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ORIGINAL ARTICLE

Comparison of the efficacy and impact of GEMOX and GDP in the treatment of patients with non-Hodgkin's lymphoma

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Summary

Purpose: *To compare the efficacy and impact of GEMOX and GDP in the treatment of patients with non-Hodgkin's lymphoma (NHL).*

Methods: *A total of 68 patients with NHL admitted to the hospitals of the authors from February 2013 to April 2016 were equally distributed into the GEMOX Group (treated with Gemcitabine and Oxaliplatin) and the GDP Group (treated with Gemcitabine, Cisplatin, and Dexamethasone), with cycle repetition every 3 weeks. The efficacy was analyzed every two weeks. The side effects were analyzed once a week. Comparison of survival was performed using Kaplan-Meier method and log-rank test and Cox univariate and multivariate regression analyses.*

Results: *Efficacy in the two groups was not statistically different ($p>0.05$). The incidence of III-IV grade of nausea and vomiting in the GDP Group was higher than in the GEMOX Group ($p<0.05$). The overall incidence decreased hemoglobin, nausea and vomiting, and renal dysfunction of the GDP Group was also higher than in the GEMOX Group ($p<0.05$). Analysis by multivariate Cox model found that the clinical classification and the grade of malignancy were independent prognostic factors ($p<0.05$). The odds ratio (OR) values of the clinical classification in the GEMOX Group and the GDP Group were 2.874 and 24.074, respectively. The OR values of the grade of malignancy in the GEMOX Group and the GDP Group were 14.034 and 6.873, respectively.*

Conclusion: *Both the GEMOX regimen and the GDP regimen had good short-term efficacy on NHL patients, but the GEMOX regimen is to be preferred since as it had fewer side effects than the GDP regimen.*

Key words: *GEMOX, GDP, non-Hodgkin's lymphoma, efficacy, impact*

Introduction

Non-Hodgkin's lymphoma (NHL) is a common hematological malignancy, with strong heterogeneity [1]. The lesions are mostly in the lymphoid organs like lymph nodes, thymus, and other parts of the lymphoid hematopoietic system [2]. In the United States, the incidence of NHL (per 100,000 people) has doubled from 10.2% in 1973 to 21.4% in 2004 and then stabilized, while the 5-year relative survival rate has increased from 42% in 1973 to 70% in 2004 [3]. However, the incidence and mortality of NHL have increased in recent years [4]. In clinical practice, the most

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common is B-cell type NHL, with a high grade of malignancy [5]. The current clinical treatment of NHL is mainly chemotherapy-based [6]. However, some patients are not sensitive to existing first-line chemotherapy drugs, not forgetting the possibility of recurrence after chemotherapy [7]. Even after the combination of second and third-line chemotherapy, the treatment effect is not satisfactory; the incidence of side effects is high and the prognosis and disease remission are not greatly improved [8].

GDP is a combination of gemcitabine with dexamethasone and cisplatin. Gemcitabine is a nucleoside analog (2'-fluoro-2'-deoxycytidine) that inhibits nucleotide metabolism. This broad-spectrum antitumor drug does not show cross-resistance with platinum drugs for the treatment of pancreatic cancer, lung cancer, breast cancer or bladder cancer [9-11]. Dexamethasone is very effective in the regression of glioma edema, but its adverse reactions include T cell-mediated immunosuppression [12]. Cisplatin is a platinum-coumpound drug that was first approved as an anti-tumor drug in 1978. Today, it is still an important and effective agent for treating a variety of cancers [13]. GDP is an effective emergency treatment for relapsed-resistant invasive NHL. Clinical treatment is better and less toxic, but the main adverse effects are bone marrow suppression, liver dysfunction, gemcitabine-related rash, elevated blood sugar and gastrointestinal toxicity [14]. GEMOX is a newly developed chemotherapy regimen of gemcitabine combined with oxaliplatin. Oxaliplatin is a third-generation platinum coumpound with broad-spectrum anticancer activity after cisplatin and carboplatin. It is the first platinum drug that has been proved to be effective for colorectal cancer and has become the standard drug for treating colorectal cancer [15]. GEMOX has achieved good results in the treatment of ovarian cancer, lymphoma and biliary tract cancer, with mild side effects and good patient tolerance [16,17]. In recent years, it has been reported that the GEMOX is effective in the treatment of refractory NHL and can prolong the progression-free survival of patients with B-cell lymphoma, especially in stage III-IV. It is currently the preferred method for the treatment of patients with refractory NHL [18], but still produce some myelosuppression.

