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Evaluation of Different Treatment Regimens for Relapsed and Refractory NHL: Single Institute Experience

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Abstract

Background and Aim: The treatment of choice for relapsed or refractory Non-Hodgkin Lymphoma (NHL) mainly, is High dose chemotherapy with autologous stem cell transplantation. However, its use is mostly restricted to patients responding to salvage chemotherapy. In this study, our aim was to evaluate outcome and toxicity of different treatment modalities of relapsed and refractory NHL. **Patient and Methods:** This retrospective study included 217 patients were diagnosed as refractory or relapsed NHL. Those patients received different treatment modalities as GDP (Gemcitabine, dexamethasone, cisplatin), DHAP (Dexamethasone, Cytarabine, and Cisplatin), MINE (Mitoxantrone, ifosfamide, etoposide and mesna), CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone), and CVP (Cyclophosphamide, vincristine and prednisone). **Results:** The median age of patients in the study was 50 years. Patients who received DHAP showed ORR of 62%, which was the highest response. The most common adverse effects were hematological which were more noticed in patients, received CHOP. Sixty one patients (54.5%) had anemia, 54 patients (48.2%) had neutropenia and 55 patients (49.1%) had thrombocytopenia, but the difference between the different lines of treatment wasn't significant p value of 0.95. The median time to relapse is 10 months and the median survival time is 40 months. The 3-year PFS rates of all patients were 49.3%, while the 3 year OS rates were 54.8%. **Conclusion:** The overall and PFS didn't show any difference between different lines of treatment.

Keywords

Non Hodgkin Lymphoma, Progression Free Survival, Overall Response Rate

1. Introduction

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of lymphoprolifer-

ative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) cells. NK/T-cell lymphomas are very rare [1]. NHL includes many clinicopathologic subtypes, each with distinct epidemiologies; etiologies; morphologic, immunophenotypic, genetic, and clinical features; and responses to therapy. With respect to prognosis, NHLs can be divided into two groups, indolent and aggressive [2]. Indolent NHL types have a relatively good prognosis with a median survival as long as 20 years, but they usually are not curable in advanced clinical stages [3]. The aggressive NHLs grow faster and have shorter survival; the number of patients cured with intensive chemotherapy currently has been increasing [4]. A large number of new therapeutic protocols based on a combination of multi-drug chemotherapy, have been introduced for the treatment of patients with high-grade NHL [5]. Multi-drug chemotherapy produces an overall survival of 50% - 60% at five years in aggressive NHL [6]. However, a significant proportion of patients relapsed, experiencing either failure after prolonged treatment, known as refractory disease, or relapsed after initial response, known as a relapsing disease [7]. The strategy for management of relapsed or refractory disease is to deliver salvage chemotherapy, followed by high dose chemotherapy and autologous stem-cell transplantation in responding patients [8]. There is no optimal salvage regimen for relapsed or refractory B-cell lymphoma; also there are no standard options of treatment for patient's response to second line regimens, nor for patients who are not eligible for transplant [9].

2. Patients and Methods

2.1. Study Type and Duration

The current retrospective study included 217 patients who were diagnosed as refractory or relapsed NHL (B or T) at Medical Oncology Department, Assiut University Hospitals from January 2011 to December 2015.

2.2. Inclusion Criteria

- Patient who are older than 18 years old;
- Histologically confirmed to have Non Hodgkin lymphoma;
- Clinically and radiologically confirmed to have relapsed and refractory;
- Stage from 1 to 4 Non Hodgkin lymphoma;
- Previously treated with CHOP, first line chemotherapy, non-metastatic;
- Furthermore, patient should have Eastern Cooperative Oncology Group performanous status (ECOG) 0 - 1 with adequate hematologic, hepatic and renal functions including hemoglobin > 10 /dl, absolute neutrophil count ≥ 1500/mm^3, platelets ≥ 100,000/mm^3, serum bilirubin < 2 mg/dl, both ALT and AST ≤ 2 × upper limit of normal (ULN), alkaline phosphates ≤ 5 × ULN, and serum creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 60 ml/min.

