

Relapse in Patients with Non-Hodgkin's Lymphoma

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ABSTRACT

Background: non Hodgkin Lymphoma is the most common hematologic malignancy and it is the 6th leading cause of cancer death. Relapses still occur in the majority of patients; overall, more than 30% of DLBCL will ultimately relapse. **Aim of study:** primary objective was to retrospectively correlate the occurrence of relapsed, refractory and in remission diffused large B cell lymphoma patients to both clinic-pathological features of the disease and line of treatment received.

Patients and Method: a total of 116 patients with aggressive high grade NHL patients (DLBCL) representing 86.6% of all patients presented to Clinical Oncology Department, Ain Shams University in the period between January 2009 and December 2015. Data were collected between January 2017 until March 2017.

Results: the mean age at diagnosis of the studied patients was 45 years. The incidence in male was higher than female (52.6% vs. 47.4%), the majority of the cases didn't have B symptoms (57.7%), high LDH level was measured among the cases (37%) and in only 36 patient's files, 16.37% of the cases had positive HCV. The most common stage at diagnosis was stage IV (33.6%) followed by stage III (29.3%). Based on response to the 1st line chemotherapy, DLBCL patients were further statistically analyzed into three categories: 24 refractory patients (20.07%), 43 relapsed patients (37.1%) and 49 patients in remission (non relapsed) (42.2%). Regarding 1st line treatment regimen by R-Chop, complete response rates were significantly higher in patients who received R-CHOP than in the group who received CHOP alone (57.1% vs 42.8%). The median disease free survival in the relapsed group was 8 months. The median survival time for the DLBCL patients was 24 months. The survival rate after 1 year was 83.7%, while after 2 years it was 52.8% and after 3 years it was 21.3%.

Conclusion: relapsed and refractory disease continues to represent the most significant challenge in treating NHL, the addition of rituximab to the CHOP regimen increased the CR rate and prolonged event-free and overall survival.

Keywords: non Hodgkin's lymphoma, DLBCL, relapsed refractory patients, CHOP vs. R-CHOP and DFS.

INTRODUCTION

The Non-Hodgkin lymphoma (NHL) is a variation gathering of lymph proliferative malignancies with different patterns of behavior and responses to treatment. Generally, NHL originates in lymphoid tissues and might spread in the different organs⁽¹⁾. Worldwide statistics Perry *et al.*⁽²⁾ recognized the following significant differences in the epidemiology of NHL in developing countries, in contrast with the developed countries:

- Higher rates of males.
- Lower median age at time of presentation for both low- and high-grade B-cell lymphoma.
- Lower frequency of B-cell lymphoma and a higher frequency of T- and NK-cell (Natural Killer-cell) lymphoma.
- Approximately 20% more cases of high-grade B-cell lymphoma furthermore 10% fewer cases of low-grade B-cell lymphoma.

The cause of most cases of NHL is obscure, however some strong risk factors have been recognized including (genetic diseases, environmental agents, and infectious agents) have been related with the development of lymphoma⁽³⁾. In 2008 The International Agency for Research on Cancer (IARC) published the 4th edition of the WHO classification of tumors of hematopoietic and lymphoid tissues reflecting better understanding of disease entities and their relationship to the immune system⁽⁴⁾. DLBCL is the most widely recognized type of NHL in the world, and accounts for 30%–40% of all adult NHLs. Although potentially treatable, 40% of patients with DLBCL were died of relapsed or refractory disease⁽⁵⁾.

The Ann Arbor staging system was utilized to create rational treatment strategies and was recommended for all NHLs, This system depended on the number and site of nodal and extranodal areas and took symptoms into account⁽⁶⁾. The Lugano modification of the Ann Arbor staging

classification was recommended for anatomic description of disease extent, This system ignores the absence or presence of disease-related symptoms and allows for other prognostic factors to direct the choice of treatment⁽⁷⁾.

A study proved the relation between achievement of early response to treatment and better survival parameters with the introduction of targeted treatments. In general, with current treatment of patients with NHL, the overall survival rate at 5 years was about 70%⁽⁸⁾. Patients with at least two risk factors had less than 50% chance of relapse-free survival and OS at 5 years and also identified patients at high risk of relapse based on particular sites of involvement, including bone marrow, CNS, liver, lung, and spleen⁽⁹⁾. The therapeutic approach for NHL was different for each subtype. Chemotherapy is considered to be the most important modality. Management can be divided into 3 groups: those presenting with localized disease, those presenting with disseminated disease, and those patients whose lymphoma recurs after an initial remission⁽¹⁰⁾. Within the last two decades, the development and utilization of rituximab had obviously improved the prognosis of NHL patients and had been the standard of care in first-line treatment regimens. Standard first-line chemotherapy included rituximab with CHOP (R-CHOP), with expected 5-year and 10-year overall survival (OS) rates of 58% and 43.5%, respectively⁽¹¹⁾. Rituximab had been utilized for both inducing and maintaining remission. Maintenance rituximab was reported to prolong PFS in patients with indolent lymphoma after induction chemotherapy. On long-term follow-up of that patient cohort, however, longer median PFS was maintained, but no significant difference in OS was noted⁽¹²⁾.

