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Original Research Article

Pediatric Hodgkin's lymphoma: experience from a tertiary cancer center in North East India

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ABSTRACT

Background: Hodgkin's lymphoma is a clonal malignant lymphoid proliferation, which originates from the germinal centers of B cells. This study was conducted to observe the socio-epidemiological profile of Hodgkin's lymphoma in a tertiary cancer care centre from North East India.
Methods: All patients from 0 to 18 years of age group with histopathologically proven diagnosis of HL, presenting to department of medical & pediatric oncology at Dr. Bhubaneswar Borooah cancer Institute during the period January 2012 to December 2019 were included in the study. Clinical parameters assessed included age, sex, locality, occupation, presenting symptoms, performance status, site of lymph node involvement, treatment modality, response to treatment, progression free survival and overall survival.
Results: A total of 64 patients with histopathologically confirmed diagnosis of HL were registered in lymphoma joint clinic of BBCI from January 2012 to December 2019. The mean age was 12.68±4.71 years. Out of 64 patients, 54 (84.4%) belonged to rural areas and 10 patients (15.6%) to urban areas. Complete response was observed in 93.5% patient with limited risk disease, 73.24% with intermediate risk and 60% with advance stage. The overall survival and event free survival rates of 91% and 78.1%, respectively, were observed at 4 years.
Conclusions: This study provides insight to incidence, demographic profile, overall response rates and survival pattern with other secondary objectives such as complete response rate, compliance rate and toxicity assessment among children with Hodgkin lymphoma belonging to Northeastern India.

Keywords: Pediatric Hodgkin's lymphoma, Epidemiology, Response rate, Survival

INTRODUCTION

Hodgkin's lymphoma (HL) is a clonal malignant lymphoid proliferation, which originates from the germinal centers of B cells. The malignant cells are in general a small minority (0.1% to 2%) of the total cellular population of involved tissues.[1] HL cases are classified into classical HL(cHL) (95%) and nodular lymphocyte-predominant HL(5%).[1] Classical HL is further subdivided into four major histological subtypes: nodular sclerosis, lymphocyte-rich, lymphocyte-depleted, and mixed cellularity.[2] Surveillance, epidemiology, and end results (SEER) program have reported HL annual incidence of 2-3 per 100,000 and constitute 0.5% of the cancer diagnosed in the USA.[3] In India, Hodgkin's lymphoma constitutes 8.3% of all pediatric cancer cases in male and 4.5% in female between 0 to 19 years of age group.[4] Hodgkin's lymphoma (HL) generally has a favorable prognosis among hematological malignancies even though it is a clinicopathologically unique, aggressive lymphoma.[4] Treatment landscape of Pediatric HL has undergone a steady change over the years

especially pertaining to advances in the imaging modalities and better knowledge about the long term complications of the treatment. The current goal of treatment is to maintain a balance between minimizing exposure to both chemotherapy and radiation therapy and choosing appropriate chemotherapy regimens so that long-term effects are negligible. Like most centers in India, we use doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) based therapy since it can be administered on day care basis, economical, and does not require frequent monitoring of blood counts, all of which are important in a resource-challenged setting. This study was conducted to observe the epidemiological profile and outcomes of Hodgkin's Lymphoma at our center.

METHODS

Bhubaneswar Borooah cancer Institute (BBCI) during the period January 2012 to December 2019 were included in the study.

Inclusion and exclusion criteria

Inclusion criteria for the study was all patients from 0 to 18 years of age group presenting with histpathologically confirmed Hodgkins lymphoma who had received treatment. Exclusion criteria was defaulting prior to the commencement of treatment.

