Original Article

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Assessment of Drug Toxicity and Mortality in Children with Classical Hodgkin Lymphoma on ABVD/COPDAC Protocol ; A Single Centre Study

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Author`s Contribution

[1,6]Substantial contributions to the conception or design of the work; or the acquisition, [5]Active participation in active methodology, [3]analysis, or interpretation of data for the work, [2,5]Drafting the work or revising it critically for important intellectual content

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ABSTRACT

Objective: To assess the frequency of drug toxicity and mortality associated with ABVD/COPDAC protocol in children with classical Hodgkin Lymphoma at IHHN, Karachi.

Methodology: A prospective observational study was conducted over six months at the pediatric Oncology Unit of IHHN, Karachi, from April 2023 to September 2023, involving patients less than 16 years diagnosed with classical Hodgkin's lymphoma and with normal cardiac function on echocardiography. The NCI Common Terminology Criteria for Adverse Events (CTCAE) was used to report toxicity and adverse effects. Toxicity was assessed over a total of eight chemotherapy cycles, and the total numbers of chemotherapy cycles assigned were based on the stage of the disease and the treatment group. Data was analyzed using SPSS version 26.

Results: 152 patients with Classical Hodgkin Lymphoma (mean age 9.45±3.43 years, male predominance 80.3%), toxicity was assessed over eight treatment cycles. In Cycle I, 5.9% had neutropenia, while 91.4% had no toxicity. In Cycle II, neutropenia was observed in 19.1%, with 76.3% reporting no toxicity. Cycle III showed 9.2% with neutropenia and 90.8% without toxicity, while Cycle IV recorded 12.5% with neutropenia and 83.6% without toxicity. Across Cycles V-VIII, neutropenia ranged from 5.3% to 14.5%, with 83.6% to 94.1% experiencing no toxicity. Cardiotoxicity and other severe toxicities were rare throughout all cycles. The overall mortality rate was low at 1.3%, with a 98.7% survival rate.

Conclusion: Study revealed varying levels of toxicity basis on treatment cycles and the overall mortality rate was low at 1.3%, with survival arte as 98.7%. Toxicity and mortality rates were statistically insignificant across the treatment groups, indicating that the ABVD/COPDAC protocol is generally safe and effective for this patient population.

Keywords: Classical Hodgkin Lymphoma, ABVD, COPDAC, toxicity, Mortality.

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Introduction

Classical Hodgkin lymphoma (CHL) is a very common hematologic neoplastic disease in children, accounting for 5-6% of all childhood cancers.[1] There is a bimodal age distribution with 1st peak between the ages of 15–35 years.[2,3] The exact cause of CHL is unknown, however, various factors including chemicals, drugs and viral agents have been associated with it, most commonly Epstein Barr virus (EBV).[4] CHL is divided into four subtypes: nodular sclerosis, mixed cellularity, lymphocyte-depleted and lymphocyte-rich.[3] The

predominant histological subtype in Pakistan and other low to middle income countries (LMICs),is the mixed cellularity subtype, with EBV infection accounting for over 80% of documented cases.[4-6] Male to female ratio is much higher in LMICs compared to high income countries.[6] Unfortunately, there is no national pediatric oncology registry in Pakistan and the exact number of pediatric malignancies is still not known. However, in one previously published study from Pakistan, CHL patients were noted to account for 6.8% of total malignant diagnosed cases annually.[7]

Management of CHL is done according to risk stratification of the disease which is based on tumor stage, bulk of disease and the presence of B symptoms. CHL in children has become a highly curable neoplasm using modern therapeutic regimens. A multi-drug regime with or without radiotherapy remains the standard of care, however, treatment-related side effects have previously been documented in survivors of CHL in Pakistan.[8] The main focus of the current pediatric CHL international clinical trials is to minimize risk of adverse events while maintaining a high cure rate.[9] In developed countries, management of CHL is according to the Children's Oncology Group (COG) and European Network Pediatric Hodgkin Lymphoma protocols with standard or intensified chemotherapy regimens to improve outcomes in higher risk patients.[10]

