Dexamethasone, Etoposide, Ifosfamide, and Cisplatin as Second-Line Therapy in Patients with Aggressive Non-Hodgkin's Lymphoma

Nissim Haim, M.D.[1]
Menachem Ben-Shahar, M.D.[1]
David Faraggi, Ph.D.[2]
Avital Tsuri-Etzioni[2]
Michelle Leviov, M.D.[1]
Ron Epelbaum, M.D.[1]

[1]Department of Oncology, Rambam Medical Center and Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

[2]Department of Statistics, University of Haifa, Haifa, Israel.

The authors wish to thank Mrs. M. Perlmutter for her assistance in the preparation of this article.

Address for reprints: Dr. Nissim Haim, Department of Oncology, Rambam Medical Center, POB 9602, Haifa 31096, Israel.

Received February 20, 1997; revision received May 21, 1997; accepted May 21, 1997.

BACKGROUND. This study analyzed the long term results of a combination of dexamethasone, etoposide, ifosfamide, and cisplatin (DVIP) used at the study center as standard second-line combination therapy in patients with aggressive non-Hodgkin's lymphoma (NHL) after prior exposure to doxorubicin.

METHODS. All drugs were given intravenously for 4 consecutive days. The maximum daily doses of etoposide, ifosfamide, and cisplatin were 75 mg/m^2, 1200 mg/m^2, and 20 mg/m^2, respectively. The dexamethasone dose was 20 mg twice daily. Cycles were repeated every 3 weeks.

RESULTS. Fifty-six patients were included in the study. Partial response was noted in 18 patients (32%) and complete response (CR) in 18 patients (32%). Pretreatment factors that predicted CR were CR with prior therapy (CR in 17 of 34 in patients with a recurrence vs. 1 of 21 in patients with primary refractory NHL) and age (CR in 12 of 25 patients age $\leq$ 65 years vs. 6 of 31 patients age $>$ 65 years). Median time to treatment failure (TTF) and median survival were 11.5 months and 30 months, respectively, for patients with a CR and 3.5 months and 8 months, respectively, for all patients. Five patients (9%) remained disease free for $>$ 24 months. By multivariate analysis, age was the only independent prognostic factor for TTF, whereas age, serum lactate dehydrogenase, and number of extranodal sites were independent predictors for survival. Myelosuppression (median granulocyte nadir and median platelet nadir of 350/mm^3 and 77,000/mm^3, respectively) was the major toxicity. There was one possible drug-related death associated with myelosuppression.

CONCLUSIONS. DVIP is a relatively safe salvage combination therapy in patients with aggressive NHL. Response to first-line therapy and age are the most important predictors for prognosis after the administration of DVIP. This regimen is highly active in patients with recurrent NHL, but relatively ineffective in patients with primary refractory NHL. ***Cancer*** **1997;80:1989–96.**
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KEYWORDS: non-Hodgkin's lymphoma, salvage chemotherapy, etoposide, ifosfamide, cisplatin.

At least 50% of patients with advanced intermediate grade or high grade non-Hodgkin's lymphoma (NHL) cannot be cured with frontline therapy using doxorubicin-containing drug combinations.[1] Most patients who fail to obtain a complete response (CR) with first-line therapy (primary refractory lymphoma) or who recur after achieving CR (recurrent lymphoma) eventually will be candidates for salvage therapy.

Because etoposide, ifosfamide, and cisplatin have been used widely in the treatment of patients with refractory lymphoma,[2] and

because the combination of these three drugs (VIP) was found to be active in patients with refractory testicular carcinoma,[3] it appeared reasonable to test a combination of these three drugs in the salvage therapy of patients with NHL. In 1989, the authors initiated a Phase II trial in patients with primary refractory and recurrent NHL that tested a modified VIP regime to which dexamethasone was added (DVIP). The preliminary results of this trial were reported previously.[4] This report focuses on the long term results and identification of prognostic factors in an unselected group of patients with histologically aggressive NHL who received DVIP as a second-line combination therapy after prior exposure to doxorubicin.

