

Role of Gemcitabine, Oxaliplatin and Prednisolone Combination as First-Line Chemotherapy in Non-Hodgkin's Lymphoma

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Non-Hodgkin's lymphomas (NHLs) are commonly treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). The prognosis is disappointing for those 50% to 60% of patients who experience primary treatment failure or relapse after an initial response. So identifying novel chemotherapeutic agents with activity against aggressive NHL is going on to improve existing combination regimens. Several encouraging trials were done to evaluate efficacy and safety of either gemcitabine or oxaliplatin as monotherapy or combined treatment in cases of refractory/relapsed NHL. The objective of the current study was to evaluate the efficacy and safety of gemcitabine, oxaliplatin and corticosteroids (GEMOX-P) as first-line treatment for patients with intermediate-high grade NHL.



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Patients and Methods

Thirty-three patients with intermediate/high-grade NHL were randomized into 2 groups first group received standard (CHOP) with Prednisolone tablets 40 mg/ m²/day for five days. The second group received (gemcitabine 1000 mg/ m² D1, 8) then (oxaliplatin 80 mg/ m² D1) and (prednisolone tablets 40 mg/ m²/day for five days) with recycling every 21 days. The primary end point was response rate. The secondary end points were disease-free survival and overall survival.

Results:

Evaluable cases were 33 patients (19 males: 14 females) with a median age of

53 years. Response rate in low risk patients was higher in (GEMOX-P) than (CHOP) as it formed (100% vs. 88.9%) respectively ($P < 0.05$). While in high risk patients, it was 66.7% and 80% in (CHOP) and (GEMOX-P) groups respectively. Complete remission occurred in 16.7% and 46.7% in high risk cases of both treatment arms respectively ($P < 0.05$). Disease-free survival and overall survival after 18 months did not show statistically significant difference in both treatment arms. Hematological, gastrointestinal tract toxicity and neurotoxicity were the main side effects in both treatment groups. Alopecia, cardiotoxicity and elevation of hepatic enzymes was higher in (CHOP)

arm, while neurotoxicity and orthostatic hypotension was higher in (GEMOX-P) arm.

Conclusion

The regimen of (GEMOX-P) had beneficial effects over (CHOP) regimen that included higher complete response rate in high risk cases and lower cardiac and hepatic toxicity, but there was no difference after 18 months in disease-free or overall survival between both treatment arms. Selection of cases that may benefit from chemotherapy treatment either (CHOP) or (GEMOX-P) is needed with balance between anticipated toxicities, treatment outcome and cost-benefit aspect.

Key words

Gemcitabine, Oxaliplatin, Non-Hodgkin's lymphoma Role of Gemcitabine, Oxaliplatin and Prednisolone Combination as First-Line Chemotherapy in Non-Hodgkin's Lymphoma

Introduction

Non-Hodgkin's lymphomas (NHLs) are commonly treated with anthracycline-containing combination chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).² Despite the fact that NHL tumors are considered chemosensitive, the prognosis is disappointing for those 50% to 60% of patients who experience primary treatment failure or relapse after an initial response. Over the past 15 years, two main strategies have been pursued to improve treatment outcome with chemotherapy for aggressive NHL. One strategy under investigation is dose-intensification of active drugs with or without autologous stem-cell transplantation.⁴ A second line of research has been aimed at identifying novel chemotherapeutic agents with activity against aggressive NHL to improve existing combination regimens.

Oxaliplatin, a recent diamminocyclohexane platinum compound, acts through DNA damage⁵ with partial or no cross-resistance with cisplatin in a

Regimen	Day	Drug	dose	No. of cases	
				Median	range
Standard CHOP	1	Cyclophosphamide	750 mg/m ² IV	5	(3-8)
		Doxorubicin	50 mg/m ² IV		
		Vincristine	1.4 mg/m ² IV (max. 2 mg)		
	1-5	Prednisolone	40 mg/m ² /day PO		
GEMOX-P	1,8	Gemcitabine	1000 mg/m ² 1/2h inf	6	(4-8)
	1	Oxaliplatin	80 mg/m ² 2h inf		
	1-5	Prednisolone	40 mg/m ² /day PO		

Table 1 - Chemotherapy regimens used for both treatment arms

Characteristic	CHOP (N=18)	GEMOX-P (N=15)
Age < 60 yr.	5 (27.7%)	4 (26.7%)
≥60 yr.	13 (72.3%)	11 (73.3%)
Male: female	10:8	9: 6
P.S		
0	3 (16.7%)	5 (33.3%)
1	11 (61.1%)	7 (46.7%)
2	4 (22.2%)	3 (20%)
Stage:		
II	4 (22.2%)	2 (13.3%)
III	6 (33.3%)	6 (40%)
IV	8 (44.4%)	7 (46.7%)
B-symptoms	8 (44.4%)	7 (46.7%)
Bulky tumor (> 10 cm)	7 (38.9%)	5 (33.3%)
BM involvement	4 (22.2%)	2 (13.3%)
Patient Risk		
0,1,2 (low)	9 (50%)	5 (33.3%)
3,4 ,5 (high)	9 (50%)	10 (66.7%)
Histopathology;		
Diffuse large	14 (77.8%)	13 (86.7%)
T-cell lymphoma	1 (5.6%)	2 (13.3%)
Anaplastic large cell	2 (11.1%)	-
Burkitt's lymphoma	1 (5.6%)	-

p >0.05 with no statistically significant difference between both treatment arms; PS, performance status

Table 2 - patient Characteristics

wide range of human tumors in vitro and in vivo⁷. Oxaliplatin shows potent in vitro cytotoxic activity against a large variety of human tumor specimens from patients using the human tumor cloning assay including colon, NSCLC⁸.

Oxaliplatin is devoid of renal toxicity and is associated with lower hematological and digestive toxicity than cisplatin, making this compound easily manage-

able for out-patient combination chemotherapy. Cumulative peripheral neuropathy, consisting of cold-enhanced paresthesia, although reversible in the majority of patients remains the main toxicity associated with oxaliplatin chemotherapy⁹.

Gemcitabine (2',2'-difluoro-deoxycytidine) is a pyrimidine nucleoside antimetabolite. It is structurally related to

1-β-D-arabinofuranosyl-cytosine (ara-C). It inhibits cellular proliferation in S phase, and causes cells to accumulate in the G1-S phase of the cell cycle¹⁰.