Follow-up strategies reflected more intensive disease surveillance in the first years after therapy, where cross-sectional routine imaging was performed with clinical follow-up to detect early relapse⁽¹³⁾. Almost a third of patients with DLBCL fails or relapses after receiving first-line treatments⁽¹⁴⁾. Refractory disease was diagnosed during response evaluation to primary treatment⁽¹⁵⁾, but in patients who were suspected of having relapsed based on imaging studies, the diagnosis was confirmed by biopsy before proceeding to second-line treatment⁽¹⁶⁾. Most relapses were developed within the first 2 years after therapy and patients who received

rituximab and relapse within a year were at highest risk for early mortality and failure of salvage therapy⁽¹⁷⁾. Patients with relapsed DLBCL treated with either R-ICE or R-DHAP followed by autologous transplant had a 3-year OS of 49% in the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study⁽¹⁶⁾. There was currently no standard treatment in the third-line setting or for patients with relapsed disease who were not candidate for stem-cell transplantation and patients were often best treated in the context of a clinical trial⁽¹⁸⁾.

PATIENTS AND METHODS

Primary objective aimed to detect the occurrence of relapsed, refractory and in remission diffused large B cell lymphoma (DLBCL) patients to both clinic-pathologic features of the disease and line of treatment received and trial to subsequently assess follow up guidelines for the DLBCL patients presented to our department.

Inclusion criteria

Age of patients (18-70).

High grade NHL.

Patients received chemotherapy CHOP or R-CHOP protocols.

Exclusion criteria

Age of patients less than 18 years old (pediatric).

Patients with multiple relapse.

METHODOLOGY

In the period between January 2009 and December 2015, one hundred thirty four patients were presented to the Department of Clinical Oncology, Ain Shams University Hospitals and diagnosed with non Hodgkin lymphoma. Data were collected between January 2017 until March 2017 looking for patients with NHL. A total of 116 patients with Aggressive High grade NHL patients (DLBCL) were included in this study representing 86.6% of all cases. DLBCL patients were further statistically analyzed into three categories based on response to the 1st line therapy into the following: 24 refractory patients (20.07%), 43 relapsed patients (37.1%) and 49 patients in remission (non relapsed) (42.2%). Among the relapsed group, 90% of the patients were relapsed in less than two years.

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

RESULTS**Table 1:** comparison between the three studied groups regarding disease characteristics of the studied patients.

Disease Characteristics		Refractory (n=24)		Relapsed (n=43)		In Remission (n=49)		Chi-square test	
		No.	%	No.	%	No.	%	X ²	P-value
B symptoms	Negative (67/116)	10	41.6%	25	58.1%	32	65.3%	5.272	0.072
	Positive (38/116)	13	54.1%	11	25.5%	14	28.5%		
	NA (11/116)	1	4.1%	7	16.2%	3	6.1%		
LDH	High (43/116)	9	37.5%	18	41.8%	16	32.6%	2.280	0.320
	Normal (18/116)	7	29.1%	5	11.6%	6	12.2%		
	NA (55/116)	8	33.3%	20	46.5%	27	55.1%		
HCV	Positive (19/116)	1	4.1%	11	25.5%	7	14.2%	10.170	0.006
	Negative (17/35)	9	37.5%	5	11.6%	3	6.1%		
	NA (80/116)	14	58.3%	27	62.7%	39	79.5%		
Stage	Stage I (14/116)	1	4.2%	7	16.3%	6	12.2%	9.705	0.138
	Stage II (28/116)	5	20.8%	11	25.6%	12	24.4%		
	Stage III (34/116)	12	50.0%	13	30.2%	9	18.3%		
	Stage IV (39/116)	6	25.0%	12	27.9%	21	42.8%		
	NA (1/116)	0	0.0%	0	0.0%	1	2.0%		
Bone Marrow affection	Positive (13/116)	3	12.5%	7	16.2%	3	6.1%	1.990	0.370
	Negative (77/116)	16	66.6%	28	65.1%	33	67.3%		
	NA (26/116)	5	20.8%	8	16.3%	13	26.5%		

