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ChlVPP Chemotherapy in Advanced Hodgkin's Disease

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Abstract—*Between March 1978 and January 1987 54 patients with advanced Hodgkin's disease (HD) or relapse following radiotherapy (RT) for Hodgkin's disease have been treated with combination chemotherapy consisting of chlorambucil, vinblastine, procarbazine and prednisolone (ChlVPP). A subgroup of five patients with bulky mediastinal disease received mantle RT in addition to ChlVPP chemotherapy.*

Forty-two patients (77.8%) entered complete remission with 33 (61.0%) remaining in unmaintained remission and 44 (81.5%) alive at a median follow up of 51 months (range: 22–103).

The treatment was generally well tolerated with minimal toxicity.

ChlVPP is effective first-line treatment for Hodgkin's disease with results which may be comparable to those achieved for MOPP but with significantly less toxicity.

INTRODUCTION

THE ADVENT of the MOPP regimen [1] resulted in a dramatic change in outlook for patients with advanced and relapsing Hodgkin's disease. For many years MOPP has been regarded as standard therapy; a recent paper reports a CR rate of 84% and relapse-free survival of 66% [2]. The toxicity of MOPP is however considerable [3]; in addition approx. 20–40% of patients will ultimately die of their disease despite this treatment.

Two main approaches to improving treatment have evolved in the last decade. Firstly, attempts have been made to reduce toxicity, whilst preserving the efficacy of treatment by drug substitution in a variety of regimens [4–11]. Secondly, a number of groups have tried to increase cure rates by using alternating regimens or by incorporating radiotherapy into the treatment strategy [12–14].

In 1977 the Royal Marsden Hospital published the results of a low toxicity regimen ChlVPP, substituting chorambucil for nitrogen mustard and vinblastine for vincristine, thus effectively reducing the acute gastrointestinal and neurological toxicity of MOPP. Comparable results have been reported with the two regimens [5].

We report here our experience of ChlVPP over a 10-year period.

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PATIENTS AND METHODS

Between March 1978 and January 1987, 54 patients with a diagnosis of Hodgkin's disease were treated by the CRC Wessex Regional Medical Oncology Unit, with ChlVPP chemotherapy (chlorambucil, vinblastine, procarbazine and prednisolone).

All histological sections were reviewed by Professor D. Wright (Dept of Pathology, Southampton General Hospital). The Rye modification of the Lukes and Butler histopathological classification [15] was used. Forty-two patients had nodular sclerosing, six mixed cellularity and six lymphocyte predominant Hodgkin's disease.

Forty patients were male and 14 female with a median age of 29 years (range 15–73). Twelve patients had relapsed after prior radiotherapy, 11 to a mantle and one to an inverted Y field (Table 1). No patient had received previous chemotherapy.

Staging was assessed according to the Ann-Arbor system [16]. Full blood counts, biochemical and liver function profiles, CXR, lymphography, abdominal ultrasound and unilateral bone marrow trephine were obtained routinely. Liver biopsy was taken where indicated, to confirm stage IV disease. Staging laparotomies were performed at diagnosis in the 11 patients relapsing from mantle radiotherapy. No other patients were staged with laparotomy.

At the commencement of ChlVPP chemotherapy, 16 patients had stage II, 27 stage III and 11 stage

Table 1. CR rate by stage

Stage	Number of patients	Number relapsing from prior radiotherapy	CR
IIA	8*	3	7
IIB	8	2	7
IIIA	12	3	11
IIIB	15	1	9
IVA			
Total	5	—	4
Bone marrow	2	—	2
Liver	1	—	1
Bone	1	—	1
Skin	1	—	0
IVB			
Total	6	3	4
Bone marrow	—	—	—
Liver	2	—	1
Liver and bone marrow	3	2	2
Lung	1	1	1
Total	54	12	42

*Includes five patients with bulky mediastinal disease treated with combined modality therapy.

IV disease (Table 1). Twenty-nine patients (54%) had B symptoms at presentation.

Patients were re-evaluated after four cycles of treatment. Treatment was planned to continue for two courses beyond complete remission or stable partial remission with a minimum of six courses to be administered per patient.

Because of evidence suggesting that the subgroup of patients with stage II disease and bulky mediastinal adenopathy (ratio of tumour size to transthoracic diameter greater than 1/3, T:M > 1/3) have an unacceptably high relapse rate when treated with RT alone [17, 18], all such patients treated after 1982 received combination chemotherapy and mantle radiotherapy. RT was sandwiched between two series of three courses of chemotherapy. A radiation dose of 35 Gray was delivered in 16 fractions in 4 weeks on an 8 MeV linear accelerator through opposed mantle fields to the chest.