Since this hospital-based study is retrospective in nature and the patient numbers are limited, all children who have received treatment has been included in the study. Information was gathered from Hospital Based Cancer Registry, Pediatric Oncology database and individual patient records. Clinical parameters assessed included age, sex, locality, occupation, presenting complaints, performance status, sites of lymph node involved, treatment modality and response to treatment. Patient received chemotherapy with Adriamycin (Doxorubicin), Bleomycin, Vinblastine, Dacarbazine (ABVD), according to their staging and risk stratification based on computerised tomography (CT) scan of neck, thorax, abdomen and pelvis and bone marrow biopsy since positron emission tomography and computed tomography (PET-CT) was not routinely available. Follow-up protocol in our institution was 3 monthly evaluations for first 2 years followed by 6 monthly till 5 years after treatment and then yearly there after till 7 years. Response assessment was based on RECIST criteria 1.1. Socioeconomic status was designated based on Kuppuswamy scale. Staging is done as per Ann Arbor staging and performance status (PS) as per ECOG, risk stratification as per. Toxicity was assessed in accordance with common toxicity criteria (CTC) version 5.0. Statistical analysis was performed using statistical package for the social sciences (SPSS) version 20.0. When a patient was lost to follow-up, the time of most recent follow-up examination was used. Qualitative data were presented as n (%), while quantitative data were presented as mean±standard deviation (SD). The rates among the categorical variables between two groups were analyzed with Chi-square and Fisher's exact tests. To compare the quantitative variables which were normally distributed, Student's t test was used; however for the comparison of the ordinal variables and the quantitative variables which were not normally distributed, Mann Whitney-U test was used. The analyses of the survival was made with Kaplan-Meier method. Statistical significance value was p=0.05.

RESULTS

A total of 64 patients with confirmed diagnosis of HL were registered in lymphoma joint clinic at our centre from January 2012 to December 2019. The mean age was 12.68±4.71 years. The number of boys were higher; 84.4%, N=54 than girls, 15.6% (N=10).

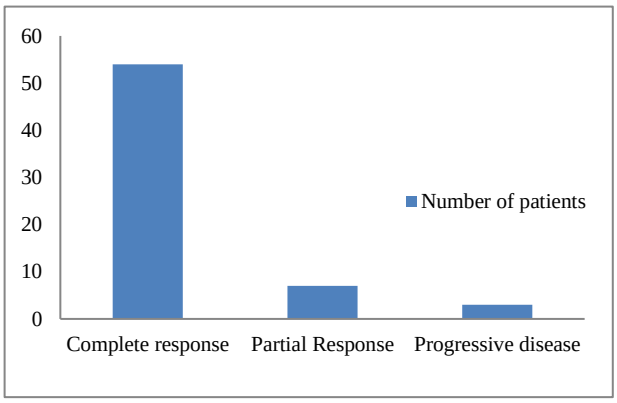

Figure 1: Response rates post ABVD chemotherapy.

Table 1: Baseline characteristics.

Demographic or clinical characteristic	N (%)
Age (years)	
≤5	8 (12.5)
6-9	13 (20.3)
≥10	43 (67.2)
Area	
Rural	54 (91.7)
Urban	10 (8.3)
Religion	
Hindu	37 (57.8)
Muslim	26 (40.6)
Christian	1 (1.6)
B symptoms	
Yes	22 (34.38)
No	42 (65.62)
Stage	
I	11 (17.2)
II	20(31.3)
III	18 (28.1)
IV	15 (23.4)
Histology	
Mixed cellularity	32 (31.3)
Nodular sclerosis	21 (20.3)
Lymphocyte rich	11 (7.8)

Out of 64 patients, 54 patients (84.4%) belonged to rural areas and 10 patients (15.6%) belonged to urban areas. Majority of the patients were Hindus (N=37, 57.8%), followed in numbers by Muslims (N=26, 40.6%), and 1 Christian (1.6%).

Table 2: Response rates among the two arms.

Stage	Response rates			
	CR N (%)	PR N (%)	PD N (%)	Total
I	11 (100)	-	-	11
II	19 (95)	-	1 (5)	20
III	11 (62)	6 (33)	1 (5)	18
IV	8 (53)	4 (27)	3 (20)	15

Mean age of presentation is 12.68±4.71 months. The majority of patients belonged to lower (33.89%) and lower middle class (28.81%) income category. Twelve patients were from upper lower class and ten patients from upper middle-class background. Thirty (46.85%) patients presented with Eastern cooperative oncology group- performance status (ECOG- PS)-0. Thirty-two (50%) patients had ECOG-PS 1 and 2 patients have ECOG-PS 3. In our study, most of the patients are in stage II and stage III comprising 34.4% and 28.1% respectively. Most common histological subtype was nodular sclerosis (30%). Main symptom at presentation was cervical swelling (90%) followed by abdominal lymphadenopathy (50%). B symptoms were observed in 26 (40%) patients at presentation. Children with early stage disease accounted for 44% while 23% children were diagnosed with metastatic disease at presentation.

