Cancer Chemother Pharmacol (1982) 7:175–177

Cancer Chemotherapy and Pharmacology

Etoposide as a Single Agent in Relapsed Advanced Lymphomas
A Phase II Study

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Summary. *Twenty-three patients with relapsed lymphomas resistant to standard chemotherapy, 13 with Hodgkin's disease and 10 with non-Hodgkin's lymphomas, were treated with etoposide 120 mg/m² i.v. daily for 5 days or orally for 7–10 days, repeated 3-weekly. This is a higher dose than has been used previously to treat these tumours. Objective responses were seen in eight of 13 (61%) patients with Hodgkin's disease (three CR, five PR) and in three of 10 (30%) patients with non-Hodgkin's lymphomas (three PR). The response rates for Hodgkin's disease are higher than those previously reported and are probably due to the greater dose of drug than has been previously employed. The dose-limiting toxicity was haematological, with gastro-intestinal toxicity occurring in a minority of patients only. It is concluded that etoposide has significant activity particularly in Hodgkin's disease. Its use in drug combinations should now be assessed.*

Introduction

The epipodophyllotoxin etoposide (VP16-213) has been shown in Phase I and II studies to have activity against a number of malignancies including lymphomas [2, 4, 6, 8]. Recent literature reviews have reported response rates of approximately 14% in Hodgkin's disease [1, 9] and 13.7% [1] and 29.7% [9] in non-Hodgkin's lymphomas. Lower response rates have been reported in a recent Phase II study [3] with no responses seen in 35 patients with non-Hodgkin's lymphomas and three of 17 (17.6%) partial regressions in patients with Hodgkin's disease. However a relatively low dose of etoposide was employed (45 mg/m² i.v. daily for 5 days repeated 3-weekly).

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In the study reported here we have treated 23 patients with previously extensively treated lymphomas with etoposide 120 mg/m² i.v. daily for 5 days or orally for 7–10 days, repeated 3-weekly. It was anticipated that this would be the maximum tolerated dose in this group of patients.

Patients and Methods

Thirteen patients with Hodgkin's disease (age range 22–69, median age 51) were included in the study. The Hodgkin's disease group include six patients with nodular sclerosing histology (NS), six with mixed cellularity (MC) and one with lymphocyte predominant disease (LD). Four patients had Stage IVA, eight patients Stage IVB and three patients Stage IIIB disease at relapse. All patients had been previously treated with a combination of chlorambucil, vinblastine, procarbazine and prednisolone (ChlVPP) [7]. Six had also been treated with the combination of adriamycin, vincristine, bleomycin and DTIC (ABVD) [11], four with mustine, vinblastine, procarbazine and prednisolone (MVPP) [12], three with mustine, vincristine, procarbazine and prednisolone (MOPP), three with chlorambucil, vincristine, procarbazine and prednisolone (ChlOPP) and one with cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP). One patient had received a combination of methotrexate and 5FU, and also CCNU and VM26 as single agents. Nine of the patients with Hodgkin's disease had received prior radiotherapy.

The non-Hodgkin's patients include the following histological subtypes, classified according to Rappaport [10] as well differentiated diffuse lymphocytic (WDLD) – 1, poorly differentiated diffuse lymphocytic (PDLD) – 5, poorly differentiated nodular lymphocytic (PDLN) – 1, nodular histiocytic (NH) – 1, diffuse histiocytic (DH) – 1 and diffuse mixed (DM) – 1.

Five patients had received prior treatment with cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP), two with chlorambucil, vincristine, procarbazine and prednisolone (ChlOPP), three with chlorambucil, vincristine and prednisolone (LOP), one with mustine, vincristine, procarbazine and prednisolone (MOPP) and one with methotrexate, bleomycin, adriamycin, cyclophosphamide, vincristine and prednisolone (MBACOP). Four patients had received a combination of chlorambucil and prednisolone, one vincristine and prednisolone and one cyclophosphamide and prednisolone. Two of the patients with non-Hodgkin's lymphomas had received prior radiotherapy.

