Original Research Article

Gemcitabine plus vinorelbine for refractory or relapsing Non-Hodgkin lymphoma: Response rate and survival

Abstract

Background: Two chemotherapeutic agents, vinorelbine and gemcitabine, have shown encouraging early results in the treatment of heavily pretreated relapsed or refractory lymphoma when used as single agents, with responses of between 20 and 47%. The aim of this work was to evaluate the role of: gemcitabin and vinorelbin in treatment of relapsed and /or refractory aggressive Non Hodjkin Lymphoma (NHL) as regard response rate, survival analysis.

Methods: This prospective study was conducted on 20 patients who had relapsed and /or refractory NHL and treated with a minimum follow up period of 6 months. All patients were subjected to full clinical examination, laboratory and radiological study. Venorelbin , Gemcitabin, dexamethasone, filgrastim (VGF) was administrated , On days 1 and 8, patients received vinorelbine 25 mg/m2, Gemcitabine 1000 mg/m2 and Dexamethasone 16mg/m2i.v, On day 9, they received peg-filgrastim 6 mg subcutaneously, Patients will receive 4 cycles of (VGF), Assessment was performed after 4th cycle of treatment and according to response during follow up period patient received 2 more cycles with minimum follow up period 6 ms and/or PET-CT will be done in all patients to evaluate response rate.

Results: Regarding status; 60 % of patients were relapsed and 40 % of them were refractory. Regarding line therapy: all patients were treated with 1st line protocol RCHOP, and 4 of them had been treated with 2nd line chemotherapy ICE. So 80% of patients received VGF chemotherapy as 2nd line, while 20% of them received it as the 3rd line. And there was no statistical difference between relapsed and refractory groups regarding lines of VGF

chemotherapy. Regarding the toxicity of VGF (toxicity criteria as defined by Cheson and WHO); 50% of patients complicated with grade III anemia, 50% of patients complicated with grade III neutropenia, 60% of patients complicated with grade III thrombocytopenia, 20% of patients complicated with grade II GIT upset, 40% of patients complicated grade II thrombo phlebitis and 40% of patients complicated with grade II neurotoxicity.

Conclusions: VGF shows substantial activity in relapsed or refractory aggressive NHL. The regimen is generally well tolerated, but hematological toxicity is common.

Keywords: Gemcitabine, vinorelbine, refractory, relapsing, Non-Hodgkin lymphoma, Response rate, survival

Introduction:

The Non Hodjkin Lymphoma (NHL) are a heterogeneous group of lymphoproliferative malignancies with differing pattern of behavior, prognosis and response to treatment [1].

The aggressive type of NHL has a shorter natural history, but a significant number of these patients can be cured with intensive combination chemotherapy regimens. In general, with modern treatment of patients with NHL, overall survival at 5 years is over 60%. Of patients with aggressive NHL, more than 50% can be cured. The vast majority of relapses occur in the first 2 years after therapy. The risk of late relapse is higher in patients who manifest both indolent and aggressive histology [2].Patients who present with or convert to aggressive forms of NHL may have sustained complete remissions with combination chemotherapy regimens or aggressive consolidation with marrow or stem cell transplantation [3].

Standard therapy for aggressive non-Hodgkin lymphoma is now well established. first-line chemotherapy utilizes the regimens of Rituximab-CHOP for aggressive histology B-cell non-Hodgkin lymphoma including diffuse large B cell (DLBCL), For patients aged less than 70 years who are refractory to or relapse following first-line therapy then second-line salvage therapy, with cis-platinum based chemotherapy followed by autologous stem cell transplantation (ASCT) is an option [4]. With this approach a significant proportion of cases will achieve a cure. Nevertheless, there remains a group of patients with ongoing disease specifically those who fail salvage therapy, and /or elderly patients ineligible for ASCT [5].

Such patients may yet respond to and benefit from further chemotherapy. Gemcitabine is a nucleoside analogue, which as a single agent in heavily pretreated advanced and aggressive non-Hodgkin lymphoma (NHL) can achieve response rates from 20–30% [6].

Vinorelbine is a vinca alkaloid and in similar patient groups can achieve response rates from 18–46%. Using these agents developed outpatient-based chemotherapy approaches for advanced lymphoma patients [7].

The aim of this work was to evaluate the role of: gemcitabin and vinorelbin in treatment of relapsed and /or refractory aggressive NHL as regard response rate, survival analysis.

Patients and Methods:

This prospective study was conducted on 20 patients who had relapsed and /or refractory NHL and treated at Clinical Oncology and Nuclear Medicine department, Tanta University Hospital and Health Insurance Hospitals throughout period from September 2017 to December 2018 with a minimum follow up period of 6 months.

Patients who had refractory or relapsed diffuse large B cell NHL, Age 18 - 70 years, WHO performance status 0-2, radiological assessment by (CT and/or PET-CT) when available were included.

