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Gemox-Vinorelbine as Pre-Transplant Salvage in Diffuse Large B Cell Non-Hodgkin Lymphoma Patients Single Institutional Prospective Phase II Study

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Abstract

***Background**: Salvage chemoimmunotherapy is given to determine the chemosensitivity of relapsed/refractory disease and to reduce the burden of disease prior to transplantation. There is no consensus regarding an optimal salvage regimen for all transplant-eligible patients, and the preferred approach varies by institution and clinician. Salvage chemoimmunotherapy comprises a combination of relatively high doses of non-cross-resistant drugs together with a monoclonal antibody against CD20 (eg, rituximab) and there is a trend towards selecting salvage regimen based on pathologic features of disease either germinal center DLBCL or Activated B-cell (ABC) DLBCL. Gemcitabine/oxaliplatin (GemOx), with or without rituximab, is a frequently used treatment of relapsed or refractory (r/r) aggressive B-cell non-Hodgkin lymphoma (B-NHL), and is NCCN -listed for transplant-eligible patients. Vinorelbine (vinca alkaloid) is a mitotic inhibitor which has shown encouraging early results in the treatment of heavily pre-treated relapsed or refractory lymphoma. In this study we explored the value of addition of vinorelbine(navelbine) to GemOx regimen in inducing more Complete remission (CR) in relapsed or refractory non-Hodgkin lymphoma.**Aim**: we investigated the efficacy and safety of Gemox-vinorelbine protocol as a pre-transplantation regimen in refractory and relapsed non Hodgkin lymphoma diffuse large B-cell type either Germinal Center B-cell or activated (ABC) B-cell type. **Methods**: Treatment consists of gemcitabine at 600mg /m2 on days 1 and 2, oxaliplatin 60 mg/m2 on days 1 and 2, vinorelbine 20mg/m2 d1 and dexamethasone 16mg/m2 d1-d4 repeated every 2 weeks d1, d15 with addition of Rituximab (375mg/m2) according to institute policy. Eligible patients were relapsed/refractory (R/R) NHL. Patients were recruited from Oncology Center Mansoura University during the period between December 2020 and September 2022 with a minimum follow of 6 months. Assessment was performed after 2-4 cycles of treatment by PET-CT. **Results:** Forty-five eligible patients (31 males ,69%) were treated with Gemox-vinorelbine ,the median number of treatment cycles was 3 (1-6).At the 1st re-evalution (after 2-4 cycles),forty one patients were eligible for treatment evalution,12 patients achieved complete remission(29.2%) , 10 patients achieved partial response(24.4%) , 3 patients had stable disease(7.3%) and 16 patients had progressive disease (39%).Patients who had partial response completed 2 more cycles (10 patients) ,4 of them achieved CR at 2nd re-evaluation (after 6 cycles) and 6 had a progressive disease .At least 3 cycles are needed for CR. A total of 16 patients achieved CR (39%). Eleven Patients proceeded to ASCT and 5 patients were rejected for bone marrow transplantation for causes like antithrombin III deficiency, one relapsed after stem cell collection, one considered to be in CR1 by bone marrow transplantation team. Gemox-vinorelbine protocol didn't affect Stem Cell harvesting nor engraftment. Any Grade toxicities were thrombocytopenia (66.6%), anemia (35.5%),*

neutropenia (33.3%), febrile neutropenia (15.5%)
Neuropathy (33.3%), mucositis (20%). Treatment related mortality occurred in one patient (NF progressed to septic shock).The median progression free survival (PFS) was 10.8 months and median OS was 12 months. Both PFS nor OS was affected by cell of origin of DLBCL either germinal Center (GC) or non-germinal center (non-GC). Significant predictors for OS were IPI, late relapse >12 months versus primary refractory and early relapse <12months and number of prior lines. ***Summary and conclusions:*** *Gemox-vinorelbine had good activity as as a salvage regimen in R/R NHL(DLBCL) especially if used as 1st salvage in transplantation candidate patients.*

Keywords: *Relapsed/ refractory non-Hodgkin lymphoma (R/ R NHL), Gemox-vinorelbine (Gemcitabine / oxaliplatin-vinorelbine), complete response (CR), Partial response (PR), progression free survival (PFS), OS (overall survival).*

1. Introduction

In the immunochemotherapy era, more than 50% of patients with advanced-stage de novo DLBCL are cured with rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (Friedberg, 2011)**.** However, depending on the number of adverse prognostic factors from the International Prognostic Score (IPI), 20% to 50% of patients with DLBCL will be refractory to R-CHOP or will relapse after achieving complete response (CR**)**(Sehn et al., 2007)**.** Among patients who progress during initial immunochemotherapy or soon after a brief CR, only 30% to 40% will respond to salvage chemotherapy and may subsequently undergo consolidation with autologous stem cell transplantation (ASCT) (Van Den Neste et al., 2016)**.**

In the relapsed setting, regimens such as if osphamide, carboplatin and etoposide (ICE), etoposide, methylprednisolone, cytarabine, cisplatin (ESHAP), and dexamethasone, high dose cytarabine and cisplatin (DHAP) all with or without rituximab (R) are often employed. Such strategies have yielded response rates of 65-85% and complete response rates of 20-30 % in younger, transplant eligible patients with DLBC or Hodgkin lymphoma. Limitations of these regimens include the inability to safely deliver high dose cytarabine to older adults, cisplatin nephrotoxicity, if osphamide neurotoxicity, and the common requirement for aggressive hydration and inpatient hospitalization for delivery of these agents (Moskowitz et al., 2010)**.**

Gemcitabine/oxaliplatin (GemOx), with or without rituximab, is Also a frequently used treatment of relapsed or refractory (r/r) aggressive B-cell non-Hodgkin lymphoma (B-NHL), and is NCCN compendium-listed for both transplant-eligible and ineligible patients based upon results in small phase II clinical trials (Schade et al., 2019)**.**

