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VIM-D salvage chemotherapy in Hodgkin's disease

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Summary. A total of 15 patients with relapsed or resistant Hodgkin's disease were treated with a combination of etoposide (VP16), ifosfamide, mitozantrone and dexamethasone (VIM-D). The regime was well tolerated, the only major toxicity being myelosuppression. Complete remissions (CRs) were obtained in 4 patients and were maintained for 2, 4, 10 and 14 months. 10 subjects subsequently received an autologous bone marrow transplant with high-dose chemotherapy (ABMT). Previous exposure to VIM-D did not appear to predict for or prejudice the response to subsequent ABMT.

Introduction

The results of salvage chemotherapy in Hodgkin's disease following failure of two or more chemotherapy regimens are poor. Recently complete remission (CR) rates of 47% have been described for a high-dose oral regime, CEP (lomustine, etoposide and prednimustine), although relapse-free survival at 30 months remains low at 22% [7]. Etoposide (VP16), ifosfamide and mitozantrone have all been shown to have single-agent activity against Hodgkin's disease [1, 2] and are not usually included in first-line therapy. It was hoped that their combination with dexamethasone (VIM-D) would prove to be effective as salvage chemotherapy.

Patients and methods

A total of 15 patients were treated with VIM-D between May 1986 and March 1988; 13 were men and the age range was 19–68 years (median, 33 years). 10 patients had nodular sclerosing (5, type I; 5, type II) 4 had mixed cellularity and 1 had lymphocyte-depleted histology. 2 patients had stage II disease; 5, stage III disease; and 8, stage IV disease. The number of previous cytotoxic agents received ranged from 3 to 8; 12 patients had received prior therapy with anthracyclines. Treatment was commenced for recurrent disease after a CR lasting for >12 months in 3 patients and for resistant disease, failure of remission induction, or recurrence at <12 months in 12 subjects. Although inevaluable for response, one additional patient was included in the toxicity assessment, as the evidence of recurrent disease remained unchanged not only after three cycles of VIM-D, but also after a further 9 months off treatment, and in retrospect was probably due to fibrosis.

The regimen consisted of 100 mg/m^2 etoposide given i.v. over 30 min on day 1; 4 g/m^2 ifosfamide given i.v. over 24 h on day 1; 1 g/m^2 mesna was given as an i.v. bolus on day 1, followed by 6 g/m^2 infused over 36 h; 10 mg/m^2 mitozantrone given as an i.v. bolus on day 1; and 40 mg dexamethasone given orally daily for 5 days. The regimen was repeated on day 28.

Dose modification. If the first midcycle neutrophil count was $>1.5\times10^9$/l, 100 mg/m^2 etoposide was given on days 1 and 2 of the second and subsequent cycles. Dose reductions were made on the basis of the neutrophil and platelet counts on day 28 of the preceding cycle. The dose of etoposide was reduced by 25% if the neutrophil count was $<2\times10^9$/l or the platelet count was $<100\times10^9$/l and was lowered by 50% if the neutrophil count was $<1.5\times10^9$/l or the platelet count was $<75\times10^9$/l; it was omitted if the neutrophil count was $<1\times10^9$/l or the platelet count was $<50\times10^9$/l. The doses of mitozantrone and ifosfamide were reduced by 25% if the neutrophil count was $<1.5\times10^9$/l or the platelet count was $<100\times10^9$/l and were lowered by 50% if the neutrophil count was $<1\times10^9$/l or the platelet count was $<75\times10^9$/l; they were omitted if the neutrophil count was $<0.5\times10^9$/l or the platelet count was $<50\times10^9$/l.

A complete remission (CR) was defined as the resolution of all evidence of disease. A partial remission (PR) was defined as a reduction of at least 50% in measurable disease. VIM-D was repeated to CR plus three cycles, provided that continued disease reduction was seen at each response assessment. None of the patients received concurrent radiotherapy. On relapse, ten patients subsequently received high-dose chemotherapy (carmustine, etoposide, cyclophosphamide; [5]) with autologous bone marrow rescue.

Results

Of 15 evaluable patients, 4 achieved a CR; their characteristics are shown in Table 1. Despite achieving a PR at 3 months, 6 subjects showed evidence of progressive disease (PD) at 6 months. All 4 patients achieving a CR relapsed, at 2,4,10 and 14 months off treatment.

