

# Gemcitabine, cisplatin, and dexamethasone and ifosfamide, carboplatin, and etoposide regimens have similar efficacy as salvage treatment for relapsed/refractory aggressive lymphoma

## A retrospectively comparative study

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### Abstract

In this study, our aim was to compare the efficacy and toxicity profiles of gemcitabine, cisplatin, and dexamethasone (GDP) and ifosfamide, carboplatin, and etoposide (ICE) regimens in the salvage treatment of relapsed/refractory lymphoma. A total of 110 patients with refractory/relapsed classical Hodgkin lymphoma (n=22) or non-Hodgkin lymphoma (n=88) who received GDP or ICE salvage regimens from January 2011 to July 2018 were retrospectively analyzed. Of the 110 patients, 50 patients received GDP, and 60 patients received ICE. The response could be evaluated in all patients. In the GDP group, 30 (60.0%) patients achieved overall response rate (ORR), and in the ICE group, the ORR was 56.6%. Of the classical Hodgkin lymphoma patients, the ORR were 72.8% and 54.6% in the GDP and ICE groups, respectively. Of the non-Hodgkin lymphoma patients, the ORR were 56.4% and 57.1% in the GDP and ICE groups, respectively. Grade I-II toxicity occurred in 16 (32.0%) patients in the GDP group and 18 patients (30.0%) in the ICE group; 14 (28.0%) patients had Grade III-IV toxicity in the GDP group, as did 20 (33.3%) patients in the ICE group. As a result, both GDP and ICE regimens are suitable for the treatment of recurrent/refractory lymphoma. The overall adverse reactions of both regimens are acceptable.

**Abbreviations:** cHL = classical Hodgkin lymphoma, CR = complete remission, GDP = gemcitabine, cisplatin, and dexamethasone, ICE = ifosfamide, carboplatin, and etoposide, NHL = non-Hodgkin lymphoma, ORR = overall response rate, OS = overall survival, PR = partly remission.

**Keywords:** hodgkin lymphoma, non-Hodgkin lymphoma, relapsed/refractory lymphoma, salvage therapy

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MM and CZ contributed equally to this work.

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## 1. Introduction

Lymphoma is one of the most complicated malignant tumors, because of difficulties with its diagnosis and classification in the clinic, and is a serious threat to patients' lives worldwide.<sup>[1]</sup> With the development of medicine, the adoption of new chemotherapy regimens, new radiotherapy techniques or immunotherapies can result in high complete remission (CR) rates; however, a significant proportion of patients with classical Hodgkin lymphoma (cHL) and non-Hodgkin lymphoma (NHL) fail to achieve CR or suffer relapse shortly after achieving CR.<sup>[2-4]</sup> In the era of new drugs, adriamycin, bleomycin, vinblastine, and dacarbazine and cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone) are still the initial treatments of cHL and most of NHL, respectively.<sup>[5,6]</sup> Nevertheless, for relapsed/refractory lymphoma, these 2 chemotherapies do not have a further benefit or lead to recovery.<sup>[1,5,7-9]</sup> Consequently, even with the best first-line treatments, a relapse might occur, emphasizing the need for salvage treatments. Moreover, as high-dose chemotherapy and autologous stem cell transplantation have become the standard treatment for relapsed/refractory lymphoma, patient response to salvage therapy plays a decisive role.<sup>[10-13]</sup>

There are several commonly used second-line chemotherapy options for lymphoma, such as etoposide, methylprednisolone, cytosine arabinoside and cisplatin, cytarabine, cisplatin, and dexamethasone, gemcitabine, cisplatin, and dexamethasone

(GDP) and ifosfamide, carboplatin, and etoposide (ICE). Response rates to these regimens in patients with relapsed/refractory lymphoma vary between 40% to 80%.<sup>[13,16–22]</sup> Nevertheless, no exact guideline has confirmed the optimal second-line treatment. Usually, the uses of these regimens depend mostly on doctor experience and the actual situation of the patients. In our hospital, the ICE regimen and the GDP regimen are 2 commonly used regimens, the effectiveness of which has been reported in related articles, but there is no relevant literature comparing the 2. In this article, we aimed to retrospectively compare the efficacy and toxicity profiles of the GDP and ICE regimens as salvage treatment in relapsed/refractory lymphoma.