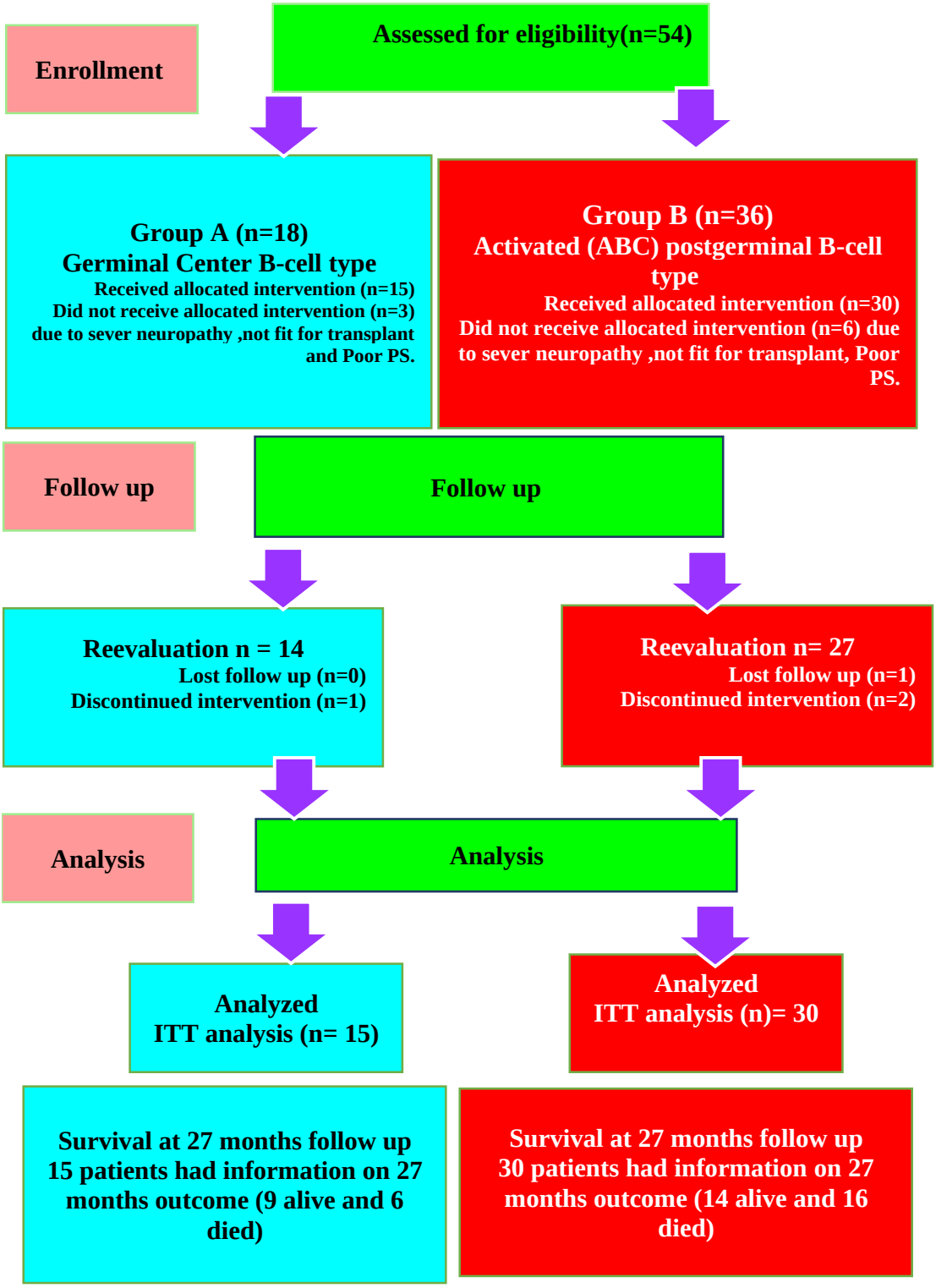
Vinorelbine is a semisynthetic vinca alkaloid with cytostatic activity against a broad range of tumor cell lines. Like other vinca alkaloids, vinorelbine is a mitotic inhibitor (‘spindle poison’) believed to exert its anti-tumor effects by binding to tubulin, thus inhibiting microtubule assembly and eventually preventing metaphasic tumor cell division (Goa et al., 1994)**.** Vinorelbine has reported single agent activity in NHL with response rates of 18–46% (Sarris et al., 2000) and in Combination with gemcitabine and prednisone (Müller-Beißenhirtz et al., 2005)**.** However, the efficacy and safety of vinorelbine combined with Gemox in patients with refractory and relapsed non-Hodgkin lymphoma have not been studied before.

2. Materials And Methods

The study designs

This was a prospective randomized study designed to assess the efficacy and safety of Gemox-vinorelbine protocol as a pre-transplant regimen in refractory and relapsed non-Hodgkin lymphoma diffuse large B-cell type either Germinal Center or activated (ABC) B-cell type. The protocol was used as either a 1st salvage therapy or subsequent. The included patients attended our Outpatient Medical Oncology Clinics at Oncology Center, Mansoura University between December 2020 and September 2022 with a minimum follow up period of 6 months.

Figure 1: Flowchart for prospective phase II Gemox/vinorelbine in R/R NHL



Treatment

Gemox-vinorelbine protocol

Consisted of gemcitabine at 600mg /m2 on days 1 and 2 (infused intravenously (IV) over 30 minutes), oxaliplatin 60 mg/m2 on days 1 and 2 (infused IV over *2* hours), vinorelbine 20mg/m2 d1 and dexamethasone 16mg/m2 d1-d4 repeated every 2 weeks d1,d15 with addition of Rituximab(375mg/m2) according to institute policy. Granulocyte colony stimulating factor GF was given prophylactic for All patients after 24 hours from end of day 2 of each D1,D15 of cycle. The

antiemetic regimen was dexamethasone 8 mg and granisteron 3 mg i.v. before chemotherapy. Treatment was repeated every 2 weeks in an outpatient setting.

The treatment was discontinued for either disease progression or loss to follow up. We considered level one dose reduction as 20% reduction of both Gemox and vinorelbine doses and level two dose reduction as 50% reduction if grade 4 hematological toxicities or grade 3 or 4 non hematological toxicities occurred.

Response evaluation

Patients were evaluated clinically& laboratory prior to each cycle and radiologically by baseline CT scan initially then after 2-4 cycles by PET-CT. If there was bone marrow infiltration at baseline, patients were re-evaluated by BMB following therapy to confirm if CR was achieved. PET CT scan was not routinely done at baseline; however, response evaluation was based on PET CT scan whenever available and to ensure CR especially in unconfirmed cases. Response assessment was performed according to the Revised Response Criteria for Malignant Lymphoma. Overall RR was defined as the number of patients with a complete remission (CR) or a partial response (PR), divided by the number of all patients with measurable lesions (Cheson et al., 2007)**.**

The response duration was dated from start of treatment until progression. The PFS was dated from imitation of treatment till progression. OS was dated from initiation of treatment till death or lost follow up or last follow-up visit if still alive. The final update for survival was performed in March 2023.

Patients with CR underwent bone marrow transplantation. Partial response (PR) continued on treatment for up to 4-6 cycles. Patients who had stationary disease (SD), progressive disease (PD) after re-evaluation were withdrawn from the study. Protocol toxicity was assessed by National Cancer Institute Common Toxicity Criteria (CTC) version 4.0**(10).**

Statistical analysis

The collected data was revised, coded, and tabulated using Statistical package for Social Science **(IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).** Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

Normality of data

Shapiro-Wilk test was done to test the normality of data distribution. Significant data was considered to be nonparametric.

Descriptive statistics:

- Mean, Standard deviation (± SD), or standard error (±SE), median and range for numerical data.
- Frequency and percentage for non-numerical data.

Analytical statistics:

- **Student T** Test was used to assess the statistical significance of the difference between two study group means.
- **Mann Whitney Test (U test)** was used to assess the statistical significance of the difference of a non-parametric variable between two study groups.
- **Chi-Square test** was used to examine the relationship between two qualitative variables. **Fisher-Exact** or **Monte-Carlo test:** was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells.
- **Kaplan–Meier test** was used for survival analysis and the statistical significance of differences among curves was determined by Log-Rank test.
- **Cox regression analysis** of factors potentially related to survival was performed to identify which independent factors might jointly have a significant influence on survival.

A hazard ratio (HR) is a measure of association between an exposure and survival. The HR represents the risk that the survival will be affected given a particular exposure, compared to the risk occurring in the absence of that exposure.
HR=1 Exposure does not affect survival.

HR>1 Exposure associated with shorter survival (risky).
HR<1 Exposure associated with longer survival (protective)

The 95 % confidence interval (CI) is used to estimate the precision of the HR. A large CI indicates a low level of precision of the HR, whereas a small CI indicates a higher precision of the HR.
Regression analysis: Logistic regression analysis was used for the prediction of risk factors when the dependent variable is categorical. An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure.

- OR=1 Exposure does not affect odds of outcome
- OR>1 Exposure associated with higher odds (risk) of outcome.
- OR<1 Exposure associated with lower odds of outcome (protective).

The 95 % confidence interval (CI) is used to estimate the precision of the OR. A large CI indicates a low level of precision of the OR, whereas a small CI indicates a higher precision of the OR.

Probability of results

- A p value is considered significant if <0.05 at confidence interval 95%.

Ethical statement:
Study protocol was registered and approved by IRB at Faculty of medicine, Mansoura University. Code number is (MD/21.01.407). Informed consent was obtained from each participant. Confidentiality and personal privacy was respected in all levels of the study. Collected data was not be used for any other purpose.

