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RESEARCH ARTICLE

CLINICOPATHOLOGICAL FEATURES AND OUTCOME OF PEDIATRIC NON-LYMPHOBLASTIC NON-HODGKINS LYMPHOMA - *AN INSTITUTIONAL EXPERIENCE*.

Arun Kumar, *Prerana Nesargi, Nuthan Kumar, Appaji, L. Aruna Kumari B.S. and Aarthi, N.

Kidwai Memorial Institute of Oncology, India

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ABSTRACT

Background: Non-Hodgkin's Lymphoma (NHL) of childhood accounts approximately 60% of lymphomas and malignant lymphomas are the third most commonest group after leukaemia, brain tumors. Need for the study: There exists paucity of data on paediatric Non Lymphoblastic Non Hodgkin's Lymphoma from developing countries, we conducted this study to know the clinic-pathological profile, treatment and survival outcome of these children. **Design/Methods:** This study is a retrospective descriptive analytical study of all the Non Lymphoblastic Non Hodgkins Lymphoma patients diagnosed and treated at department of paediatric oncology, Kidwai cancer institute from January 2009 to December 2014. **Results:** Seventy one patients aged less than 15 years were included in this study, there were males (n=53) and females (n=18) with male: female ration being 3:1. The most common site involved at the time of presentation was intrabdominal (n=32,45%) The most common pathological subtype was Burkitt lymphoma(37,52%) followed by ALCL(20,28%),DLBCL(14,20%),majority of children were stage lll (n=54,76%) as per St Judes staging for Non Hodgkins Lymphoma. 42 (71.2%) patients were treated with MCP 842 and 17(28.8%) were treated COMP protocols. The 3 year DFS was for Burkitt, ALCL, DLBCL were 90%, 66.7%,90% respectively. **Conclusion:** The outcomes in non lymphoblastic NHL from our centre were almost equivalent to western data, short intensive chemotherapy and good supportive care has pivotal role in the management of these tumours even in advanced stages of the tumours.

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INTRODUCTION

Non Hodgkins Lymphoma(NHL) of childhood accounts approximately 60% of lymphomas and malignant lymphomas are the third most commonest group after leukaemias , brain tumours .In India incidence of NHL varies from 12 to 25% of all childhood cancers compared to 7–10% in west. and are high grade histologically. The 4 major pathologic subtypes of child hood NHL are Lymphoblastic, Burkitts Lymphoma, Diffuse large B Cell Lymphoma (DLBCL), Anaplastic Large Cell Lymphoma(ALCL) [Naresh, 2000]. The incidence of lymphoma varies by age and considerably in different world region.In the developed countries malignant lymphoma (including Hodgkins and Non Hodgkins) comprise the third most commonest group of malignancies under the age of 20 years whereas the reported incidence of lymphomas in India varies from12 to 25% of all childhood cancers compared to 7–10% in west, In India, the estimated incidence is between 1.9–5.6/million/year in girls and 9.2–15.7/million/year in boys in major cancer registries (Mumbai, Bengaluru, Chennai,and Delhi) similar to west with B cell lymphomas contributing 80-85% and rest 15-20% by T cell lymphomas [Arora, 2009]. In paediatric age group NHL is more common in age group less than 10 years and male predominance is seen in all age groups and subtypes with male preponderance noted. As there exists paucity of data on paediatric Non Lymphoblastic Non Hodgkins Lymphoma from developing countries, we conducted this study to know the clinic-pathological profile, treatment and survival outcome of these children.

Corresponding author:* **Prerana Nesargi,
Kidwai Memorial Institute of Oncology, India.

MATERIALS AND METHODS

Patients: All the Non Lymphoblastic Non Hodgkins Lymphoma patients diagnosed and treated at department of paediatric oncology, Kidwai memorial institute of oncology from January 2009 to December 2014 were included in this study. The clinical pathological and treatment data were collected from their case records and were studied retrospectively

Evaluation and staging: The diagnosis was established based on biopsy analysis done from nodal/extranodal sites as applicable, review of biopsy block carried out whenever required by haematopathologist at our centre followed by histological classification according to WHO classification 2008 and were staged by St Jude staging system for which all patients had underwent CECT of thorax/abdomen/pelvis, bone marrow examination and cerebrospinal fluid [Rosolen, 2015].