MATERIALS AND METHODS

Patient Eligibility

All patients had a histologically confirmed diagnosis of intermediate grade or large cell immunoblastic NHL according to the working formulation.[5] They had to have recurrent or primary refactory disease after prior therapy that was comprised of only one regimen and included doxorubicin. No age limit was instituted. Other eligibility criteria included a World Health Organization (WHO) performance status of 0–3, normal serum creatinine, an interval of at least 3 weeks since last chemotherapy, and no prior therapy with etoposide, ifosfamide, or cisplatin. Patients with central nervous system (CNS) involvement were eligible unless the CNS was the only known site of disease. Because of the vigorous hydration, adequate cardiac function was required. The protocol was approved by the Institutional Ethics Committee and informed consent was obtained from all patients.

Pretreatment Evaluation

Baseline investigations for all patients included a complete history and physical examination, complete blood count, blood chemistry (including lactate dehydrogenase [LDH]) and urinalysis. Baseline staging procedures included computerized tomography (CT) scan of the chest in 50 of the 56 patients, CT scan of the abdomen and pelvis in 54 patients, ^{67}Ga scan in 30 patients, and bone marrow biopsy in 33 patients.

Treatment Plan

Patients were hospitalized and all drugs were given over 4 consecutive days. The DVIP schedule is shown in Table 1. Mesna uroprotection (maximal daily dose, 720 mg/m^2) was given intravenously (i.v.) in three divided doses; the first dose was given in a mixture with ifosfamide; and the second and third doses were given i.v. in 150 mL of saline over 15 minutes, 4 hours, and 8 hours, respectively, after the beginning of the ifosfamide infusion. Prior to cisplatin administration, patients received hydration with 1 L of saline over 1.5 hours. Furosemide, 40 mg, was given by i.v. bolus before cisplatin and after the end of ifosfamide administration. Hydration with 2 L of saline was continued over a period of 6 hours after the end of ifosfamide administration.

Full doses of the 3 myelotoxic drugs were given in the first cycle of DVIP to patients age $\leq$ 60 years with a WHO performance status of 0–2 and in whom the interval between DVIP and the last chemotherapy was $\geq$ 6 months. Patients age $\leq$ 60 years who did not fulfill these criteria and those age 60–70 years received 75% of etoposide, ifosfamide, and cisplatin during the first cycle. Patients age $>$ 70 years received 60% of the myelotoxic drug doses during the first cycle. Only 40% of full doses of the myelotoxic drugs were given during the first cycle to patients with initial neutrophil counts of $<$1500/mm^3 and/or platelet counts of $<$100,000/mm^3, which were not related to the myelosuppressive effect of prior therapy. Cycles were repeated on Day 22 if the neutrophil count was $\geq$1500/mm^3 and the platelet count was $\geq$100,000/mm^3. Doses of all 3 myelotoxic agents were reduced by 25% in subsequent courses if neutropenic fever that required i.v. administration of antibiotics developed, and/or if the leukocyte nadir was $<$1000/mm^3 and/or the neutrophil nadir was $<$ 500/mm^3 and/or the platelet nadir was $<$ 30,000/mm^3. Hematopoietic colony–stimulating factors (CSFs) were not used routinely.

Laboratory Monitoring and Evaluation of Response

Clinical evaluation and blood chemistry were evaluated before each cycle. A complete blood count was performed on Days 1, 8, and 15 of each cycle, and urinalysis was performed on each day of treatment. Response to therapy was evaluated according to standard criteria.[6] The first detailed evaluation usually was performed after the second DVIP cycle, unless the clinical evaluation showed clear evidence of tumor progression after the first cycle.

Duration of DVIP and Consolidation Therapy

Responders received two cycles after the maximal response was documented but not less than six cycles unless consolidation with high dose chemotherapy (HDCT) was given. HDCT was not an integral of this trial because the role of consolidation with HDCT was unclear at the time this study was initiated. Generally, this approach was considered in patients age $<$ 60 years who achieved CR or good partial response (PR) with DVIP. DVIP was withdrawn if disease progression was noted.

TABLE 1
Schedule of DVIP Regimen Given Every 3 Weeks

Drug	Daily dose	Mode of administration	Days
Cisplatin	20 mg/m^2	IV in saline (250 mL) over 30 mins	1–4
Etoposide	75 mg/m^2	IV in saline (500 mL) over 1 hr	1–4
Ifosfamide	1200 mg/m^2	IV in saline (300 mL) over 2 hrs	1–4
Dexamethasone	40 mg	IV bolus, 20 mg before cisplatin and 20 mg after ifosfamide infusion	1–4

DVIP: dexamethasone, etoposide, ifosfamide, and cisplatin; iv: intravenously.
These doses of cisplatin, etoposide, and ifosfamide are the maximum daily doses.

