SPECIAL REPORT

Retrospective analysis of baseline Prognostic factors on the outcome of Paediatric Hodgkin's Lymphoma in a tertiary care cancer center

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Abstract

Prognostic factors in Hodgkin's Lymphoma has categorized the disease into early stage and advanced stage. The aim of our study was to identify baseline prognostic factors effect on the outcome of Paediatric Hodgkin's Lymphoma patients. A total of 357 patients with newly diagnosed, biopsy proven Hodgkin's lymphoma stage I -IV were included from April 2012 to October 2015 treated with Cyclophosphamide, vincristine ,prednisone, decarbazine (COPDac) and adriamycin, bleomycin, vinblastine, decrabazine (ABVD) chemotherapy alone or with involved field radiotherapy. Erythrocyte sedimentation rate, Haemoglobin and albumin were independent risk factors for advanced stage Hodgkin Lymphoma.

Keywords: Pediatric Hodgkin lymphoma, Prognostic factor, involved field radiotherapy, event free survival, overall survival

Introduction

Paediatric Hodgkin's lymphoma constitutes 5 to 6 % of all the children with cancer.[1] The incidence of Hodgkin's Lymphoma is age related, it is highest among adolescents aged 15 to 19 years (29 cases per 1million per year), with children ages 10 to 14 years, 5 to 9 years, and 0 to 4 years having approximately threefold, eightfold, and 30-fold lower rates, respectively.[2] In developing countries, there is a similar rate in young adults but a much higher incidence in childhood[3] Cure rates approach 80-90%; however, 15-20% of patients have resistance to therapy or relapse after treatment.[4] The exact cause is unknown but patients who are infected with Epstein Barr Virus(EBV), Acquired Immunodeficiency Virus (AIDS) and have immunodeficiency disorders are more prone to acquire the disease. Survival of patients with Hodgkin's lymphoma has markedly improved due to different combination of chemotherapy drugs and low dose involved field radiotherapy.[5] Prognostic factors help to define risk stratified treatment and identify patients at risk for failure. Several prognostic factors had been evaluated which included Gender, Weight, presence of B symptoms (i.e., fevers, drenching night sweats, or significant weight loss of more than 10% in last 6 months), erythrocyte sedimentation rate ,Bulk volume, Albumin, Haemoglobin, Platelet count.[6] By these Prognostic factors Hodgkin Lymphoma is categorized into early stage and advanced stage disease. In recent trials, patients with favourable prognostic factors have been candidates for evaluating combined modality therapy with fewer chemotherapy cycles, further reduction in radiation therapy (RT) field doses or even chemotherapy alone.[7,8] The aim of our study was to see the impact of baseline prognostic factors such as Gender, weight, B symptoms, ESR, Bulk Volume, Albumin, Haemoglobin, Platelet count on the outcome of Paediatric Hodgkin Lymphoma.in our institution.

Methodology

A cross-sectional study was conducted in Shaukat Khanum Memorial Cancer Hospital Lahore, Pakistan. Records were reviewed retrospectively for patients with newly diagnosed Hodgkin's Lymphoma on histopathology between April 2012 and October 2015 and age less than 20 years at the time of diagnosis. Data was collected on each patient's age, gender, pathology, B symptoms, stage, and bulk volume, ESR albumin, haemoglobin, staging workup, treatment cycles, reevaluation scans and follow-up. The Institutional Review Board (IRB) approved the study. Each new patient underwent staging F18 FDG PET-CT scan, by which tumour bulk was measured by using software based volumetry. The largest contiguous lymph node mass of more than > 200ml was labeled as bulk volume.[9] B symptoms were defined as at least one of the following systemic symptoms such as inexplicable weight loss of more than 10% within last 6 months, unexplained persisting or recurrent temperature above38^{o}C, and drenching night sweats.[9]

Stage classification was done according to Cotswold's revision of the classical Ann Arbor staging system[9] for

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Table-1: Descriptive statistics with bivariate analysis.