It is an analog of cytarabine that has more effective cellular kinetics, including intracellular incorporation, phosphorylation and retention¹¹. Gemcitabine has activity against a variety of epithelial tumors. However, it has not been widely studied in patients with hematological malignancies. In comparison with many other cytotoxic agents, gemcitabine has a favorable toxicity profile and is now commonly used in treating patients with solid tumors such as those of pancreas, bladder and lung^{12,12,14}. Single-agent gemcitabine has shown activity in Hodgkin's disease^{15,16} and in a variety of histological subtypes of non-Hodgkin's lym-

The addition of cisplatin to gemcitabine has shown synergistic activity in vitro, and the combination of cisplatin and gemcitabine has become standard in the treatment of advanced bladder and non-small-cell lung cancer

phoma^{17,18}. The addition of cisplatin to gemcitabine has shown synergistic activity in vitro¹⁹, and the combination of cisplatin and gemcitabine has become standard in the treatment of advanced bladder and non-small-cell lung cancer^{12,14}.

Several trials were done to evaluate efficacy and safety of either gemcitabine or oxaliplatin as monotherapy in treatment of refractory/relapsed NHL^{17,18,20}. Other trials evaluated the combination of gemcitabine, cisplatin and corticosteroids in treatment of NHL²¹.

Treatment Response		CHOP		GEMOX-P		p-value
		No.	%	No.	%	
RR	Low Risk	8/9	88.9	5/5	100	< 0.05
	High Risk	6/9	66.7	8/10	80	NS
Disease Progression	Low Risk	1/9	11.1	0/5	-	NS
	High Risk	3/9	33.3	2/10	20	NS

Table 3-A - Treatment response in both treatment arms according to different risk groups with 18 months follow-up:

Treatment Response		CHOP (No.=18)		GEMOX-P (No.=15)		p-value
		No.	%	No.	%	
CR/CRu	Low Risk	8	44.4	5	33.3	NS
	High Risk	3	16.7	7	46.7	< 0.05
PR	Low Risk	-	-	-	-	NS
	High Risk	3	16.7	1	6.7	NS
Disease Progression	Low Risk	1	5.6	-	-	NS
	High Risk	3	16.7	2	13.3	NS

Table 3 - Treatment response in both treatment arms according to different risk groups with 18 months follow-up:

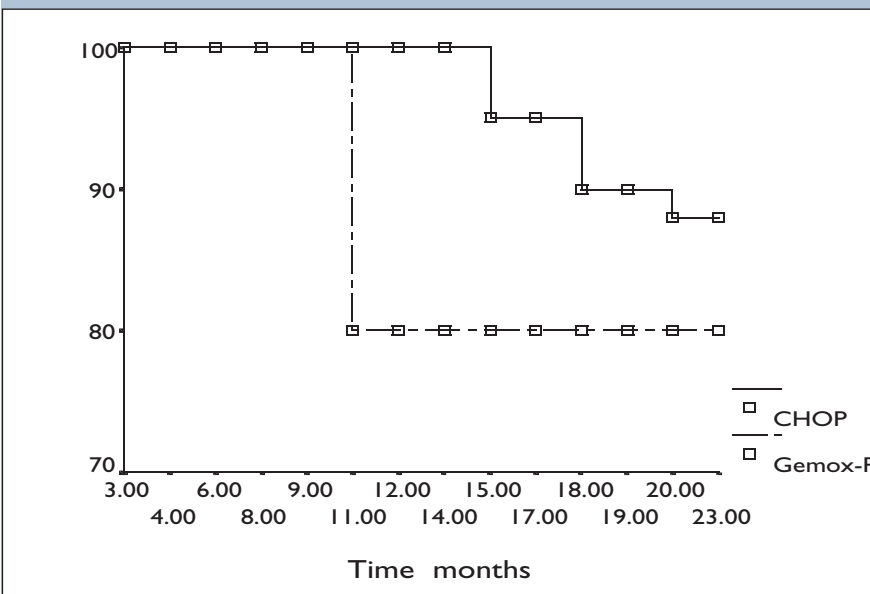


Figure 1 - DFS in low risk patients in both treatment arms in the study

Given the encouraging single-agent activity of gemcitabine seen in patients with Non-Hodgkin's disease²², single-agent oxaliplatin with response rate of 40% in relapsed/refractory NHL²⁰ and oxaliplatin-based treatment in relapsed NHL²³, added to that the relatively moderate toxicities observed with gemcitabine-platinum combinations in

patients with solid tumors, the current study was planned to use gemcitabine, oxaliplatin and prednisolone as first-line treatment in patients of intermediate-/high-grade NHL without previous chemotherapy.

The objective of the current study was to evaluate the efficacy and safety of gemcitabine, oxaliplatin and corticosteroids

as first-line treatment for patients with intermediate-high grade NHL.

Patients and Methods

Thirty-three patients with intermediate or high-grade Non-Hodgkin's lymphoma from December, 2001 to February, 2004 were enrolled in this study among multiple oncology centers. Nineteen men and 14 women with median age of 53 years (range 22–75) were included. Patients were randomized into 2 groups to receive standard (CHOP) or gemcitabine, oxaliplatin and prednisone (GEMOX-P) chemotherapy regimens. To simplify the statistical data the cases were stratified into low or high risk patients after estimating the International Prognostic Index (IPI) score that depends on age, Ann Arbor stage, performance status, LDH and number of extra-nodal sites. Patients with score of (0-2) and (3-5) were classified as low and high risk patients respectively. Patients were eligible for participation in this trial if they had a histological diagnosis of intermediate or high-grade Non-Hodgkin's lymphoma. Other inclusion criteria included:

- ◆ Age > 16 years < 75 years.
- ◆ ECOG scale performance status of 0–2.
- ◆ Stage II, III or IV disease.
- ◆ At least one site of bi-dimensionally measurable tumor as assessed by clinical examination, computed tomography (CT) or magnetic resonance imaging had to be identified.
- ◆ Life expectancy of > 3 months.
- ◆ No previous chemotherapy or radiotherapy prior to the study.
- ◆ Adequate hematopoietic reserve: absolute neutrophil count >1.5 x 10⁹/l, platelets >100 x 10⁹/l with adequate hepatic and renal function: serum creatinine <1.5 times the upper normal limit (UNL), creatinine clearance >60 ml/min, serum bilirubin, AST and ALT <1.5 times UNL.
- ◆ All patients were required to provide signed informed consent.

