ORIGINAL ARTICLE

Response Rate After Modified Regime DHAP and Toxicity with Refractory and Relapsed Disease in Lymphoma Patients

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ABSTRACT

Objective: To assess the response rate and toxicity of a modified regimen DHAP (dexamethasone, cytarabine, and cisplatin) and to compare treatment response and toxicity profile with disease status in patients with refractory and relapsed lymphoma who presented to a public hospital in Karachi, Pakistan.

Study Design: A cross sectional study.

Place and Duration of Study: The study was conducted at the Oncology Department of Jinnah Postgraduate Medical College, Karachi, Pakistan, from December 2021 to October 2022.

Methods: Modified DHAP was used to treat all individuals with lymphoma who had refractory disease or had relapse. The modified DHAP treatment includes intravenous infusions of dexamethasone 40 mg every 15 minutes on days 1 through 4, cisplatin 25 mg every 3 hours on days 1 through 4, and cytarabine 2x0.5 g/m^2 every hour on days 1 through 4. Cycles were repeated every three weeks. Following each cycle, toxicity was evaluated using WHO criteria. A CT scan and a physical examination were used to assess the therapy response.

Results: The median age was 41, ranging from 20 to 74 years. Most of the patients were males (73.9%). Of 92 patients, 32 had refractory disease, and 60 had relapse. Twenty-nine patients had a complete response, 45 patients had a partial response, and the overall response rate of modified DHAP was 80.4%. The most frequent toxicity of modified DHAP was pancytopenia (46.7%), followed by febrile neutropenia (14.1%), respectively. Mortality occurred in 4 patients (13%). Febrile neutropenia was reported more in non-Hodgkin's lymphoma patients than in Hodgkin's lymphoma patients, with a *p*-value=0.014.

Conclusion: Modified DHAP has a better overall response rate and manageable toxicity profile in patients with refractory or relapsed lymphoma.

Keywords: *Lymphoma, Modified DHAP, Relapse Lymphoma, Refractory Disease, Toxicity.*

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Introduction

Patients with Hodgkin's lympoma (HL) or non-Hodgkin's lymphoma (NHL) who have refractory or relapsed lymphoma typically have a poor prognosis.[1] Relapses occurred in about 20% of patients with stage I–II diseases with favorable characteristics and approximately 40% of people with advanced diseases.[2] So, choosing the appropriate salvage chemotherapy for these cases is still challenging.[3]

Relapse and refractory cases of HL and NHL entail complex challenges. While often curable, HL can experience relapses—early or late—necessitating treatments like intensified chemotherapy, targeted therapies, and stem cell transplantation.[4] Refractory HL involves poor responses to initial treatments, warranting aggressive approaches such as high-dose chemotherapy and immunotherapies like

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checkpoint inhibitors. NHL, with its diverse subtypes, exhibits varying relapse risks. Aggressive forms may be prone to relapse, necessitating tailored strategies such as further chemotherapy, radiation, immunotherapy, or stem cell transplantation.[5] Refractory NHL, where initial treatments fail, demands intricate therapies, including targeted agents and CAR T-cell therapy, often in the context of clinical trials. The evolving landscape of treatment options underscores the importance of individualized, multidisciplinary care for patients facing these challenging scenarios.[4,5]

The DHAP regimen (dexamethasone, cytarabine, and cisplatin) is frequently used to treat refractory and relapse lymphoma.[4-7] Patients with NHL have an overall response rate of DHAP of up to 70% after 2 to 3 cycles; however only 50% of the responding patients may be treated with sequential autologous stem cell transplantation.[8] However, data are scarce regarding the efficacy of DHAP as a salvage therapy regimen in HL patients.[3] The conventional DHAP regimen needs patients to be hospitalized, which is a significant drawback of this therapy.[3,8] Infections and severe myelosuppression are two additional adverse effects that have been linked to treatment-associated death. These side effects are often observed after DHAP cycles. Additionally, up to 20% of patients receiving DHAP treatment experienced permanent or temporary renal damage, mainly related to a single-day cisplatin infusion.[3,8]

