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ESHAP versus GEMOX in Management of Relapsed or Refractory Lymphoma: A Prospective Randomized Study

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Background: There is lack of evidence about the best chemotherapy regimen in treatment of relapsed/refractory Hodgkin's lymphoma (HL) and aggressive non-Hodgkin's lymphoma (NHL) lymphoma.
Aim: To compare GEMOX (gemcitabine, oxaliplatin) with ESHAP (etoposide, methylprednisolone, cytarabine arbinoside, cisplatin) regimes as 2nd line in lymphomas.
Methods: This was a prospective randomized study that included relapsed/refractory HL and aggressive NHL patients who failed 1st line chemotherapy. After assessment for eligibility, patients were randomized to receive GEMOX or ESHAP.
Results: The study included 41 patients, 21 of them received GEMOX and 20 received ESHAP. The response rate did not differ significantly between the GEMOX and ESHAP arms (28.6% vs. 35%, p=0.793) as well as progression free survival (8.7 months vs. 6.6 months, p=0.711). By univariate analysis for the whole group, the response rate differed significantly according to disease status at relapse, time to relapse, lactate dehydrogenase, International Prognostic Index (IPI) and secondary age-adjusted IPI (2ry aa-IPI). Hematological toxicity was not statistically different between the two treatment arms. GEMOX was associated with significantly less vomiting of any grade (p=0.013). Acute renal toxicity of any grade was significantly lower in GEMOX compared to ESHAP (p=0.003). In terms of peripheral neuropathy, GEMOX was associated with significantly higher all grades (p=0.0001).
Conclusion: The current study results suggest that the response rate and progression free survival of GEMOX and ESHAP are comparable with different toxicity profile.

Keywords: Relapsed/refractory lymphoma, GEMOX, ESHAP
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INTRODUCTION

Numerous chemotherapy protocols have been used as 2nd line treatment in relapsed or refractory aggressive non-Hodgkin's lymphoma (NHL) / Hodgkin's lymphoma (HL). An ideal regimen excludes agents that the patient has been exposed to recently, has no cross resistance to initial therapy and would allow for future stem cell collection [1].

Two randomized trials have compared salvage regimens as 2nd line. In the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) trial, patients were randomized to R-ICE (rituximab, ifosfamide, etoposide, carboplatin) or R-DHAP (rituximab, dexamethasone, high dose Ara-C, cisplatin) [2]. In the second study, NCIC CTG LY12 trial, patients with aggressive lymphoma were randomized to either GDP (gemcitabine, dexamethasone, cisplatin) or DHAP [3]. In both trials, the response rate (RR), progression free survival (PFS) and overall survival (OS) were comparable.

Accordingly, there is lack of data regarding the best chemotherapy regimen in the 2nd line setting. ESHAP (etoposide, methylprednisolone, cytarabine arbinoside, cisplatin) have been used as salvage chemotherapy protocol for years [4-7]. GEMOX (gemcitabine, oxaliplatin) is another regimen that has shown promising results in multiple phase 2 trials in patients who were not eligible for transplant [8-12].

The aim of this study was to compare GEMOX to ESHAP as 2nd line for patients with relapsed/refractory HL and aggressive NHL.

METHODS

This was a prospective randomized study including patients with relapsed/refractory HL or aggressive NHL between July 2014 and March 2016.

Eligible patients included those who relapsed after 1st line chemotherapy or were refractory to it with an age ranging from 18 to 65 years, and an Eastern Cooperative Oncology Group (ECOG) performance status 0-2. Exclusion criteria included ECOG performance status 3-4, central nervous system involvement, history of another malignant disease excluding skin basal cell

carcinoma and squamous cell carcinoma, significant cardiovascular disease with ejection fraction below 50%, non-compliance to 1st line treatment, and serious concomitant medical condition which may compromise participation in the study.

