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Original Article

Pediatric Nonblastic Non-Hodgkin's Lymphoma: A Perspective from India

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Abstract

Background: There is a paucity of data on pediatric nonblastic non-Hodgkin's lymphoma (NHL) from developing countries. We conducted this study to study outcome and identify risk factors that can predict survival in pediatric nonblastic NHL at our center. **Methods:** Patients <18 years of age who were diagnosed with nonlymphoblastic NHL at our hospital from January 1, 2005, to December 31, 2014, were included. Data were collected retrospectively from case records. **Results:** One hundred and two patients with median age of 12 years (range: 1–18) were included in the study. There were 69/102 (68%) male and 33/102 (32%) female patients. The most common histological diagnosis was Burkitt's lymphoma (BL) in 59/102 (58%) patients followed by anaplastic large cell lymphoma (ALCL) in 28/102 (28%) patients and diffuse large B-cell lymphoma (DLBCL) in 12/102 (12%) patients, T-cell lymphoma in 2/102 patients, and primary mediastinal B-cell lymphoma in 1/102 patients. The LMB-89 protocol was the most common protocol used for treatment in 74/102 (72%) patients. The 2-year event-free survival (EFS) for patients with BL, ALCL, and DLBCL was 72%, 55.8%, and 27.5%, respectively (P = 0.037). On univariate analysis, factors that significantly predicted poor EFS included non-BL histological subtype, poor performance status, malnutrition, use of less intense chemotherapy, and not achieving complete response on interim radiological assessment. **Conclusions:** Outcomes in nonblastic NHL from our center are worse compared to data from the west. This is because a large proportion of patients present with advanced stage and in moribund condition. Patients with BL have better outcome compared to other subtypes.

Keywords: *Chemotherapy, non-Hodgkin lymphoma, survival*

Introduction

More than 80% of children with pediatric non-Hodgkin's lymphoma (NHL) can be cured currently.[1] However, results of this success story seen in the developed world have not been replicated in developing countries.[2] There is a paucity of published literature on pediatric NHL from developing countries. We, therefore, conducted this study at our center to find the outcome of pediatric patients with nonblastic NHL and identify risk factors for disease relapse.

Methods

Data of all consecutive pediatric patients with newly diagnosed nonblastic NHL, <18 years of age, who were treated at our center from January 1, 2006, to December 31, 2014, were analyzed. The data were retrospectively retrieved from case records of the patients. Diagnosis of NHL was confirmed by histopathological examination of biopsy specimen and immunohistochemistry. Patients with lymphoblastic lymphoma were excluded from the study. Staging and response assessment was performed using computed tomography scan with contrast of neck, chest, abdomen, and pelvis. All patients underwent unilateral iliac crest bone marrow aspiration and bone marrow biopsy to look for bone marrow involvement. Patients were staged according to the Murphy staging system.[3] Cytogenetic testing or molecular studies to identify specific translocations were not performed.

Patients with Burkitt's lymphoma (BL) were treated using the LMB-89 protocol, whereas patients with diffuse large B-cell lymphoma (DLBCL) were treated with either LMB-89 protocol or CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone) chemotherapy.[1] Patients with anaplastic large cell lymphoma (ALCL) were treated with either LMB-89 protocol or BFM-90 ALCL protocol or MCP-842 protocol.[1,2,4] Patients with primary mediastinal B-cell lymphoma (PMBCL) were treated with MACOP-B protocol.[5]

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The Eastern Cooperative Oncology Group (ECOG) criteria were used for recording the performance status (PS) of the patients. However, the ECOG PS score is designed for adults and not for children. Patients were defined as moribund if they were severely malnourished and/or had disease-related complications such as hemodynamic instability, respiratory failure, bleeding diathesis, or altered sensorium making them unsuitable for intensive chemotherapy regimens. Moribund patients were treated with prednisolone and cyclophosphamide till their physical status improved, and they could tolerate more intensive chemotherapy. Undernutrition was defined as weight-for-age less than third centile on the World Health Organization growth charts.[6]

Event was defined as death due to any cause or relapse or progression of disease. Event-free survival (EFS) was calculated from date of initiation of treatment to date of relapse or documented progression or death. Patients were censored at the date of the event or date of last follow-up. EFS was estimated using Kaplan–Meier method and variables were compared using the log rank test. $P < 0.05$ was considered statistically significant. Statistical analysis was done using SPSS Software (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0., Chicago: SPSS Inc).

