

## Retrospective analysis of clinical features and treatment outcomes of children with Hodgkin's Lymphoma treated with different chemotherapy protocols at a tertiary care center in Pakistan

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### Abstract

**Purpose:** Hodgkin lymphoma (HL) is one of the most curable paediatric cancers, with long-term survival rates now exceeding 90% after treatment with chemotherapy alone or combined with radiotherapy (RT). Treatment options for Hodgkin's Lymphoma differ among various study groups and there is still no consensus regarding the standard treatment for Hodgkin's lymphoma. Taking into account the impact of treatment-related mortality in low- and middle-income countries we propose to study the the clinical features and treatment outcomes by using different chemotherapy protocols in Hodgkins's Lymphoma children's at Shaukat Khanam hospital Lahore.

**Methods:** Clinical data from a large regional cancer center Pediatrics patients with Hodgkin's Lymphoma from January 2009 till December 2015 was retrospectively collected after Institutional Review Board (IRB) approval.

**Results:** A total of 748 patients were reviewed retrospectively. Mostly (45%) were in 6-10 years age group. Male showed predominance ,male to female ratio was 4:1. B symptoms were present in 51%, bulky disease in 44% and ESR was more than 30mm in 26% of patients. CD 30 was positive in 95%, Bone marrow involved in 13% of patients. Stage I in 8%, stage- II in 27%, stage -III in 39% and stage IV in 26% was seen. COPDac/ABVD was given in 412 patients, CHLVPP/ABVD in 176 patients, OEPA/COPP in 57 patients, OEPA in 35 patients, OEPA/COPDac in 33 Patients and remaining 33 received various chemotherapy protocol combination. XRT was given in 17% of patients. Of these 86% of patients were alive ,5% patients died , 3% patients abandoned, 6% patients relapsed ,3% patients progressed while on chemotherapy. Five years Overall survival was 94% and 5 Years Event free survival was 91%. Minimum haematological and other toxicity was seen in patients who had received COPDac/ABVD when compared to other regimen.

**Conclusion:** Hodgkin's lymphoma patients had good outcome with different chemotherapy regimens, however our experience showed that the COPDac/ABVD regimen was better tolerated with minimum toxicity

**Keywords:** Clinical features, outcomes, Hodgkins lymphoma, over all survival , event free survival, XRT. (JPMA 69: 1266; 2019)

### Introduction

Hodgkin Lymphoma (HL) is one of the most curable paediatric cancers, with long-term survival rates now exceeding 90% and estimated 5-year survival rates exceeding 98%,after treatment with chemotherapy alone or combined with radiotherapy (RT).<sup>1</sup> There is bimodal age distribution with an initial peak for the most part in adolescents and young adults aged 15-34 years of age the second peak occurs in older adults over 55 years of

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age. HL is uncommon in children under 10 years of age and is rarely seen in children less than five years of age, there is slight male overall predominance.<sup>2</sup> The exact cause of HL is unknown various factors including chemicals, drugs and viral agents have been associated. Epstein bar virus is the commonest of all.<sup>2,3</sup> The most common clinical features in the paediatric population include a generalized adenopathy with the frequent association of B symptoms in 30% of patients, consist of the triad of fever, drenching night sweats and unexplained weight loss of greater than or equal to 10%

of body weight and involvement of extra nodal sites such as liver, lung, bone and bone marrow. Bone marrow involvement is seen in approximately 5% of cases.<sup>4,5</sup> Treatment options for Hodgkin's Lymphoma differ among various study groups, and various chemotherapeutic agents with or without radiotherapy have been used and there is still no consensus regarding the standard treatment for Hodgkin's lymphoma. In combination with chemotherapy, Radiotherapy may be employed in reduced doses (from 36-44 Gy to 15-25 Gy), with excellent therapeutic results, to reduce long-term toxicity in children.<sup>16,11</sup> Taking into account the impact of treatment-related mortality in low- and middle-income countries we propose to study the clinical features and treatment outcomes of children with Hodgkin's Lymphoma by using different chemotherapy regimens at tertiary care centre.

