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Third line Treatment in Relapsed/Refractory Hodgkin's Lymphoma and Aggressive non-Hodgkin Lymphoma after 2nd line ESHAP or GEMOX

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Background: Treatment after failure of 2nd line chemotherapy in patients with Hodgkin's lymphoma (HL) or aggressive non-Hodgkin's lymphoma (NHL) is not well studied.
Aim: To assess the value of 3rd line treatment in a cohort of HL and aggressive NHL patients.
Methods: This was a retrospective study of patients with relapsed/refractory HL or aggressive NHL treated with 3rd line treatment based on physician choice. Response rate as well as overall survival (OS) and factors affecting it were assessed.
Results: Fifteen (41%) out of 37 patients who failed 2nd line received 3rd line. The remaining 22 received single-agent palliative chemotherapy or best supportive care only. Third line treatment was IGEV (ifosfamide, gemcitabine, navelbine) in 7 (47%) patients, lenalidomide in 4 (26%), ESHAP (etoposide, methylprednisolone, cytosine arabinoside, cisplatin) in 2 (13%) and GEMOX (gemcitabine, oxaliplatin) in 2 (l3%). Four (27%) patients achieved complete remission (2 with IGEV and 2 with lenalidomide) and 3 of them underwent autologous stem cell transplantation. One (7%) patient achieved partial response and another one (7%) had stable disease. The median OS for the whole group was 4.7 months. For patients who received 3rd line the OS was significantly longer than those who didn't (13.4 vs. 3.4 months, p=0.001). Among the whole set of patients, performance status, lactate dehydrogenase, tertiary age-adjusted International Prognostic Index, 3rd line treatment, response to 3rd line and transplantation had significant impact on OS.
Conclusion: Third line treatment may be feasible in selected HL and aggressive NHL patients who failed 2nd line.

Keywords: Hodgkin's lymphoma, Non-Hodgkin's lymphoma, Relapsed, Refractory, 3rd line treatment
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INTRODUCTION

Second line chemotherapy followed by autologous stem cell transplantation (ASCT) is the standard of care treatment for diffuse large B-cell lymphoma and Hodgkin's lymphoma (HL) patients who failed first line treatment [1, 2].

The value of treatment of patients failing 2nd line is not well studied.

Van Den Neste et al studied the outcome of 203 patients who failed 2nd line treatment after the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study [3, 4]. The median overall survival (OS) for the whole group in their study was 4.4 months. However, patients who received 3rd line achieved high overall response rate (39%) with a complete response rate of 27%. Multivariate analysis showed that tertiary international prognostic index (IPI) >2 and transplantation achievement were associated with better OS (p< 0.0001 and = 0.0002, respectively) [3].

Other smaller studies like that of Elstrom et al reported the outcome of 27 patients who failed 2nd line. The median OS for the whole group was 4 months. However, median OS for patients who received 3rd line was much better (10 months) [5]. Seshadri et al also reported the outcome of 120 patients after failure of 2nd line platinum-based chemotherapy. Seventy-three of them received 3rd line with low response rate of 14% [6]. The response rate was higher (52% overall response rate and 14% complete remission) in the study of Simpson et al that included 21 patients treated with ICE (ifosfamide, carboplatin, etoposide) after failure of 2nd line DHAP (dexamethasone, high-dose cytarabine and cisplatin) [7].

The aim of this retrospective study was to report the outcome of treatment with 3rd line in a cohort of patients with relapsed/refractory HL and aggressive non-Hodgkin's lymphoma (NHL) who failed 2nd line treatment.

METHODS

The original study of 2nd line chemotherapy was a prospective study that included 41 patients with relapsed/ refractory HL or aggressive NHL randomized between either GEMOX (gemcitabine, oxaliplatin) or ESHAP (etoposide, methylprednisolone, cytosine arabinoside, cisplatin).[8] During follow up that continued until May 2017, 37 out of those 41 patients failed

treatment and represent the population of the current study.