Treatment plan: Patients had been treated as per two protocols COMP and MCP 842 protocol[4,5] based on the general status of the patient to withstand the toxicities of chemotherapy at the time of diagnosis.

Statistical methods: This study was a retrospective survival analysis study Overall survival (OS) was calculated from the day of diagnosis to the day of death from any cause or till the last follow up or contact of the patients who were alive. Disease free survival (DFS) was calculated from the day of completion of chemotherapy to an event which was defined as death due to disease, relapse or progression or the day of last contact or follow up of those who did not have an event. OS and DFS were calculated by Kaplan Meier method. Log rank test and Cox regression model were used for univariate and multivariate analysis respectively. Data were censored on 31 Dec 2017

RESULTS

Of the 71 de novo pediatric NHL patients during the study period, males were(n=53) females were(n=18) with ratio being 3:1 with most common clinical presentation being abdominal distension and the Table-1 shows the frequency and order of anatomical site of primary tumour, the mean duration of symptoms was 25 days. patients presented to us with emergencies like Tumour lysis syndrome(n-2) intususception(n-2), spinal cord compression(n-2)massive GI bleed (n-1).

Table 1. Primary site distribution

Primary site	BL	DLBCL	ALCL
Head and neck	5	5	
mediastinum		3	
Abdomen	25	3	
GIT	2		
Renal			
Testicular	2		
retroperitoneum	4		
CNS		2	
Brain		1	
spinal			

The primary site of presentation of all the patients diagnosed are depicted in table-1 ,there were rare sites like brain and stomach involved, the subtype distribution of non lymphoblastic NHL was as follows was Burkitt lymphoma (37,52%) followed by ALCL(20,28%), DLBCL(14,20%) in our study. among all the subtypes stage III (n=54,76%) at presentation was predominant. Out of these 71 patients 10(14.08%).refused treatment at diagnosis 2(2%) died before the start of chemotherapy about 42(71.12%) (BL n-21, DLBCL n-9, ALCL n-12)received MCP 842 and 17(28.8%) (BL n -10, DLBCL n-3ALCL n-4) COMP. out of 59 who had received treatment n- 6(10.16%) relapsed 4(66.67%) had received 842 and 2 (33.33%)

Table 2. summary of the data analysed

Category	*Number of cases(n)*	*Percentage*
Total cases diagnosed	71	100%
Burkitt lymphoma	37	52.11%
ALCL	20	28.16%
DLBCL	14	19.71%
MC site of presentation	Intrabdominal(31)	43.66%
Predominant Stage(ST JUDES)	STAGE III(55)	77.46
Refusal of treatment	10	14.98%
Died Before Chemotherapy	2	2.8%
COMP	17	28.81%
MCP 842	42	71.18%
Died during Chemotherapy	4	6.77%
On MCP 842	2	
On COMP	2	
MC cause of death	Febrile neutropenia(4)	
Relapse(burkitt,DLBCL,ALCL)	6	10.19%
Received MCP 842		
COMP	4	
Early	2	
Late		
Salvage chemotharapy	nil	

Table 3. ICMR data on Paediatric NHL [8]

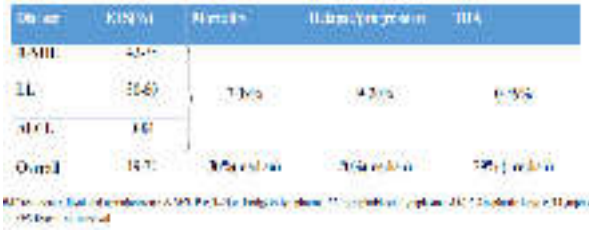

Table 4. 5yr EFS of various risk groups of B cell NHL [9-12]

Table 5. risk stratification for ALCL [13]

COMP and the site of recurrence was in their primary site of their first disgnosis and 4 (6.77%)died while on chemotherapy .

