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Treatment Outcome of Refractory/Relapsed High-Grade Non-Hodgkin Lymphoma and Classical Hodgkin Lymphoma at Tikur Anbessa Specialized Hospital: A Retrospective Cross-Sectional Study

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A Thesis to be submitted to the Department of Internal Medicine, School of Medicine, College of Health Sciences, Addis Ababa University, in partial fulfillment of the Sub-specialty Certificate in Clinical Hematology

March 2024 G.C.

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ACKNOWLEDGEMENT

First, I am grateful to express my gratitude to Dr. Amha Gebremedhin for his invaluable guidance and constructive comments throughout this research project. I would also like to thank the department of internal medicine and hematology unit for giving me an opportunity to conduct research for a fellowship program. I would also like to acknowledge AAU, college of health sciences for supporting this research project financially. Finally, I would like to acknowledge TASH outpatient department and the nursing staffs in hematology unit and staff at card room who were very cooperative and helpful in providing all the necessary records that enabled me to collect the data.

ABSTRACT

BACKGROUND: High-dose chemotherapy followed by autologous HSCT is the main stay of treatment for eligible patients with primary refractory or first relapsed high-grade NHL and classic Hodgkin's lymphoma (cHL). In centers where this modality of treatment is not readily available, outcome of salvage chemotherapy alone in this group of patients is not known. In this single center retrospective study, we evaluated the outcome of refractory/relapsed high-grade NHL and cHL treated with salvage chemotherapy alone.

METHODS: An institution-based cross sectional retrospective study was conducted to review the outcome of refractory/relapsed lymphomas treated with salvage chemotherapy from January 2019 to September 2023 at Tikur Anbessa Specialized Hospital (TASH). Data was collected from HMIS log book and electronic medical records of the patients and analyzed using SPSS statistical Software. Bivariate and multivariate logistic regression analysis was performed to identify the predictors of treatment outcome with 95% confidence interval and $p<0.05$ being considered as statistically significant. Survival analysis was performed using Kaplan-Meir method.

RESULTS: A total of 18 cHL (6 refractory and 12 relapsed) and 17 NHL (6 refractory and 11 relapsed) patients were included in the study. Ten (55.5%) of cHL and 9 (53%) of NHL patients were males and the median age was 29 and 42 years for the cHL and NHL groups respectively. The main salvage chemotherapy regimens were DHAP (72%) and GDP (28%) for cHL while R-DHAP (50%) and R-GDP (17.6%) for NHL. The ORR to salvage chemotherapy was significantly better for cHL than NHL group, 77.8% and 52.9% respectively, ($p=0.027$). The median PFS for cHL and high-grade NHL was 5 and 3 months, and the OS rate was 16 and 7 months, respectively. For both histologic groups, primary refractory disease, advanced stage at diagnosis and failure to achieve CR after salvage chemotherapy were associated with trend towards inferior OS. Nausea/vomiting and hematologic adverse effects were the main treatment related toxicities in both groups.

CONCLUSION: Three-fourth of patients with RR cHL and half of RR high-grade NHL respond to salvage chemotherapy alone at our center but the duration of response was not durable and long-term survival was limited.

FUND: This study was be funded by Addis Ababa university, College of Health Sciences

KEY WORDS: Lymphoma, Relapse, Refractory, Salvage chemotherapy, Treatment outcome

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LIST OF ABBREVIATIONS AND ACRONYMS

