ORIGINAL ARTICLE

Comparison of Presentation and Outcome in 100 Pediatric Hodgkin Lymphoma Patients Treated at Children Hospital, Lahore, Pakistan and Royal Marsden Hospital, UK

Mahwish Faizan[1], Mary M. Taj[2], Saadia Anwar[3], Nyla Asghar[3], Alia Ahmad[3], Donna Lancaster[2], Ayad Atra[2] and Agha Shabbir Ali[4]

ABSTRACT

Objective: To compare differences in demographics and outcomes in childhood Hodgkin lymphoma (HL) presenting at the Children's Hospital Lahore (CHL), and Royal Marsden Hospital (RMH), UK.

Study Design: An observational comparative study.

Place and Duration of Study: From January 2011 to February 2012 at CH, Lahore and from October 2008 to February 2012 at RMH, UK.

Methodology: Consecutive HL patients (50 from each hospital) were inducted. Data regarding age, gender, staging, histopathology and outcome were analysed. Clinical and pathological staging done according to Ann-Arbor and World Health Organization classification. Treatment duration was 6-8 months. They were followed for 6 months post-treatment. Frequencies of variables were noted and compared. Chi-square test was used for determining significance.

Results: Patients from Children's Hospital, Lahore were younger (mean 7.9 years) with male predominance (n=42, 84%). Histopathology showed Mixed Cellularity (MC) in 32 (64%), Nodular Sclerosis (NS) in 5 (10%), Lymphocyte Rich in 4 (8%) and lymphocyte depleted in 1 (2%), nodular lymphocyte predominant (NLP) in 1 (2%) each. Majority presented in stage IV (n=25,50%), or stage III (n=20,40%). Constitutional B symptoms were present in 37 (74%). Bone marrow involvement observed in 23 (46%). Remission was achieved in 42 (84%) patients; 2 (4%) relapsed, 4 (8%) expired and 2 (4%) left against medical advice. In contrast, RMH patients were older (mean 11.8 years.) and 30 (60%) were males. NS (n=40,80%) and NLP (n=6,12%) types were predominant. Two (4%) patients were in stage I, 27 (54%) in stage II, 12 (24%) in stage III and 9 (18%) presented in stage IV. Fourteen (28%) had B-symptoms. None had bone marrow disease. Event free survival was 46 (92%). Four (8%) patients relapsed. Three responded to second line therapy and one relapsed postautologous transplant.

Conclusion: Significant differences were observed in age at presentation, stage, histopathology and extent of bone marrow involvement between the groups. Of interest is the bone marrow involvement in stage IV patients in Pakistan. Delayed diagnosis account for advanced stage but difference in pathological subtype needs further study.

Key Words: *Childhood. Hodgkin lymphoma. Pakistan. Mixed cellularity. Nodular sclerosis. UK.*

INTRODUCTION

Hodgkin's lymphoma (HL) is a common and curable malignancy. For children and adolescents, 5-year survival rate has increased from 81 to 94% between 1975 and 2002.[1] The most common treatment is combination chemotherapy[2], and radiotherapy. The focus now is on developing strategies to minimise long-term side effects of treatment. HL is the third most common malignancy in developed nations.[3] However, data from developing countries indicate that HL is the second commonest malignancy after acute leukemia.[4,5] It usually shows a bimodal age distribution,[6,7] which is not seen in the data from the developing nations.[8]

In Pakistan, small studies and anecdotal data indicate that HL patients have different features from those seen in the developed world. To address this, a retrospective study was conducted to compare differences in age at presentation, stage, histopathology and outcome between Children's Hospital, Lahore (CHL), Pakistan and Royal Marsden Hospital (RMH), London, UK.

METHODOLOGY

Fifty consecutive children each, from January 2011 till February 2012, from The Children's Hospital (CH) and Institute of Child Health (ICH), Lahore, Pakistan, and

[1] *Department of Paediatric Haematology/Oncology and Bone Marrow Transplant, Birmingham Children Hospital, Steel House Lane, B4 6NH Birmingham, UK.*

[2] *Department of Paediatric Oncology, Royal Marsden Hospital, Downs Road, Sutton, London, UK SM2 5PT.*

[3] *Department of Haematology/Oncology, The Children Hospital and ICH, Ferozepur Road, Lahore, Pakistan.*