Table 2: comparison between the three studied groups regarding 1st line chemotherapy treatment of the studied patients

Treatment data		Refractory (n=24)		Relapsed (n=43)		In Remission (n=49)		Chi-square test	
		No.	%	No.	%	No.	%	X ²	P-value
1st line chemotherapy	Chop (n= 70)	19	79.1%	30	69.7%	21	42.8%	3.74	0.154
	R-CHOP (n= 46)	5	20.8%	13	30.2%	28	57.1%	15.98	0.001

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Table 3: showing treatment outcome among the relapsed group after 1st line therapy estimated by disease free survival rate (DFS) in months

Disease free survival (months)		95% Confidence Interval		Survival rate		
Median (IQR)	SE	Lower	Upper	1 year	2 years	3 years
8 (5-13)	0.99	6.06	9.94	20.80%	10.40%	4.20%

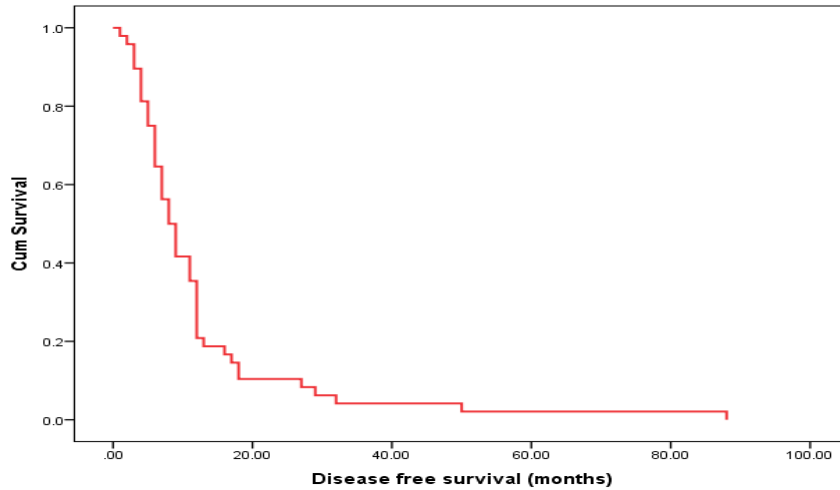


Figure 1: disease free survival in months among the relapsed group

Table 4: showing the overall survival in allDLBCL patients

Overall survival (months)		95% Confidence Interval		Survival rate		
Median (IQR)	SE	Lower	Upper	1 year	2 years	3 years
24 (16-31)	1.579	20.905	27.095	83.7%	52.8%	21.3%

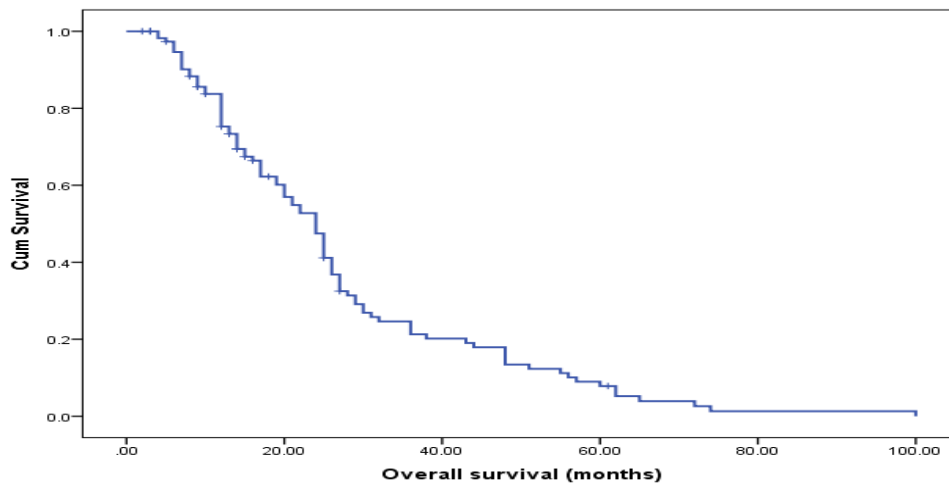


Figure 2: the overall survival (months) in all DLBCL patients

Table 5: Kaplan-Meier analysis for correlations between the three studied groups regarding overall survival in months

	Median	SE	95% Confidence Interval		Log rank test	
			Lower	Upper	X ²	P-value
Refractory	12	2.084	7.915	16.085	12.207	0.002
Relapsed	25	2.07	20.944	29.056		
In Remission	25	2.183	20.721	29.279		