Patients who were aged > 70 years, with renal, or hepatic morbidity, Pregnant or lactating females, WHO performance status > 2, or Patients with unacceptable co-morbidities as ventricular arrythmia, congestive heart failure or documented myocardial infarction were excluded.

Approval of the study was obtained from the Ethical Committee of Scientific Research, Faculty of Medicine, Tanta University (Approval code: 31729/08/17.). Written informed consent was taken from the patients enrolled in this study.

All eligible patients were subjected to full clinical examination, laboratory and radiological study. Full history taking: Detailed history taking including; presenting complaint, history of present illness, medications history and history of past illness. And previous chemotherapy received. Full clinical examination:

1- General examination including: general comment on patient conscious and mental state, vital signs (pulse, blood pressure, capillary filling time, respiratory rate and temperature), and lymph nodes examination.

2- Systemic examination including: respiratory System: For detection of any abnormal breath sound, adventitious sounds and respiratory distress, Cardiac examination: For detection of heart sounds and murmers, Gastrointestinal Tract (GIT) and Abdomen: For presence of organomegaly or ascites and finally Central Nervous System (CNS) including power, tone and reflexes, Signs of meningeal irritation, Presence of abnormal movement.

3- Investigations: Routine lab. Investigations as: Complete blood count (CBC), Erythrocyte sedimentation rate (ESR), Liver function tests (ALT, AST, bilirubin and albumin), Coagulation tests (PT, PTT and INR) and Kidney function test (urea, uric acid and creatinine). Bone marrow aspiration and/or biopsy, Lactate dehydrogenase (LDH), CT chest, abdomen and pelvis, PET-CT, when available and Echocardiography.

Regarding prior chemotherapy received, 20 patients have been treated with 1st line protocol R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone, plus rituximab). For patients were treated with ICE (ifosfamide, carboplatin and etoposide). Performance status of the patients was scored according to ECOG**.** The patients were staged according to Ann Arbor staging with Cotswolds modification**.** International prognostic index (IPI) was used to assess the prognosis**.** All patents were treated with chemotherapy after assessing the stage. Venorelbin , Gemcitabin, dexamethasone, filgrastim (VGF) was administrated , On days 1 and 8, patients received vinorelbine 25 mg/m2, Gemcitabine 1000 mg/m2 and Dexamethasone 16mg/m2i.v, On day 9, all patient received filgrastim as a prophylactic SC. Assessment was performed after 4th cycle of treatment and according to response during follow up period patient received 2 more cycles with minimum follow up period 6 ms, by CT will be done in all patients to evaluate response rate and/or PET-CT when available.Standard response and toxicity criteria as defined by Cheson and WHO were used [8].Following

completion of all trial therapy, response was classified as CR (complete remission), CRU (CR unconfirmed), PR (partial remission), SD (stable disease) or PD (progressive disease) as per published standardized criteria [6].

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA) Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Chi-Square test X^2 was used to test the association variables for categorical data. Student's t-test was used to assess the statistical significance of the difference between two population means in a study involving independent samples. Survival and progression free survival were calculated by using the Kaplan–Meier method. The accepted level of significance was 0.05.

Results:

As regarding the characters of the studied cases; 60% of cases were males and 40% were females. And 20% of cases were between 30 and 50 years old, 55% were between 50 and 60 years old and 25% of patients were older than 60 years old. Regarding to staging (according to Ann Arbor staging with Cotswolds modification): 80% of patients presented with stage III, while 20% presented with stage IV. Regarding to symptoms: 80% of patients presented with B symptoms. Regarding status; 60 % of patients were relapsed and 40 % of them were refractory. Regarding extranodal disease; 80% of patients had no extranodal manifestations, One patient had > 2 extra nodal sites and 3 patients had <2 extra nodal sites. Regarding performance status (PS) according to ECOG; 90% of patients had performance status 0-1 and 10% of them had performance status 2. Regarding to LDH: 40% of patients had elevated LDH levels, while 60% of patients had normal LDH levels. Regarding international prognostic index (IPI): 20 % of patients were intermediate risk group, and 80% were high risk group. Regarding previous chemotherapy: 20 patients were treated with 1st line protocol

RCHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone, plus rituximab), and only 4 of them had been treated with 2nd line chemotherapy ICE (ifosfamide, carboplatin and etoposide). **[Table 1]**

Table 1: Characteristics, staging, symptoms, status, extranodal disease, performance status(PS), LDH, International Prognostic Index(IPI) and previous chemotherapy of the studied cases.

	N	%
Gender		
Male	12	60
Female	8	40
Age		
30 – < 50	4	20
50 – 60	11	55
> 60	5	25
Stage		
III	16	80
IV	4	20
B Symptoms		
Absent(A)	4	20
Present(B)	16	80
Disease Status		
Relapse	12	60
Refractory	8	40
Extenodal disease		
0	16	80
≥ 2	1	5
< 2	3	15
PS		
0 – 1	18	90
2	2	10
LDH		
Elevated	8	40
Normal	12	60
IPI		

Intermediate risk	4	20
High risk	16	80
Previous chemotherapy		
1st line	20	100
2nd line	4	20

IPI: International prognostic index, PS: Performance status, LDH: lactate dehydrogenase.

