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Original Article

Clinical Profile and Outcomes of Non-Hodgkin's Lymphoma in Children: A Report from a Tertiary Care Hospital from India

Abstract

Background: Non-Hodgkin's lymphoma (NHL) is an aggressive malignancy. Its outcome has improved over the past decades. Although it accounts for 8%–10% of all childhood cancers, very less information about its clinical presentation and outcomes is available from India. Our objective was to study the clinical presentation and outcomes in children (<15 years) with NHL at our center. **Methodology:** We retrospectively analyzed 26 children diagnosed with NHL at our center from August 2008 to June 2014 and followed them up to May 2017. **Results:** The median age at the time of diagnosis was 7.7 years (2.5–13 years). Abdominal distension and an abdominal lump were the most common presenting features occurring in 75%, followed by fever (73.8%) and weight loss (46.2%). Most patients had advanced-stage (Stage III/IV, 92.3%) disease at presentation. The primary presentation was extranodal in 57.7%, nodal in 26.9%, and combined in 15.4%. Burkitt's lymphoma (BL) was the most common subtype (46.2%), followed by T-lymphoblastic lymphoma, diffuse large B-cell lymphoma, and anaplastic large-cell lymphoma. Three patients did not take treatment. The median follow-up of patients was 48 months (36–99 months). Nineteen patients achieved remission and four had progressive disease. Significantly better event-free survival (EFS) was found with younger age and lower stage of presentation. The EFS did not significantly differ with sex, group of disease, lactate dehydrogenase levels, and presenting features. **Conclusions:** Our cohort of patients with NHL showed characteristics similar to those reported from other developing countries. NHL occurred at a younger age, with a higher incidence of BL. The outcome for patients aged >10 years was poor. The outcome of NHL was comparable to that of other centers in the world.

Keywords: *India, non-Hodgkin's lymphoma, pediatrics*

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Introduction

Malignant lymphomas (including non-Hodgkin's lymphoma [NHL] and HL) are the third most common group of malignancies in children after leukemias and brain tumors. They account for 15% of all childhood malignancies in children younger than 20 years.[1] Approximately 60% of pediatric lymphomas are NHL, whereas the rest are HL.[2]

Most NHLs in children present as an aggressive disseminated disease. Potential clinical emergencies in patients with NHL prior to diagnosis are superior/inferior vena cava obstruction, acute airway obstruction, spinal cord compression, pericardial tamponade, intussusception/intestinal obstruction, and central nervous system (CNS) complications. The outcome of childhood NHL has improved progressively over the past decade to about 80%–90% with intensive risk-adapted multiagent therapy.[3-5]

In developing countries, there are many obstacles to the treatment of childhood lymphomas. The most important are late diagnosis, low socioeconomic status, and poor nutrition.[6-8] The lack of awareness at primary care level, universal health-care provision, and poor socioeconomic status lead to late presentations with advanced stage disease, thus influencing outcomes.

There is a scarcity of data on the clinical profile and outcomes of treatment of childhood NHL in India. Here, we present the experience in the management of childhood NHL from a single tertiary center in a large metropolitan urban setting, focusing specifically on the clinical profile and outcome of these children.

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Methodology

Eligibility, staging, and diagnosis

The data of children younger than 15 years diagnosed with NHL at the All India Institute of Medical Sciences, New Delhi, diagnosed with NHL over 6 years from August 2008 to June 2014, were retrospectively analyzed. The study was approved by our Institutional Ethics Committee. Twenty-six patients who had been diagnosed with NHL during this period were identified, and data regarding clinical features, diagnostic and staging workup, and treatment outcomes were collected.

The workup for all patients included a detailed history; physical examination; standard blood tests including lactate dehydrogenase (LDH); computed tomography (CT) scan of the primary site along with neck, chest, abdomen, and pelvis; and bone marrow (BM) aspiration and biopsy. NHL was staged according to St Jude/Murphy staging system[9] before treatment initiation.