3. Results and Discussion

Patients' demographic criteria

Our study included 45 patients diagnosed with refractory and relapsed DLBCL. Thirty-one patients (68.9%) were males, median age at diagnosis was 45 years. Seventeen patients (37.7%) were ≥ 50 years old. B symptoms were detected in 6 patients (13.3%). Nine patients (20%) had bulky disease. The spleen was involved in 14 patients (31.1%). Extra nodal sites were involved in 28 patients (62.2%). At time of diagnosis, most patients were stage III-IV (77.8%). BM infiltration was detected in 4 patients. International prognostic index (IPI) at diagnosis was low in 10 patients (22.2%), low intermediate in 15 patients (33.3%), high intermediate in 15 patient (33.3%) and high in 5 patients (11.1%). Thirty patients (66.7%) were refractory or had early relapse (<12months) while 15 patients (33.3%) had late relapse (>12months). According to cell of origin of DLBCL ,15 patients had germinal center origin (33.3%) while 30 patients had non germinal center origin (66.6%). Thirty-three patient (73.3%) received Gemox-vinorelbine as 1st salvage,11 patient (24.4%) as 2nd salvage and 1 patient (2.2%) as 3rd salvage.

Table 1. demographic criteria of cases.

		No	%
Age group (years)	< 50	28	62.2%
	≥ 50	17	37.7%
Sex	Male	31	68.9%
	Female	14	31.1%
Performance status	PS I	41	91.1%
	PS II	4	8.8%
Diabetes	Yes	4	8.8%
	No	41	91.1%
Virology	Negative	30	66.6%
	HCV	14	31.1%
B-symptoms	Absent	39	86.6%
	Present	6	13.3%
Bulky	Yes	9	20%

	No	36	80%
Splenic Involvement	Yes	14	31.1%
	No	31	68.8%
Extranodal involvement	Yes	28	62.2%
	No	17	37.7%
Number of extranodal sites	No	17	37.7%
	Single	14	31.1%
	Multiple	14	31.1%
bone marrow involvement	Yes	4	8.9%
	No	41	91.1%
LDH	High	34	75.5%
	Normal	11	24.4%
Staging I-II vs III-IV	stage I	2	4.4%
	stage II	8	17.8%
	stage III	16	35.6%
	stage IV	19	42.2%
international prognostic index at diagnosis	Low	10	22.2%
	low intermediate	15	33.3%
	high intermediate	15	33.3%
	High	5	11.1%
Subtype	Germinal center	15	33.3%
	Non germinal center	30	66.7%
Refractoriness/early vs late relapse	Primary refractory or relapse <12 month	30	66.7%
	Late relapse >12 month	15	33.3%

Distribution of Gemox-vinorelbine in the different lines of treatment		
1 salvage	33	73.3%
2 salvage	11	24.4%
3 salvage	1	2.2%
Previous protocols		
R-CHOP/CHOP	40	88.8%
R-DA-EPOCH	4	8.9%
MiniCHOP	1	2.2%
ICE	4	8.9%
GDP	2	4.4%
DHAP	3	6.7%
R-ESHAP	4	8.9%
Gemox	2	4.4%

Gemox- vinorelbine treatment

Radiotherapy was used at some point in therapy course in 9 (20%) patients either for curative purposes like single residual lesion pre-transplantation or for palliative purposes for large tonsillar lesion or bulky lymphadenopathy.

The median number of received cycles was 3 cycles of Gemox-vinorelbine with range from one to six cycles. Two patients (4.4%) received only one cycle, 13 patients (28.8%) received 2 cycles, 12 patients (26.6%) received 3 cycles, 5 patients (11.1%) received 4 cycles, 3 patients (6.6%) received 5 cycles, 10 patients (22.2%) received 6 cycles.

Gemox-vinorelbine combination was received as a 1st salvage for 33 patients (73.3%) and 12 patients as a 2nd salvage or beyond (26.6%). Seventeen patients (37.7%) received Rituximab with Gemox-vinorelbine most of them were of non-GC origin. Prior protocols were ESHAP for 4 patients, ICE for

4 patients, DHAP for 3 patients and gemcitabine-based combination in form of GDP for 2 patients and gemcitabine/oxaliplatin for 2 patients.

Gemox-vinorelbine combination was discontinued for 26(57.7%) patients. The most common cause for treatment discontinuation was disease progression. Level 1 dose reduction occurred in 22(48.8%) patients while level 2 dose reduction occurred only in 3 patients.

Regarding hematological toxicity of Gemox-vinorelbine protocol; Sixteen patients (35.5%) of the studied population developed grade 3 or 4 anemia, twelve patients (26.6%) developed grade 3 or 4 neutropenia, seven patients (15.5%) developed febrile neutropenia and nineteen patients (42.2%) developed grade 3 or 4 thrombocytopenia.

Regarding non hematological toxicity of Gemox-vinorelbine protocol; four patients (8.8%) developed grade 3 or 4 neuropathy, four patients (8.8%) developed grade 3 or 4 mucositis, three patients (6.6%) developed grade 3 or 4 diarrhea, and one patient (2.2%) developed grade 3 or 4 hepatotoxicity. One patient died from treatment related complications (neutropenic fever progressed to septic shock).

Neutropenia was more common in non-germinal center origin (43.3%) than GC(13.3%).

Response to Gemox-vinorelbine

Our study enrolled 45 patients but only 41 were evaluable for response as four patients either lost follow up or died before evaluation.

At time of 1st re-evaluation (after 2-4 cycles of Gemox-vinorelbine),41 patients were eligible for response evaluation. Twelve patient (29.2%) achieved CR, 16 patients (39%) progressed, 10 patients (24.4%) achieved PR, and 3 patients (7.3%) had stable disease. Patients with progressive or stationary disease were withdrawn from the study.

At time of 2nd reevaluation (after 4-6 cycles of Gemox/vinorelbine),10 patients were eligible for response evaluation (who achieved PR). Four patients (40%) achieved CR and 6 patients (60%) had progressive disease. In Total 16 patients achieved CR (39%) with Overall response rate (ORR) reached 53.6%.

The Patients who received Gemox-vinorelbine as 1st salvage were more likely to achieve CR 13 out of 33 patients (39.4%) than who received Gemox-vinorelbine as a 2nd salvage or beyond 3 out of 12 patients (20%).

The mortality rate among lymphoma patients was 48.9%. The most common cause of mortality was disease progression.

Table 2. Treatment characteristics & Toxicity

		No	%
Radiotherapy	Radiotherapy	9	20%
	No radiotherapy	36	80%
Discontinuation due to disease progression	No	23	51.1%
	Yes	22	48.8%
Dose reduction	No	20	44.4%
	Level 1	22	48.8%
	Level 2	3	6.6%
Hematological Toxicity			
Anemia	All Grades	16	35.5%
Anemia (G3-4)	G3-4	16	35.5%
Neutropenia	All Grades	15	33.3%
Neutropenia (G3-4)	G3-4	12	26.6%
Neutropenic fever	Yes	7	15.5%
Thrombocytopenia	All Grades	30	66.6%
Thrombocytopenia (G3-4)	G3-4	19	42.2%
Peripheral neuropathy	All Grades	15	33.3%

Peripheral neuropathy(G3-4)	G3-4	4	8.8%
Mucositis (G3-4)	G3-4	4	8.8%
Diarrhea (G3-4)	G3-4	3	6.6%
Hepatotoxicity	All Grades	7	15.5%
Hepatotoxicity (G3-4)	G3-4	1	2.2%
Treatment related mortality	Yes	1	2.2%

Table 3. Assessment of response

		No	%
Interim Evaluation (after 2-4 cycles) (41 patients evaluable for response)	CR	12	29.2%
	PR	10	24.4%
	SD	3	7.3%
	PD	16	39%
2nd Treatment Evaluation (after 4-6 cycles) (10 patients evaluable for response, patients who achieved PR after 1st evaluation)	CR	4	40%
	PR	6	60%
End of Treatment Evaluation (41 patients evaluable for response)	CR+PR	22	53.6%
	No Response	19	46.3%