## 2. Patients and methods

### 2.1. Patients

We retrospectively studied 110 patients with relapsed/refractory lymphoma diagnosed in the hospital between 2011 and 2018. The inclusion criteria were as follows: patients with an initial pathological diagnosis of cHL or NHL with histopathologically confirmed recurrence or any radiologic evidence of residue lesions after the first-line treatment; and patients who received the GDP or ICE chemotherapy regimen as the second-line treatment. Lymphoma classification was performed according to the World Health Organization classification (2008 edition) and all patients were staged according to the Ann Arbor staging system. The study was approved by the local Ethics Committee, and informed consent was not required because there were no conflicts of interest or damage to patients in this retrospective study.

### 2.2. Treatment regimens

Fifty patients were treated with the GDP regimen consisting of gemcitabine (1000 mg/m<sup>2</sup>, days 1 and 8), dexamethasone (40 mg/m<sup>2</sup>, days 1–4), and cisplatin (100 mg/m<sup>2</sup>, day 1) as described in T. Baetzl's study.<sup>[23]</sup> Sixty patients received an ICE regimen consisting of etoposide (100 mg/m<sup>2</sup>, days 1–3); carboplatin (AUC 5, maximum dose 800 mg, day 2), ifosfamide (5000 mg/m<sup>2</sup>, day 2). Rituximab (R) 375 mg/m<sup>2</sup> was added in CD20-positive, B-cell NHL.

### 2.3. Assessment

Staging or restaging was performed according to the results of physical examination, computed tomography scans, and bone marrow aspirates and biopsy samples, and PET, if performed. The response was evaluated using the International Working Group Recommendations after the second or fourth cycle of chemotherapy. Any response less than partial response was considered a failure of treatment, and the treatment regimen should be changed. Chemotherapy side effects were evaluated based on the Common Terminology Criteria for Adverse Events Version 4.0.

### 2.4. Statistical analysis

Curves for overall survival (OS) were established using the Kaplan-Meier method and survival comparisons were performed using the log-rank test. Pearson chi-squared test was used when comparisons of categorical data of different groups were done. All *P* values ≤.05 were considered statistically significant. Data

analysis was performed by SPSS, version 25.0, and GraphPad Prism 7.0.

## 3. Results

### 3.1. Patients' characteristics

We included 110 patients; 30 (27%) were female, and the median age was 50 years (range:14–73). In all histological subtypes, there were 22 patients with classical Hodgkin disease, 55 patients with diffuse large B cell lymphoma, 8 patients with mantle cell lymphoma, 5 patients with peripheral T cell lymphoma, 4 patients with follicular lymphoma, and 16 patients with other NHL. The clinicopathological characteristics of the patients are summarized in Table 1. No patients received autologous stem cell transplantation.

### 3.2. Response

**3.2.1. Whole group.** The response was evaluated in all patients. In the GDP group, 20% of patients achieved CR, and 40% of patients achieved partly remission (PR), leading to an overall response rate (ORR) of 60%. In the ICE group, the CR rate, PR rate, and ORR were 13.3%, 43.3%, and 56.6%, respectively (Table 2). There was no difference in overall response rates between the GDP and ICE regimens (*P* = .72).

The median follow-up for OS of the GDP group and ICE group was 26.5 months (range, 3–81 months) and 20.5 months (range, 2–72 months), respectively. The median survival time of the GDP