At present, there are few reports on the comparison of the efficacy and safety of the two treatment options. In order to better guide the clinical use of drugs, 68 NHL patients were evaluated in this GEMOX and GDP study. The efficacy and safety of the two treatments were analyzed to provide reference for clinical treatment of NHL.

Methods

General Information

Sixty-eight patients with NHL admitted to the authors' hospitals from February 2013 to April 2016 were included as experimental subjects. The patients were equally divided by random number table into the GEMOX Group (21 men and 13 women, aged from 23-73 years with an average age of 36.84±5.72 years) and the GDP Group (20 males and 14 females, aged from 25-75 years with an average age of 36.84±5.36 years).

Inclusion criteria: 1) all patients were pathologically diagnosed with NHL , in line with NHL diagnostic criteria [19]; 2) patients with evaluable lesions and patients treated with CHOP first-line regimen; 3) patients with a Karnofsky performance status (KPS) score higher than 70 points on admission [20] and with white blood cells (WBC) more than 3×10^9/L, and those with poor results when treated with CHOP or other chemotherapy regimens; 4) all patients suffered from relapsed and refractory NHL; 5) the WBCs was more than 3×10^9/L, and of the platelet (Plt) was more than 80×10^9g/L.

Exclusion criteria: 1) patients with chemotherapy contraindications such as hematopoietic dysfunction, chemotherapeutic drug allergy, etc.; 2) patients who received radiotherapy and chemotherapy within 6 months before this study; 3) patients with heart, brain, liver and kidney dysfunction or other severe organic diseases.

Chemotherapy

Patients in the GEMOX Group were treated as follows: intravenous drip of Gemcitabine hydrochloride (Ningbo Team Pharmaceutical Co., Ltd., H20040957) from the 1st day to the 8th day, 1000 mg/m^2; intravenous drip of Oxaliplatin (Suzhou Lixin Pharmaceutical Co., Ltd., H20113144) in the 1st day, 120 mg/m^2.

Patients in the GDP Group were treated as follows: Gemcitabine hydrochloride (Ningbo Team Pharmaceutical Co., Ltd., H20040957) 1000 mg/m^2, intravenous drip, d1, d8; Dexamethasone (Guangxi Wonder Pharmaceutical Co., Ltd., H20113234) 20 mg/m^2 intravenous drip, d1-5; Cisplatin (Luoxin Pharmaceutical Group Co., Ltd., Shandong, H20046375) 25 mg/m^2 intravenous drip, d1-3.

Cycle repetition in both groups was every 3 weeks with gastric protection and antiemetics. Routine blood tests of the patients were performed after the end of each chemotherapy cycle to make sure the WBC were over 1×10^9/L and the platelets were over 3×10^9/L. If the WBC or platelets were lower, preventive treatment or course delay were performed.

Observation indicators

All patients were evaluated every R cycles to assess their physical condition. According to the response evaluation criteria in solid tumors (Lugano response criteria) [21], the treatment efficacy was divided into four categories: complete response (CR): all lesions disappeared completely for 4 or more weeks; partial response (PR): the sum of the longest diameters of all tumor lesions was reduced by at least 30% and maintained for

more than 4 weeks; stable disease (SD): the sum of all the longest diameters of all tumor lesions was longer than that of the PR situation but shorter than that of the PD category; progressive disease (PD): the sum of the longest diameters of all tumors increased by more than 20%, or new lesions appeared. Objective response rates (ORRs) and the disease control rate (DCR) of the two groups were calculated and compared: ORR = (number of patients in CR+number of patients in PR)/total patients number of the group * 100%; DCR = (number of patients in CR+number of patients in PR+number of patients in SD)/total patients number of the group * 100%. According to the National Cancer Institute Common Toxicity Criteria (NCI-CTC.4.0) [22], the incidence of side effects of the two groups was assessed weekly and compared.

