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ORIGINAL PAPER

Phase II study of low-dose fixed-rate infusion of gemcitabine combined with cisplatin and dexamethasone in resistant non-Hodgkin lymphoma and correlation with Bcl-2 and MDR expression

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Abstract This study aims to assess the efficacy of low-dose fixed-rate infusion of gemcitabine, cisplatin and dexamethasone in resistant non-Hodgkin lymphoma (NHL) patients in addition to evaluating the prognostic value of B cell lymphoma 2 (Bcl-2) and multidrug resistant (MDR) expression in this cohort of patients. Patients with relapsed/refractory NHL following at least two chemotherapy regimens were enrolled. They received gemcitabine 800 mg/m^2 in fixed infusion rate of 10 mg/m^2/min, cisplatin 35 mg/m^2 in days 1, 15 and dexamethasone 20 mg days 1–4, 15–18 every 28 day. Response to treatment, time to disease progression (TTP) and 1-year progression-free survival (PFS) were assessed together with their association with Bcl-2, MDR expression and other prognostic variables. Overall response to treatment was 32 % (14 % complete response). Median TTP and 1-year PFS were 2 months and 31.3 %, respectively. Predictors of response to treatment were early stage [odd ratio (OR) = 4.6, 95 % CI 1.3–16.4], low/low intermediate International Prognostic Index (IPI) (OR = 6.2, 95 % CI 1.2–31.7), negative/low Bcl-2 expression (OR = 6.2, 95 % CI 1.2–31.7) and negative/low MDR expression (OR = 18, 95 % CI 1.4–28.9). However, IPI status lost its value in multivariate analysis. TTP and 1-year PFS were significantly associated with Bcl-2 expression ($p = 0.04$), tumor status before enrollment (relapse vs. refractory, $p < 0.0001$) and tumor stage ($p < 0.000$). In multivariate analysis, clinical stage was the only predictor of TTP and 1-year PFS. Fixed-rate gemcitabine infusion with cisplatin and dexamethasone had reasonable activity in resistant NHL. Clinical stage, Bcl-2 and MDR expressions were predictors of response to treatment, while only clinical stage was associated with TTP and 1-year PFS.

Keywords Lymphoma · Gemcitabine · Bcl-2 · MDR · Refractory · Relapse

Introduction

Hodgkin and non-Hodgkin lymphomas (NHL) represent 4–5 % of all new cancer cases and the fifth leading cause of cancer death in the USA. A remarkable increase in NHL incidence rates has occurred over the past four decades with the greatest increase occurred in aggressive lymphomas [1].

Following relapse, management of patients' refractory to salvage chemotherapy and those with multiple relapses is still unsatisfactory and constitutes a therapeutic challenge [2]. Gemcitabine has demonstrated efficacy in relapsed/refractory NHL, not only as a single agent, but also in combination with cisplatin and dexamethasone with objective tumor responses in approximately half of patients [3, 4].

To exert its activity, gemcitabine needs to be phosphorylated by deoxycytidine kinase (dCK). However, the

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rate of phosphorylation and intracellular accumulation of the active form of the drug is saturated at gemcitabine concentration of 15–20 μM in plasma as demonstrated by clinical pharmacokinetic studies. This concentration is achieved with gemcitabine infusions rate of 8–10 mg/m^2/min, and prolonged infusion with this rate leads to the maintenance of effective plasma gemcitabine concentration for prolonged period of time, which was hypothesized to result in a higher antitumor activity [5].

Reduced drug accumulation via the multidrug resistant (MDR) gene product, P-glycoprotein, constitutes a common mechanism of resistance both in vitro and in vivo [6]. MDR expression is particularly high (50–70 %) in recurrent NHL cases [7]. In addition, several studies reported that MDR expression is correlated with lower response to chemotherapy and higher relapse rate in NHL [8, 9].