Mortality	Alive	23	51.1%
	Dead/censored	22	48.9%

CR complete remission, PR partial response, SD stationary disease, PD progressive disease

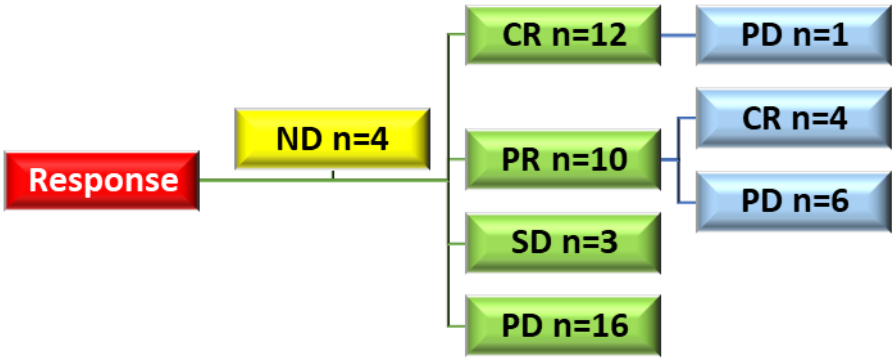


Figure 2. Organization chart for response among lymphoma patients.

Table 4. assessment of the response according to Gemox-vinorelbine distribution in salvage line

No of salvage	1st re-evaluation		No 2nd re-evaluation		%
1st salvage (33 patients,3 not evaluated)	CR	9			21.9%
	PR	10	CR	4	24.3%
			PD	6	
	SD	2			4.8%
	PD	9			21.9%
2nd salvage (11 patients ,1 not evaluated)	CR	3			7.3%
	SD	1			2.4%
	PD	6			14.6%
3rd salvage	PD	1			2.4%

CR complete remission, PR partial response, SD stationary disease, PD progressive disease

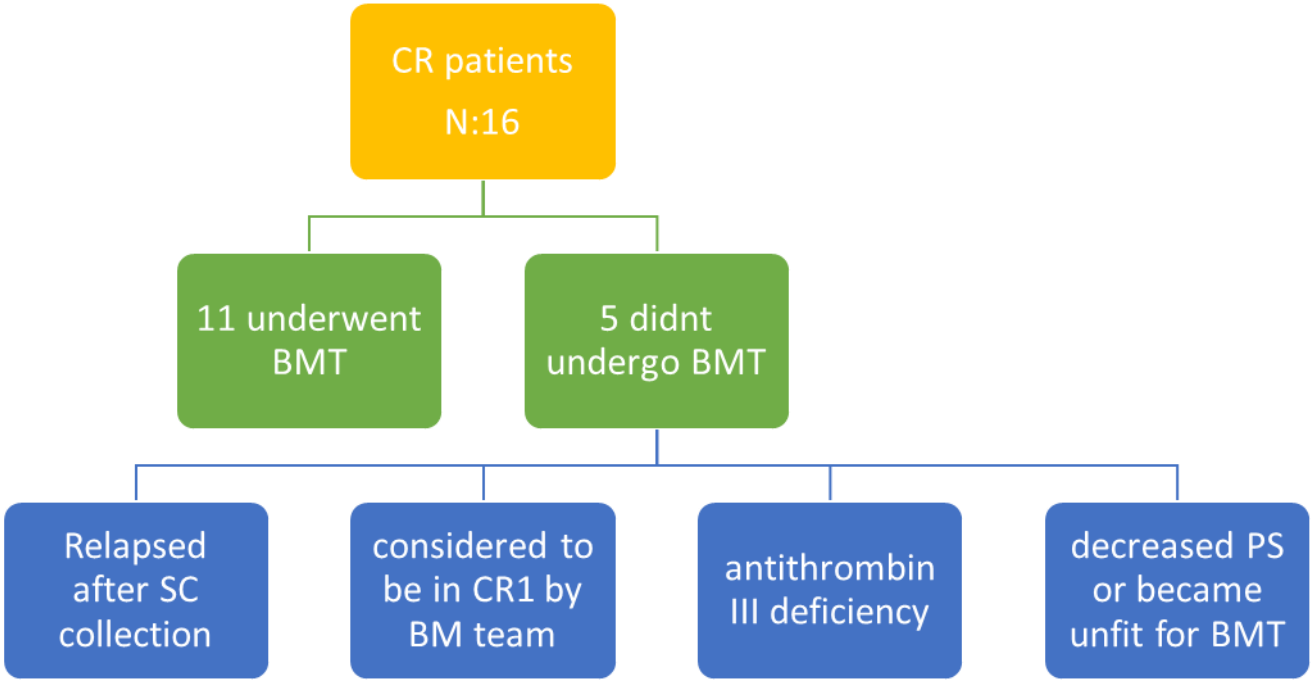


Figure 3. organization chart for Complete responders.

Eleven of responding patients underwent autologous bone marrow transplantation and 5 patients were rejected for bone marrow transplantation for causes like antithrombin III deficiency, one relapsed after stem cell collection, one considered to be in CR1 by bone marrow transplant team and two for declining PS and became unfit for BMT. Gemox-vinorelbine didn't affect stem cell harvesting nor the successful engraftment. The median amount of Stem Cell collection was 3.95 million/Kg. The median duration of days between the last cycle and harvesting was 88.5 day due to long waiting list and logistic problems. One of them needed the use of plerixafor for stem cell collection. The cell of origin (GC vs non-GC) didn't show any impact on the outcomes of transplantation.

Table 5. BMT among lymphoma patients.

	All cohort N = 45	
	№	***%***
Referred for transplant		
No	*29*	*64.4%*
Yes	*16*	*35.6%*
Transplant		
No	34	75.6%
Yes	11	24.4%
Harvesting stem cell amount n=12		
Yes	12	26.7%
Mean ± SE.		5.48 ± 0.97
Median (Range)		3.95 (2.00 –12.50)
Duration last cycle-harvesting n=12		
Mean ± SE.		103.17 ± 17.05
Median (Range)		88.5 (37.0 – 244.0)
Use of plerixafor n=12	1	8.3%
Engraftment n=11		
Successful engraftment	10	91%
Delayed engraftment	1	9%

When we reviewed the eleven patients who underwent BMT, we found that they were four males and seven females. Ten of them received the protocol as first salvage and One as 2nd salvage. Five patients were primary refractory or had early relapse <12 months while Six patients had late relapse >12 months. Five of them were non germinal and six were germinal center cell of origin. All of them had EGOG PS1. According to IPI, Patients who had low IPI were 4 patients, Low intermediate IPI were 5 patients and two were High intermediate. None of them was >60 years old. Two of them presented with bone marrow infiltration. At least, Three cycles of Gemox-vinorelbine were received with or without dose reduction to achieve CR.