In Pakistan, different chemotherapeutic regimes are used for treatment of CHL after staging and risk stratification. One study conducted at Children Hospital Lahore as per EuroNet-PHL-C1 protocol - OEPA/COPDAC chemotherapy regimen, when compared to HIC showed higher rate of treatment related mortality.[5] In another study conducted in Combined Military Hospital (CMH) Rawalpindi using the same EuroNet-PHL-C1 protocol, febrile neutropenia was seen as the most common complication while using the OEPA chemotherapy cycles, and vincristine associated toxicity was next common complication observed. Treatment related mortality was also high in patients who were suffering from stage IV disease.[11] A retrospective study conducted at Indus hospital Karachi on the basis of ABVD/COPDAC protocol in CHL treatment, showed improved survival rate.[12] In a single institute study in Shaukat Khanum Memorial Cancer Hospital in patients with CHL using different chemotherapy protocol including COPDAC/ABVD, OEPA/COPP, OEPA/COPDAC, CHLVPP/ABVD and OEPA over the duration of 6 years, when compared with ABVD/COPDAC protocol minimum toxicity was observed.[8]

In Pakistan and other low- and middle-income countries, pediatric oncology patients often face high rates of malnutrition and are thus at increased risk for severe infections. This situation is exacerbated by limited hospital resources, such as inadequate bed availability and supportive care. In response to these challenges, many pediatric oncology units in Pakistan have adopted the COPDAC/ABVD regimen. At the Pediatric Oncology Department of Indus Hospital in Karachi, over 1,000 pediatric cancer cases are registered annually, with Classical Hodgkin Lymphoma patients representing approximately 5-6% of these cases. These patients are treated using the PSPO CHL protocol, which involves the ABVD/COPDAC regimen based on their risk stratification. This hybrid chemotherapy approach is deemed a safer and more cost-effective alternative, with survival rates comparable to other treatment regimens.[12] The current study aims to evaluate drug-associated toxicity and mortality rates in pediatric patients with CHL receiving the ABVD/COPDAC regimen, providing crucial insights into its safety and effectiveness in this population.

Methodology

A prospective observational study was conducted at the Pediatric Oncology Unit of the Indus Hospital and Health Network (IHHN), Karachi, over a six-month period from April 2023 to September 2023, after obtaining ethical approval from the Institutional Review Board (IRB) of the Indus Hospital. A sample size of 150 patients was calculated using the WHO sample size calculator, based on a 10.9% mortality rate among patients treated with ABVD/COPDAC for Hodgkin's lymphoma (HL), with a 95% confidence level and a 5% margin of error.

All pediatric patients under 16 years of age at the time of diagnosis, of both genders, with a confirmed diagnosis of classical Hodgkin's lymphoma and normal cardiac function (Ejection Fraction > 55% and Fractional Shortening [FS] > 27%) were included in the study. Patients were excluded if they had a history of chemotherapy for other malignancies, known hypersensitivity or contraindications to the drugs, relapsed classical Hodgkin's lymphoma, hepatic, renal, or cardiac dysfunction, or if they did not provide consent to participate in the study.

Before data collection, informed written consent was obtained from the guardians of eligible patients. After a

clinical examination and a review of demographic and medical history, patients were assessed for drug toxicity, related factors, and mortality associated with the ABVD/COPDAC protocol. Any cases with missing, incomplete, or inaccurate data were excluded. Patients were stratified into three treatment groups (TG) based on risk. The treatment groups were as follows:

1. TG -1: all patients with stage IA, IB, IIA

2. TG -2: all patients with stages IEA/B, IIEA, IIB, IIA

3. TG -3: all patients with stages IIEB, IIIEA/B, IIIBS, IVA/B

The NCI Common Terminology Criteria for Adverse Events (CTCAE) was used to report toxicity and adverse effects. Investigations included complete blood count (CBC), electrolytes, calcium levels, renal and liver function tests, coagulation profile, urinalysis, and echocardiography.

Echocardiography was repeated during chemotherapy if clinically indicated and at the end of chemotherapy for all patients. Chest X-ray (CXR), abdominal ultrasound (U/S), and PET-CT scan were performed in all patients before starting chemotherapy for risk assessment and staging.

Baseline laboratory tests, including CBC, electrolytes, and liver and renal function tests, were repeated after each chemotherapy cycle. A PET scan was repeated after four chemotherapy cycles in all patients. Toxicity was assessed over a total of eight chemotherapy cycles, with the total number of assigned chemotherapy cycles depending on the disease stage and treatment group.

Data was collected using a questionnaire-based study proforma, and SPSS version 26 was used for analysis.

