Original Article

Childhood Lymphoblastic Lymphoma: Hospital Based Study.

Samaher A. Fadhil* **FIBMS**
Amir F. Al-Darraji* **FIBMS**
Raghad M. Al-saeed* **FICMS**
Salma Al-Hadad** **CABP, MRCPCH**

Summary:

Background: Lymphoblastic lymphomas (LBL) are neoplasms of precursor T cells and B cells, or lymphoblasts. The term lymphoblastic lymphoma has been used to describe predominantly lymph node–based disease; however, clinical distinction between LBL and acute lymphoblastic leukemia (ALL) has been arbitrary and has varied among different studies and institutions

Objectives: To determine the frequency of LBL among all Non-Hodgkin's lymphoma (NHL) patients in children and to study the clinical and pathological features of LBL and assess the treatment outcome.

Methods: A retrospective study included 28 children with newly diagnosed LBL (based on morphology) below the age of 14 years over 8 years period from January 1st, 2000 to December 31st, 2007 All the patients except one were treated by modified Medical Research Council UK National Randomized Trial For Children and young Adult with Acute Lymphoblastic Leukemia (MRC UKALL) regimen, one patient was misdiagnosed as B-cell NHL and treated with United Kingdom Children's Cancer Study Group (UKCCSG) Non-Hodgkin's Lymphoma protocol.

Results: LBL forms 28/376 (7.1%) among NHL diagnosed in Children Welfare Teaching Hospital (CWTH) in the same period. The median age was 8.95 years (range 2 to 13.25 years) with male to female ratio of 3.7:1. Lymphadenopathy was present in 22 (78 .6%) of patients. The median duration of onset of symptoms was 7.25 months (range 1 week to 18 months). In response to treatment, 20 (71.4%) patients achieved complete remission (CR), 1 (3.6%) died during induction and 7 (25%) patients were non-responder (4 died and 3 abandoned). Of the 20 patients who achieved complete remission (CR); thirteen (46.4%) remained in continuous complete remission with a median follow up of 32.3 months, 3 (10.7%) patients died while in CR in an average of 16.6 weeks, 2 (7.1%) patients abandoned treatment and 2 (7.1%) patients relapsed.

Conclusion: The study showed a low frequency of LBL in comparison with other studies which might be due to inadequate diagnostic facilities which differentiate LBL from other types of NHL, low survival rate might be due to advanced stages at presentation in addition to abandonment of treatment in some patients.

Key words: Lymphoblastic lymphoma, children, outcome.

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Introduction:

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of lymphoid neoplasms. The distribution of subtypes according to the (World Health Organization Classification) (1) is significantly different in childhood and adulthood. In children, lymphoblastic lymphoma (LBL) of the precursor B- or T-cell type, Burkitt lymphoma (BL), leukemia (B-ALL), and anaplastic large-cell lymphoma (ALCL) predominate, while the proportion of diffuse large B-cell lymphoma (DLBCL) increases with increasing age (2). Lymphoblastic lymphomas are neoplasms of precursor T cells and B cells, or lymphoblasts. The term LBL has been used to describe predominantly lymph node–based disease; however, clinical distinction between lymphoblastic lymphoma and acute lymphoblastic leukemia (ALL) has been arbitrary and has varied among different studies and institutions (3). LBL is classified as a high grade tumor according to the National Cancer Institute (NCI) Working Formulation, and accounts for approximately 30% of the NHL occurring in children. The vast majority are of T-cell immunophenotype and typically present with an anterior mediastinal mass (stage III). The bone marrow may also be involved when there is greater than 25% marrow replacement by Lymphoblast (4).

The cells are morphologically indistinguishable from the blast cells of acute lymphocytic leukemia (ALL) (5).