Variables	Characteristics	Frequency n (%)	Early stage 117 (32.8%)	Advance stage 240 (67.2%)	*p*-value
Sex	Male	294 (82.4%)	94 (32.0%)	200 (68.0%)	0.49
	Female	63 (17.6%)	23 (36.5%)	40 (63.5%)	
Weight (kilogram)	0-20	181 (50.7%)	71 (39.2%)	110 (60.8%)	0.03
	21-40	131 (36.7%)	33 (25.2%)	98 (74.8%)	
	Above 40	45 (12.6%)	13 (28.9%)	32 (71.1%)	
B - symptoms	Negative	286 (80.1%)	95 (33.2%)	191 (66.8%)	0.72
	Positive	71 (19.9%)	22 (31.0%)	49 (69.0%)	
Erythrocyte sedimentation rate	Less than 30	161 (45.1%)	81 (50.3%)	80 (49.7%)	0.001
	Above 30	196 (54.9%)	36 (18.4%)	160 (81.6%)	
Radiotherapy	No	303 (84.9%)	112 (37.0%)	191 (63.0%)	0.001
	Yes	54 (15.1%)	5 (9.3%)	49 (90.7%)	
Patients status	Alive	347 (97.2%)	115 (33.1%)	232 (66.9%)	0.51
	Death	10 (2.8%)	2 (20.0%)	8 (80.0%)	
Relapse	No relapse	340 (95.2%)	110 (32.4%)	230 (67.6%)	0.45
	Relapse	17 (4.8%)	7 (41.2%)	10 (58.8%)	
Albumin	Mean ± SD*	3.92 ± 0.81	4.32 ± 0.57	3.72 ± 0.83	0.001
Haemoglobin	Mean ± SD*	10.76 ± 5.74	12.52 ± 9.16	9.91 ± 2.47	0.001
Platelets	Mean ± SD*	389.05 ± 164.45	392.12 ± 143.98	387.55 ± 173.82	0.81

Hodgkin's lymphoma into stage I, II, III, IV. Treatment protocol used at our hospital is institutional, COPDac (cyclophosphamide, vincristine,prednisone, decrabazine)/ABVD(Adriamycin,bleomycin,vinblastine, decarbazine) which is modified version of ChIVVP/ABVD in UKCCSG HODGKIN'S DISEASE PROTOCOL 2000 and involved field radiation.[10] This protocol has been used since 2012 and it was well tolerated with minimum toxicity and excellent outcomes. Patients got 2 cycles each of COPDAc/AVBD and then re-assessment FDG - PET scans were done. Stage IA and IIA were treated as TG1 and given 2 cycles of COPDac/ABVD each followed by re-assessment scans and then discussed in Multi-disciplinary meeting about radiation if there is incomplete metabolic or morphological response. Patient was upstaged to TG2 if ESR > 30mm/Ist hour and bulk volume > 200ml. These patients got one more cycle of COPDac/ABVD each. Stage IV patients were treated as TG3 and received 4 cycles of COPDAC/ABVD alone or with involved field radiotherapy.

Statistical analysis was carried out using the SPSS software (version 20.0; SPSS, Chicago, IL, USA). Percentages (proportion) were used for categorical variables while mean and standard deviation was used for continuous variables. Chi square or Fisher exact test (when necessary) were used for bivariate analysis of categorical variables and independent t-test was used to check the mean difference between continuous variables Table 1. Univariable and multivariable logistic regression model was done to identify the independent risk factors of Hodgkin lymphoma in children. All factors with $p<0.05$ were considered significant independent risk factors causing advanced stage Hodgkin lymphoma. The Kaplan-Meier method was used to estimate survival as a function of time.

Results

A total of 357 patients with Hodgkin's Lymphoma were evaluated at our institution during the study period. The median follow up of cohort was 40 months. All patients were treated with COPDAC/ABVD Protocol. There were four age groups categories. The one to five years patients were 91(25.5%), six to ten years were 168(47 %), eleven to fifteen years were 74(20.7%), and above fifteen years were 24(6.7%). Stage I patients were 19(5 %), stage IB 7(2 %), stage II 74(20.7%), stage IIB 17(4.8%), Stage III

Table-2: Risk Factors.

