Outcome of Hodgkin's Disease in Children with Chemotherapy alone in a Resource Limited Country

Rahman Atikur ATM¹, Yasmin F², Begum M³, Ahammed T⁴, Islam A⁵

Abstract:

**Background:** Treatment of Hodgkin's lymphoma involves both chemotherapy and radiotherapy. But radiotherapy in children is associated with risk of development of long term complications like the development of second malignancy. Novel therapeutic strategies with combination chemotherapy without radiotherapy are being used to reduce such complications while maintaining the optimum response. **Objective:** To investigate the outcome of treatment of Hodgkin's lymphoma with combination chemotherapy ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) alone. **Patients and methods:** A quasi-experimental open label clinical study was done on 48 children with Hodgkin's lymphoma in the Paediatric Haematology-Oncology department of Bangabandhu Sheikh Mujib Medical University (BSMMU) with eight cycle ABVD regime on an outpatient basis over a period of 8 months to see the outcome of treatment. **Results:** The mean age of the patients was 10.3 years (range 3-16). There were 42 males and 6 females. Mixed cellularity cHL was the commonest histological subtype observed 20/48 (42%) patients. Forty-two (88%) patients achieved complete response (CR), 5 (10%) had partial response (PR) and one patient did not respond at all. Fifteen patients (31%) are known to be dead and the rest are alive and tumour free. Median EFS and OS were not achieved. The EFS and OS at 5 years were 63% and 67% respectively. **Conclusion:** ABVD combination should be regarded at the present moment as the simplest and most effective drug therapy for treating childhood Hodgkin's disease.

**Keywords:** Hodgkin's disease, Chemotherapy, Children, Resource Limited Country

Introduction

Hodgkin's lymphoma (HL) is a malignant disease of the lymphatic system. HL comprises approximately 11% of all lymphomas in western countries and has a bimodal age distribution, with a first peak in young adults and a second peak around 59 years of age.¹ During the last 20 years the introduction of combined chemotherapy (CT) protocols with or without radiotherapy (RT) improved significantly the outcome of children with HD. The 5-year event-free survival (EFS) in childhood and adolescence exceeds 90% for patients with early stage disease and 70 to 80% for those with advanced stage.² There is an ongoing debate about the use of radiotherapy in children due its association with long term adverse effect, in particular, the development of secondary malignancy. Therefore, novel therapeutic strategies are being designed to reduce these complications.³-⁶ Also in some low-income countries due to the limited availability of RT children with HL are necessarily treated with chemotherapy only.

**Aim and Objective of the Study**

The aim and objective of this study is to assess the outcome of treatment of HL in all stages with combination chemotherapy alone and thus adjust the treatment plan in a resource limited country like Bangladesh.

**Patients and Methods**

This was an open label quasi experimental non-randomized clinical study. Previously untreated patients with HL in children under 16 years of age were registered in this study between January 2004 and December 2010 in the Paediatric Haematology and Oncology department of Bangabandhu Sheikh Mujib Medical University (BSMMU). Demographic and clinical data, histopathological subtypes and stage of the disease were recorded and analysed.
**Treatment Protocol:** Regardless of their stage, all patients received eight 28-day cycles of ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, and dacarbazine) on an outpatient basis over a period of 8 months. Chemotherapy was withheld if leukocyte count was lower than 2.5x10^9/L or neutrophil count lower than 1.0x10^9/L. Complete remission (CR) was defined as the complete regression of clinical and radiological lesions. Partial remission (PR) was defined as the reduction of disease in all sites by at least 50% compared with the initial involvement. Disease progression was defined as increase by 25% or more of at least one measurable lesion, or by the appearance of a new lesion.

**Follow-Up:** After completion of therapy, all patients were asked to attend the follow-up clinic every 3 months during the first year, every 6 months until the fifth year, and then once a year. Thorough clinical examination and ESR test were performed at each visit; chest X-ray as well as CECT of thorax, abdomen, and pelvis was performed every year for the first 5 years. Follow up was updated on 1 August 2014. Return postcards were sent to get information about vital status of patients who had been lost to follow up.

**Statistical Methods:** OS was calculated from diagnosis to death or last visit (censored). Event-free survival (EFS) was calculated from diagnosis to death, progression of the disease, relapse, and second malignancy, whichever came first or last visit (censored). Patients with early LFU were excluded from EFS analysis. OS and EFS were estimated by Kaplan-Meier actuarial survival method. The effect of stage on survival was studied by Kaplan-Meier method and Log rank test was used to see survival difference according to its categories.

**Results**

Patients Characteristics: 48 children with Hodgkin's disease were studied. The mean age was 10.3 years (range 3-16). There were 42 males and 6 females giving a male: female ratio of 7:1. Among the histopathological subtypes, mixed cellularity is the commonest subtype observed in 20 of 48 (42%) patients. Only 5 (10%) patients had lymphocyte predominant type of histology. The largest single stage observed was stage IIIIB. Sixteen of 48 (33%) patients had stage IIIB disease.