All patients underwent an initial evaluation, including a detailed clinical history and examination. Laboratory investigations included: complete blood count, liver function assessment (aspartate aminotransferase , alanine aminotransferase , and total bilirubin), fasting blood sugar, serum creatinine, serum uric acid, lactate dehydrogenase (LDH) , hepatitis B-surface antigen and hepatitis C virus antibody. Staging was done according to Ann Arbor staging system by computerized tomography of chest, abdomen, aand pelvis, and bone marrow aspirate/biopsy. Refractory or relapse disease was defined based on Lugano criteria for response assessment [13]. The histologic diagnosis was documented by biopsy at relapse, while in refractory disease, no biopsy was required

Patients were randomly assigned to GEMOX or ESHAP, both given every 21 days. GEMOX regimen consisted of gemcitabine (1200 mg/m^2, IV, days 1 and 8) and oxaliplatin (120 mg/m^2, IV, day 1). ESHAP regimen consisted of etoposide (40 mg/m^2, IV, days 1 to 4), methylprednisolone (500 mg, IV, day 1), cytarabine (2000 mg/m^2, IV, day 5) and cisplatin (25 mg/m^2, 24 hour IV infusion, days 1 to 4).

Patients were assessed for response with each treatment cycle clinically and after 3 cycles by computerized tomography according to the International Working Group criteria [13]. Adverse events were graded according to the common terminology criteria for adverse effects (CTCAE) version 4.0. A complete blood count, serum creatinine, aspartate aminotransferase, alanine aminotransferase, and bilirubin were carried out before each chemotherapy cycle to assess for the hematological, renal and hepatic toxicity and to adjust doses of chemotherapy if necessary. Patients who achieved complete remission (CR) were referred for autologous stem cell transplant (ASCT) and those who achieved less than CR continued chemotherapy for 6 cycles.

The 1ry end point was the RR, while the 2ry end points were PFS and chemotherapy toxicity. The trial was approved by the institutional research ethics committee.

All statistics were done by SPSS software (statistical package for social science) version 17. Progression free survival was defined as the time from entry into the study until disease progression (PD) or death as a result of any cause. Survival analysis was done using the Kaplan-Meier method and compared by log-rank test for significance. All reported p values were two-sided, and p value <0.05 was considered significant.

RESULTS

Forty-one patients were included in the current study, 21 in the GEMOX arm and 20 in the ESHAP arm, and the majority had an advanced stage (III/IV) (81% and 80%, respectively).

Table 1. Patients' characteristics

Characteristic	GEMOX (n=21) n(%)	ESHAP (n=20) n(%)	P value
Age (years)			
<60	17 (81)	18(90)	0.35
>60	4 (19)	2(10)	
Median (range)	40 (26-65)	43 (20-63)	0.99
Gender			
Male	10 (52.4)	10(50)	0.56
Female	11 (47.6)	10(50)	
Pathology			
Hodgkin's lymphoma	6 (28.6)	5(25)	0.33
DLBCL	15 (71.4)	13(65)	
T-cell lymphoma	0	2(10)	
Prior chemotherapy			
ABVD	6(28.6)	5(25)	0.39
CHOP	14(66.6)	14(70)	
EPOCH	1(4.8)	0	
HyperCVAD	0	1(5)	
Number of cycles			
Median (range)	4 (3-8)	6 (2-8)	0.84
Prior 1st line rituximab	3(14.3)	2(15)	0.54
Hepatitis C virus positive	3(14.3)	5(25)	0.31
Ann Arbor Stage at relapse			
II	4(19)	4(20)	0.97
III	7(33.3)	6(30)	
IV	10(47.7)	10(50)	
Lactate dehydrogenase			
Above normal	10(47.7)	7(35)	0.55
Normal	3(14.3)	2(10)	
ECOG performance scale			
0-1	14(66.3)	10(50)	0.31
2-3	7(33.7)	10(50)	
Extranodal involvement	8(38)	9(45)	0.8
>1 extranodal site	2(9.5)	2(10)	0.97
Bone marrow involved	5(23)	4(20)	0.85
B symptoms	9(42.9)	7(35)	0.42
Largest tumor diameter			
≤10 cm	17(81)	14(70)	0.32
>10 cm	4(19)	6(30)	
Disease status			
Relapsed	10(47.6)	7(35)	0.30
Refractory	11(52.4)	13(65)	
Time to relapse			
>12 months	7(33.3)	6(30)	0.54
≤12 months	14(66.7)	14(70)	
2ry aa-IPI for DLBCL			
Low (0-1)	3(14.3)	3(15)	0.95
Intermediate (2)	8(38)	6(30)	
High (3)	4(19)	4(20)	
IPI for DLBCL at relapse			
Low (0-1)	2(9.5)	3(15)	0.61
Intermediate (2-3)	8(38)	7(35)	
High (4-5)	5(23.8)	3(15)	
Diabetes			
Yes	3(14.3)	3(15)	0.64
No	18(85.7)	17(85)	