Results

During the study period, 102 patients with pediatric nonblastic NHL were treated at our hospital. The median age of the patients was 12 years (range: 1–18 years). There were 69 male and 33 female patients in the study. The duration of symptoms was <1 month in 50/102 (49%) patients. The most common histological diagnosis was BL in 59/102 (58%) patients followed by ALCL in 28/102 (27%), DLBCL in 12/102 (12%), T-cell lymphoma in 2/102, and PMBCL in 1/102 patient. Stage III was the most common stage and was seen in 62/102 (61%) patients. The most common site of disease involvement was the abdomen followed by neck and mediastinum. Baseline demographic data are shown in Table 1.

Table 1: Demographic features of the study patients

Parameter	*n*
Stage	
I	11/102
II	12/102
III	62/102
IV	17/102
Gender	
Male	69/104
Female	33/104
Age	
Median (range)	12 (1-18)
<5 years	23/102
5-10 years	21/102
>10 years	58/102
Sites of disease	
Neck	43
Thorax	25
Abdomen	73
CNS	5
BM	10
Bone	5
Pathological subtype	
Burkitt's lymphoma	59/102
DLBCL	12/102
PMBCL	1/102
ALCL	28/102
PTCL	2/102
Chemotherapy protocol	
LMB-89	74
CHOP	8
BFM-90 ALCL	8
MACOP-B	1
MCP-842	2
Cyclophosphamide and steroid	6
Not treated	3

CNS – Central nervous system; BM – Bone marrow; DLBCL – Diffuse large B-cell lymphoma; PMBCL – Primary mediastinal B-cell lymphoma; PTCL – Peripheral T-cell lymphoma; ALCL – Anaplastic large-cell lymphoma; BFM – Berlin-Frankfurt-Muenster

Survival outcome

The mean and median duration of follow-up of study patients was 38.04 months and 26.7 months, respectively. The 2-year EFS of the entire cohort was 62.6%. The 2-year EFS for patients with BL, DLBCL, and ALCL was 72.0%, 27.5%, and 55.8%, respectively.

Among the 12 patients with diagnosis of DLBCL, 4/12 received CHOP chemotherapy, 1/12 received oral cyclophosphamide, and 7/12 received LMB-89 protocol. Among the 7 patients who received LMB-89 protocol, 3/7 had disease relapse and 2/7 died due to neutropenic sepsis. Among the 5 patients who received CHOP or oral cyclophosphamide, 3/5 had disease relapse. Ten of the 12 patients with DLBCL had Stage III disease at presentation, and 1 patient each had Stage I and II, respectively.

On univariate analysis, factors that significantly predicted poor EFS included non-BL histological subtype, poor PS, not achieving complete response (CR) on interim assessment, malnutrition, and use of less intensive chemotherapy [Figures 1 and 2]. Table 2 shows the univariate analysis for various parameters. On multivariate analysis, interim radiological response and PS were significantly associated with EFS. Gender, serum albumin, elevated LDH, hemoglobin, and delay in presentation of more than 1 month did not significantly predict EFS.