[4] *Department of Paediatrics, Lahore General Hospital and PGMI, Lahore, Pakistan.*

Correspondence: Dr. Mahwish Faizan, Department of Paediatric Haematology/Oncology and Bone Marrow Transplant, Birmingham Children Hospital, Steel House Lane, B4 6NH Birmingham, UK.
E-mail: mahwishfz@gmail.com

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from October 2008 till February 2012 from Royal Marsden Hospital (RMH), UK, were studied and compared. Treatment duration was 6-8 months, depending on clinical stage. Children were followed-up 6 months post-treatment. Approval was taken from both hospitals, institutional review boards. Children with biopsy proven HL of both gender were included in the study. Children receiving partial treatment at other centres or relapsed HL patients were excluded from the study. The sample size was calculated using the formula n=N/1+N times e^2, where n=sample size, N=total population, and e^2 = error of tolerance.

Data regarding age, gender, staging, histopathology, and outcome were analysed. Staging investigations included chest X-ray, abdominal ultrasound, CT scan, bone marrow aspirates and trephine biopsies. Patients from RMH also had PET scans. Clinical and pathological staging was done according to Ann-Arbor and new World Health Organization classification (WHO-REAL), respectively. Patients were treated according to Euro Net-PHL-C1 protocol. Both groups received 2 cycles of OEPA (Vincristine, Etoposide, Prednisolone, Adriamycin) and 2-4 cycles of COPDAC (Cyclophosphamide, Vincristine, Prednisolone, Dacarbazine) chemotherapy, according to stage. In CHL 19.8 Gy radiotherapy was given to all involved sites with 10 Gy boosters to sites showing inadequate response (< 75% after two cycles of chemotherapy). In RMH, a reassessment CT and PET-CT was done after 2 courses of OEPA. Patients who had less than 50% response on CT and those with inadequate metabolic response on PET were given 19.8 Gy involved field radiotherapy.

All data were entered into SPSS version 20. Chi-square test was applied and frequencies and percentages calculated. P-value < 0.001 was taken as significant with confidence level of 95%.

Table I: Patient characteristics.

	Children Hospital, Lahore (no=50)	Royal Marsden Hospital, London (no=50)	p-value
Age			
1-5 years	11 (22%)	1 (2%)	<0.001
5-10 years	32 (64%)	14 (28%)	
10-15 years	7 (14%)	35 (70%)	
Gender			
Female	8 (16%)	20 (40%)	0.008
Male	42 (84%)	30 (60%)	
Histopathology			
Mixed cellularity	32 (64%)	1 (2%)	<0.001
Nodular sclerosis	05 (10%)	40 (80%)	
Lymphocyte rich	04 (8%)	01(2%)	
Nodular lymphocyte predominant	01 (02%)	06 (12%)	
Lymphocyte depleted	01 (02%)	0	
Unspecified	07(14%)	2 (4%)	
Stage			
I	0	02 (4%)	<0.001
II	4 (8%)	27 (54%)	
III	20 (40%)	12 (24%)	
IV	25 (50%)	09 (18%)	
Unspecified	01(2%)	0	
B-symptoms present Data not available	38 (76%) 04 (08%)	14 (28%) 0	
Bone marrow involvement	23 (46%)	0	
Lung nodules present	02 (4%)	9 (18%)	

Table II: Patient outcome.

	CHL	RMH
Event free survival	42 (84%)	46 (92%)
Relapse / refractory	02 (4%)	04 (8%)
Left against medical advice (LAMA)	02 (4%)	00
Expired	04 (08%)	00
With sepsis	02	
With disease progression	02	
Total	50	50

RESULTS

A total of 100 patients, 50 from each centre, were included. At CH, Lahore, mean age of presentation was 7.9 ±3.56 years (median=7 years). There was male predominance 42 (84%). Majority of the patients (n=32, 64%) were between 5-10 years of age. RMH patients also showed male predominance 30 (60%) but were older with 35 (70%) between 10-15 years of age, mean=11.8 ±4.01, median=11.5 years.

Thirty-two (64%) patients from CH Lahore had mixed cellularity (MC) disease and 5 (10%) had nodular sclerosis (NS) disease. In contrast, 40 (80%) of RMH patients had NS disease, while one (2%) had mixed cellularity disease (Table I, p < 0.005).