No virus association has been observed with LBL, nor is there a single specific chromosomal abnormality associated with LBL, which appears to be similar to T-cell ALL with respect to its genetic lesions. Even though LBLs are predominantly of T-cell origin, a small fraction have pre–B-cell characteristics. It seems likely that LBL encompasses several etiologically distinct diseases. In Southeast Asia, virus-associated hemophagocytic syndrome (usually EBV) is associated with an increased risk of T-cell lymphoma development, and peripheral T-cell lymphomas represent a higher fraction of

** Corresponding author:Dr. Amir Fadhil Mohammed Ridha Al-Darraji,Children Welfare Teaching Hospital.*
*** Dept. of pediatric, Baghdad College of medicine, Ministry of higher education.*

NHL in this world region (6).

Patients and Methods

From January 1st 2000 to December 31st 2007; 376 patients with NHL were newly diagnosed and admitted to the pediatric oncology unit in CWTH and considered eligible for the study. The diagnosis was based on morphology only.

Twenty eight patients with LBL were included in this study from the total number of NHL cases.

The information regarding (age, sex, clinical presentation, residence, diagnostic procedure, staging, treatment modality with its complications and outcome) was taken from the inpatient files and from the records of the oncology consultation clinic.

Clinical staging was based on St. Jude staging system (7). Histopathological classification was done according to International Working Formulation (IWF) as defined by National Cancer Institution (NCI), 1982 (8).

Immunophenotyping or karyotyping studies, histochemical stains, gallium scan, bone scan were not done because of lack of facilities.

Before starting chemotherapy all patients received supportive care in form of hydration and allopurinol 300 mg/m^2/day for at least 24-48 hours before starting chemotherapy and continue for 7 days thereafter as preventive and therapeutic measures for acute tumor lysis syndrome.

The patients were classified and treated with protocols modified from Medical Research Council MRC 97 modified 1999 (9) & MRC 2003 (10) for 27 cases, one patient who was presented with jaw mass for which incisional biopsy suggested diagnosis of B-cell NHL and he was treated with UKCCSG 96 protocol for B NHL (11).

Statistical analysis: The data were presented as number and percentage as it is descriptive study.

Result:

This retrospective analysis identified 28 (7.1%) patients who met the diagnosis of LBL out of 376 patients below the age of 14 years diagnosed as having NHL in the same period.

The detailed characteristics of the 28 patients are presented in Table 1. The median age was 8.95 years (range 2 years to 13.25 years), 22 (78.6%) were Males and 6 (21.4%) were females. Male: female ratio was 3.7:1; the median duration of onset of symptoms was 7.25 months (range 1 week to 18 months).

Fever was reported in 16 (57.1%), pallor in 14 (50%) and lymphadenopathy in 22 (78 .6%) patients.

Hepatomegaly and splenomegaly (≥5 cm below costal margin) were recorded in 8 (28.6%) and 2 (7.1%) patients respectively. Testicular swelling and palpable kidney were recorded in 2 (7.1%) patients. There were 16 (57.1%) patients with respiratory distress.

Table 3 shows the profile of laboratory and radiological findings: The hemoglobin level range between 5.5-14.6 g/dl with a mean ± SD of 10.8 g/dl. Leukocyte count ranged from 0.4 to 24 ×10^9/L with a median of 7×10^9/L. The median Platelets count was 175× 10^9/L (range 20 to 609 ×10^9/L). Thrombocytopenia was observed in 3 patients. Initial bone marrow involvement was present in 9/28 (32.1%) patients. Initial CNS involvement was present in 1/20 (5%) patient as the other eight patients were not analysed with CSF cytospin because of lack of facilities. Mediastinal mass was detected by chest X-ray in 23/28 (82.1%) patients, pleural effusion was present in 4/28 (14.3%) patients and pericardial effusion in 4/28 (14.3%) patients. One patient (3.6%) stage I, 17 (60.7%) patients stage III and 10 (35.7%) patients IV as shown in table 3.