Specific exclusion criteria

Patients were excluded if they had

received previous chemotherapy or radiotherapy. Patients who had indolent lymphoma or had active infections (including positive human immunodeficiency virus or unresolved hepatitis B patients), evidence of more than grade (1) peripheral neuropathy according to institutional and national guidelines, or bone lesions as the only evidence of disease, central nervous disease manifestations, inadequate liver or renal functions. Also patients who were pregnant or breast feeding, or had a second malignancy or other serious concomitant medical disorders were excluded from the study.

All patients were to receive at least three cycles, except in case of progression and/or unacceptable toxicity or patient refusal.

Study design:

This study was a comparative randomized study. The regimen of (CHOP) is the most widely used regimens, so it was chosen as the control treatment arm for this study. The first group received (Cyclophosphamide 750mg/ m² (IV) D1, Doxorubicin 50 mg/ m² (IV) D1, Vincristine at dose of 1.4 mg/m² (IV) D1 with a maximum dose of 2 mg and Prednisolone tablets 40 mg/ m²/day for five days) with recycling every 21 days. The second group received (gemcitabine 1000 mg/ m² D1, 8) then (oxaliplatin 80 mg/ m² D1) and (prednisolone tablets 40 mg/ m²/day for five days) with recycling every 21 days. The plan was to discontinue the study on the second group if there was a disease progression in > 25% of first 8 cases after 2 cycles from starting (GEMOX-P) chemotherapy.

Drug administration

The regimen of (CHOP) was given on D1 as bolus IV injection of cyclophosphamide, doxorubicin, vincristine after dilution with 20-50 ml normal saline, with premedication with 8 mg i.v. ondansetron combined with 80 mg i.v. methylprednisolone, administered 15 min before the start of chemotherapy. Prednisolone

tablets with a dose of 40 mg/m² were given daily after meals for five days.

The (GEMOX-P) regimen was given as follows; gemcitabine was diluted with normal saline to obtain a final solution containing 10 mg/ml or less, and given as an intravenous infusion over 30 min, followed by oxaliplatin diluted in 500 ml of 5% glucose solution and administered as i.v. infusion over 2 h, starting 15 min after the end of the day 1 gemcitabine infusion. No specific hydration was given with oxaliplatin being devoid of nephrotoxicity. All patients received prophylactic anti-emetics, including at least one standard dose of 5-hydroxytryptamine-3-receptor agonists, premedication consisted of 8 mg i.v. ondansetron combined with 80 mg i.v.

Cotrimoxazole was given at a dose of 480 mg twice a day thrice weekly to all patients throughout their disease for prophylaxis against *Pneumocystis carinii* pneumonia

methylprednisolone, administered 30 min before the start of gemcitabine infusion. Prednisolone tablets with a dose of 40 mg/m² were given daily after meals for five days.

Patients were given allopurinol 300 mg once daily for the first 2 cycles. Cotrimoxazole was given at a dose of 480 mg twice a day thrice weekly to all patients throughout their disease for prophylaxis against *Pneumocystis carinii* pneumonia.

Pretreatment assessment

Before enrollment in the study, patients underwent a complete history taking and physical examination, including evaluation of performance status,

assessment for the presence of constitutional symptoms or concurrent co-morbid conditions with estimation of weight, height, blood pressure, pulse rate and measurement of palpable or visual tumor lesions. Measurement of blood pressure was done on 2 consecutive days before, one week and 2 weeks after treatment. Orthostatic hypotension (OH) is a fall in blood pressure (BP) after assuming an upright position due to cerebral hypo-perfusion. A drop in systolic BP of 20 to 30 mmHg within 3

All patients had disease reassessment by physical examination and CT scan of the chest, abdomen and pelvis

minutes of standing, with resulting complaints, is thought to be adequate for the diagnosis of OH as reported by Freeman R, (1993)²⁴. In normal individuals, systolic BP drops no more than 10 mmHg on assuming an upright position. In tandem with these changes, diastolic BP will rise and the pulse rate will increase from 5 to 10 beats per minute; but in case of OH, such a rise will not occur.²⁴

Laboratory studies included a complete blood count (CBC) with white blood cell differential count, urine analysis, biochemistry profile (including sodium, potassium, calcium, creatinine, urea, uric acid, bilirubin, AST, ALT, alkaline phosphatase, LDH, glucose, total protein and albumin). Electrocardiogram and bone marrow examination were required. Radiological examinations, including a chest radiograph and CT scanning of the chest, abdomen and pelvis, were required within 3 weeks of starting treatment. Gallium scanning was recommended but not required.

Patient Monitoring and Toxicity Assessment

During therapy, performance status, weight, blood pressure, pulse rate, and full-blood counts were obtained before each drug infusion. In addition, a complete medical history, including assessment of subjective (non-laboratory assessments) and objective (laboratory assessments) toxicity according to the WHO Common Toxicity Criteria (CTC)²⁵, were obtained before the start of each new cycle.

In this study, dose-limiting toxicity (DLT) was defined, using the WHO CTC 25, as any of the following events that occurred during the first two cycles of treatment: (i) grade 4 neutropenia lasting >7 days and/or associated with fever > 38.5°C; (ii) grade 4 thrombocytopenia; (iii) grade 3 thrombocytopenia associated with hemorrhage; (iv) grade 3 non-hematological toxicity (excluding alopecia, nausea and vomiting); and (v) persistence of non-hematological toxicity (excluding alopecia) of CTC >2 at the scheduled retreatment. For oxaliplatin-induced neurotoxicity, it is graded according to an oxaliplatin-specific scale²⁶ defined as follows:

- ◆ Grade 1, hypoesthesia or paresthesia which completely resolved before the next cycle.
- ◆ Grade 2, hypoesthesia or paresthesia which persist between cycles, without functional impairment.
- ◆ Grade 3, permanent functional impairment.

Grade 3 neuropathy was considered as a DLT. A delay of up to 2 weeks was permitted to allow the blood count to return to < grade 1 toxicity level (National Cancer Institute common toxicity criteria).

