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Early Complete Response after Chemotherapy as A Prognostic Indicator for Final Outcome in High Grade Non-Hodgkin's Lymphoma Patients

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ABSTRACT

Background: In spite of progress in management of high-grade Non-Hodgkin's Lymphoma (NHL), more than 30% will ultimately relapse after standard treatment. **Aim of study**: was to estimate early complete response (CR) as a prognostic factor for final outcome and benefit of early switching to second line chemotherapy for slow responders. **Patients and Method:** Newly diagnosed patients with high-grade NHL were randomized to either Group A or Group B. All patients received 3 cycles of CHOP/RCHOP while, only patients in the group B who didn't achieve early CR were shifted to second line chemotherapy. **Results**: The clinicopathological characteristics of patients included in the two groups were comparable. Assessment of treatment results after the 6th cycle showed that 10 patients achieved late CR, 4 patients in group A (40%-4/10) and 6 patients in group B (6/7–85.7%). This difference was statistically significant (p-value 0.04). Out of the early CR group (24 patients), one patient died and another developed CNS relapse thus, both mortality (1/24) and relapse rate (1/23) of early CR group is 4%. Two patients of late CR group relapse (2/10-20%). The difference between the relapse rates of early CR (4%) and late CR (20%) wasn't statistically significant. The remaining 22 patients (22/23-95.7%) achieved early CR and 8 achieved late CR (8/10-80%) were in maintained remission. Regarding toxicity profile, there was no significant difference between both groups.

Conclusion: Early shifting to second-line chemotherapy is tolerable and promising. However, studies with larger number of patients are mandatory to identify who may need this approach.

Keywords: NHLs, early complete response and shifting to second line in NHLs.

Introduction

Although major advances have been made over the last decades in the management of aggressive non-Hodgkin`s lymphoma, not all patients achieving a response go-on to achieve a cure. Relapses are observed in a significant proportion of patients. Consequently, the aim remains to identify patients who are at risk for relapse and may benefit from intensification of initial therapy [(1)].

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 [(2)].

Although RCHOP regimen is the standard treatment for patients with aggressive NHL about 30% to 50% of patients are not cured by this treatment, 20% suffer from primary refractory disease, whereas 30% relapse after achieving CR depending on disease stage or prognostic index [(3)].

Patients with relapsed DLBCL treated with either R-ICE or R-DHAP followed by autologous stem cell transplant had a 3-year OS of 49% in the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study and there was no statistically difference between the two regimens as second line treatment [(4)].

The aim of the current study was to estimate early complete response (CR) as a

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prognostic factor for final outcome and benefit of early switching to second line chemotherapy for slow responders.

Patients and Methods

This prospective study included a total of 41 patients with pathologically confirmed diagnosis of high-grade NHL, attending the Clinical Oncology and Nuclear Medicine Department, El Hussein University Hospital, Faculty of Medicine, Al-Azhar University. Approval of the ethical committee and a written informed consent from all the subjects were obtained. This study was conducted between September 2014 and July 2017.

Inclusion criteria:

- Pathologically proven diagnosis of high-grade NHL.
- Performance Status ≤ 2 ECOG scale.
- Adequate renal and liver function tests.
- Ejection fraction > 55%.
- No prior chemotherapy or radiotherapy.
- Age more than 18 years and less than 65 of both genders.

Exclusion criteria:

- HIV positive patients.
- Burkett's lymphoma.
- Primary CNS NHL or CNS involvement at presentation.
- Associated malignant tumor other than NHL.

All patients were subjected to a series of laboratory and radiological investigations to assess the extent of disease and the presence of co-morbidity if any. The subtype of high-grade NHL was determined according to the WHO classification [(5)]. The stage of disease was assessed according to the Ann Arbor classification System [(6)]. The International Prognostic Index was determined according to the recommendation of Ziepert et al. (2010) [(7)].

Treatment protocol:-

Before starting treatment, the study group was randomized to two subgroups: -Group (A): -Standard group and Group (B): -Experimental group

The treatment protocol for the whole study group was divided into two phases: -Phase I and phase II

Phase (I) treatment:

The treatment protocol in phase I was the same for patients in group A and group B. They received 3 cycles of standard CHOP/RCHOP repeated every 21 days. Due to administrative reasons, Rituximab was sometimes available after more than one month from diagnosis. Therefore, it was accepted in our study to start with CHOP without Rituximab in order not to delay starting of treatment.