Recently, a modified DHAP treatment protocol with a different time of administration and dosage has been tested in refractory or recurrent lymphomas in order to evaluate the efficacy and toxicity profile.[3,8,9] Kanat et al. used a modified DHAP regimen containing dexamethasone(40 mg intravenously on days 1 to 4), cytarabine (2 g/m^2 intravenously as 3 hour-infusion on days 3 in the morning and days 2 in the evening), and cisplatin (35 mg/m^2 intravenously as two hour infusion on days 1 to 3) and found a 88% overall response rate.[3] Whereas, Kroschinsky et al. discovered 55% overall response rate in lymphomas that were refractory or had relapsed after administration of modified DHAP [i.e. dexamethasone 40 mg 15 min intravenously infusion on days 1 to 4, cisplatin 25 mg/m^2 24 hour intravenously infusion on days 1 to 4 and cytarabine 2 × 0.5 g/m^2 one hour intravenously infusion on days 1 to 4]. Additionally, they discovered that just 1.7% of treatment-related deaths and infections were reported to be less than 40%.[8]

Data on the effectiveness of modified DHAP in lymphoma patients are lacking in Pakistan. Therefore, the current study sought to assess the response rate and toxicity of a modified regimen DHAP and to compare treatment response and toxicity profile with disease status in patients with refractory and relapsed lymphoma who presented to a tertiary care hospital in Karachi, Pakistan. In patients with poor prognoses, this study will help improve protocol safety and treatment outcomes overall.

Methods

This cross-sectional study was carried out at the Oncology Department of Jinnah Postgraduate Medical College, Karachi, Pakistan, from December 2021 to October 2022. A sample size of 92 was estimated using Open Epi sample size calculator by taking statistics of the complete response rate of DHAP as 39.2%[3], margin of error as 10%, and confidence level as 95%. Patients of age more than 18 years, both genders with refractory (Refractory lymphoma indicates a lack of meaningful reduction in tumor size or activity in response to the prescribed therapeutic regimen) or relapse (Relapse lymphoma involves the reappearance of active cancer cells after a period of apparent absence or dormancy following successful treatment) lymphoma were included in the study. Patients with cardiovascular disease, central nervous system involvement, and active infections were excluded from the study. Samples were selected using a non-probability consecutive sampling technique.

The study's ethical approval was obtained from the institute's ethical review committee vide letter no (ERC# NO.F.2.81/2022-GENL/178/JPMC) dated May 25, 2022. The written informed consent was obtained from all the eligible patients before the initiation of data collection. Data was kept secured in locked computers. Participants' names were coded, and data were only accessible to the researcher.

All 92 patients with refractory or relapsed lymphoma were treated with modified DHAP. Modified DHAP protocol included dexamethasone 40 mg 15 min

intravenously infusion on days 1 to 4, cisplatin 25 mg/m^2 as 3 hours intravenously infusion on days 1 to 4, and cytarabine 2 × 0.5 g/m^2 one hour intravenously infusion on days 1 to 4. Every three weeks, cycles were repeated. Intensified oral supportive medication was used to avoid chemotherapy-induced nausea and vomiting.

Following each cycle, toxicity was evaluated using WHO criteria.[3] A CT scan and a physical examination were used to measure how well the treatment responded. After three months of therapy, a complete response was defined as the lack of disease signs or symptoms—a partial response referred to any previously identified abnormalities that had decreased by over 50%. Patients without a complete or partial response were categorized as having stable disease.

Within three months following the end of treatment,

Table 1: Patient characteristics (n=92)

Variables	n (%) or Median (IQR)
Age (years)	41 (20-74)
Gender	
Male	68 (73.9)
Female	24 (26.1)
Lymphoma type	
HL	45 (48.9)
NHL	47 (51.1)
Disease status	
Refractory	32 (34.8)
Relapse	60 (65.2)
Stage of lymphoma	
II	11 (12)
III	40 (43.5)
IV	41 (44.6)
Histology	
DLBCL NHL	37 (40.2)
Follicular lymphoma NHL	3 (3.3)
Mixed cellularity HL	20 (21.7)
Nodular sclerosis HL	23 (25)
Other NHL type	8 (8.7)
Unspecified	1 (1.1)
Extranodal involvement	
Yes	22 (23.9)
No	70 (76.1)
ECOG status	
0	37 (40.2)
1	44 (47.8)
2	11 (12)
Previous regimens	
ABVD	48 (52.2)
R-CHOP	44 (47.8)
Number of previous chemotherapy cycles	1 (1-4)