Statistics

The experimental data were statistically analyzed using SPSS19.0 statistical software (SPSS Inc., Chicago, IL, USA). The count data (%) were compared by group using the chi-square (x^2) test. The measurement data (mean±standard deviation/SD) were compared by group using the *t*-test. The survival was analyzed using the Kaplan-Meier method and log-rank test. The prognostic factors were analyzed by using the univariate and multivariate Cox model. Statistical significance was set at $p<0.05$.

Results

Comparison of general data

As shown in Table 1, in the GEMOX Group, the first locations of 6 patients were in the oropharynx ring, 12 patients in the cervical lymph nodes, 9 patients in the inguinal lymph nodes, and 7 patients in other locations. Thirteen patients had I-II clinical stage and 21 had III-IV clinical stage. In the GDP Group, the first locations of 9 patients were in the oropharynx ring, 11 patients in the cervical lymph nodes, 9 patients in the inguinal lymph nodes, and 5 patients in other locations. Twelve patients had I-II clinical stage and 22 had III-IV clinical stage. No statistical difference was seen between the GEMOX Group and the GDP Group in terms of age, gender, first location, clinical classification and pathological type ($p>0.05$). Detailed data are shown in Table 1.

Table 1. Comparison of general clinical data

Clinical factors	*GEMOX Group (n=34)*	*GDP Group (n=34)*	*t/x²*	*p*
Age (years)	36.34±5.72	36.84±5.36	0.372	0.711
Body mass index (kg/m²)	20.63±2.58	21.22±2.41	0.974	0.334
Gender, n (%)			0.061	0.804
Male	21 (61.76)	20 (58.82)		
Female	13 (38.24)	14 (41.18)		
First attacked location, n (%)			0.977	0.807
Oropharynx ring	6 (17.65)	9 (26.47)		
Cervical lymph nodes	12 (35.29)	11 (32.35)		
Inguinal lymph nodes	9 (26.47)	9 (26.47)		
Other locations	7 (20.59)	5 (14.71)		
Clinical classification			0.063	0.801
I/II	13 (38.24)	12 (35.29)		
III/IV	21 (61.76)	22 (64.71)		
Pathological type, n (%)			0.264	0.877
B cell	19 (55.88)	21 (61.76)		
T cell	10 (29.41)	9 (26.47)		
NK/T cell	5 (14.71)	4 (11.76)		
Malignant degree, n (%)			0.619	0.734
Inert	4 (11.77)	6 (17.65)		
Invasive	27 (79.41)	26 (76.47)		
Highly invasive	3 (8.82)	2 (5.88)		
The longest diameter of the tumor (cm), n (%)			0.078	0.779
<10	26 (76.47)	25 (73.53)		
≥10	8 (23.53)	9 (26.47)		
ECOG score, n (%)			0.086	0.770
0-1	27 (79.41)	26 (76.47)		
2-5	7 (20.59)	8 (23.53)		

Comparison of the efficacy between the GEMOX Group and the GDP Group

According to the evaluation of efficacy, the two groups were not statistically different because the GEMOX Group had ORR of 61.76% and DCR of 88.24%, while the GDP Group had ORR of 55.88%, and DCR of 85.29%. In the GEMOX Group, 6 patients achieved CR, 15 patients PR, 9 patients had SD, and 4 patients had PD. In the GDP Group, 5 patients achieved CR, 14 patients achieved PR, 10 patients had SD, and 5 patients had PD (p>0.05) (Table 2).