As regarding the order of VGF chemotherapy; 80% of patients received VGF chemotherapy as 2nd line, while 20% of them received it as the 3rd line. **[Figure 1]**

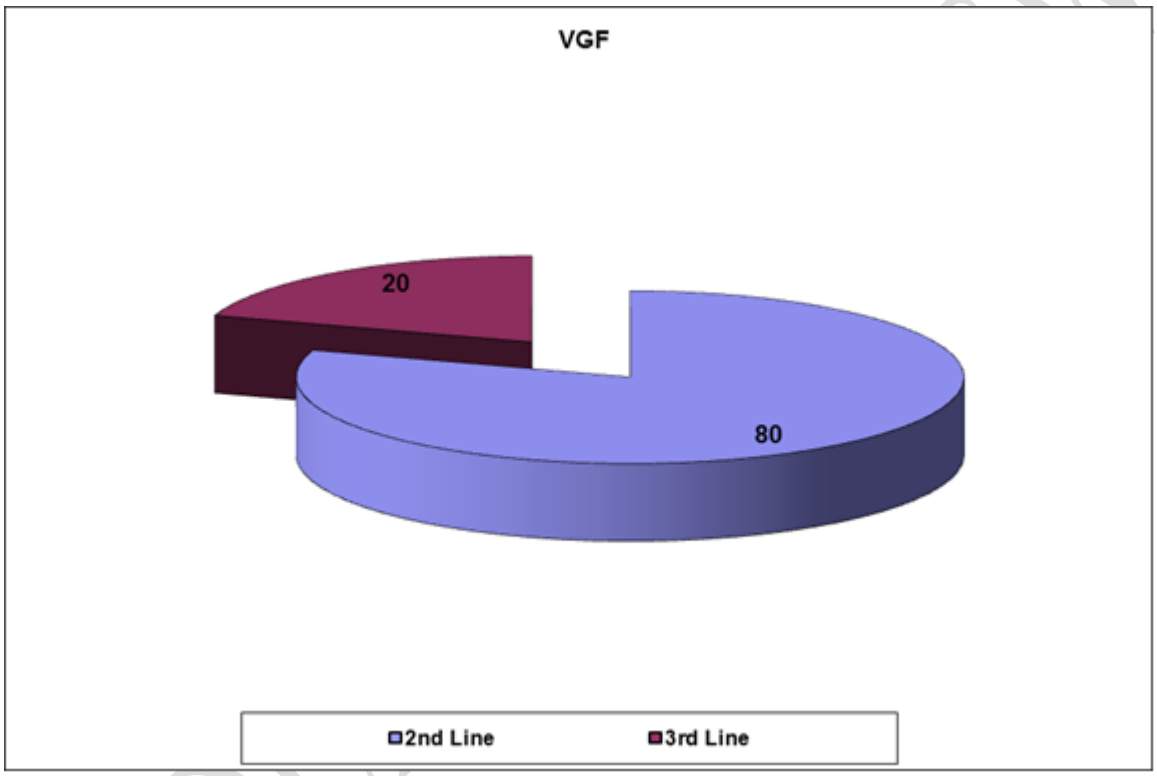


Figure 1: Lines of VGF chemotherapy in studied patients

As regarding the lines of VGF chemotherapy in studied patients; in patients with relapsed NHL; 10 patients received 2nd line and 2 patients received 3rd line. Compared patients with refractory NHL; 6 patients received the 2nd line and 2 patients received 3rd line. With no statistical difference between relapsed and refractory groups regarding lines of VGF chemotherapy. **[Figure 2]**