The diagnosis was on the basis of either ultrasound or CT-guided core needle or excisional biopsy. The presence of neoplastic cells in the cerebrospinal fluid and the clinical sign of CNS involvement defined CNS disease. To evaluate malnutrition, the Z-scores were used for each patient's weight for age (undernutrition), height for age (stunting), and weight for height (wasting) (WHO Z-scores in children <5 years of age[10] and Indian Academy of Pediatrics Z-scores in children >5 years of age).[11]

Stratification

Therapy was stratified into three risk groups[3] according to the following criteria: risk Group 1 (R1) was defined as patients having lymphoma with initial complete resection; risk Group 2 (R2) was defined as patients diagnosed with lymphoma with no or incomplete resection and involvement of only extra-abdominal sites and LDH level <500 U/L, measured before starting chemotherapy; and risk Group 3 (R3) was defined as patients diagnosed with lymphoma, with no or incomplete resection of abdominal lymphoma and LDH ≥500 U/L, all patients with BM involvement and/or CNS disease, and/or multifocal bone involvement.

Treatment

The patients were stratified by risk factors (stage and LDH level) and treated with the NHL-Berlin–Frankfurt–Münster (BFM 90) protocol.[3,12] At diagnosis, all patients were treated with vigorous hydration and allopurinol to prevent tumor lysis syndrome (TLS). All patients received a cytoreductive phase with prednisone and cyclophosphamide. After the 5th day of prephase, the first course of chemotherapy was initiated the next day depending on the condition of the patient. In our patients' group, no one was in Group R1. Patients in Group R2 received four courses of multiagent chemotherapy (AA-BB-AA-BB). Patients in Group R3 received six courses, i.e., AA-BB-AA-BB-AA-BB. Conditions for starting the subsequent course of therapy were as follows: platelets >100,000/μL and neutrophils >1000/μL after the nadir of postchemotherapeutic cytopenia. The minimal interval between the two successive courses was at least 4 weeks.

Patients in risk groups R2 and R3 who had a residual tumor after two therapy courses received therapy course CC. Patients were re-evaluated after course CC. If no viable lymphoma tissue was found, therapy was continued with three more courses (AA-BB-CC).

Patients of lymphoblastic lymphoma (LBL) were treated with the International Network for Cancer Treatment and Research (INCTR), an unpublished study protocol for LBL/lymphoma and the MCP 841 protocol.

Response evaluation

Physical examination of all clinically documented sites of disease was performed prior to the initiation of each cycle. All patients underwent a CT scan of the neck, chest, and abdomen upfront. A CT or positron emission tomography (PET) scan study was performed after the first two cycles of chemotherapy. Follow-up evaluations included history, physical examination, and laboratory examinations every 3 months during the 1st year after the end of the therapy and at 4–6-month intervals during the following 3 years and yearly thereafter. PET or CT scans were performed when clinically indicated. Progression was defined as a recurrence of tumor documented by clinical examination, X-rays, ultrasound, and CT scan or PET scan studies. Patients with initial BM and CNS involvement were evaluated with punctures of BM and CNS until clearing of blasts. Complete response was defined as the complete disappearance of clinical and radiological lesions. Disease progression was defined as increase by ≥25% of at least one measurable lesion, or by the appearance of a new lesion. Event-free survival (EFS) was determined as the time from the initiation of treatment to progression, death, or the most recent follow-up examination.

Statistical analysis

Data were statistically described as frequencies (number of cases) and percentages where appropriate. Descriptive statistics were used to calculate the relative frequencies of age, sex, histopathologic types, and clinical and laboratory features. Survival curves were plotted using the Kaplan–Meier method, and comparison was made using the log-rank test. $P < 0.05$ was considered to be statistically significant. The statistical analysis was performed using SPSS statistics version 16.0 for analysis (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc).

Results

Patient characteristics and presentation

There were 26 patients of NHL who were treated at our center during the above period. The median age at the

time of diagnosis was 7.7 years (2.5–13 years). There were 21 males. The presenting clinical characteristics of patients are shown in Table 1. The abdominal distension/lump was the most common presenting feature occurring in twenty patients (76.9%), followed by fever (73.1%), weight loss (46.2%), breathlessness (34.6%), pallor (34.6%), lymphadenopathy (26.9%), and bone pain (19.2%). The physical/radiological findings of the cohort are shown in Table 2. An abdominal mass (69.2%) was the most common finding. Pleural effusion was present in 46% of patients and about 19% of the patients presented with a superior mediastinum syndrome/superior vena cava syndrome.

Disease localization and staging

Highly elevated serum LDH (LDH ≥1000 IU/L) was seen in 50% of patients. Nineteen patients (73.1%) were in Group R3 and seven patients (26.9%) were in R2 risk group. The primary presentation was extranodal in 57.7%, followed by nodal (26.9%) and combined (15.4%). The most common nodal presentation was cervical lymphadenopathy (46.2%), and the most common extranodal presentation was gastrointestinal tract (69.2%) followed by liver and BM (15.4% each).