0344-5704/82/0007/0175/$01.00

Table 1. Clinical details of responding patients

Patient	Histology	Previous chemotherapy		Previous radiotherapy	Response to etoposide	Response duration (weeks)	No. of courses to response (oral/i.v.)	Total no. of courses
1	HD (NS)	ChlVPP ABVD MOPP MTX/5FU VM 26 CCNU	× 3 × 6 × 1 × 1 × 1 × 1	Mantle, Whole brain	PR (skin nodule + ulcer)	12	1 (i.v.)	4
2	HD (MC)	ChlVPP ChlOPP	× 5 × 2	Total nodal irradiation	CR (Axillary node, skin nodule)	14	2 (i.v.)	6
3	HD (NS)	MVPP MOPP ChlVPP	× 10 × 6 × 12	Total nodal irradiation	PR (Lung infiltration)	52+	2 (oral)	14
4	HD (NS)	MVPP ChlVPP	× 6 × 12	Mantle	CR (Cervical + axillary nodes, pleural effusion)	20	3 (i.v.)	6
5	HD (MC)	MVPP ChlVPP ABVD	× 13 × 11 × 5		PR (Axillary nodes, liver)	34+	5 (i.v.)	6
6	HD (NS)	ChlVPP	× 10		CR (Inguinal node)	20	5 (i.v.)	6
7	WDLD	Chlor/pred LOP Cyclo/pred	× a[a] × 2 × b[a]		PR (Cervical + axillary nodes)	32+	1 (oral)	3
8	DM	MBACOP	× 2		PR (Cervical + axillary nodes)	4	1 (oral)	2
9	DH	CHOP	× 5		PR (Axillary + hilar nodes, lung infiltration	12	1 (oral)	2
10	HD (MC)	MOPP ChlVPP	× 6 × 10	Total nodal irradiation	PR (Lung)	4+	2 (i.v.)	2[b]
11	HD (NS)	ChlVPP ABVD	× 18 × 6	Whole lung, left breast	PR (Lung)	8+	1 (oral)	4

[a] Continuous low dose therapy for a) 20 months, b) 5 months
[b] Continued therapy with etoposide/adriamycin/bleomycin

Patients were treated with etoposide 120 mg/m^2 i.v. daily for 5 days or orally for 7–10 days, repeated 3-weekly as toxicity allowed.

Complete regression (CR) was defined as disappearance of all clinically and radiologically measurable disease for at least 1 month.

Partial regression (PR) was defined as a greater than 50% reduction in the product of the two largest perpendicular diameters of any measurable lesion, in the absence of any new lesions developing elsewhere or further progression of known lesions, for at least 1 month.

Results

Twelve patients with Hodgkin's disease were assessable for response, and one patient died of progressive disease 2 weeks after starting therapy. Objective responses were seen in eight patients (61%), CR in three of 13 (23%), PR in five of 13 (38%), No response (NR) in four of 13 (30%). The median duration of response was 20 weeks (range 4+ to 52+ weeks).

One patient who achieved a partial regression in the lung after two courses of etoposide was subsequently treated with a combination of etoposide, adriamycin and bleomycin, with continued regression of his disease.

Nine patients with non-Hodgkin's lymphomas were evaluable for response, with 1 patient dying of septicaemia 2 weeks after starting therapy. Objective responses were seen in three patients (30%), CR – zero, PR – three of ten (30%), NR – seven of ten (70%).

Table 1 shows histology, previous treatment, sites and duration of response and number of courses of etoposide given to the responding patients.

Table 2. Toxicity of etoposide in patients with advanced lymphomas

Toxicity	Hodgkin's disease (%)	Non-Hodgkin's lymphomas (%)	All patients (%)
Anaemia Hb < 10 g	3 (23)	4 (40)	7 (30)
Leucopenia WBC < 2,000/cu.mm	5 (38)	3 (30)	8 (35)
Thrombocytopenia Plat. < 100,000/cu.mm	5 (38)	4 (40)	9 (39)
Neutropenia related infection	3 (23)	2 (20)	5 (22)
Nausea	3 (23)	1 (10)	4 (17)
Phlebitis	1 (8)	–	1 (4)
Alopecia	13 (100)	10 (100)	23 (100)

Toxicity

Details of toxicity are given in Table 2. Haematological toxicity was dose limiting, and occurred usually on days 8–12, although in some cases it persisted until day 21. Three patients had one or more courses of etoposide delayed because of leucopenia. Infection related to neutropenia was seen in five patients, with one of these dying 2 weeks after starting therapy. In all these patients the neutrophil count was lower than 500/cu.mm. All patients experienced varying degrees of alopecia, and gastrointestinal toxicity (nausea) was experienced by four patients, three of whom were receiving the oral preparation.

Discussion

This study shows that etoposide in a higher dose than previously reported has significant activity against lymphomas, with objective response rates of 30% in non-Hodgkin's lymphomas and 61% in Hodgkin's disease occuring in heavily pretreated patients.

The dose limiting toxicity is haematological, with gastrointestinal toxicity seen in a minority of patients only.

Lower response rates have been seen in earlier phase I and II studies of etoposide in Hodgkin's disease [2–6, 8] and it seems likely that the response rate of 60% demonstrated in our study has resulted from the relatively high dose of etoposide employed.

It is concluded that etoposide is active against lymphomas, its toxicity is predictable and tolerable, and its use in combinations should be evaluated.

Acknowledgements. We wish to thank Sandoz Ltd for original supplies of drug and Bristol Myers Ltd for continued support.

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Accepted July, 1981