The data collected included age, gender, Ann Arbor stage at failure, Eastern Cooperative Oncology Group (ECOG) performance scale, lactate dehydrogenase (LDH), 3rd line treatment protocol, and tertiary age-adjusted International Prognostic Index (aaIPI). International Working Group criteria were used to assess response to 3rd line treatment [9]. Patients who achieved complete remission in response to 3rd line were scheduled to undergo autologous stem cell transplant (ASCT).

Response assessment was done clinically with each cycle and by computerized tomography scan after 3 cycles and bone marrow biopsy was repeated if it was abnormal before starting treatment. Overall survival (OS) was calculated as the time from the date of failure to 2nd line until death.

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

SPSS software (statistical package for social science) version 17 was used for statistical analysis. All data statistically studied by descriptive analysis. Survival analysis was done according to possible prognostic factors by Kaplan-Meier method and compared by log-rank test for significance. All reported *p* values are two-sided, and $P < 0.05$ was considered significant.

RESULTS

During the study period from March 2016 till May 2017, 37 patients failed 2nd line treatment. Their characteristics are listed in table 1. The majority (78.1%) of patients had aggressive NHL and most (78.3%) of them had an advanced stage of III or IV.

Out of 37 patients who failed 2nd line chemotherapy 15 (40.5%) patients received 3rd line treatment. IGEV (ifosfamide, gemcitabine, navelbine) was the most commonly used regimen (in 7 [47%] patients). Other treatment regimens used were lenalidomide in 4 (26%) patients, ESHAP (etoposide, methylprednisolone, cytosine arabinoside, cisplatin) in 2 (13%) and GEMOX (gemcitabine, oxaliplatin) in 2 (13%). The total number of cycles was 62 and the median number per patient was 4 (range: 3-8). The remaining 22 patients received palliative single agent chemotherapy or best supportive care only.

Four (26.6%) patients achieved complete remission with 3rd line treatment (2 with IGEV and 2 with lenalidomide) and 3 of them underwent ASCT while the 4th lost to follow up. One (6.6%) patient achieved PR and another one (6.6%) had stable disease. Disease progression was observed in 9 (60.2%) patients.

Median OS was 4.7 months (95% Confidence Interval: 2.1-7.2) for the all patients who failed 2nd line (figure 1) and the 1-year survival rate was 37%. The median OS was significantly longer in patients who receive 3rd line treatment compared to those who received best supportive care (13.4 vs. 3.4 months, p=0.001) (figure 2).

Table 1. Characteristics of 37 lymphoma patients who failed 2nd line chemotherapy

	No.	%
Age (years)		
<60	31	83.7
>60	6	16.3
Median	43	
Range	26-65	
Gender		
Male	17	46
Female	20	54
Pathology		
HL	8	21.7
DLBCL	27	72.9
T-cell lymphoma	2	5.4
Prior 2nd line chemotherapy		
ESHAP	17	46
GEMOX	20	54
No. of cycles of 2nd line chemotherapy		
Median	4	
Range	3-8	
Ann Arbor stage at relapse		
II	8	21.7
III	11	29.7
IV	18	48.6
LDH		
Above normal	16	43.2
Normal	5	13.6
Unknown	16	43.2
ECOG performance scale		
1	10	27.1
2	11	29.7
3, 4	16	43.2
Extranodal involvement >1 site	3	8.1
Bone marrow involvement	8	21.7
B symptoms	13	36.1
Diameter of the largest tumor		
≤10 cm	27	72.9
>10 cm	10	27.1
Tertiary aaIPI (29 NHL patients)		
Low (0-1)	3	8.1
Intermediate (2)	15	40.5
High (3)	11	29.7

HL: Hodgkin lymphoma, **DLBCL**: diffuse large B-cell lymphoma: **LDH**: lactate dehydrogenase, **ECOG**: Eastern cooperative oncology group, **aaIPI**: Age-adjusted International Prognostic Index