Complete remission was defined as disappearance of clinical radiological, biochemical and haematological evidence of Hodgkin's disease. Disease-free survival was calculated from the date of completion of chemotherapy and survival from date of presentation or relapse from radiotherapy.

Chemotherapy was administered at 28 day intervals. Chlorambucil was given at a dose of 6 mg/m^2 orally daily days 1–14 (max. dose 10 mg/day); procarbazine at a dose of 100 mg/m^2 orally daily, days 1–14, prednisolone at a dose of 40 mg orally daily, days 1–14 and vinblastine at a dose of 6 mg/m^2 i.v. days 1 and 8 (max. single dose 10 mg). Appropriate dose reductions or delays in therapy were made according to blood counts performed on days 1 and 8 using published criteria [5].

RESULTS

Forty-two of 54 patients (77.8%), including all five patients treated with chemotherapy and radiotherapy, achieved a complete remission (CR) with 33 (61.6%) remaining in continuous CR at a median follow up of 51 months (range 22–103, Fig. 1). Nine patients (21.4%) have relapsed from CR at a median of 3.5 months (range 1–14). Four of these patients achieved a further CR with second-line adriamycin containing combination chemotherapy and two remain in CR at 32 and 40 months. Two patients have been lost to follow up, both of whom were in CR at last review at 32 and 60 months from chemotherapy.

Twelve patients did not achieve complete remission with ChlVPP. Four subsequently achieved CR, three with adriamycin containing chemotherapy and one with high dose chemotherapy and autologous marrow rescue, all four remain in CR at 10, 22, 40 and 92 months from treatment. Two of the remaining patients are alive with disease and five have died with progressive Hodgkin's disease, all after second-line therapy. One patient died during ChlVPP chemotherapy.

Differences in CR rate and survival according to age, sex, stage, presence of symptoms and histology are given in Table 2. Statistical significance was not assessed due to the small numbers in each group.

Forty-four patients (81.5%) are alive at a median follow up of 51 months (range 22–103, Fig. 2). Ten (18.5%) patients have died, eight with progressive Hodgkin's disease, one from meningitis whilst apparently in CR and one from *Legionella* pneumonia during his initial course of chemotherapy.

The five patients who received combined modality therapy for bulky mediastinal disease all remain in continuous CR, 17, 56, 71, 74 and 91 months from completing treatment.

DRUG ADMINISTRATION AND TOXICITY

The chemotherapy was easy to administer according to schedule and was well tolerated. All patients were treated on an out-patient basis.

Five patients required substitution of one of the regimen drugs because of specific side-effects; in three patients procarbazine was discontinued after the development of severe cutaneous reactions and in two patients vinblastine was discontinued because of unacceptable neurotoxicity. Of the remaining 49 patients, nine required a total of 13 treatment delays of between 1 and 2 weeks for delayed haematological recovery. Ninety-three per cent of the calculated ideal dose of chlorambucil,

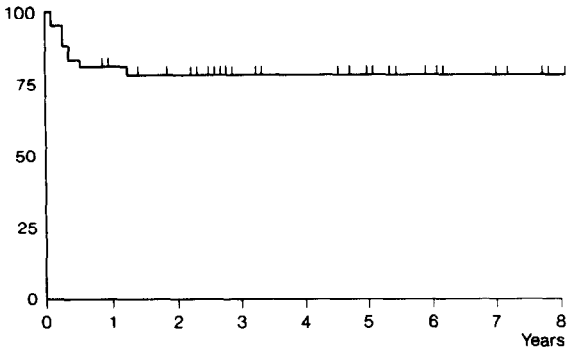

Fig. 1. ChlVPP relapse-free survival.

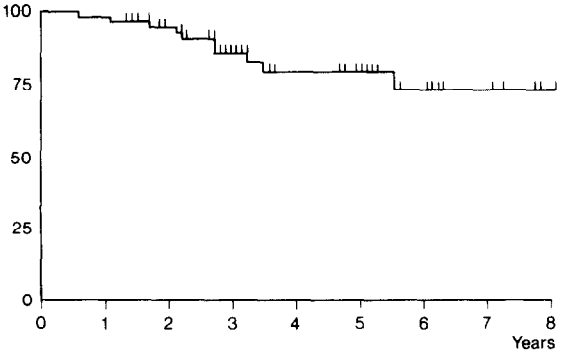

Fig. 2. ChlVPP overall survival.