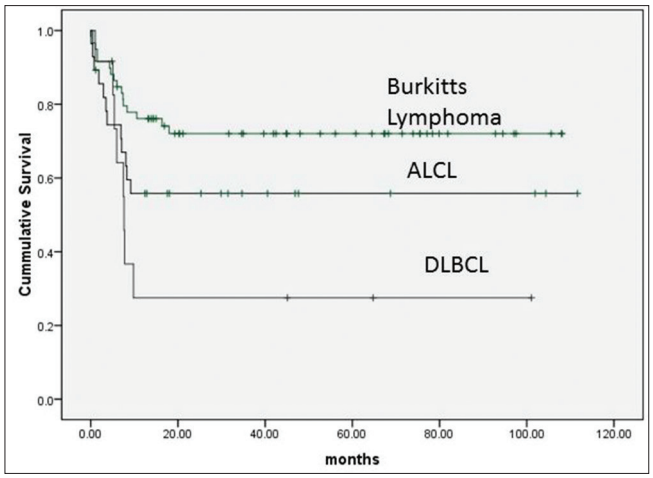

Figure 1: Event-free survival according to pathological subtype

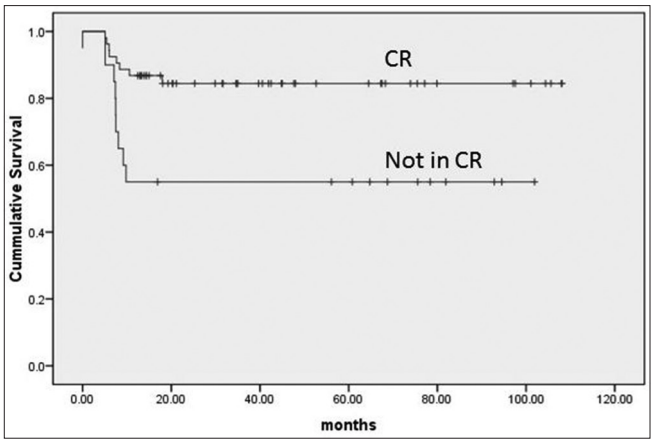

Figure 2: Event-free survival according to interim assessment

Events

The total number of events among the 102 patients was 37. Disease relapse or progression contributed to 27/37 events; 8/37 events were due to treatment-related toxicity death, 1/37 due to a patient developing colonic adenocarcinoma, and 1/37 patient died due to unknown cause in remission.

There were 8/102 (7.8%) treatment-related deaths, 3/8 deaths in patients with BL, 3/8 in patients with ALCL, and 2/8 in patients with DLBCL. The most common protocol associated with treatment-related mortality was LMB-89, which was used in 6/8 patients, 2/8 patients received BFM-90 ALCL protocol and MCP-842 protocol, respectively. All the eight treatment-related deaths were due to neutropenic sepsis.

The mean and median duration of disease relapse/progression was 5.28 and 5.97 months, respectively (range: 0–10.57 months). Three patients expired before treatment could be started and 2/3 had BL and 1/3 had ALCL. Six patients were treated with oral cyclophosphamide and steroids as they were moribund at presentation, 4/6 have expired, and status of the remaining 2/6 patients is not known as they were lost to follow-up. To summarize, definitive treatment for NHL could not be given to 9/102 patients.

Salvage chemotherapy and stem cell transplantation

Salvage chemotherapy was offered to 6 patients, 4/6 patients had DLBCL, 1 patient each had BL and ALCL, respectively. Two patients with DLBCL underwent autologous peripheral blood hematopoietic stem cell transplantation (ASCT) after achieving CR with salvage chemotherapy; they are well on follow-up and are currently in CR. The remaining 4/6 patients had disease progression after salvage and have died; they did not undergo ASCT.