Data Analysis

Survival and time to treatment failure (TTF), in which failure is tumor progression or death in a patient, were measured from the beginning of DVIP treatment. Because consolidation with HDCT may increase TTF and survival in patients with recurrent NHL,[7] the four patients who received HDCT were censored at the onset of that therapy. Calculations of survival and TTF were performed according to the method of Kaplan and Meier.[8] Factors that were assessed for their influence on the CR rate, TTF, and survival included age, gender, performance status, presence of B symptoms, histology (intermediate grade vs. high grade), hemoglobin level, presence of bulky disease ($\geq$10 cm), serum LDH, number of extranodal sites, number of involved sites, response to prior therapy, TTF from the beginning of prior chemotherapy, and average dose intensity (DI) of the 3 myelotoxic drugs of DVIP during the first cycle and during the first 3 and first 6 cycles. Calculation of DI was performed according to the method of Hryniuk and Bush.[9] The log rank test[10] was used to evaluate binary prognostic factors in univariate analysis. Multivariate analysis was performed on both TTF and survival using the Cox proportional hazards regression model.[11] The influence of prognostic factors on the response rate and on the long term disease free survival rate was examined by Fisher's exact test.[12] The logistic model[12] was used in a multivariate analysis of CR.

RESULTS

Patients

Between November 1989 and October 1995, 65 patients were eligible for this study. Nine of these patients did not enter the study for the following reasons: five received other types of salvage therapy, two were treated outside the study center, one refused to enter the protocol, and one was excluded after the first day of therapy due to an allergic reaction to ifosfamide. Characteristics of the 56 patients included in the study are shown in Table 2. The median age of the patients was 68 years. Approximately 46% of the patients had a poor performance status (WHO Grades 2 and 3), 39% had B symptoms, 25% had bulky disease, and 64% had elevated serum LDH. Approximately 38% had not achieved CR with front-line therapy.

Treatment

All patients completed therapy and were evaluable for response and toxicity. The number of DVIP cycles ranged between one and seven (median, 4 cycles) and the total number of cycles given was 204. CSFs were given to 13 patients over 30 cycles. DVIP was discontinued in 24 patients after maximal response was documented. In the remaining 32 patients, DVIP was given until treatment failure was noted. Consolidation with HDCT after DVIP was given to four of eight patients to whom such an approach was offered. Two of these four patients responded to DVIP with a CR and two with a PR. HDCT was not given to the remaining four patients due to patient refusal or lack of cooperation.

Response

CR was observed in 18 patients (32%) (95% confidence interval [CI], 20–44%) and PR in 18 patients (32%), for a total response rate of 64% (95% CI, 52–77%). Seven patients (13%) had stable disease and tumor progression was noted in 13 patients (23%). Response to DVIP usually was evident after the second cycle. Factors associated with a significantly higher CR rate included CR with prior therapy (17 of 34 patients [50%] in recurrent NHL vs. 1 of 21 patients [5%] in primary refractory NHL; $P = 0.0003$), younger age (12 of 25 patients, [48%] in patients age $\leq$ 65 years vs. 6 of 31 patients [19%] in patients age $>$ 65 years, $P = 0.042$], and longer TTF with prior therapy (12 of 23 patients [52%] in patients with TTF $>$ 12 months vs. 6 of 33 patients [18%] in patients with shorter TTF; $P = 0.01$). A logistic regression model revealed that CR with prior therapy and

TABLE 2
Patient Characteristics

Male/female	27/29
Median age (yrs) (range)	68 (21–89)
WHO performance status	
0 + 1	30
2 + 3	26
B symptoms	
Present	22
Absent	34
Histology [WF]	
Intermediate grade	26
Large cell immunoblastic	16
Diffuse, large cell, unclassified	14
Greatest dimension ≥10 cm	
Yes	14
No	42
Serum LDH	
Normal	20
Elevated	36
Extranodal disease	
Yes	32
No	24
Prior chemotherapy	
CHOP	51
MACOP-B	5
Prior radiotherapy	
Yes	10
No	46
Prior CR	
Yes	34
No	21
Unknown	1
Median interval from last chemotherapy (mos) (range)	6.5 (1–58)

WHO: World Health Organization; WF: working formulation; LDH: lactate dehydrogenase; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; MACOP-B: methotrexate with leucovorin rescue, doxorubicin, cyclosphosphamide, vincristine, prednisone, and bleomycin; CR: complete response.

age ≤ 65 years were independent factors for CR (P = 0.0053 and P = 0.0358, respectively).

