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Research Article

Pediatric Hodgkin Lymphoma; Experience with Euronet Pediatric Hodgkin Lymphoma Protocol in a Developing Country

Tariq Ghafoor[1,2*], Raheel Iftikhar[1], Imtenan Sharif[1], Tanveer Ashraf[2], Shakeel Ahmed[2], Farrah Bashir[2]

[1]Armed Forces Bone Marrow Transplant Centre, Pakistan
[2]Department of Paediatric Oncology, Pakistan

***Corresponding author:** Tariq Ghafoor, Paediatric Oncologist and Bone Marrow Transplant Specialist, Armed Forces Bone Marrow Transplant Centre, CMH Medical Complex, Rawalpindi, Pakistan

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Abstract

Objective: To analyse outcome of Paediatric Hodgkin Lymphoma (HL) patients treated with Euronet Paediatric Hodgkin Lymphoma treatment protocol in a developing country.

Patients and Methods: This is a prospective study conducted at Paediatric Oncology department at Combined Military Hospital (CMH) Rawalpindi, Pakistan. All newly diagnosed cases of HL, less than 18years registered from January 2012 onwards that completed their treatment until 30th June 2018 were included. Data regarding age, sex, staging, histopathology and outcome were analysed.

Results: Total 102 patients including 80 (78.4%) males and 22 (21.6%) females were analysed. The mean age was 7.54±2.77 years. B symptoms were present in 58 (56.9%) patients. Ten (9.8%) patients had stage I disease, 33 (32.4%) stage II, 41 (40.2%) stage III and 18 (17.6%) stage IV disease. Mixed cellularity was the commonest histological subtype seen in 74 (72.5%) patients. Involved field radiotherapy was given to 17 (16.7%) patients having inadequate response after 2 cycles of OEPA chemotherapy. Eight (7.8%) patients died of treatment related complications and 10 (9.8%) patients relapsed. Nine of the relapsed (90%) cases responded to 2nd line treatment including one requiring autologous stem cell transplant. One relapsed patient died of progressive disease. Overall Survival (OS) and Event Free Survival (EFS) was 91.2% and 82.4% respectively.

Conclusion: In Pakistan, mixed cellularity is the commonest HL subtype seen in young males. Long duration of disease before presentation, malnutrition, presence of B symptoms, bone marrow and lungs involvement and advanced disease is associated with decreased OS and EFS.

Keywords: Hodgkin lymphoma; Treatment outcome; Developing country; Pakistan; Euronet PHL protocol

Introduction

Treatment of Paediatric Hodgkin Lymphoma (PHL) is one of the important success stories of the previous century. Treatment protocols of PHL have evolved over many years with a consideration of reduction of acute and long-term toxicity of chemotherapy and radiotherapy. Initial treatment protocols incorporated unacceptably high radiation doses for children.

In the study GPOH-HD 95, radiotherapy was restricted to patients not in complete remission after chemotherapy [1]. Current treatment protocols are based upon a risk-based and response-adapted approach in which patients receive multi-agent chemotherapy with or without low-dose involved-field or involved-site radiation therapy [2].

Most European centres are following protocols formulated by European Network for Paediatric Hodgkin Lymphoma (EuroNet-PHL) while the Paediatric Oncology Group and Children's Cancer Group have merged to form the Children's Oncology Group (COG), widely practised in North and South America. In developed countries, the 5-year survival rate of PHL increased from 81% to more than 95% between 1975 and 2010 [3]. However, survival in developing countries is still significantly lower, because of late presentation, abandonment of therapy and inadequate supportive and critical care [4-6]. Data of few published studies from Pakistan shows overall survival ranging from 76% to 84% [7]. There is no uniform protocol for treatment of PHL in Pakistan. We conducted this study using treatment as per The EuroNet-PHL-C1 protocol.

Materials and Methods

This is a prospective on-going study being carried out in the department of Paediatric Oncology at Combined Military Hospital Rawalpindi, Pakistan. The hospital ethical committee approved the study and informed consent was obtained from parents of the patients. Data collection was started in January 2012. All newly diagnosed patients with histologically confirmed primary diagnosis of classical HL, less than 18 years of age were included in the study. Patients having prior chemotherapy or radiotherapy for other malignancies, pre-treatment of HL, (except for 7-10 days steroid pre-phase of a

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Table 1: Patient characteristics.