Dose reductions were based on blood counts and nonhematologic toxicity before infusion. Doses were reduced by the following percentages if patients had blood counts within the specified ranges: 0% for leukocyte count >2 x 10⁹/L, granulocyte count >1.5 x 10⁹/L, or platelet count >100 x 10⁹/L; 25% for leukocyte

count less than 2.0 x 10⁹/L and >1.0 x 10⁹/L, granulocyte count less than 1.5 x 10⁹/L and >1.0 x 10⁹/L, or platelet count less than 100 x 10⁹/L and >50 x 10⁹/L. Doses were omitted for leukocyte count less than 1.0 x 10⁹/L, granulocyte count less than 1.0 x 10⁹/L, or platelet count < 50 x 10⁹/L. Doses were reduced by 25% when a nonhematologic toxicity of WHO grade 3 occurred in the previous cycle and were reduced by 50% or omitted after a previous nonhematologic toxicity of WHO grade 4. Granulocyte-macrophage colony-stimulating factor (GM-CSF) was planned to be given in subsequent cycles in order to maintain dose intensity in case of occurrence of episode of febrile neutropenia or after one dose delay of chemotherapy. In case of a treatment delay > 2 weeks or in case of permanent paresthesia, the oxaliplatin dose was reduced, whereas in case of grade 3 neurotoxicity, which was assessed according to the oxaliplatin-specific neurotoxicity scale, oxaliplatin was discontinued. Supportive care that includes blood-product transfusions, antibiotics, anti-emetics, analgesics and growth factors were given as appropriate.

Assessment of outcome

The primary end point of this study was response rate (RR). All patients had disease reassessment by physical examination and CT scan of the chest, abdomen and pelvis. Other scans or X-rays were performed as indicated. Bone marrow biopsy was repeated after 2nd cycle if the marrow was involved by disease at baseline examination. The treatment response was categorized according to the International Workshop Criteria after 6 cycles of chemotherapy. The response was classified as complete response (CR), unconfirmed CR (CRu), partial response (PR), stable disease (SD) or progressive disease (PD). A minimum duration of four weeks was needed to document response.

CR was defined as the resolution of all pretreatment lymphoma-related abnormalities after completion of all chemotherapy cycles. This reassessment

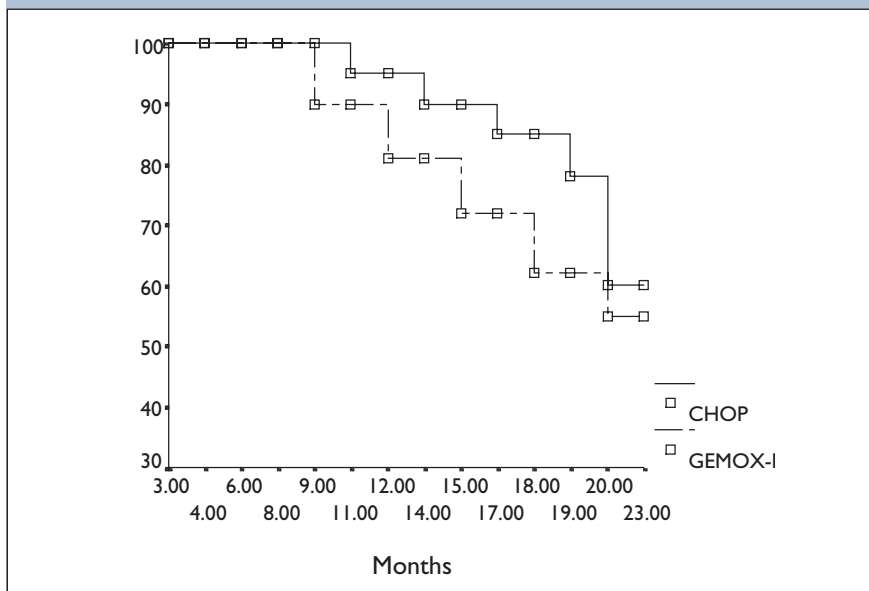


Figure 2 - DFS in high risk patients in both treatment arms in the study

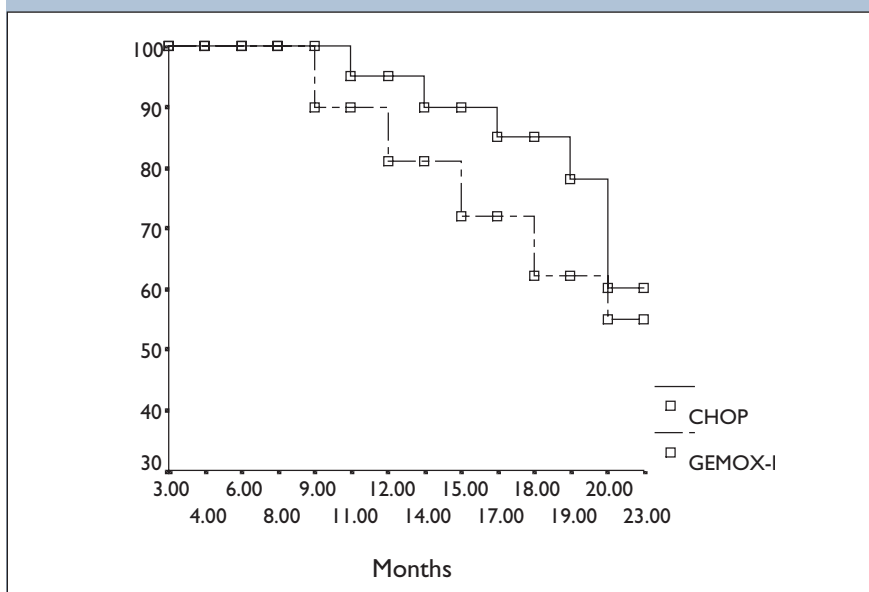


Figure 2 - Overall survival in high risk patients in both treatment arms in the study

Survival and statistical methods

For survival analysis, the date of randomization was considered the date of enrollment in the study. The primary end point was treatment efficacy after at least three chemotherapy cycles as measured by the objective RR (CR + CRu + PR) as defined by the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma 27, and the secondary end points were disease-free survival (DFS) and overall survival (OAS). Disease-free survival was calculated from the date of entry into the study to the date of progression or relapse. Overall survival rate was measured from date of entry to date of death, regardless its cause, or date of last follow-up evaluation. Surviving patients were estimated after 6, 12 and 18 months of starting treatment. Survival curves were estimated using the Kaplan-Meier²⁸ method and comparisons with the log rank test. Treatment was continued until evidence of disease progression or occurrence of an unacceptable toxicity. The Kaplan-Meier method was employed to determine medians and 95% confidence intervals (CI) of the time-related parameters.