Discussion

There is a paucity of published literature on pediatric NHL from developing countries.[7,8] The 2-year EFS in patients with BL in our cohort was 72%, whereas the 5-year EFS in the LMB-89 trial was 91%.[1] Patients with Stage I and II BL had 100% EFS. Advani *et al*. from Mumbai, India, reported an EFS of 68% in patients with small noncleaved and large cell lymphoma using MCP-842 protocol.[2] Bakhshi *et al*. reported a progression-free survival of 72.8% in a cohort of 38 nonblastic NHL patients at a median follow-up of 20.3 months.[9] Our results in BL are comparable to reports from other centers in India. The 2-year EFS in patients with DLBCL in our cohort is 27.5% which is inferior compared to what has been reported in the literature. Patients with DLBCL were treated with either intensive LMB-89 protocol (n = 7) or less intensive CHOP protocol (n = 4) or oral cyclophosphamide (n = 1) based on physician preference. However, the events in LMB-89 and CHOP group were similar. The poor outcome in the DLBCL cohort compared to BL or ALCL group in our study cannot be explained. The 2-year EFS in patients with ALCL in our study was 55.8%. Lakshmaiah *et al*. reported an EFS of 66.7% in pediatric patients with ALCL at a median follow-up of 36 months.[10] Advanced stage, malnutrition, treatment-related toxicity, and poor general condition contribute toward the inferior outcome in our cohort.

None of the patients in our study abandoned treatment. We could not ascertain the overall survival (OS) status because majority of the patients who relapsed or progressed were sent home on best supportive care and their survival outcome could not be ascertained by postal or telephonic contact.

In our study, BL was the most common histology followed by ALCL and DLBCL. We had excluded patients with lymphoblastic lymphoma from our study because they are treated with acute lymphoblastic leukemia protocols rather than the short course intensive chemotherapy protocol used in nonblastic NHL. In a study of 252 pediatric NHL patients from Christian Medical College, Vellore, India, the most common subtype of NHL was lymphoblastic lymphoma (43.2%) followed by BL (22.2%),

Table 2: Univariate analysis of parameters for event-free survival

Parameter (*n*)	2-year EFS (SE)	*P**
Stage		
I (11)	100	0.06
II (12)	72.7 (13.4)	
III (62)	55.4 (6.4)	
IV (17)	58.8 (11.9)	
BL stage		
I (6)	100	0.12
II (8)	100	
III (34)	64 (8.4)	
IV (11)	63.6 (14.5)	
ALCL stage		
I (4)	100	0.4
II (3)	33.3 (27.2)	
III (16)	50 (12.5)	
IV (5)	60 (21.9)	
Chemotherapy+		
Intensive (80)	69.2 (5.1)	0.002
Standard (19)	33.7 (12.2)	
Gender		
Male (69)	68.3 (5.8)	0.08
Female (33)	51.1 (8.8)	
Pathological subtype		
Burkitt's (59)	72.0 (6.0)	0.01
DLBCL (12)	27.5 (13.5)	
ALCL (28)	55.8 (9.5)	
Interim assessment		
CR (53)	84.4 (5.1)	0.005
Not in CR (20)	55.0 (11.1)	
Duration of symptoms		
Less than a month (50)	61.1 (7.0)	0.64
More than a month (52)	64.0 (6.8)	
PS		
PS1 (53)	72.8 (6.2)	0.003
PS2 (30)	62.2 (9)	
PS3 (15)	30 (12.3)	
PS4 (2)	50 (35.4)	
Undernourished		
Yes (36)	52.3 (8.4)	0.02
No (41)	77.7 (6.6)	

*Log rank test, +$P < 0.05$. Intensive protocols – LMB-89; BFM-90; BFM-95. Standard protocols – CHOP oral cyclophosphamide; MCP 842. *n* – Number of patients; EFS – Event-free survival; CR – Complete Response; SE – Standard error; DLBCL – Diffuse large B-cell lymphoma; ALCL – Anaplastic large cell lymphoma; PS – Performance status; BL – Burkitt's lymphoma

ALCL (11.5%), and DLBCL (8.7%).[11] The distribution of nonlymphoblastic subtypes seen at Vellore is similar to our study.