BL-Burkitt Lymphoma
BR-Bendamustine and Rituximab
CHOP-Cyclophosphamide, Hydroxy Adriamycin, Oncovin, Prednisolone
CIT-Chemoimmunotherapy
CR-Complete Response
daR-EPOCH-dose adjusted Etoposide, prednisolone, Oncovin, Cyclophosphamide and Adriamycin
DHAP-Cisplatin, Cytarabine and Prednisolone
DLBCL- Diffuse Large B-Cell Lymphoma
ECOG PS-Eastern Cooperative Oncology Group Performance Status
GDP-Gemcitabine, Cisplatin and Prednisolone
cHL-Classic Hodgkin Lymphoma
HSCT-Hematopoietic Stem Cell Transplantation
NHL-Non-Hodgkin's Lymphoma
IPI-International Prognostic Index
OS-Overall Survival
ORR-Overall Response rate
PD-Progressive Disease
PFS-Progression Free Survival
PR-Partial Response
R-DHAP-Rituximab plus DHAP
RECIST-Response Evaluation Criteria In Solid Tumors
R-GDP-Rituximab plus GDP
RT-Radiotherapy
SD-Stable Disease
R/R- Relapsed or Refractory

1. INTRODUCTION

Two-third of patients with diffuse large B cell lymphoma (DLBCL) are cured with frontline treatment with chemoimmunotherapy (CIT). However, 10% of patients do not respond adequately to initial treatment (primary resistance), and nearly one-third of patients will later relapse after achieving an initial complete response.[1] The treatment of refractory or relapsed DLBCL is challenging and depends on timing of relapse.[2] High dose-chemotherapy followed by autologous HSCT generally showed superior ORR and long-term survival in fit patients when compared to salvage chemotherapy alone.[3, 4]

Recently CD19-directed CART cell therapy demonstrated better event free survival than autologous HSCT in patients with DLBCL refractory to frontline CIT and/or relapsed within 12 months of frontline treatment.[56]

The cure rate of Hodgkin's lymphoma with front line multimodality treatment is >85%. However, 5% of patients with limited stage disease and 1/3 of those with advanced stage disease develop relapse even following multimodality therapy.[7,8] For these patients, different treatment regimens have been studied in second line and beyond; however, high dose chemotherapy followed by autologous HSCT was associated with superior survival outcomes in second line settings.[9] Novel drugs like anti-CD30 monoclonal antibody brentuximab vedotin (BV) and PD1-inhibitors also showed significant response in refractory and relapsed cHL patients as a second and/or third line after autologous HCT.[10–12]

For patients with refractory/relapsed high-grade NHL and cHL ineligible for autologous HSCT, the response to salvage chemotherapy alone is short-lived and survival is limited.[13,14] Similarly in centers where HSCT was not available more than 60% of these patients responded to salvage chemotherapy but the duration of response was short-lived.[15,16]

In Ethiopia HSCT and targeted treatments for refractory/relapsed cHL and high-grade NHL are not available so far. Therefore, except for few patients who seek treatment abroad, majority of these high-risk patients are treated with salvage chemotherapy alone. However, their treatment outcome was not known. Hence this

retrospective cross-sectional study was aimed to evaluate the treatment response of high-grade lymphomas treated with salvage chemotherapy alone at a single center.

2. METHODS

An institution based retrospective cross-sectional study was conducted at TASH including patients ≥15-years of age with refractory and/or relapsed cHL and high-grade NHL and treated with at least one salvage chemotherapy regimen from January 1, 2019 to September 30, 2023. The lower cut of 15 years was used because transition from pediatrics to adult care in our hospital is 15 years. High-grade NHL in this study refers to NHLs reported histologically as high-grade, excluding Burkitt's type. Refractory disease was defined as a lack of complete response to front-line treatment while relapsed disease was defined as histologically confirmed disease recurrence after achieving CR after 1st-line treatment. The diagnosis of the relapsed disease was made based on the pathologists' report of the lymph node biopsy and with/without IHC and the staging of the disease was determined by cross-sectional imaging, mainly CT-scan of the chest, abdomino-pelvis ± neck. As the PET scan was not available in Ethiopia, the response assessment of the treated patients was based on clinical data and interim and end of treatment CT-scan.

Patients with a diagnosis of Burkitt's lymphoma and low-grade lymphomas were excluded from the study. Moreover, patients with refractory and relapsed lymphoma but didn't receive at least one salvage treatment or with unknown outcome after the salvage treatment were excluded.