The overall response rate in patients with recurrent NHL was significantly higher than in primary refractory NHL (27 of 34 patients, [79%] vs. 9 of 21 patients, [43%]; P = 0.0087).

Time to Treatment Failure

Median TTF was 3.5 months for the entire group, 11.5 months for patients with a CR, 3.8 months for patients with a PR, and 1.0 months for nonresponders. Parameters that were significantly correlated with longer TTF by univariate analysis (Table 3) included age, performance status, constitutional symptoms, CR with prior therapy, TTF from first therapy, and dose intensity during the first cycle and during the first three and first six cycles. Multivariate analysis demonstrated that age was the only significant independent factor for a longer TTF (P = 0.006).

Survival

The median survival time was 8 months for the entire group, 30 months for patients with a CR and 8 months for patients with a PR. The actuarial 2-year survival for the entire group was 25%. Significant associations between various parameters and survival by univariate analysis are shown in Table 3. By multivariate analysis, only 3 factors remained as having significant influence on survival: age (P = 0.0014), serum LDH (P = 0.0029), and number of extranodal sites (P = 0.0209).

Follow-up and Long Term (≥ 24 Months) Disease Free Survival

Except for 1 patient who was alive with no evidence of disease at 11+ months after DVIP and HDCT at last follow-up, all the other patients were available for analysis of long term disease free survival. Thirty-nine of the 55 patients died with lymphoma, 11 were alive with progressive lymphoma, and 5 (9%) remained disease free for > 24 months. Three of these five were alive at 46+, 68+, and 75+ months after treatment with DVIP alone. These three patients had achieved CR with first-line therapy and recurred after 19, 22, and 11 months, respectively, from the onset of therapy. Another patient who achieved CR with DVIP and then received HDCT was disease free at 51+ months. The fifth patient achieved PR with DVIP and then obtained a CR with HDCT. She was disease free at 37+ months from the beginning of DVIP.

The rate of long term disease free survival was significantly higher in patients who achieved a CR with DVIP (4 of 17 patients, [24%] vs. 1 of 38 patients [3%] in noncomplete responders, P = 0.028). The long term disease free survival rate also was higher in patients with recurrent lymphoma (5 of 33 patients [15%] vs. none of the 21 patients with primary refractory lymphoma) and in younger patients (4 of 24 patients [17%] in patients age ≤ 65 years vs. 1 of 31 patients [3%] in patients age > 65 years). However, these differences were not statistically significant.

Toxicity

Myelosuppression was the major toxicity encountered (Table 4). WHO Grade 4 granulocytopenia developed in 37 patients (66%) during at least 1 cycle. In all, 30 episodes of granulocytopenic fever requiring hospitalization and the i.v. administration of antibiotics developed in 26 patients (46% of patients and 15% of all cycles). Three of these episodes were associated with documented sepsis. The median duration of i.v. antibiotic therapy was 5 days. Pronounced neutropenia developed with all dose levels of DVIP. Among 52 patients who received the first cycle without CSFs, neutropenic fever developed during the first cycle in 4 of

TABLE 3
Prognostic Factors for Time to Treatment Failure and Survival

Factor (no. of patients)	Median TTF (mos)	*P* value	Median survival (mos)	*P* value
Age (yrs)				
≤65 (25)	6.0	0.006	18.0	0.002
>65 (31)	2.3		5.0	
WHO PS				
0 + 1 (30)	5.0	0.0002	11.0	0.0023
2 + 3 (26)	1.6		5.0	
B symptoms				
Present (22)	1.9	0.0009	4.3	0.0178
Absent (34)	5.0		9.0	
Serum LDH				
Normal (20)	4.0	NS	16.0	0.0038
Elevated (36)	2.6		5.0	
No. of extranodal sites				
0 + 1 (44)	3.5	NS	8.0	0.0114
≥2 (12)	2.0		4.0	
Prior CR				
Yes (34)	5.5	0.0062	9.0	0.0343
No (21)	2.0		5.0	
TTF from first therapy				
≤12 mos (33)	2.3	0.0348	5.0	NS
>12 mos (23)	6.0		11.0	
DI during first cycle				
<75% (27)	2.0	0.0184	5.0	0.021
≥75% (29)	5.0		16.0	
DI during first 3 cycles				
≤60% (18)	2.0	0.0004	5.0	0.0011
>60% (17)	6.0		46.0	
DI during first 6 cycles				
≤60% (9)	2.5	0.0011	6.0	0.0136
>60% (8)	14.5		46.0	

TTF: time to treatment failure; WHO: World Health Organization; PS: performance status; LDH: lactate dehydrogenase; CR: complete response; DI: dose intensity; NS: not significant.