Comparison of side effects between the GEMOX Group and the GDP Group

The incidence of side effects of the GEMOX Group and the GDP Group was recorded to compare the incidence of III-IV grade of adverse reac-

Table 2. Comparison of the efficacy between the GEMOX Group and the GDP Group

	CR *n (%)*	*PR* *n (%)*	*SD* *n (%)*	*PD* *n (%)*	*ORR* *n (%)*	*DCR* *n (%)*
GEMOX Group	6 (17.65)	15 (44.12)	9 (26.47)	4 (11.76)	21 (61.76)	30 (88.24)
GDP Group	5 (14.71)	14 (41.18)	10 (29.41)	5 (14.71)	19 (55.88)	29 (85.29)
x^2	0.109	0.060	0.073	0.128	0.243	0.128
P	0.742	0.806	0.270	0.721	0.622	0.721

Table 3. Comparison of the side effects between the GEMOX Group and the GDP Group

Side effects	*GEMOX Group (n=34)*			*GDP Group (n=34)*			*p (III+IV)*	*p (overall incidence)*
	I+II *n (%)*	*III+IV* *n (%)*	*Overall incidence* *n (%)*	*I+II* *n (%)*	*III+IV* *n (%)*	*Overall incidence* *n (%)*		
Decrease in WBC	58.82	20.59	79.41	64.71	26.47	91.18	0.568	0.171
Decrease in PLT	58.82	26.47	85.29	61.76	26.47	88.24	1.000	0.721
Decrease in HGB	55.88	2.94	58.82	70.59	14.71	85.29	0.087	0.015
Decrease in NE	17.65	0.00	17.65	23.53	2.94	26.47	0.314	0.380
Nausea and vomiting	52.94	2.94	55.88	61.76	32.35	94.12	0.002*	0.001
Liver dysfunction	23.53	0.00	23.53	20.59	2.94	23.53	0.314	1.000
Renal dysfunction	5.88	0.00	5.88	26.47	0.00	26.47	-	0.021

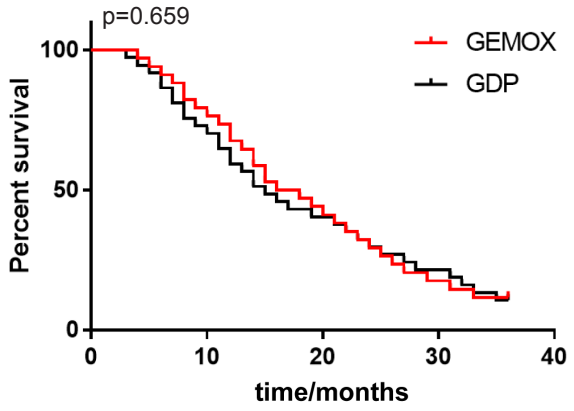

Figure 1. Comparison of the overall survival between the GEMOX Group and the GDP Group. Kaplan-Meier curves showing no statistical difference between the GEMOX Group and the GDP Group as the median survival times of the GEMOX Group and the GDP Group were 17 and 15 months, respectively, and the 3-year survival rates were 11.76% and 2.94%, respectively. (p>0.659).

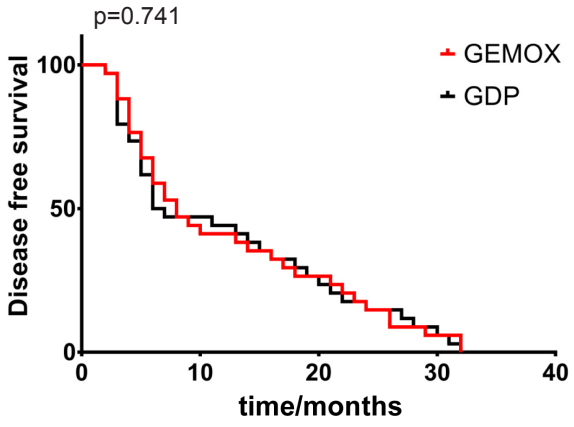

Figure 2. Comparison of the progression-free survival between the GEMOX Group and the GDP Group. Kaplan-Meier curves indicating that the GEMOX Group and the GDP Group were not statistically different in the percentage of disease-free survival (p>0.741).

tions and the overall incidence between the two groups. The incidence of III-IV grade of nausea and vomiting in the GDP Group was higher than in the GEMOX Group (p<0.05). The overall incidence of a decrease in hemoglobin, nausea and vomiting, and renal dysfunction of the GDP Group was also higher than in the GEMOX Group (p<0.05) (Table 3).