The study was conducted in compliance with the principles of the Declaration of Helsinki and after the study protocol was approved by ethical review board of College of Health Sciences, AAU. Data was collected from medical records of patients including HMIS log book, charts, electronic medical records and death summaries of the hospital, using structured questionnaire. Patients with undocumented survival status were called on the phone number registered on their

medical records to obtain their survival status or date of death from their close attendants. Patients were censored at the last date of follow up if their exact date of death was not obtained with all efforts.

The primary end point of the study was overall response rate (the combination of partial response and complete response rates) to salvage chemotherapy. The secondary end points were event free survival EFS), overall survival (OS) and occurrence of adverse events. EFS was defined as the time from initiation of salvage chemotherapy to the time of disease progression or death from any cause, whichever occurred first while OS was a time between the date of diagnosis of the refractory/relapsed disease and date of death or last date of follow-up.

Descriptive statistics was used to describe clinico-pathologic characteristics and treatment modalities of the patients with refractory and relapsed high-grade NHL and cHL. The correlation between dependent and independent variables was analysed using chi-square test with 95 % CI, and two-sided p-value of 0.05, considered as statistically significant. The duration of response and survival analysis was performed using Kaplan-Meir and the effect of independent variable on survival analysis was evaluated using log rank test.

3. RESULTS

Patients

Between January 2019 and September 2023, total of 47 patients diagnosed with refractory/relapsed high-grade NHL and cHL were identified. Twelve patients were excluded (for 11 patients, documentation regarding salvage chemotherapy and their outcome was not obtained and 1 patient underwent autologous HSCT immediately after 2 cycles of GDP). The remaining 35 patients (18 (51%) cHL and 17 (49%) high-grade NHL) were included in the analysis. Ten (55.5%) of cHL and 9 (53%) of NHL patients were males and the median age was 29 and 42 years for the cHL and NHL groups respectively. The baseline characteristics of the patients are depicted in **table 1.** Seventy six percent of patients with high-grade NHL and 78% of cHL had stage 3/4 disease at the time of diagnosis of RR disease. Results of IHC from lymph node biopsy was documented for 11 patients with cHL and 11(65%) of patients with

high-grade NHL. From 11 patients with RR NHL whose IHC result was known, 9 (82%) had DLBCL-ABC type and the remaining 2 patients had DLBCL-GC type.

Table 1. Baseline characteristics of patients with R/R cHL and high-grade NHL

Characteristics	Total (n=35)	cHL (n=18)	NHL (n=17)
Age, median (range)	42 (16-66)	29 (16-47)	50 (26-66)
Male, n (%) Female	19 (54) 16 (46)	10 (55.5) 8 (44.5)	9 (53) 8 (47)
Disease status, n (%) Refractory Relapsed	 12 (34.3) 23 (65.7)	 6 (33) 12 (67)	 6 (35.3) 11 (64.7)
Stage of primary disease, n (%) Stage I-II Stage III-IV Unknown	 5 (14.3) 21 (60%) 9 (25.7)	 2 (11.1) 12 (66.7) 4 (22.2)	 3 (17.6) 9 (52.9) 5 (29.4)
Frontline chemotherapy regimen, n (%) ABVD CHOP R-CHOP da-R-EPOCH	 18 6 10 1	 18 (100)	 6 (35.3) 10 (58.8) 1 (5.9)
Time to relapse from 1st chemotherapy Refractory < 12 months ≥12 months	 12 (34.3) 9 (25.7) 14 (40)	 6 (33.3) 4 (22.2) 8 (44.4)	 6 (35.3) 5 (29.4) 6 (35.3)
HIV Positive, n (%)	8 (23)	4 (22.2)	4 (23.5)
Stage at relapse Stage I-II Stage III-IV	 8 (33) 27 (77)	 4 (22) 14 (78)	 4 (23.5) 13 (76.5)
IHC of Relapsed disease cHL DLBCL ABC DLBCL GC Unknown	 11 (31.4) 9 (25.7) 2 (5.7) 13 (37.1)	 11 (61) 7 (39)	 9 (52.9) 2 (11.8) 6 (35.3)
ECOG PS 0-2 ≥ 3 Unknown	 22 (63) 4 (11.4) 9 (25.7)	 14 (77.8) 1 (5.6) 3 (16.7)	 8 (47.1) 3 (17.6) 6 (35.3)