	Number (n)	Percentage (%)
Total number	102	100
Age		
5-Jan	24	23.5
>5-10	60	58.8
>10-15	18	17.6
Sex		
Male	80	78.4
Female	22	21.6
Nutrition Status		
Well-nourished	76	74.5
Under-nourished	26	25.5
Duration of symptoms	Mean 8.97 ± 8.65 months	
	Median 6 months	
	(Range; 1-48 months)	
Presentation		
Cervical Lymphadenopathy	85	83.3
Abdominal Lymphadenopathy	6	6.3
Mediastinal Lymphadenopathy	44	43.1
Type B symptoms	58	56.9
Visceromegaly	24	25
B Symptoms		
Yes	58	56.3
No	44	43.1
Fever	57	55.9
Weight loss	27	26.5
Sweating	32	31
Histological subtype		
Mixed cellularity	74	72.5
Nodular sclerosis	23	22.5
Lymphocyte depletion	2	2
Unspecified	3	3
Immunohistochemistry		
CD 30 positive	91	89.2
CD 15 positive	50	49
Stage		
I	10	9.8
II	33	32.4
III	41	40.2
IV	18	17.6
Bone marrow involvement	8	7.8
Lungs involvement	13	12.7
Liver involvement	4	3.9
Spleen involvement	24	23.5
Radiotherapy administered	17	16.7
Treatment group		
1	21	20.6
2	37	36.3
3	44	43.1
Outcome		
Overall survival	93	91.2
Event free survival	84	82.4

large mediastinal tumor), diagnosis of lymphocyte-predominant Hodgkin's lymphoma, post-transplant Hodgkin lymphoma and patients abandoning the treatment, were excluded from the study.

Detailed medical history, clinical examination, excision biopsy of the involved lymph node for histopathology and immunohistochemistry, echocardiography, LDH, ESR and baseline chemistry was performed for all patients. All the patients were weighed at the time of admission before start of the chemotherapy. The weight was recorded in kilograms and plotted on the standard WHO Z-score chart for age and sex. The patients were categorized as No Malnutrition, Moderate Malnutrition and Severe Malnutrition if they had Z score >-2, between ≤-2 to >-3 and ≤-3 respectively.

The disease was classified as per World health organization 2008 classification of HL. For staging purpose, Contrast Enhanced Computed Tomography (CECT) of neck, chest, abdomen, pelvis was done in all cases. Bulky disease was considered when the lymph node was 7 cm or more in size on CT, or when the mediastinal mass occupied more than one-third of the chest diameter. Because of limited availability, Positron Emission Tomography (PET) scanning was done in few cases. All patients with a stage >IIA had bilateral bone marrow aspiration and trephine biopsy. Ann Arbor staging with Cotswolds modification was used for staging purpose.

Eligible patients received chemotherapy as per EURONET-PHL protocol 2006 and were stratified into three Treatment Groups (TG). TG-1: patients of stages IA/B & IIA without bulk and without ESR ≥30 mm/hr, TG-2: patients of stages IEA/B, IIEA, IIB or III A and patients of stages IA/B and IIA with bulk and/or ≥30 mm/hr and TG-3: patients of stages IIEB, IIIEA/B, IIIB or IVA/B. All patients received 2 cycles of OEPA (Vincristine, Etoposide, Prednisolone, and Adriamycin) chemotherapy. Patients in TG-1 had no further chemotherapy while patients in TG-2 and TG-3 had two and four courses of COPDAC (Cyclophosphamide, Vincristine, Prednisolone, Dacarbazine) chemotherapy respectively. After two courses of OEPA chemotherapy response assessment was done with CECT scan or PET scan.

Patients with Inadequate Response (IR) received involved field radiotherapy after the end of chemotherapy. Radiotherapy dose was 19.8 Gy to all initially involved fields. Those patients with a poor response (less than 75% reduction of tumor volume in some areas or a residual mass of more than 100 ml) received another 10 Gy boost to these regions. Patients were followed up three monthly in first 2 years, four monthly in third year and six monthly in fourth and fifth year after achieving remission. Patients having relapsed or refractory disease had 2nd line chemotherapy; ABVD (Doxorubicin, Bleomycin, Vinblastine and Dacarbazine) and IEP (Ifosfamide, Etoposide and

Table 2: Patient outcome (n=102).

Stage	I	II	III	IV	Total
Relapse / refractory	1 (10%)	3 (9.1%)	5 (12.2%)	1 (5.6%)	10 (7.8%)
Expired	0 (0%)	3 (9.1%)	2 (5.0%)	4 (22.2%)	9 (8.8%)
TRM		3 (9.1%)	2 (5.0%)	3 (16.7%)	8 (7.8%)
With disease progression		0 (0%)	0 (0%)	1 (5.6%)	1 (1%)
Event free survival	9 (90%)	27 (81.8%)	34 (82.9%)	14 (77.8%)	84 (82.4%)
Overall survival	10 (100%)	30 (90.9%)	39 (95.1%)	14 (77.8%)	93 (91.2%)
Total	10	33	41	18	102

Table 3: Comparison of current study with others studies of PHL.