Two weeks after the 3rdcycle, patients were subjected to clinical examination, laboratory and radiological investigations (CT with contrast neck, chest, abdomen and pelvis and PET-CT for some patients) to assess the treatment response. The response was classified as complete remission, Partial Remission, Stationary disease or Disease Progression according to the Standardized International Workshop Criteria and the Deauville five point's scale [(8-9)].

Patients achieved complete remission after phase I treatment constituted the early CR group. Those who achieved partial remission constituted the PR group.

Phase (II) treatment:

After the 3rdcycle, the treatment protocol was different for patients in the two groups (Group A and Group B).

Phase II - Group A

Patients achieved early CR, PR or SD after 3 cycles of CHOP/RCHOP received 3 more cycles of the same regimen before final disease assessment. Patients who showed progressive disease were prepared for salvage therapy and were excluded from the study.

After each cycle, patients were assessed at day 10 for chemotherapy related toxicity by

clinical, laboratory and radiological investigations as required to detect the occurrence of treatment related toxicity if any. The toxicity was graded according to the NCI common toxicity criteria (CTCAE Version; 4). Treatment related toxicity was assessed by its impact on the delay during receiving the chemotherapy protocol. For the sake of the current study, patients who received the 3 cycles of chemotherapy (CHOP/RCHOP) within ≤ 45 days (≤ 5% delay) were considered to have no delay or grade 0 or I toxicity. Patients who received the 3 cycles within 46-50 days (> 5% and ≤ 10% delays) were considered to have short delay or grade II toxicity. Patients who received the 3 cycles within more than 50 days (> 10% delay) were considered to have long delay or grade III and IV toxicity.

Phase II- Group B

Only patients who achieved early CR after 3 cycles of CHOP/ RCHOP received 3 more cycles of the same regimen as in group A. Patients with PR and SD received 3 cycles of second line chemotherapy before final disease assessment. Patients who showed progressive disease were prepared for salvage therapy and were excluded from the study.

Second line combination chemotherapy was either ICE or DHAP regimen repeated every 21 days. After each cycle, patients were assessed at day 10 for chemotherapy related toxicity as in phase I.

Two weeks after the 6th cycle, patients were subjected to clinical examination; laboratory and radiological investigations to assess the treatment response. The response was classified as CR, PR, SD or DP as for phase (I) treatment. Patients achieved complete remission after phase II treatment constitutes the late CR group. Patients achieved PR, SD or DP after phase II treatment constitutes the no CR group; they were prepared for salvage chemotherapy and were excluded from the study.

Follow-up

Patients achieved CR (early and late) of both groups (A and B) was kept under regular follow-up till relapse, death or end of study.

CNS prophylaxis

CNS prophylaxis was given for patients at high risk for CNS relapse. These patients received intrathecal methotrexate on day 15 of the cycle for 4 to 6 doses as recommended by Jonathan et al (2012)[10].

Consolidation radiotherapy

Radiotherapy was given after the phase II treatment for patients in CR with extra-nodal disease and bulky nodal disease (>7.5cm) according to the recommendations of Hu C et al (2015) [11]. Involved site irradiation was given for these patients to a total dose between 24 and 40 Gy on linear accelerator 5 fractions per week. The technique of radiotherapy was tailored according to the site of disease involvement.

Statistical Methods

The clinical characteristics, response rate, relapse and the overall as well as the disease–free survival for patients in group A and those of group B were compared. Comparisons between the two groups with respect to normally distributed numeric variables were done using the t-test. P-values ≤0.05 were considered significant.

Results

The current prospective study included 41 patients with pathologically confirmed diagnosis of high-grade NHL. The clinicopathologic characteristics of the study group (table 1):

The mean age at diagnosis was 47 years. The incidence in male was higher than female (56% vs. 44%), most of the cases didn't have special habits (56%), high LDH level was measured among the cases (58.5%), in only 36.5% of the studied patients had bulky disease and 26.8 % of the cases had positive HCV. The most frequent presenting symptoms were

painless swelling (63.4%) while 48% had B symptoms. The most common stage at diagnosis was stage II (41.6%) followed by stage IV (31.7%). The clinico-pathological characteristics of patients included in the two groups (A and B) were comparable except for the special habits. Smoking was more prevalent among patients in Group B (60%-12/20) than among those included in group A (28.6%-6/21). Table (1)