Response to salvage chemotherapy

The major salvage chemotherapy regimens were DHAP and GDP accounting for 72% and 28% respectively for RR cHL and R-DHAP (50%) and R-GDP (17.6%) for high grade NHL. The median number of salvage chemotherapy cycles was 3 (range 2-6 for cHL and 1-7cycles for NHL). The ORR to salvage chemotherapy was 77.8% (27.8% CR and 50% PR) and 52.9% (11.7 CR and 41.2 % PR) for cHL and high-grade NHL respectively; (*p=0.027*).

Table 2. Salvage chemotherapy and response status

	Total (n=35)	cHL (n=18)	NHL (n=17)
Salvage regimen			
DHAP	16 (45.6)	13 (72.2)	3 (17.6)
R-DHAP	8 (23)		8 (47.1)
GDP	6 (17.1)	5 (27.8)	1 (5.9)
R-GDP	3 (8.6)		3 (17.6)
BR	2 (5.7)		2 (11.8)
Number of cycles			
Median (range)	3 (1-7)	4 (2-6)	3 (1-7)
Overall response, n (%)	23 (65.7)	14 (77.8)	9 (52.9)
CR	7 (20)	5 (27.8)	2 (11.8)
PR	16 (45.7)	9 (50)	7 (41.1)
No response	12 (34.3)	4 (22.2)	8 (47.1)

Table 3. Response status to salvage chemotherapy according to patient characteristics

Characteristics	Number of patients (n)					
	CR	PR	No Response	ORR	*Odds ratio [95% CI]*	Total, n (%)
All	7 (20)	16 (45.7)	12 (34.3)	23 (65.7)		35 (100)
Histologic Subtype						35 (100)
cHL	5	9	4	14 (77.8)	*2.8 [1.28-6.84]*	
HG NHL	2	7	8	9 (52.9)		
Relapse time						35 (100)
Relapse ≥ 12 months	5	5	4	10 (71)	*1.3 [0.51-3.2]*	
Relapse <12 months	2	11	8	13 (61)		
Stage at relapse						35 (100)
Stage I-II	1	5	2	6 (75)	*1.56 [0.37-6.6]*	
Stage III-IV	6	11	10	17 (62.9)		

There was no statistically significant difference between DHAP and GDP treated patients in terms of ORR or rate of CR in both histologic groups. Among patients with NHL who had IHC results, DLBCL with ABC signature by Han's algorithm showed significantly lower ORR to salvage chemotherapy when compared to other subtypes (OR 3.08 [95% CI 1.12-13.46; *p=0.018*]). In Both cHL and high-grade NHL, patients with primary refractory disease, early relapse and stage III/IV disease had trend towards lower ORR but statistically there was no significant difference.

Survival Outcomes

The median PFS was 5 months [95% CI; 2.9-7] for cHL and 3 months for high-grade NHL. When compared with refractory and early relapse (relapse within 1 year), patients relapsed beyond 1 year had better PFS in both cHL and NHL but the difference was not statistically significant. The median OS for cHL and high-grade NHL was 16 months [95% CI; 14.5-17.4] and 7 months [95% CI; 4.2-9.8] respectively (*p=0.004)*. Their respective 6-month, 1-year and 2-year OS rates were 100%, 72% and 11% for cHL and 58.9%, 11.8% and 5.9% for NHL respectively. For the overall cohort, OS rate was superior for relapsed disease as opposed to refractory disease (10 months vs 14 months; *p=0.02*), early-stage disease at relapse (20 months vs 10 months; p=0.06) and those who achieved CR after salvage chemotherapy (22 months vs 9.7 months for PR and 7 months for no response; p=0.039). As of December 31, 2023, with a median follow up of 16 months, 5/18 of the cHL and 4/17 of the high-grade NHL patients were alive.