Table 1: Clinical characteristics (presenting complaints) of non-Hodgkin's lymphoma patients

Characteristics	*n* (%)
Abdominal distension/lump	20 (76.9)
Fever	19 (73.1)
Weight loss	12 (46.2)
Breathlessness	9 (34.6)
Pallor	9 (34.6)
Lymphadenopathy	7 (26.9)
Bone pain	5 (19.2)
Abdominal pain	4 (15.4)
Facial swelling	4 (15.4)
Cough/dysphagia/vomiting	3 each
Pedal edema/voice change/chronic diarrhea	2 each
Bleeding manifestations/fecal/urinary incontinence/jaundice	1 each

Table 2: Physical/radiological findings of non-Hodgkin's lymphoma patients

Signs/physical findings	*n* (%)
Abdominal mass	18 (69.2)
Pallor	15 (57.7)
Hepatomegaly	15 (57.7)
Lymphadenopathy	15 (57.7)
Pleural effusion	12 (46.2)
SMS/SVCS	5 (19.2)
Ascites	5 (19.2)
Splenomegaly	4 (15.4)
Bone lesions	3 (11.5)
Bone tenderness	2 (7.7)

SMS/SVCS – Superior mediastinum syndrome/superior vena cava syndrome

Types of non-Hodgkin's lymphoma

Burkitt's lymphoma (BL) was the most common NHL subtype (46.2%), followed by T-LBL (T-LBL), diffuse large B-cell lymphoma (DLBCL), and anaplastic large-cell lymphoma (ALCL), accounting for 15.4%, 7.7%, and 3.8% of the cases, respectively. Seven patients (26.9%) could not be classified in specific subtype [Table 3].

Treatment

Fifteen patients (57.7%) received chemotherapy alone. Three patients (11.5%) (T-LBL) received a combination of chemotherapy and radiotherapy (cranial radiation therapy). Five patients (19.2%) received combined therapy of chemotherapy and surgery. Two patients (BL) required surgery for residual tumor. Three patients required surgery for intestinal obstruction (1 BL, 1 DLBCL, and 1 B-cell-NHL [B-NHL] [unclassified]). Eighteen patients (69.2%) were treated with NHL-BFM protocol, four patients of T-LBL were treated with INCTR (n = 3) and MCP 841 (n = 1) protocol, and one patient of peripheral T-cell lymphoma was treated with four chemotherapy cycles of cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone. Three patients did not take treatment. Five patients (21.7%) out of 23 who received treatment had TLS (4, BL and 1, T-LBL); out of them, two required recombinant urate oxidase (rasburicase) and hemodialysis.

Survival outcomes

The median follow-up in patients was 48 months (36–99 months). A total of 19 patients achieved complete remission and 4 (17.4%) patients had progressive disease. The 3-year EFS rate of our study was 82.6% [Figure 1]. The 3-year EFS compared between the age groups of <10 years and ≥10 years was statistically significant (94.1% vs. 66.7%; P = 0.008) [Figure 2]. The sex of the patient, risk group, LDH levels, and primary presentation characteristics did not significantly affect the EFS.

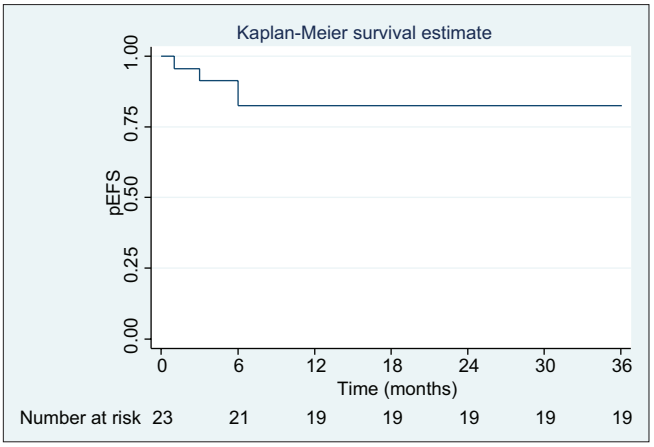

Figure 1: Event-free survival of all non-Hodgkin lymphoma patients

Table 3: Summary of demographic and laboratory characteristics, risk stratification, stage, presentation, histology subtypes, and treatment modality of non-Hodgkin's lymphoma patients (*n*=26)