## Patients and Methods

Data of 748 Paediatrics patients from single institute, Shaukat Khanum Memorial Cancer Hospital with Hodgkin's lymphoma from January 2009 till December 2015 was retrospectively collected after IRB approval. Data was reviewed for patients with Hodgkin lymphoma on histopathology and age less than 18 years. The UKCCGC Protocol for Hodgkin's Lymphoma HD-2002-02 was used at the hospital since the start of 2007 which included CHLVPP/ ABVD (Chlorambucil, Vincristine, Procarbazine, Prednisolone) / (Adriamycin, Bleomycin, Vinblastin, Dacarbazine).<sup>10,12</sup> The chemotherapy protocol was then switched to OEPA/COPP (Vincristine, Etoposide, Prednisolone, Doxorubicin / Cyclophosphamide, Vincristine, Prednisolone, Procarbazine), OEPA/COPDAC (Vincristine, Etoposide, Prednisolone, Doxorubicin / Cyclophosphamide, Vincristine, Dacarbazine, Prednisolone and OEPA ( Vincristine, Etoposide, Prednisolone, Doxorubicin ) for a short period of time. Since 2012 COPDAC/ABVD has been used, this is the modified version of CHLVPP/ABVD. A few number of patients received various other chemotherapy protocol combinations. Re-assessment was done after 2 cycles of each combination and decision of Radiotherapy was made at that point. Risk stratification was done according to stage, B symptoms, ESR and bulk of >200 ml. Overall survival (OS) and event-free survival (EFS) were estimated by the Kaplan-Meier method and prognostic variables were compared using the log-rank test. OS was

defined as the times from diagnosis to last follow up visit while EFS was calculated as the time from diagnosis to the first event (relapse or death). All p values were 2-sided. A univariate analysis was utilized to evaluate for predictors of EFS.

Data of 748 patients was collected. Demographic features, clinical characteristics, and different treatment protocols and outcome were analyzed. The Institutional Review Board (IRB) approved the study.

All patients underwent Staging Computerized tomography scan (CT) or Positron emission tomography ( PET/CT) scan, Ct was done in 425 patients and PET in 323 patients. Complete blood count, bone marrow exam and ESR levels to determine extent of disease. The Ann Arbor Staging Classification was used to classify the extent of disease.<sup>11,13</sup>

## Results

A total of 748 patients were reviewed retrospectively by using hospital information system. Out of all 161 (21%) were in 1-5 years age group, 336 (45%) in 6-10 years age, 170 (23%) in 11-15 years age and 81 (11%) in >15 years age group. Male showed predominance with a total of 603 (81%) males and 149 (19%) females. B symptoms were present in 384 (51%), of patients and absent in 364 (49%). Bulky disease was present in 331 (44%) and absent in 417 (56%) of patients. ESR >30mm was present in 243 (26%) and <30 in 191 (25%) of patients. ESR was not done in 314 (42%) of patients.

Excisional biopsy was done to confirm histopathologic diagnosis, CD30 was positive in 713 (95%) and negative in 11 (1.5%) of patients. CD 15 was positive in 325 (44%) and negative in 170 (23%) of patients. Mixed cellularity in 83% of patients, Nodular sclerosis in 15% and Lymphocyte predominant in 2% of patients was seen. Bone marrow was positive in 98 (13%) of patients. Stage -I was seen in 57 (8%), stage -II in 209 (27%), stage -III in 290 (39%) and stage IV in 192 (26%) of patients was seen. COPDAC/ABVD was given in 412 patients, CHLVPP/ABVD in 176 patients, OEPA/COPP in 57 patients, OEPA in 35 patients, OEPA/COPDAC in 33 patients and the remaining 35 received various different combinations of chemotherapy protocols. XRT was given in 124 (17%) of patients at end of treatment in those achieving Partial response after 2 cycles of chemotherapy. XRT to neck was given in 46%, to neck and chest in 23%, neck chest and abdomen in 39% and neck to pelvis in 16% of patients.