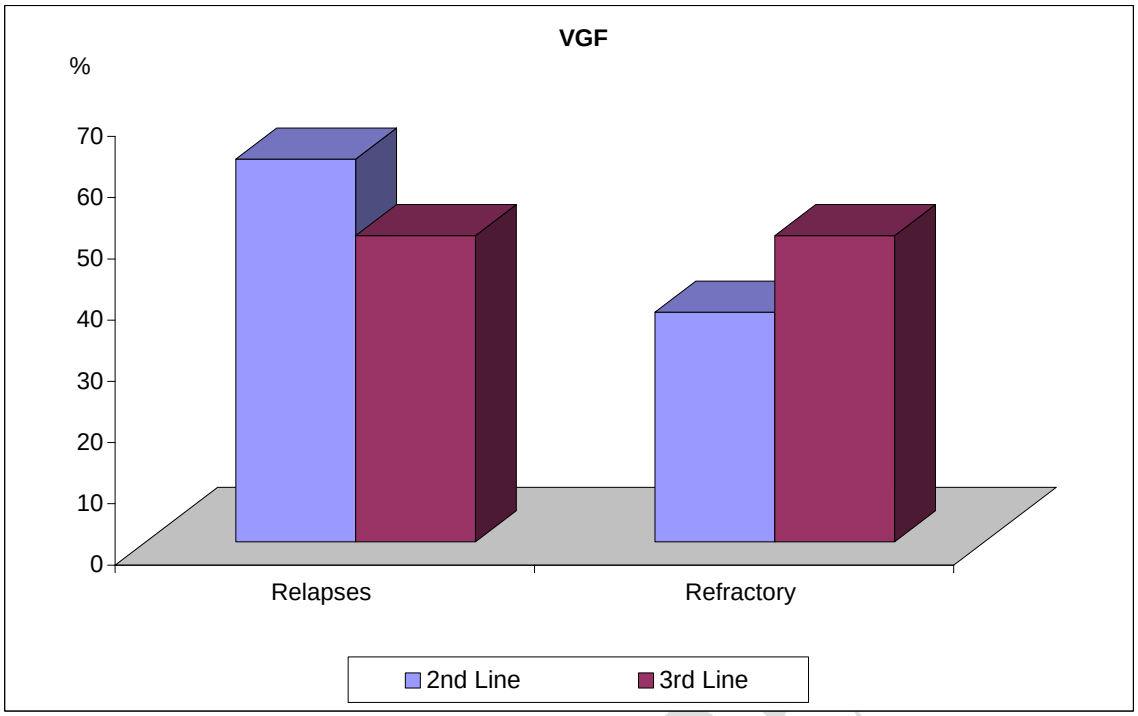


Figure 2: Comparison between patients with relapsing NHL and Patients with refractory NHL according to Lines of VGF chemotherapy

As regarding the toxicity of VGF; 50% of patients complicated with grade III anemia, 50% of patients complicated with grade III neutropenia, 60% of patients complicated with grade III thrombocytopenia, 20% of patients complicated with grade II GIT upset, 40% of patients complicated grade II thrombo phlebitis and 40% of patients complicated with grade II neurotoxicity. **[Figure 3]**

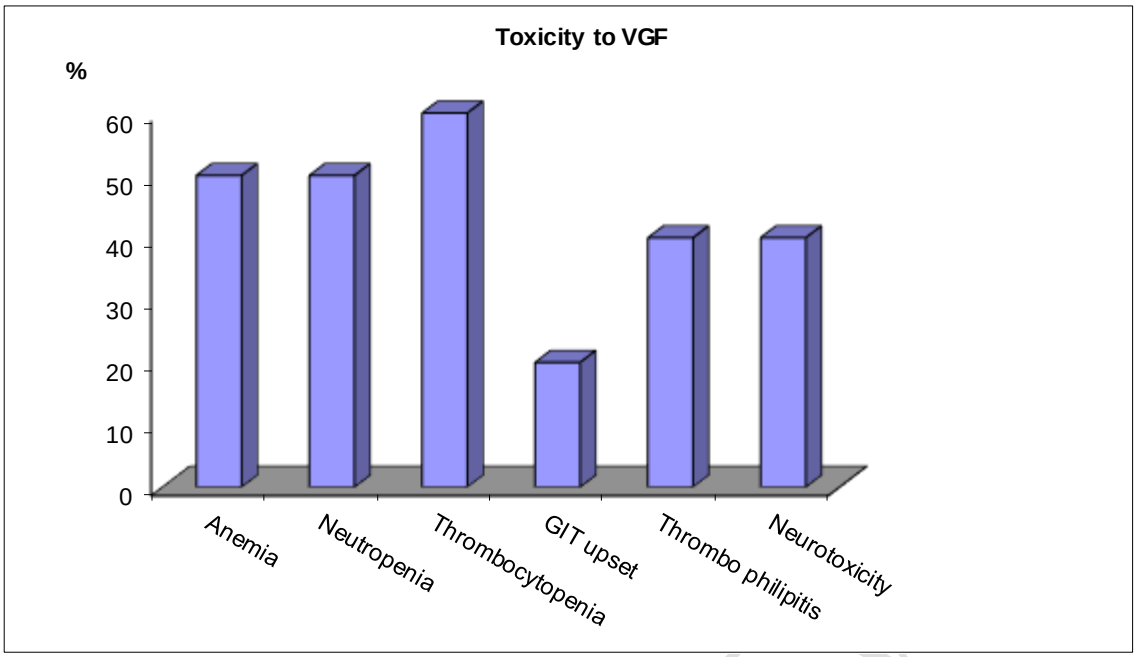


Figure 3: Observed treatment toxicity of VGF

As regarding the respond to treatment in patients with relapsing NHL and patients with refractory NHL; After finishing treatment of VGF; 12 patients had complete remission (CR); 8 patients with relapsed NHL and 4 patients with refractory disease, 2 patients with relapsed NHL had partial remission (PR). And 6 patients had stable disease (SD); 2 patients with relapsed NHL and 4 patients with refractory NHL. No patients had progressive disease (PD). With no statistical difference between patients with relapsing NHL and patients with refractory NHL regarding to respond to treatment. **[Figure 4]**