Survival Outcome: The data was analysed for survival outcomes using Kaplan meier curves, log rank tests and cox regression. Overall survival time was taken as duration from date of diagnosis to last date of follow up/date of death. Disease free survival was the duration from date of completion of chemotherapy and declaration of disease remission to date of last follow up/relapse/death due to malignancy. The median duration of follow up of the study patients was 64(CI-57-70.9),49.8(CI 38.9-60.7),45.6(CI 38.7-50.4) months for BL, DLBCL, ALCL respectively, the 3 year DFS of BL,DLBCL,ALCL was 91.7, 90.3% ,66.2%and overall survival(OS) of the entire cohort for 3 years was 86.7%.

Salvage chemotherapy and Stem cell transplant: Out of6 patients who relapsed/progressed option of salvage chemotherapy and autologus stem cell transplant were explained and prognosticated but opted only for palliative supportive care.

DISCUSSION

There is a paucity of published literature or data on paediatric NHL from India. This study was ant attempt to know the outcomes of paediatric non blastic NHL in india as principles of treating these lymphomas differs from lymphoblastic lymphomas which are mostly treated on acute lymphoblastc leukaemia protocols. In our study male predominance was noted similar to the reports in the literature and the frequency of non lymphoblastic NHL in decreasing order was Burkitt lymphoma (n-37), ALCL(n-20),DLBCL(n-14) similar distribution was reported by V radhakrishnan et al at in their study conducted at chennai but in Lymphoma registry at Tata Memorial Hospital (TMH) in 2001 suggested an almost equal distribution of B and T-cell tumors. Of B-cell, DLBCL was the commonest (22.9%) followed by BL (15.3%) and in TCell, LL was the commonest (31.5%) followed by ALCL in 11.1% cases. However, impact of referral bias could not be ruled out. The 3 yr DFS of Burkitt lymphoma DLBCL,ALCL was 91.7, 90.3% ,66.2% in our study,Advani et al from Mumbai India reported EFS of 68% in patients with small non cleaved large cell lymphoma using MCP842 [Advani, 1997], Vradhkrishnan et al from Chennai reported 2 yr EFS for patients with BL, ALCL ,DLBCL- 72 ,55.8 ,27.5 with LMB 89 protocol [Radhakrishna].

According to ICMR consensus on treatment of paediatric NHL 5 year EFS of Mature B cell NHL for localised disease ranges from 90-94% and advanced disease 73-88% using various established protocols including MCP 842 and COMP as they mention clearly that in centres with limited supportive care infrastructure,and/or facility/experience with methotrexate delivery or cost-constraints, MCP-842 (8 cycles–6 mo) is a good option with excellent outcomes [Neerav, 2017]. In ALCL we got 3 year DFS 66.3% which is comparatively inferior to other two subtypes similar to the 2 yr PFS was reported by 65.7% in alk negative and 85.7% in ALK positive ALCL cases by Manoj Sanger et al using MCP 842 protocol however poor outcome can be attributed to systemic disease and poor general condition of patients, similar study conducted at our centre by lakshmaiah et al reported that at a median follow-up of 36 months (range: 6-72 months) ALK− ALCL had a poor outcome. The 3 year event free survival in pediatric ALCL was 66.7%. In adults, this was 60% ALK+ ALCL was 60% and 20% in ALK− ALCL. In our study, emergencies encountered at the time of diagnosis and during therapy were tumour lysis syndrome, intussusception, perforation, massive GI bleed, febrile neutropenia. Most common toxicity was myelosuppression predisposing to severe infections followed by mucositis, the cause of mortality was febrile neutropenia and progression of malignancy in our patients.

Conclusion

In resource limited setting short intensive chemotherapy protocols like MCP 842 can reproduce similar outcomes as per western data however robust supportive care and nutrition remains backbone of management efforts, malnourishment poor general condition lack of appropriate supportive care can have huge influence on the outcomes.

Limitations of the study: In our study stage wise or risk strata wise outcomes are not analysed and also risk factors predisposing to decreased survival are not assessed as these guide us in risk stratifying and improving the management.

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