Table (1): The clinicopathologic characteristics of the study group

clinicopathologic characteristics	Group A (21)		Group B (20)		Total (41)		P-value
	No.	%	No.	%	No.	%	
Mean (SD)	48(±13)		46(±10)		47(11.3)		0.59
Age (Years)							
≤ 40	6	28.6	5	25	11	26	0.79
>40	15	71.4	15	75	30	74	
Sex							
Male	9	42.9	14	70	23	56	0.08
Female	12	57.1	6	30	18	44	
Special habits (smoking)							
No	6	28.6	12	60	18	44	0.04
Yes	15	71.4	8	40	23	56	
Co-morbidity							
No	10	47.6	10	50	20	48	0.78
Yes	11	52.4	10	50	21	52	
HCV							
Positive	4	19	7	35	11	26.8	0.249
Negative	17	81	13	65	30	73.2	
LDH level (U/L)							
High	14	66.7	10	50.0	24	58.5	0.27
Normal	7	33.3	10	50.0	17	41.5	
Extent of disease							
No extra-nodal	14	66.7	8	40.0	22	53.7	0.05
Extra-nodal disease	4	19.0	11	55.0	15	36.6	
Nodal & extra-nodal	3	14.3	1	5.0	4	9.7	
Bulky disease							
Present	9	42.9	6	30.0	15	36.5	0.393
Absent	12	57.1	14	70.0	26	63.5	
Stage							
I	1	4.8	1	5.0	2	4.8	NA
II	8	38.2	9	45	17	41.6	
III	6	28.5	3	15	9	21.9	
IV	6	28.5	7	35	13	31.7	
B-symptoms							
No	11	52.3	9	45	20	48	0.636
Yes	10	47.7	11	55	21	52	
International PI							
Low	5	23.8	6	30	11	26.8	0.69
Intermediate	12	57.1	12	60	24	58.6	
High	4	19.1	2	10	6	14.6	
Swelling							
Yes	12	57	14	70	26	63.4	0.39
No	9	43	6	30	15	36.6	

Assessment after phase (I) treatment:-

Assessment after phase I showed that early CR was achieved in 58.5% of the whole study group. PR was documented in 41.5% of all patients there was no statistically significant difference between the two groups as regards remission achieved. (Table 2)

Table (2): Assessment of response after Phase I treatment

	Group A		Group B		Total		P value
	No.	%	No.	%	No.	%	
CR	11	52.4	13	65	24	58.5	0.26
PR	10	47.6	7	35	17	41.5	
Total	21	52	20	48	41	100%	

Treatment related toxicity (mucositis and mylosuppression with or without infective problems) were more frequently encountered as a cause of delay among patients in the group B than in group A. However, this difference was not significant. Table (3)

Table (3): Prevalence of treatment related toxicity causing treatment delay in Phase I treatment.

	Group A		Group B		Total		P-value
	No.	%	No.	%	No.	%	
No delay (≤5%)	15	71.4	10	50	25	61	0.16
Short delay (> 5% - ≤ 10%)	6*	28.6	9**	45	15	35.5	
Long delay (>10%)	-		1	5	1	2.5	
Total	21	52	20	48	41	100	

Treatment delay was due to administrative and / or social reasons for * 3 and ** 1 patients.

Assessment after Phase I treatment:-

Assessment of treatment results after the 6th cycle showed that 10 patients achieved late CR, 4 patients in group A (40%-4/10) and 6 patients in group B (6/7–85.7%) This difference was statistically significant (p 0.04) (Table 4)

Table (4) Assessment of response after phase II treatment for PR group

	Group A		Group B		Total		P value
	No.	%	No.	%	No.	%	
Late CR	4	40	6	85.7	10	58.8	0.04
No CR	6	60	1	14.3	7	41.2	
Total	10	100	7	100	17	100	

About 32% (11/34) of patients who received CHOP/RCHOP during phase II completed the treatment without delay versus about 43% of the second line group (3/7) while long delay was observed more among patients received second line 42.8% versus 32.3% of the other group. However, these differences are not significant. Table (5)