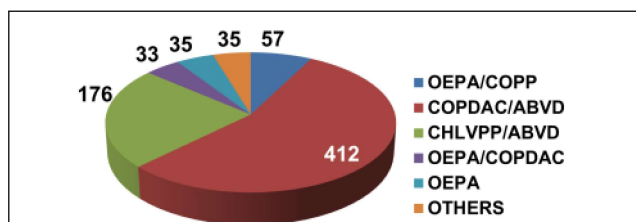
**Table-1:** Characteristics of patients according to age, gender, stage, B symptoms, Bulk volume, Bone marrow involvement, ESR and Histologic markers.

Characteristics	n (%)
<b>Age</b>	
1 - 5 years	161 (21)
6 - 10 years	336 (45)
11 - 15 years	170 (23)
> 15 years	81 (11)
<b>Gender</b>	
Male	603 (81)
Female	145 (19)
<b>B symptoms</b>	
Positive	384 (51)
Negative	364 (49)
<b>Stage</b>	
I	59 (8)
II	209 (27)
III	<b>286 (39)</b>
IV	194 (26)
<b>Nodal Bulky Disease</b>	
Present	331 (44)
Absent	417 (56)
<b>ESR</b>	
> 30	243 (26)
< 30	191 (25)
<b>Bone Marrow</b>	
Positive	98 (13)
Negative	575 (77)
<b>CD 30</b>	
Positive	713 (95)
Negative	11 (1.5)
<b>CD 15</b>	
Positive	325 (44)
Negative	170 (23)

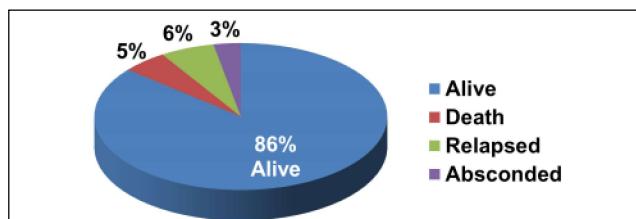
**Table-2:** Chemotherapy protocols and Death of patients with specific protocol: COPDAC/ABVD was used in 412 patients, 11 patients died on this regimen. OEPA/COPP was used in 57 patients, 11 patients died receiving this regimen. Similarly OEPA/COPDAC and CHLVPP/ABVD was used in 33 and 176 patients, there were 3 and 12 deaths respectively on these chemotherapy regimens.

Chemotherapy protocol	Number of patients who received	Patients died with specific protocol n (%)
COPDAC/ABVD	412	11 (2.6)
OEPA/COPP	57	11 (21)
OEPA/COPDAC	33	3 (9)
CHLVPP/ABVD	176	12 (6.8)

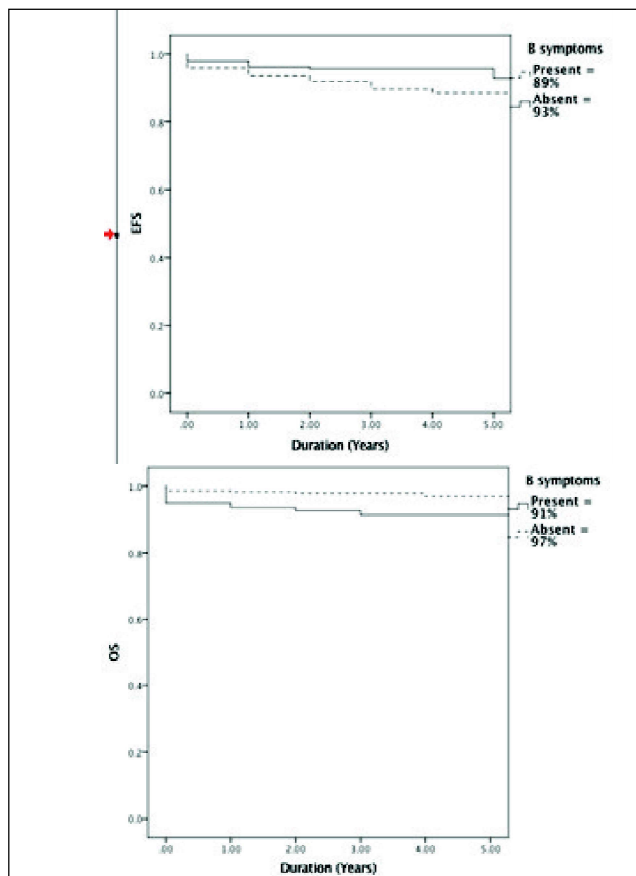
Of the 748 patients 641 (86%) of patients were alive, 37 patients (5%) died, 22 (3%) patients abandoned, 48 (6%) patients relapsed. Overall (OS) survival at 5 years was 94% and Event Free (EFS) was 91%. Median duration of follow up was 2 years. Most of deaths were due to haematological toxicity leading to sepsis. There was only one death related to disease, 22 patients died due to sepsis, 11 due to respiratory failure and 3 treatment