2.3. Exclusion Criteria

- Prior history of cardiac disease (serious arrhythmia, heart failure, myocardial

infarction, or unstable angina within the last 6 months);

- Active serious infection or a psychiatric illness.

2.4. Study Design

Patients were divided into 6 groups:

Group (1): 54 patients received Dexamethasone, Cytarabine, and Cisplatin (DHAP).

Group (2): 25 patients received Mitoxantrone, ifosfamide, etoposide and mesna (MINE).

Group (3): 13 patients received fludarabine, cyclophosphamide (FC).

Group (4): 8 patients received Cyclophosphamide, vincristine and prednisone (CVP).

Group (5): 5 patients received Gemcitabine, Cisplatin and Dexamethasone.

Group (6): 112 patients received Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP).

All studied patients were subjected to the following: Full history taking, Complete physical examination, Laboratory investigations including CBC, liver function test, kidney function test, LDH, and bone marrow aspirate and biopsy., MSCT chest & abdomen, Excisional lymph node biopsy, International Prognostic Index calculation, Evaluation of the patients (toxicity and response) done by*:*

a) Evaluate toxicity: signs of GIT toxicity as nausea, vomiting and diarrhea, signs of neurological toxicity as mood changes, restless, sleeping problems, unsteadiness, signs of hepatic toxicity as hyperbilirubinemia and raised liver enzymes (AST level > 38 U/L, ALT level > 41 U/L), and signs of anemia as complete blood count with differential count.

b) Evaluate response: by physical examination, MSCT chest and abdomen and Lugano response criteria for NHL [10] observed at the end of treatment of 6 cycles as complete response, partial response, stable disease, progressive disease.

2.5. Statistical Analysis

The results of study were tabulated and statistical analysis was carried out using statistical package spss version 23. using significant level ($p < 0.05$), chi square test was used to compare frequencies, M ANOVA, Survival curves were estimated with Kaplan Mayer method [11] and compared using Log-rank test.

3. Results

3.1. Patient Characteristics (n = 217)

The median age of patients in the study was 50 years old with 116 (53.5%) of patients were females. One hundred and twelve patients (51.6%) were with ECOG performance status of 1133 patients (61.3%) with B symptoms and the median LDH was 277. Most of the patients were B-NHL; 185 patients (85.3%), 119 patients (54.8%) were in stage 3 and 200 of patients (92.2%) received CHOP as 1st line. One hundred and thirteen (52.1%) of patients were refractory after receiving 1st line, 59 (56.7%) of patients were relapsed before 1 year and 45 (43.3%)

after 1 year. Most of the patients 85 (39.2%) were with low intermediate IPI, as shown in Table 1 & Table 2.

Table 1. Base line patient's characteristics.

	No. (n = 217)	%
Age		
Range	51 - 69	
Mean ± SD	47.70 ± 13.18	
Median (IQ)	50.00	
Sex		
Male	101	46.5
Female	116	53.5
Performance status		
0	25	11.5
1	112	51.6
2	80	36.9
B symtom		
Positive	133	61.3
Negative	84	38.7
LDH		
Range	689 - 781	
Mean ± SD	307.9954 ± 150.3	
Median (IQ)	277	
Pathology		
B cell-NHL	185	85.3
T cell-NHL	32	14.7
Stage		
1A	6	2.8
1B	6	2.8
2A	40	18.4
2B	7	3.2
3A	78	35.9
3B	41	18.9
4	39	18.0
1st line		
CHOP	200	92.2
R-CHOP	17	7.8
Response		
Refractory	113	52.1
Relapse	104	47.9
Before 1 Y	59	56.7
After 1 Y	45	43.3
International prognostic index		
Low risk	50	23
Low intermediate	85	39.2
High intermediate	46	21.2
High risk	36	16.6

Table 2. Patient's characteristic of different treatment groups.