Author/ Study	Country	Year	N	Chemotherapy	IFRT	EFS (%)	OS (%)
Present study	Pakistan	2017	96	OEPA and COPDAC	19.8 Gy 10 Gy boost	82.4	91.2
Faizan et al [7]	Pakistan	2016	50	OEPA and COPDAC	19.8 Gy 10 Gy boost	84	92
Fadoo et al [13]	Pakistan	2010	17	COPP and ABVD	Dose not mentioned	94	94
Faizan et al [7]	UK	2016	50	OEPA and COPDAC	19.8 Gy 10 Gy boost	92	100
Arya et al [14]	India	2006	148	COPP and ABVD	20-25 Gy	87.9	91.5
Trehan et al [9]	India	2013	207	MOPP, COPP and ABVD	Dose not mentioned	77.7	92.7
Bhethanabhotla et al [12]	India	2017		ABVD	25 Gy (to bulky site)	84.8	95.3
Sherief et al [8]	Egypt	2015	59	ABVD	21-35 Gy	84.7	96.6
Geel et al [19]	South Africa	2017	294	ABVD, COPP OPPA/OEPA ChlVPP	14-44 Gy		79
Castellanos et al [10]	Central America	2014	216	COPP, ABV	No	71	
Zubizarreta et al [20]	Argentina	2017	165	ABVD	25 Gy	84	95

Prednisone) chemotherapy.

Supportive care

All patients were hospitalized for the initiation of chemotherapy. Subsequent chemotherapy was given as inpatient or in day care as outdoor cases. Outdoor cases were admitted immediately in case of fever or any other problem. Patients not admitted in the hospital were reviewed at least twice weekly in outdoor clinics. No prophylactic antimicrobials and colony stimulating factors were used during neutropenic period. However, all cases of febrile neutropenia were treated as inpatient with broad-spectrum intravenous antibiotics. Fever was defined as a single oral temperature of >38˚C or 2 readings >37.5˚C at least 2 hours apart. Neutropenia was defined as Absolute Neutrophil Count (ANC) of < 1000 cells per microliter. Febrile patients with ANC < 1000 were treated with a combination of Pipracillin-Tazobactam and Amikacin. Vancomycin or Teicoplanin were added if central venous line infection was suspected. Pipracillin-tazobactam was swapped with Meropenam if fever continued after 48 hours. Amphotericin B was added empirically if fever continued beyond 96hours.

Blood and blood products transfusion was given on regular basis. Haemoglobin transfusion threshold was 8.0g/dL. Thresholds for Platelet transfusion were $10x10^9$/L for asymptomatic patients, and 20x109/L for febrile patients.

Statistical analysis

Survival analyses were performed using the Kaplan-Meier method in SPSS 22. Chi-square test was applied and frequencies and percentages calculated. Relapse-Free Survival (RFS) was defined as the time from completion of treatment until progression of disease or relapse (RFS). Overall Survival (OS) was defined as the time from the date of diagnosis till last follow-up or death from any cause (OS). Log rank tests were used to compare survival differences. $P \leq 0.05$ was considered statistically significant.

Results

During the study period, total 102 new patients of Hodgkin lymphoma were enrolled in the Paediatric oncology department at Combined Military Hospital Rawalpindi. Age at diagnosis ranged from 2.5 to 15 years and the mean and median age was 7.54 (± 2.77) years and 7.0 years respectively. Majority of cases, 60 (58.8%) were between 5 and 10 years of age. There were 80 (78.4%) males and 22 (21.6%) females. There were 76 (74.5%) well-nourished and 26 (25.5%) under-nourished children. The mean duration between symptom onset and consultation of oncologist was 8.97 ± 8.65 months (range from 1.0 to 48 months. Cervical lymphadenopathy was the

most common presentation seen in 85 (83.3%) cases. Twenty (19.6%) patients received anti-tuberculosis treatment for variable duration before being referred to pediatric oncologist. Mixed cellularity was the most common histological subtype seen in 74 (72.5%) cases followed by nodular sclerosis in 23 (22.5%) cases. Immunohistochemistry demonstrated CD 30 positivity in 91 (89.2%) patients and CD 15 positivity in 50 (49%) patients. Demographic characteristics of the study group are summarized in (Table 1).