**Table 1**  
Clinical and pathological characteristics of the patients.

	GDP (n=50 (%))	ICE (n=60 (%))	P-value
Age (median, range)	(51, 23–70)	(47, 14–73)	.10
Sex			.88
Male	36 (72.0)	44 (73.3)	
Female	14 (28.0)	16 (26.8)	
Histology			
cHL	11 (22.0)	11 (18.3)	.63
DLBCL	25 (50.0)	30 (50.0)	1.00
FL	3 (6.0)	1 (1.7)	.23
PTCL	3 (6.0)	2 (3.3)	.50
MCL	0 (0.0)	8 (13.3)	.007
Others	8 (16.0)	8 (13.3)	.69
Stage			.56
I, II	15 (30.0)	15 (25.0)	
III, IV	35 (70.0)	45 (75.0)	
IPI* risk group			
Low	14 (28.0)	22 (36.7)	.42
Intermediate	23 (46.0)	23 (38.3)	.44
High	2 (4.0)	4 (6.7)	.69
BM involvement			.86
Yes	20 (40.0)	25 (41.7)	
No	30 (60.0)	35 (58.3)	
With Rituximab			.54
Yes	7 (14.0)	11 (18.3)	
No	43 (86.0)	49 (81.7)	
Numbers of prior therapies			.50
≤2	47 (94.0)	58 (96.7)	
>2	3 (6.0)	2 (3.3)	

BM = bone marrow, cHL = classical Hodgkin's lymphoma, DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, GDP = gemcitabine, cisplatin, and dexamethasone, ICE = ifosfamide, carboplatin, and etoposide, IPI = International Prognostic Index, MCL = mantle cell lymphoma, NHL = non-Hodgkin lymphoma, PTCL = peripheral T-cell lymphoma.

\*Used only in the evaluation of NHL patients.

**Table 2**  
**Response of relapsed/refractory lymphoma patients.**

Response	GDP		ICE	
	cHL (n = 11 (%))	NHL (n = 39 (%))	cHL (n = 11 (%))	NHL (n = 49 (%))
CR	4 (36.4)	6 (15.4)	2 (18.2)	6 (12.2)
PR	4 (36.4)	16 (41.0)	4 (36.4)	22 (44.9)
ORR	8 (72.8)	22 (56.4)	6 (54.6)	28 (57.1)

cHL = classical Hodgkin's lymphoma, CR = complete response, GDP = gemcitabine, cisplatin, and dexamethasone, ICE = ifosfamide, carboplatin, and etoposide, NHL = non- Hodgkin lymphoma, ORR = overall response rate, PR = partial response.

group was 36 months, while the ICE group did not reach the median survival time. The 1-year OS and 3-year OS of the GDP group were 81.9% and 62.4%, respectively, and in the ICE group, the 1-year OS and 3-year OS values were 68.2% and 59.8%, respectively. No statistically significant difference was observed between the 2 salvage treatment groups (1-year OS:  $P = .13$ , 3-year OS:  $P = .85$ ).

Seven patients in the GDP group received the rituximab therapy and 11 patients in the ICE group received the rituximab therapy. The OS between the R-GDP group and R-ICE group had no statistical difference either (supplement figure 1, <http://links.lww.com/MD/F290>).

**3.2.2. Patients with Hodgkin lymphoma.** Of the 22 patients with cHL, 11 patients received the GDP regimen, and 11 patients received the ICE regimen. In the GDP group, 4 patients (36.4%) achieved CR, and 4 (36.4%) patients achieved PR, leading to an ORR of 72.8%. In the ICE group, 2 (18.2%) patients achieved CR, and 4 (36.4%) patients achieved PR, leading to an ORR of 54.6%.

**3.2.3. Patients with NHL.** Of the 88 patients with NHL, 39 patients received the GDP regimen, and 49 patients received the ICE regimen. In the GDP group, 6 patients (15.4%) achieved CR, and 16 (41.0%) patients achieved PR, leading to an ORR of 56.4%. In the ICE group, 6 (12.2%) patients achieved CR, and 22 (44.9%) patients achieved PR, leading to an ORR of 57.1%.

As for DLBCL accounts for the highest proportion of NHL, we analyzed the results of DLBCL independently. In the GDP group, the DLBCL patients achieved CR, PR, and ORR values of 24%, 28%, and 52%, respectively. In the ICE group, the CR, PR, and ORR values of DLBCL patients were 13.3%, 50%, and 63.3%, respectively.

The survival analysis showed that the survival of relapsed/refractory NHL or cHL patients using the GDP regimen was

similar to that of patients using the ICE regimen, and the p values were .79 and .93, respectively. The survival curves mentioned above are shown in Figure 1.