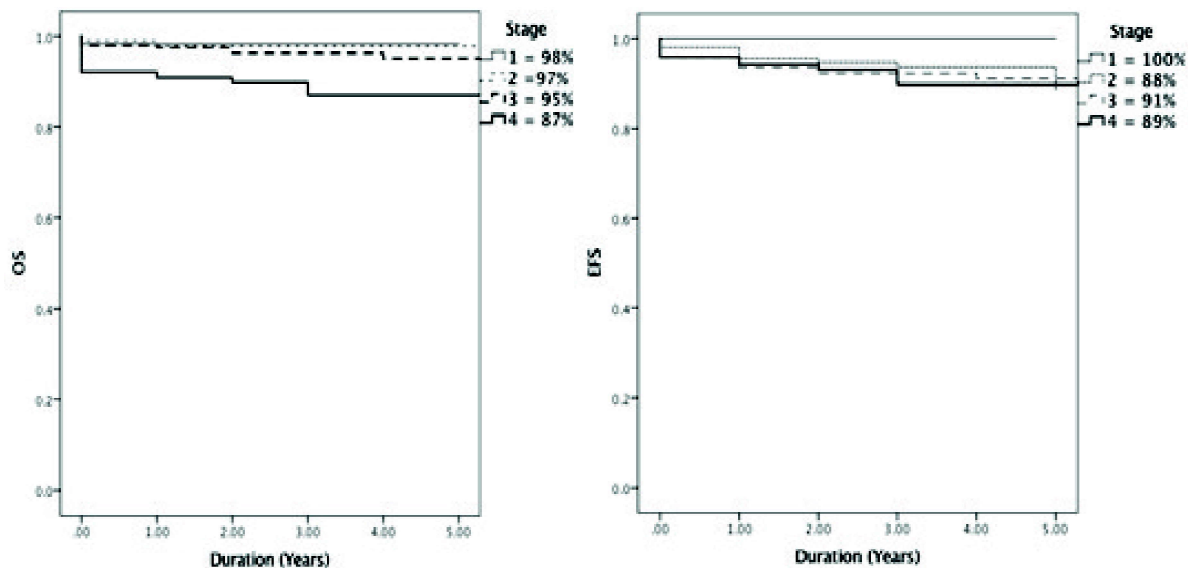
**Figure-1:** Nummber of patients who received different chemotherapy regimens: 412 received COPDAC/ABVD, 176 received CHLVPP/ABVD, 57 received OEPA/COPP, 35 received OEPA, 33 OEPA/COPDAC and 33 received different combinations.



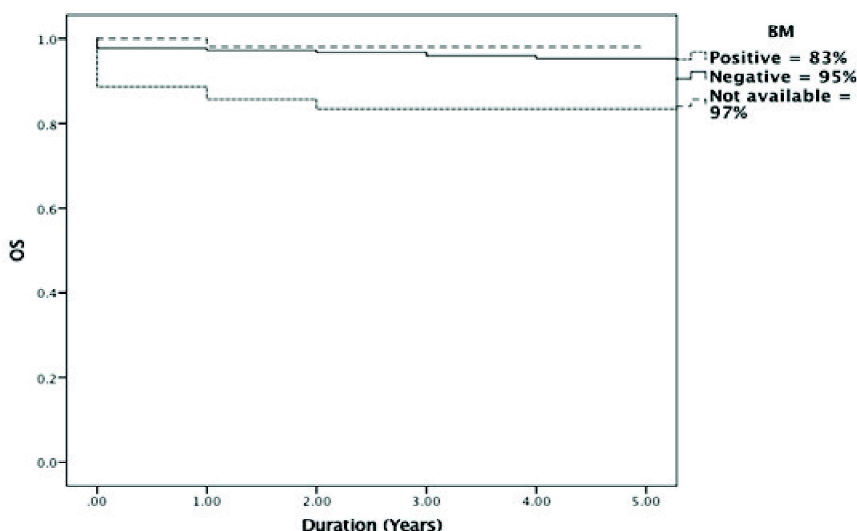
**Figure-2:** Percentage of patients who were died , relapsed, absconded and who are alive: 86% are alive, 6% relapsed, 5 % died and 3% abandoned treatment.



