Original Article

Treatment Outcome of Childhood Hodgkin Lymphoma after Chemotherapy Alone

Hodgkin Lymphoma

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ABSTRACT

Objective: To find the outcome of Hodgkin lymphoma treatment in children without radiotherapy using chemotherapy as a single treatment modality.

Study Design: Descriptive retrospective study.

Place and Duration of the Study: This study was conducted at the Pediatric Oncology Department, Children's Hospital & Institute of Child Health, Multan from January, 2006 to January, 2014.

Materials and Methods: All newly diagnosed children with Hodgkin lymphoma up to the age of 15 years were included in the study. Diagnosis was made on history, clinical examination and lymph node biopsy for histopathology & immunohistochemical staining. X-Ray chest, CT scan of the abdomen, bone scan and bone marrow biopsy were done for staging the disease. Chemotherapy was given to all children according to UKCCSG (United Kingdom Childhood Cancer Study Group) protocol for treatment of Hodgkin lymphoma. Response to treatment was noted after completion of chemotherapy.

Results: Among 60 children with Hodgkin lymphoma, 55(92%) were male with M: F = 11.5:1.Age range at presentation was 3.5-15 years with mean of 8.5 years. Cervical lymphadenopathy was noted in 52(87%) & mediastinal lymphadenopathy in 8(13%) patients. Stage I, II, III & IV were found in 13(22%), 4(7%), 34(56%) & 9(15%) respectively. Mixed cellularity (MC) was the most common histopathological type, found in 43(72%) patients, followed by nodular sclerosis(NS) in 13(22%) and lymphocyte predominant (LP) in 3(5%).Lymphocyte depleted(LD) type was found in only one patient. On immunohistochemical staining CD30 was positive in all patients. So far, 53 (88%) children have completed their treatment and showed complete response to chemotherapy alone, 4(7%) got relapse & 3(5%) expired during treatment.

Conclusion: Most of the children with Hodgkin lymphoma show complete response to the chemotherapy alone and can be treated without radiotherapy. However more patients and long-term follow up is needed for making definite conclusions.

Key Words: Hodgkin Lymphoma, Lymph Node Biopsy, Immunohistochemical Staining, Chemotherapy.

INTRODUCTION

Treatment for children with Hodgkin lymphoma may involve radiotherapy, chemotherapy or combined modality therapy. High-dose large volume radiotherapy administered to young and prepubescent children is known to result in impairment of soft tissue and bone growth. The growth disturbance is related largely to the age of the child at the time of radiotherapy and the radiation dose administered.[1] The most marked impairment is observed when radiation dose >35 Gy are given to children <13 years old.[2] The risk of Hypothyroidism appears to be related to radiation dose.[3] Among children who receive neck irradiation of < 26 Gy, the incidence of hypothyroidism is only 17%compared with 78% incidence among children who receive dose > 26 Gy.[4] Standard-dose radiotherapy has also been implicated in the development of late thyroid, cardiac, and pulmonary toxicity.[5,6] A major late effect among survivors of pediatric Hodgkin's disease is an increased risk for second malignant tumors, particularly breast cancer or other solid tumors, which commonly occur in previously irradiated fields.[7,8,9,10] Therapeutic trials in adults with Hodgkin's disease have compared outcome between patients treated with chemotherapy alone and those treated with combined-modality Therapy. In some studies, patients treated with combined modality therapy have an event-free survival (EFS) benefit but no increased survival benefit. In other studies, EFS and overall survival (OS) are similar.[11] One pediatric trial that compared chemotherapy with or without radiation for patients with advanced stage Hodgkin's disease indicated no benefit with the addition of radiation. [12] The British experience of radiation alone as a single treatment for stage 1 showed a 92 % overall survival, but 30 % of the children relapsed and required salvage chemotherapy. [13] This rate seems too high considering the results of the similar patients treated by a short chemotherapy course and low dose radiation.[14, 15]

The rationale for most protocols based on chemotherapy alone was always based on the experience of the Olweny et al. [16] in Uganda where radiotherapy machines were not available. On the basis

of these encouraging results, the earliest chemotherapy-alone studies used 6-12 courses of MOPP (nitrogen mustard,oncovin,prednisolone,procarbazine) or MOPP like regimens.[17,18,19] In pediatric and adult experience ,six cycles of MOPP induce male sterility in > 90% of the patients[20] as well as an increased risk of secondary leukemia [21] that were considered unjustifiable. In 1984, Chemotherapy was changed from MOPP to ABVD (Adriamycin , Bleomycin , Vincristine & Dacarbazine) which was reported to be less toxic owing to the lower dosages of alkylating agents [22],but high relapse rate was observed with this regimen[23] Treatment was switched to combination of MOPP and ABVD in all Hodgkin lymphoma cases irrespective of stage or size of the involved lymph nodes ,considering the fact that cure can be achieved using non cross-resistant drugs from onset and because male gonadal dysfunction is reported to be reversible after three MOPP courses[24]

Our study analyzes the results of chemotherapy-alone modality for treatment of Hodgkin lymphoma at the Children's Hospital and the Institute of Child Health, Multan according to UKCCSG protocol for Hodgkin Lymphoma (HD 2000-2002).