Furthermore, over expression of the anti-apoptotic protein B cell lymphoma 2 (Bcl-2) prevents cell death induced by cytotoxic drugs and irradiation [10]. Three different studies have reported that Bcl-2-positive cases had worse disease-free survival (DFS) and cause-specific survival, but without significant difference in overall survival (OS) [11]. In contrast, Gascoyne et al. found significant differences for OS, DFS, and recurrence-free survival (RFS) according to Bcl-2 expression status [12].

The present study aims to assess the efficacy of low-dose fixed-rate infusion of gemcitabine in combination with cisplatin and dexamethasone in relapsed and refractory NHL cases in addition to evaluating the prognostic value of Bcl-2 and MDR expression in this cohort of patients.

Methods

Patients

The study included 50 patients with relapsed/refractory NHL presented to outpatient clinic in Oncology Center of Mansoura University, Egypt, from April 2009 to December 2010. Patients with relapsed, refractory NHL aged ≥18 to <70 years with World Health Organization (WHO) performance status 0–2 were included (0 indicates that the patient is fully active and able to carry on all pre-disease activities without restriction; 1 indicates that the patient is restricted in physically strenuous activity, but is ambulatory and able to carry out work of a light or sedentary nature; and 2 indicates that the patient is ambulatory more than 50 % of waking hours and is capable of all self-care, but unable to carry out any work activities). Patients must have been previously treated with at least two chemotherapy regimens and showing resistance or relapse after second-line chemotherapy. Other key eligibility criteria included the presence of measurable disease before enrollment as assessed according to the response evaluation criteria in solid tumours (RECIST), version 1.1, in addition to adequate bone marrow function, liver and renal profile. Patients were ineligible if they had prior or concurrent second malignancy or CNS involvement with NHL. In addition, pregnant/lactating females, and patients with active/uncontrolled infection or bleeding were excluded. The protocol was approved by the institutional review board, and the study was conducted in accordance with Good Clinical Practice principles. All patients provided written informed consent.

Study design

This is a single-arm phase II study where enrolled patients received chemotherapy regimen as described below. Response to chemotherapy, time to disease progression (TTP) and progression-free survival (PFS) were assessed. These parameters were correlated with tumor stage, International Prognostic Index (IPI) status (assessed at the time of enrollment), Bcl-2 and MDR expression status to check for possible predictors of the efficacy of this chemotherapy regimen in this cohort of patients.

Pretreatment evaluation

Eligible patients had thorough history and physical examination, and routine laboratory investigations in addition to assessment for IPI. Baseline staging CT of neck, chest, abdomen and pelvis and bone marrow aspiration/biopsy were done. Assessments of MDR and Bcl-2 expressions by immunohistochemistry on paraffin blocks of the initial pathological specimens—taken at the time of diagnosis—were also performed.

Treatment schedule

Gemcitabine 800 mg/m^2 was administered at a fixed infusion rate of 10 mg/m^2/min over 80 min in days 1 and 15. Cisplatin 35 mg/m^2 was given over 2 h on days 1 and 15 in addition to dexamethasone 20 mg intravenous (IV) in days 1–4 and 15–18. Gemcitabine was given 1 h before cisplatin infusion. The regimen was given in 28-days cycle. Treatment was given for six cycles or up to disease progression or development of grade 4 toxicity whichever occurred first.

Follow-up assessment

Clinical assessment of response to toxicity was carried out before each cycle. Toxicity was evaluated and graded

according to common toxicity criteria, NCI Canada. Complete blood count (CBC), chemistry and lactate dehydrogenase (LDH) tests were repeated before each cycle. CT of neck, chest, abdomen and pelvis were repeated every two cycles. Bone marrow aspiration and/or biopsy was repeated after second cycle only if marrow is involved before starting the study protocol.

Pathology

Pathological assessments of MDR and Bcl-2 expressions were done for only 40 patients with available pathological material using antihuman monoclonal mouse antibodies. Bcl-2 antibody was provided in liquid form as tissue culture supernatant in 0.05 mol/L concentration, pH 7.6 with 0.015 mol/L sodium azide as a preservative (Dako, code no M0887). Also, P-glycoprotein expression was detected by immunohistochemistry using antihuman monoclonal mouse antibody provided in liquid form with concentration of 0.1 mg/ml with 0.1 % sodium azide preservative (Dako, code no M3527).