	DHAP N = 54	MINE N = 25	Fludara + Endoxan N = 13	CVP N = 8	GDP N = 5	CHOP N = 112	P value
Age			44.62.62 ± 13.9				
Mean ± SD	52.53 ± 8.3	52.48 ± 8.3	44.63 ± 13.9	48 ± 5.88	32 ± 2.24	45.55 ± 3.2	0.000
Sex							
Male	32 (59.3%)	12 (48%)	5 (38.5%)	0 (0%)	0 (0%)	52 (46.4%)	0.01
Female	22 (40.7%)	13 (52%)	8 (61.5%)	8 (100%)	5 (100%)	60 (53.6%)	
PS							
0	5 (9.3%)	2 (8%)	3 (23.1%)	0 (0%)	4 (80%)	11 (9.8%)	0.000
1	33 (61.1%)	16 (63%)	6 (46.2%)	3 (37.5%)	0 (0%)	54 (48.2%)	
2	16 (29.6%)	7 (28%)	4 (30.8%)	5 (62.5%)	1 (20%)	47 (42%)	
Pathology							
B cell NHL	46 (58.2%)	18 (72%)	10 (76.9%)	7 (87.5%)	4 (80%)	100 (89.3%)	0.32
T cell NHL	8 (14.8%)	7 (28%)	3 (23.1%)	1 (12.5%)	1 (20%)	12 (10.7%)	
LDH							
mean ± SD	295.32 ± 123.20	277.24 ± 98.39	319.92 ± 55.86	204 ± 5.3	384 ± 8.9	325.2 ± 13.2	0.162
B symptom							
Positive	33 (61.1%)	23 (92%)	7 (53.8%)	5 (62.5%)	5 (100%)	60 (53.6%)	0.006
Negative	21 (38.9%)	2 (8%)	6 (46.2%)	3 (37.5%)	0 (0%)	52 (46.4%)	
Stage							
1A	1 (1.9%)	0 (0%)	4 (30.8%)	0 (0%)	0 (0%)	1 (0.9%)	0.000
1B	1 (1.9%)	4 (16%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	
2A	12 (22.2%)	5 (20%)	0 (0%)	0 (0%)	0 (0%)	23 (20.5%)	
2B	1 (1.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (5.4%)	
3A	23 (42.6%)	12 (48%)	1 (7.7%)	0 (0%)	1 (20%)	41 (36.6%)	
3B	12 (22.2%)	0 (0%)	8 (61.5%)	4 (50%)	4 (80%)	13 (11.6%)	
4	4 (7.4%)	4 (16%)	0 (0%)	4 (50%)	0 (0%)	27 (24.1%)	
1st line							
CHOP	54 (100%)	25 (100%)	13 (100%)	8 (100%)	5 (100%)	95 (84.8%)	0.016
R-CHOP	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	17 (15.2%)	
1st Response							
Refractory	25 (46.3%)	8 (32%)	9 (69.2%)	0 (0%)	4 (80%)	67 (59.8%)	
Relapsed	29 (53.7%)	17 (30.8%)	4 (30.8%)	8 (100%)	1 (20%)	45 (40.2%)	0.002
Before 1 y	28 (96.5%)	6 (35.3%)	2 (50%)	5 (62.5%)	0 (0%)	18 (40%)	
After 1 y	1 (3.4%)	11 (64.7%)	2 (50%)	3 (37.5%)	1 (100%)	27 (60%)	0.89
IPI							
Low risk	7 (13%)	9 (36%)	3 (23.1%)	1 (12.5%)	4 (80%)	26 (23.2%)	
Low intermediate	24 (44.4%)	11 (44%)	4 (30.8%)	5 (62.5%)	1 (20%)	40 (35.7%)	0.05
High intermediate	9 (16.7%)	4 (16%)	4 (30.8%)	1 (12.5%)	0 (0%)	28 (25%)	
High risk	14 (25.9%)	1 (4%)	2 (15.4%)	1 (12.5%)	0 (0%)	18 (16.1%)	

3.2. Treatment Outcome

Response to 2nd line was shown in Table 3.

Toxicity of different treatment lines was shown in Table 4.

Survival of patients was shown in Figures 1-4.