Results

The mean age of the participants was 9.45 years with a standard deviation of 3.43 years. Of the total participants, 19.7% were female, and 80.3% were male. The ethnic distribution shows that 13.2% were Balochi, 18.4% Pathan/Pushtun, 16.4% Punjabi, and the majority, 52.0%, was Sindhi. Regarding the stages of disease, the distribution was varied, with the most common stage being IVBS (17.1%, n=26), followed by IIIBS (15.8%, n=24). Other notable stages included IIB (13.2%, n=20) and IIA (11.2%, n=17). Less frequent stages were IA, IIAE, IIBSE, IIIBS, and others, each occurring in less than 1% of cases. Table I

Table I: Descriptive statistics of demographic information. (n=152)

Variables	N	%
Gender		
Female	30	19.7
Male	122	80.3
Ethnicity		
Balochi	20	13.2
Pathan / Pushtu	28	18.4
Punjabi	25	16.4
Sindhi	79	52.0
Stages		
IA	1	0.7
IB	5	3.3
IIA	17	11.2
IIAE	1	0.7
IIAS	4	2.6
IIB	20	13.2
IIBE	2	1.3
IIBS	10	6.6
IIBSE	1	0.7
IIIA	10	6.6
IIIAS	12	7.9
IIIB	4	2.6
IIIBE	1	0.7
IIIBS	24	15.8
IIIBSE	3	2.0
IIIBS	1	0.7
IVAS	5	3.3
IVB	3	2.0
IVBS	26	17.1
IVBSE	2	1.3
Mean age (Mean±SD)	9.45±3.43 years	

Across Cycles I-IV, the most common toxicity observed among children with Classical Hodgkin Lymphoma on the ABVD/COPDAC protocol was neutropenia, especially in TG3. In Cycle I, neutropenia occurred only in TG3 (5.9%), and 91.4% of participants experienced no toxicity. Cycle II had the highest rate of neutropenia (19.1%), predominantly in TG3, while other toxicities, such as Neutropenia/mucositis and Cardiotoxicity, were rare. In Cycle III, neutropenia was noted in 9.2% of participants, with the majority (90.8%) showing no toxicity. In Cycle IV, neutropenia was reported in 12.5% of participants, mainly in TG2 and TG3, with other toxicities like Neutropenia/hepatitis, Neutropenia/ pancytopenia, Cardiotoxicity, and Thrombocytopenia being infrequent. In Cycle V, 5.3% experienced neutropenia, mostly in TG3, while 92.1% had no toxicity.

Cardiotoxicity/mucositis and thrombocytopenia were rare (each 0.7-1.3%). During Cycle VI, neutropenia was the most common toxicity (14.5%), with TG3 having the highest occurrence. Most participants (83.6%) had no toxicity. In Cycles VII and VIII, the pattern was similar, with neutropenia affecting 5.3% of participants, mainly in

TG3, and the majority (91.4%) showing no toxicity. Overall, most participants experienced no toxicity in all cycles, and the differences in toxicity across treatment groups were not statistically significant in any cycle (p->0.05). Table II & III

Table II: Drug Toxicity in Children with Classical Hodgkin Lymphoma on ABVD/COPDAC Protocol at cycle I-IV (n=152)

Toxicity basis on cycle	Treatment groups (TG)			Total	p-value
	TG1	TG2	TG3		
Cycle-I					
Neutropenia	0	0	9	9	
	0.0%	0.0%	5.9%	5.9%	
Neutropenia/mucositis	0	1	2	3	
	0.0%	0.7%	1.3%	2.0%	
Neutropenia/hepatitis	0	1	0	1	0.110
	0.0%	0.7%	0.0%	0.7%	
No toxicity	20	46	73	139	
	13.2%	30.3%	48.0%	91.4%	
Cycle-II					
Cardiotoxicity	0	0	1	1	
	0.0%	0.0%	0.7%	0.7%	
Neutropenia	7	7	15	29	
	4.6%	4.6%	9.9%	19.1%	
Neutropenia/fever	0	0	1	1	
	0.0%	0.0%	0.7%	0.7%	
Neutropenia/mucositis	0	1	2	3	
	0.0%	0.7%	1.3%	2.0%	0.436
Neutropenia/mucositis/ fever	0	2	0	2	
	0.0%	1.3%	0.0%	1.3%	
No toxicity	13	38	65	116	
	8.6%	25.0%	42.8%	76.3%	
Cycle-III					
Neutropenia	1	5	8	14	
	0.7%	3.3%	5.3%	9.2%	
No toxicity	19	43	76	138	0.772
	12.5%	28.3%	50.0%	90.8%	
Cycle-IV					
Cardiotoxicity	0	0	1	1	
	0.0%	0.0%	0.7%	0.7%	
Neutropenia	0	7	12	19	
	0.0%	4.6%	7.9%	12.5%	
Neutropenia/hepatitis	1	2	0	3	
	0.7%	1.3%	0.0%	2.0%	
Neutropenia/ pancytopenia	1	0	0	1	
	0.7%	0.0%	0.0%	0.7%	
No toxicity	18	39	70	127	0.133
	11.8%	25.7%	46.1%	83.6%	
Thrombocytopenia	0	0	1	1	
	0.0%	0.0%	0.7%	0.7%	