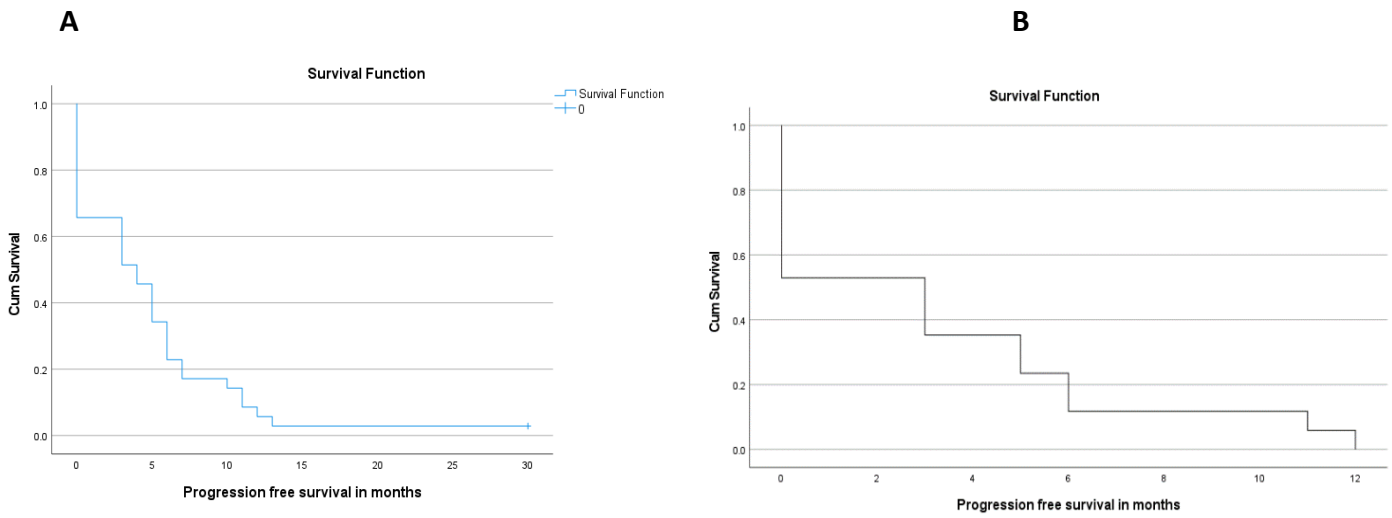

Fig. 1 Kaplan-Meier analysis of PFS: A) cHL, B) high-grade NHL

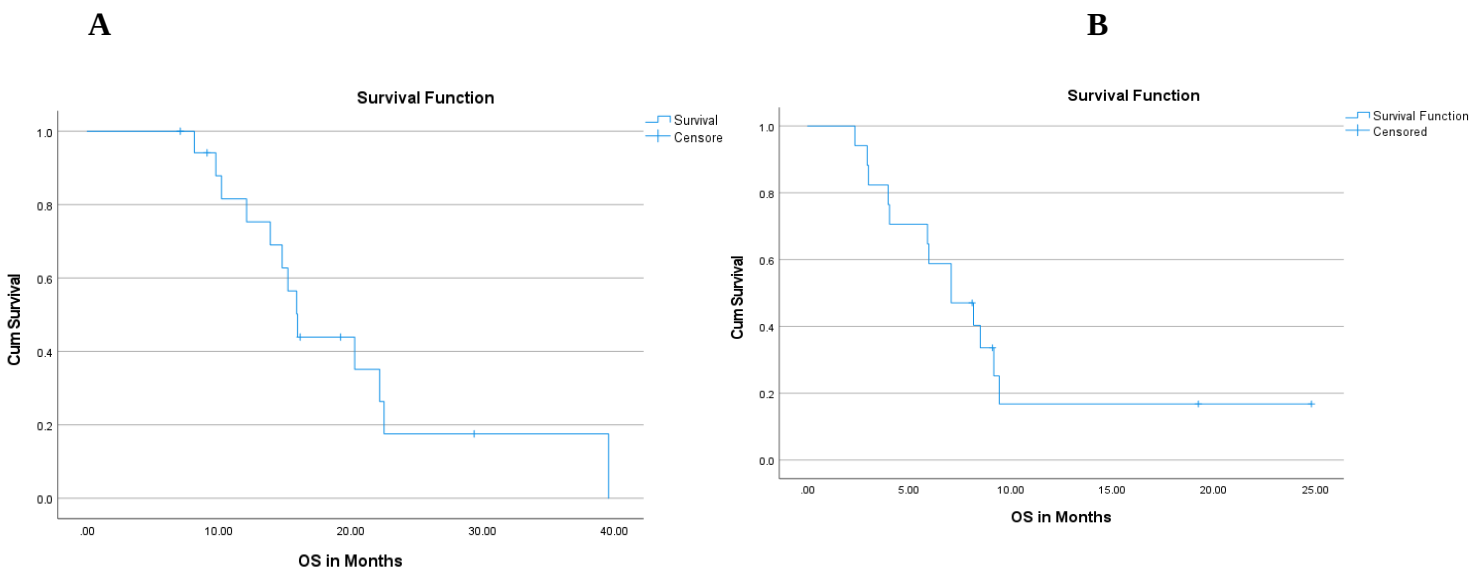

Fig. 2 Kaplan-Meier analysis of OS of RR: A) cHL and B) high-grade NHL

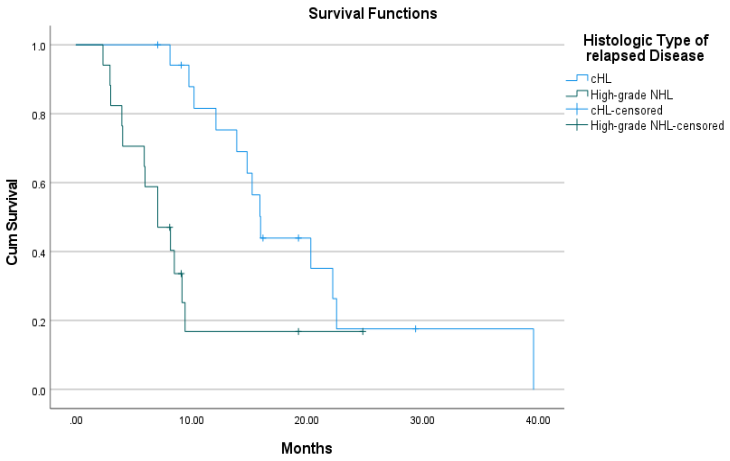

Fig. 3 Kaplan-Meier of OS in Histologic Subtypes of R/R Lymphoma

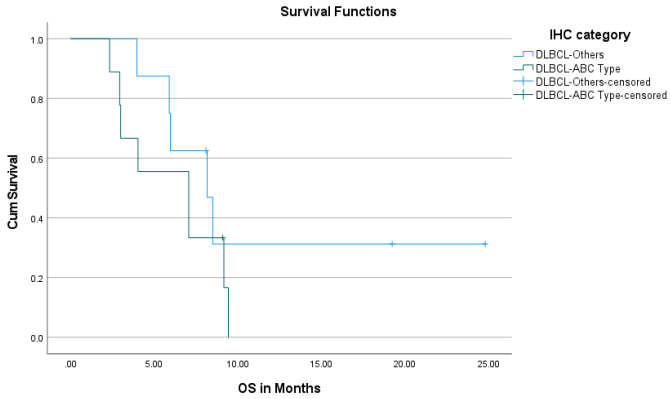

Fig. 4 Kaplan-Meier of OS in NHL based on IHC subtypes

Adverse Events

Regarding the toxicities, any grade anemia occurred in 42.4% of patients while grade 3/4 was in 15%. Twenty three percent and 28.6% of the patients had grade 3/4 thrombocytopenia and neutropenia respectively. Overall occurrence of grade 3/4 neutropenia and thrombocytopenia was similar between cHL and NHL as well as GDP and DHAP based treatment groups. Grade 3/4 nausea and vomiting occurred in 23%, and acute kidney injury was seen in 8 (23%). The incidences of

nausea/vomiting and AKI were more common in DHAP group but the difference was not statistically significant (OR=1.287 [95% CI; 0.884-1.873]). There were two deaths presumed to be treatment related. One patient with refractory DLBCL and HIV died of sepsis while on the 2nd cycle of R-DHAP and the other patient with relapsed DLBCL had interactable vomiting following the 1st cycle of R-DHAP and presented with hypotension, hypoglycemia and mental status change, 4 days after discharge from the hospital and succumbed despite resuscitative measures.