Ten (9.8%) patients had stage I disease, 33 (32.4%) had stage II, 41 (40.2%) had stage III and 18 (17.6%) had stage IV disease. Constitutional B-symptoms were present in 58 (56.9%) patients. Bulky disease was seen in 42 (41.2%) cases. Bone marrow aspiration and trephine biopsy was done in patients having >II A disease. Out of 75/102 (73.5%) patients having bone marrow examination only 8/102 (7.8%) had bone marrow involvement. Two patients had evidence of Haemophagocytic Lympho Histiocytosis (HLH) on bone marrow examination. Lung involvement was seen in 13 (12.7%) patients. Liver and spleen involvement was documented in 4 (3.9%) and 24 (23.5%) cases. Fine Needle Aspiration Cytology (FNAC) was performed in 29 (28.4%) cases having lymphadenopathy. However, only three cases were diagnosed as Hodgkin Lymphoma on FNAC, making only 10% specificity of this procedure.

Response and Disease Outcome

Patients were divided into three Treatment Groups (TG) as per protocol; 21 (20.6%) patients were in TG-1, 37 (36.3 %) in TG-2 and 44 (43.1%) in TG-3. Tumor response assessment was done after two cycles of OEPA chemotherapy. Eight patients (8.3%) expired before response assessment. Out of the remaining 94 patients adequate and inadequate response was documented in 73/94 (77.6%) and 21 (22.3%) cases respectively. Involved Field Radiotherapy (IFRT) was administered to patients having inadequate response. However, four patients did not get IFRT and are still in remission.

Out of 10 patients having stage I disease, only one patient relapsed and was rescued with second line chemotherapy. Event Free Survival (EFS) and Overall Survival (OS) was 90% and 100% respectively in stage I disease. Out of 33 patients having stage II disease, three patients died of treatment related complications and three patients relapsed and were rescued with second line chemotherapy. EFS and OS was 81.8% and 90.9% respectively in stage II disease. Out of 41 patients having stage III disease, two patients died of treatment related complications and five patients relapsed and were rescued with second line chemotherapy. EFS and OS was 82.9% and 95.1% respectively in stage III disease. Out of 18 patients having stage IV disease, three patients died of treatment related complications and one patient relapsed. The relapsed case did not respond to second line chemotherapy and expired of progressive disease. EFS and OS was 77.8 % in stage IV disease.

Out of total 102 patients in our cohort 10 patients relapsed and 9/10 were rescued with 2nd line chemotherapy. One relapsed patient required autologous stem cell transplant after ABVD & IEP chemotherapy and one relapsed patient died of progressive disease. Eight patients (7.8%) died of treatment related complications. Median follow-up time of our study was 1021.11 ± 677.43 days, ranging from 22 to 2488 days from end of treatment. At the time of analysis EFS and OS and was 84 (82.4%) and 93 (91.2%) respectively (Table 2).

Table 4: Results of statistical tests of association between OS and EFS and study variables in Hodgkin Lymphoma patients.

Variable	OS		EFS	
	Log Rank	*P*	*Log Rank*	*P*
Reporting time to oncologist	17.21	0	10.46	0
Anti-tuberculosis treatment	16.24	0	13.78	0
B Symptoms	4.165	0.04	4.115	0.04
Bone Marrow involvement	10.43	0	9.23	0
Lungs involvement	10.5	0	9.162	0
Histological Subtype	48.93	0	30.36	0
Nutritional Status	5.726	0.06	4.001	0.14
Stage of disease	6.114	0.11	5.758	0.12
Treatment Group (TG)	2.449	0.29	2.283	0.32

Febrile neutropenia was the most common complication seen in 38/94 (40%) and 28/94 (29.8%) cases in 1st and 2nd OEPA chemotherapy courses. No episode of febrile neutropenia was documented during COPDAC chemotherapy. Mucositis was seen in 12/94 (12.8%) and 8/94 (8.5%) cases in 1st and 2nd OEPA chemotherapy courses. Vincristine induced peripheral neuropathy was seen in two (2%) cases and improved after reducing the dose of vincristine. Total 8 (7.8%) died due to treatment related complications. Neutropenic sepsis was the main cause of death seen in 5/8 (62.5%) cases. Treatment Related Mortality (TRM) was 17.6 % in stage IV disease.

Presence of B symptoms, bone marrow involvement, duration of symptoms before start of treatment has statistically significant difference in OS and EFS of pediatric HL in the study. Age and sex were not statistically associated with outcome. (Table 3 and Figures 1-4).

Discussion

Hodgkin Lymphoma (HL) accounts for 5% to 6% of all childhood cancer [8]. There is no pediatric oncology registry in Pakistan and exact number of pediatric malignant disorders is not known. However, in the present study, HL patients were 6.8% of total new cases making it in accordance with the international data.

