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An effective oral combination in advanced relapsed Hodgkin's disease prednisolone, etoposide, chlorambucil and CCNU

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Summary. Many patients with advanced Hodgkin's disease continue to need palliative therapy, but where there is no curative intent, patients and doctors may prefer oral treatment only. This paper describes the preliminary experience of such a schedule. A total of 15 patients with advanced relapsed Hodgkin's disease were treated with an oral regimen, PECC (prednisolone at 40 mg daily for 7 days, etoposide at 200 mg/m^2 on days 1–3, chlorambucil at 20 mg/m^2 on days 1–4 and CCNU at 100 mg/m^2 on day 1 only), repeated every 4–6 weeks. 12 patients had been extensively pretreated. 11 patients had extranodal disease and 8 had B symptoms when treatment was started. Eight patients achieved a complete remission, with a median duration of 7+ months, and five achieved a partial remission; the overall response rate was 86%. Haematological toxicity was the major side effect. There were no treatment-related deaths. All patients tolerated treatment well and the oral route has particular advantages for those unwilling or unable to accept intravenous treatment.

Introduction

The first-line treatment of advanced Hodgkin's disease is well described. Most patients are treated with MOPP (mechlorethamine, vincristine, procarbazine and prednisolone) or the MOPP-related combinations CLVPP (chlorambucil, vinblastine, procarbazine, prednisone) and MVPP (mustine, vinblastine, procarbazine, prednisone). Some centres use ABVD (Adriamycin, bleomycin, vinblastine and dacarbazine) as first-line chemotherapy. A number of randomized trials are in progress, comparing ABVD with standard MOPP and MOPP/ABVD alternating regimens with MOPP or ABVD alone. Newer combinations containing etoposide are also under evaluation as first-line treatment. Complete response rates of 70%–80% are achieved but, in the long term, 40%–50% of patients presenting with advanced Hodgkin's disease eventually require further treatment because of relapse or progressive disease [4].

Such patients present a chemotherapeutic challenge and various second-line options have been studied [5–7, 11, 13, 15, 16]. If these options fail, effective salvage treatment can be difficult and toxic. Three reported regimens [3, 8, 17, 18] attained complete remission rates of 14%–37%, with median disease-free survival of 15 [3, 17] and 19 months [18] and median survival of 50 weeks [8].

In 1987 our group developed the oral combination of prednisolone, etoposide, chlorambucil and CCNU (PECC) for use in patients with either progressive disease not responsive to standard regimens or advanced chronic, relapsing Hodgkin's disease [14]. The original intention was to provide effective palliation in end-stage patients, and the oral approach was chosen because many such patients are reluctant to consider further treatment involving intravenous injections.

The first two patients to receive PECC had been extensively pretreated, and both had extranodal disease that caused distressing symptoms. Each showed a good partial response to PECC after only two courses. This experience led us to carry out a phase II study of the oral combination in a larger number of patients. The study was subsequently expanded to include some patients who relapsed (<12 months) after primary chemotherapy.

Patients and methods

Between January 1987 and August 1988, 15 patients with relapsed advanced Hodgkin's disease or chronic relapsing Hodgkin's disease were studied. Their age and sex distribution, histology, stage at presentation and treatment prior to entry in the study are shown in Table 1.

The treatment schedule comprised 40 mg prednisolone daily for 7 days, 200 mg/m^2 etoposide on days 1–3, 20 mg/m^2 chlorambucil on days 1–4 and 100 mg/m^2 CCNU on day 1. Treatment was repeated every 4–6 weeks, depending on the peripheral blood count and on patient response. Some patients were treated only when symptomatic, in cases in which the intention was palliative rather than curative. A complete re-

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Table 1. Patient characteristics