**Figure-3:** Overall survival and Event free survival with and without B symptoms: OS and EFS was superior in patient without B symptoms as compared to those with B symptoms.



**Figure-4:** Overall survival and event free survival with stage: OS and EFS was better in patients with stage-I as compared to those with stage-IV.



**Figure-5:** Overall survival of patients with and without Bone marrow involvement: OS in patients without Bone marrow involvement was good as compared to those with Bone marrow involvement.

related hepatic failure. There were 11 deaths (21%) in patients treated on OEPA/COPP, 12 deaths (6.8%) in patients treated with CHLVPP/ABVD, 3 deaths (9%) treated on OEPA/COPDac and only 11 deaths (2.6%) in patients treated on COPDac/ABVD. Minimum haematological and other toxicity was seen in patients who had received COPDac/ABVD when compared to other regimen. 124 patients received XRT, 4 Patients (3.2%) who received XRT died. EFS In patients receiving

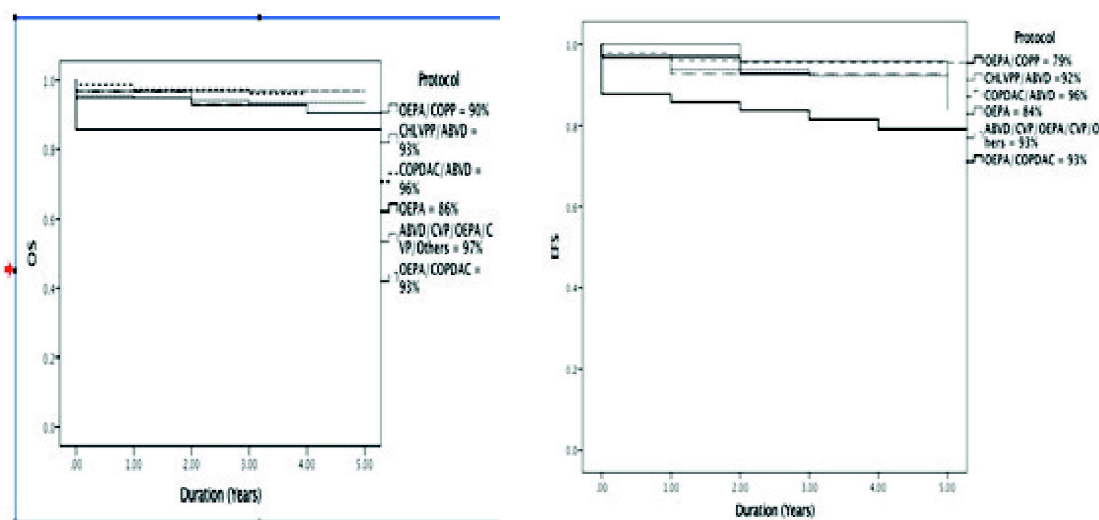
XRT were 88.7% and OS was 96.8%.

The log-rank test was performed to identify factors affecting survival. Age at diagnosis, gender, stage, presence of B symptoms, lymph node involvement, extra nodal involvement, and the different types of treatment protocol were evaluated. There were statistically significant factors affecting OS and EFS. Advanced stage (stages III and IV), the presence of B symptoms, and bone marrow involvement were identified as poor prognostic factors for EFS and OS ( $P < 0.001$ ). But ESR and bulk has no impact on OS or EFS.

In patients with B symptoms OS was 91% compared to 97% with no B symptoms. OS was 83% in patients having bone marrow involvement

compared to 95% with normal marrows. Similarly Stage I patients have OS of 98%, Stage II 97%, Stage III 95% and Stage IV 87%. Overall survival in patients treated with COPDac/ABVD was 96%, CHLVPP/ABVD 93%, OEPA/COPDac 93%, OEPA/COPP 90% and 86% in patients with OEPA chemotherapy.