Progression free survival & Overall survival

1st as a whole population

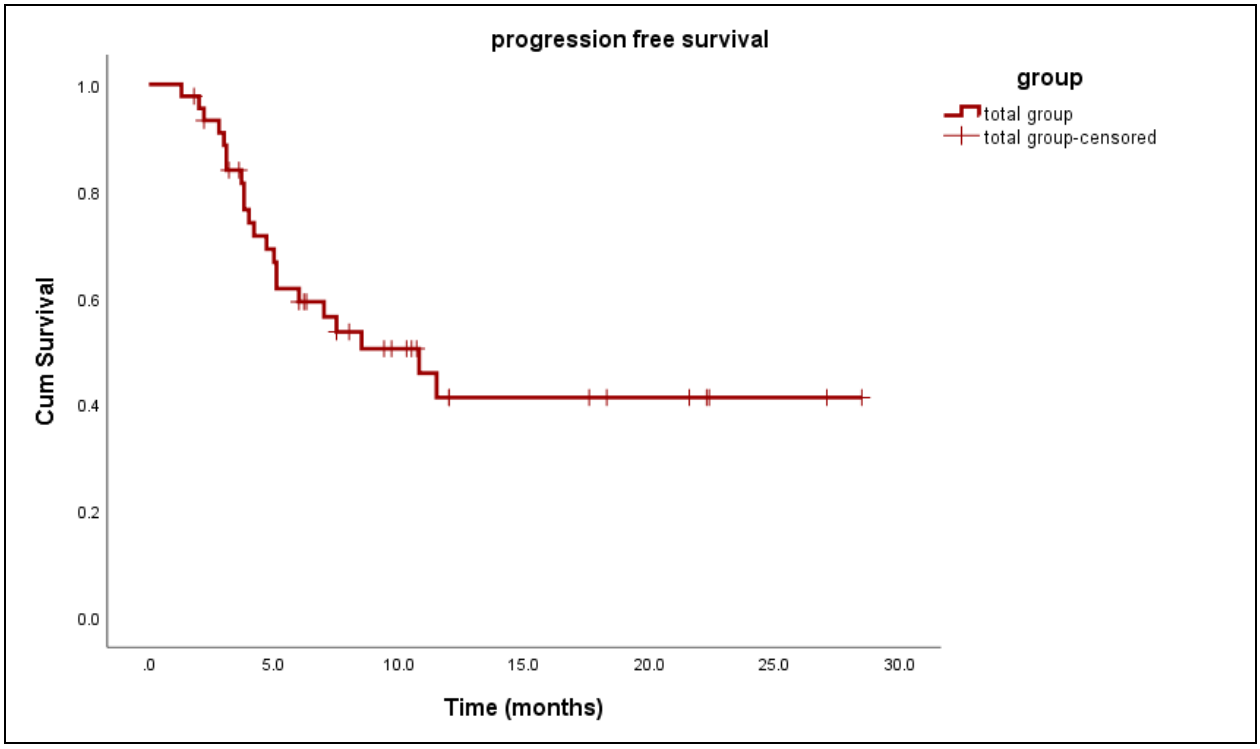


Figure 4. The Progression Free Survival at 2 years

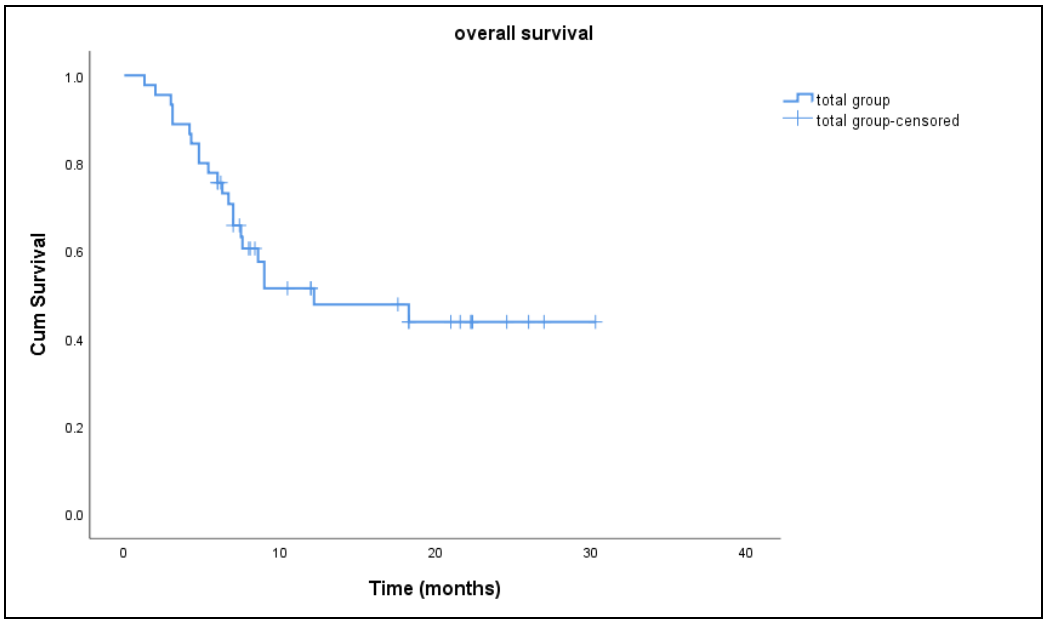


Figure 5. The Overall Survival at two years

After median follow up period of 12-month, Median PFS was 10.8 months and median OS was 12 months. The overall survival at two years was 45%.
Here in, we discuss the subgroups analysis and their impact on PFS and on OS

- Cell of origin (COO)germinal vs non germinal DLBCL
- The disease status (refractory or early relapse <12m / late relapse >12m),
- Gemox-vinorelbine protocol as 1st salvage versus as ≥ 2nd salvage line
- International prognostic index (IPI)

The median progression free survival (PFS) of studied patients was 10.8 months (95% CI 5.8-15.7 months). Median PFS for germinal center (GC) was not reached (NR) versus only 7.5 months for non-germinal center (non-GC). PFS didn't show any statistically significant difference as regard COO with log rank=0.4, P value 0.52. Also, PFS wasn't affected by IPI.

The median PFS was not reached for patients who had late relapse (>12 months) versus only 6 months for those with primary refractory or early relapse (<12 months). The difference was significant with log rank= 4.9, P value 0.026. Additionally, the median PFS was not reached (NR) when gemox-vinorelbine was given early as 1st salvage versus only 4.7 months when given as a 2nd salvage or beyond. The difference was significant with log rank =6.2, P-value 0.013 as show in figures 6 (a ,b,c)

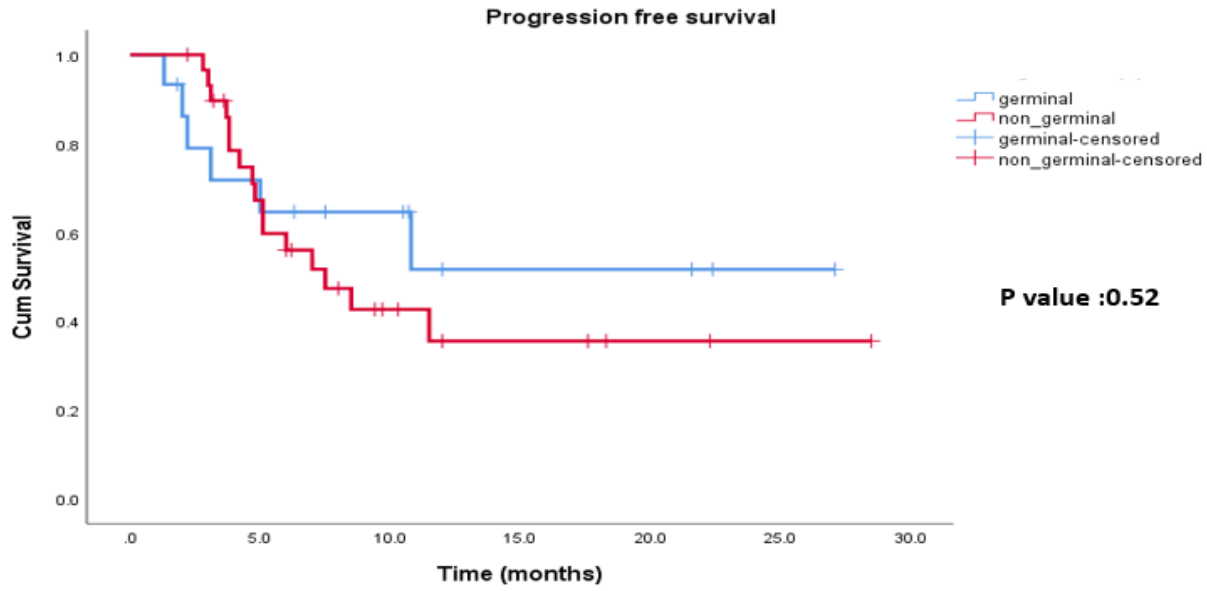


Figure 6a. PFS according to germinal or non-germinal nature of disease.