Table 3. Response to different 2nd line regimens.

	DHAP N = 54	MINE N = 25	Fludara + Endoxan N = 13	CVP N = 8	GDP N = 5	CHOP N = 112
CR	14 (25.9%)	7 (28.0%)	3 (23.1%)	2 (25.0%)	2 (40.0%)	19 (17.0%)
PR	20 (37.0%)	3 (12.0%)	2 (15.4%)	2 (25.0%)	1 (20.0%)	18 (16.1%)
Progression	12 (22.2%)	8 (32.0%)	5 (38.5%)	2 (25.0%)	1 (20.0%)	38 (33.9%)
Stationary	8 (14.8%)	7 (28.0%)	3 (23.1%)	2 (25.0%)	1 (20.0%)	37 (33.0%)

Table 4. Toxicity of different 2nd line regimens.

	DHAP N = 54	MINE N = 25	Fludara + Endoxan N = 13	CVP N = 8	GDP N = 5	CHOP N = 112	P value
Anemia	34 (63%)	12 (48%)	12 (92.3%)	4 (50%)	3 (60%)	61 (54.5%)	0.12
Neutropenia	22 (40.7%)	11 (44%)	7 (53.8%)	1 (12.5%)	1 (20%)	54 (48.2%)	0.31
Thrombocytopenia	27 (50%)	14 (56%)	7 (53.8%)	5 (62.5%)	2 (40%)	55 (49.1%)	0.95
Nausea	32 (59.3%)	10 (40%)	7 (53.8%)	5 (62.5%)	3 (60%)	60 (53.6%)	0.71
V vomiting	31 (57.4%)	14 (56%)	5 (38.5%)	4 (50%)	3 (60%)	62 (55.4%)	0.88
Diarrhea	17 (31.5%)	12 (48%)	5 (38.5%)	2 (25%)	1 (20%)	40 (35.7%)	0.68
Neurotoxicity	22 (40.7%)	12 (48%)	6 (46.2%)	4 (50%)	4 (80%)	39 (34.8%)	0.32
Hepatotoxicity	21 (38.9%)	10 (40%)	2 (15.4%)	1 (12.5%)	0 (0%)	34 (30.4%)	0.18
Renal toxicity	18 (33.3%)	7 (28%)	5 (38.5%)	3 (37.5%)	3 (60%)	40 (41.1%)	0.69

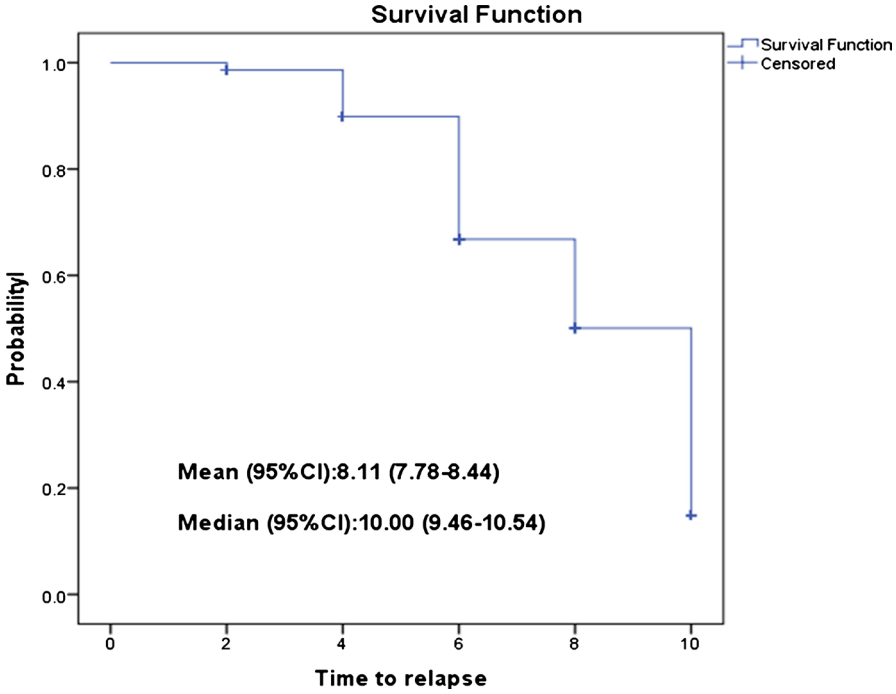

Figure 1. PFS of all patients; the median time to relapse was 10 months; *p* value = 0.679.