**Treatment response:** Forty-two (88%) patients achieved complete response, 5 (10%) had partial response and one patient did not respond at all. The influence of stage on treatment response is shown in Table II. All the early stage patients achieved complete remission. Fourteen of 15 patients with good prognostic histological subtypes (lymphocyte predominant and nodular sclerosis) attained complete response. Among the 42 complete responders, 11 (26%) have so far relapsed. There is no significant difference in the pattern of relapse between the early and late stage disease. One of the early stage patients developed Burkitt's lymphoma after 4 months remission, and died of the same 22 months later. Among the 11 relapsing patients, 6 relapsed within 12 months, and 5 of them are dead and only one is alive and disease free.
gynaecomastia appears to be related to germinal epithelial damage. Other complications occurred were tropical ulcers in 6 cases, haemolytic anaemia and pulmonary tuberculosis in 2 cases each, Pseudomonas septicaemia and peripheral neuropathy in 1 case respectively.

**Survival:** The Event free survival (EFS) and Overall Survival (OS) at 5 years was 63% and 67% respectively. Median OS was not achieved till the last follow up. Three patients (Stages IIA, IIIA, and IVB) were lost after 2, 6 and 20 months of follow-up. Fifteen patients (31%) are known to be dead and the rest are alive and tumour free. Four early stage patients have died: one from Burkitt's lymphoma, another from disseminated herpes simplex and the remaining 2 (both stage IIB) from progressive Hodgkin's disease. All the 11 late stage deaths were due to disease progression and drug resistant to treatment. In addition, 2 patients had pulmonary tuberculosis, 1 developed terminal pseudomonas septicaemia and another had evidence of disseminated intravascular coagulation. Figure 2 shows the life table analysis of survival. Sixty-seven percent of the entire group is currently alive. For the early stage patients 75% are alive and disease free while only 60% of the late stage patients enjoy the same status.

**Table II:** Childhood Hodgkin's lymphoma: Treatment response by stage and histological subtype

<table>
<thead>
<tr>
<th>Stage</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>NR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>4/4 (8.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIA</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IIB</td>
<td>5/5 (10%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIIA</td>
<td>2/2 (4.3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIIB</td>
<td>7/7 (14.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IVA</td>
<td>14/16 (29.2%)</td>
<td>2/16 (4.3%)</td>
<td>0</td>
</tr>
<tr>
<td>IVB</td>
<td>1/1 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>9/13 (18.5%)</td>
<td>3/13 (6.2%)</td>
<td>1/13 (2%)</td>
</tr>
</tbody>
</table>

CR-Complete response, PR-Partial response, NR-No response

**Complications:** The commonest complications were Herpes zosterinfection and gynaecomastia observed in 10 and 9 children respectively. Development of gynaeomastia appears to be related to germinal epithelial damage. Other complications occurred were tropical ulcers in 6 cases, haemolytic anaemia and pulmonary tuberculosis in 2 cases each, Pseudomonas septicaemia and peripheral neuropathy in 1 case respectively.

**Figure 1:** Overall Response of the Patients

**Figure 2:** Life table analysis of survival by stage of children with Hodgkin's disease

**Discussion**

Among the four different subtypes of classical Hodgkin's lymphoma nodular sclerosing subtype are the most common among the children in the western countries, whereas in developing countries MC, known to be more aggressive in adults, is the commonest subtype, accounting for at least 60% of the cases. In our study, 42% had MC subtype, but this did not have any significant adverse impact on survival. The absence of prognostic significance of histology in childhood HD was shown in a study conducted by the United Kingdom Children's Cancer Study Group.
The complete response rate in this study is 88% and 31 of the 42 (74%) complete responders are still enjoying their first remission. All the 18 early stage patients achieved complete responses and 14 (78%) of them have sustained initial remissions, with 10 in excess of 60 months. These results confirm our previous observations of the excellent response in childhood Hodgkin's disease in Bangladesh treated with ABVD chemotherapy alone. This is in similar to the suggestions by earlier investigators of the clinical response to treatment. It has been stated that ABVD treatment in children is known to produce fewer complete responses as compared to MOPP therapy in adults. This is thought to be related to the preponderance of nodular sclerosis which responds less favourably to MOPP than other histologic subtypes. The relatively few cases of nodular sclerosis in the present study may explain the very high rate of observed complete response. The 74% relapse-free individuals in this study compares favourably with the figures of 66% and 52% quoted by others. The median survival of the entire group has not been reached and 67% are still too small to permit any meaningful conclusions to be made. In comparison with other reports the number of children with this complication is probably less than expected. The 100% complete remission as well as the 75% disease free survival for the early stage patients at 7 years raises an important question of whether ABVD chemotherapy should be used for all children with Hodgkin's disease. The results observed in this study are even more impressive if preponderance of poor prognostic histology is taken into consideration.

Conclusion

The treatment of HL has changed over the last several years and continues to evolve. Early-stage HL patients are no longer exposed to extended field radiation, reducing the risk of long term complications. ABVD has been used extensively for more than 20 years and it does not pose a significant risk for leukaemia or infertility compared to prior therapies. The expense involved in accurate staging coupled with the cost of radiotherapy equipment and lack of trained personnel leaves little doubt as to the value of chemotherapy especially in developing countries. ABVD combination should be regarded at the present moment as the simplest and most effective drug therapy for treating childhood Hodgkin's lymphoma for a resource limited country.

References