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EVA treatment for recurrent or unresponsive Hodgkin's disease

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Summary. Nineteen patients with recurrent or unresponsive Hodgkin's disease who had previously received combination chemotherapy comprising mustine or chlorambucil with vinblastine, prednisolone and procarbazine (MVPP or ChlVPP), were treated with a combination of etoposide, vincristine and adriamycin (EVA). Clinical remission (complete, CR + good partial, GPR) was achieved in eleven of the nineteen patients (58%). The remission rate was similar for patients who had previously responded well to chemotherapy and for those who had previously been poorly responsive. Six patients have relapsed between 3 and 5 months after completion of therapy. The remainder continue in remission, two without further therapy at 7 and 8 months, respectively, and three having had additional radiotherapy while in remission. Myelosuppression was the most important toxicity, but in general this was manageable. These results suggest that EVA may be non-cross-resistant with MVPP and ChlVPP and that it is of potential value in combination chemotherapy for previously untreated patients, even though it is unlikely to be curative when treatment with either MVPP or ChlVPP has failed.

Introduction

The prognosis for patients with advanced Hodgkin's disease improved dramatically with the introduction of cyclical combination chemotherapy comprising mustine, vincristine, procarbazine and prednisolone (MOPP) or its variants [5, 10]. However, the prognosis for the approximately 30% of patients who fail to achieve CR with primary therapy remains poor. Patients who achieve CR but subsequently relapse may respond again to further MOPP therapy, especially if the first remission duration exceeds 12 months, but a prolonged second response is only seen in a minority of patients [6].

Many attempts have been made to develop alternative combinations, the most widely used being that of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD), each drug having been reported to yield remission in Hodgkin's disease [1]. (Vinblastine is used in this regimen, as patients who have previously been treated with MOPP have been exposed to vincristine.) Santoro and Bonadonna [9] have reported impressive results with ABVD, both in patients who have relapsed following remission induced with MOPP and in those who have responded poorly to MOPP, but results from other centres have been conflicting [2].

The demonstration of the activity of etoposide in Hodgkin's disease [4, 7, 8] combined with the significant toxicity of bleomycin and dacarbazine and the previous poor results at St Bartholomew's Hospital with ABVD [11] led to a study of EVA (Table 1). Vincristine was used as the patients had previously received vinblastine.

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Patients and methods

1. Patients

Nineteen patients (age range 18–64 years, median 34 years) with recurrent or poorly responsive Hodgkin's disease form the basis of this study. Details of previous therapy and responsiveness are shown in Table 2. Eleven patients had previously achieved a CR lasting 12 months or more with chemotherapy. However, three of these had subsequently shown poor responses (fail, partial response, and CR lasting less than 3 months) to chemotherapy at relapse. The remaining eight patients had responded poorly to first-line chemotherapy, and two of these had also been poorly responsive to several further drug regimens. Three of the nineteen patients had previously been exposed to two or more of the constituents of the EVA regimen.

Details of the extent of disease at the time of treatment with EVA are shown in Table 3.

2. Assessment

Pretreatment assessment was made by clinical examination, biochemical tests of liver function, chest X-ray and CT scan of chest if appropriate, abdominal CT scan or lymphography, and bone marrow biopsy. Isotope bone

Table 1. EVA treatment regimen

Drug		Dosage	Route	Day(s)
E	Etoposide (VP16)	200 mg/m^2	p.o.	1–5
V	Vincristine	2 mg	i.v.	1
A	Adriamycin	50 mg/m^2	i.v.	1

Interval 21–28 days
Median number of cycles given 4
Range 1–6

Table 2. Details of previous therapy

	1st Therapy	Response	Duration (months)	2nd Therapy	Response	Duration (months)	3rd, 4th and 5th Therapy	Response	Duration (months)
1	MVPP	CR	12						
2	MVPP	CR	18						
3	MVPP	CR	32						
4	MVPP	CR	40						
5	MVPP	CR	17	MRT	CR	4			
6	MVPP	CR	17	MRT	CR	71			
7	MVPP	CR	108	IYRT	CR	48			
8	MRT	CR	108	MVPP	CR	7			
9	TNI	CR	84	MVPP	CR	24	ChlVPP	PR	–
10	Cyclo	CR	24	MVPP	CR	3	MRT	CR	108
11	MVPP	CR	18	ChlOMP	PR	–	Chl + CCNU	F	–
							BE	PR	–
							A	PR	–
12	ChlVPP	PR	–						
13	ChlVPP	PR	–						
14	MVPP	PR	–						
15	ChlVPP	PR	–						
16	ChlVPP	PR	–						
17	MRT	CR	40	ChlVPP	F	–			
18	MRT	CR	36	MVPP	PR	–	MOPP	F	–
							Chl + CCNU	PR	–
							CVEP	F	–
19	MVPP	PR	–	OPEC	F	–	Chl + CCNU	PR	–

MVPP, mustine, vinblastine, procarbazine, prednisolone; ChlVPP, chlorambucil, vinblastine, procarbazine, prednisolone; ChlOMP, chlorambucil, vincristine, methotrexate, prednisolone; Chl + CCNU, chlorambucil + CCNU; BE, bleomycin + etoposide; CVEP, Cyclophosphamide, vinblastine, etoposide, prednisolone; OPEC, vincristine, prednisolone, etoposide, chlorambucil; MRT, mantle radiotherapy; IYRT, inverted Y radiotherapy; TNI, total node irradiation; A, adriamycin; CR, complete remission; PR, partial response; F, fail

Table 3. Extent of disease at start of EVA therapy

Extent	No. of patients
Nodal disease only	9
Extranodal disease only	5
Nodal + extranodal disease	5

Sites of extranodal disease: lung (5 patients); bone (2); liver + lung (1); liver + bone marrow (1); and bone + bone marrow (1)

scan was performed if clinically indicated or if the alkaline phosphatase was raised. Liver involvement was assessed according to the Ann Arbor criteria [3].