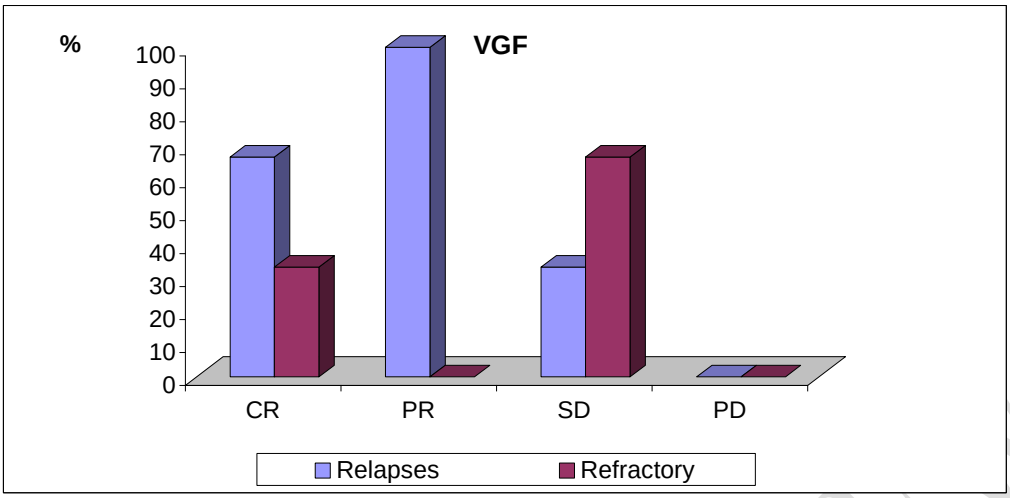


Figure 4: Comparison between patients with relapsing NHL and patients with refractory NHL according to respond to VGF chemotherapy

A comparison between patients with 4 cycles and patients with 6 cycles of VGF chemotherapy according to their respond. In the group with 4 cycles of VGF; 2 patients had complete response (CR), 10 patients had partial response (PR) and 8 patients had stable disease (SD). While in the group with 6 cycles; 12 patients had complete response (CR), 2 patients had partial response (PR) and 6 patients had stable disease (SD). With a statistical difference between groups, p=0.002. **[Figure 5]**

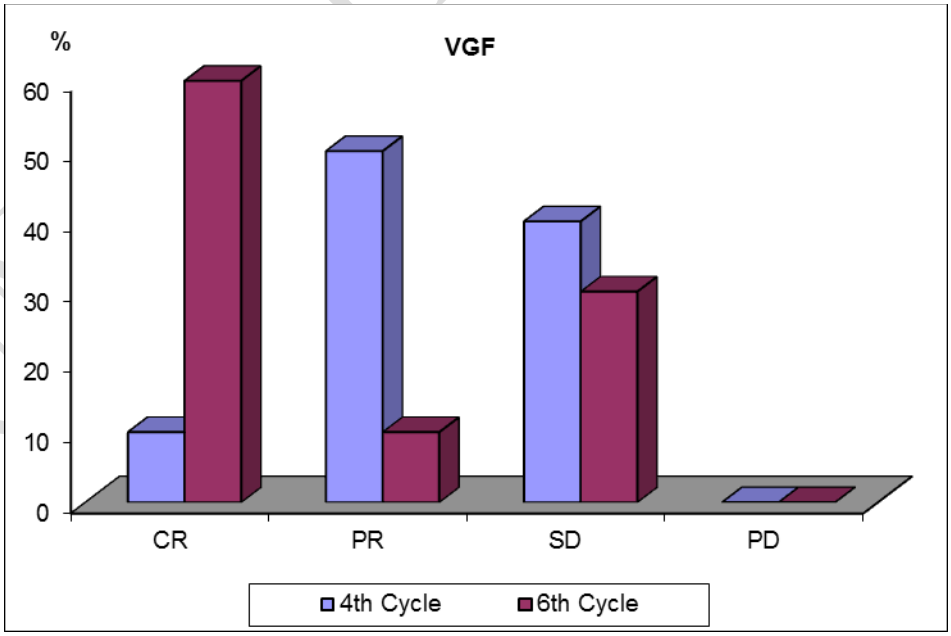


Figure 5: Comparison between patients with 4 cycles and patients with 6 cycles of VGF chemotherapy according to their respond

As regarding correlation of patient's response and patient's criteria; there was difference in response rate in correlation with disease stage, PS, presence of symptoms, or IPI but no statistical difference of significance. **[Table 2]**