NHL=Non Hodgkin's Lymphoma, DLBCL=Diffuse large B cell lymphoma, Hodgkin's lymphoma, ABDV=Adriamycin, bleomycin, vinblastine, dacarbazine, R-CHOP=Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolon

progressive illness was defined as the development of any new lesions or an expansion of any lesions that had already been identified. The percentage of patients who reacted completely or partially was used to compute the overall response rate.

SPSS version 23 was used to analyze data. Median and range were calculated for numeric variables like age and number of previous chemo cycles. Frequency and percentage were computed for categorical variables like gender, lymphoma type, disease status, lymphoma stage, histology, extranodal involvement, ECOG status, previous regimen, treatment response, mortality, and toxicity profile. Comparison between disease status and treatment response and toxicity profile was done using the Chi-square test or Fisher exact test. The level of significance was set at 5%.

Results

The baseline characteristics of included participants are displayed in Table 1. The median age was 41 years, ranging from 20 to 74 years. Most of the patients were males (73.9%). Of 92 patients, 32 had refractory disease, and 60 patients had relapse. Almost 88.1% of the patients had advanced stage of lymphoma (stage III or stage IV).

The majority of the patients had Diffuse large B cell lymphoma (DLBCL) NHL, followed by nodular sclerosis HL (25%). About 55 patients had ECOG status 1 to 2 and 23.9% had extra-nodal involvement. Of 92 patients, 52.2% of the patients had ABDV (*Adriamycin, bleomycin, vinblastine, dacarbazine*) as previous chemotherapy regimen, whereas 47.8% had R-CHOP (*Rituximab,* cyclophosphamide, doxorubicin, vincristine, and prednisolon) with overall median number of previous chemo cycle as 1.

Table 2 presents the treatment response and toxicity profile of individuals with refractory and relapse lymphoma. About 49 individuals had partial response, 29 had complete response, 6 had stable disease, and 12 had progressing disease. The modified DHAP had an overall response rate of 80.4%. The most frequent toxicity of modified DHAP was pancytopenia (46.7%), followed by febrile neutropenia (14.1%), respectively. Mortality occurred in 4 patients (13%).

Response to treatment was almost similar in patients with HL and NHL with *p*-value>0.05. The toxicity profile of patients with HL and NHL was statistically similar except febrile neutropenia. Febrile neutropenia was reported more in NHL patients as compared to HL patients with *p*-value=0.014. (Table 3)

Table 2: Response to the treatment and toxicity profile (n=92)

Response to treatment	**n (%)**
Partial response	45 (48.9)
Complete response	29 (31.5)
Progressive disease	12 (13)
Stable disease	6 (6.5)
Overall response	74 (80.4)
Mortality	
Yes	4 (4.3)
No	88 (95.7)
Toxicity profile	
Anemia	1 (1.1)
Electrolyte imbalance	11 (12)
Febrile neutropenia	13 (14.1)
Gastrointestinal illness	5 (5.4)
Infection	1 (1.1)
Nausea Vomiting	6 (6.5)
Pancytopenia	43 (46.7)

Discussion

Previously, in order to assess the effectiveness and toxicity profile, a modified DHAP therapy regimen

Table 3: Comparison of disease status with treatment response, mortality and toxicity (n=92)

Response to treatment	HL	NHL	*p*-value
Complete response	15 (33.3%)	14 (29.8%)	0.606
Partial response	22 (48.9%)	23 (48.9%)	
Stable disease	4 (8.9%)	2 (4.3%)	
No response/Progressive disease	4 (8.9%)	8 (17%)	
Toxicity profile			
Pancytopenia	25 (55.6%)	18 (38.3%)	0.097
Anemia	0	1 (2.1%)	0.999
Electrolyte imbalance	7 (15.6%)	4 (8.5%)	0.349
Febrile neutropenia	2 (4.4%)	11 (23.4%)	0.014*
Gastrointestinal illness	3 (6.7%)	2 (4.3%)	0.674
Infection	0	1 (2.1%)	0.999
Nausea/ vomiting	3 (6.7%)	3 (6.4%)	0.999