Table (5) Prevalence of delay in phase II Treatment

	3 cycles CHOP/RCHOP		Second line treatment		Total		P-value
	No	%	No	%	No	%	
No delay (≤5%)	11	32.3	3	42.8	14	34.1	NA
Short delay (> 5% - ≤ 10%)	12*	35.4	1	14.4	13	31.8	
Long delay (> 10%)	11**	32.3	3*	42.8	14	34.1	
Total	34	82.9	7	17.1	41	100	

*Treatment delay was due to administrative and / or social reasons in 1 patient

** One patient developed severe Mylosuppression for about 15 days and eventually died from septic shock

Fate of early CR group

Out of the early CR group (24 patients), one patient died with septic shock 12 days after the 5th cycle. Another patient developed CNS relapse after 6 months from date of CR documented by positive CSF and brain SOL. Thus, the mortality rate of early CR group is 4% (1/24) and the relapse rate 4%. (1/23) (Figure 1)

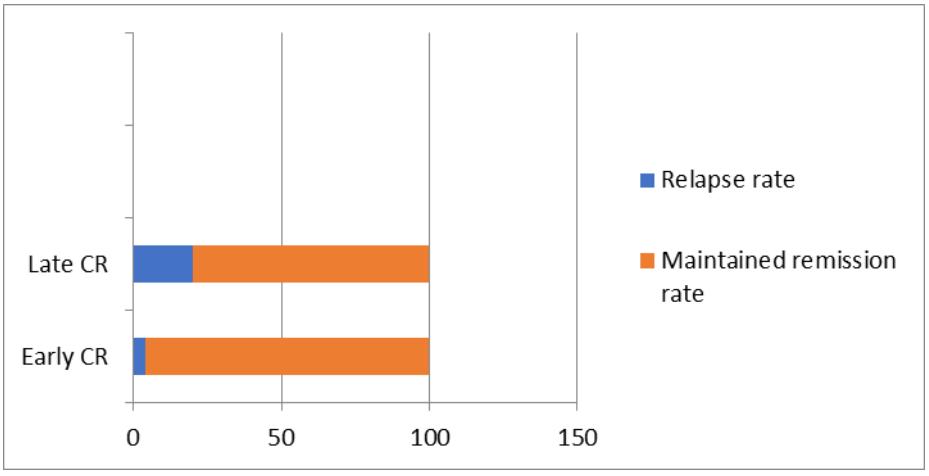
With a median follow-up of 24 months (range 13-44 months), the remaining 22 (22/23-95.7%) patients who achieved early CR were in maintained remission till the end of study.

Fate of late CR group

Two patients of late CR group relapsed (2/10-20%) after 13 months and 15 months, one patient from group A and the other from group B. The site of relapse in the two patients was peripheral groups of lymph nodes with bone marrow involvement in one of them. The difference between the relapse rates of early CR group (4%-1/23) and that of late CR group (20%-2/10) wasn't statistically significant (figure 1).

With a median follow-up of 29 months (range 18-41 months), the remaining 8 (8/10-80%) patients who achieved late CR were in maintained remission till the end of study.

Figure (1) Relapse rate for the early CR and late CR groups



Survival rates:

The median overall survival in the whole study group has not been reached. The 2-year disease free survival (DFS) for the whole study group is 75.5% while Overall survival (OS) is 82.9%. (Figure 2-3)The 2-year disease free survival (DFS) for the early CR group is 70.3% while the 2-year disease free survival (DFS) for the late CR is 65.6%. The 2-year Overall survival (OS) for the early CR group is 75.4% while Overall survival (OS) for the late CR is 80%. (Figure 4-5) There was no significant difference between the all subgroups.

Figure (2): Disease -free survival for the whole study group.