The most common reason of events in our cohort was disease relapse or progression; all the relapses occurred within first 10 months of treatment. We did not modify the treatment protocols to reduce the intensity, and therefore, this could not be a reason for higher relapse rate. About 7.8% of patients died due to febrile neutropenia, which is high compared to western settings. Patients have access to broad spectrum antibiotics and intensive care facilities at our hospital. We feel that the neutropenic deaths were because of the patient's poor nutritional status rather than access to adequate facilities. Tumor lysis syndrome (TLS) was effectively managed with hydration and allopurinol. No child required dialysis. Only one child with TLS was given rasburicase; she presented in a moribund condition and died before definitive treatment could be started.

Epidemiologically, our patients had features of sporadic BL unlike the endemic BL seen in Africa. Abdominal mass was the most common presentation and none of our patients with BL had jaw tumor.

Our study has limitations; these include the retrospective nature and lack of OS data. However, there are few curative options after progression or relapse in pediatric nonblastic NHL, especially in BL, and therefore, the EFS should reflect the OS.

Conclusion

Malnutrition and poor physical condition at presentation are important factors responsible for the inferior outcomes seen with pediatric nonblastic NHL at our center when compared to the western data. Patients with DLBCL had inferior outcomes in comparison to patients, with BL or ALCL.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Patte C, Auperin A, Michon J, Behrendt H, Leverger G, Frappaz D, *et al.* The Société Française D'oncologie Pédiatrique LMB89 protocol: Highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. Blood 2001;97:3370-9.
2. Advani S, Pai S, Adde M, Vaidya S, Vats T, Naresh K, *et al.* Preliminary report of an intensified, short duration chemotherapy protocol for the treatment of pediatric non-Hodgkin's lymphoma in India. Ann Oncol 1997;8:893-7.
3. Murphy SB, Fairclough DL, Hutchison RE, Berard CW. Non-Hodgkin's lymphomas of childhood: An analysis of the histology, staging, and response to treatment of 338 cases at a single institution. J Clin Oncol 1989;7:186-93.
4. Seidemann K, Tiemann M, Schrappe M, Yakisan E, Simonitsch I, Janka-Schaub G, *et al.* Short-pulse B-non-Hodgkin lymphoma-type chemotherapy is efficacious treatment for pediatric anaplastic large cell lymphoma: A report of the Berlin-Frankfurt-Münster Group Trial NHL-BFM 90. Blood 2001;97:3699-706.
5. Klimo P, Connors JM. MACOP-B chemotherapy for the

treatment of diffuse large-cell lymphoma. Ann Intern Med 1985;102:596-602.
6. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age: Methods and Development. Geneva: World Health Organization; 2006.
7. Ahmad N, Zaidi A, Badar F, Maaz AU, Akram MS. Clinical characteristics and outcome analysis of pediatric B-cell non-Hodgkin's lymphoma. Experience with FAB-LMB 96 and UKCCSG B-cell NHL guidelines in a developing country. Asia Pac J Clin Oncol 2010;6:49-56.
8. Moleti ML, Al-Hadad SA, Al-Jadiry MF, Al-Darraji AF, Al-Saeed RM, De Vellis A, *et al.* Treatment of children with B-cell non-Hodgkin lymphoma in a low-income country. Pediatr Blood Cancer 2011;56:560-7.
9. Bakhshi S, Radhakrishnan V, Sharma P, Kumar R, Thulkar S, Vishnubhatla S, *et al.* Pediatric nonlymphoblastic non-Hodgkin lymphoma: Baseline, interim, and posttreatment PET/CT versus contrast-enhanced CT for evaluation – A prospective study. Radiology 2012;262:956-68.
10. Lakshmaiah KC, Guruprasad B, Shah A, Kavitha S, Abraham LJ, Govindbabu K, *et al.* Anaplastic large cell lymphoma: A single institution experience from India. J Cancer Res Ther 2013;9:649-52.
11. Manipadam MT, Nair S, Viswabandya A, Mathew L, Srivastava A, Chandy M, *et al.* Non-Hodgkin lymphoma in childhood and adolescence: Frequency and distribution of immunomorphological types from a tertiary care center in South India. World J Pediatr 2011;7:318-25.