EFS in patients with B symptoms was 89% compared to 93% in absence of B symptoms, EFS In patients with stage -I was 100%, Stage -II 88%, Stage -III 91%, Stage



**Figure-6:** Overall survival and Event free survival in patients with different chemotherapy regimens: Both EFS, OS was higher in patients who received COPDAC/ABVD as compared to other regimens.

-IV 89%.EFS with chemotherapy COPDAC/ABVD was 96%, OEPA/COPDAC 93%, CHLVPP/ABVD 92%,OEPA 84%,OEPA/COPP 79% and 93% with different chemotherapy drug combinations .No difference in EFS with or without BM Involvement , bulk and ESR.

## Discussion

Like many other diseases, lymphoma also shows geographical variations in natural history and clinical presentation. In present study Hodgkin's Lymphoma has male predominance which is consistent with studies in both developed and developing countries. The early peak in 5-10 years age group in our study is comparable when seen with other studies from developing countries. In our study 45% of patients were in 5-10 year age group and 21% below 5 year of age. Reports from other developing countries show that paediatric HL occurs at a younger age with as many as 15 to 30% of cases occurring before 5 years of age, against some 5% in developed countries.<sup>9</sup> The bimodal distribution of lymphoma may be due to the relative immune deficient status in these age groups. This in turn is dependent upon environmental influences, such as common viral infections and socioeconomic factors.<sup>10,11</sup> Epstein Barr virus, for example, has a strong causal association with Hodgkin's disease. Improving the standard of living delays the early peak of occurrence of lymphoma up to young adulthood. This may explain the early peak of lymphoma in developing countries, as also observed in our study.<sup>12</sup>

In our study there were statistically significant factors affecting OS and EFS. Advanced stage (stages III and IV), the presence of B symptoms, and bone marrow involvement were identified as poor prognostic factors for EFS and OS. In patients with B symptoms OS was 91% compared to 97% with no B symptoms, 83% in patients having bone marrow involvement compared to 95% with normal marrows. Similarly Stage I patients have OS of 98%, Stage II 97%, Stage III 95% and Stage IV 87%. EFS in patients with B symptoms was 89% compared to 93% in absence of B symptoms, EFS In patients with stage -I was 100%, Stage -II 88%, Stage -III 91%, Stage -IV 89%. ( $P < 0.001$ ). But ESR and Bulk has no impact on OS or EFS. Studies by Wolden S L et al showed that patients with B symptoms at diagnosis had a 10 year EFS of 71.7% compared with 87.5% for patients with no B symptoms ( $P < 0.001$ ). For patients with bulk disease, 10-year EFS were 75.6% compared with 87.2% for patients without bulk disease ( $P < 0.001$ ).<sup>13</sup> Santoro A et al also showed low EFS & OS in patient with B symptoms. EFS of patients with A versus B symptoms was 94.2% versus 76% ( $p < 0.004$ ).<sup>14</sup> Uysal K M et al showed impact of staging on EFS & OS. In stage I-II patients EFS was 90%, and 82%, at 5 and 10 years, respectively. OS was 100% at both 5 and 10 years. In Stage III-IV patients EFS was 59% at 5 and 10 years. OS was 92% at 5 year and 81% at 10 year.<sup>15</sup> In our study ESR and Bulk have no effect on EFS And OS.

We had used PET/CT as base line in 612 patients, CT scan in 136 patients. Over the past few years, evidence has

confirmed the potential role of F-FDG PET/CT in the staging and monitoring treatment outcomes in lymphomas. FDG-PET/CT scan response after one to two cycles of chemotherapy may predict outcome and may identify patients less likely to relapse after chemotherapy alone. Thus F-FDG PET/CT had greater sensitivity and positive predictive values after the first cycle (82% versus 45.5% and 90% versus 83%, respectively) than after the last cycle. Early interim FDG-PET/CT scan after 2 cycles of chemotherapy may help risk adapted treatment strategies by selecting good-prognosis HL patients for less intensive and less morbid treatment and intensifying treatment with poor risk group.<sup>16-18</sup>