Survival

All patients were followed up for 2-36 months, with an average follow-up time of 18.68 months. According to Kaplan-Meier method, the GEMOX Group and the GDP Group had not statistical difference in survival since the median survival of the GEMOX Group and the GDP Group were 17 and 15 months, respectively. The 3-year survival rates were 11.76% and 2.94%, respectively (p<0.05). The median progression-free survival of the GEMOX Group and the GDP Group were 8 (3-32) months and 6.5 (3-32) months, respectively (p>0.05). Detailed data are shown in Figures 1 and 2. Analysis of survival of the two groups by the univariate and multivariate Cox model indicated that the clini-

Table 4. Cox univariate analysis of prognostic factors of the GEMOX Group and the GDP Group

Clinical factors	*GEMOX Group (n=34)*		*GDP Group (n=34)*	
	HR (95%CI)	*p*	*HR (95%CI)*	*p*
Age, years				
<60	1	0.058	1	0.378
≥60	0.464 (0.210-1.027)		1.452 (0.633-3.329)	
Gender				
Male	1	0.381	1	0.594
Female	1.423 (0.646-3.134)		1.254 (0.545-2.888)	
Clinical classification				
I/II	1	0.023	1	0.004
III/IV	2.874 (1.158-7.133)		24.074 (2.772-209.075)	
Pathological type				
B cell	1	0.662	1	0.652
Others	1.201 (0.528-2.733)		1.216 (0.520-2.842)	
Degree of malignancy				
Inert	1	0.027	1	0.031
Invasive and highly invasive	14.034 (1.359-144.930)		6.873 (1.198-39.433)	

Table 5. Cox multivariate analysis of prognostic factors of the GEMOX and the GDP groups

Clinical factors	*GEMOX Group (n=34)*		*GDP Group (n=34)*	
	OR (95%CI)	*p*	*OR (95%CI)*	*p*
Age, years				
<60	1	0.058	1	0.378
≥60	0.464 (0.210-1.027)		1.452 (0.633-3.329)	
Gender				
Male	1	0.381	1	0.594
Female	1.423 (0.646-3.134)		1.254 (0.545-2.888)	
Clinical classification				
I/II	1	0.023	1	0.004
III/IV	2.874 (1.158-7.133)		24.074 (2.772-209.075)	
Pathological type				
B cell	1	0.662	1	0.652
Others	1.201 (0.528-2.733)		1.216 (0.520-2.842)	
Grade of malignancy				
Inert	1	0.027	1	0.031
Invasive and highly invasive	14.034 (1.359-144.930)		6.873 (1.198-39.433)	

cal stage and the grade of malignancy were independent prognostic factors of the NHL patients in the two groups ($p<0.05$). The OR values of the clinical stage in the GEMOX Group and the GDP Group were 2.874 and 24.074, respectively ($p<0.05$). The OR values of the grade of malignancy in the GEMOX Group and the GDP Group were 14.034 and 6.873, respectively ($p<0.05$, Tables 4 and 5).

Discussion

As a group of independent diseases originating from lymph nodes and related lymphatic system, NHL greatly impacts patient life because in some patients NHL has strong invasiveness [23]. After current clinical first-line chemotherapy, NHL regresses in many patients who may be even cured [24]. However, after chemotherapy, some patients can still develop metastasis or recurrence [25].

