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Short communication

VP-16, ifosfamide, and methotrexate combination chemotherapy for aggressive non-Hodgkin's lymphomas after failure of the LNH 84 regimen

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Summary. A total of 20 patients with intermediate or high-grade non-Hodgkin's lymphomas who failed to LNH 84 regimen were treated with a combination of VP 16, ifosfamide and methotrexate (VIM regimen). Nineteen patients are evaluable for response. Eight patients (42%) achieved complete responses and four (21%) attained partial responses. Most of the complete responders are still in remission with a follow-up of more than 30 months for 5 patients.

Introduction

LNH 84 is an intensive, first-line chemotherapy regimen for the treatment of intermediate and high-grade non-Hodgkin's lymphomas (NHL). It includes high-dose Adriamycin (75 mg/m^2 per course) induction therapy and has produced a 76% complete response rate and a 2-year survival rate of 62% [3]. However, NHL patients who fail or relapse after initial intensive therapy have a very poor prognosis. We assessed the efficacy of a three-drug chemotherapy protocol combining VP-16, ifosfamide and methotrexate (VIM) in 20 patients who had failed the LNH 84 regimen. This VIM combination is derived from the IMVP-16 regimen previously reported by Cabanillas et al. [1].

Patients and methods

A total of 20 patients who had failed the LNH 84 regimen were treated. In 16 cases, failure was established after 3 or 4 induction cycles; 7 of these patients were non-responders and 9 were partial responders. The 4 remaining patients had relapsed either during LNH 84 consolidation (1 case) or after completing the whole treatment programme (3 cases). The histological diagnosis, performance status, and clinical stage of the patients are shown in Table 1. Those with CNS involvement were not included in this study.

The VIM regimen consisted of 100 mg/m^2 VP-16 in 250 cc normal saline given over 1 h on days 1, 3 and 5; 1 g/m^2 ifosfamide in 500 cc dextrose solution given over 1 h daily for 5 consecutive days (days 1–5); and 30 mg/m^2 i.v. methotrexate on days 1 and 5. Hydration with 3 l dextrose solution per day was given over the 5 days; neither mesna nor leucovorin were used. Courses were repeated every 21 days. In cases of myelosuppression, the next course was delayed and given at the full dose on day 28. Treatment was continued until progression of disease or for a maximum of six courses.

A complete response (CR) was defined as the disappearance of all tumor lesions for a period of at least 2 months. A partial response (PR) corresponded to a decrease of $>50\%$ in the total measurable tumor and the absence of new lesions or of progression in any other lesion for a period of at least 2 months.

Results

In all, 19 patients were evaluable for response, as 1 died immediately after the first course and was evaluable only for toxicity. A total of 8 patients (42%) achieved CRs and 4 (21%) attained PRs for an overall response rate of 63%. Treatment failed in 7 cases (37%). Table 2 shows the response to VIM therapy as a function of the initial response to the LNH 84 regimen. Interestingly, five of eight patients (63%) who had a PR after LNH 84 induction therapy achieved CRs with VIM salvage chemotherapy. Of the eight complete responders to VIM, two relapsed after 4 and 14 months, respectively, and six are currently alive, with no evidence of disease after 13, 33, 34, 40, 41 and 43 months, respectively.

Myelotoxicity was the most common side effect. A total of 89 courses of VIM were given. Eight infectious episodes related to neutropenia, one of which was fatal, were recorded in five patients. No renal or liver dysfunction was observed and no hemorrhagic cystitis occurred.

Discussion and conclusion

All patients in this study had aggressive non-Hodgkin's lymphoma and failed an intensive, first-line, Adriamycin-containing combination chemotherapy regimen. Most cases were clinical stage IV. The response rates (42% CRs and 21% PRs) we observed with the VIM salvage therapy are similar to those reported by Cabanillas et al. [1] with the IMVP-16 regimen (37% CRs and 25% PRs) as second-line treatment for aggressive NHL. IMVP-16 and VIM dif-

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Table 1. Characteristics of the 20 patients

Mean age (range)		46 years (21–68)
Performance status (WHO criteria):		
	<2	10
	⩾2	10
Clinical stage:	I E	1
	II–II E	3
	III	2
	IV (bone marrow +)	14 (7)
Histological type		
diffuse, small cleaved cell		2
diffuse, mixed cell		7
diffuse, large cell		1
large cell, immunoblastic		3
lymphoblastic		5
small non-cleaved cell		1
histiocytic		1

Table 2. Tumor response according to the response to initial induction therapy with LNH 84 (19 evaluable patients)

Type of response to LNH 84	Number	Response to VIM		
		CR (%)	PR (%)	Failure (%)
Absence of response	7	2 (29)	1 (14)	4 (57)
Partial response	8	5 (63)	0	3 (37)
Relapse after complete response	4	1 (25)	3 (75)	0
All patients	19	8 (42)	4 (21)	7 (37)

fer only in the timing of methotrexate injections. The addition of methyl-glyoxal (MIME regimen) or bleomycin (VIM-Bleo regimen) does not improve the results, with published overall response rates of 60% and 62%, respectively [2, 4]. Special emphasis must be placed on the 63% CR rate obtained with VIM in patients who responded partially to LNH 84 induction therapy and on the prolonged remissions and survival of most CR patients.

References

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