Treating Hodgkin's Lymphoma in a Resource Poor Setting: Challenges and Outcome

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Abstract Objectives: To assess the problems encountered in managing children with Hodgkin's Lymphoma (HL) in a resource poor Indian setting and to describe the clinical profile and outcome of these children. Materials and Methods: Case records of 184 previously untreated children (age 0-18yr) diagnosed to have HL at our centre between 1994 and 2012 were reviewed. The clinical characteristics, treatments offered and outcomes of these children were analyzed. Results: There were 162 boys and 22 girls with a median age of 8yrs. Sixty two percent children came from rural areas and 60% children were malnourished. Median duration of symptoms prior to treatment was 12 months (range 1-96 months). Eighty two percent children had advanced disease (Stage IIB-IV) at presentation. Abandonment rates were high (20%) and 12% children died during treatment. Treatment related complications were seen in a large number of patients and there was a high incidence of acquiring Hepatitis B and C during the treatment course. The 5-year overall survival and event-free survival rates were 79.4% and 53.1%, respectively. Conclusions: Children with HL coming to our centre tend to have a delayed presentation with advanced disease. Abandonment rates are high and a large proportion of patients experience complications during treatment. But despite these challenges, reasonably good outcomes were attained using simple chemotherapy protocols.

Keywords Hodgkin's Lymphoma, Outcome, Challenges, Complications

1. Introduction

In India, Hodgkin's Lymphoma (HL) is the fourth most common malignancy after acute lymphoblastic leukemia, brain tumors and retinoblastoma [1]. The outcome for children with HL has vastly improved over the last 3-4 decades in resource rich countries. Even the well-established oncology centers in India have reported outcomes comparable to the resource rich countries. However, there is

lack of data on the survival and complications in children with HL treated in resource poor settings. The state of Uttar Pradesh with a population of 220 million does not have a dedicated pediatric oncology centre and many of the patients cannot afford to travel to other states for their treatment. The pediatric hematology-oncology unit was started in the Department of Pediatrics at King George's Medical University, Lucknow, Uttar Pradesh in 1994 with the intent to provide treatment to pediatric cancer patients in this region.

In the present paper we describe the clinical profile and outcome of children with HL treated at our centre. We also describe the complications encountered during and after treatment in these children.

2. Patients and Methods

Study design

This was a retrospective observational study carried out in the Pediatric hematology-oncology unit of our department.

Patients

Previously untreated children with age less than 15yrs at the time of diagnosis with histologically proven HL, between January 1994 to December 2012 were included in the study.

Staging and Diagnostic evaluation

Demographic parameters including age, sex, residence (rural/urban), duration of illness, and clinical symptoms were recorded. Physical finding records included groups of involved lymph nodes, presence of liver and spleen enlargement, anemia, and nutritional status. Laboratory investigations included blood counts, liver function tests (LFT), kidney function tests (KFT) and LDH. Ann Arbor classification scheme was followed for staging [2]. CT scans of the neck, thorax, abdomen and pelvis were obtained for staging whenever possible. When CT could not be done, X-ray chest and ultrasound abdomen were obtained. Bone marrow biopsy was done to look for bone marrow involvement. Histopathological classification was

established according to Rye criteria [3]. All the patients were screened for HIV, hepatitis B and hepatitis C by HIV ELISA, HbsAg and Anti HCV respectively before starting treatment.

Treatment Protocol

Multiagent chemotherapy was the prime modality of treatment at our center. Table 1 summarizes the various treatment protocols used at our center. Radiotherapy was reserved for patients with advanced disease, incomplete responders or relapsed disease. Patients with early stage HL (stages IA, IB, and IIA) were administered 4-6 cycles of chemotherapy. All others were planned for 6-8 cycles of chemotherapy. No child received stem cell transplantation. Chemotherapy was administered on outpatient's basis in the day care facility.

Response was assessed clinically at each visit and radiologically at the end of planned therapy. Complete response (CR) was defined as complete resolution of disease at all sites clinically and on CT scan. Incomplete response (IR) was defined as decrease in size of lesions by $\geq 50\%$, while increase in size of lesions or appearance of new lesions were labeled as no response (NR).