Interpretation of the immunostaining reaction

Slides were visualized under light microscopy (DAB chromogen × 100). Immunoreactivities were evaluated with a semi-quantitative method and graded as negative, low (+), moderate (++) or high (+++) immunostaining.

Response criteria (according to RECIST criteria version 1.1)

Complete response (CR) was defined as the complete disappearance of all target lesions, and all pathological lymph nodes must have decreased to <10 mm in short axis. Partial response (PR) was defined as at least 30 % decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. Progressive disease (PD) was defined as at least 20 % increase in the sum of diameters of target lesions taking as reference the smallest sum on study. Stable disease refers to disease that neither applied to PR or PD. Response evaluation was performed after the first two cycles and thereafter every two cycles in non-progressing patients.

Statistical analysis

The data were analyzed by using SPSS version 17 (SPSS Inc., Chicago, IL, USA) and subjected to descriptive analysis, while qualitative data were analyzed by chi-square test and Fisher's exact test where appropriate. Moreover, the associations of response to the chemotherapy regimen with multiple variables were demonstrated by odds ratio with 95 % confidence interval. TTP and one-year PFS were assessed using Kaplan–Meier curves, while the differences in survival distributions according to the levels of IPI status, tumor clinical staging, tumor status before enrollment, Bcl-2 and MDR expressions were evaluated via log-rank test. Multivariate analysis was performed including factors that were found to be significant predictors in univariate analysis. An α level of <0.05 was considered as significant.

Table 1 Patients' baseline characteristics

Variable	*N*	%
Gender		
Male	33	66
Female	17	34
PS		
0	5	10
1	35	70
2	10	20
B-symptoms		
Yes	15	30
No	35	70
Pathological type		
DLBL	41	82
T cell	3	6
High-grade follicular	3	6
Indolent	3	6
Pre-treatment status		
Refractory	34	68
Relapse	16	32
Tumor stage		
I	7	14
II	12	24
III	17	34
IV	14	28
IPI status		
Low	11	22
Low intermediate	21	42
High intermediate	14	28
High	4	4
MDR expression ($n = 40$)		
Negative, low	12	30
Moderate, high	28	70
Bcl-2 expression ($n = 40$)		
Negative, low	13	32.5
Moderate, high	27	67.5

PS WHO performance status, *DLBL* diffuse large B cell lymphoma, *IPI* International Prognostic Index, *Bcl-2* B cell lymphoma 2, *MDR* multidrug resistance protein

Table 2 Relation of Bcl-2 and MDR expression with tumor stage and IPS status

Variables	Bcl-2 expression			MDR expression		
	Negative to low $n = 13$	Moderate to high $n = 27$	p value	Negative to low $n = 12$	Moderate to high $n = 28$	p value
Tumor stage						
Early (I, II)	9 (69.2)	5 (18.5)	0.002	4 (33.3)	11 (39.3)	0.72
Advanced (III, IV)	4 (30.8)	22 (81.5)		8 (66.6)	17 (60.7)	
IPI status						
Low to low intermediate	9 (69.2)	18 (66.7)	0.87	9 (75)	18 (64.3)	0.5
High intermediate to high	4 (30.8)	9 (33.3)		3 (25)	10 (35.7)	

Data have been presented in n (%)

Bcl-2 B cell lymphoma 2, *MDR* multidrug resistance protein, *IPI* International Prognostic Index

Table 3 Toxicity of gemcitabine, cisplatin and dexamethasone regimen

	G1	G2	G3	G4	Treatment delay
Vomiting	11	31	8	0	0
Mucositis	3	2	0	0	0
Diarrhea	5	9	2	0	1
Neutropenia	11	9	2	1	3
Anemia	14	11	5	2	5
Thrombocytopenia	12	4	2	0	1
Renal (↑creatinine)	4	5	0	0	5
Hepatic (↑enzymes)	1	3	0	0	2
Neurotoxicity	2	1	0	0	0