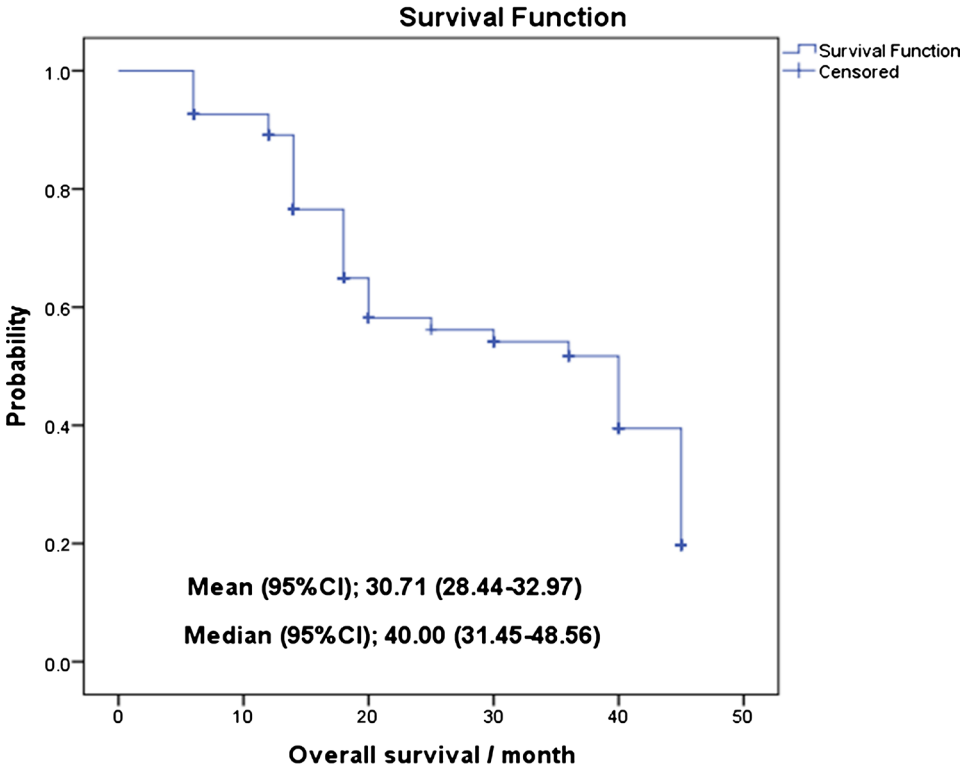

Figure 2. OS of all patients; the median survival time was 40 months; *p* value = 0.917.