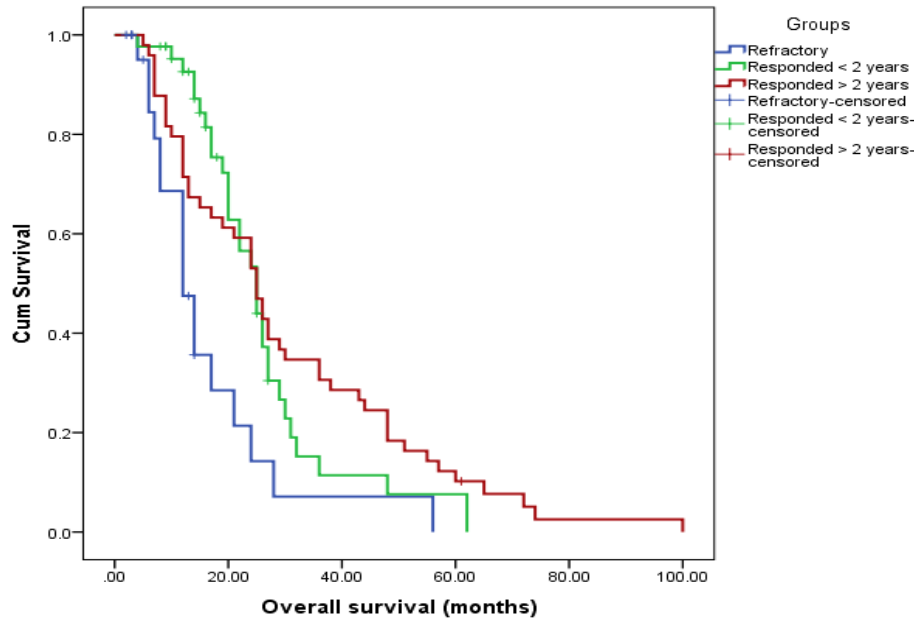


Figure 3: overall survival of the studied population estimated with Kaplan-Meier method.

DISCUSSION

According to the Middle East Cancer Consortium in Egypt, the NHLs age-standardized incidence rates are (16.3/100 000 person). This very high incidence makes NHLs the third most common cancer in Egyptian men and the second most common cancer in women as reported by the National Cancer Institute (NCI), accounting for 10.9% of all cancers in Egypt diagnosed every year. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL in Egypt, representing about 49% of all NHL cases presenting to the NCI⁽¹⁹⁾.

The present retrospective study analyzed the clinico-pathological profile of 116 pathologically confirmed aggressive high grade NHL patients (DLBCL) who were diagnosed and treated over a period of 5 years at our center. In our study the incidence of NHL in males (52.6%) was higher than in females (47.4%). As compared to UK population-based case-control study of 791 cases including 316 DLBCLs patients representing 53.5% in male and 46.5% in females reflecting the same male predominance for DLBCL incidence⁽²⁰⁾. The mean age at diagnosis of the study population was 45 years ranging from 19-70, which was similar to a large Egyptian retrospective study of 224 patients with DLBCL-NHL at NCI-Egypt between 1999 to 2006 that revealed the median age was 47 years⁽²¹⁾. In our study, in only 36 patient's files we found that up to 16.37% patients were HCV positive. This was similar to a study by **FIL, Italian Lymphoma Foundation** which was carried out a multicenter retrospective study on a large consecutive series of

DLBCL patients between 1995 to 2010 revealing HCV-positive cases made up to 17% of all registered cases of DLBCL⁽²²⁾.

In our study, the most common stage at diagnosis was stage IV (33.6%), followed by stage III (29.3%). the majority of patients in our study presented with advanced stage disease (stage III, IV). This finding was more strengthened by a retrospective pilot descriptive study conducted by **Gad Allah *et al.***⁽¹⁹⁾ who evaluated the outcome of different treatment methodologies of lymphoma patients in the Clinical Hematology and Bone Marrow Transplantation Units in Ain-Shams University Hospital over 2 years (2011 and 2013). Their study included 74 patients, 33 with aggressive NHL with stage IV (54.55%) and stage III (39.39%).