GEMOX: Gemcitabine, oxaliplatin; **ESHAP**: etoposide, methylprednisolone, cytarabine arbinoside, cisplatin; **DLBCL**: Diffuse large B-cell lymphoma; **ABVD**: Adriamycin, bleomycin, vinblastine, dactinomycin; **CHOP**: Cyclophosphamide, adriamycin, oncovin, prednisone; **EPOCH**: Etoposide, prednisone, oncovin, cyclophosphamide, adriamycin; **HyperCVAD**: Cyclophosphamide, vincristine, adriamycin, dexamethasone, methotrexate, cytarabine; **ECOG**: Eastern Cooperative Oncology Group), **aa-IPI**: age-adjusted International Prognostic Index .

Almost half (52.4%) in GEMOX had refractory disease, while it represented two thirds (65%) in ESHAP arm. Patients' characteristics were not significantly different between the 2 treatment arms (table 1).

During the study period, 63 cycles of GEMOX were administered with a median of 3 cycles (range: 1-6) compared to 68 cycles of ESHAP with a median of 3 cycles (range: 1-6). Eight (38%) patients in the GEMOX arm experienced treatment delay compared to 9 (45%) in the ESHAP with total number of 80 days and a median of 7 days in the GEMOX arm compared to 73 days and a median of 8.5 days in the ESHAP arm. The main cause of chemotherapy delay was grade 3 neutropenia in 4 (19%) patients in the GEMOX arm and 5 (25%) patients in the ESHAP arm. One patient in each arm had also grade 3 thrombocytopenia and grade 3 nausea and vomiting. The 2nd common cause of treatment delay was non-compliance in 2 (14.2% and 10%) patients in each of the treatment arms. Other causes in the ESHAP arm were grade 3 nausea and vomiting in 2 patients and grade 3 anemia in 1 patient. Other causes in the GEMOX arm were grade 3 hepatic toxicity in 1 patient and grade 3 peripheral neuropathy in another 1. Two patients in the GEMOX arm had 25% dose reduction due to persistent grade 3 neutropenia and grade 3 hepatic toxicity while only 1 patient in ESHAP arm had 25% dose reduction due to persistent grade 3 neutropenia.

The median follow up was 9.8 months (range 2-21.7 months). The RR was 28.6% in the GEMOX arm vs. 35% in the ESHAP with no significant difference. Progression free survival did not differ significantly between both arms (8.7 months [95%CI=3.6-10.4] for GEMOX vs. 6.6 months [95%CI=2.6-10.9] for ESHAP; p=0.711) (table 2, figure 1).

Table 2. Response to GEMOX and ESHAP

Response	GEMOX n=21	ESHAP n=20	P value
	n (%)	**n (%)**	
Complete response	2 (9.6)	2 (10)	0.79
Partial response	4 (19)	5 (25)	
Stable disease	3 (14.2)	2 (10)	
Disease progression	12 (57.2)	11 (55)	

GEMOX: Gemcitabine, oxaliplatin; **ESHAP**: etoposide, methylprednisolone, cytarabine arbinoside, cisplatin

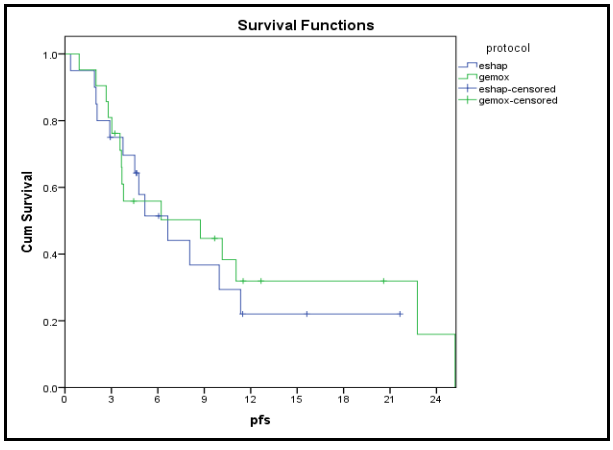

Figure 1. Progression free survival curves of GEMOX and ESHAP arms

Among the whole patients' set, disease status at relapse, time to relapse, LDH, IPI and 2ry age adjusted IPI (aa-IPI) had significant impact on response (table 3).