8 patients treated with full doses, in 5 of 20 patients treated with a 25% dose reduction, in 9 of 20 patients treated with a 40% dose reduction, and in 1 of 4 patients treated with a 60% dose reduction. The rate of neutropenic fever in patients age ≤ 65 years (11 of 25 patients [44%]) was similar to that in patients age > 65 years (15 of 31 patients [48%]). Platelet transfusions were required in 4 patients (7%), 2 of whom developed life-threatening bleeding. Red blood cell transfusions were given during therapy to 23 patients (41%).

There was one possible drug-related death. After the first cycle, this patient developed neutropenic fever, severe thrombocytopenia, and gastrointestinal bleeding and died with rapidly progressing disease.

Due to myelosuppression, drug doses were reduced during the second cycle in 20 of 42 patients (48%) who received ≥ 2 cycles.

Nonhematologic toxicity was moderate. WHO Grades 2 and 3 alopecia developed in 47 of 52 patients (90%). Alopecia was nonevaluable in four patients due to preexisting alopecia from previous chemotherapy. WHO Grades 2 and 3 nausea and emesis occurred in 23 patients (41%) but was less common after serotonin antagonists were introduced. Other side effects included WHO Grades 2 and 3 mucositis in 16 patients (29%), mild to moderate paresthesia in 11 patients (20%), mild ototoxicity in 2 patients (4%), transient elevation of serum creatinine to values between 1.4–2.3 mg/dL (upper normal range, 1.3 mg/dL) in 10 patients (18%), and transient microscopic hematuria (5–20 red blood cells/high-power field) in 10 patients (18%).

DISCUSSION

In the largest series to date of salvage chemotherapy in patients with NHL reported from the M. D. Anderson Cancer Center,[13–16] the response rate ranged from 55–69% and the CR rate from 24–48%. Salvage chemotherapy trials in patients with NHL that included the three drugs comprising the VIP regimen were reported

TABLE 4
Myelotoxicity of DVIP: 204 Courses Given to 56 Patients

Median nadir counts	
Leukocytes/mm^3	1000
Granulocytes/mm^3	350
Platelets/mm^3	77.000
Hb (g/dL)	8.2
WHO Grade 4 (no. of patients)	
Leukopenia	23 (41%)
Granulocytopenia	37 (66%)
Thrombocytopenia	7 (13%)
Hospitalization due to granulocytopenic fever	
No. of patients	26 (46%)
No. of courses	30 (15%)
Platelet transfusions	
No. of patients	4 (7%)
No. of courses	4 (2%)
Red blood cell transfusions	
No. of patients	23 (41%)

DVIP: dexamethasone, etoposide, ifosfamide, and cisplatin; Hb: hemoglobin; WHO: World Health Organization.

by two other groups of investigators.[17,18] Nichols et al.[17] used the VIP combination and found an objective response in 8 of 22 patients (36%) patients. Goss et al.[18] recently reported a series of 36 patients treated with a combination of dexamethasone, ifosfamide, cisplatin, and etoposide. The objective response rate was 67% and the CR rate was 23%. Because patient selection significantly can influence the results of salvage therapy in patients with lymphoma, it is difficult to compare the present results with those reported by others. Nevertheless, the relatively high response rate (64% with a 32% CR) obtained in the current trial cannot be attributed to patient selection bias. This series was comprised of the majority (86%) of all eligible patients treated at the study center and included a substantial proportion of patients with a poor prognosis. It is noteworthy that the median age in this series (68 years) was higher than in most other reported series, including the large series from M. D. Anderson in which the median age was $<$ 60 years.[14–16]

Several disease and patient characteristics known to be risk factors in the front-line treatment of patients with aggressive NHL also were found to be prognostic factors in this study. Of these characteristics, age was the most important risk factor; age was an independent factor for achieving a second CR and was the most important independent factor for TTF and survival by multivariate analysis. It is interesting to note that the three pretreatment parameters found in the current study to be independent prognostic factors for survival (i.e., age, serum LDH, and number of extranodal sites) are independent prognostic factors for survival in the front-line therapy of patients with aggressive lymphoma according to the International Index.[19]