Table 1. Chemotherapy protocols used at our centre

Protocol	Stage		Total
	Early (Stage IA/IB/IIA)	Advanced (Stage IIB/IIIA/IIIB/IV)	
<i>COPP/ABV</i>	29 (85.4)	96 (64)	125 (67.9)
<i>COPP</i>	3 (8.8)	21 (14)	24 (13.0)
<i>ABVD</i>	1 (2.9)	18 (12)	19 (10.3)
<i>No Treatment</i>	1 (2.9)	15 (10)	16 (8.8)
Total	34 (100)	150 (100)	184 (100)

The numbers in parenthesis indicate percentage.

COPP/ABV: cyclophosphamide 600 mg/m², vincristine 1.5 mg/m²; procarbazine 100 mg/m²; prednisolone 60 mg/m², adriamycin 25 mg/m²; bleomycin 10 mg/m²; vinblastine 6 mg/m². cyclophosphamide and vincristine IV on day 1; adriamycin, bleomycin and vinblastine IV on day 8; procarbazine PO day 1 – day 7; prednisolone PO day 1 – day 14.

COPP: cyclophosphamide 600 mg/m², vincristine 1.5 mg/m²; procarbazine 100 mg/m²; prednisolone 60 mg/m². cyclophosphamide and vincristine IV: days 1 and 8; prednisolone and procarbazine PO x14 d.

ABVD: adriamycin 25 mg/m²; bleomycin 10 mg/m²; dacarbazine 375 mg/m²; vinblastine 6 mg/m². All drugs IV on days 1 and 14.

Follow-up

Patients with complete response were followed monthly for the first 6 months, 3 monthly for the next 1 yr and 6 monthly thereafter. A detailed physical examination was done at each visit. Repeat imaging studies were done when deemed to be necessary. Patients with IR or NR after first-line therapy or those who relapsed were offered second-line chemotherapy $\pm$ radiotherapy.

Statistical Analysis

Overall survival (OS) was defined as time from the start of treatment till last follow-up. Event free survival (EFS) was defined as time from the start of treatment till abandonment,

relapse, progressive disease or death due to any cause. Survival was estimated by the Kaplan–Meier method. Analysis was done using the SPSS version 15 (SPSS Inc. IL)

3. Results

Patient characteristics

From January 1994 to December 2012, 184 children (mean age 8 ± 2.6 yr) with proven HL were registered at the Pediatric Hematology-Oncology Clinic, 162 boys and 22 girls (male to female ratio 7.4:1). Their characteristics are depicted in Table 2. During initial years, 5-8 patients were treated every year. However, from 2005 onwards, when the treatment became highly subsidized at our center, the number of patients increased to 15-20/year.

Sixty percent (111/184) patients were malnourished and 52 % (96/184) were stunted. The median duration of symptoms prior to hospital admission was 12 months (1mo-96mo). Cervical lymphadenopathy was the most common presenting feature (seen in 86% cases). Seventy nine percent (146/184) patients had B symptoms. Advanced disease (stage IIB - IV) was present in 81.7% (150/184) cases. A total of 35 patients (19.1%) had bulky disease at presentation. Splenic involvement, mediastinal mass and bone marrow involvement were present in 41.8%, 16.2%, and 1.6% cases respectively. Mixed cellularity was the most common histological subtype (61/160), followed by nodular sclerosis (52/160).

Table 2. Clinical and laboratory characteristics of patients with Hodgkin's lymphoma (n=184)

Parameter	Number (%)
Age	
<5yr	15 (8.2)
5-10yr	136 (73.9)
>10yr	33 (17.9)
Clinical Stage	
I	24 (13)
II	34 (18.5)
III	99 (53.8)
IV	27 (14.7)
B symptoms	146 (79.3)
Bulky disease	35 (19.1)
Hb level	
<10.5g/dl	122 (66.2)
>10.5g/dl	62 (33.8)
LDH (n=143)	
>460 U/L	107 (74.8)
Albumin (n=96)	
≤ 4 g/dl	66 (68.7)
>4 g/dl	30 (31.3)
Histopathology (n=160) ^a	
Mixed Cellularity	61 (38.1)
Nodular Sclerosis	52 (32.5)
Lymphocyte Predominant	22 (13.7)
Lymphocyte Depletion	3 (1.9)
Nodular Lymphocyte Predominant	2 (1.2)
Not specified	20 (12.5)

^a Twenty four cases were excluded because of lack of adequate tissue

Figure 1. Flow diagram showing outcome of children with Hodgkin's lymphoma

Treatment

Response to first-line treatment: Out of the total 184 patients, first-line treatment could be completed in only 126 (36 abandoned and 22 died during first-line treatment) (Figure 1). Fifty-five percent (104/184) patients achieved CR, 11% (20/184) patients had IR and 1% (2/184) patients had NR. Of the 36 abandonments, there was upfront refusal for treatment in 16 patients, while the remaining 20 abandoned before completion of the first-line treatment. Of the 22 patients who died during first-line treatment, 11 died due to chemotherapy related immune-suppression, 9 due to advanced disease, 1 due to Procarbazine toxicity, and 1 unrelated death due to CNS Tuberculosis.