Gemcitabine is a new type of antitumor drug. At present, experts at home and abroad believed that gemcitabine can be used as first-line chemotherapy for advanced pancreatic cancer and rectal cancer after combined with oxaliplatin, because gemcitabine has less side effects and better patient tolerance so as to greatly improve the patient survival situation with advanced cancer [26,27]. Cisplatin is a common anticancer drug in clinical practice, often combined with other drugs such as gemcitabine and dexamethasone to create the second-line treatment, providing good efficacy for various lymph cancers, but has obvious side effects [28]. There are currently few studies on the treatment plans for patients with NHL, so this study compared the efficacy of the GEMOX and GDP regimens in patients with NHL through analysis of factors such as side effects and prognosis.

The results of this study showed that the ORR and DCR of the GEMOX Group were 61.76% and 88.24%, respectively ($p>0.05$) and the ORR and DCR of the GDP Group were 55.88% and 85.29%, respectively ($p>0.05$). The median survival of the GEMOX Group and the GDP Group were 17 and 15 months, respectively ($p>0.05$). The 3-year survival rates of the GEMOX Group was 11.76%, significantly higher than in the GDP group (2.94%, $p<0.05$ respectively. The median progression-free survival times of the GEMOX Group and the GDP Group were 8 months and 6.5 months, respectively ($p>0.05$). Analysis by the multivariate Cox model found that the clinical stage and the grade of malignancy were independent prognostic factors in the NHL patients from the two groups, proving that both GEMOX Group and GDP Group achieved good efficacy in patients with NHL (the prognosis of the GEMOX Group was a little bit better than that of the GDP Group, but the two groups were not statistically different). Currently, second-line chemotherapy regimens such as MVP-16 have an ORR value of no more than 50%, which is not ideal for the prognosis and survival of patients [29]. Some authors showed that GEMOX could be the first choice for patients with refractory NHL as it could significantly prolong the progression-free survival of patients with B-cell NHL [30]. One previous study showed that GEMOX could achieve an ORR of 83% in the treatment of refractory mantle cell lymphoma [31], and high ORR which might partly due to the additional use of rituximab. Another previous study showed that the GDP could achieve satisfactory efficacy in the treatment of NHL, with an ORR of 65.4% [32], slightly higher than the ORR of this study, because of the use of dexamethasone in this study, instead of prednisolone which has been proved in clinical practice to have strong liver and kidney toxicity [33]. Therefore, this study insisted on the use of dexamethasone instead of prednisolone. In this study, the incidence of III-IV grade of nausea and vomiting in the GDP Group was higher than in the GEMOX Group ($p<0.05$), and the overall incidence of decrease in hemoglobin, nausea and vomiting, and renal dysfunction of the GDP Group was also higher than that of GEMOX Group, proving that the GDP Group suffered from more side effects than the GEMOX Group, which may be related to the difference of medication in the two treatment regimens. As a third-generation platinum compound, oxaliplatin has better efficacy than other platinum drugs and has less adverse reactions in the digestive system than cisplatin [34,35]. The reason may be that aminogroups at the 1,2 position of cisplatin are replaced by diaminocyclohexane groups [35]. In the GDP regimen of this study, glucocorticoids such as dexamethasone were used to neutralize the side effects of cisplatin, but the overdoses of glucocorticoids brought more risks to patients [36]. Therefore, the GEMOX regimen was significantly better than the GDP regimen considering the side effects.

For the first time, the side effects of GDP were compared with those of the GEMOX in this study. Moreover, the changes of hemogram before and after treatment in the two groups were compared, and the subjective symptoms were analyzed in detail.

Many shortcomings existed in this study, such as the small sample size due to the limitations of experimental conditions, which need expanded case collection (sample fusion between multiple

regions is a good choice). Besides, comparison of the efficacy of the two treatment regimens in patients with different clinical stages should have been made except for the comparison of the efficacy between the two treatment regimens.

In summary, both the GEMOX and the GDP achieved better efficacy in patients with NHL, and prolonged the median overall survival and median progression-free survival of NHL patients, but the GEMOX is worthy of further study as its side effects were significantly less than the GDP.

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Conflict of interests

The authors declare no conflict of interests.

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