In our study and according to the response to treatment, DLBCL patients were further statistically analyzed into three categories: 24 refractory patients (20.07%), 43 relapsed patients (37.1%) and 49 patients in remission (non relapsed) (42.2%). Regarding clinic-pathologic data, our 43 Relapsed DLBCL patients were comparable to a retrospective study on 45 Relapsed DLBCL patients at two centers in Lyon, France, between 1985 and 2003 who had a biopsy-proven relapse 5 years or later⁽²⁴⁾, since patients in the current study showed female predominance regarding male to female (46.5% : 53.5% vs. 71% : 29%), were relatively younger (median 47 vs. 57 years), had more B symptoms (25.5% vs. 23 %), closer results of high LDH above normal (41.8% vs. 43%), majority presented with advanced stage (III and IV) more

than early stage (I and II) (58.1% : 41.9% vs. 33% : 67%) had relatively close results regarding bone marrow affection (7 vs. 6 patients) and according to another study carried out by **Ferreri et al.**⁽²⁴⁾ on 41 relapsed DLBCL patients revealed similar results to our study regarding HCV level in 12 vs. 11 patients. Rituximab was recommended for use in combination with a regimen of (CHOP) for first-line treatment⁽²⁵⁾, which was similar to our results regarding the 1st line chemotherapy treatment by both Chop and R-Chop in the studied patients as there was a statistically highly significant difference between the three studied groups regarding the 1st line chemotherapy treatment by R-Chop in the studied patients with p-value 0.000, but the most commonly used first line chemotherapy regimen was Chop being used in 19 refractory patients (79.1%), 30 relapsed patients (69.76%) and 21 patients in remission (42.8%), this was strengthened by a study on 45 relapsed DLBCL patients conducted by **Larouche et al.**⁽²³⁾ with higher percentage of CHOP which had been used as a first line therapy in 87% of the patients. According to our study, response evaluation showed that among the 70 patients of the three studied groups who received CHOP, the majority of the patients 30 patients (69.7%) from 43 patients who received CHOP were relapsed and out of the 24 patients, 19 patients (79.1%) were refractory and only 21 patients (42.8%) from 49 patients who were in Remission. However, response evaluation showed better outcome with the three studied groups who received R-CHOP as among the total 46 patients of the three studied groups who received R-CHOP, 28 patients (57.1%) from 49 patients were in remission, while 13 patients (30.2%) from the 43 patients relapsed and only 5 patients (20.8%) from 24 patients were refractory, So we found out that the complete response rates were significantly higher in patients who received R-CHOP than in the group who received CHOP alone (57.1% vs 42.8% with p value 0.000) as these patients presented a better response to chemotherapy.

Similar to our results, the **Groupe d' Etude des Lymphomes de l' Adulte (GELA)**⁽²⁶⁾ published a study that compared CHOP plus rituximab (R-CHOP) with CHOP alone in patients older than age 60 years. On the basis of phase 2 studies in which R-CHOP had a good safety profile and induced response rates in more than 90% of patients in aggressive lymphoma, The complete response rates were higher in patients who received R-CHOP than those who received CHOP alone (76% vs 63%; $P = .0005$), revealing that adding rituximab to CHOP resulted in favorable outcomes compared with

CHOP alone which is similar to our study results. In our study the median disease free survival (DFS) in the relapsed group was 8 months and the range was 5-13 months. Close to our study results, a retrospective study of 312 DLBCL patients at the Haematology Department of Cerrahpasa Medical Faculty, Istanbul University, from January 2000 to May 2011, among the relapsed patients, the median time to relapse was 10 months⁽²⁷⁾.

In the survival analysis performed in our study, the median survival time for all DLBCL patients was 24 months, This finding is similar to a retrospective study which was conducted to investigate clinical and pathological data of DLBCL patients that revealed the median survival time for DLBCL-NHL patients was also 24 months⁽²⁸⁾. The survival rate in our study for all DLBCL after 3 years was 21.3% which was lower than that reported by **Yang et al.**⁽²⁸⁾ that revealed the survival rate after 3 years was 48.5%, Also on another study of DLBCL patients positive for HCV serology diagnosed and treated between 1995 and 2010 at 16 Italian major hematologic institutions belonging to the FIL, that showed 3 years OS rate was 71% which is higher than that of our study results⁽²²⁾.

CONCLUSION

In conclusion non Hodgkin's lymphoma is the most common hematologic malignancy and it is the 6th leading cause of cancer death. DLBCL is the most common type. The prognosis for patients with NHL depends on the following factors: tumor histology, tumor stage, patient age, tumor bulk, performance status, serum LDH level.

Relapses still occur in the majority of patients; overall, more than 30% of DLBCL were ultimately relapse. Relapsed and refractory disease continued to represent the most significant challenge in treating NHL. The addition of rituximab to the CHOP regimen increased the CR rate and prolongs event-free and overall survival. More research was under way to establish the optimal schedule, timing and duration for maintenance rituximab. The current study summarized differences between DLBCL-NHL patients with respect to disease incidence, clinical characteristics and response to therapy in the rituximab era.

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