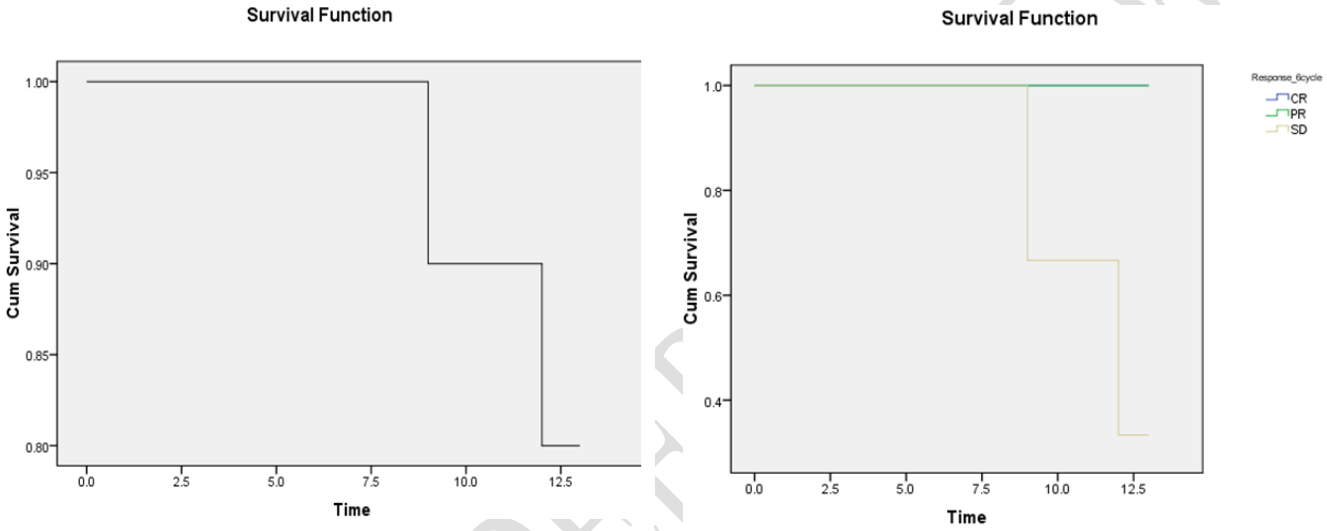
Table 2: Correlation of disease response and prognostic factors.

Patients' characteristics	Response after VGF therapy								P value (Fisher's Exact test)
	Complete response (CR)		Partial response (PR)		Stable disease (SD)		Total		
	N	%	N	%	N	%	N	%	
Gender									0.378
Male	6	50	2	16.7	4	33.3	12	60	
Female	6	75	0	0	2	25	8	40	
Age									0.189
30 – < 50	4	100	0	0	0	0	4	20	
50 – 60	5	45.5	2	18.2	4	36.4	11	55	
>60	3	60	0	0	2	40	5	25	
Stage									0.535
III	10	62.5	2	12.5	4	25	16	80	
IV	2	50	0	0	2	50	4	20	
Extenodal disease									0.248
0	10	62.5	2	12.5	4	25	16	80	
≥ 2	0	0	0	0	1	100	1	5	
< 2	2	10	0	0	1	5	3	15	
LDH									0.189
Elevated	6	75	0	0	2	25	8	40	
Normal	6	50	4	33.3	2	16.7	12	60	
PS									0.093
0 – 1	12	66.7	2	11.1	4	22.2	18	90	
2	0	0	0	0	2	100	2	10	
B symptoms	8	50	2	12.5	6	37.5	16	80	0.189
IPI									0.189
Intermediate risk	4	100	0	0	0	0	4	20	

High risk	8	50	2	12.5	6	37.5	16	80	

IPI: international prognostic index, PS: Performance status, LDH: lactate dehydrogenase.

The 12 months OS rate was 80% with no treatment related deaths, 4 cases of deaths were related to other comorbidities. All patients were evaluable for response to treatment. Survival curve according to sixth cycle response. Mean survival time is 11.5 months. All patients who achieved CR, no one of them develop disease relapse during 1 year follow up. **[**Error! Reference source not found.**]**



(A) **(B)**

Figure 6: Overall survival(OS) of the 20 patients with NHL treated with VGF chemotherapy (A) and Progression from survival of patients with complete response(CR), patients with partial response(PR) and patients with stable disease(SD) after treatment with VGF chemotherapy (B).

Discussion

Since the early 1970s the incidence of non-Hodgkin lymphoma (NHL) has increased by almost 60% in both men and women, blacks and whites, making it, along with malignant melanoma and lung cancer in women, one of the most rapidly increasingly diagnosed malignancies in the industrialized world [9]. Two new chemotherapeutic agents, vinorelbine and gemcitabine, have shown encouraging early results in the treatment of heavily pretreated relapsed or refractory lymphoma when used as single agents, with responses of between 20 and 47% [10]**.** Vinorelbine is a semisynthetic vinca alkaloid whereas gemcitabine is a novel

nucleoside analogue of deoxycytidine, both can be safely given in the outpatient setting through short i.e. infusions, have differing mechanisms of action and have little overlapping toxicity [6].

