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VM26 in Malignant Hematological Diseases

A Phase II Study

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Summary. *From August 1979 to April 1981, 33 consecutive patients with malignant hematological diseases, entered this phase II study. Sixteen patients had NHL, eight CLL, four Myeloma, three HD, one ALL, and one Polycythaemia vera. Two patients were unevaluable because of early death. The median age was 67 years. Eight patients were not pretreated with drugs. Two CR (5+, 20+ weeks) were obtained among NHL patients, whereas five PR were observed among two NHL, one CLL, one Myeloma, and one HD patients, respectively. Toxicity was almost exclusively hematologic and occurred in ten patients, in one of them causing severe myelosuppression. Moreover, severe asthenia, attributable to VM26, was encountered in three patients, in one requiring the suspension of the treatment.*

Introduction

Since 1970, VM26 has been employed in a large number of patients with Hodgkin (HD) and non-Hodgkin Lymphoma (NHL), with overall response rates ranging from 27%–56% and 23%–52%, respectively [2]. However, a significant number of these patients were treated within broad phase I and II studies, in which sufficient information regarding the schedules employed, the definitions of response and the durations of remission were not provided. Moreover, old terms such as "reticulum cell sarcoma" or "lymphosarcoma" were used in many studies, making difficult the comparison with the results of more recent trials. In addition, VM26 has never been tested in malignant hematological diseases such as chronic lymphocytic leukemia (CLL), multiple myeloma (MM) and mycosis fungoides (MF). In August 1979, we undertook a phase II trial of VM26 in the treatment of malignant hematological diseases. The study was designed to determine: 1) the efficacy of VM26 both in untreated and in pretreated patients with NHL classified according to the modified Rappaport classification [3], 2) the efficacy of VM26 in other malignant hematological diseases in which VM26 has never been thus far employed, 3) the toxicity of VM26 in malignant hematological diseases.

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Patients and Methods

Criteria of patient selection for this trial were: patients with NHL, HD, MM, acute lymphoblastic leukemia (ALL) resistant to conventional treatment, according to ongoing clinical protocols of our Institution; untreated patients with NHL, HD, MM, in poor general condition and/or older than 70 years; patients with CLL and Polycythaemia vera (PV), even prior to conventional treatment. From August, 1, 1979 to April, 30, 1981, 33 consecutive patients with malignant hematological diseases entered this study. All histological diagnoses were reviewed by one of us (A.C.). Sixteen patients had NHL, eight CLL, four MM, three HD, one ALL, and one PV. Two patients were unevaluable because of early death. The median age was 67 years (7–79). Eight patients were not pretreated with drugs. Patients with NHL were classified according to the modified Rappaport classification [2]: five patients had MF, seven diffuse lymphocytic poorly differentiated (DLPD), two "Histiocytic", two lymphoblastic, one nodular lymphocytic poorly differentiated (NLPD), one diffuse mixed (DM), and one malignant histiocytosis. VM26 was given as a more than 30 min i.v. infusion at 100 mg/m^2 weekly for at least three cycles to NHL, HD, and ALL patients, six cycles to MM patients and nine cycles to CLL and PV patients, prior to evaluation of response. Dose modifications were adjusted according to peripheral blood counts. In patients who obtained complete remission, four cycles of consolidation were given and then treatment discontinued. If only partial or minimal remission was obtained, treatment was continued until maximum clinical response was thought to be achieved. Response criteria for NHL and HD patients were: CR, complete resolution of all measurable and known disease; PR, a decrease of greater than 50% in the sum of the products of perpendicular diameters of measurable lesions; MR, a decrease less than 50% in the sum of the products of perpendicular diameters of measurable

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lesions. Response criteria for CLL patients were: PR, a decrease greater than 50% of marrow infiltration and lymphnodal and visceral involvement; MR, a decrease less than 50% of marrow infiltration and lymphnodal and visceral involvement. Response criteria for MM patients were those of University of Arizona [1]. The evaluation of responses was made at June, 30, 1981.

Results

Overall results are reported in Table 1.

Two CR were obtained among NHL patients (one MF and one "Histiocytic"), whereas five PR were observed among two NHL, one CLL, one MM, and one HD patients, respectively. The results obtained in NHL patients, classified according to modified Rappaport classification [3] are reported in Table 2. Of the two CR, one was obtained in a patient not previously treated, another in a patient previously treated with regimens including Vincristine and Vinblastine. The latter CR was achieved after many cycles of VM26 and a long period of only PR. Toxicity was almost exclusively hematologic and occurred in ten patients. In one of them, extensively pretreated and with fungal infection, VM26 caused a severe myelosuppression with subsequent death. Neither hypotension nor alopecia were encountered, whereas one patient experienced nausea and another amenorrhea. In three patients, severe asthenia, attributable to VM26, was encountered, in one requiring the suspension of the treatment. Among the eight previously untreated patients, no bone marrow toxicity nor other side effects were so far encountered.

Table 1. Overall results with VM26 in malignant hematological diseases

Histology	No. of patients		Response (in weeks)		
	Entered	Evaluable	CR	PR	MR
NHL	16	15	2 (5+, 20+)	2 (10, 20)	2 (2, 5)
CLL	8	8	–	1 (9)	6 (2, 2, 2, 6, 12, 14)
MM	4	3	–	1 (4)	
HD	3	3	–	1 (4)	2 (5, 24)
ALL	1	1	–	–	–
PV	1	1	–	–	–
Total	33	31	2	5	
				22%	

Table 2. VM26 in NHL

Histology (2)	No. of patients evaluable	Response (in weeks)		
		CR	PR	MR
Mycosis fungoides	5	1 (20+)	1 (20)	1 (5)
DLPD	4	–	1 (10)	–
„Histiocytic"	2	1 (5+)	–	1 (2)
NLPD	1	–	–	–
Lymphoblastic	1	–	–	–
DM	1	–	–	–
Malignant histiocytosis	1	–	–	–
Total	15	2	2	
			26%	

Discussion

Our preliminary results show that VM26 is an effective drug in NHL (CR + PR: 26%) and in particular in MF (CR + PR: 40%). In the latter disease, no previous experience with VM26 has been thus far reported. It is noteworthy that all patients with MF were extensively pretreated and in particular with Vinca Alkaloids. Moreover, in the only patient with previously untreated NHL ("histiocytic" sub-type), VM26 was able to induce CR. So far, only Chiuten et al. [2] have reported CR obtained with VM26 in two NHL patients (diffuse histiocytic sub-type), previously treated. More patients are necessary in the other malignant hematological diseases of this trial to draw definitive conclusions. Toxicity seems acceptable even in heavily pretreated patients.

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