There is substantial variation in epidemiological, clinical, and pathological features of PHL, according to various geographic areas. Patients in developing countries tend to present at a younger age as compared with the western world where the mean age of presentation is between 12 and 15 years [4,9,10]. In the present study, the mean age of diagnosis was 7.5 years and the majority of cases (58.8%) were between 5 and 10 years of age. Other studies report similar age of diagnosis from developing countries in Asia and Africa, indicating the association of HL with Epstein-Barr Virus (EBV) infection in these countries [4,7-11]. Many authors have reported male predominance in HL [4,6,8,12]. In our study, male to female ratio was 3:6:1. Similar male to female ratio is reported from another study from Pakistan [7]. The reason for this male predominance is not clearly understood. One reason may be gender discrimination still prevalent in many developing countries.

Patients were referred to pediatric oncologist very late. The mean reporting time to pediatric oncologist was 8.97 ± 8.65 months. This

delayed presentation was associated with statistically significant difference in EFS and OS. This can be due to the fact that delayed presentation leads to more advanced stage. Because tuberculosis is very common in Pakistan and children presenting with fever, weight loss and cervical lymphadenopathy are suspected to have tuberculosis. In the present study, cervical lymphadenopathy was seen in 85 (83.3%) cases and B symptoms were present in 58 (56.3%) cases. Twenty (19.6%) patients received anti-tuberculosis treatment for variable duration before reporting to paediatric oncologist. Faizan et al [7] have also documented use of anti-tuberculosis treatment for several weeks before initiating investigations for lymphoma.

In the present study, the most common histological subtype was mixed cellularity. Faizan et al, [7] reported that 64 % children had MC in their study. Other studies from developing countries have reported similar results [4,7-9,13,14]. The earlier presentation of MC subtype of HL in young males in low-income countries is associated with high prevalence of EBV infection, overcrowding and malnutrition [4,6,7,13].

In the present study, majority of patients (about 58%) had advanced stage (Stage III and IV) disease. Similar pattern of advanced disease is reported by other authors from low-income countries, most likely due to delay in diagnosis and referral to oncologists [7-9,14]. Contrary to this, in the western world, most of the newly diagnosed patients have early stage (stage I-II) disease [8].

Over the last three decades, treatment protocols for PHL have been modified with an aim to reduce radiotherapy and modify chemotherapy to achieve high cure rates with minimal toxicity and long-term side effects [1,15-18]. There is no uniform treatment protocol for HL in Pakistan and other developing countries. In the present study, EURONET-PHL protocol 2006 was used for treatment. The patients were stratified into three Treatment Groups (TG). The patients in TG 1 and 2 having low stage disease showed better overall survival as compare to children with advanced disease. In the present study, the 5-years OS and EFS was 91.2% and 82.4% respectively. Faizan et al [7] from Pakistan used same treatment protocol and reported very similar 5-years OS and EFS as 92 % and 84 % respectively. Other studies from developing countries reported similar results [7-10,12-14,19, 20]. (Summarized in Table 3).

In the present study, eight patients died, resulting in Treatment Related Mortality (TRM) of 7.8%. Neutropenic sepsis was the leading cause of death in five cases. Other causes included respiratory failure due to bilateral lung involvement in one case, hepatic failure due to disease involvement in one case and sudden death at home in one case. Presence of B symptoms, delayed presentation to pediatric oncologist, bone marrow involvement at the time of diagnosis and histological subtype had statistically significant impact on overall survival. Nutritional status also had impact on survival though it was not statistically significant. Survival was 94.7% in children having normal nutritional status and it decreased to 75% in children suffering from severe malnutrition (log rank p=0.057). Other studies have also documented increased TRM and inferior EFS in malnourished children [6,21,22]. Delay in start of treatment for HL also had statistically significant impact on OS and EFS. OS decreased from 95.5% to 61.5% (log rank p=0.000) in children presenting before and after one year from onset of symptoms. A delay in diagnosis especially in the presence of B symptoms results in worsening of the nutritional status of the children due to decreased caloric intake because of loss of appetite and increased basal metabolic rate secondary to fever and infection. Delay in diagnosis also leads to bone marrow involvement, which is also a bad prognostic factor. Please see (Table 4) for Results of Statistical Tests of Association between OS and EFS and Study Variables.

Conclusion

The present study has documented that young males having cervical lymphadenopathy with B symptoms is the common presentation of PHL in Pakistan. Mixed cellularity is the most common subtype of PHL. Long duration of disease before presentation, malnutrition, presence of B symptoms, bone marrow and lungs involvement and advanced disease is associated with decreased OS and EFS.

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