Median PFS for germinal center (GC) was not reached (NR) versus only 7.5 months for non-germinal center (non-GC). PFS didn't show any statistically significant difference as regard COO with log rank=0.4 ,P value 0.52.

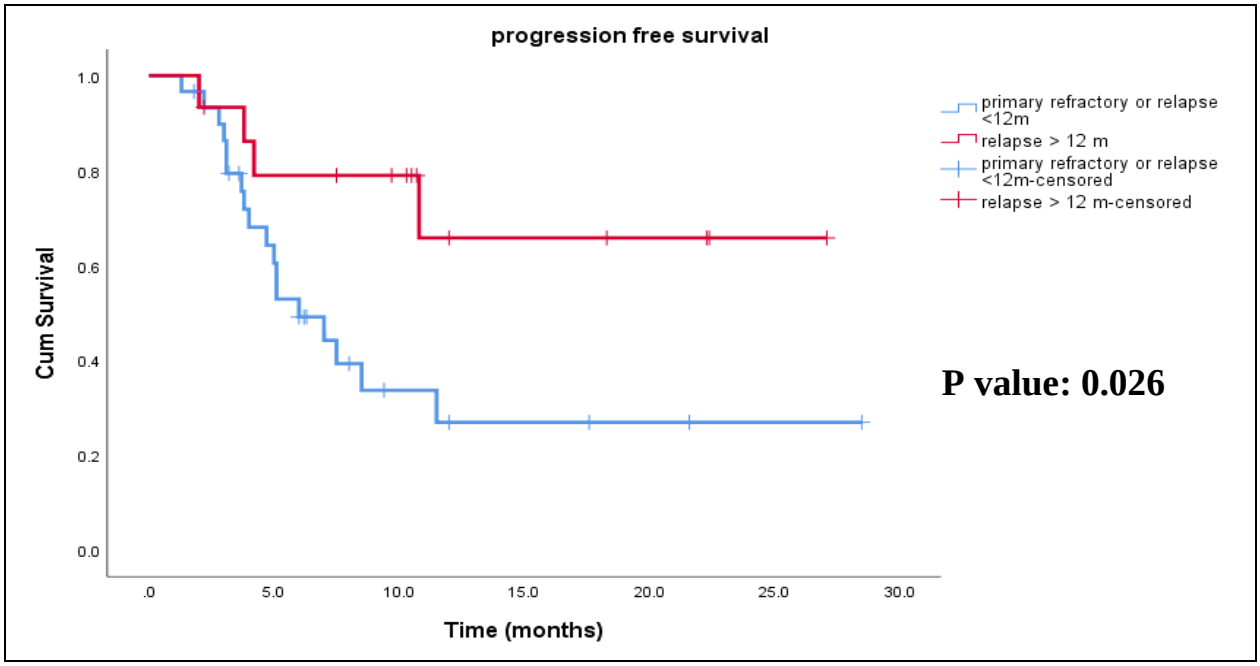


Figure 6b. PFS according to disease status

The median PFS was not reached for patients who had late relapse (>12 months) versus only 6 months for those with primary refractory or early relapse (<12 months). The difference was significant with log rank= 4.9, P value 0.026.

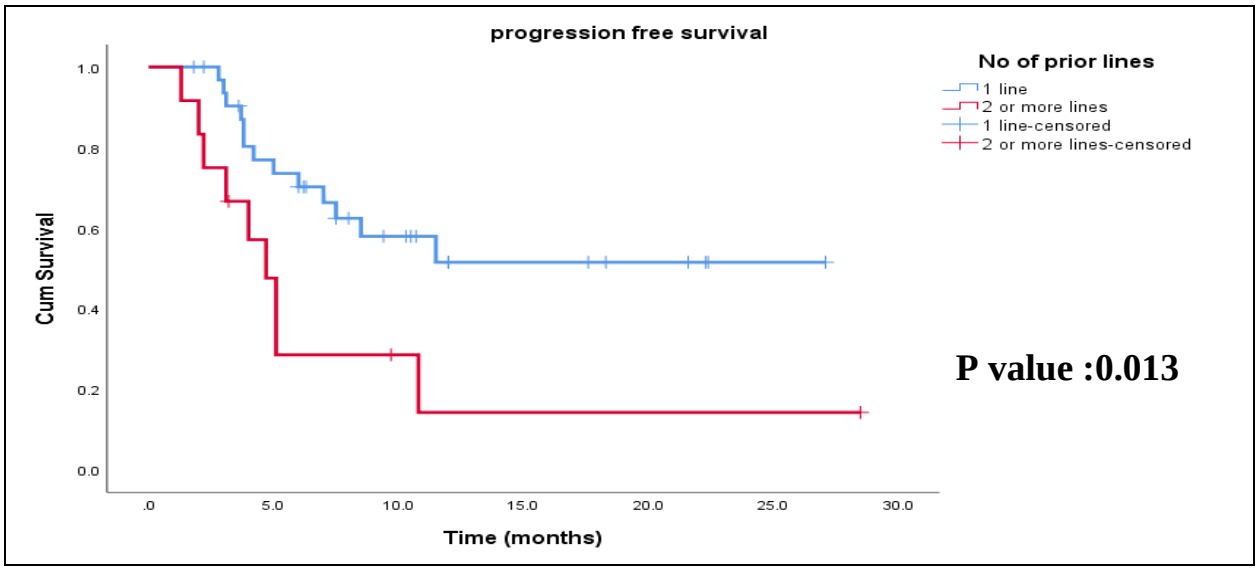


Figure 6c. PFS according to Gemox-vinorelbine distribution in different lines of treatment

The median PFS was not reached (NR) when gemox-vinorelbine was given early as 1st salvage versus only 4.7 months when given as 2nd salvage or beyond. The difference was significant with log rank =6.2, P-value 0.013.

Median Overall Survival (OS) of studied cases was 12 months (95% CI 0.76-23.6 months). Median OS in GC patients was NR (not reached) versus only 9 months in non-GC patients. Overall Survival at two years was 53% in GC group versus only 39.6 % in non-GC group. The difference between two groups was not statistically significant with log rank =0.4 ,p value of 0.5 but may be on longer follow up become significant as there is already separation of curves.

Median OS was not reached (NR) for patients with late relapse versus 7.6 months for primary refractory or early relapse <12 months.The survival at two years was 70% in patients with late relapse versus 30% in patients with primary refractory or early relapse ,the difference was significant with log

rank =5.3, P value 0.020. Additionally Median OS was Not reached when gemox-vinorelbine was given as a lst salvage versus 5.4 months for 2nd salvage or beyond. The survival at two years was 55% in patients who received gemox-vinorelbine as 1st salvage versus 20% for those who received it as a 2nd salvage or beyond ,the difference was significant with log rank =5,P value 0.023. as shown in figures 7(a,b,c).Finally OS which was markedly affected by IPI with significant P value of 0.001.