Results

Fifty patients comprised the study subjects with 34 (68 %) having refractory disease, while the rest having relapsed disease at the time of enrollment following at least two lines of chemotherapy. Median follow-up period of enrolled patients was 18 months (range 12–22 months).The subjects' mean age was 42.9 years (range 19–70) with male predominance (66 %). The majority of patients had PS 1(70 %) with only 30 % of cases having B-symptoms at the time of enrollment. Diffuse large B cell lymphoma was the most frequent type encountered (82 %). Majority of the subjects (62 %) had advanced clinical stage (stage III, IV) at the time of enrollment. Regarding IPI status of studied cases, low and low–intermediate categories were more frequent (64 %). The majority of patients assessed for Bcl-2 and MDR expressions had moderate and high expressions (67.5 and 70 %, respectively) (Table 1).

Only two cases received prior three chemotherapy regimens, while the remaining cases received only two previous regimens. Most cases received R-CHOP as first-line (46/50) and DHAP (dexamethasone, high dose Ara-C, cisplatin) as second-line chemotherapy (70 %), while the rest of patients received MINE (mesna, ifosfamide, novantrone, etoposide) regimen as a second-line chemotherapy.

The relation between Bcl-2 expression and tumor stage was studied where cases with negative to low expression had more commonly early-stage disease (69.2 %), while 81.5 % of cases with moderate or high expression had advanced-stage disease ($p = 0.002$). However, no significant relation was found between MDR expression and tumor stage. In addition, no significant relation was found between Bcl-2 or MDR expressions with IPI status (Table 2).

Toxicity

Overall, chemotherapy regimen in our study was well tolerated. Most patients experienced either G1 or G2 toxicity, while only three patients had grade 4 toxicity, i.e., one with neutropenia, two with anemia. Some patients had delay of their treatment mainly due to anemia (five patients), renal toxicity (five patients) or neutropenia (three patients) (Table 3).

Response to chemotherapy

Sixteen (32 %) cases responded to the treatment with 7(14 %) showing CR (mean response duration 12.5 months, range 3–22 months), while 9 (18 %) showing PR (mean response duration 5.2 months, range 2–8 months) and 52 % of cases having clinical benefit from the treatment, i.e., responsive (32 %) and stationary cases (20 %). Cases with early clinical stage (OR = 4.6, 95 % CI 1.3–16.4, $p = 0.02$), low to low intermediate IPI status (OR = 6.2, 95 % CI 1.2–31.7, $p = 0.03$), negative to low Bcl-2 (OR = 6.4, 95 % CI 3.3–96.7, $p = 0.02$) and MDR (OR = 18, 95 % 1.4–28.9, $p = 0.002$) expression were significantly more likely to respond to treatment (Table 4). Relapsed cases had better response to treatment than cases refractory to second-line chemotherapy (43.7 vs. 25 %,

Table 4 Subjects' response to GDP treatment versus tumor status, clinical staging, IPI status, MDR and BCL-2 expression

	Response	OR	95 % CI	*p* value
Tumor status				
Refractory/relapsed	9/7	0.46	0.13–1.6	0.22
Clinical staging				
Early (I, II)/advanced (III, IV)	10/6	4.6	1.3–16.4	0.02
IPI status				
Low to low intermediate/high intermediate to high	14/2	6.2	1.2–31.7	0.03
MDR*				
Negative to low/moderate to high	7/5	6.4	1.4–28.9	0.02
Bcl-2*				
Negative to low/moderate to high	9/3	18	3.3–96.7	0.0008

OR odd ratio, *CI* confidence interval, *GDP* gemcitabine, dexamethasone, and cisplatin, *Response* response to GDP, i.e., complete and partial response, data are presented in numbers, *Bcl2* B cell lymphoma 2, *MDR* multidrug resistance protein, *IPI* International Prognostic Index

* Forty patients have been considered for MDR and Bcl-2 expression analysis

respectively); however, the difference was not statistically significant ($p = 0.22$) (Table 4). Multivariate analysis of factors predicting response to treatment in univariate analysis was performed where clinical stage (p value 0.001), BCL2 expression (p value 0.017) and MDR expression (p value 0.048) were found to be independent predictors of response, while IPI status was not (p value 0.309).