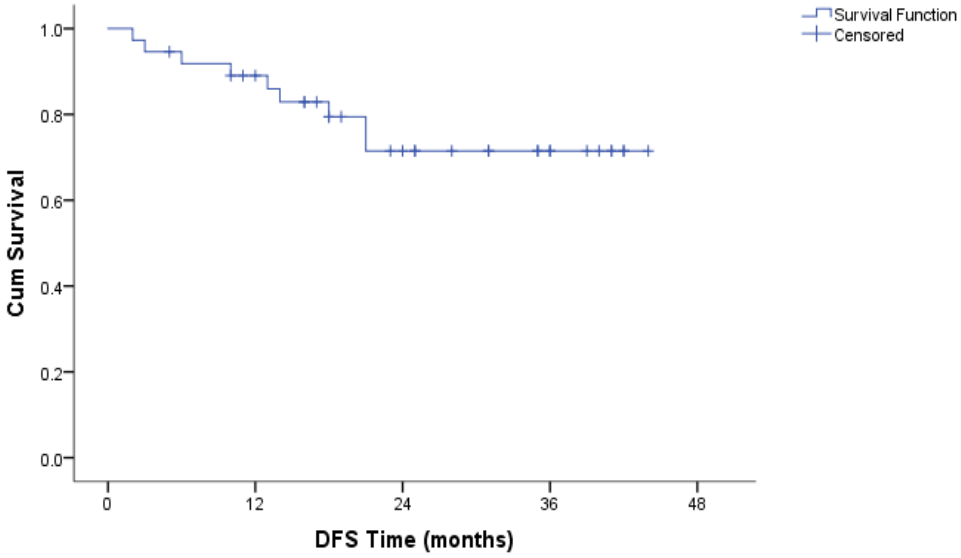


Figure (3): Over-all survival for the whole study group.

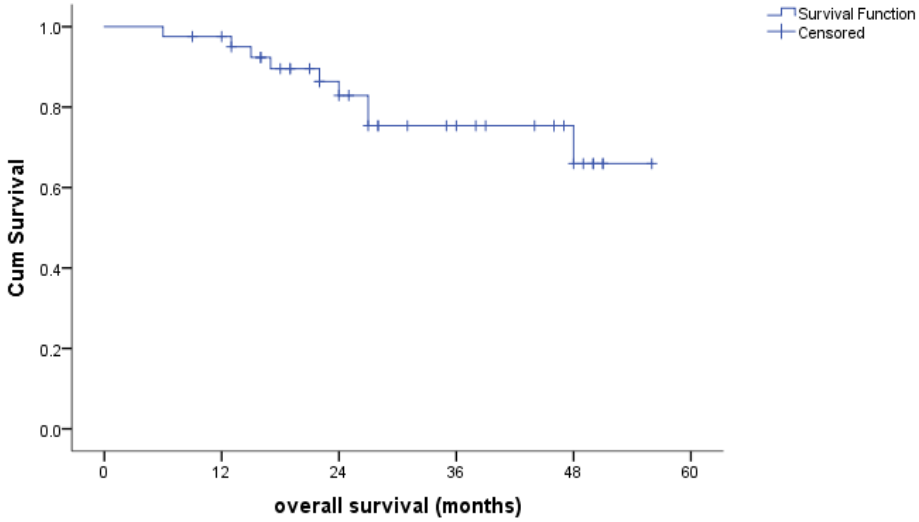


Figure (4): The DFS survival for early CR and late CR.