Table 3. Univariate analysis for factors affecting response

Variable	CR/PR (n=13) n (%)	SD/DP (n=28) n (%)	P value
Age (years)			
<60	11(84.6)	24(85.7)	0.62
>60	2(15.4)	4(14.3)	
Prior 1st line Rituximab	2(15.3)	3(10.7)	0.51
Ann Arbor Stage at relapse			
II	4(19)	4(20)	0.97
III-IV	9(69.3)	24(85.7)	
Lactate dehydrogenase			
Above normal	4(30)	13(46.5)	0.02
Normal	3(23	2(7)	
ECOG performance scale			
0-1	9(69.2)	15(53.5)	0.55
2-3	4(30.8)	13(46.5)	
Extranodal involvement	3(23)	14(50)	0.64
>1 extranodal site	1(7.6)	4(14.7)	0.81
Bone marrow involvement	2(15.3)	7(25)	0.35
B symptoms	4(30.6)	12(42.8)	0.35
largest tumor diameter			
≤10 cm	1(7.6)	9(32.1)	0.09
>10 cm	12(92.4)	19(67.9)	
Disease status			
Relapsed	10(76.9)	7(33.3)	0.30
Refractory	3(23.1)	21(66.7)	
Time to relapse after diagnosis			
>12 months	7(53.8)	6(21.4)	0.04
≤12 months	6(46.2)	22(78.6)	
2ry aa-IPI (DLBCL patients)			
Low (0-1)	3(23)	3(10.8)	0.03
Intermediate (2)	5(38.5)	9(32)	
High (3)	0	8(28.6)	
IPI at relapse (DLBCL patients)			
Low (0-1)	3(23)	2(7.5)	0.03
Intermediate (2-3)	5(38.5)	10(35.7)	
High (4-5)	0	8(28.6)	

CR/PR: Complete response/partial response; **SD/DP**: Stable disease/ disease progression; **ECOG**: Eastern Cooperative Oncology Group; **aa-IPI**: age-adjusted International Prognostic Index: **IPI**: International Prognostic Index; **DLBCL**: Diffuse large B-cell lymphoma.

The most common hematological toxicities in both arms were anemia, neutropenia and thrombocytopenia respectively, with no statistically significant difference between them. Platelet transfusion was given to 1 patient in the GEMOX arm due to grade 4 thrombocytopenia and hematuria. Febrile neutropenia was observed in 3 patients in the GEMOX arm and 6 in the ESHAP arm with no toxicity related deaths reported during the study period.

The most common non-hematological toxicities in both arms were nausea and vomiting. The prevalence of nausea did not differ significantly; however, GEMOX was associated with significantly less vomiting of any grade (p=0.013). Acute renal toxicity of any grade was significantly lower in GEMOX (P=0.003). In terms of

peripheral neuropathy, GEMOX was associated with significantly higher all grades (p=0.0001). Toxicities are summarized in table 4.

Table 4. Toxicity profile of the two treatment groups

Toxicity	GEMOX (n=21)	ESHAP (n=20)	P value
	n (%)	n (%)	
Hematological toxicity			
Anemia			
Any grade	17(80.9)	14(70)	0.62
Grade1-2	13(61.9)	9(45)	0.53
Grade 3-4	4(19)	5(25)	
Neutropenia			
Any grade	10(47.6)	13(65)	0.21
Grade1-2	6(28.5)	8(40)	0.47
Grade3-4	4(19)	5(25)	
Thrombocytopenia			
Any grade	7(33.3)	5(25)	0.40
Grade1-2	5(23.8)	3(15)	0.56
Grade3-4	2(9.5)	2(10)	
Febrile neutropenia	3(14.2)	6(30)	0.2
Non-hematological			
Acute renal toxicity			
Any grade	0	6(30)	0.003
Grade1-2	0	6(30)	0.003
Grade 3-4	0	0	
Hepatic toxicity			
Any grade	7(33.3)	3(15)	0.15
Grade1-2	6(28.5)	3(15)	0.26
Grade 3-4	1(4.7)	0	
Diarrhea			
Any grade	5(23.8)	3(15)	0.3
Grade1-2	4(19)	3(15)	0.48
Grade3-4	1(4.8)	0	
Vomiting			
Any grade	11(52.3)	17(85)	0.01
Grade1-2	10(47.6)	15(75)	0.01
Grade3-4	1(4.7)	2(10)	
Nausea			
Any grade	14(66.6)	18(90)	0.07
Grade1-2	13(61.9)	15(75)	0.59
Grade3-4	1(4.7)	3(15)	
Mucositis			
Any grade	8(38)	9(45)	0.44
Grade 1-2	7(33.3)	8(40)	0.84
Grade3-4	1(4.7)	1(5)	
Peripheral neuropathy			
Any grade	18(85.7)	1(5)	0.001
Grade1-2	17(80.9)	1(5)	0.001
Grade3-4	1(4.8)	0	
Laryngo-pharyngeal dysesthesia	14(66.6)	0	0.001