Second-line treatment and treatment after relapse: Twenty-two patients who did not achieve CR with 1st line treatment were given 2nd line treatment. Twelve of these patients were also given radiotherapy. Twenty-one patients achieved CR with 2nd line therapy, and the remaining one patient died due to advanced disease during the 2nd line

treatment. Out of the total 125 remissions (104 CR after 1st line and 21 after 2nd line treatment), 18 patients relapsed after a median duration of 24 months (range 6-130 months). Of these 18 relapses, 14 received second-line treatment and 9 achieved second CR. The remaining 5 five patients died due to treatment failure.

Survival: The OS and EFS were estimated for all 184 patients. With a median follow-up duration of 24.5 months, the projected OS at 5 years of the entire group was 79.4 % (standard error (SE) 3.6%) and the EFS 53.1% (SE 4.3%) (Figure 2). The 5yr OS in early stage disease was 90.1% (SE 5.4%) while that in advanced stage disease was 77% (SE 4.1%) (P=0.204). The EFS rates in early and advanced stage disease were 70.7% (SE 8.4%) and 49.6% (SE 4.7%) respectively (P=0.128). There was no significant difference in the OS of patients with (77.6%) or without B symptoms (85.8%) (P=0.505). Presence of a Bulky disease also did not adversely affect the OS (OS in patients with Bulky disease 76.5%, without Bulky disease 80.4%).

Figure 2. Overall Survival and Event Free Survival in Hodgkin's lymphoma

Complications

Complications during first-line treatment: Treatment related complications were seen in 77 patients with 12 deaths (11 died due to chemotherapy related immune-suppression, and 1 due to procarbazine toxicity). The commonly encountered complications during the first-line treatment included febrile episodes, jaundice / deranged liver function tests, anemia, and neutropenia (Table 3). Thirty nine patients acquired Hepatitis B, seven Hepatitis C, and two Parvo B19 virus infection during their treatment. Of the 126 patients who completed the first-line treatment, 36 (28.6%) had chemotherapy delays of ≥ 7 days (Median delay 17 days, Range 7-60 days).

Table 3. Complications during management of Hodgkin's lymphoma

Complications during treatment (n=148)	Number (%)
No complication	57 (38)
Febrile episode (requiring hospitalization)	33 (22)
Jaundice	39 (26)
Anemia	20 (13)
Hepatitis B infection	39 (26)
Hepatitis C infection	7 (5)
Parvo virus B19 infection	2 (1.3)
Procarbazine toxicity	1 (0.6)
Mania	1 (0.6)
Chemotherapy delay (n=126)	
No delay	90 (71)
Delay	36 (29)
Reason for delay	
Febrile Neutropenia	7 (6)
Deranged LFT	25 (20)
Social	4 (3)
Long term complications (n=73)	
Hepatitis B infection*	19 (26)
Hepatitis C infection#	22 (30)
Hypothyroidism	5 (7)
Azoospermia	2 (3)
Psychosis	1 (1)

*HbsAg or HBV DNA PCR positivity

HCV RNA PCR positivity

Long term complications: Long term follow up (more than 5 years) data is available for 73 patients. Among these 73, 22 cases are positive for Hepatitis C (HCV RNA PCR), 19 are positive for Hepatitis B (HbsAg or HBV DNA PCR), 5 have hypothyroidism, 2 have azoospermia and 1 has developed psychosis. None of the survivors has developed second malignancy so far.

4. Discussion

HL cases in developed and developing countries display differences regarding their clinical, epidemiological and pathological characteristics. The present study describes the epidemiological and clinical features and outcome of children with HL from a centre with limited facilities using chemotherapy and very rarely radiotherapy. It also highlights the challenges we faced in managing these children.