Patient number	Age/sex	Stage	Histology	Initial treatment	Response	Remission duration (months)	Subsequent treatment	Response	Remission duration (months)
1	37/F	IIB	NK	Mantle	PR		MOPP	NR	
							Chlor/Pred/para aortic DXT	CR	9
2	39/M	IIIB	MC	CLVPP/ EVAP	CR	6	CHLVPP	CR	2
							LVB	PR	
3	61/M	IVA	MC	CLVPP	CR	14	LOPP/EVAP	CR	5
							DXT	NR	
							LVB	NR	
4	26/F	IVA	MC	OPEC/ABV Mantle	CR	11			
5	20/M	IVB	NK	MOPP Mantle	PR		ABVD	PR	
							Ifosfamide/VP16	CR	24
							Cytosine/mitoxantrone	NR	
6	34/M	IIIB	MC	CLVPP	CR	5			
7	25/F	IIA	NS	Mantle	CR	50	CLVPP	PR	
8	10/M	IIA	MC	Mantle	CR	23	Local DXT	CR	39
							Local DXT	CR	21
							MVPP	CR	53
							CLVPP	CR	25
							LVB	CR	18
							Chlor/Pred	CR	7
							Chlor/VP16/CCNU/DXT	CR	19
9	22/M	IIIA	MC	ABVD/ CLVPP DXT	CR	10			
10	23/M	IIIB	MC	CLVPP	CR	14	Methotrexate	NR	
							ABVM/DXT	PR	
							LVB	PR	
11	35/M	IIIB	NS	CLVPP	CR	12	LVB	CR	13
12	21/M	IIIB	NS	CLVPP Mantle	CR	15	DXT	NR	
							Mitoxantrone/cytosine	NR	
13	20/F	IIIA	NS	CLVPP + DXT	CR	12	CLVPP/LVB	PR	
							CLVPP/DXT	NR	
14	21/M	IIIB	NS	CLOPP	CR	22	DXT	CR	28
							CLVPP	CR	14
							CLVPP	NR	
15	17/M	IA	NS	Mantle	CR	24	MOPP	CR	8

MOPP: mechlorethamine, vincristine, procarbazine, prednisolone; CHLVPP: chlorambucil, vinblastine, procarbazine, prednisolone; EVAP: etoposide, vinblastine, Adriamycin, prednisolone; LVB: lomustine, vindesine, bleomycin; LOPP/CLOPP: chlorambucil, vincristine, procarbazine, prednisolone; OPEC: vincristine, prednisolone, etoposide, chlorambucil; ABV: Adriamycin, bleomycin, vinblastine; ABVD: Adriamycin, bleomycin, vinblastine, decarbazine; MVPP: mechlorethamine, vinblastine, procarbazine, prednisolone; chlor, chlorambucil; Pred, prednisolone; DXT, radiotherapy to involved fields

sponse was defined as the disappearance of symptoms and physical signs and the complete resolution of changes on X-rays and/or scans. A partial response was defined as the disappearance of symptoms and a reduction of >50% in measurable disease on scans or X-rays.

Results

The response to PECC treatment is shown in Table 2. Of 15 patients treated, 8 achieved a CR and 5, a PR, for an overall response rate of 86%. In two patients disease was progressive. Four patients who achieved CRs have relapsed at 5, 6, 8 and 10 months; one has again achieved a CR after additional courses of PECC. The remaining patients who achieved CRs continue well in CR at 4, 6, 9 and 10 months follow-up; two of these patients had only nodal disease at relapse and in one, the CR has been consolidated by radiotherapy. Of 11 patients with extranodal disease at treatment with PECC, 5 have achieved CRs (3 have since relapsed) and 4 have achieved PRs.

At the time of treatment with PECC, eight patients had B symptoms and seven did not. Four patients with B symptoms achieved CRs, three of which have been maintained. All patients with B symptoms improved symptomatically on treatment, including those whose disease ultimately progressed. PECC treatment was particularly effective in abolishing severe pruritus (patient 1), which had been refractory to all previous treatments. Of five patients who achieved PRs, one has since died of Hodgkin's disease and the remaining four continue in PR.