Variables	Characteristics	Unadjusted OR (CI), *p*-value	Adjusted OR (CI), *p*-value
B - symptoms	Negative	Ref	Ref
	Positive	1.11 (0.63 1.94), 0.72	0.65 (0.34 1.25), 0.20
Erythrocyte sedimentation rate	Less than 30	Ref	Ref
	Above 30	4.50 (2.80 7.24), 0.001	2.40 (1.34 4.27), 0.003
Haemoglobin		0.67 (0.60 0.76), 0.001	0.82 (0.69 0.97), 0.02
Platelets		1.00 (0.99 1.01), 0.80	0.99 (0.99 1.00), 0.05
Albumin		0.27 (0.20 0.41), 0.001	0.47 (0.30 0.82), 0.01

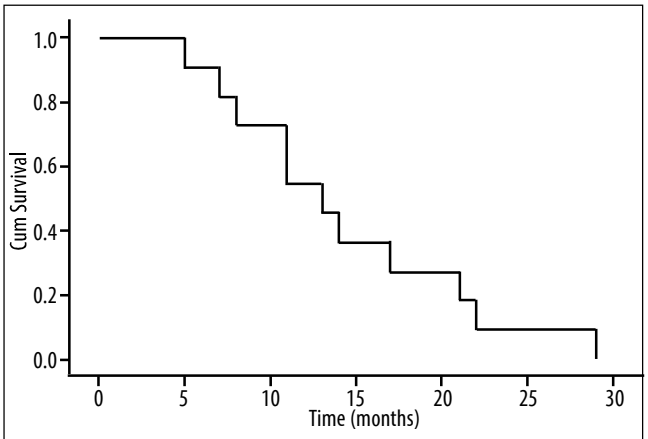

Figure-1: Kaplan-Meier curve displaying the 3-years event free survival of pediatric Hodgkin lymphoma.

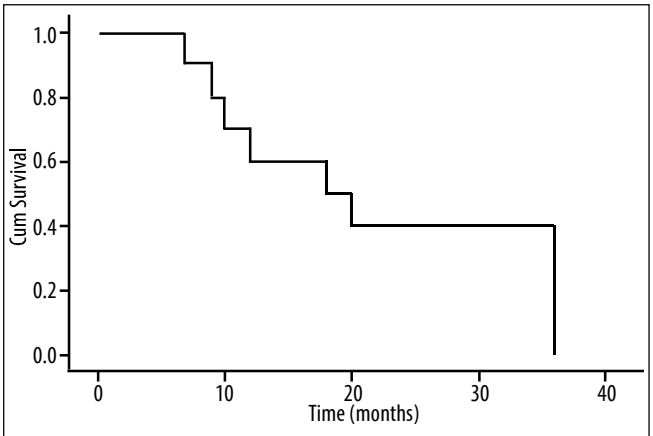

Figure-2: Kaplan-Meier curve displaying the 3-years overall survival of pediatric Hodgkin lymphoma.

137(38.4%), Stage IIIB 11(3.1 %), Stage IV 80(22.4%), Stage IVB 12(3.4%).Males patients were 294(82%) and females were 36(18%).B symptoms were positive in 71(20%) and negative in 286(80%).ESR was more than 30 in 196(55%) and less than 30 in 161(45%) patients.

Early stage disease patients were 117(39%) and advanced disease patients were 240(67%).Three categories of bulk volume, 0-100ml 83(23%), 101-200ml 148(49%), above 200 ml 100(28%).Bone marrow involvement 48(13%), no involvement 297(83%) and bone marrow not done in 12(3.4%).

Radiotherapy was received in 54(15%) and not received in 303(85%).17(4.8%) patients had a relapse. Median event free survival and overall survival were 13±4.48 and 18±6.32 months respectively (Figure 1&2).

In multivariate analysis, three variables were identified as significant independent risk factors for advanced stage Hodgkin's lymphoma: ESR (above 30) (adjusted odds ratio [AOR] 2.40; 95% confidence interval [CI] (1.34 4.27), p-value (0.003), haemoglobin; (AOR 0.82; 95% CI (0.69 0.97), 0.02 and albumin (AOR 0.47; 95% CI (0.30 0.82), 0.01. Furthermore, platelets were marginally significant in multivariable model as shown in Table 2.