**3.2.4. Toxicity.** Toxicity analysis between the 2 treatment groups was performed, and the results are as follows: Grade 1 to 2 toxicity occurred in 16 (32%) patients in the GDP group and 18 (30%) patients in the ICE group. Fourteen (28.0%) patients had Grade 3 to 4 toxicity in the GDP group, and 20 (33.3%) patients had Grade 3 to 4 toxicity in the ICE group.

The main toxicity of the GDP regimen was hematological symptoms with thrombocytopenia (Grade 3–4) in 5 (10%) patients and leukopenia (Grade 3–4) in 5 (10%) patients. 2 (4%) patients developed Grade 3 to 4 anemia. Three (6%) patients developed Grade 3 to 4 hepatic dysfunction.

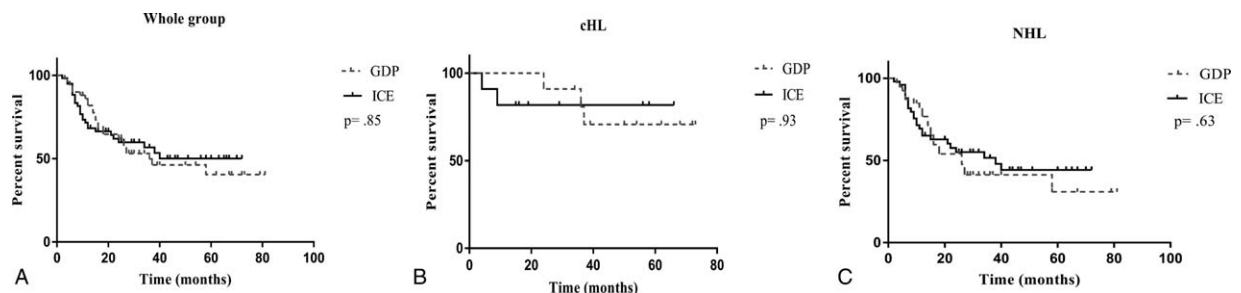
The main toxicity of the ICE regimen was also hematological. Thrombocytopenia (grade 3–4) and leukopenia (grade 3–4) had the same incidence, 13.3%, in patients treated with ICE. Grade 3 to 4 anemia occurred in 4 (6.7%) patients, and grade 3 to 4 hepatic dysfunction only occurred in 1 (1.7%) patient.

In patients with cHL, 3 (27.3%) patients had grade 1–2 toxicity and 2 (18.2%) patients had grade 3 to 4 toxicity within the use of the GDP therapy. 3 (27.3%) patients had grade 1 to 2 toxicity and 4 (36.4%) patients had grade 3 to 4 toxicity by using the ICE therapy.

In patients with NHL patients, 13 (33.3%) patients had grade 1–2 toxicity and 12 (30.8%) patients had grade 3 to 4 toxicity within the use of GDP therapy. 15 (30.6%) patients had grade 1 to 2 toxicity and 16 (32.7%) patients had grade 3 to 4 toxicity for use of the ICE therapy.

**4. Discussion**

For primary refractory/relapsed patients, the treatment outcomes of conventional-dose salvage chemotherapy regimens are not



**Figure 1.** Survival analysis indicated the overall survival (OS) of patients with relapsed and refractory lymphoma after GDP (gemcitabine, cisplatin, and dexamethasone) and ICE (ifosfamide, carboplatin, and etoposide) treatments. (A) OS of the whole group,  $P = .85$ . (B) OS of classical Hodgkin lymphoma (cHL) patients,  $P = .93$ . (C) OS of non-Hodgkin lymphoma (NHL) patients,  $P = .63$ .

satisfactory.<sup>[4–8]</sup> To avoid drug resistance, second-line chemotherapy should feature drugs that have not been used before, which is one of the principles of treatment planning. Cytarabine, cisplatin, and dexamethasone, ICE, GDP, and etoposide, methylprednisolone, cytosine arabinoside and cisplatin are regimens that are more commonly used to treat relapsed/refractory lymphoma patients than newly diagnosed patients, and response rates to these second-line regimens vary between 40% and 80%.<sup>[10–19]</sup> There is currently no consensus regarding the optimal salvage regimen. In this retrospective study, the efficacy and toxicity of the GDP and ICE regimens were compared first, and the results demonstrated that these 2 regimens had similar efficacy as salvage treatment for relapsed/refractory aggressive lymphoma.