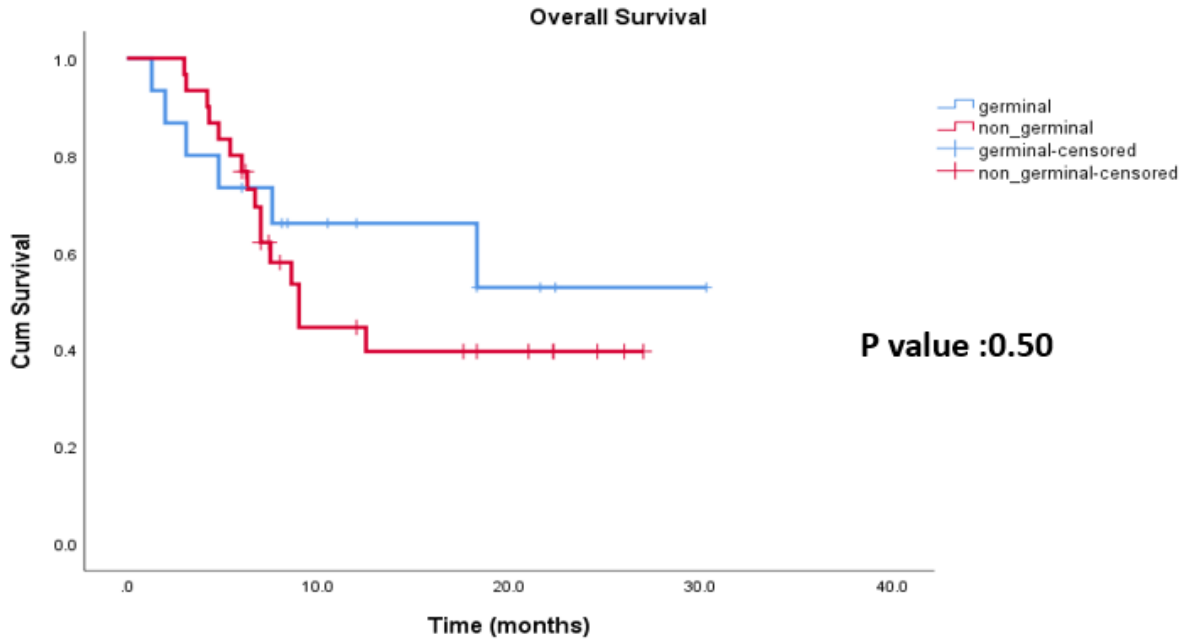


Figure 7a. OS according to germinal or non-germinal nature of disease.

Median OS in GC patients was NR (not reached) versus only 9 months in non-GC patients. Overall Survival at two years was 53% in GC group versus only 39.6 % in non-GC group. The difference between two groups was not statistically significant with log rank =0.4 ,p value of 0.5 but may be on longer follow up become significant as there is already separation of curves.

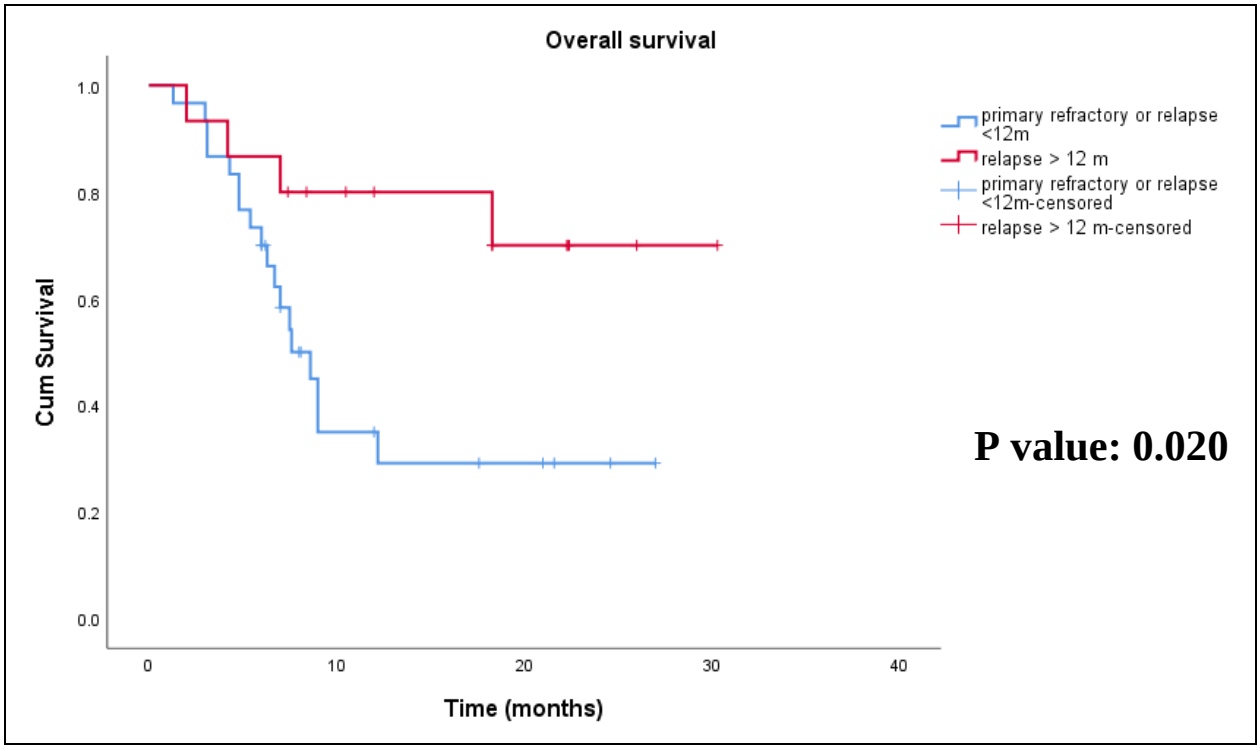


Figure 7b. OS according to disease status

Median OS was not reached (NR) for patients with late relapse versus 7.6 months for primary refractory or early relapse <12 months. The survival at two years was 70% in patients with late relapse versus 30% in patients with primary refractory or early relapse ,the difference was significant with log rank =5.3, P value 0.020.

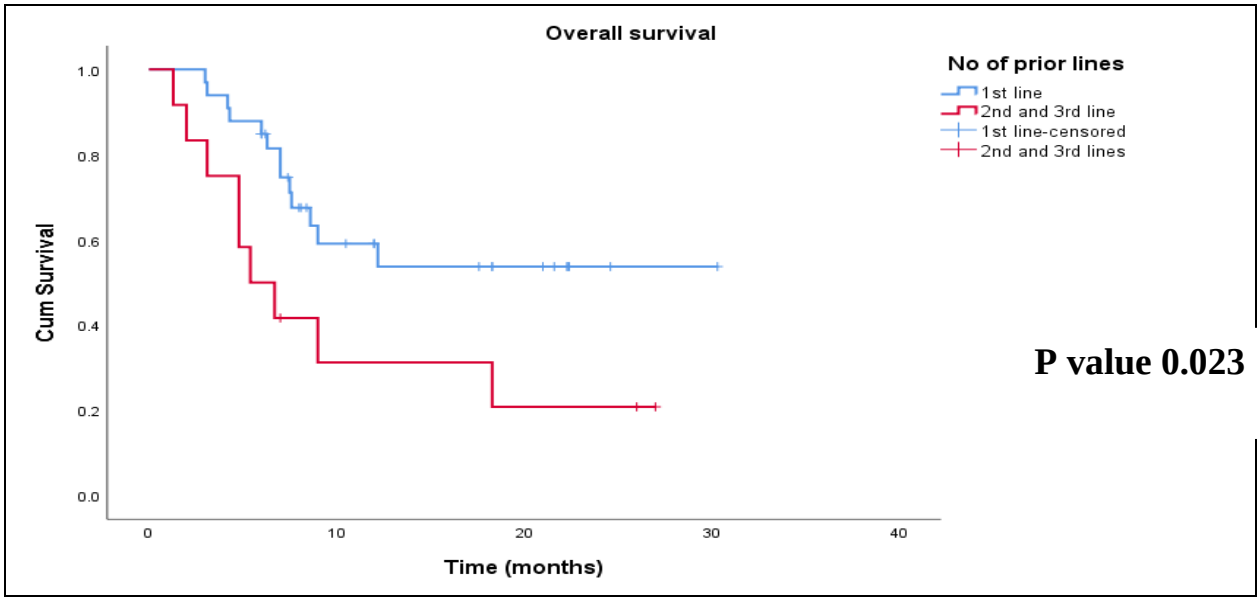


Figure 7c. OS according to Gemox-vinorelbine distribution in different lines of treatment

Median OS was Not reached when Gemox-vinorelbine was given as lst salvage versus 5.4 months for 2nd salvage or beyond. The survival at two years was 55% in patients who received Gemox-vinorelbine as 1st salvage versus 20% for those who received it as a 2nd salvage or beyond. The difference was significant with log rank =5,P value 0.023.