Survival patterns

The Kaplan–Meier survival estimates showed that the median TTP and 1-year PFS of the studied cases were 2 months (95 % CI 0.95–3.1 months) and 31.3 %, respectively. The mean TTP was 15.1 months (range 5–25 months) in patients with CR in contrast to 9 months (range 4–15) in patients with PR.

Log-rank test showed significant difference of TTP and 1-year PFS according to (a) Bcl-2 expression, i.e., negative and low intermediate versus high intermediate and high, $p = 0.04$, (b) tumor status before treatment, i.e., relapse versus refractory, $p < 0.0001$, and (c) tumor stage, i.e., early versus advanced, $p < 0.0001$(Table 5; Figs. 1, 2). Noteworthy, 1-year PFS was 0 % in refractory versus 78 % in relapsed cases and 19 % in cases with moderate/high versus 61 % in negative/low Bcl-2 expression. Meanwhile, no significant difference in TTP and 1-year PFS according to MDR expression ($p = 0.14$) or IPI status ($p = 0.08$) (Table 5; Figs. 1, 2). By multivariate analysis incorporating clinical stage, tumor status before treatment and BCL2 expression, only clinical stage remained predictor of TTP and 1-year PFS (p value 0.006).

Discussion

In the present study, we evaluated the efficacy and toxicity of gemcitabine given in low-dose fixed-rate infusion

Table 5 Relation of TTP and 1-year PFS with tumor status, clinical staging, IPI status, MDR and Bcl-2 expression

Variable	Median TTP*	95 % CI	1-year PFS (%)	95 %CI	*p* value
Tumor status					
Refractory	2	1.6–2.4	0	0	<0.0001
Relapsed	NR	NA	78	54–99.8	
Tumor stage					
Early	NR	NA	71.4	47.8–95.1	<0.0001
Advanced	2	1.3–2.7	7.7	0–20.4	
IPI status					
Low, low intermediate	2	2-NA	39	19.6–58.2	0.08
High intermediate, high	2	1–3	15	0–35	
MDR expression					
Negative to low	10	2-NA	48.6	19.6–77.6	0.14
Moderate to high	2	1.4–2.6	25	9–45	
Bcl-2 expression					
Negative to low	NR	NA	61	33.5–87.7	0.004
Moderate to high	2	1.4–2.6	19	3.9–33.2	

p value by log-rank test

CI confidence interval, *NR* not reached, *NA* not available, *Bcl-2* B cell lymphoma 2 protein, *MDR* multidrug resistance protein, *IPI* International Prognostic Index, *PFS* progression-free survival

* Median time to disease progression is in months

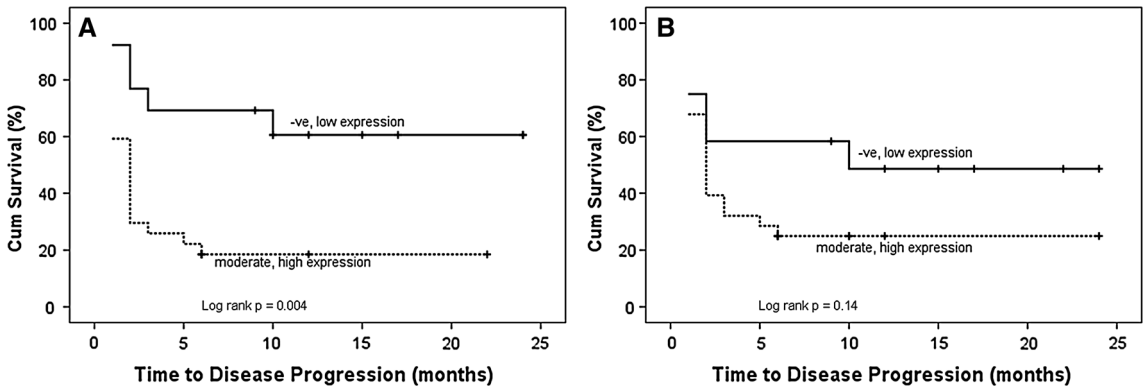

Fig. 1 Kaplan–Meier survival analysis ($n = 40$). **a** B cell lymphoma 2 (Bcl-2) expression and time to disease progression. **b** Multidrug resistant (MDR) gene expression and time to disease progression (in univariate analysis)