A multivariate Cox model²⁹ was used to assess the effect and relationship between the pre-treatment prognostic factors according to IPI score (age, PS, LDH level, Ann Arbor stage, and the number of extranodal sites) on disease-free and overall survival for patients who received CHOP or (GEMOX-P).

T test was done to estimate the P value of all results.

Cost of chemotherapy cycles was estimated to assess the cost-effective benefits in both treatment groups.

Results

Table (1) shows the chemotherapy regimens used in both treatment arms. Eighteen cases in (CHOP) arm received a median of 5 cycles with a range of (3 to 8 cycles), while 15 patients of (GEMOX-P) arm received a median of 6 with a

included re-evaluation of all initially abnormal laboratory tests, physical examination findings, and radiographs, including CT scans. An unconfirmed CR was defined as a complete response with persistence of some radiological abnormalities, which had at least 75% regression in size. PR was defined as regression of all measurable lesions by more than 50%, disappearance of non-measurable lesions and the absence of new lesions. Stable disease was defined as regression of any measurable lesion by < 50% or no change for the non-measurable lesions. Progressive disease was defined as the

appearance of new lesion or growth of any measurable lesion that had regressed during treatment by more than 50% from its smallest dimension. After completion of therapy, patients were monitored every 2 to 3 months for the first 2 years, then every 4-6 months thereafter.

Radiotherapy or changing chemotherapy treatment was permitted after three cycles in patients of (GEMOX-P) group who showed stable disease (SD) and at any time if disease progression (PD), if considered useful by treating physician.

range of (4 to 8 cycles).

Evaluable cases were 33 patients (19 males: 14 females). Age ranged from (22-75) years with a median age of 53 years. Low risk cases with IPI score of (0-2) constituted 50% and 33.3% of CHOP group and (GEMOX-P) group respec-

After completion of therapy, patients were monitored every 2 to 3 months for the first 2 years, then every 4-6 months thereafter

tively, while high risk cases with IPI score of (3-5) formed 50% and 66.7% of both treatment arms respectively. The most common pathological type was diffuse large B-cell lymphoma in 77.8% and 86.7% of (CHOP) and (GEMOX-P) groups respectively. Other types - such as peripheral T-cell, Burkitt's lymphoma and anaplastic large cell - formed the rest of the cases with no statistically significant difference between both treatment arms as shown in table (2).

Table (3-A) showed the response according to risk factors in both treatment arms. It was found that response rate in low risk patients was higher in (GEMOX-P) arm as it formed 100% of cases compared to 88.9% in (CHOP) group with statistically significant difference ($P < 0.05$). While in high risk patients, the response rate was 66.7% and 80% in (CHOP) group and (GEMOX-P) respectively. No cases of low risk patients had experienced disease progression in (GEMOX-P) group compared to 11.1% of (CHOP) arm. The median response duration was 15.3 and 10.5 months of low and high risk groups of (CHOP) arm, while it was 14.2 and 8.8 months of low and high risk patients in (GEMOX-P) arm respectively.

Table (3-B) showed that CR/CRu

occurred in 44.4% and 33.3% in low risk cases of (CHOP) and (GEMOX-P) groups respectively without statistically significant difference, while it occurred in 16.7% and 46.7% in high risk group of both treatment arms respectively with statistically significant difference. Partial response was present in 3/18 (16.7%) and 1/15 (6.7%) in high risk cases of (CHOP) and (GEMOX-P) arms respectively with no statistically significant difference. Progression of disease occurred only in one patient (5.6%) with low risk in (CHOP) arm, while it occurred in (16.7%) and (13.3%) in patient with high risk factors in (CHOP) and (GEMOX-P) groups respectively as shown in table (3-B).

Tables (4-A, B) showed the disease-free survival (DFS) and overall survival (OS) after 18 months according to risk factors in both treatment arms. Disease-free survival after 18 months in low risk cases constituted 88.9% and 80% in (CHOP) group and (GEMOX-P) arm respectively, while it formed 66.7% and 60% in both treatment arms respectively in high risk cases without statistically significant difference. Overall survival after 18 months was 100% in low risk cases in both treatment arms, while it was 33.3% and 40% in high risk patients in (CHOP) and (GEMOX-P) arms respectively without statistically significant difference.

Table (4-C) represents DFS after 6, 12 and 18 months according to different risk factors in both treatment arms. After a median follow up duration of 74 weeks (range, 20 to 94 weeks), it was found that median time to disease progression in low risk cases was 66 and 62 weeks in (CHOP) and (GEMOX-P) arms respectively. While median DFS in high risk cases was 53 and 49 weeks in both treatment arms respectively as shown in table (4-C) and Figures (1, 2). Disease-free survival was higher and statistically significant in (CHOP) group than (GEMOX-P) arm after 6 and 12 months in low and high risk cases respectively. Overall survival was presented in table (4-D) and figure (3) according to different risk factors in both treatment arms

without any statistical significant difference. Median overall survival in low risk cases was 77 and 78 weeks in (CHOP) and (GEMOX-P) arms respectively. While median OS in high risk cases was 49 and 53 weeks in both treatment arms respectively. 18-months survival was 33.3% and 40% in high risk cases in (CHOP) and (GEMOX-P) arms respectively as shown in table (4-D) and Fig. (3).