In this study; 60% of cases were males and 40% were females. And 20% of cases were between 30 and 50 years old, 55% were between 50 and 60 years old and 25% of patients were older than 60 years old. This was in agreement with ***(Gopal et al., 2010)***[11] study, on patients with relapsed/refractory lymphoma, as the median age in the study group was 58 years (range: 19 – 79) and females represents 41% of cases. Also in ***(Sivam et al., 2012)***[5] study the median age of the studied patients was 67 years (range 19–87) also there was a male predominance, male/female: 13/9.

Regarding staging (according to Ann Arbor staging with Cotswolds modification): 80% of patients presented with stage III, while 20% presented with stage IV. This was in agreement with ***(Gopal et al., 2010)***[11] as stage III and IV represent most of the study group, 90.2%. While in (***Müller-Beißenhirtz et al., 2005)***[12] study, 53.3% of patients presented with stage IV, 20% with stage III, 6.7% with stage II and 20% with stage I.

Regarding international prognostic index (IPI): 20 % of patients were intermediate risk group, and 80% were high risk group. This didn't match with previous studies as in ***(Müller-Beißenhirtz et al., 2005)***[12] study, 40% of patients were high risk and the rest were intermediate risk and in ***(Papageorgiou et al., 2005)***[13] study 45% of cases were intermediate risk, 41% were low risk and only 14% were high risk

Regarding performance status (PS) according to ECOG; 90% of patients had performance status 0-1 and 10% of them had performance status 2. This was in agreement with ***(Müller-Beißenhirtz et al., 2005)*** [12], as the median performance status in their study was 1 (range 0-2). While in ***(Papageorgiou et al., 2005)***[13] study, PS was 0 in 32% of patients, 1 in 36% of patients, 2 in 27% of patients, and 3 in 4.5% of patients

Regarding to LDH: 40% of patients had elevated LDH levels, while 60% of patients had normal LDH levels. This was in agree with many previous studies as LDH was elevated in 36.5% in ***(Sivam et al., 2012)***[5] study, 37% of cases in ***(Gopal et al., 2010)*** study, and 44% in ***(Pasricha et al., 2008; Spencer et al., 2007)***[6, 7] studied. However in ***(Müller-Beißenhirtz et al., 2005)***[12] , 73.3% of patients had elevated LDH.

Regarding status; 60 % of patients were relapsed and 40 % of them were refractory. This was comparable with ***(Spencer et al., 2007)***[6] study, as 30% of patients were 1st relapse, 30% were 2nd relapse, and 40% were refractory. In ***(Sivam et al., 2012)***[5] study, 50% of cases were relapsed and the other 50% were refractory.

Regarding line therapy: all patients were treated with 1st line protocol RCHOP, and 4 of them had been treated with 2nd line chemotherapy ICE. So, 80% of patients received VGF chemotherapy as 2nd line, while 20% of them received it as the 3rd line. And there was no statistical difference between relapsed and refractory groups regarding lines of VGF chemotherapy. In ***(Sivam et al., 2012)***[5] study, the median number of prior chemotherapy regimens was 2 (range: 1-5). In ***(Papageorgiou et al., 2005***) [13] study, 64% of patients had single prior regimen, 32% had 2 prior regimens and 4% had 3 prior regimens.

Regarding the toxicity of VGF (toxicity criteria as defined by Cheson and WHO); 50% of patients complicated with grade III anemia, 50% of patients complicated with grade III neutropenia, 60% of patients complicated with grade III thrombocytopenia, 20% of patients complicated with grade II GIT upset, 40% of patients complicated grade II thrombo phlebitis and 40% of patients complicated with grade II neurotoxicity. This was comparable with ***(Sivam et al., 2012)***[5], who observed that haematological toxicity of WHO grade 3 or 4 severity was seen in 55% of patients. Neutropenic sepsis necessitating in-patient treatment occurred in five cycles (23%). And in ***(Gopal et al., 2010)*** [11] study, Grade 3 and 4 hematologic toxicities were observed in (22%) and (76%) of patients,

respectively, but there were and no life-threatening bleeding or infectious complications or treatment-related deaths. Rates of grade 4 thrombocytopenia by cycle for all patients were: 1=57%, 2=36%, 3=33%, 4=39%. For the 28 patients that received 4 cycles of therapy the rates of grade 4 thrombocytopenia for cycles 1–4 were 50%, 25%, 32%, and 39%, respectively. There were 4 (2.5%/cycle) episodes of febrile neutropenia. The most common (>10%) non-hematologic adverse events of grade 3 or higher included laboratory abnormalities (22%), cardiovascular (14%), and pain (12%). In contrast to ***(Spencer et al., 2007)***[6], who observed that therapy was generally well tolerated with low rates of grades 4 thrombocytopenia (15%) and neutropenia (13%), Non-haematological toxicities were uncommon, the most frequent being fatigue (21% of cycles) and phlebitis (20% of cycles) secondary to vinorelbine. And ***(Pasricha et al., 2008)***[7], who observed that the VGF regimen was well tolerated, with few unplanned hospital admissions and with grade 3 of 4 hematologic toxicities occurring in fewer than one-third of patients.