Table 4. Treatment toxicities among patients with R/R lymphoma receiving GDP and DHAP regimens

	Total (n=35)	**GDP ± R**	**DHAP ± R**
Anemia n (%)	14 (42.4)	4 (44)	10 (41)
Grade 3/4	5 (15)	2 (22)	3 (12.5)
Neutropenia	17 (48.6)	5 (55)	12 (50)
Grade 3/4	10 (28.6)	3 (33)	7 (26)
Thrombocytopenia	8 (22.8)	2 (22)	6 (25)
Grade 3/4	6 (17)	1 (11)	4 (16.6)
Nausea/Vomiting	15 (42.8)	3 (30)	12 (50)
Grade 3/4	8 (23)	1	7 (29)
AKI	8 (23)	1	7 (29)
Sepsis	7 (20)	2	5
DILI	2 (5.7)		2
Steroid induced DM	2 (5.7)	2	
Sinus tachycardia	1 (2.9)		1

4. DISCUSSION

Although high dose chemotherapy followed by autologous HSCT remains the standard of care for most of R/R high grade NHL and cHL patients in resource rich settings, only limited number of patients in our center have access to this modality of treatment due to unavailability. Hence patients with R/R high grade lymphomas

are treated with salvage chemotherapy alone. In this study we reported the outcomes of R/R high grade NHL and cHL patients treated with mainly DHAP and GDP (± Rituximab for CD20 Positive B-cell lymphomas). Two-third (65.7%, 77.8% of cHL and 52.3% of NHL) of our patients responded to these regimens. This is consistent with *Alden A. Moccia et al* from Canada who reported ORR of 49% and 71% for patients with DLBCL and HL, respectively to GDP regimen.[17] *Kaimila et al* from Malawi also reported similar findings, where the ORR was 71%, using EPIC regimen (etoposide, prednisolone, ifosfamide and cisplatin) for relapsed and refractory lymphomas.[15]. *H. Abalı et al* reported an ORR of 70% for 13 cHL and 50% for 41 NHL patients using ICE and DHAP regimens without statistically significant difference between the two regimens.[18] In a study by *Julie Lignon et al* of refractory and relapsed B-cell NHLs treated with R-DHAP regimen, the ORR in DLBCL subgroup was 59.5%.[19] However, in Egyptian study that included refractory and relapsed NHLs treated with GDP and DHAP reported higher ORR of 70% and 64 % respectively.[16] In contrast, in our study, for patients with NHL sub-group, an ORR was 53%. The lower ORR in our study could be explained by high number of DLBCLABC-type in our NHL group, which showed significantly lower response to salvage chemotherapy and inferior OS than other immunophenotypic sub-types. DLBCL-ABC type was shown to be associated with inferior response to CIT and survival in several studies.[20,21]