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Table 1. VIM-D in Hodgkin's disease: complete responders

Patient number	Previous treatment	Response to previous treatment	Stage at relapse	Histology	Duration of response to VIM-D	Cycles of VIM-D to CR
1	ChlVPP/ABV, alternating	PD	IVB	MC	2 months	6
2	LOPP	CR (11 months)	IIIB	MC	4 months	3
3	LOPP/ABV, alternating	PD	IVB	MC	10 months	3
4	MVPP→LOPP	CR (48 months)	IIIB	NS type II	14 months	3

PD, progressive disease; CR, complete remission; MC, mixed cellularity; NS, nodular sclerosing; ChlVPP = chlorambucil, vinblastine, prednisolone, procarbazine [4]; ABV = Adriamycin, bleomycin, vinblastine [6]; LOPP = lomustine, vincristine, prednisone, procarbazine [3]; MVPP = mustine, vinblastine, prednisolone, procarbazine [3]

Table 2. Toxicity of VIM-D

	All WHO grades	WHO grade III–IV
Clinical[a]:		
Mucositis	35	0
Nausea/vomiting	26	9
Abdominal pain	21	1
Dyspepsia	16	2
Peripheral neuropathy	13	0
Impaired consciousness	6	3
Haematuria	4	0
Cardiotoxicity	2	1
Laboratory:		
Neutropenia	$<2.0 \times 10^9$/l	$<1 \times 10^9$/l
	62	36
Anaemia	<11 g/dl	<8 g/dl
	39	1
Thrombocytopenia	$<100 \times 10^9$/l	$<50 \times 10^9$/l
	16	3
Raised hepatic transferases	>50 µmol/l	>225 µmol/l
	15	5

Data represent the percentage of cycles during which toxicity occurred ($n = 75$)

[a] Alopecia was seen in 13/16 patients and was complete in 1 case

Clinical and laboratory toxicities were assessed on days 14 and 28 of each cycle and are summarised in Table 2. The median neutrophil nadir on day 14 was 1.4×10^9/l, with a range of $0.2–5 \times 10^9$/l in cycle 1; in all cases, recovery to at least 1.3×10^9/l was seen by day 28. The severity of nadir neutropenia could not be explained by the presence or absence of marrow involvement with Hodgkin's disease. In a total of 75 cycles, 2 serious infections occurred: 1 case of *Staphylococcus aureus* septicaemia and 1 fatal case of bronchopneumonia, both of which were associated with neutropenia.

No treatment delays were required. Four patients who had previously received vinca alkaloids complained of peripheral paraesthesiae, but in no case was this associated with clinically detectable sensory loss. Two subjects experienced transient somnolence lasting for 24–48 h after each course of chemotherapy. One patient died of sudden-onset left ventricular failure after two cycles of VIM-D, having received a total of 31 mg mitozantrone and 540 mg Adriamycin.

The duration of therapy ranged from 2 to 6 months. The mean percentage of the intended dose actually given was as follows: etoposide, 111%; ifosfamide, 93%; mitozantrone, 96%; dexamethasone, 98%. 10 patients received the standard regimen throughout; 3 subjects tolerated standard doses, plus 100 mg/m^2 i.v. etoposide on day 2; only 1 patient received <75% of the planned cytotoxic doses, due to thrombocytopenia.

Autologous bone marrow transplantation

Of the ten patients who underwent an autologous bone marrow transplant (ABMT), one died at day 6 of a *Pseudomonas* septicaemia. Of nine evaluable patients, six achieved a CR and three showed a PR. The duration of CRs was <6 months in two cases, but four patients remain in CR at 10, 12, 14 and 18 months post-ABMT. The response to ABMT was not related to the previous response to VIM-D: only one of three subjects who achieved a CR on VIM-D also attained a CR after ABMT, but five of the remaining seven patients who did not achieve a CR on VIM-D (three PRs and two PDs) did reach a CR after ABMT.

Discussion

The CR rate in the group of patients treated with VIM-D was 27%, with 95% confidence limits of 5%–49%. Thus, VIM-D cannot be expected to give a significantly greater response rate than that reported for CEP in a similar group of patients. In addition, the remission duration was short. Therapeutic efficacy might be improved by giving etoposide at a lower dose over an extended period, a schedule that has been shown to be dramatically better than a single high-dose schedule in small-cell lung cancer [8]. Our data confirm the high response rates seen in Hodgkin's disease patients treated with high-dose chemotherapy and autologous marrow rescue.

In the present study, exposure to VIM-D did not prejudice the subsequent response to ABMT. Treatment with VIM-D, although not curative, may be useful for palliation in some patients deemed unsuitable for ABMT and in controlling tumour bulk prior to transplantation.

In conclusion, the VIM-D regimen is effective in a small proportion of patients with relapsed and resistant Hodgkin's disease. The major toxicity is myelosuppression.

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