Different grades of treatment-related toxicity were presented in table (5). Hematological, gastrointestinal tract toxicity and neurotoxicity were the main side effects in both treatment groups. Grade 3/4 leukopenia, neutropenia and thrombocytopenia occurred in 33.3%, 33.3% and 20% in (GEMOX-P) group compared to 11.1%, 22.2% and 5.6% of (CHOP) arm respectively ($P > 0.05$). Grade 3/4 toxicities were higher in (GEMOX-P) arm than (CHOP) group without statistically significant difference, except orthostatic hypotension had statistically significant difference. Grade 3/4 nausea and vomiting occurred in 20% of (CHOP) arm com-

Average cost of 6 chemotherapy cycles of (CHOP) was about 2340 Egyptian pounds

pared to 5.6% in (GEMOX-P) group with no statistically significant difference. Alopecia occurred in all cases of (CHOP) arm compared to 66.7% in (GEMOX-P) group. Grade 1/2 alopecia was present in 83.3% of (CHOP) arm compared to 46.7% in (GEMOX-P) group with statistically significant difference.

Table (5) showed that neurotoxicity (peripheral neuropathy of grade 3/4) was higher in (GEMOX-P) group than group of (CHOP) that constituted (20%) and (5.6%) respectively, without statis-

Treatment outcome in Low Risk cases	CHOP (No. = 9)		GEMOX-P (No. = 5)		P value
	No.	%	No.	%	
DFS (18 ms)	8	88.9	4	80	NS
OS (18ms)	9	100	5	100	NS

Table 4-A - Treatment outcome in both treatment arms in low risk group in the study

Treatment outcome in High Risk cases	CHOP (No. = 9)		GEMOX-P (No. = 10)		P value
	No.	%	No.	%	
DFS (18 ms)	6	66.7	6	60	NS
OS (18ms)	3	33.3	4	40	NS

Table 4-B - Treatment outcome in both treatment arms in high risk group in the study

DFS	CHOP		GEMOX-P	
Low risk (No.)	9		5	
• Median DFS	66 weeks	(48-82)	62 weeks	(38-84)
• 6- month Survival	9/9	100%	5/5	100%
• 12- months Survival	9/9	100%*	4/5	80%*
• 18- months Survival	8/9	88.9%	4/5	80%
High Risk (No.)	9		10	
• Median DFS	53 weeks	(28-81)	49 weeks	(22-78)
• 6- month Survival	9/9	100%*	9/10	90%*
• 12- months Survival	7/9	77.8%	7/10	70%
• 18- months Survival	6/9	66.7%	6/10	60%

* p < 0.05

Table 4-C - DFS in both treatment arms according to different risk groups

OS	CHOP		GEMOX-P	
Low risk (No.)	9		5	
• Median OS	77 weeks	(73-89)	78 weeks	(72-94)
• 6- month Survival	9/9	100%	5/5	100%
• 12- months Survival	9/9	100%	5/5	100%
• 18- months Survival	9/9	100%	5/5	100%
High Risk (No.)	9		10	
• Median OS	49 weeks	(23-75)	53 weeks	(20-81)
• 6- month Survival	8/9	88.9%	8/10	80%
• 12- months Survival	5/9	55.6%	5/10	50%
• 18- months Survival	3/9	33.3%	4/10	40%

P > 0.05

Table 4-D - OS in both treatment arms according to different risk groups

tically significant difference. Mild to moderate elevation of hepatic enzymes was present in 38.9% of (CHOP) arm compared to 13.3% in (GEMOX-P) group with (P < 0.05). Cardiac toxicity

was present in about one third of cases (33.4%) of (CHOP) group compared to 6.7% of (GEMOX-P) arm without any statistical significant difference. Orthostatic hypotension was the main side

effect in patients who received oxaliplatin, gemcitabine and prednisolone. It was present in all cases (100%) of (GEMOX-P) arm as compared to 5.6% of (CHOP) group with statistically significant difference. It was severe (grade 3/4) in one third of cases with marked postural hypotension with symptoms ranging from light-headedness to pre-syncope or syncope complaints.

Average cost of 6 chemotherapy cycles of (CHOP) was about 2340 Egyptian pounds, as compared to 6 cycles of (gemcitabine, oxaliplatin and prednisolone) that cost average of 35,400 Egyptian pounds as shown in table (6).

Discussion

Tables (1, 2) showed the chemotherapy regimens used in the study and the general characteristics of Non-Hodgkin's lymphoma patients in the current study without any statistical significant difference between both treatment groups. More than two thirds of the patients in both treatment groups were > 60 years old. For a purpose of simplification to compare between both treatments' arms according to different risk factors, the patients were stratified into low or high risk groups. Patients with IPI score of 0-2 were classified as low risk, while those with score of 3-5 were classified as high risk cases. Low risk patients were present in 50% and 33.3%, while high risk cases were present in 50% and 66.3% in (CHOP) and (GEMOX-P) groups respectively. The most common pathological type was diffuse large B-cell lymphoma in 77.8% and 86.7% of (CHOP) and (GEMOX-P) groups respectively. Table (3-A) showed that the objective overall response rate for all cases including low and high risk patients was 77.8% and 86.7% for (CHOP) and (GEMOX-P) respectively. The treatment outcome of (CHOP) group including response rate and disease progression in the current study coincides with the results reported by Coiffier and others. (1997)30; Younes and others. (2001)31 and Pfreundschun and others. (2000)32.

Response rate in low risk patients was higher in (GEMOX-P) arm as it formed 100% of cases compared to 88.9% in (CHOP) group with statistically significant difference ($P < 0.05$). High risk patients showed response rate of 66.7% and 80% in (CHOP) and (GEMOX-P) groups respectively. Although the current study used 1st line treatment in patients without previous chemotherapy, but these data are comparable to results of Chau I, and others. (2001)23 who used oxaliplatin-based chemotherapy in patients with relapsed or refractory intermediate/high grade NHL. They found that response rate was 77% for high risk patients treated after first relapse.

The results of current study coincides with results of Chau Ian, and others. (2003)33 who studied gemcitabine, cisplatin, methylprednisolone in poor primarily progressive or relapsed NHL. They found that response rate was 80% and 50% for whole study group and primarily progressive cases respectively.

A response rate of 60% was achieved by gemcitabine and oxaliplatin combination when tested in heavily pretreated refractory and relapsed NHL patients34. Table (3-B) showed that complete response and/or unconfirmed complete response in high risk patients was higher in (GEMOX-P) arm as it formed 46.7% of cases compared to 16.7% in (CHOP) group with statistically significant difference ($P < 0.05$). However, it was not statistically significant in low risk cases. It occurred in 44.4% and 33.3% in (CHOP) and (GEMOX-P) groups respectively. Partial response and disease progression were not statistically significant in low or high risk patients in both treatment arms.