Variables like older age, poor performance status, advanced stage of the disease and early relapse were predictors of poor ORR to salvage chemotherapy and mainly of survival in both RR cHL and DLBCL in several studies.[22–24] In another study, by *Crump et al* comparing GDP and DHAP as pretransplant salvage chemotherapy for RR aggressive lymphomas these factors were not predictors of ORR but overall survival.[25] We didn't observe statistically significant difference in overall response by time to relapse, stage of the disease and type of salvage regimen (GDP vs DHAP ± Rituximab) in this study in both histologic sub-types. Due to its small sample size our study may not be powered to assess the differences in response in these subgroups.

Only 8/35 (4 cHL and 4 NHL) (22%) of patients were HIV positive in our study. HIV positive patients had inferior OS in NHL group with median OS of 4 months and 8 months for HIV positive and negative patients respectively; (p=0.3).

There was no difference in survival based on HIV status in cHL subgroup. No difference in response was reported in Malawi between 13 HIV positive and 8 HIV negative patients with RR lymphomas.[15] However, we emphasize that it is difficult to evaluate the prognostic impact of HIV on treatment outcomes of RR lymphomas based on our study as the sample size and the number of HIV positive patients was small.

In our study, despite high-rate of initial response to salvage chemotherapy, the median duration of response was short (5 months for cHL and 3 months for high-grade NHL). These findings were notably similar to what was reported in resource-rich settings when salvage chemotherapy was not followed by consolidative high-dose therapy with autologous stem cell rescue.[14,26,27]

The median OS was significantly better in cHL than NHL group (16 months for and 7 months; *p=0.004)* in our study. For both cHL and NHL, survival was significantly lower than what was reported with autologous transplantation where 2-year PFS and OS were 36% and 46% for DLBCL and 58% and 85% for cHL, respectively.[17] Variables like, advanced stage, high IPI score, ECOG PS >2 and primary refractory or early relapse were shown to be predictors of poor survival in several studies.[217] In our study however, the impact of these factors on survival was not statistically significant when cHL and NHL were analyzed separately. This is due to small number of patients in each subgroup, limiting the statistical power of the study.

The incidence of treatment related adverse events were similar between cHL and NHL groups. Overall, the most commonly reported adverse events were, anemia, neutropenia and nausea/vomiting. Grade 3/4 hematologic toxicities were similar between DHAP and GDP groups. This in contrast to lower incidence of neutropenia with GDP than DHAP based treatment in other studies.[16,25] The difference may be due to small number of patients treated with GDP based regimen in our study. The incidence of grade 3/4 nausea/vomiting, sepsis and renal impairment was higher in DHAP than GDP based regimen, but the difference was not statistically significant. Two patients were died of presumed treatment related complications.

This study had several limitations. First, as it's a retrospective study some of the follow up data, mainly for the primary disease were incomplete. We tried to analyze cHL and NHL groups separately but due to small sample size, our study has limited

statistical power to assess the effect of different factors on outcomes of salvage chemotherapy on each histologic sub-type.

With all the limitations, this is the only study that reported the outcomes of salvage chemotherapy alone in refractory and relapsed high-grade lymphomas in Ethiopia. Short duration of response and limited survival with salvage chemotherapy alone in our study shows that there is an urgent need of other better modalities of treatment like HSCT and targeted agents for these high-risk patients. Prospective studies with higher sample size that separately look into refractory and relapsed cHL and high-grade NHL subtypes, are warranted to more specifically evaluate outcome of salvage chemotherapy and associated factors.

In summary, three-fourth of patients with RR cHL and half of RR high-grade NHL respond to salvage chemotherapy alone at our center but the duration of response was short-lived and long-term survival was limited.

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