Discussion

This study aimed to see the impact of baseline prognostic factors on the outcome of Hodgkin's lymphoma. Hodgkin's lymphoma is further classified into low risk, intermediate risk and high risk by clinical criteria present at diagnosis such as stage of disease, bulk volume and presence of systemic symptoms.[11] Male gender is more commonly affected all around the world, similarly in this study, male population was more than 80%. Malnutrition is a significant problem in developing nations and it is associated with poor outcome in Paediatric malignancies.[12] Patients with body weight less than 20 kilogram had advanced disease.

Exploratory laparotomy with splenectomy, bipedal lymphangiography and systemic bone marrow biopsy have been replaced by the modern imaging techniques CT of the chest, abdomen and pelvis , magnetic resonance imaging, FDG- Positron Emission Tomography (PET).[13] Hodgkin's lymphoma lymph nodes show strong avidity to FDG in 97-100%. In staging workup FDG PET scan has more sensitivity and specificity than CT,MRI, ultrasound, bone scan or bone marrow biopsy.[14] In our study we used FDG -PET scan for baseline staging, to see mid treatment response and was also used as end of treatment scan in those patients who did not achieve complete response after 2 cycles of chemotherapy. Erythrocyte sedimentation rate (ESR), is an acute phase reactant, has prognostic significance in patients with Hodgkin's lymphoma, various studies have different values for baseline ESR being significant.[15] In Euronet PHL ESR more than 30 mm /hr is significant.In our study 80% patients in advanced stage had ESR more than 30mm/hr with a significant p value 0.003.

A study reported that B symptoms are present in 10-25% patients with early stage disease, and up to 70% of patients with advanced stage disease. In our study, it was present in 22% in early stage disease and 49% in advanced stage disease.[4]

Paolo G Gobbi in his study concluded that tumour burden (TB) was an important prognostic factor. The

tumour burden taken in terms of body surface area, is the relative tumour burden (rTB), and is expressed as cm^3/m^2. This study proved that there was a statistically significant difference between relative tumour burden and number of involved sites, disease free survival and overall survival.[13] In contrast to this study, bulk volume was not identified as a risk factor for Hodgkin's lymphoma.

Baseline Haemoglobin level had a great impact on survival of patients as shown by Aynur Oguz, S.J.P Belle.[16,17] Similarly, patients who had a haemoglobin level of 9.91±2.47 had advanced Hodgkin's lymphoma.

Baseline Albumin level is an international prognostic factor and level less than 4 is significant. In our study patients with albumin level less than 4 had advanced disease ($p<0.01$).

Radiotherapy, the main modality of treatment alone or in combination with chemotherapy, has many acute and long term complications. To reduce the risk of secondary malignancies many centers use radiotherapy in low dose in those patients who show partial response to chemotherapy or are refractory to chemotherapy.[5] Similarly in this study only 15% had received radiotherapy and 14% had advanced stage Hodgkin's lymphoma.

In the study conducted by Asim Belgaumi and another by Cindy L. Schwartz, showed that less than 80% patient is with advanced disease had event free survival, in contrast to our study event free survival was 94% for early stage patients and 96% for advanced stage patients.[18,19]

There are certain molecular and genetics biomarkers in paediatric Hodgkin's lymphoma. To Assess their prognostic significance further studies, are required. These prognostics are p53, bcl-2, Ki -67,IL-10/IL-12. Targeted Hodgkin's lymphoma therapy with the antibody-drug conjugate Brentuximab vedotin (Bv) has proven to be superior to conventional salvage chemotherapy and clinical trials are being conducted to incorporate Bv into frontline therapy that substitutes Bv for alkylating agents to minimize secondary malignancies.[20]

Conclusion

Our data illustrated that there was significant impact of baseline prognostic factors such as Erythrocyte sedimentation rate, Haemoglobin and albumin on the survival of patients with Hodgkin's lymphoma. Further prospective trials for emerging biomarkers will be required for risk stratification of patients.

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