First-line chemotherapy of (gemcitabine, oxaliplatin, prednisolone) had higher response rate and complete remission in high risk patients than standard (CHOP) regimen in the current study.

Gemcitabine has response rates ranging from 20% to 30%. Oxaliplatin has demonstrated potent antitumor activity, at least equivalent to cisplatin, along

Event	Grade 1 or 2			Grade 3 or 4		
	CHOP	GEMOX-P	P-value	CHOP	GEMOX-P	P-value
Leukopenia	12 (66.7%)	7 (46.7%)	NS	2 (11.1%)	5 (33.3%)	NS
Febrile neutropenia	11 (61.1%)	7 (46.7%)	NS	4 (22.2%)	5 (33.3%)	NS
Anemia	2 (11.1%)	2 (13.3%)	NS	1 (5.6%)	1 (6.7%)	NS
Thrombocytopenia	2 (11.1%)	5 (33.3%)	NS	1 (5.6%)	3 (20%)	NS
Infection	7 (38.9%)	6 (40%)	NS	4 (22.2%)	5 (33.3%)	NS
Nausea, vomiting	7 (38.9%)	5 (33.3%)	NS	1 (5.6%)	3 (20%)	NS
Diarrhea	5 (27.8%)	2 (13.3%)	NS	1 (5.6%)	1 (6.7%)	NS
Constipation	7 (38.9%)	4 (26.7%)	NS	-	2 (13.3%)	NS
Mucositis	5 (27.8%)	2 (13.3%)	NS	1 (5.6%)	1 (6.7%)	NS
Alopecia	15 (83.3%)*	7 (46.7%)*	< 0.05	3 (16.7%)	3 (20%)	NS
neuropathy	6 (33.3%)	6 (40%)	NS	1 (5.6%)	3 (20%)	NS
Liver enzymes elevation	7 (38.9%)*	2 (13.3%)*	< 0.05	1 (5.6%)	1 (6.7%)	NS
Renal toxicity	2 (11.1%)	2 (13.3%)	NS	-	1 (6.7%)	NS
Cardiac toxicity	5 (27.8%)	1 (6.7%)	NS	1 (5.6%)	--	NS
Hypotension	1 (5.6%)*	10 (66.7%)*	< 0.05	-	5 (33.3%)	< 0.05

Table 5 - Treatment-related toxicity in both treatment arms

Chemotherapy cycles	CHOP	GEMOX-P
One Cycle	390 ± 90	5900 ± 190
6 Cycles	2340 ± 130	35,400 ± 320

Table 6 - Average cost of both chemotherapy arms in the study

with lower incidence of toxicity. Gemcitabine and oxaliplatin are both active in a number of tumors, with no overlapping toxicity. In vitro, this combination has been demonstrated to be synergistic in several human cancer cell lines, with a sequence-dependency that favors the administration of gemcitabine followed by oxaliplatin. The basic mechanisms of this synergistic interaction are likely to take place at the DNA level, as the incorporation of the anti-metabolite into DNA may increase platinum binding to DNA35.

Tables (4:A-D) and figures (1-3) represented that overall survival and disease free-survival after 18 months did not show any statistically significant difference between both treatment arms in low and high risk cases of the study.

Although, there was no statistically significant difference of disease-free survival after 18 months between both treatment arms, DFS was higher and statistically significant in (CHOP) group than (GEMOX-P) arm after 6 and 12 months in low and high risk cases

respectively as shown in table (4-C) and figures (1,2). This may be attributed to lower duration periods of achieved response in (GEMOX-P) arm than (CHOP) arm.

Chau Ian, and others. (2003)33 studied gemcitabine, cisplatin, methylprednisolone in poor primarily progressive or relapsed NHL. They found that probability of one-year overall and disease-free survival were 60.8% and 40.4% respectively. These results seem to be lower than the current study results, which may be attributed to difference in chemotherapeutic drugs used (cisplatin vs. oxaliplatin) and/or difference in inclusion criteria (refractory-relapsed NHL cases vs. patients without previous chemotherapy).

Table (5) showed the different toxicities in both treatment arms of the study. One third (33.3%) of cases of (GEMOX-P) group had experienced grade 3/4 leukopenia and febrile neutropenia without statistically significant difference when compared to (CHOP) group. Grade 3/4 thrombocytopenia occurred

in 5.6% and 20% in (CHOP) and (GEMOX-P) arms respectively. The duration of neutropenia and thrombocytopenia was usually <7 days. Recovery to normal at time of the subsequent planned infusion was experienced in majority of cases. Febrile neutropenia that needed GM-CSF, isolation and antibiotics was present in 22.2% of (CHOP) cases compared to 5 cases (33.3%) of (GEMOX-P) group. The febrile neutropenia was successfully treated with GM-CSF and broad-spectrum antibiotics. Grade 3–4 neutropenia and thrombocytopenia occurred generally between 2nd and 6th cycles. Sustained thrombocytopenia led to a total of 2 cycles being postponed. The full recommended dose could not be administered on consecutive cycles as planned in a total of 7 cycles because of the frequency, severity and duration of neutropenia that imposed multiple

treatment delays and/or 25% dose reductions. Reversible grade 3 anemia was reported in one patient at both treatment groups. These toxicities were still tolerable and acceptable. There were no

In the California trial, the dose limiting toxicities occurred at the dose of gemcitabine 1250 mg/m² were grade 4 thrombocytopenia

treatment-related deaths.

Two other phase I trials had reported data on combination of

(gemcitabine–oxaliplatin) using different schedules. Mavroudis and others (2000) used gemcitabine 1000–1600 mg/m² on days 1 and 8, combined with oxaliplatin 60–120 mg/m² on day 8, every 21 days, in patients with advanced tumors. Overall, the incidence of grade 3–4 hematological toxicity was comparable to results of the current study. These data showed that combination of gemcitabine with oxaliplatin can be well tolerated in both untreated and previously treated patients with grade 3/4 hematological toxicities < 10% which was lower than current study results. The California Consortium trial had reported the results of gemcitabine 700–1750 mg/m² on days 1 and 8, plus a fixed dose of oxaliplatin 130 mg/m² on day 1, every 21 days, in patients with advanced tumors^{37,38}. In the California trial, the dose limiting toxicities occurred at the dose of gemcitabine

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1250 mg/m² were grade 4 thrombocytopenia. This schedule appears to be associated with more severe grade 3/4 hematological toxicity in about 30% to 33% of cycles which is consistent with the current study results of (GEMOX-P) that constituted 20-33.3%.