Characteristics	*n* (%)
Gender	
Male	21 (80.8)
Female	5 (19.2)
Hb	
≤10 (g/dl)	13 (50)
>10	13 (50)
TLC	
≤11,000	15 (57.7)
>11,000	11 (42.3)
Platelets	
≤50,000	3 (11.5)
>50,000	23 (88.5)
LDH	
<500	6 (23.1)
500-999	7 (26.9)
≥1000	13 (50)
NHL risk stratification schema	
R1	0 (0)
R2	7 (26.9)
R3	19 (73.1)
BM aspiration/biopsy	
Involvement	4 (15.4)
No involvement	22 (84.6)
Primary presentation	
Nodal	7 (26.9)
Extranodal	15 (57.7)
Combined	4 (15.4)
Presence of nodal disease	
Cervical	12 (46.2)
Inguinal	5 (19.2)
Mediastinal	5 (19.2)
Abdominal	3 (11.5)
Axillary	3 (11.5)
Supraclavicular	1 (3.8)
Presence of extranodal disease	
GIT	18 (69.2)
Liver	4 (15.4)
BM	4 (15.4)
Bone	3 (11.5)
Spleen	2 (7.7)
Soft tissue	1 (3.8)
Lung	1 (3.8)
CNS	1 (3.8)
Subtype histology	
Burkitt's lymphoma	12 (46.2)
T-lymphoblastic lymphoma	4 (15.4)
Diffuse large B-cell lymphoma	2 (7.7)
Anaplastic large cell lymphoma	1 (3.8)
B-NHL (unclassified)	3 (11.5)
B-NHL high grade (unclassified)	1
NHL (NOS)	2
PTCL (NOS)	1
Treatment	
CT alone	15 (57.7)
CT + RT	3 (11.5)
CT+ surgery	5 (19.2)
Abandonment	3 (11.5)
Chemotherapy regimen	
NHL-BFM 90 protocol	18 (69.2)
INCTR	3 (11.5)
MCP 841	1 (3.8)
CHOEP	1 (3.8)

TLC – Total leukocyte count; LDH – Lactate dehydrogenase; NHL – Non-Hodgkin's lymphoma; GIT – Gastrointestinal tract; CNS – Central nervous system; NOS – Not otherwise specified; PTCL – Peripheral T-cell cutaneous lymphoma; CT – Chemotherapy; RT – Radiotherapy; CHOEP – Cyclophosphamide; doxorubicin; vincristine; etoposide, and prednisone; INCTR – International Network for Cancer Treatment and Research; BM – Bone marrow; BFM 90 – Berlin–Frankfurt–Münster-90; Hb – Hemoglobin

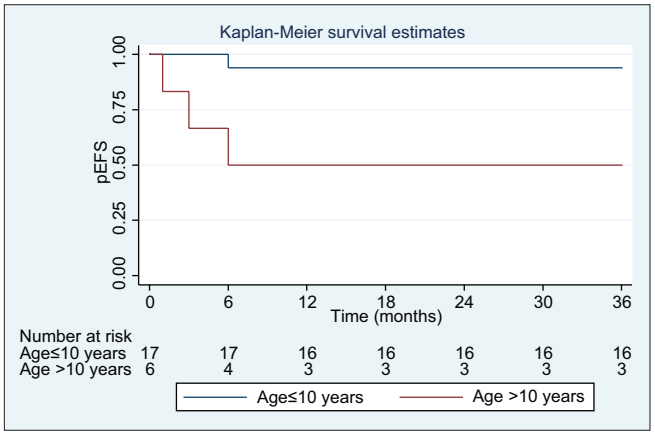

Figure 2: Event-free survival of all non-Hodgkin lymphoma patients according to age

Discussion

The outcome of NHL in children has improved considerably over the years with the risk stratification and treatment modifications. NHL in children is an aggressive malignancy and requires early intervention and intensive chemotherapy. Data about the clinical profile and outcomes of childhood NHL from many developing countries, including India, are scanty. This study included NHL patients <15 years old diagnosed at our department from August 2008 to June 2014. Our hospital is a tertiary care hospital and referral bias cannot be excluded.