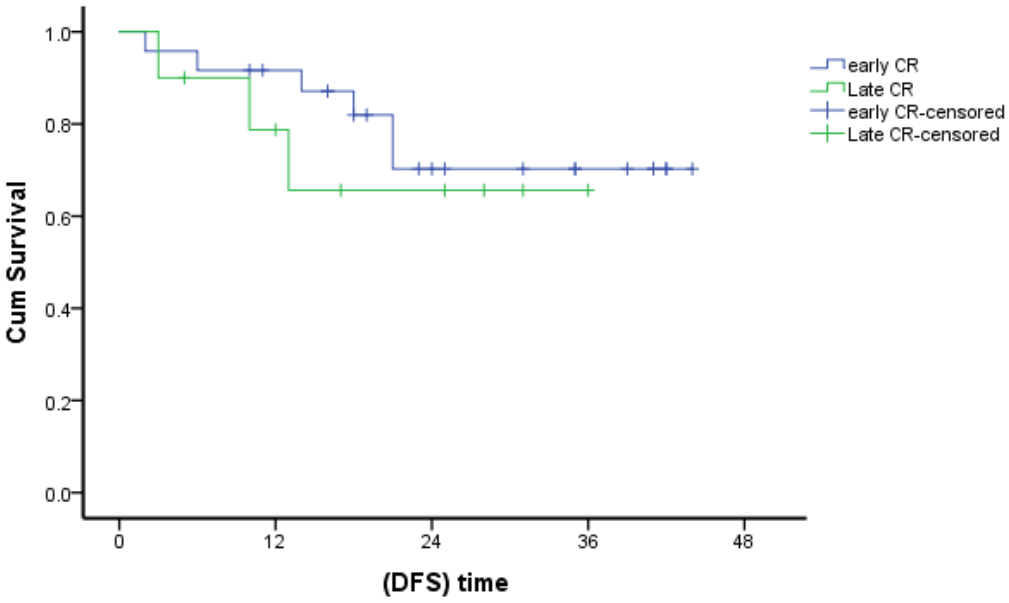
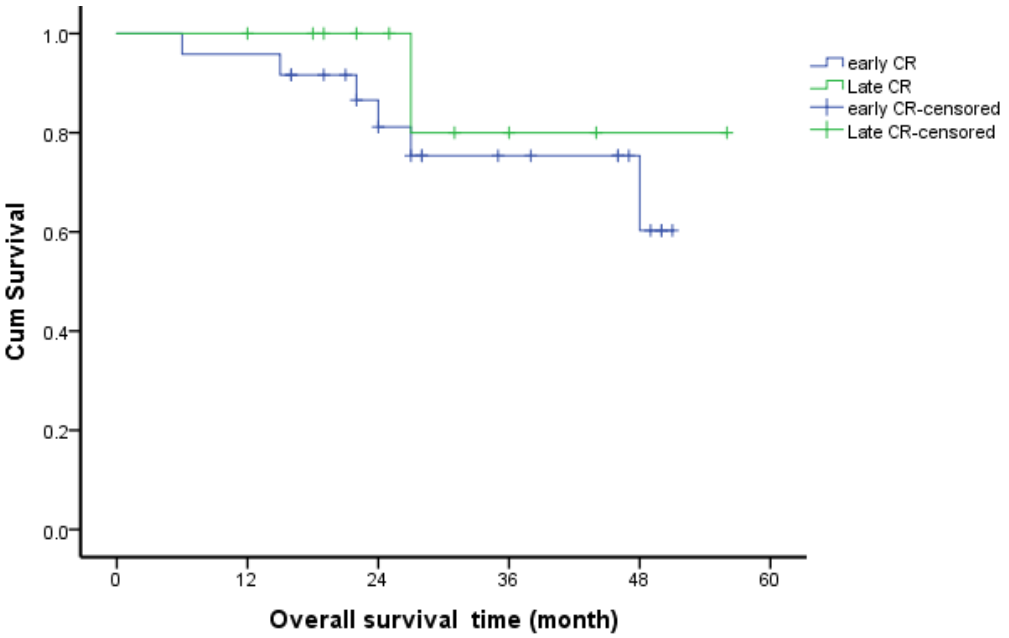


Figure (5): The overall survival for early CR and late CR.



DISCUSSION

In 1986, Armitage [12] identified the time required to achieve CR as an important prognostic variable in aggressive NHL. In their series, only 40% of patients who required more than 5 cycles of standard therapy to achieve CR remained disease free whereas 80% of patients who needed less than 3 cycles of therapy to achieve CR remained disease free at 2 years. Moreover, Engelhard et al (1991) [13] subsequently identifies time to CR as the most important prognostic determinant of overall survival in their series of 548 patients with aggressive NHL [14].

The general idea of the current prospective study is to save using ineffective therapy and overcome the emerging of resistant clones by early introduction of second line chemotherapy in patients does not achieve CR after 3 cycles of chemotherapy. This policy may theoretically, improve the response and consequently the survival.

About half of the study group had no special habits. However, 44% of our patients were smokers. Geyer et al [15] reported a higher incidence of smokers (70%) among their patients with NHL in the United States. In the current study, smoking was significantly more prevalent among patients in group B. We noticed that delay during receiving chemotherapy was more frequent among this group (group B) secondary to medical causes (mucositis and Mylosuppression). We concluded that smoking may play a role in the tolerance of patients to chemotherapy and subsequently may affect the treatment results.

Our patients tolerated phase I treatment well only one patient (1/41–2.4%) had mylosuppression with severe infection necessitating long periods of antibiotics, eleven more patients (11/41-26.8) developed mild degree of toxicity causing short term delay. As reported in the literature, CHOP regimen is mostly well tolerated by patients with NHLs. The most encountered treatment related toxicity is fatigue, alopecia, mucositis and mylosuppression. The treatment related toxicity is generally managed without affecting the treatment course [16-17].