Investigations for which abnormal results were recorded were repeated 1 month after the completion of therapy.

3. Definitions

a) Clinical remission. (i) Complete remission (CR): Disappearance of all symptoms and signs of disease with complete resolution of all previous evidence of disease on X-rays, biochemical tests, bone marrow biopsy and radioisotope studies.

(ii) Good partial remission (GPR): Disappearance of all clinical evidence of disease, but with equivocal residual abnormalities remaining on radiological, biochemical or radioisotope studies.

b) Poor partial remission (PPR). More than 50% reduction in tumour bulk, but with definite evidence of residual disease.

c) Fail. Less than 50% reduction in tumour bulk.

Results

1. Response

Clinical remission was achieved in 11 of the 19 (58%) patients (6/19 CR, 5/19 GPR) and PPR in 2. One patient was not assessable for response as she had had a lobectomy for recurrent Hodgkin's disease of the lung and had no measurable disease at the time of therapy. The clinical remission rate for evaluable patients was therefore 11 out of 18 (61%). Two patients who died during the first cycle of therapy are included as therapy failures in the assessment of response.

The response rates for patients with nodal and extranodal disease were similar. Clinical remission was achieved in six out of nine patients with nodal disease only, compared with five out of nine evaluable patients with extranodal disease.

The three patients who had previously been exposed to two or more drugs in the EVA regimen failed to respond to the combination. Responsiveness to EVA was not related to responsiveness to previous chemotherapy for the remaining fifteen evaluable patients. Six out of eight patients who had shown an initial poor response to chemotherapy (6 patients) or had become refractory to chemotherapy (2 patients) achieved clinical remission with EVA. Five out of seven patients who had been previously responsive to chemotherapy (CR more than 12 months) achieved a further clinical remission with EVA.

Duration of remission. Five remain in remission, three having received radiotherapy as consolidation 2 months after completing treatment. The other two patients remain in remission without further therapy after 7 and 8 months, re-

spectively (1 CR, 1 GPR). Six patients have relapsed following clinical remission lasting 3–5 months.

2. Toxicity

Myelosuppression was the most serious toxicity. The neutrophil count fell below $0.5 \times 10^9/l$ in 11 of the 19 patients, and 7 patients developed pyrexia while neutropenic, requiring admission to hospital for i. v. antibiotics. The platelet count fell below $20 \times 10^9/l$ in 1 patient. Bleeding due to thrombocytopenia was not otherwise encountered.

Myelosuppression was related to proximity to previous treatment (chemotherapy or radiotherapy). Eleven patients received EVA within 15 months of their preceding treatment; 9 developed severe myelosuppression, compared with 1 out of 8 patients for whom the interval was longer. Myelosuppression was not, however, related to the extent of previous therapy. There were 9 patients who had received only a single previous therapy, and 5 of these experienced severe myelosuppression, compared with 3 out of 5 who had received two previous treatments and 3 out of 5 who had received more than this.

Two patients died during treatment. One with extensive pulmonary Hodgkin's disease died 2 weeks after the institution of therapy from pneumonia. The second death occurred in a patient with bone marrow and liver infiltration, who died after prolonged cytopenia and jaundice. Post-mortem examination revealed extensive cytomegalovirus infection of the lungs and regression of Hodgkin's disease.

Nausea and vomiting were common, and six patients had moderate or severe oral ulceration. Treatment was stopped in three patients because of the resulting debility. All patients developed alopecia.

Discussion

The activity of the combination of etoposide, vincristine and adriamycin (EVA) in recurrent or unresponsive Hodgkin's disease has been demonstrated by this study. The CR rate of 6 out of 18 evaluable patients (33%) and clinical remission (CR + GPR) rate of 11 out of 18 (61%) are encouraging, and are higher than have been achieved previously at St Bartholomew's Hospital with other salvage regimens [12]. Furthermore, good responses were not only seen in patients who had previously responded well to chemotherapy, but also in patients with a poor response to first-line therapy and in two patients who had become refractory to alternative chemotherapy. However, the duration of remission, in keeping with most other reports of salvage therapy in Hodgkin's disease, was disappointingly short.

Myelosuppression was the most serious toxicity encountered and was at least a contributory factor in the two deaths. For the remaining patients it was manageable. The relationship between myelosuppression and proximity to previous therapy suggests that modifications of the dosage or scheduling of the three drugs may be necessary for some patients.

These results suggest that EVA is non-cross-resistant with MVPP, although probably not curative for patients failing MVPP therapy. This has prompted the incorporation of these three drugs into a regimen for primary therapy for advanced Hodgkin's disease.

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