Treatment outcome: All the patients were treated by MRC UKALL regimen for treatment of ALL except one patient who was treated with UKCCSG B-cell Non-Hodgkin's Lymphoma protocol. After receiving induction chemotherapy; 20 (71.4%) patients achieved complete remission (CR), 1 (3.6%) patient died during induction and 7 (25%) patients were non-responder (4 died and 3 abandoned thereafter). (Table 4) Of the 20 patients who achieved CR following induction; thirteen (46.4%) patients remained in continuous complete remission with a median follow up of 32.3 months (range; 5 to 51.3 months), 3 (10.7%) died while in remission in an average of 16.6 weeks (one due to diabetic ketoacidosis as complication of chemotherapy, 2 due to febrile neutropenia), 2 (7.1%) patients abandoned treatment and 2 (7.1%) patients relapsed (one died after prolonged neutropenia with presumptive fungal infection at 163rd week chemotherapy, second one was diagnosed initially as B cell NHL and treated with UKCCSG 96 protocol then he got testicular relapse 6 months off treatment, the diagnosis was changed to LBL after doing testicular biopsy, he died during re-induction with MRC UKALL protocol.

Table1: Clinical Data of 28 patients treated at the CWTH in the years 2000-2007

		No. of patients	%
Overall		28	100
Age (years)	<5	8	28.6
5-10		11	39.3
≥10-<14		9	32.1
Sex	Males	22	78.6
Females		6	21.4
Duration of onset	<6 weeks	12	42.9
6 weeks-6 months		13	46.4
>6 months		3	10.7
Signs	Lymphadenopathy	22	78.6
Fever		16	57.1
Respiratory distress		16	57.1
Pallor		14	50
Hepatomegaly ≥ 5 cm BCM		8	28.6
Splenomegaly ≥ 5 cm BCM		2	7.1
Palpable kidney		2	7.1
Testicular swelling		2	7.1

Table2: Initial Laboratory & Radiological results of 28 Patients with lymphoblastic lymphoma

	No. of patients	%
Overall	28	100
HB(g/dl) <6	1	3.6
6-10	7	25
>10	20	71.4
WBC($\times 10^9$/L) < 5	8	28.6
5-10	12	42.8
> 10	8	28.6
Platelets($\times 10^9$/L) <20	1	3.6
20-<100	2	7.1
≥100	25	89.3
Bone marrow involvement yes	9	32.1
No	19	67.9
Mediastinal mass Present	23	82.1
Absent	5	17.9
Pleural effusion Present	4	14.3
Absent	24	85.7
Pericardial effusion Present	4	14.3
Absent	24	85.7

Table 3. Staging system in patients with lymphoblastic lymphoma

Stage	No. of patients	%
I	1	3.6
II	0	0
III	17	60.7
IV	10	35.7

Table 4. Response to Treatment of 28 patients with lymphoblastic lymphoma in CWTH:

Treatment phase	No. of patients	%
Total	28	100
Induction Phase Remission	20	71.4
Failures	7	25
Deaths	1	3.6
Post Induction Phases Total	20	71.4
Continuous Complete Remission (CCR)	13	46.4
Deaths in remission	3	10.7
Relapse	2	7.1
Abandonment	2	7.1

Discussion:

In pediatric NHL, the intensive regimens used by several cooperative groups have resulted in event free survival rates ranging between 80 and 90% in B-cell lymphomas (12), and only slightly lower in LBL and anaplastic large cell lymphomas (13). In countries with limited resources, however, unavailability of some active drugs, inadequate supportive care to face life-threatening toxicities of modern chemotherapy and low protocol compliance by patients or physicians may significantly reduce patient outcome. LBL in this study forms 28/376 (7.1%) among NHL diagnosed in CWTH in the same period. This figure is lower than other studies; a study done by Magrath IT in the pediatric branch of the NCI in United States on 65 patients below age of 35 years, showed 14/65 (21.5%) of patients had LBL (14). In Hemato-Oncology department of La Mascota children's hospital of Managua in Nicaragua, Baez F, et al. found LBL to be 16/53 (30.2%) among NHL cases from the period of 1996 to 2003 (15). This low incidence in this study might be attributed to underestimation due to misdiagnosis of LBL with other types of NHL due to limitation in the diagnostic tools in our settings. On the other hand, there might be some cases diagnosed as having ALL because of bone marrow involvement more than 25% of blast cells. The median age was 8.9 years (range 2-13.25) which is slightly lower than Baez F, et al. (15) study of 9.7 (range 4.7-16.7), this might be due to the higher age group of patients taken in Baez F, et al.(15) study which was below 18 years compared to 14 years in this study. In the leukemia-lymphoma division, St Jude Children's Research hospital, a study done by Dahl GV et al (16) which included 24 children with stage III & IV lymphoblastic NHL only, the median age was 11.5 years (range, 21 months to 18 years) which is higher than our results. Male to female ratio was 3.7:1 in our study slightly higher than 3:1 in Baez F, et al. (15) study, while it was only 1.4:1 in Dahl GV (16) study. Duration of symptoms before diagnosis was less than 6 weeks in 12 (42.9%) patients with a median duration of 7.25 months, this was higher than Mora et al. (17) study which showed duration of less than 35 days in 56/81 (69.1%) while 25/81 (30.9%) presented with symptoms of >60 days (range, 60-300 days). This might explain the advanced stage of disease in our patients due to delay in diagnosis and /or referral, which is the usual setting in the developing countries. Mediastinal mass was present in 24 (85.7%) cases while lymphadenopathy was the presenting sign in 22 (78.6%) cases. Dahl GV (16) studied 24 cases with stage III and IV LBL; 21/24 (87.5%) presented with mediastinal mass and 14/24 (58.3%) had lymph node enlargement which is similar to our results. In Baez F, et al. (15) study; the mediastinal mass was the presenting sign of 11/16 (68.8%) cases and lymph nodes in only 4/16 (25%). Wright D (18) studied 84 cases of LBL; Twenty seven (32.1%) presented with mediastinal mass while 32 (38.1%) cases presented with peripheral lymph node enlargement, this lower figures might be due to inclusion of early stages of LBL in the study. This study showed 17/28 (60.7%) stage III &10/28 stage (35.7%) IV, Dahl GV (16) study who studied advanced cases, showed stage III in 17/24 (70.8%) and stage IV in 7/24 (29.2%), the current study showed more stage IV than Dahl GV

(16) study which might be due to late diagnosis and referral. Another explanation is that we might have a high incidence of aggressive type of disease. The complete remission after induction was seen in 20/28 (71.4%) which is slightly lower than 75% which is the induction rate in the treatment of ALL in the same unit with the same protocol in a study done by Aljadiry MF (19) and also less than other studies, in Baez F, et al.(15) Nicaraguan's study 13/16 (81.25%), Dahl's study (16) in 1984 22/23 (95.7%), Magrath's study (14) of 89%. In developing countries, there are many obstacles for treatment of childhood lymphomas. The most important are late diagnosis, low socioeconomic status and under-nourishment. In developing countries patients with these conditions may be at increased risk for therapy-related toxicity, including life-threatening infections (20), Seven cases (25%) showed no response to induction treatment which might be explained by the modest therapy in our setting due to poor supportive facilities. Only 13 (46.4%) remained in Continuous Complete Remission (CCR) with a median follow up period of 32 months which is much lower than other studies; in Dahl study (16) four year overall survival was 73%, compared to Baez F. et al (15); with a median follow up period of 3 years (range: 0.1-9 years), 34 (64%) patients are alive, 15 (28%) died, and 4 (8%) abandoned therapy during induction phase before obtaining a CR.

Conclusion:

Lower frequency of the disease than studies done abroad, Lower median age of patients with advanced stages of disease were predominant, the remission induction was low, relatively low survival rate due to limitation in diagnosis and treatment.

Authors Contribution

Study conception and design: Dr. Salma Al-Hadad

Acquisition of data analysis: Dr. Samahir Abdulrazzaq Fadhil , Dr. Amir Fadhil Al-Darraji

Interpretation of data, drafting of manuscript and critical revision: Dr. Raghad M Al-Saeed , Dr. Salma Al-Hadad.

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