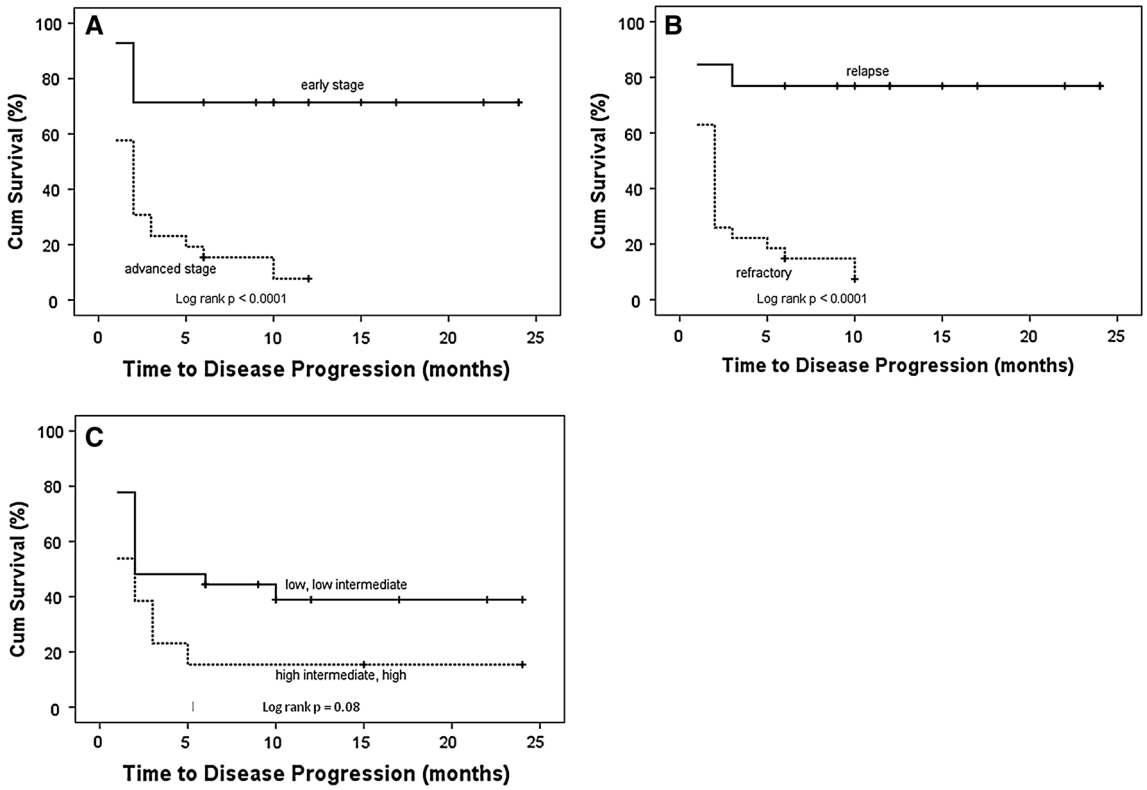

Fig. 2 Kaplan–Meier survival analysis ($n = 50$). The relation of time to disease progression with **a** tumor stage, **b** tumor status before treatment, **c** International Prognostic Index (IPI) (in univariate analysis)

together with cisplatin and dexamethasone in 50 patients with resistant NHL who were refractory or relapsed after at least two lines of chemotherapy. In addition, we evaluated the prognostic value of MDR and Bcl2 expression in this group of patients.