Table 3: Toxicities of chemotherapy.

Variable	Treatment-induced toxicity			
	I	II	III	IV
Hematologic toxicity	-	-	-	-
Anemia	12	9	2	-
Neutropenia	3	3	5	13
Thrombocytopenia	9	1	4	2
Neutropenic fever	-	-	8	-
Gastrointestinal toxicity	-	-	-	-
Nausea	1	-	-	-
Stomatitis	3	-	-	-
Esophagitis	-	-	-	-
Pulmonary toxicity	-	-	-	-
Cough	-	-	-	-
Dyspnea	-	-	-	-

In the present study, 82.81% of patients with HL achieved complete clinical and radiological response after chemotherapy with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) with or without radiation therapy (RT). Partial response was documented in 17.19% of children, achieved with 4 cycles of ABVD chemotherapy.

Hematological toxicities such as neutropenia and anemia were observed in fifteen patients (20.31%). Eight (12.5%) patients experienced episodes of febrile neutropenia. Grade 4 hematological toxicities were noted in 5(7.8%) patients. No other toxicities were noted (Table 3). Majority of the patients (80%) had complete response (CR), and 8 children (12.5%) had partial response (PR) while 5 children (7.8%) had progressive disease (PD). Non-significantly better CR was observed in male than female patients (81.48% vs 70%). Patients with limited risk disease had 93.5% complete response whereas in intermediate and Advanced stage disease, complete response were observed in 73.24% and 60% patients respectively (Table 2).

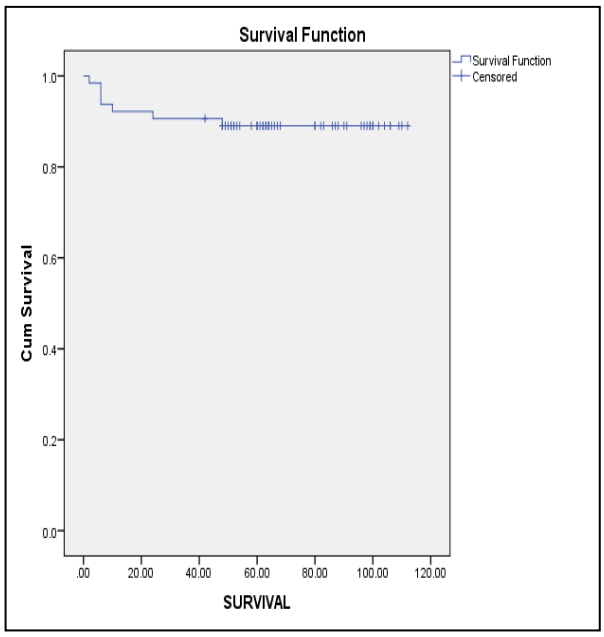

Figure 2: Overall survival in Hodgkins lymphoma.

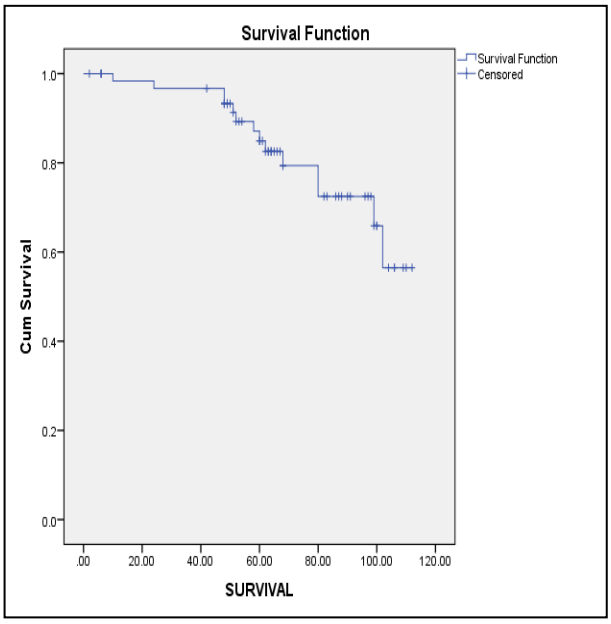

Figure 3: Event free survival in Hodgkins lymphoma.