Hodgkin Lymphoma (HL) was one of the first malignancies for which curative chemotherapeutic regimens were developed. MOPP/ABVD have been mainstays of therapy for decades. Despite late sequelae (infertility, second malignancy, cardiopulmonary toxicity) and knowledge that total dose and rate of drug delivery impact treatment efficacy, the adequacy of these low-intensity regimens deterred efforts to improve them. Over the past two decades, treatment of Hodgkin's disease has evolved considerably. Focus is on minimizing toxicity and late effects and preserving high cure rates. Treatments were modified for children by reducing radiation dose and field size and relying on chemotherapy across all disease stages. Procarbazine has been gradually eliminated to reduce the risk of infertility, and etoposide and doxorubicin substituted to reduce the cumulative alkylating agent dose.<sup>17</sup>

In our study different protocols were used over the duration of 6 years and modified to have minimal toxicity and achieving better outcomes. COPDac/ABVD, OEPA/COPP, OEPA/COPDac, CHLVPP/ABVD, OEPA only and CVP average 5-years OS was 94% and 5-years EFS was 91%, which is superior to many previous studies using same chemotherapy protocols with or without radiotherapy. Wolden S L et al compared the results of chemotherapy with and without radiotherapy for children with Hodgkin's Lymphoma, 10-year EFS and OS rates were 83.5% and 92.5%.<sup>13</sup> Santoro A et al studied superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy, combined modality treatment for intermediate stages of Hodgkin's disease, ABVD followed by wide-field radiotherapy is confirmed to represent a valid therapeutic alternative to MOPP plus radiotherapy, apparently devoid of sterility and leukemogenesis, and not associated with

cardiotoxicity<sup>14</sup> ChIVPP were reported to produce less gastrointestinal toxicity and neurotoxicity than MOPP, ABVD represented the first new effective adjuvant regimen randomly tested versus MOPP to evaluate the comparative incidence of acute leukemia and sterility.<sup>19</sup>

In our study EFS in patients receiving XRT with chemotherapy was 88.7% and OS was 96.8%. which is comparable to different studies. Uysal K M et al showed the result of COPP and/or ABVD + radiotherapy (RT) and GPOH-HD 90 + RT. The 5-year EFS and OS rates for the whole study group were 77% and 96%, respectively.<sup>15</sup> Baez F et al showed EFS 75% after using COPP or COPP-ABV (hybrid) regimens without RT.<sup>20</sup> Schwartz C L et al showed EFS Of 84% and OS 95% after using ABVE-PC and IFRT.<sup>21</sup> Schellong G et al showed result of using OEPA with and without IFRT, The probability of EFS and OS at 5 years is 91% and 98%, respectively.<sup>22</sup> Dorffel W et al studied results by using different chemotherapy (OEPA & OPPA), overall survival and event-free survival at 10 years were 96.3%, and 85.4% respectively.<sup>23</sup>

In our study 6% patients relapsed, 3% have primary progressive disease. We did not study the treatment and outcome of these patients in the present study. There are 15-20% of patients who will have resistance to therapy or relapse after treatment.

The outcome of children with HL has greatly improved with 5-year overall survival rates greater than 95%, and 5-year EFS greater than 90% for all stages for the last two decades. Treatment results have shown considerable improvement even in developing countries. The main challenge today is finding a balance between maximizing cure and minimizing the late effects. Therefore, emphasis is now on tailoring therapy according to the risk groups which should be based on well defined prognostic factors. Several study groups from the developed countries have been searching for the efficacy of risk-based therapies using risk factors determined in their own populations.

## Conclusion

Treatment of patient with Hodgkin's Lymphoma has been a great challenge, as there has been a great variation in selection of chemotherapy protocol among various institutes even in same area and same country. In our present study by using various chemotherapy drugs combinations, we have seen better outcome and less deaths with COPDac/ABVD. There is a need of close collaboration among different institutes in Pakistan, so

that same chemotherapy protocol with best outcome can be implicated.

**Disclaimer:** None to declare.

**Conflict of Interest:** None to declare.

**Funding Sources:** None to declare.

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