MATERIALS AND METHODS

It is a retrospective descriptive study conducted at the Children's Hospital and the Institute of Child Health, Multan from January, 2006 to January, 2014. Sixty newly diagnosed children with Hodgkin Lymphoma up to the age of 15 years were included in the study. Patients with relapsed Hodgkin lymphoma and those who were already given chemotherapy at some other center were excluded from the study. Data was collected from the record of all patients registered for the treatment of Hodgkin lymphoma and age,sex ,clinical presentation & previous drug history specially for anti tuberculosis drugs were noted. Local examination of the involved lymph nodes for site, size & consistency was noted. Abdominal examination for hepatosplenomegaly and chest examination for any signs & symptoms related to mediastinal mass were noted. Lymph node biopsy of the primary site was sent for histopathology & immunohistochemical staining to the histopathologist at Shaukat Khanam Memorial Cancer Hospital & Research Center Lahore.CD 30 staining was done in all patients but CD 15 & CD 20 could not be done due to limited financial resources. X-Ray chest was done in all patients for the detection of any mediastinal mass. CT scan of the neck, chest, abdomen & pelvis, bone scan and bone marrow trephine biopsy were done for staging the disease.

Chemotherapy was given to all children according to UKCCSG protocol for Hodgkin Lymphoma (HD 2000-2002). We used the hybrid regimen with alternating courses of ChlVPP and ABVD to lessen the pulmonary and cardiac toxicity associated with ABVD. ChlVPP regimen consists of Chlorambucil , Vinblastine , Procarbazine & Prednisolone and ABVD consists of Adriamycin , Bleomycin , Vincristine & Dacarbazine .Four to eight courses were given depending upon the stage of the Hodgkin lymphoma. At the end of the treatment, response to chemotherapy was assessed by regression/persistence of the lymph nodes clinically and on CT scan.

Data was analyzed using statistical software SPSS 19.Descriptive statistics were applied to analyze the data. The quantitative variables were calculated by mean and standard deviation and qualitative variables by percentages and frequencies.

RESULTS

Among 60 children with Hodgkin Lymphoma, 55(92%) were male with M: F = 11.5:1.Age range at presentation was 3.5-15 years with mean age of 8.5 years. Most of the patients were referred from different areas of Southern Punjab and remaining belonged to some areas of Baluchistan. Previous history of receiving anti tuberculosis drugs for a duration of 3 - 9 months was noted in 12(20 %) patients. Cervical lymphadenopathy was noted in 52(87%), being the most common site of Hodgkin lymphoma presentation ,axillary in 3(5%) and generalized in 5(8%) patients with a variable duration of 3 months to 3 years**.** Mediastinal lymphadenopathy was noted in 8(13%) children (table 1). Stage I, II, III & IV were found in 13(22%), 4(7%), 34(56%) & 9(15%) respectively (table 2). Among the four known histological types of classical Hodgkin lymphoma; Mixed cellularity (MC) was the most common histopathological type, found in 43(72%) patients, followed by nodular sclerosis(NS) in 13(22%) lymphocyte predominant (LP) in 3(5%) & Lymphocyte depleted(LD) type in only one patient.(Table. 3) .On immunohistochemical staining CD30 was positive in all patients. So far, 53 (88%) children have completed their treatment and showed complete response to chemotherapy, 4(7%) got relapse & were given EPIC regimen (Etoposide, Prednisolone,Ifosfamide,cisplatin). During chemotherapy, 3(5%) patients expired due to herpes encephalitis, tuberculous meningitis and pulmonary aspergillosis. (Table 4).

Table No.I: Clinical characteristics of the patients (n=60)

Clinical Characteristics	Patients
Age	3.5 – 15 Yrs
Mean Age	8.5 Years
Males	55 (92%)
Females	05(08%)
Male: Female	11.5 :0 1
Took ATT	12(20%)
Cervical Lymphadenopathy	52 (87%)
Pallor	42 (70%)
Fever	40 (67%)
Weight Loss	12 (20%)
Mediastinal Mass	08 (13%)

Table No.2: Staging Distribution of Hodgkin Lymphoma (n=60)

Stages	Patients
Stage I	13(22%)
Stage II	04(07%)
Stage III	34(56%)
Stage IV	09(15%)

Table No.3: Histopathological Types of Hodgkin Lymphoma (n=60)

Histopathological Type	Patients
Mixed Celularity	43 (72%)
Nodular Sclerosis	13 (22%)
Lymphocyte Predominant	03(05%)
Lymphocyte Depleted Type	01 (01%)