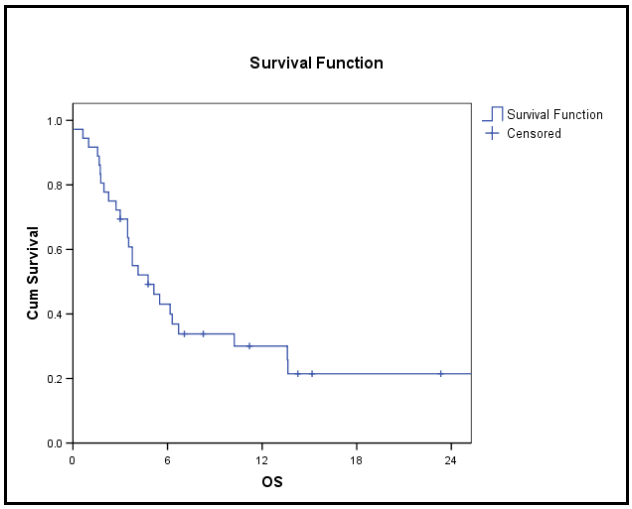

Figure 1. Overall survival curve of 37 lymphoma patients who failed 2nd line chemotherapy

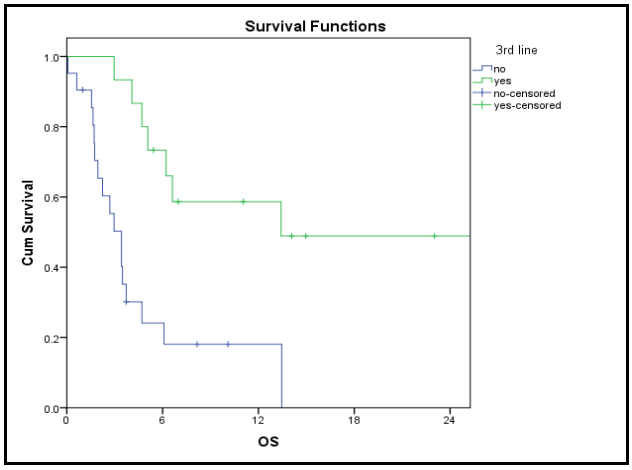

Figure 2. Overall survival curves of 3rd line versus best supportive care

Other variables that correlated significantly with the OS of the whole group in univariate analysis included ECOG performance status, LDH, and tertiary aaIPI , response to 3rd line and transplantation (table 2).

DISCUSSION

Aggressive NHL and HL failing 2nd line chemotherapy have very poor prognosis and represent a challenge for clinicians.

The largest data about the value of 3rd line comes from the analysis of patients failing 2nd line in the CORAL study [3]. Overall response rate for patients who received 3rd line was 39% and complete response rate was 27%. The response rate in another study of Seshadri et al which included 73 patients failed 2nd line platinum-based chemotherapy and received 3rd line was 14% [6]. Another study conducted by Simpson et al showed a response rate of 52% with 14% complete response for 21 patients who received ICE after failure of 2nd line DHAP [7]. In our study, from 37 patients failing 2nd line, 15 received 3rd line and 22 patients received palliative single agent chemotherapy or no active treatment with best supportive care. The overall response rate was 33.2% and 4 (26.6%) patients achieved complete remission (2 with IGEV and 2 with lenalidomide) and 3 of them underwent ASCT. The results of the current study are comparable to those of Van Den Neste et al [3]. Response rates to 3rd line treatment in the other aforementioned studies that included relatively small number of patients were variable [6, 7].