GEMOX: Gemcitabine, oxaliplatin; **ESHAP**: Etoposide, methylprednisolone, cytarabine arbinoside, cisplatin.

At the time of analysis (May 2016), 1 of the 2 patients in the GEMOX arm who achieved CR was referred for ASCT and the other developed PD. Similarly, 1 of the 2 patients who achieved CR in the ESHAP arm was referred for ASCT and the other lost to follow up.

DISCUSSION

Treatment of relapsed/refractory aggressive NHL and HL represents a challenge for both patients and clinicians, since more than half of these patients cannot be cured even with the addition of rituximab [14, 15]. Autologous stem cell transplantation is the standard of care in chemotherapy-sensitive relapsed/refractory aggressive NHL and HL [16, 17].

An ideal salvage therapy regimen for use prior to ASCT should have a high response rate, low hematologic and non-hematologic toxicity, and should not impair the harvesting of stem cells [18]**.** There is lack of evidence regarding which the best chemotherapy that can be used in the 2nd line setting. GEMOX regimen has shown promising results in multiple phase 2 trials in patients who were not eligible for transplant. Therefore, in our study we compared GEMOX against the standard ESHAP regimen [8-12].

In the majority of studies testing ESHAP as a 2nd line, the overall RR ranged between 53% and 73% (CR 37–50 %) [4-7]. On the other hand, R-GEMOX overall RR ranged between 43% and 83% (CR 34–50%) [9-11]**.** The overall RR to GEMOX without rituximab in DLBCL was 57%, with 30% CR achievement [12]. For HL, a study that included 24 patients reported 71% RR (38% CR) [8]**.**

In the current study, there was no statistically significant difference in RR between GEMOX and ESHAP (28.6% vs. 35% respectively and CR was equal in both arms (9.6 % vs. 10% respectively). These results are inferior when compared to the international figures. This could be attributed to the high percentage of 1ry refractory disease in our study, the fact that only one third of patients had a time to relapse >12 months; and unfortunately, rituximab was not given due to logistic and financial reasons.

In the present study, factors affecting RR were disease status at relapse, time to relapse after 1st line, IPI at relapse, LDH and 2ry aa-IPI. These results are consistent with previously published studies [2, 19-22]**.**

As regards to the toxicity profile of GEMOX and ESHAP, the hematologic toxicity rates were similar in both arms. In contrast, the non-hematologic toxicities were different between both groups. Renal toxicity and vomiting were less with GEMOX while neurotoxicity was lower in ESHAP. Thus GEMOX may be considered in frail patients with renal impairment.

Successful stem cell collection is a fundamental prerequisite for salvage chemotherapy regimens. However, due to the limited number of patients who received GEMOX and referred for ASCT, this point cannot be answered in our study. Quality of life was not assessed in the current study. GEMOX could be more convenient because this regimen is typically administered on an outpatient basis, compared to 5 days admission in ESHAP regimen. However, the price of individual drugs in GEMOX is more costly in comparison to ESHAP, plus the hospitalization costs.

Limitations of this study were the small sample size and the lack of response assessment by functional imaging. Other limitation was that, in DLBCL patients, cell of origin studies were not performed. The cell of

origin remains a major and independent factor in relapsed/ refractory DLBCL, with a better response to R-DHAP in GCB-like DLBCL [23].

Conclusion

GEMOX regimen is comparable to ESHAP regarding RR and PFS. The hematologic toxicity rates were similar in both arms; however, renal toxicity and vomiting were less with GEMOX while neurotoxicity was lower in ESHAP. GEMOX may be considered in frail patients with renal impairment.

Conflict of Interest

None to declare.

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