Assessment after 3 cycles of CHOP/RCHOP showed that early CR was documented in 58.5% (24/41) of our study group. The remaining of patients showed early PR (41.5%). There was no statistically significant difference between the two groups as regards remission achieved. These figures are comparable to that reported in the literature [16,17,18,19].

In the current study, all patients showed good early response on CHOP/R CHOP (CR or PR). This means that this regimen is still good first line chemotherapy for high-grade NHLs. However, there may a subset of patients that should be treated by more intensified regimen to achieve early CR after 3 cycles of chemotherapy. In an attempt to identify this subgroup, the clinical characteristics of patients achieved early CR were compared to those achieved early PR. We found that early CR was more frequently encountered among patients more than 40 years old and with Co-morbidity. However, these differences are not statistically significant. Studies with larger number of patients may be required to reach firm conclusions.

The main aim of this study is to assess the possibility of improving the prognosis through early introduction of second line non-cross resistant regimen for patients not achieving early complete response after 3 cycles of CHOP. In the current study we selected ICE/DHAP regimens because of well tolerability and availability of drugs. Moreover, ***Gisslbrecht et al.*** [4] concluded that there is no statistically difference between the two regimens as second line treatment.

To assess the efficacy of early shifting to second line chemotherapy, the 7 early PR patients of group B received 3 cycles of second line chemotherapy ; ICE (3patients) or DHAP (4 patients). While, the 10 early PR patients of group A received 3 more cycles of CHOP/RCHOP.

Late CR could be achieved in 85.7% (6/7) of patients in group B versus 40% (4/10) of patients in group A. This difference is statistically significant (p-value 0.04). These results confirm that early introduction of second line chemotherapy may improve the number of patients achieving late CR. Moreover, there was no significant difference between second line chemotherapy and CHOP/R CHOP as regards treatment related toxicity and delay during phase II treatment. However, more studies with larger number of patients are needed for firm conclusions.

As documented before by ***Armitage*** [(12)] ***and Engelhard et al.*** [(13)] time to CR may be considered an important prognostic determinant for survival in patients with NHL. The impact of early achieving CR on cure is evident in the current study. After a median period 27 month follow-up, the relapse rate of the early CR group was 4% (1/23) while that of the late CR group was 20% (2/10). However, this difference is not statistically significant. Moreover, the site of relapse in the early CR patient was the CNS. It is considered a sanctuary site to which chemotherapy may not reach in effective doses. While the site of relapse in the late CR cases was peripheral groups of lymph nodes with bone marrow involvement in one of them however, more studies with larger number of patients are needed for firm conclusion.

Coiffier and Sarkozy [(3)] stated that among patients for whom R-CHOP therapy fails, 20% suffer from primary refractory disease, whereas 30% relapse after achieving CR. In the current study, we reported a comparable figure for the refractory cases where the no CR group (refractory cases) constituted 17% (7/41). However, we reported a lower relapse rate (7.5%-3/41). This can be explained by the short period of follow-up (27 months)

Although RCHOP regimen is the standard treatment for patients with aggressive NHL about 30% to 50% of patients are not cured by this treatment, depending on disease stage or prognostic index [(3)]. In the current study we reported a similar finding. The 2 year's survival rate in the current study was around 70% for the all subgroups. There was no significant difference between the all subgroups.

New strategies should be explored to obtain better CR rates and fewer relapses for patients with high grade NHL. Early shifting to second line chemotherapy is promising. However, more studies with larger number of patients are mandatory to identify the category of patients who may need this approach. Moreover, new drugs will most likely be introduced over the next few years and will probably be different for relapsing and refractory patients

Conclusion

The prognosis for patients with NHL depends on many factors: histological type, tumor stage, patient age, performance status, serum LDH level, tumor bulk and presence of extra-nodal disease. Relapse still occur in the majority of patients. Overall, more than 30% of high grades NHL were ultimately relapse.

New strategies should be explored to obtain better CR rates and fewer relapses for patients with high-grade NHLs. The current study established early CR prolongs event free and overall survival and early shifting to second line chemotherapy is promising. However, more studies with larger number of patients are mandatory to identify the category of patients who may need this approach.

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