Mortality was observed in 1.3% (n=2) of the total population, with one death each in TG2 and TG3 (0.7% each). No mortality was recorded in TG1. The vast majority, 98.7% (n=150), survived, with the highest proportion in TG3 (54.6%), followed by TG2 (30.9%) and TG1 (13.2%). Although the mortality between the treatment groups were not statistically significant (p=0.781). Table IV

Table III: Drug Toxicity in Children with Classical Hodgkin Lymphoma on ABVD/COPDAC Protocol at cycle V-VIII. (n=152)

Toxicity basis on cycle	Treatment groups (TG)			Total	p-value
	TG1	TG2	TG3		
Cycle-V					
Cardiotoxicity /mucositis	0	0	1	1	
	0.0%	0.0%	0.7%	0.7%	
Neutropenia	0	2	6	8	
	0.0%	1.3%	3.9%	5.3%	
No toxicity	20	45	75	140	
	13.2%	29.6%	49.3%	92.1%	
Severe neutropenia /mucositis	0	1	0	1	0.558
	0.0%	0.7%	0.0%	0.7%	
Thrombocytopenia	0	0	2	2	
	0.0%	0.0%	1.3%	1.3%	
Cycle-VI					
Cardiotoxicity	0	1	1	2	
	0.0%	0.7%	0.7%	1.3%	
Neutropenia	0	8	14	22	
	0.0%	5.3%	9.2%	14.5%	
No toxicity	20	38	69	127	
	13.2%	25.0%	45.4%	83.6%	0.343
Severe neutropenia	0	1	0	1	
	0.0%	0.7%	0.0%	0.7%	
Cycle-VII					
Cardiotoxicity	0	1	1	2	
	0.0%	0.7%	0.7%	1.3%	
Neutropenia	0	0	8	8	
	0.0%	0.0%	5.3%	5.3%	
Neutropenia/hepatitis	0	0	2	2	
	0.0%	0.0%	1.3%	1.3%	
No toxicity	20	47	72	139	0.260
	13.2%	30.9%	47.4%	91.4%	
Severe neutropenia /mucositis /fever	0	0	1	1	
	0.0%	0.0%	0.7%	0.7%	
Cycle-VIII					
Cardiotoxicity	0	1	1	2	
	0.0%	0.7%	0.7%	1.3%	
Neutropenia	0	0	8	8	
	0.0%	0.0%	5.3%	5.3%	
Neutropenia/hepatitis	0	0	2	2	0.600
	0.0%	0.0%	1.3%	1.3%	
No toxicity	20	47	72	139	
	13.2%	30.9%	47.4%	91.4%	
Severe neutropenia /mucositis /fever	0	0	1	1	
	0.0%	0.0%	0.7%	0.7%	

Table IV: Mortality in Children with Classical Hodgkin Lymphoma on ABVD/COPDAC Protocol. (n=152)

Mortality	Treatment groups (TG)			Total	p-value
	TG1	TG2	TG3		
Yes	0	1	1	2	
	0.0%	0.7%	0.7%	1.3%	
No	20	47	83	150	0.781
	13.2%	30.9%	54.6%	98.7%	
Total	20	48	84	152	
	13.2%	31.6%	55.3%	100.0%	

