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Short communication

Salvage therapy for non-Hodgkin's lymphoma with a combination of dexamethasone, etoposide, ifosfamide, and cisplatin*

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Summary. A total of 30 consecutive patients with refractory or relapsing non-Hodgkin's lymphoma (NHL) were treated with a combination of dexamethasone, etoposide (VP-16), ifosfamide, and cisplatin (DVIP). In all, 9 subjects (30%) showed a partial response and 10 (33%) achieved a complete response (CR) lasting from 2.5 to 24+ months. Aggressive histology, no prior therapy with VP-16, a CR to previous chemotherapy, and a treatment-free interval of >6 months prior to the present study were associated with the high CR rate. DVIP caused pronounced myelosuppression (median granulocyte nadir and median platelet nadir, 380/mm^3 and 73.000/mm^3, respectively), but no drug-related death occurred. We conclude that DVIP is an effective salvage combination, especially in aggressive NHL, that produces acceptable toxicity.

Introduction

The combination of etoposide (VP-16), ifosfamide, and cisplatin (VIP) is active in patients with recurrent germ-cell tumors [5]. Since the majority of modern chemotherapy regimens for the treatment of refractory non-Hodgkin's lymphoma (NHL) are based on the constituent drugs comprising the VIP regimen [1, 2], there is a rationale for the use of combinations that include all three of these drugs in the salvage therapy of NHL. However, the data in the literature on such drug combinations are sparse [4, 7]. Our preliminary experience with a modified VIP combination to which dexamethasone had been added (DVIP) is reported herein.

Patients and methods

Between November 1989 and December 1991, 30 consecutive patients with refractory or relapsing NHL (other than lymphoblastic and Burkitt's type) were treated with DVIP. The main characteristics of our patients are shown in Table 1. All patients had undergone prior therapy that included both Adriamycin and cyclophosphamide (CHOP in 20 cases, ProMACE/MOPP in 6 and MACOP-B in 4). Prior therapy had included more than one regimen in 9 patients, VP-16 in 9 subjects, and radiotherapy in 6 others. The median interval between the present study and the last chemotherapy treatment was 5.5 months (range, 1 month to 4.5 years).

DVIP (maximal daily doses during the first cycle) consisted of 20 mg dexamethasone $\times 2$ given i.v. on days 1–4, 75 mg/m^2 VP-16 given i.v. on days 1–4, 1,200 mg/m^2 ifosfamide given i.v. on days 1–4 (plus mesna given i.v. at 60% of the ifosfamide dose in 3 divided daily doses), and 20 mg/m^2 cisplatin given i.v. on days 1–4. During the first cycle, full doses were given only to patients aged <60 years whose performance status was 0–2 and who had received no previous extensive radiotherapy and no prior chemotherapy that had been associated with grade 4 myelotoxicity or that had been given during the last 6 months prior to the present study. In all other subjects, doses were reduced during the first cycle by 25%, 40%, or 60%. DVIP administration was repeated every 3 weeks when the WBC amounted to $\geq$4,000/mm^3 and the platelet count was $\geq$100,000/mm^3. Both the response to therapy and the resultant toxicity were evaluated according to standard WHO criteria [6]. Response was measured from the onset of therapy.

Results

All 30 patients completed the therapy and were evaluable for response and toxicity. In all, 9 subjects (30%) showed a partial response (PR) lasting 2–6 months (median, 3.5 months) and 10 patients (33%) achieved a CR lasting from 2.5 to 24+ months; 5 of the latter remain disease-free at 5+, 6+, 19+, 21+, and 24+ months, respectively. Stable disease was seen in 3 patients for 2–4 months, and tumor progression was evident in 8 subjects after the 1st cycle. The overall median survival cannot yet be fully evaluated.

Factors that were associated with the high CR rate included (a) aggressive histology (10/23 patients vs 0/7 subjects with low-grade histology), (b) no prior treatment with VP-16 (8/21 patients vs 2/9 subjects who had previously received VP-16), (c) a CR to prior chemotherapy (8/15 patients vs 2/14 subjects who had previously failed to achieve a CR), and (d) a treatment-free interval of

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Table 1. Patients' characteristics

Sex (M/F)	14/16
Median age (range)	63 (28–84) years
Performance status (grade):	
0 + 1	12
2	11
3	7
"B" symptoms:	
Present	15
Absent	15
Pathology (Working Formulation):	
Low-grade	7
Intermediate grade + high-grade	23
Extra nodal sites involved:	
Yes	14
No	16
Tumor burden:	
Maximal diameter, ⩾ 10 cm	12
Maximal diameter, <10 cm	18
Serum LDH levels:	
Elevated	19
Normal	11

>6 months (7/14 patients vs 3/16 subjects whose treatment-free interval amounted to ⩽6 months).