Survival

The 4-year median overall survival was 90.6% (Figure 2). The OS rates in patients without and with B symptoms were 96% and 87%, respectively. This difference was not statistically significant (p=0.211). The 4-year OS in early-stage disease was statistically higher (97%) as compared to 82% in late-stage disease (p=0.05). Four-year overall survival in stage I, II, III, IV were 100%, 95%, 89% and 80% respectively. The 4-year EFS was 78.1% (Figure 3) in overall population with 90% in early and 67% in advanced stages (p=0.02).

DISCUSSION

The primary objective of our retrospective study was to estimate the incidence, demographic profile and overall response rates with other secondary objectives such as complete response rate, compliance rate and toxicity assessment. Most cases (85%) in this study were >5 years of age and 15% cases below 5 years. Reports from other developing countries also reported 15% to 30% of cases occurring before 5 years of age, against 5% in developed countries.[5-8] In our study the mean age was 12.68±4.71 years. Similar findings have been reported by a study conducted in Malaysian population.[9] A bimodal age-specific incidence pattern with a relatively high proportion of cases in adolescents and young adults is commonly observed in Western industrialized countries.[10] Male predominance in HL was reported by many authors in developing and developed countries.[11-13] In a study reported from India, 21% of all Hodgkin's disease was seen in the pediatric age groups at the Tata Memorial Center from 1975 to 1982, with male:female ratio of 5.5:1.[4]

In our study, out of 59 patients, 49 patients (89.05%) belonged to rural areas and 10 patients (16.95%) to urban areas. The majority of patients belonged to lower (33.89%) and lower middle class (28.81%) income category. In the published literatures, lower socioeconomic status (SES) is independently associated with shorter survival in Hodgkin's Lymphoma patients. Potential underlying mechanisms associated with the impact of SES are delayed diagnosis and poorer education. Educational and socio-economic support interventions must be tested in this vulnerable population.[14] In our study, 27 (45.76%) patients were ECOG-PS 0. ECOG-PS 1 is reported in 28 (47.46%) patients and 4 patients have ECOG-PS 3. Majority of patients presented with stage I and stage II (24.56% and 50.87% respectively). Advanced stages (Stage III and IV) were present in 10.5% and 14.1% of patients respectively. Limited risk patients were 44% and advanced risk patient reported were 23%. Published studies have reported different data on stages. In one study, 52.1% presented with stage II disease and the rest (46.8%) presented with stage III and IV disease.[9] In another study majority (64.7%) presented in advanced stage (Stage III and IV) disease.[15] In a study from Tata Memorial Hospital, Mumbai reported 54% of the patients in stages I and II of which 20% had B symptoms. Remaining 46% of patients presented in stages III and IV with B symptoms in 67%.[4] In studies from United States and Europe, 60 to 70% of the patients had early-stage disease (stage I and IIA), while advanced-stage disease is more common among patients from developing countries.[16-19] Jain et al reported stage IV disease in 37% patients (N=46) with B symptoms in 75% of the study population. International prognostic score (IPS) ≤4 was seen in 95/112 (85%) patients in their study.[20] In developing countries lack of awareness may lead to a delay in diagnosis when the patient notices lymph node masses. Moreover, some patients choose to seek complementary and alternative medicine before seeing a physician and this further delays the diagnosis. Secondly, FNAC is never sufficient for a new HL diagnosis and may delay a definite diagnosis. In our study approximately 75% patients presented with early stages (Stage I and Stage II) which in compliance with data reported from western studies, however higher than developing countries such as India.[19] The higher number of patients in early stages in our study might be due to awareness, early diagnosis and availability of tertiary care. However these associative factors need to be proven by conducting prospective studies and high sampled studies. In our study, 26 (44%) out of 59 patients reported B symptoms. In different published literature B symptoms were observed in 57% to 75% of patients.[14,19,21,25] The higher rate of advanced stage and B-symptoms in these studies may be due to delayed diagnoses and late referral of HL cases from primary health care centers. However, these are tertiary centers, and referral bias for such complicated and complex cases should be taken into account. Lower B symptoms in our study might be due to early reporting and early stage disease. Most common toxicity reported in our study was fatigue (23.81%). Fever was observed in four patients (19.04%). Hematological toxicities such as neutropenia and anemia were observed in four patients (19.04%) each. In the literature, Bleomycin pulmonary toxicity was observed in 10% of the patients and febrile neutropenia in 9% of the patients.[17]