Toxicity

A total of 70 courses of treatment were given. In all, 11 courses were given after a 4-week treatment-free interval, 4 were given after 5 weeks and 24 were given after 6

weeks. Ten courses of treatment were delayed beyond 6 weeks because of cytopenia. When a patient had difficulty in meeting the 6-week schedule because of persistent cytopenia, the dose of CCNU was halved; the other drugs were given at full doses. The remaining courses of treatment were deliberately delayed by the physician in charge of the case and were used only on an ad hoc basis when the patient was symptomatic. Full details of haematological toxicity are shown in Table 3.

Four patients required transfusion during their treatment period. A total of 21 courses of antibiotics were given (13 courses to only 3 patients), and 10 periods of in-patient treatment were required for treatment of infection (5, septicaemia; 4, chest infection; 1, diarrhoea). One patient developed herpes zoster whilst on treatment. All patients developed alopecia and most had grade II nausea and vomiting for 24 h at the beginning of each course. No patient refused treatment because of side effects.

Table 2. Patient response to PECC

Patient number	Site of disease at start of PECC	B symptoms at start of PECC	Response to PECCC	Duration of response (months)
1	Nodes ? Liver	+	CR	9+
2	Nodes Liver	+	PR	–
3	Nodes	–	PR	–
4	Mediastinum Nodes	–	CR	6
5	Mediastinum Marrow Lungs Bone	+	PR	–
6	Mediastinum Lung	–	CR	5
7	Nodes	–	CR[a]	6+
8	Nodes	+	CR	8
9	Nodes Liver	+	PD	–
10	Liver Nodes	–	CR	10
11	Mediastinum Lung Nodes Bone	–	PR	–
12	Bone Soft-tissue back	+	NR/PD	–
13	Mediastinum Lung Nodes Bone	–	PR	–
14	Nodes Marrow ? Liver	+	CR	10+
15	Nodes	+	CR	4+

[a] Treatment with PECC was followed by DXT

Discussion

This oral combination was piloted as a salvage regime in heavily pretreated patients who did not wish to receive further treatment involving intravenous injections. All four drugs have previously been used in the treatment of advanced Hodgkin's disease, either as part of a different combination (chlorambucil, prednisolone) or as single agents (etoposide, CCNU), and all have demonstrated activity in advanced Hodgkin's disease [1, 2, 9, 10].

The CR rate of 53% and overall response rate of 86% compare favourably with reports of other salvage regimens (summarized in Table 4), as far as such comparisons can be made. It must be emphasized that the numbers of patients in these studies were necessarily small and that the extent and type of prior chemo/radiotherapy varied from centre to centre.

Cervantes et al. [3] used lomustine, etoposide and prednimustine (LEP) in an oral combination to treat patients resistant to CVPP (cyclophosphamide, vinblastine, procarbazine and prednisolone) and ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine). Three instances of severe myelosuppression occurred. Santoro et al. [17] used the same LEP regimen to treat patients with disease resistant to both MOPP and ABVD. The treatment was generally well tolerated and all toxic signs were reversible. Two patients with extensive previous irradiation required hospitalization because of severe thrombocytopenia, and three patients refused further cycles of treatment.

Table 3. NCI toxicity grades[a]

	Haemoglobin (Hb): 0 1 2 3 4	WBC count: 0 1 2 3 4	Platelets: 0 1 2 3 4
At start of PECC	12 3	13 2	15
After PECC 1	5 5 4 1	3 3 5 4	8 4 3
After PECC 2	9 4 1	4 5 2 3	9 3 2
After PECC 3	5 4 3	2 2 4 4	7 1 3 1
After PECC 4	5 1 5 1	4 4 3 1	7 1 3 1
After PECC 5	7 1 1	3 3 2 1	5 2 2
After PECC 6	5 2	4 1 1 1	5 1 1

[a] Key to NCI toxicity grades:

	0 = None	1 = Minimal	2 = Moderate	3 = Severe	4 = Life threatening
Hb (g/dl)	>11.0	9.5–10.9	7.5–9.4	5.0–7.4	<5.0
WBC ($\times 10^9$/l)	>4.5	3.0–4.4	2.0–2.9	1.0–1.9	<1.0
Platelets ($\times 10^9$/l)	>130	90–129	50–49	25–49	<25

Table 4. Salvage regimens in relapsed Hodgkin's disease

Reference	Regimen	Patients (*n*)	Complete (*n*)	Remission: (%)	Response duration	Overall response (CR + PR)
[3]	LEP	15	4	27	2 with no evidence of disease at 7 and 18 months	40
[17]	LEP	58	23	40	Median duration of CR, >15 months	54
[8]	MIME	47	11	23	Median survival 50 weeks	63
[18]	LEM	32	4	13	Median duration of CR, >33 months	48
[12]	CEVD	32	14	44	Median duration of CR, >10 months	56

LEP: lomustine, etoposide, prednimustine; MIME: methyl-GAG, ifosfamide, methotrexate, etoposide; LEM: lomustine, etoposide, methotrexate; CEVD: lomustine, etoposide, vindesine, dexamethasone

A total of 47 patients with relapsed Hodgkin's disease were treated with methyl-GAG, ifosfamide, methotrexate and etoposide (MIME) [8]. All patients had previously received MOPP or similar regimens and doxorubicin-containing combinations; many had received extensive irradiation. Chances of achieving a CR were adversely influenced by the presence of extranodal disease, by serum LDH and haemoglobin values and by the number of relapses before MIME. Toxicity was significant, including infections (23%), neutropenic fever (34%) and haemorrhagic cystitis (23%).

Tseng et al. [18] treated 32 patients resistant to MOPP, ABVD and prior irradiation (20 patients) with lomustine, etoposide and methotrexate (LEM). The majority of patients (23 cases) had B symptoms and the major site of disease was nodal (22 patients). The major toxic effect was severe myelosuppression, which occurred in six patients.

The most recent report of an effective salvage regimen for relapsed advanced Hodgkin's disease is from the German Hodgkin's study group [8]. In this multi-centre trial, 32 patients resistant to cyclophosphamide, vincristine, procarbazine and prednisolone (COPP)) and ABVD were treated with lomustine, etoposide, vindesine and dexamethasone (CEVD). Treatment was well tolerated, with only one episode of septicaemia. Overall, 25% of courses were delayed because of neutropenia and 10% because of thrombocytopenia. One patient refused to complete the treatment for psychological reasons.

It is clear that third-line salvage combinations can rescue some patients with relapsed advanced Hodgkin's disease, but the chances of success are better if the patient has only nodal disease and no B symptoms and has shown a good response to first-line treatment. We are now investigating the possibility of using PECC as second-line treatment in cases of progressive disease or early relapse and consolidating CR with radiotherapy and/or autotransplant. We were encouraged to do this after seeing marked subjective improvement and five CRs in patients we had previously considered as having end-stage disease and for whom treatment was intended to be palliative. We used high doses of drugs, but haematological toxicity was not too severe. No patient refused treatment. Infection was the commonest reason for hospital admission, with three patients accounting for >60% of the total amount of antibiotics used.

In conclusion, we submit that PECC is an effective salvage combination in Hodgkin's disease. It is well tolerated by the patients and has particular advantages for those with difficult venous access or those unwilling to accept further intravenous chemotherapy.