Majority of patients from CHL presented in advanced stage as compared to RMH patients (p < 0.005). The number of patients in stage IV was 25 (50%) and stage III was 20 (40%). Four (8%) were in stage II while none had stage 1 disease. Constitutional B-symptoms were present in 38 (76%) patients. Bone marrow involvement was documented in 23 (46%) patients. Lung involvement was seen in 2 (4%) patients. Royal Marsden Hospital data showed, stage I in 2 (4%), stage II in 27 (54%), stage III in 12 (24%) and stage IV in 9 (18%). Fourteen (28%) patients had B-symptoms. No patient had bone marrow disease. Lung nodules were seen in 9 (18%) patients.

Overall survival was comparable, 42 (84%) and 46 (92%) for CHL and RMH, respectively. Among the CH patients, 2 (4%) relapsed after going into complete remission. Mortality rate of 4 (8%) patients during treatment was high for CH as compared to RMH. Out of these 2 (4%) died of sepsis and 2 (4%) of disease progression with concomitant septicemia in one. Two patients (4%) left against medical advice. At RMH 4 (8%) patients relapsed including one following autologous transplant, while none expired.

DISCUSSION

Hodgkin lymphoma is the most common solid malignancy being referred to CHL. In Western countries, childhood HL is the third most common malignancy after acute leukemia and brain tumours . The reason for this is not entirely clear.

The bimodal age distribution seen in western countries with a first peak at 15 - 35 years and a second peak at more than 50 years of age is not seen in this and other studies from developing countries. A large study from Pakistan that included 658 patients from 1 to 84 years of age also did not show the bimodal age distribution.[9] The earlier onset could be because of poor nutrition, and earlier and more frequent exposure to infectious agents including Ebstein Barr virus which has a proven role in pediatric HL.[3] EBV positivity is more common in children younger than 10 years,[10] compared with adolescents and young adults.[11] EBV is positive in tumour cell in 15 - 25% patients in studies from the western world, implying that the virus may have a causative role in HL.[12,13]

The male:female ratio of 5:1 for patients from developing countries like Pakistan is not clearly understood. One reason may be gender discrimination still prevalent in many developing countries.[8]

In this study, 45 (90%) patients from CHL presented in stage III or IV of disease, while the majority of patients from RMH had stage II or III; a reflection of delayed diagnosis and poor socioeconomic conditions. As the disease primarily presents with cervical lymphadenopathy and tuberculosis is common, some patients are given anti-tuberculous therapy for several weeks before being referred/investigated for lymphoma.

An interesting observation was the significant bone marrow involvement seen in 23 (46%) patients from CHL as compared to none in RMH patients ($p < 0.001$). This difference is also seen in other studies from Pakistan. The incidence of bone marrow involvement in HL generally shows considerable variability according to pathologic subtype. Predominance of MC histology may be one explanation for this high percentage, but needs further studies.

Mixed cellularity was the predominant histological subtype in patients from CHL, which is also in studies from other developing countries.[15,16] The majority of patients from RMH had nodular sclerosis HL, which is also the experience of other centres in the developed world.[17,18] The rationale for this could be that EBV is very common in the developing countries and occurs at an earlier age. It combined with other social and environmental conditions like malnutrition and infections affecting immunity may be the reason why it is common in younger children and mixed cellularity in type.

The overall survival is comparable in the two groups using OEPA based chemotherapy. Deaths due to sepsis at CHL were low 2 (4%), although significant when compared with none at RMH. A significant contributor to sepsis is lower socioeconomic conditions, poor hygiene and lack of education, especially in people from rural areas. A large study conducted in Turkey over 34-year period showed how improved socioeconomic conditions changed the disease behaviour.[19] Survival can be increased by improving patient access to cancer centres, manpower training, and use of standard protocols.[20]

CONCLUSION

Patients with HL vary markedly in the two cohorts, in terms of age, histological type and stage at presentation. Delayed diagnosis could account for advanced stage but difference in pathological subtype mixed cellularity v-nodular sclerosis needs to be explored further. While nutrition and infections could play a part, the role of genetics/racial variation cannot be excluded. Of interest is bone marrow involvement, seen only in stage IV patients in Pakistan. Not noted previously is pulmonary involvement, seen in all cases of stage IV disease at RMH and only 2 (4%) patients at Children Hospital Lahore, despite delayed presentation. Further research is required in this regard.

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