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(Seshadri et al., 2008). In this study Out of 45 patients with relapsed or refractory diffuse large B-cell lymphoma,Gemox-vinorelbine achieved ORR(CR+ PR) of 53.6% with 39% Complete remission (CR).More than 80% of CR was achieved when Gemox-vinorelbine was used as a first salvage.

The ORR of the Gemox-vinorelbine regimen reported here was similar to that observed in CORAL study, a phase III multicenter randomized trial that compared the efficacy of three R-DHAP or R-ICE cycles, followed by ASCT with or without rituximab maintenance in patients aged 18–65 years with previously treated DLBCL, provided comparable ORR of 62.8 and 63.5% respectively with 37% CR in both arms (Gisselbrecht et al., 2012).

Also it was comparable to what reported in LY12 study which compared the R-DHAP and R-GDP regimens in patients with relapsed /refractory aggressive lymphoma to treatment and responding patients proceeded to stem-cell collection and ASCT, provided ORR of 45% and 42% respectively (Crump et al., 2014a) however Gemox-vinorelbine achieved more than doubling for CR rates achieved in this study indicating that Gemox-vinorelbine could be used as a pre-transplant salvage as achieving PET-CT negativity pre-transplant was crucial for bone marrow transplantation in our locality.

R-GemOx regimen was assessed in refractory/relapsed diffuse large B-cell lymphoma patients ineligible for autologous stem cell transplantation and achieved ORR of 54 % with 33% CR rates (Cazelles et al., 2021). However, in our study, we recruited transplant eligible patients and achieved very similar ORR with higher CR which confirm the efficacy of R-Gemox-vinorelbine as a pre-transplant salvage regimen.

Gemox regimen wasn't assessed in large studies for R/R DLBCL transplant eligible patients. To our knowledge, this is the 1st study to assess Gemox-vinorelbine as a pre-transplant salvage regimen for Relapsed/Refractory DLBCL.

Concerning the toxicity of our regimen, the most frequent Grade 3-4 adverse events were the hematological AEs including thrombocytopenia (42.2%), anemia (35.5%), neutropenia (26.6%) and neutropenic fever (15.5%). These results were comparable to what reported with other regimens as DHAP and GDP where they required more platelet transfusions reaching 47% ,31% respectively. Febrile neutropenia incidence was lower in our study than that described with DHAP (23%) but was higher than GDP protocol (9%). One advantage of GDP and Gemox-vinorelbine was that both regimens administered on an Outpatient basis therefore less frequent hospitalization compared with DHAP (Crump et al., 2014b).

Inquiring about the addition of vinorelbine to Gemox would increase the toxicity of protocol. R-Gemox regimen in patients with refractory /relapsing diffuse large cell lymphoma not candidate for ASCT consolidation showed G3-4 neutropenia and thrombocytopenia in 43% of patients (López et al., 2008) which was parallel to our results however our study recruited transplant eligible patients requiring higher ORR and CRs which is an important achievement for autologous stem cell transplantation.

The most common non hematological Grade 3-4 adverse event associated with our regimen was peripheral neuropathy (8.8%) attributed to oxaliplatin administration which was parallel to that reported with R-Gemox in Spanish study (López et al., 2008).

As regard to the transplantation rate ,the most commonly used salvage chemotherapy regimens including R-DHAP, R-ICE,R-GDP achieved nearly 50% (Crump et al., 2014a; Van Den Neste et al., 2016) While in Our study it was only 24.4 %.This difference may be explained by higher percentage of primary refractory and early relapsed cases(66.7%), higher secondary IPI (66.6%) and small number of patients .Moreover, only the patients in complete remission (CR) underwent bone marrow transplantation in our study. Our results were in parallel with transplantation rate documented with various salvages received in OCMU reached 27% which is generally low attributed to logistic factors like the availability of hospital beds and financial issues.

With respect to the rate of successful stem mobilization in our study, it reached 91.6% while it was 87.9% in the GDP group and 82.2% in the DHAP group (Crump et al., 2014b).

Predicted poor mobilizers are defined by baseline patient or disease characteristics which are associated with poor mobilization. These factors included old age, advanced stage of underlying disease and high number of prior treatment lines. In a recent published study assessed GDP regimen as a salvage and mobilization chemotherapy before ASCT in relapsed and refractory Hodgkin lymphoma patients, PBSC collections were adequate in all patients with a median number of 11.01 × 10^6/kg CD34+ cells (Gokmen et al., 2022) while in our study, mobilization was done with G-CSF with or without plerixafor, the median number of CD34+ cells were 3.95 x106 /kg CD34+ cells which was markedly lower than that reported in this study. Also according to CORAL trial , the Median CD34+ cells collected was 4.5 x10^6 cells/kg for ICE versus 4.9 x10^6 cells/Kg for DHAP which was also higher than our study

This discrepancy may be due to lower median age in Hodgkin study (32 years old) in contrast to higher median age in our study (45 years old) and higher percentage of patients with advanced disease and more refractory /early relapsed patients.

This difference in collected CD34+ cells didn't affect transplantation and was sufficient for successful engraftment but larger studies are needed to confirm these results.

The three-year PFS after commonly used salvage regimens e.g R-ICE ,R-DHAP, R-GDP and R-ESHAP was 31%, 42%,28% and 57% respectively(Crump et al., 2014b), (Martín et al., 2008).This results are similar to our study's 2 year PFS rate of 40% ,but taking in consideration that longer follow up is needed for fair comparison.

Median PFS with R-Gemox was 5 months which was doubled (10.8 month) in overall population in our study with addition of vinorelbine. Subgroup analysis showed that median PFS for germinal center (GC) was higher than non-germinal center (non-GC) but with no statistically significant difference as regard COO which was near to that reported by Cazelles where Having a GC or non-GC phenotype did not affect the outcome (Cazelles et al., 2021).

As regard the two-year OS, our study achieved 45% which was comparable to what described with R-DHAP and R-ICE achieving 48%. Subgroup analysis in our study showed that median OS in GC patients was higher than non GC patients but this difference wasn't statistically significant. This was in contrast to what showed in Retrospective analysis of the CORAL study that reported that outcomes varied according to COO status and that for patients with GCB-like DLBCL, treatment with R-DHAP was associated with better outcomes than patients treated with R-ICE (Thieblemont et al., 2011b).

In our study both PFS and OS were affected by the number of prior lines of therapy This contradicts Corazzelli and his colleagues who studied R GEMOX in transplant ineligible patients.They reported that the number of prior lines had no effect on neither PFS nor OS (Corazzelli et al., 2009).

Factors that affected 3-year OS included second-line age-adjusted IPI of ≥2, relapse <12 months after completion of first-line therapy and prior rituximab exposure in the front-line setting (Flowers et al., 2010), which are the same factors affecting our Overall survival.

Other proposed explanations to our finding could be related to the complexity & heterogeneity of molecular and genetic alternation in refractory and relapsed NHL (Coccaro et al., 2020) intrinsic and acquired resistance to gemcitabine are common (De Sousa Cavalcante & Monteiro, 2014)**.** Also, there are no large randomized trials that examined Gemox-vinorelbine in transplant candidate patients. Personalized therapy is still the unreached goal in treatment of refractory / relapsed NHL.

4. Conclusion

Gemox-vinorelbine has good activity as a salvage regimen in R/R NHL especially if used as 1st salvage. It could be used as a pre-transplant salvage with increasing CR with manageable toxicity and also with no effect on harvesting SC and successful engraftment.

Conflict of interest

Authors declare no conflict of interest and this research was not funded by any organization.

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