The overall response rate (ORR) to chemotherapy regimen in the present study is lower than that reported from other studies that used gemcitabine, cisplatin and dexamethasone combination. For example, the ORRs in the studies of Fan et al. and Ng et al. were 58.3 and 79 %, respectively. The first study recruited 24 patients who had previously received at least one chemotherapy regimen, while in the second study, higher doses of cisplatin (100 mg/m^2/cycle) and steroid (methylprednisolone 1,000 mg on days 1–5) were given. These differences may account for the higher response rates in these studies [13, 14].

Emmanouilides et al. explored the efficacy of the same chemotherapy regimen used in our study in 22 patients with relapsed Hodgkin's and non-Hodgkin's lymphoma

with 45 % ORR. However, incorporation of patients with Hodgkin lymphoma and the small number of patients may make the comparison inconclusive [15]. In addition, most cases in the present study received DHAP (including cisplatin and dexamethasone) as second-line treatment, which may explain lower response rate.

The principal toxicities from chemotherapy regimen in the present study were vomiting and hematological toxicity (mostly grade 1 and 2). In the study of Emmanouilides et al. [15] who explored the same chemotherapy regimen, higher frequency of grade 4 hematological toxicities was described (thrombocytopenia 41 %, neutropenia 18 %), which may be related to accrual of more heavily pretreated group in this study with a median number of four previous chemotherapy regimens. Similarly, greater proportions of grade 3/4 toxicities were observed in the studies of Fan et al. [13] and Ng et al. [14] Different treatment schedule of gemcitabine in the first and greater doses and different schedule of chemotherapy in the second study may account for higher grade 3/4 toxicities.

B cell lymphoma 2 protein expression has been found in 44–55 % of aggressive lymphomas according to reports from several studies that evaluated previously untreated patients [11, 12, 16]. However, moderate/high Bcl-2 expression was found in 67.5 % of patients in our study, which may be related to selection of only chemotherapy-resistant cases.

In the present study, subjects with negative to low Bcl-2 expression were more likely to respond to treatment than those with moderate to high expression. The prognostic significance of Bcl-2 protein expression and Bcl-2 gene rearrangement in diffuse large cell lymphomas (DLCL) is controversial in different studies. Wilson et al. [17] found no significant association between Bcl-2 expression and PFS or OS. Other studies have displayed that the DFS for patients with tumors expressing Bcl-2 was significantly poorer [11, 12, 16].

The available evidence suggests that MDR expression is relatively low in untreated patients (10–20 % of lymphomas positive), but increases in patients with recurrent disease (50–70 % positive) [18]. However, in our study, moderate/high expression has been detected in 70 % of cases in the initial pathological specimen. This may be related to selecting patients that has been found to be resistant to chemotherapy (intrinsically resistant cases).

Several studies reported that MDR expression is correlated with poor response to chemotherapy [18–20]. In addition, Yuen and Sikic [18] reported worse survival in those with MDR expression. We have displayed a significant relationship between MDR expression status and response to chemotherapy in univariate analysis only. However, no significant relation was found between MDR expression status and TTP neither in univariate nor multivariate analyses. This may be explained by the small number of patients assessed for MDR expression.

The present study has some limitations; first, Bcl-2 and MDR expressions were assessed in only 40 patients which may limit proper evaluation of their prognostic value. Second, rituximab was not used in second-line chemotherapy regimens given to recruited patients due to financial restrictions at our institute. Third, the majority of recruited patients received DHAP chemotherapy regimen as a second line (containing cisplatin and dexamethasone), which may explain the low response rate in our study, suggesting that the chemotherapy regimen used in our study should be explored in patients not previously treated with cisplatin containing regimens.

In conclusion, chemotherapy in the present study was well tolerated, but with relatively low ORR. However, it can provide reasonable efficacy in selected group of patients. Early clinical stage, low to low intermediate IPI status, negative to low Bcl-2 were independent predictors of response to chemotherapy, while clinical stage was the only independent predictor of TTP and PFS.