After finishing treatment of VGF; 12 patients had complete remission (CR); 8 patients with relapsed NHL and 4 patients with refractory disease, 2 patients with relapsed NHL had partial remission (PR). And 6 patients had stable disease (SD); 2 patients with relapsed NHL and 4 patients with refractory NHL. No patients had progressive disease (PD). With no statistical difference between patients with relapsing NHL and patients with refractory NHL regarding to respond to treatment. This was in agree with ***(Spencer et al., 2002)***[6], who reported that the combination of gemcitabine, vinorelbine and filgrastim result in an overall response rate of 55% in patients with advanced Hodgkin's disease or diverse types of non-Hodgkin's lymphomas. This remission rate is remarkably similar to the remission rate in our study. While in ***(Müller-Beißenhirtz et al., 2005)***[12] study, 5 patients (33%) had complete remission (CR); all with relapsed disease, 3 patients (20.5%) had partial remission (PR); all with refractory disease, 2 patients (14.5%) had stable disease (SD); 1 patient with relapsed NHL

and 1 patient with refractory NHL. 5 patients (33%) had progressive disease (PD); 1 patient with relapsed NHL and 5 patients with refractory NHL. And in ***(Sivam et al., 2012)***[5] study, 3 patients (14%) achieved a complete response and eight patients achieved a partial response (36%) for an overall response rate of 50%.

On comparison between patients with 4 cycles and patients with 6 cycles of VGF chemotherapy according to their respond. In the group with 4 cycles of VGF; 2 patients had complete response (CR), 10 patients had partial response (PR) and 8 patients had stable disease (SD). While in the group with 6 cycles; 12 patients had complete response (CR), 2 patients had partial response (PR) and 6 patients had stable disease (SD). With a statistical difference between groups.

On comparison between patients with complete response (DR), patients with partial response (PR) and patients with stable disease (SD); there was no statistical difference between groups as regarding to their age, gender, stage, extenodal site, LDH, IPI, PS, presence of symptoms, occurrence of anemia, neutropenia or thrombo phlebitis. While there was a statistical difference between groups as regarding to occurrence of thrombocytopenia and GIT upset. This wasn't in agree with ***(Müller-Beißenhirtz et al., 2005)***[12]**,** who observed that disease status at the time of study inclusion (refractory vs. relapsed) proved to be a good predictor of outcome. Also, the international prognostic index was a valuable factor predicting response to GVP. Patients with low or low-intermediate risk (IPI 0–2) achieved an overall response rate of 100%. By contrast, in patients with high intermediate or high risk (IPI 4 and 5), treatment with GVP resulted in an overall response rate of only 33%.

In this study, Overall survival (OS) of the 20 patients with NHL treated with VGF chemotherapy, The 12 months OS rate was 80% with no treatment related deaths, 4 cases of deaths were related to other comorbidities. All patients were evaluable for response to treatment. All patients who achieved CR, no one of them develop disease relapse during 1

year follow up period. In ***(Di Renzo et al., 2006)***[14] study, At the end of therapy, complete remission (CR) rate was 23%, 3-year relapse free survival rate was 40% and 3-year overall survival rate was 25% for the whole series (29% and 20% for relapsed and refractory patients, respectively). In ***(Kirk et al., 2007)***[15] study, All 22 patients were evaluated for response to treatment. Three patients (14%) achieved complete remission and eight patients (36%) had partial remission accounting for an overall response rate of 50%. The duration of CR of the three patients was 4, 5, and 42+ months. As of today, 15 patients have died, 14 from disease and one patient from acute myocardial infraction. With a median follow up of 44 months, the median TTP for all patients was 8.1 months (range: 1–54+), while the median OS was 12.9 months (range: 4–54+)In ***(Pasricha et al., 2008)***[7] study, Ninety patients were enrolled. Group 1 comprised patients with "good" risk disease, Group 2 comprised patients with "high" risk disease, and Group 3 comprised patients relapsing after prior stem cell transplant. Overall response for Groups 1, 2 and 3, respectively was 76%, 39% and 50%, with median overall survival of 28, 9 and 30 months.

Conclusions:

VGF shows substantial activity in relapsed or refractory aggressive NHL. The regimen is generally well tolerated, but haematological toxicity is common.

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COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement

of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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