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References

1. Cavalli F (1985) VP16 in the treatment of malignant lymphomas – a report from the Swiss group for Clinical Cancer Research (SAKK). Semin Oncol 12: 33–36
2. Cecil JW, Quagliana JM, Coltman CA, Al-Sarraf M, Thigpen T, Groppe CWJ (1978) Evaluation of VP-16-213 in malignant lymphoma and melanoma. Cancer Chemother Rep 62: 801–803
3. Cervantes F, Reverter JC, Montserrat E, Rozman C (1986) Treatment of advanced resistant Hodgkin's disease with lomustine, etoposide and prednimustine. Cancer Treat Rep 70: 665–667
4. De Vita VT Jr, Simon RM, Hubbard SM, Young RC, Berard CW, Moxley JH, Frei E III, Carbone PP, Canellos GP (1980) Curability of advanced Hodgkin's disease with chemotherapy: long term follow up of MOPP-treated patients at the National Cancer Institute. Ann Intern Med 92: 587–595
5. Fisher RI, De Vita VT Jr, Hubbard SP, Simon R, Young RC (1979) Prolonged disease free survival in Hodgkin's disease with MOPP reinduction after first relapse. Ann Intern Med 90: 761–763
6. Goldman JM, Dawson AA (1975) Combination therapy for advanced resistant Hodgkin's disease. Lancet II: 1224–1227
7. Goldman JM, Dawson AA (1981) Chemotherapy for advanced resistant Hodgkin's disease. Lancet I: 252
8. Hagemeister FB, Tannir N, Mclaughlin P, Salvador P, Riggs S, Velasquez WS, Cabanillas F (1987) MIME chemotherapy (methyl-GAG, ifosfamide, methotrexate, etoposide) as treatment for recurrent Hodgkin's disease. J Clin Oncol 5: 556–561
9. Hansen HH, Selawry OS, Pajak TF, Spurr CL, Falkson G, Brunner K, Cutner J, Nissen NI, Holland JF (1981) The superiority of CCNU in the treatment of advanced Hodgkin's disease: Cancer and Leukaemia Group B study. Cancer 47: 14–18
10. Kaye SB, Juttner CA, Smith IE, Barrett A, Austin DE, Peckham MJ, McElwain TJ (1979) Three years' experience with ChLVPP (a combination of drugs of low toxicity) for the treatment of Hodgkin's disease. Br J Cancer 39: 168–174
11. Lennard AL, Proctor SJ, Dawson AA, Allan NC, Prescott RJ, Parker AC, Leonard RCF, Angus B, Dobson C, Ritchie GL, Lucraft HH, Scott S (1989) Lomustine, vindesine and bleomycin (LVB) used in the treatment of relapsed advanced Hodgkin's disease. Haematol Oncol 7: 77–86
12. Pfreundschuh MG, Schoppe WD, Fuchs R, Pfluger KH, Loeffler M, Diehl V (1987) Lomustine,, etoposide, vindesine and dexamethasone (CEVD) in Hodgkin's lymphoma refractory to cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) and doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD): a multicentre trial of the German Hodgkin's study group. Cancer Treat Rep 71: 1203–1207

13. Porzig KJ, Portlock CS, Robertson A, Rosenberg SA (1978) Treatment of advanced Hodgkin's disease with B-CAVe following MOPP failure. Cancer 41: 1670–1675
14. Proctor SJ, Evans RGBE (1985) Recognition of a chronic relapsing form of Hodgkin's disease in a population of patients demonstrating no second tumours. Clin Radiol 36: 461–464
15. Roach M III, Kapp DS, Rosenberg SA, Hoppe RT (1987) Radiotherapy with curative intent: an option in selected patients relapsing after chemotherapy for advanced Hodgkin's disease. J Clin Oncol 5: 550–555
16. Santoro A, Bonfanta V, Bonadonna G (1982) Salvage chemotherapy with ABVD in MOPP resistant Hodgkin's disease. Ann Intern Med 96: 139–143
17. Santoro A, Viviani S, Valagussa P, Bonfante V, Bonadonna G (1986) CCNU, etoposide and prednimustine (CEP) in refractory Hodgkin's disease. Semin Oncol 13: 23–26
18. Tseng A Jr, Jacobs C, Coleman CN, Horning SJ, Lewis BJ, Rosenberg SA (1987) Third-line chemotherapy for resistant Hodgkin's disease with lomustine, etoposide and methotrexate. Cancer Treat Rep 71: 475–478