The current trial also demonstrated that the response to front-line therapy was the most significant independent factor for achieving a second CR. The authors found a relatively high CR rate in patients with recurrent NHL (17 of 34 patients [50%]), indicating that DVIP has a curative potential in this group of patients. In contrast, only 1 of 21 patients with primary refractory NHL responded with CR. Nevertheless, the overall response rate of 43% in patients with primary refractory lymphoma indicates that DVIP can be used as a palliative therapy in these patients. It also suggests that this regimen may be noncross-resistant with doxorubicin-containing combinations. An association also was found between TTF after first-line therapy and response to second-line therapy. Longer TTF ($>$12 months) after first-line therapy was associated with a higher CR rate and, by univariate analysis, predicted longer TTF with DVIP. An association between response to front-line therapy and to salvage therapy also has been reported by other investigators.[13,18,20–22] However, Velasquez et al.[14] failed to show a significant difference in the CR rate with high dose cytarabine and dexamethasone between NHL patients who had achieved CR with front-line therapy and those who had not achieved CR with prior therapy.

Although conventional dose chemotherapy can induce CR in $>$ 20% of patients with aggressive NHL, durable remissions rarely are reported in these patients. In the current study, 5 patients (9%) achieved long term disease free survival. As might be anticipated, the probability of attaining durable remission was related to the response to salvage therapy and to first-line therapy. Long term disease free survival was achieved in only 1 of the 38 patients who failed to respond to DVIP with CR and was not observed in any of the 21 patients with primary refractory lymphoma. Conversely, durable remissions were observed in 4 of 17 patients who achieved CR with DVIP and in 5 of 33 patients with recurrent NHL. Durable CR also was less common in older patients (1 of 31 patients [3%] in patients age $>$ 65 years vs. 4 of 24 patients [17%] in patients age $\leq$ 65 years).

Consolidation with HDCT may increase the curability rate in patients with recurrent or refractory aggressive NHL.[7] In the current study, consolidation of response with HDCT was given to four patients, two of whom were long term disease free survivors. However, the statistical analysis of TTF and survival was not influenced by the administration of HDCT, because patients who received HDCT were censored before the onset of that treatment. The sensitivity of the disease

to conventional salvage chemotherapy is considered to be one of the major prognostic factors that predicts long term disease free survival after HDCT.[23] Therefore, the high response rate (64%) observed in this study suggests that DVIP may provide effective cytoreduction before HDCT. In patients who are resistant to first-line salvage chemotherapy (i.e., DVIP), second-line salvage chemotherapy, such as prolonged daily administration of oral etoposide[24] or mini-BEAM (carmustine, etoposide, cytarabine, and melphalan),[25] could be used to reduce tumor bulk prior to HDCT.

Generally, DVIP was well tolerated. Pronounced myelosuppression developed despite the relatively moderate drug doses, but usually was of short duration and resulted in only one treatment-related death. Nonhematologic toxicity was not dose limiting. Noteworthy was the lack of serious nephrotoxicity, which may be attributed to the vigorous hydration given during hospitalization.

The American Society of Clinical Oncology recommends primary administration of CSFs if the expected incidence of febrile neutropenia is $\geq$ 40%.[26] In the current study, febrile neutropenia developed during the first cycle in 19 of 52 patients (37%) who received the first cycle without CSFs. Furthermore, 46% of all patients developed at least 1 episode of granulocytopenic fever. Therefore, the routine use of CSFs with DVIP should be considered. This could significantly decrease the toxicity of this regimen and also could be cost-effective. Furthermore, because leukopenia was more pronounced than thrombocytopenia, dose escalation is expected to be feasible with the routine use of CSFs. DI was found to be a significant prognostic factor for TTF and survival by univariate analysis and therefore dose escalation may improve the therapeutic results of DVIP.

DVIP can be used relatively safely as a second-line combination in unselected patients with aggressive NHL if proper dose modifications are made. Response to first-line doxorubicin-containing chemotherapy and age are the most important pretreatment factors that predict prognosis after DVIP. Although this regimen induces a high response rate and may even be curative in patients with recurrent NHL, it is relatively ineffective in patients with primary refractory NHL.

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