Discussion

Classical Hodgkin Lymphoma is the frequent lymphoma in children and adolescents and a highly curable cancer,

particularly when treated with chemotherapy protocols such as ABVD and COPDAC. Despite their great effectiveness, these treatment methods are linked to severe toxicity, which can affect the quality of life and prognosis for children patients. The present study done to evaluate drug associated toxicity in the pediatric population with CHL who are managed using ABVD/COPDAC consisting 152 patients with mean age of 9.45 years male predominance (80.3% male and 19.7% female). CHL primarily affects young people, including studies revealing that the average age at diagnosis is 34 years for Hispanic individuals and 39 years for non-Hispanic patients.[13,14] The male-to-female ratio fluctuates, although males consistently account for a higher proportion of cases across all populations. For example, in a cohort from the SEER database, males made up around 54.1% of non-Hispanic patients and 55.3% of Hispanic patients. The typical age in old populations is approximately 66 years, with males being predominant.[15]

In this study across the treatment cycles, the most common toxicity observed among children with Classical Hodgkin Lymphoma on the ABVD/COPDAC protocol was neutropenia, especially in TG3. In Cycle I, neutropenia was exclusive to TG3 (5.9%), and 91.4% experienced no toxicity. Cycle II had the highest neutropenia rate (19.1%), again predominantly in TG3, while other toxicities like Neutropenia/mucositis and Cardiotoxicity were rare. In Cycle III, 9.2% had neutropenia, and 90.8% had no toxicity. In Cycle IV, neutropenia occurred in 12.5%, mostly in TG2 and TG3, with other toxicities being infrequent. Neutropenia affected 5.3% in Cycle V, mainly in TG3, and 92.1% had no toxicity. Cycle VI showed neutropenia as the most frequent toxicity (14.5%), with TG3 having the highest occurrence, and 83.6% experienced no toxicity. Cycles VII and VIII followed a similar pattern, with 5.3% affected by neutropenia, mostly in TG3, and the majority (91.4%) showing no toxicity. Overall, most participants had no toxicity in all cycles, and toxicity differences across treatment groups were not statistically significant ($p>0.05$).

Comparatively, Bekhit et al[16] reported that in the OEPA-COPDAC regimen, toxicity occurred in 49.5% of chemotherapy phases, with neutropenia being the most frequent adverse event, affecting 85% of participants during early cycles. This higher frequency of neutropenia in the OEPA-COPDAC regimen compared to ABVD/COPDAC could be due to differences in chemotherapy agents or dosing schedules. The relatively lower incidence of neutropenia in the current study might reflect the specific supportive care measures or patient management strategies employed. Additionally, according to a study ABVD/COPDAC treatments have shown encouraging survival rates, with up to 93.5% survival after four years, indicating that despite the occurrence of neutropenia, the regimen remains effective and potentially life-saving for children with Classical Hodgkin Lymphoma.[17] The manageable toxicity profile and favorable survival outcomes underscore the protocol's suitability in pediatric oncology settings.

In this study, the overall mortality rate was 1.3%, with one death occurring in each of the TG2 and TG3 groups. The majority of patients, 98.7%, survived, with the highest survival rate observed in TG3 (54.6%), followed by TG2 (30.9%), and TG1 (13.2%). The differences in mortality rates among the treatment groups were not statistically significant ($p=0.781$), suggesting that the treatment regimens did not differ significantly in terms of survival outcomes. In comparison, Ahmed M et al[18] reported no deaths during or after treatment among their cohort, highlighting a more favorable outcome in their study. Among the 62 patients in that study, 15% experienced disease progression during treatment, and 6% had a recurrence after completing therapy. This contrast underscores the variability in patient outcomes and the potential impact of different treatment protocols.

Both ABVD and COPDAC regimens have proven effective, but they exhibit different toxicity profiles. This necessitates careful monitoring and potential adjustments based on individual patient responses and long-term outcomes. However, the current findings are limited by a small sample size and a lack of long-term follow-up. Therefore, further large-scale, longitudinal studies are needed to validate these results and provide more definitive conclusions.

Conclusion

Study revealed a male predominance and across eight treatment cycles, varying levels of toxicity were observed, with the majority of patients experiencing no toxicity in each cycle. The overall mortality rate was low at 1.3%, with survival arte as 98.7%. Toxicity and mortality rates among the treatment groups were statistically insignificant ($p>0.05$), indicating that the ABVD/COPDAC protocol is generally safe and effective for this patient population. Although due to some study

limitations, further large-scale longitudinal studies are recommended to validate the findings.

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