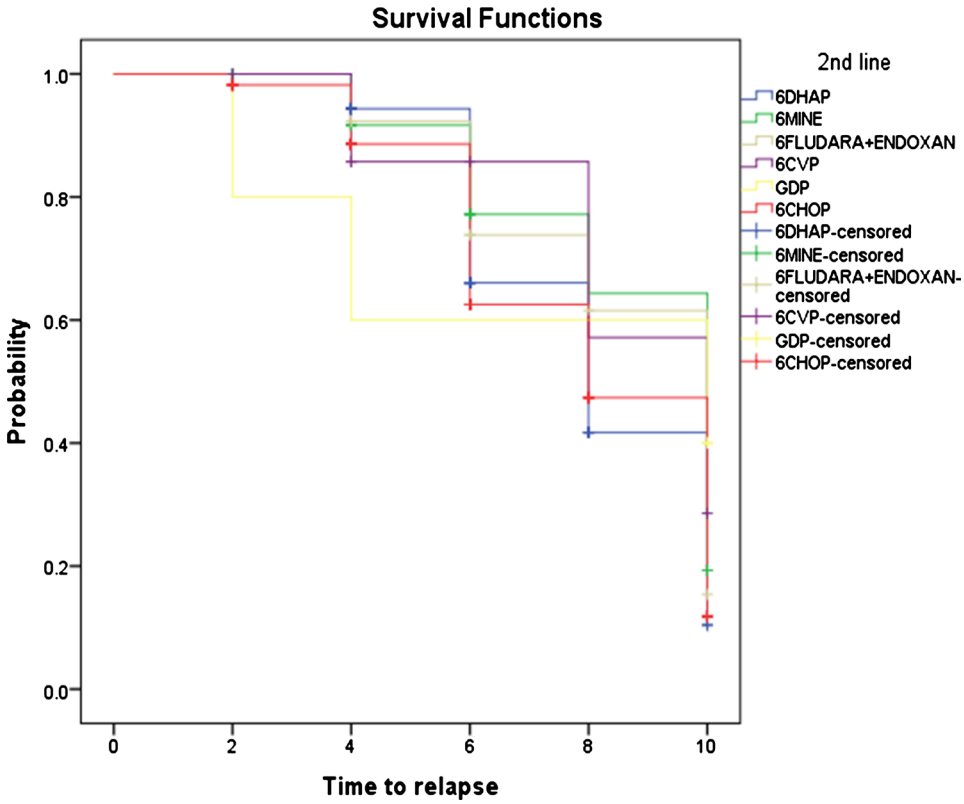

Figure 3. PFS of different treatment regimens; The median times to relapse were 8 months, 10 months, 10 months, 10 months and 8 months for patients who had received DHAP, MINE, Fludarabine & Cyclophosphamide, CVP, GDP and CHOP with no significant difference; *p* value = 0.679.

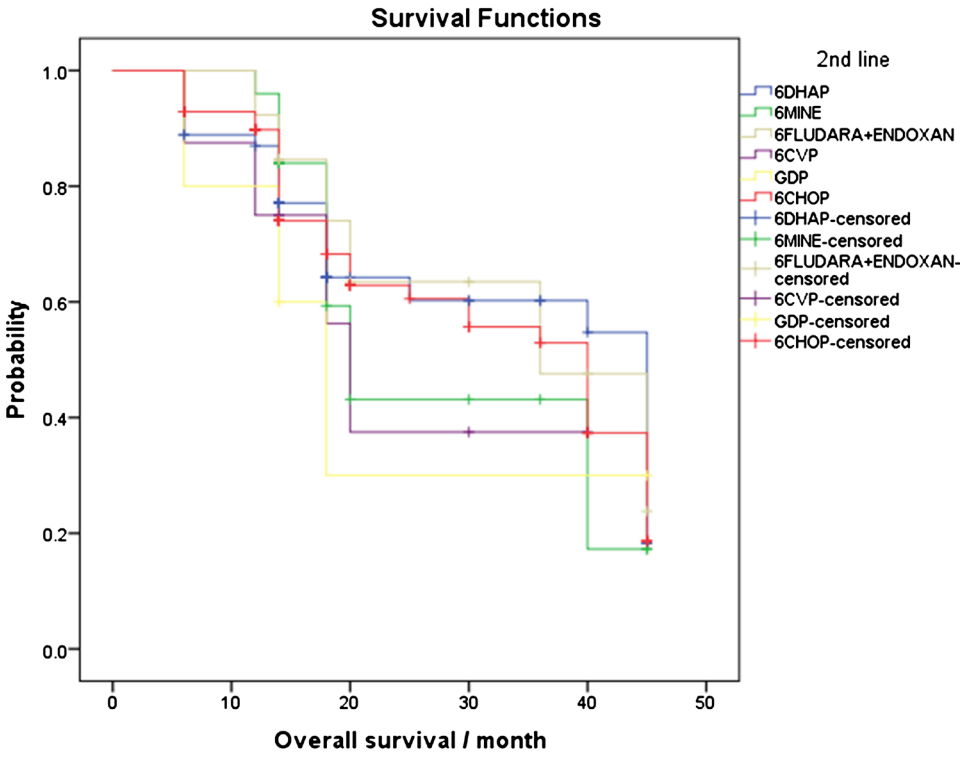

Figure 4. OS of different treatment regimens; The Median survival times were 45 months, 20 months, 36 months, 20 months, 18 months and 40 months for patients who received DHAP, MINE, Fludarabine and Cyclophosphamide, CVP, GDP and CHOP, with no significant difference; p value = 0.917.