Conflict of interest The authors have declared no conflicts of interest.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics. CA Cancer J Clin. 2007;57(1):43.
2. Sweetenham J. Diffuse large B-cell lymphoma: risk stratification and management of relapsed disease. Hematology. 2005;1:252–9.
3. Smith MR, Joshi I, Jin F, et al. Enhanced efficacy of gemcitabine in combination with anti CD-20 against CD-20+ non-Hodgkin lymphoma cell lines. BMC Cancer. 2005;5:103.
4. Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer. 2004;101(8):1835–42.
5. Veltkamp S, Beijnen J, Schellens J. Prolonged versus standard gemcitabine infusion: translation of molecular pharmacology to new treatment strategy. Oncologist. 2008;13(3):261–76.
6. Borst P, Elferink RO. Mammalian ABC transporters in health and disease. Annu Rev Biochem. 2002;71:537–92.
7. Duhem C, Ries F, Dicato M. What does multidrug resistance (MDR) expression mean in the clinic? Oncologist. 1996;1(3):151–8.
8. Xu YC, Lin YM, Zhang FC. The relationship between abnormal MDR gene expression and chemotherapy response in lymphoid malignancies. Zhonghua Zhong Liu Za Zhi. 2006;28(5):353–6.
9. Gascoyne R, Hoskins P, Connors J, et al. A study of clinical and pathologic variables affecting disease specific survival (DSS) of patients with diffuse large cell lymphoma treated with MACOP-B or VACOP-B—univariate and multivariate analysis. Proc Am Soc Clin Oncol. 1999;13:374a.
10. Küppers R, Dalla-Favera R. Mechanisms of chromosomal translocations in B cell lymphomas. Oncogene. 2001;20(40):5580–94.
11. Hermine O, Haioun C, Lepage E, et al. Prognostic significance of bcl-2 protein expression in aggressive non-Hodgkin's lymphomas. Blood. 1996;87(1):265–72.

12. Gascoyne RD, Adomat SA, Krajewski S, et al. Prognostic significance of Bcl-2 protein expression and Bcl-2 gene rearrangement in diffuse aggressive non-Hodgkin's lymphoma. Blood. 1997;90(1):244–51.
13. Fan Y, Huang ZY, Luo LH, et al. Efficacy of GDP regimen (gemcitabine, dexamethasone, and cisplatin) on relapsed or refractory aggressive non-Hodgkin's lymphoma: a report of 24 cases. Ai Zheng. 2008;27(11):1222–5.
14. Ng M, Waters J, Cunningham D, et al. Gemcitabine, cisplatin and methylprednisolone (GEM-P) is an effective salvage regimen in patients with relapsed and refractory lymphoma. Br J Cancer. 2005;92(8):1352–7.
15. Emmanouilides C, Colovos C, Pinter-Brown L, et al. Pilot study of fixed-infusion rate gemcitabine with cisplatin and dexamethasone in patients with relapsed or refractory lymphoma. Clin Lymphoma Myeloma Leuk. 2004;5(1):45–9.
16. Hill ME, MacLennan KA, Cunningham DC, et al. Prognostic significance of bcl-2 expression and bcl-2 major breakpoint region rearrangement in diffuse large cell non-Hodgkin's lymphoma: a British national lymphoma investigation study. Blood. 1996;88(3):1046–51.
17. Wilson WH, Teruya-Feldstein J, Fest T, et al. Relationship of p53, bcl-2, and tumor proliferation to clinical drug resistance in non-Hodgkin's lymphomas. Blood. 1997;89(2):601–9.
18. Yuen AR, Sikic BI. Multidrug resistance in lymphomas. J Clin Oncol. 1994;12(11):2453–9.
19. Yang X, Jia L, Wei L, et al. Correlation of expression levels of multidrug resistance gene 1 (mdr1) mRNA, multidrug resistance-associated protein (MRP), and P-glycoprotein (P-gp) with chemotherapy efficacy in malignant lymphomas. Zhonghua Yi Xue Za Zhi. 2002;82(17):1177–9.
20. Li L, Su LP, Ma L, et al. Expression and significance of P-gp/mdr1 mRNA, MRP and LRP in non-Hodgkin's lymphoma. Zhonghua Zhong Liu Za Zhi. 2009;31(3):199–202.