with a different time of administration and dose has been performed in patients with refractory or recurrent lymphomas.[3,8, 10-12] In the current study, we have also evaluated DHAP's effect and safety. The high overall response rate of 80.4% and complete response rate of 31.5% were achieved in patients with refractory and relapse lymphoma. Our study highlighted that this modified DHAP is a feasible and promising salvage treatment for the patients with lymphoma in Pakistan. The satisfactory outcomes achieved in the current study might be due to demographic characteristics of the included patients. First of all, the median age was 41, showing most of the patients were adults. Secondly, at the start of the study, the majority of the patients (88%) had good ECOG status (0 or 1).

In a similar study by Kanat O et al. also revealed high proportion of overall response of DHAP salvage therapy as 88.3% and complete response in 39.2% of the patients with lymphoma.[3] In another recent study by Frank et al. the overall response rate was 55%, wherein complete response achieved in 16% and partial response achieved in 39% of the patients of refractory disease or relapse lymphoma after modified DHAP therapy.[8] Hu J et al. in their study found overall response rate was 50% after combining DAC with a modified DHAP, whereas complete response rate was 35%, stable disease was 25% and disease control rate was 75%.[6] Abali H et al. conducted a comparative study of ICE and DHAP and found overall response rate in ICE group as 68% and in DHAP group as 48%.[13] They concluded that ICE had a better response rate as compared DHAP in patients with refractory or relapsed HL or NHL.[13] In the study by Josting et al. the complete response rate was achieved in 21% of the patients and partial response rate was achieved in 68% of the patients hence, overall response rate was 89% after 2 cycles of DHAP in patients with relapse or refractory disease.[14] In patients with refractory or recurrent DLBL, Kong et al. gave decitabine intravenously for five days (10 mg per day), followed by a modified DHAP, and obtained an overall response rate of 33%.[15]

In the current study, only four out of 92 lymphoma patients (4.3%) had mortality related to modified DHAP therapy. Kroschinsky et al. also found only two lymphoma patients died (1.7%) due to treatment-related complications.[8] Whereas, in the series of standard DHAP therapy by Velasquez et al., treatment related mortality was reported in 10 cases out of 90 cases.[16] In another study by Aparicio et al., 22 refractory or relapse lymphoma patients received modified DHAP including etoposide 40 mg/m^2 for 4 days and reported 5% treatment related mortality.[17]

Literature has revealed that salvage chemotherapy regimens are associated with side effects like infection, myelosuppression and renal toxicity which resulted in discontinuation therapy.[7,18-22] In the present study, most common toxicity of modified DHAP observed was pancytopenia, followed by

febrile neutropenia. We also observed that febrile neutropenia was significantly higher in NHL patients than HL patients (p=0.014). Abali et al. reported none of the patients had mortality because of treatment and the most frequent toxicities observed were anemia (15%), neutropenia (14%), febrile neutropenia and thrombocytopenia (10% each).[13] Lisenko et al. in their trial observed no renal toxicity in patients who received modified DHAP.[23] While, in the study by Sheha H et al., the standard DHAP was administered and found that the most frequent toxicities were anemia (63%), thrombocytopenia (50%), vomiting (57%), and nausea (59%).[22]

Our study has a few limitations. The patients included were heterogeneous concerning age, gender, disease status, and lymphoma types. Only modified DHAP was administered; however, comparison with another chemotherapy regimen like standard DHAP, ICE, or CHOP could generate evidence related to the best therapy for Pakistani patients with refractory or relapsed lymphoma disease. The patients were selected from a single institute, which also lacks the generalizability of the findings. To validate the results of the current study, more randomized control trials, including patients from different institutes, should be conducted.

Conclusion

Modified DHAP has a better overall response rate and manageable toxicity profile in patients with refractory or relapsed lymphoma.

Authors Contribution

RK: Idea, concept of study and literature review
GH: Critical review and concept of study
NA: Literature review and methods
AS: Data analysis and interpretation
TS: Literature review and methods
KA: Manuscript writing, critical appraisal and verification of results

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