In our study of GDP versus ICE, we compared the 2 regimens in terms of efficacy, and the ORR values for the entire cohort were 60% and 56.6%, respectively. There were no significant differences between the 2 groups, but a little different in cHL and NHL groups, and our results were similar to those of previous studies.

In the GDP group, the rates of CR and PR for the group of patients with cHL were 36.4% and 36.4%, respectively, leading to an ORR of 72.8%. The results of the present study exhibited similar response rates to the 69% ORR reported for cHL patients of Baetz et al.<sup>[23]</sup> In our studies, the rates of CR and PR in NHL patients were 15.4% and 41%, respectively, leading to an ORR of 56.4%. We also analyzed the efficacy in DLBCL patients, who accounted for 64.1% in our NHL patients, and found CR, PR, and ORR values of 24%, 28%, and 52%, respectively, which was similar to the 49% ORR in DLBCL with a GDP salvage regimen reported by Crump et al.<sup>[24,25]</sup> Notably, the GDP regimen had a better response to cHL patients than NHL patients.

In the ICE group, for cHL patients, the CR rate, PR rate, and ORR were 18.2%, 36.4%, and 54.6%, respectively, which showed a better result than the study of Valiollah et al. of the ORR of relapsed/refractory Hodgkin lymphoma being 39% with an ICE salvage regimen.<sup>[26]</sup> Of the NHL patients in our study, 12.2% achieved CR and 44.9% achieved PR, leading to an ORR of 57.1%, which demonstrated a little worse result than the study of Moskowitz et al. with the ORR of 66%.<sup>[28]</sup> And, more remarkable, for DLBCL patients with ICE in our patients, the ORR value was 63.3%, which seemed to show a better response rate than patients with GDP (ORR:52%).

The survival of patients after the use of the 2 chemotherapy regimens was also similar. The median follow-up for OS of the GDP group and ICE group was 26.5 months (range, 3–81 months) and 20.5 months (range, 2–72 months), respectively. The 1-year OS and 3-year OS values of the GDP group were 81.9% and 62.4%, respectively, and of the ICE group, the 1-year OS and 3-year OS values were 68.2% and 59.8%, respectively. There was a trend toward better OS in cHL patients than NHL patients regardless of the use of the GDP or ICE regimen.

Considering the toxicity profiles, for both groups, the Grade I–II toxicity incidence was similar linked (30.0% versus 32.0%), and the main side effects were hematological symptoms. However, the ICE group had more patients with Grade III–IV toxicity than the GDP group (33.3% versus 28.0%), and the incidences of leukopenia and thrombocytopenia induced by ICE were significantly higher than those caused by GDP. Among the other adverse reactions, the incidence was the same in the 2

groups. Besides, whether using GDP therapy or ICE therapy, the toxicity effect on cHL patients and NHL patients were similar.

Our study has the following limitations. First, it is a retrospective analysis. Second, the small sample size limits its statistical power. However, to the best of our knowledge, there is no prospective randomized trial comparing salvage GDP versus ICE regimens. Third, the initially unmatched treatment groups revealed differences in patient clinicopathological characteristics. Finally, the follow-up time was not long enough and the PFS values were not counted, which may affect the utility of our results for making conclusions regarding treatment benefit.

Different regimens of salvage chemotherapy have been recommended in literatures to achieve higher efficiency and minimum side effects.<sup>[11,27–29]</sup> Despite its limitations, our study provided an idea of the efficacy and tolerability of GDP and ICE treatments in patients with relapsed/refractory lymphoma. Toxicity with both regimens was within acceptable limits, and both regimens are suitable options for relapsed/refractory lymphoma.

## 5. Conclusion

Considering the aforementioned analysis, both the GDP and ICE regimens are suitable options for relapsed/refractory lymphoma in terms of the risk and benefit ratio. For definitive conclusions, the results of an ongoing prospective randomized trial should be awaited.

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## Correction

The corresponding author has been corrected from Juan Li to Liling Zhang.

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