The gastro-intestinal tract (GIT) toxicity of (gemcitabine, oxaliplatin and prednisolone) was well tolerated. It was comparable to GIT toxicity of (CHOP) group without any statistically significant difference. Nausea, vomiting, diarrhea/constipation and mucositis were mild in the majority of patients and did not result in any clinically significant problems. Digestive tract toxicity of grades (1, 2) was easily manageable with classical anti-emetics, antispasmodic and anti-diarrhea treatment. Grade 3/4

nausea and vomiting was present in 5.6% and 20% in cases treated with (CHOP) and (GEMOX-P) respectively without statistically significant difference ($P > 0.05$).

Alopecia was the most common side effect in patients treated with (CHOP). It occurred in all patients of (CHOP) compared to 2/3 patients of (GEMOX-P) arm. Grade I, 2 alopecia of (CHOP) arm was higher and statistically significant when compared to (GEMOX-P) arm.

Toxicity of gemcitabine was reported to be limited to mild myelosuppression, asthenia and nausea/vomiting, which is usually controlled with standard supportive symptomatic treatment. Oxaliplatin has a specific neurotoxic profile with both acute and chronic symptoms. Neurotoxic symptoms were frequent

but limited to grade 1, 2 in most of the patients (33.3% vs 40%) in (CHOP) and (GEMOX-P) arms respectively. Neurotoxicity was experienced in the first three treatment cycles. No patients had worsening of neurotoxicity after treatment discontinuation.

Table (5) showed that grade (1, 2) elevation of hepatic enzymes was higher in (CHOP) than (GEMOX-P) arm which constituted (38.9% vs. 13.3%) respectively with statistically significant difference ($P < 0.05$). Nephrotoxicity occurred in limited number of patients (11.1%) and (20%) in (CHOP) group and (GEMOX-P) arm respectively with no statistically significant difference. Cardiac toxicity was not apparent as a frequent toxicity in (GEMOX-P) group, so it may be suitable for NHL patients with

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mild/moderate cardiac dysfunction to use (GEMOX-P) instead of (CHOP) treatment. A large scale trial including more number of patients is recommended to confirm the use of (GEMOX-P) as a substitute regimen for NHL cases with hepatic or cardiac impairment.

Beneficial agents used for treatment of severe cases are fludrocortisone, midodrine, caffeine and erythropoietin alfa

Orthostatic hypotension occurred only in one case of (CHOP) group and in all patients of (GEMOX-P) arm, with statistically significant difference ($P < 0.05$) between both treatment groups. Grade 3/4 occurred in one third of cases of (GEMOX-P) arm. Symptoms ranged from light-headedness to presyncopal or syncopal complaints. Functional activity was often greatly compromised by these symptoms, that included dimming of vision and visual blurring, neck pain (often the only symptom present), weakness or buckling of the legs, cognitive slowing, headache, seizures (usually clonic jerks) and postprandial angina pectoris. Symptoms were also worse after sudden postural changes, prolonged standing, exposure to hot environments (e.g. a hot bath or shower, summer weather), when febrile, exercise and hyperventilation may also provoke symptoms. Bonema JD, and others.³⁹, (1992) reported that greater than 20% of the elderly population can be expected to experience a systolic BP drop of more than 20 mmHg on standing. This problem is accentuated by the combination of side effects from medication and a greater incidence of chronic illnesses. Secondary orthostatic hypotension may also be associated with diabetes mellitus, malignancy, encephalopathy and/or peripheral neu-

ropathy. Beneficial agents used for treatment of severe cases are fludrocortisone, midodrine, caffeine and erythropoietin alfa⁴⁰.

In this study, the main cause of treatment modification (delay or dose reduction) in (CHOP) group was thrombocytopenia, leukopenia, febrile neutropenia and/or elevated liver enzymes. While in (GEMOX-P) arm, it was hematological toxicity and/or elevated cumulative toxicities as asthenia, orthostatic hypotension and parasthesia.

Average cost of chemotherapy of both regimens was estimated in table (6). Average cost of 6 chemotherapy cycles of (gemcitabine, oxaliplatin, prednisolone) was about 35.400 Egyptian pounds, as compared to 6 cycles of standard (CHOP) regimen that cost about 2.340 Egyptian pounds. Cost estimates are always difficult and debatable. The cost of chemotherapy not only varies from one national health system to another but also changes within the country depending on individual hospital policy. Although these costs are only estimates, they show that an increase in the cost of chemotherapy could affect the ranking order of strategy costs (Benson R, and others., 1998)⁴¹. This indicates that good selection of cases that may benefit from this regimen is an important issue. It may be used as substitution to (CHOP) in NHL patients with cardiac or hepatic impairment.

Conclusion

The current comparative study was done between (CHOP) and (GEMOX-P) regimens as first-line chemotherapy in intermediate and high grade Non-Hodgkin's lymphoma. It was found that; (gemcitabine, oxaliplatin, and prednisolone) had more frequent attacks of hematological, neuro-toxicities and orthostatic hypotension, but lower incidence of cardiac and hepatic toxicity than (CHOP) regimen. The main cause of (GEMOX-P) treatment delay was thrombocytopenia, febrile neutropenia and/or cumulative toxicities as asthenia, orthostatic hypotension, and paresthe-

sia. Nearly one third of (GEMOX-P) cases experienced grade 3/4 leukopenia and febrile neutropenia with no statistically significant difference between the two treatment groups. Orthostatic hypotension occurred in all cases of (GEMOX-P) group with statistically significant difference when compared to (CHOP) regimen. The regimen of (GEMOX-P) had beneficial effects over (CHOP) regimen that included higher complete response rate in high risk cases and lower cardiac and hepatic toxicity, but there was no difference after 18 months in disease-free or overall survival between both treatment arms. Selection of cases that may benefit from chemotherapy treatment either (CHOP) or (GEMOX-P) is needed with balance between anticipated toxicities, treatment outcome and cost-benefit aspect.