Table 2. Univariate analysis for factors affecting OS

Variable	Median OS (months)	95% CI	P value
Age (years)			
<60	4.4	2.5-6.3	0.5
≥60	5.3	1.8-8.3	
Gender			
Male	4	2.3-5.8	0.6
Female	5.1	1.3-8.7	
Prior 2nd line			
ESHAP	9.1	2.9-6.4	0.6
GEMOX	13.4	.01-14	
Ann Arbor Stage at relapse			
I-II	6.6	2.7-6.6	0.22
III-IV	4.7	2.4-7.2	
ECOG performance scale			
1	NR	NR	0.003
2	3.7	2.1-7.2	
3,4	1.7	1.6-1.8	
LDH			
Above normal	2.9	1.6-4.2	0.05
Normal	NR	NR	
B symptoms			
Yes	2.6	0.9-4.4	0.07
No	6	3.8-8.3	
Tertiary aaIPI (29 NHL patients)			
Low (0-1)	NR	NR	0 .04
Intermediate (2)	4.7	2-6.1	
High (3)	1.9	0.1-3.7	
Response			
CR/PR	NR	NR	0.012
SD/PD	5.4	2.2-8.6	
Transplant			
Yes	NR	NR	.02
No	3.7	2.4-7.5	

OS: Overall survival, **CI**: Confidence interval, **ESHAP**: Etoposide, methylprednisolone, cytosine arabinoside, cisplatin, **GEMOX**: Gemcitabine, oxaliplatin, **ECOG**: Eastern cooperative oncology group, **LDH**: Lactate dehydrogenase, **aaIPI**: Age-adjusted International Prognostic Index, **CR/PR**: Complete response/partial response, **SD/DP**: Stable disease/disease progression

Median OS in the present study for the whole group of patients was 4.7 months which is relatively short. This is comparable to the studies of Elstrom et al, Van Den Neste et al and Simpson et al who reported a median OS of 4, 4.4 and 4.7 months, respectively [5, 3, 7]. However, there was a subset of patients who had longer OS. This was shown in Van Den Neste et al study which reported a median OS of 11.1 months in patients who were eventually transplanted (31.5%) compared to 3.3 months in those who were not. Multivariate analysis of median OS showed that IPI >2 and transplantation were independently associated with OS ($p<0.0001$, HR, 2.74 and $p=0.0002$, HR, 2.667; respectively) [3]. This was also shown in the study conducted by Seshadri et al in which the 2-year PFS for patients who underwent ASCT after 3rd line was comparable to those who underwent ASCT after 2nd line. Factors affecting response rate were progression on primary therapy, high LDH level and tumor bulk [6]. Simpson et al also reported that response to 3rd line and transplantation were significant predictors of OS in patients who received 3rd line [7]. In our study patients who achieved complete remission/partial remission after 3rd line had a better median OS (not reached) in comparison to those who had stable disease/progressive disease (5.4 months). Also, patients who underwent ASCT had a better median OS (not reached) than those who did not (3.7 months).

Two patients treated with lenalidomide as 3rd line achieved complete remission and one of them underwent ASCT. In a relatively large international phase II study; 217 patients with relapsed or refractory diffuse large B-cell lymphoma, mantle cell lymphoma, follicular grade 3 lymphoma, or transformed lymphoma received lenalidomide single agent. The overall response rate was 35% with 13% complete remission. The median response duration was 10.6 months for 77 responsive patients and it was not reached for the 29 patients who achieved complete remission [10]. Lenalidomide looks promising in this setting.

A limitation of the current study is that rituximab ,which changed significantly CD-20 positive NHL map both in 1stand 2nd line treatment, was not given due to logistic and financial reasons. Other limitations included being a retrospective design and the inclusion of small number of patient. Another important limitation is that molecular subtyping for cell of origin, which is an important independent prognostic factor in relapsed/ refractory diffuse large B-cell lymphoma [11], was not performed.

Conclusion

Third line treatment is feasible in selected relapsed/refractory HL and aggressive NHL patients. The current study suggests some prognostic factors for overall survival in 3rd line treatment as ECOG performance status, LDH, tertiary aaIPI, response to 3rd line and transplantation.

Conflict of interest

The authors declare that they have no conflict of interest.

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