The mean age at presentation in our study group was 8 years, which is similar to that found in countries with sub-optimal socioeconomic conditions (8–9 years), and lower than developed countries (12–15 years) [4–9]. The male to female ratio in our study was 7.3:1. This striking male preponderance has been reported from all over India with ratios ranging from 6:1 to 10.5:1 [7,10]. The exact reason for this striking preponderance is still not known, but it may be partly related to the poor health care access for females, reflecting the cultural disinterest in the female child. The median duration of symptoms of 12 months, before these children were admitted to our center indicates a significant delay on the part of patients before seeking medical opinion as well as referral delay on the part of primary care physicians. In fact, in India there is a tendency to treat any lymphnode enlargement empirically with anti-tubercular drugs and many of our patients had taken anti-tubercular drugs before coming to our center. This delay in referral and diagnosis probably accounts for the fact that

most of our patients (81.7%) had advanced disease at presentation, an observation made by other Indian researchers as well [11-13].

Contemporary treatment strategies in HL typically use chemotherapy, followed by low-dose radiotherapy (RT) to lymph node regions. Combined therapy trials have shown excellent results, with EFS of 75% to 100%. But, because of the issues around availability as well as adverse effects of RT, some recent studies, especially from developing countries have assessed the role of 'chemotherapy only' protocols in management of HL. The results of these studies have been encouraging with OS ranging from 80-92% and EFS 77-87% [7,12,14]. In the present study, multiagent chemotherapy was the mainstay of treatment, and contrary to the usual practice of giving RT to all initial sites of bulky disease, we reserved RT only for children who did not achieve complete response after the first line treatment. The difference in 5-year OS between patients with and without bulky disease was not significant. This provided evidence for our practice of omitting RT to all initially bulky sites. Omission of RT is particularly useful in younger children as it avoids long-term sequelae such as premature epiphyseal fusion, and secondary solid tumors in radiation fields.

We were able to achieve a 5yr OS of 79% and a 5yr EFS of 53%. A poor EFS in our series is partly attributable to the high abandonment rate of 20%. We also experienced a higher death rate of 12% during the first line treatment. Fifty percent of these deaths were due to infections caused by chemotherapy related immune suppression. A possible reason for this finding is that most of our patients were malnourished and were from poor socio-economic status, thus at risk of recurrent infections, which is also evident from the fact that 22% of our patients experienced febrile episodes requiring hospitalization. Another interesting observation in the present study was that 29% patients had chemotherapy treatment delays. Treatment delay results in reduced dose intensity, a factor critical in the outcome. Studies have suggested that even minor delays in treatment could adversely impact the survival by compromising chemotherapy dose intensity [13,15].

An important complication encountered in our cohort was Hepatitis, which also led to chemotherapy delays in 20% children. There was a high incidence of acquiring Hepatitis B and C. These viruses were acquired by transfusions of blood and blood products, or due to direct exposure to HBV or HCV carriers in the hospital [16]. While some of these children were detected during the chemotherapy phase itself, others (especially Hepatitis C) could be detected only in their follow-up period. Acute HCV is commonly asymptomatic and often results in chronic disease. However, symptoms related to chronic disease may not appear for years. Hence, it is important that a high index of suspicion be maintained and all cancer survivors (especially those treated before the introduction of blood donor screening tests for HCV) be screened for HCV infection in follow up [17,18]. The incidence of Hepatitis B and C in our patients have decreased significantly in the last 3 yrs, since the introduction of mandatory nucleic acid amplification testing (NAAT) of

blood products for HBV, HCV and HIV in our blood bank and routine pre-chemotherapy HBV vaccination in all children. This decrease in the incidence of hepatitis has also been partly brought down by increased stress on universal precautions and safe injection techniques.

The present study is a retrospective analysis and thus carries inherent problems like selection bias. But, what this paper reflects is that, reasonably good outcomes can be attained using simple protocols even in centers with limited facilities. Treatment modalities in these settings should be tailored to the available local resources in order to achieve maximum benefit while minimizing the adverse effects. Outcomes at these centers can be further improved by efforts to ensure early diagnosis of childhood cancer and efforts to reduce abandonment rates. Spreading knowledge regarding the diagnosis and treatment of pediatric cancers through workshops, scientific meetings and public awareness campaigns will help in reducing the patient and physician related delay. Moreover, dedicated social workers should be available in all pediatric cancer units in order to ensure proper support and counseling for the family. This would help in reducing the abandonment rates.

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