Myelosuppression was the major toxicity encountered. The median granulocyte, platelet, and hemoglobin nadirs were 380/mm^3, 73,000/mm^3 and 8.4 g/dl, respectively. Grade 4 granulocytopenia developed in 18 subjects (60%) during at least 1 cycle, and its median duration was 4 days (range, 2–7 days). In all, 13 episodes of granulocytopenic fever developed in 12 patients (40%); none of these episodes was associated with sepsis as proven by positive blood cultures. The median duration of hospitalization for i.v. antibiotic therapy was 5 days (range, 3–10 days). Grade 3 and 4 thrombocytopenia developed in 9 patients (30%) and was not associated with life-threatening hemorrhaging. Packed red-blood-cell (RBC) transfusions were required in 11 subjects (37%). The 1st course was associated with grade 4 myelotoxicity in 3/4 courses given at the full dose, in 5/13 cycles given at a 25% dose reduction, in 3/9 courses given at a 40% dose reduction, and in 1/4 cycles given at a 60% dose reduction.

Subtotal or total alopecia occurred in all patients, grade 2 or 3 vomiting was experienced by 20 subjects (67%), transient microscopic hematuria (5–20 RBC/high-power field) developed in 11 cases (37%), grade 2 and 3 mucositis occurred in 9 patients (30%), and mild paresthesia was noted in 3 subjects (10%). An elevation of serum creatinine values to 1.4–1.6 mg/dl (upper-normal range, 1.3 mg/dl) was observed in 5 patients (17%), but these values returned to normal levels (<1.3 mg/dl) in all cases. There was no treatment-related death.

Discussion

The present overall response rate of 63% and the CR rate of 33% indicate that DVIP is active in refractory or relapsing NHL following prior Adriamycin-containing therapy. Furthermore, since long-term remissions were seen, this regimen may be curative. Investigations of chemotherapy for refractory NHL that includes VP-16, ifosfamide, and cisplatin have been reported by two other groups of investigators. In one of these series, an objective response was noted in only 8/22 subjects (36%) [7], and in the other series, which also involved 22 patients, the overall response rate was 77% and the CR rate was 27% [4]. The largest series involving salvage chemotherapy in NHL have been those testing MIME (mitoguazone, ifosfamide, methotrexate, and VP-16) [3] and DHAP (dexamethasone, high-dose ara-C, and cisplatin) [8], which resulted in CR rates of 24% and 31%, respectively. Only 25% of the patients who achieve a CR during MIME salvage therapy may be cured [2]. Due to the small numbers of patients involved, our series cannot be compared either with the other two series in which similar combinations were used [4, 7] or with larger series.

The effect of the histological subtype of NHL on the response to salvage chemotherapy has not been conclusively determined. Whereas the MIME regimen has produced response rates in patients with aggressive histology that are higher than those obtained in cases of indolent histology [3], the response to DHAP has been independent of the histological subtype involved [8]. The present response to DVIP noted in aggressive NHL was obviously better than that observed in indolent NHL (CR, 10/23 vs 0/7 patients). Despite our use of drug doses that were lower than those given in other studies in which similar combinations were tested [4, 5, 7], we found that DVIP was associated with pronounced myelosuppression. However, toxicity, was reversible, and no drug-related death occurred. We therefore feel that the drug doses and the criteria for dose modification used in the present study were suitable for our heavily pretreated patients.

References

1. Armitage JO, Vose JM, Bierman PJ (1990) Salvage therapy for patients with non-Hodgkin's lymphoma. J Natl Cancer Inst Monogr 10: 39
2. Cabanillas F (1991) Experience with salvage regimens at the M. D. Anderson Hospital. Ann Oncol 2 [Suppl 1] 2: 31
3. Cabanillas F, Hagemeister FB, McLaughlin P, Velasquez WS, Riggs S, Fuller L, Smith T (1987) Results of MIME salvage regimen for recurrent or refractory lymphoma. J Clin Oncol 5: 407
4. Goss PE, Shepherd FA, Scott JG, Warner E, Baker MA, Sutton D, Farquharson HA, Buick S, Sutcliffe S (1991) Dexamethasone, ifosfamide, cisplatin, etoposide (DICE) as therapy for patients with advanced refractory non-Hodgkin's lymphoma. Preliminary report of a phase II study. Ann Oncol 2 [Suppl 1]: 43
5. Loehrer PJ, Lauer R, Roth BJ, Williams SD, Kalasinski LA, Einhorn LH (1988) Salvage therapy in recurrent germ cell cancer. Ifosfamide and cisplatin plus either vinblastine or etoposide. Ann Intern Med 109: 540
6. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207
7. Nichols CR, Loehrer PJ, Greist A, Kubilis PS, Hoffman R (1988) Salvage chemotherapy for lymphoma with VP-16, ifosfamide and cisplatin. Med Pediatr Oncol 16: 12
8. Velasquez WS, Cabanillas F, Salvador P, McLaughlin P, Fridrik M, Tucker S, Jagannath S, Hagemeister FB, Redman JR, Swan F, Barlogie B (1988) Effective salvage therapy for lymphoma with cisplatin in combination with high-dose ara-C and dexamethasone (DHAP). Blood 71: 117