Table No.4: Outcome

Total Patients	60
Compete Response to treatment	53(88%)
Relapse	04(07%)
Expired	03(05%)

DISCUSSION

Since the introduction of MOPP chemotherapy in addition to extended field radiotherapy, combined therapy has become a standard mode of treatment for Hodgkin lymphoma in most centers [25, 26] The first report on children treated without radiotherapy was from Ziegler et al [27]In 1978, Olweny et al. reported survival rates of 75% and 60% for low and high stage patients respectively.[28] In 1988, Ekert et al, gave disease free survival rates (DFS) of 92% for all stages using chemotherapy only.[29] In 1989, a randomized study showed equal results using chemotherapy with or without radiotherapy [30]

In our study, all patients were enrolled onto a single protocol regardless of the stage and histopathological type of the Hodgkin lymphoma. Chemotherapy alone modality was used with ChlVVP -ABVD regimen for a duration of 4-8 months depending upon the stage of the disease. Majority of the patients i.e. 88% showed complete response to treatment with regression of lymph nodes at the primary site clinically and on CT scan. These results of our study are in concordance with a study conducted in Costa Rica where Lobo-Sanahuja et al. gave results of 86 children treated with chemotherapy alone with DFS rates of 90% and 60% for stage I- IIIA and IIIB- IV, respectively. [31]The reported decrease in DFS in patients with more advanced stage is not seen in our patients. But in our series only a few stage IV patients i.e 09(15%) are included, also the case in many other reports. From a retrospective analysis on several reports, Bader et al. concluded that only stage IVB patients benefit from combined therapy. [32] The data from our patients are in line with mentioned reports.

Although the follow-up for our study is not yet long enough to conclude that survival will be equivalent in our patients to the patients receiving radiotherapy, other studies that have longer follow-up have indicated no survival benefit for post-chemotherapy radiation therapy. [33] Loffler et al. conducted a meta-analysis that included eight trials for patients with Hodgkin's disease in which the randomized study question was chemotherapy with or without additional radiation therapy. Overall, patients who received radiation had an 11% higher rate of continuous complete remission at 10 years (15% higher for patients with stage I to III disease). The advantage was less pronounced for patients with mixed-cellularity Hodgkin's disease, and same response might be expected in our patients as mixed-cellularity was the most common type in our patients i.e. 72%. However, overall survival was better in the chemotherapy-alone arm because of an increased rate of death after relapse and from non–relapse-related causes in patients who received radiation before relapse. In the only other randomized study of radiotherapy versus no further treatment in children with Hodgkin's disease achieving a complete response to initial chemotherapy, Weiner et al [34] treated patients with advanced-stage disease who achieved complete responses to eight cycles of MOPP-ABVD with total nodal radiation or no further therapy. There was no difference in EFS or overall survival at 5 years for patients in the two randomized treatment groups.

Although survival is an excellent measure of outcome, EFS is equally important end point when treating patients with Hodgkin's disease. Although many patients who relapse can be cured, salvage therapy is more toxic and is associated with a high rate of late effects. In a study of survivors of pediatric Hodgkin's disease from Stanford, [35] relapse was the most significant risk factor for the development of a second malignancy. In our study, relapse was observed in 4(7%) patients and these patients were given salvage therapy with EPIC regimen. The follow-up for our study is not yet long enough to conclude about the toxicity and late effects of this salvage therapy. Considering long-term effects, it is known that ABVD courses combined with radiotherapy cause parenchymal lung damage. Gonadal toxicity is lower using ABVD instead of MOPP. [36, 37] The occurrence of secondary malignancies for MOPP or ABVD in combination with radiotherapy is probably similar.[38] The use of hybrid chemotherapy programs that decrease total exposure to alkylating agents, anthracyclines, and bleomycin has decreased, but not eliminated, the incidence of chemotherapy-associated late effects. These observations are in concordance with our study, as we did not found these effects associated with chemotherapy in our patients. Similarly, no

endocrinological dysfunction was noted in our patients during chemotherapy after regular evaluation by endocrinologist of our hospital. This observation may be due to use of hybrid regimen with alternating ChlVVP - ABVD courses, secondly the follow-up for our patients is not yet long enough to conclude about the late effects.

In our study, 3(5%) patients expired during the treatment due to causes other than the disease itself or the chemotherapy. One patient expired due to complicated tuberculos meningitis, other due to pulmonary aspergillosis and third one due to herpes encephalitis. These causes of death are due to increased risk of infections in these children as they are immunocompromised due to disease itself and chemotherapy as well.

CONCLUSION

Chemotherapy alone with ChlVVP – ABVD regimen gives a high cure rate in all children with Hodgkin lymphoma without use of radiotherapy. This treatment modality is effective and safe, however more patients and long-term follow up is needed for making definite conclusions.

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