Lymphomas are the third most common malignancy in children, accounting for 15% of all childhood malignancies in children younger than 20 years.[1] In contrast to a NHL/HL ratio of 3:2 in Western countries, it is either equal or often reversed in India.[1,13]

In our study, BL was the most common lymphoma and constituted 46.2% of the cases, similar to what has been reported by other authors.[14-16] Other studies from India[17-20] have shown that LBL is more common than BL. The incidence of BL varies markedly worldwide, being predominantly high in Equatorial Africa, which is likely due to early infection by Epstein–Barr virus (EBV) and chronic exposure to malaria. The exposure to EBV is commonly seen in the lower socioeconomic strata, and BL is commonly associated with EBV worldwide.[21]

LBL was the second most common subtype of NHL, comprising 15.4% of all NHLs similar to other studies.[14,22-24] In a Brazilian epidemiologic study, LBL represented 36% of all NHLs and T-LBL was the most prevalent (60%) followed by B-LBL (25%) and the remaining (15%) were unclassified.[25] The overall frequency of T-LBL (6%–7.2%) in India[26,27] has been reported to be slightly higher than that in other countries. The cause for this high frequency may be due to the role of genetic factors and environmental factors in developing countries.[28] There are studies for the possible association between T-LBL in children and risk factors such as EBV infection[29,30] and methylene tetrahydrofolate reductase gene polymorphisms.[31]

DLBCL constituted 7.7% of all NHLs in our study. The frequency of DLBCL was higher in other studies at 21.6%.[16,24,32] Occasionally, differentiation of BL can be difficult from high-grade DLBCL. Childhood DLBCL is biologically different from adult and has a good prognosis. The good prognosis of DLBCL is accredited to the fact that most of the childhood DLBCLs are of the germinal center phenotype and lack the (8:14) translocation.[33] In our study, ALCL constituted about 3.8% of all NHLs.

NHL in children is generally considered to be a widely disseminated disease from the beginning. In the present study, 92.3% of NHL patients had advanced stage (Stage III/IV) disease; similar results were reported by several previous studies.[16,22,24,32] Multiple reasons may be responsible for presentation in an advanced stage, and they include lack of early referral, insufficient knowledge about the disease, and wide use of alternative medicine, which may delay seeking proper medical advice. In this study, three patients received prior antitubercular drug, one patient had got methylprednisolone and intravenous immunoglobulin, and one patient received alternative medicine prior coming to our center.

NHL in children is commonly found extranodally and is more difficult to diagnose, clinically as well as histopathologically, in comparison to HL.[34] In our study of 26 patients with NHL, abdominal involvement was the most common presentation (69.2%), followed by cervical lymph node involvement (46.2%), whereas BM infiltration (15.4%) was the most common site of metastasis. In other studies, the abdominal involvement was the most common presentation (73.2%), followed by mediastinal involvement (16.2%).[16,22] The incidence of TLS (21.7%) and mucositis (23.7%) in our study was similar to that reported by Alavi *et al*. at 23.7%[35] and Tiwari *et al*. at 26.1%, respectively.[36]

The 3-year EFS in the present study was 82.6%. The survival of our patients is comparable with the results presented by the international treatment groups, reporting a survival rate of ~80–90% for patients with NHL.[12,15,22,37,38] With regard to prognostic factors, no statistically significant associations were observed between gender, LDH, risk stratification groups, and primary presentations. The difference in 3-year EFSs between the age groups of <10 years and ≥10 years was significant. Similarly, Hwang *et al*.[23] reported that the overall survival for patients in the age group of 21–31 years was significantly inferior to that of the other younger age group in Korea ($P = 0.014$).

Conclusions

Our cohort of pediatric patients with NHL showed characteristics that were similar to those reported from other developing countries. NHL occurs at a younger age among pediatric patients in India, with a higher incidence of BL and the most common presentation of abdominal involvement. The outcome for patients with higher age (>10 years) was poor. Age (>10 years) might serve as a criterion for risk stratification in these subtypes of NHL. The outcome of NHL in our center was satisfactory, approaching the international rates although most patients presented in advanced stage of the disease. This study may help to establish baseline data for future studies, which may serve as a guideline for the management and may help improve the outcome for children with NHL in India.

Some limitations in our study were the small sample size and retrospective design; future prospective studies with larger sample size are needed to confirm our study results.

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Conflicts of interest

There are no conflicts of interest.

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