4. Discussion

Several attempts have been made to prolong survival of patients with relapsed and refractory NHL [12]. Refractory or progressive disease is identified during the post-treatment response evaluation. The treatment of patients with relapsed or refractory lymphomas remains challenging. In general, the standard care is high-dose chemotherapy followed by autologous stem cell transplant (ASCT) for patients who are sensitive to salvage chemotherapy. There are no standard options of treatment for patients who show no response to second-line regimens, nor for patients who are not eligible for transplants [13]. In developing countries with limited resources as Egypt, high dose chemotherapy followed by ASCT is not always an option of treatment in relapsed and refractory lymphomas due to a small number of transplant centers across the country, long waiting lists and limited resources [14].

Regarding the response rate, the ORR in this study was higher in patients receiving DHAP and GDP but there was no statistical difference between the different lines of treatment. These findings were in agreement with that of *Ismaeil., et al.* who reported that the ORR was 65% and 67.6% in patients who had received GDP and DHAP respectively [15]. Conversely, this finding was higher than that of Abali, *et al.* who reported ORR of 48% in the DHAP group [16].

As regard treatment toxicity, the most common adverse effect was hemato-

logical toxicity which was more noticed with patients received CHOP but the difference between the different lines of treatment wasn't significant. Neutropenia and anemia in patients who had received CHOP were slightly higher than that of KLAUS, *et al.* who reported a rate of 42% and 44% in their patients respectively [17].

Furthermore, there was no significant difference between different regimens in the occurrence of thrombocytopenia. Crump, *et al.* reported that thrombocytopenia occurred in 31% and 47% of patients who had received GDP and DHAP respectively [18].

As regard the non-hematological toxicities, nausea, vomiting, and diarrhea were the most common adverse effect which were more in patients who had received DHAP, but the difference wasn't significant. This finding was in agreement with that of Ismaeil, *et al.* who reported that nausea and vomiting were the most common non-hematologic toxicities in the majority of patients who received GDP and DHAP with a non-significant difference [15].

As regard the survival analysis performed in this study, the 3-year survival rate of patients received MINE was higher than that of Haung, *et al.* who reported the 1- and 2-year survival rates of 34.2% and 7.9%, respectively [19].

The survival rates were moderate in patients who had received DHAP. This finding was higher than that of Li, *et al.* who reported a median survival time of 8.3 months, and 1-year and 2-year survival rates of 30.8% and 19.3%, respectively [20].

The 3-year survival rate of patients received GDP was higher than that of Fan, *et al.* who reported 1-year overall survival rate of 41.7% [21].

Wang, *et al.* reported the 1- and 2-year PFS rates of 54.5% and 45.4% and the 1- and 2-year OS rates of 72.7% and 54.7% for patients who had received GDP [22].

As regard CVP regimen, the 3 year PFS was low. Hochster, *et al.* reported PFS estimates at 2 and 4 years of 42% and 34%, which was higher than that of our results. The difference may be attributed to the addition of Rituximab to their CVP regimen [23].

5. Conclusion

From the results of the current study, we conclude that relapsed and refractory disease continued to represent the most significant challenge in treating NHL with no difference between different lines of treatment. The hematological toxicity, GIT toxicity, hepatoxocitiy, neurotoxicity and renal toxicity didn't show a significant difference between investigated lines of treatment. The overall and PFS didn't show any difference between different lines of treatment while the low response and survival rates mandate the need to add rituximab to 2nd line treatment and to proceed to bone marrow transplantation in eligible patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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