In the present study, 82.22% of patients with Hodgkin's lymphoma achieved complete response after successive treatment with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) with or without radiation therapy and 17.78% partial response. Patient with limited risk disease had 100% complete radiological response. Complete response (CR) were observed in 73.24% cases with intermediate risk and 60% with advanced stage disease. Similar findings were observed in some other studies in literature. In a Malaysian study, among the 92 patients evaluated after front-line treatment, 70 (76.1%) achieved CR and 15 (16.3%) had partial response (PR) , the CR rates for early and advanced disease being 84.2% and 70.4% respectively.[9] In another study, the complete response rate was seen in 76% (96/125).[20] In our study, there was no significant association between type of response (partial or complete) with age, gender, systemic symptoms (p>0.05); however, a significant association was seen in treatment response across the risk groups (p<0.05). Limited risk patients had reported higher complete response rate

compared to intermediate and advanced risk group. Smaller sample size needs to be considered when interpreting clinical importance. Other studies also reported similar CR like 91%, 73.65%, 76.1% at completion of initial therapy.[9,19-21] The outcomes were comparable with studies published in developed countries for early-stage disease (early favorable and unfavorable), but inferior for advanced-stage disease.[22-25] The CR rates with ABVD regimen reported in the literature range from 68% to 92%, the largest of which is the U.S intergroup trial wherein CR rate was 76% and progressive disease was seen in 2.1% children.[21,23,26,27]

Limited risk group children in our study have achieved statistically higher complete response rates (p value=0.001), again in accordance with various other reported literatures. A retrospective analysis from Tata Memorial Hospital, Mumbai reported that on univariate and multivariate analysis, International prognostic score or IPS (>4), age (>45 years), and end of therapy response (failure to achieve complete response) adversely affected the response rates, whereas only PS >4 showed negative impact on the response rates.[20] In literature, age, extranodal disease, advanced stage and high-risk IPS are described as significant prognostic factors.[9.17,20] Multi-agent chemotherapy was the mainstay of treatment. Local radiation to the site of disease was given to 3 patients, deviating from protocol, because of poor response. General treatment strategy in HL typically uses combination chemotherapy, followed by low-dose RT to lymph node regions as indicated. ABVD therapy was the backbone of therapy for Hodgkins lymphoma. Combined therapy trials have shown excellent results, with EFS of 75% to 100% depending upon the stage of the disease, in North American, European, and South American studies.[28-32] Contemporary chemotherapy-only trials have used alternating non–cross-resistant regimens. The results from various cancer groups demonstrate treatment outcomes similar to those achieved with combined modality therapy with an EFS of 75% to 80% and an OS of 80% to 96%(28–32). We have used ABVD regimen and has OS and EFS rates of 91% and 78.1%, respectively, at 4 years. Despite advances in therapy, 10% to 20% of children eventually relapse. Cases of relapse were documented in 14 (22%) patients. Most of the relapses occurred in patients with advanced-stage disease (78%). Treatment modalities in low-income countries have to be tailored to the resources of the local health teams. Protocols have to be easily adaptable as low-income countries do not have all the facilities available in the developed world. We have achieved an OS and EFS comparable to those of developed nations using chemotherapy alone in our setup.

Limitations

Limitations of current study were; in the present PET guided era, therapy for HL is risk adapted. During the trial period, PET/CT was not available at our centre. Hence risk adapted therapy, the current standard of care couldn't be delivered to the children. Further subgroup analysis couldn't be performed due to the limited sample size. We are on our way with the data collection with the follow up study rectifying our limitations and giving the risk adapted therapy to our children.

CONCLUSION

This study provides insight to incidence, demographic profile, overall response rates, progression free survival and overall survival with other secondary objectives such as complete response rate and toxicity assessment among children with Hodgkin lymphoma belonging to Northeastern India. The age and male preponderance reported by our study is found to be in compliance with the studies reported in western world and form India. Secondary to retrospective nature of study and small sample size, we could not find the association of lower socioeconomic status SES with shorter survival in Hodgkin Lymphoma patients. Lower B symptoms in our study might be due to early reporting and early-stage disease. In our study, there was no significant association between type of response (partial or complete), age, gender, systemic symptoms. However, a significant association was seen in treatment response across the risk groups. The complete remission rate reported by our study is similar as reported by the literature. The survival patterns in our centre were equivalent to those in published literature.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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