursors of T cells mainly. 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 primary 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]. The cure rate 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.

2. 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

Table 1. Induction Protocol I (9 weeks)

- Prednisone: 60 mg/m²/day orally days 1 to day 38
- Vincristine: 1.5 mg/m² /day iv, on d8, d15, d22 and d29.
- Doxorubicin: 30 mg/m² /day iv on days 8, 15, 22 and 29.
- L-Asparaginase: 10,000 mg/m^2/day iv on d12; d18; d24; d30.
- Cyclophosphamide: 1000 mg/m²/day iv over 2h on days 36 and 64.
- Cytarabine: 75 mg/m^2/day infuse over 1 hr 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 orally on days 36 and 64.

Table 2. Protocol M (8 weeks)

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

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

- Dexamethasone: (10 mg/m^2/d) orally from days 1 to 30.
- Vincristine (1.5 mg/m²/d) iv on day 8, 15, 22 and 29.
- Adriamycin: (30 mg/m²/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/m²/d) iv infusion over 2hrs on day 36
- Cytarabine (75 mg/m^2/d) iv infusion over 1 hour on days 38 to 40 and 45 to 49
- Methotrexate 15 mg +hydrocortisone 15mg IT on days 38 and 45.

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.

2.1 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.

2.2 Progressive Disease

A 25% increase in the size of one or more measurable lesions, compared to pre-study volume or compared to volume of best prior response.

2.3 Statistical Analysis

The follow-up time for each patient was counted from inclusion in the study to the latest information. To estimate overall survival (OS), all deaths were considered regardless of causes and survival times of alive patients were censored at the date of last contact with the patient up to the date of study closure. To estimate event-free survival, first tumour recurrence at any site or death without recurrence were considered as events (times were censored at the date the patient was alive without tumour recurrence). The data obtained from the medical records of patients were analyzed on IBM SPSS version 20 (SPSS Inc., Chicago, IT).

3. RESULTS

From 01/10/2009 to 30/04/2016 ten patients with LBL were diagnosed. 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 percent 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 (the disease had a T-cell phenotype in these two patients). The 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 were 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. The overall survival rate was 30%. The duration of follow-up was 72 months. The characteristics of the patients included are detailed in Table 4.

4. 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

Table 4. Patient characteristics

Characteristics	Number	Percentage (%)
Sex		
Male	3	30
Female	7	70
Age (year)		
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
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 discontinuation	2	20
Overall Survival	10	30
Deaths	5	50

diagnosis was eight 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 was low 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 OS [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 small 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.

5. CONCLUSION

LBL remains unrepresentative of non-Hodgkin's malignant lymphomas in children and is a relatively rare cancer in sub-Saharan Africa. Treatment discontinuation, unavailability of chemotherapy medications and supportive care are limited factors for survival of lymphoma patients in sub-Saharan Africa A large multicenter study will allow us to broadly evaluate the epidemiological and therapeutic aspects of this pathology in Africa.

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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sandlund JT, Downing JR, Crist WM. Non-Hodgkin's lymphoma in childhood. N Engl J Med. 1996;334(19):1238-48.
2. Hoelzer D, Gokbuget N. T-cell lymphoblastic lymphoma and T-cell acute lymphoblastic leukemia: A separate entity? Clin Lymphoma Myeloma. 2009;9(3):214-21.
3. Schmidt E, Burkhardt B. Lymphoblastic lymphoma in childhood and adolescence. Pediatr Hematol Oncol. 2013;30(6):484-508.
4. Oschlies I, Burkhardt B, Chassagne-Clement C, d'Amore ES, Hansson U, Hebeda K, et al. Diagnosis and immunophenotype of 188 pediatric lymphoblastic lymphomas treated within a randomized prospective trial: Experiences and preliminary recommendations from the European childhood lymphoma pathology panel. Am J Surg Pathol. 2011;35(6):836-44.
5. Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: Dissimilarities from lymphomas in adults. Semin Oncol. 1980;7(3):332-9.
6. Georgakis MK, Karalexi MA, Agius D, Antunes L, Bastos J, Coza D, et al. Incidence and time trends of childhood lymphomas: Findings from 14 Southern and Eastern European cancer registries and the surveillance, epidemiology and end results, USA. Cancer Causes Control. 2016;27(11):1381-1394.
7. Oliveira MC, Sampaio KC, Oliveira AC, Santos AD, Castro LP, Viana MB. Outcome of children and adolescents with lymphoblastic lymphoma. Rev Assoc Med Bras. 2016;62(1):59-64.
8. Gualco G, Klumb CE, Barber GN, Weiss LM, Bacchi CE. Pediatric lymphomas in Brazil. Clinics. 2010;65(12):1267-77.
9. Katz OB, Ben Barak A, Abrahami G, Arad N, Burstein Y, Dvir R, et al. Treatment of T cell lymphoblastic lymphoma in children and adolescents: Israel Society of Pediatric Hematology Oncology retrospective study. Isr Med Assoc J. 2011;13(3):161-5.
10. Pillon M, Arico` M, Mussolin L, Carraro E, Conter V, Sala A, et al. Long-term results of the AIEOP LNH-97 protocol for childhood lymphoblastic lymphoma. Pediatr Blood Cancer. 2015;62(8):1388-9.
11. Reiter A, Schrappe M, Ludwig WD, Tiemann M, Parwaresch R, Zimmermann M, et al. Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell

lymphoblastic lymphoma: A BFM group report. Blood. 2000;95(2):416-21.
12. Gao Y, Pan C, Tang JY, Lu FJ, Chen J, Xue HL, et al. Clinical outcome of childhood lymphoblastic lymphoma in Shanghai China 2001–2010. Pediatr Blood Cancer. 2014;61(4):659-63.
13. Harif M, Traore F, Hessissen L, Moreira C, Atteby JJ. Challenges for paediatric oncology in Africa. The Lancet Oncology. 2013;14(4):279-81.
14. Ribeiro RC, Steliarova-Foucher E, Magrath I, et al. Baseline status of paediatric oncology care in ten low-income or mid-income countries receiving My Child Matters support: A descriptive study. Lancet Oncol. 2008;9(8):721-29.
15. Pilozzi E, Pulford K, Jones M, et al. Co-expression of CD79a (JCB117) and CD3 by lymphoblastic lymphoma. J Pathol. 1998;186(2):140-3.
16. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: Evolving concepts and practical applications. Blood. 2011;117(19):5019–5032.
17. Copelan EA, McGuire EA. The biology and treatment of acute lymphoblastic leukemia in adults. Blood. 1995;85(5):1151-68.
18. Colgan JP, Andersen J, Habermann TM, Earle JD, O'Connell MJ, Neiman RS, et al. Long-term follow-up of a CHOP-based regimen with maintenance therapy and central nervous system prophylaxis in lymphoblastic non-Hodgkin's lymphoma. Leuk Lymphoma. 1994;15(3-4):291-6.
19. Hoelzer D, Gokbuget N, Digel W, Faak T, Kneba T, Reutzel R, et al. Leukemia GMAIL: Outcome of adult patients with T lymphoblastic lymphoma treated according to protocols for acute lymphoblastic leukemia. Blood. 2002;99(12):4379-85.
20. Sandlund JT, Pui CH, Zhou Y, Behm FG, Onciu M, Razzouk BI, et al. Effective treatment of advanced-stage childhood lymphoblastic lymphoma without prophylactic cranial irradiation: Results of St Jude NHL13 study. Leukemia. 2009;23(6):1127-30.

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