94% of vinblastine, 91% of procarbazine and 95% of prednisolone was actually administered.

Non-haematological toxicity was mild with a majority of patients experiencing either no nausea or vomiting or mild nausea with the vinblastine injections and/or procarbazine tablets. Only three patients experienced moderate nausea and vomiting. Three patients had documented mild neuropathy related to vinblastine administration in addition to the two who experienced severe neuropathy requiring cessation of that drug. No patient had more than minimal hair thinning and most lost no hair. No patient refused therapy. There have been no cases of second malignancy or myelodysplastic syndrome (Table 3).

There were six episodes of neutropenic fever in three of which no organism was recovered; three documented infections also occurred, one resulting in death from *Legionella* pneumonia.

DISCUSSION

For two decades MOPP has been the standard with which other treatments of advanced Hodgkin's disease have been compared. During this period a

Table 2. Patient characterisics

	Number of patients (%)	Number achieving CR (%)	Number continuously free of disease (%) (median follow up 47 months)
Total	54	42 (77.8)	33 (61.6)
Age			
<40 years	43 (79.6)	33 (76.7)	27 (62.8)
>40 years	11 (20.4)	9 (81.8)	9 (81.8)
Sex			
Males	40 (74.1)	32 (80)	24 (60)
Females	14 (25.9)	10 (71.4)	9 (64.3)
B Symptoms			
Yes	29 (53.7)	21 (72.4)	14 (48.3)
No	25 (46.3)	21 (84.0)	19 (76.0)
Histology			
NS	42 (77.8)	31 (73.6)	23 (54.8)
MC	6 (11.1)	5 (83.3)	4 (66.7)
LP	6 (11.1)	6 (100)	6 (100)
Stage			
II	16 (29.6)	14 (87.5)	12 (75)
III	27 (50.0)	20 (74.1)	15 (55.6)
IV	11 (20.4)	8 (72.7)	6 (54.5)
Prior RT	12 (22.2)	10 (83.3)	8 (66.7)
No prior RT	42 (77.8)	32 (76.2)	25 (59.5)
Combined CT and RT (mantle)	5 (9.3)	5 (100)	5 (100)

NS = Nodular sclerosing; MC = mixed cellularity; LP = lymphocyte predominant; RT = radiotherapy; CT = chemotherapy.

Table 3. Non-haematological toxicity

Toxicity	*n*
Nausea and vomiting	
WHO grade 0	31
WHO grade 1	20
WHO grade 2	3
Neuropathy	
WHO grade 0	49
WHO grade 1	3
WHO grade 3	2
Alopecia	0
Second malignancy	0

number of alternative regimens have been adopted in an attempt both to improve cure rates and to reduce treatment toxicity.

There have been few randomized trials comparing MOPP with its less toxic 'drug substitution' alternatives. There is however a consensus that they are of equal efficacy [3]; quite clearly they are also far more acceptable to patients.

With regard to long-term toxicities, namely sterility and second malignancy, there is probably little difference between ChlVPP and MOPP. Whilst we have seen no patients develop second malignancy or myelodysplasia following ChlVPP, the actual rate remains uncertain.

Problems of sterility in males can, to an extent, be overcome by sperm banking prior to therapy [19] and by *in vitro* fertilization techniques for patients oligospermic after therapy [20]. Despite this, the concern of sterility remains for the majority of patients.

The drug combination ABVD, promoted primarily by the Milan group [7], has the advantage of being less toxic to the germinal epithelium and apparently less leukaemogenic than MOPP. It has also been tested against MOPP in clinical trials [21, 22], and in terms of efficacy is probably comparable. However, ABVD causes severe gastrointestinal toxicity and the long-term toxic effects of adriamycin and bleomycin are of concern [20].

The results of a variety of alternating drug combinations have now been published [8, 12], and recently a randomized trial of MOPP alternating with ABVD vs. ABVD alone and MOPP alone was reported [21]. In this trial both the alternating arm and the ABVD alone arm showed a modest increase in CR rate and freedom from progression over MOPP alone. This study, as with other trials of MOPP against ABVD [12], has been criticized as drug delivery in the MOPP arm has been poor [22]. Mature results of this and other such studies are awaited with interest.

What should be the standard first line chemotherapy for Hodgkin's disease? ChlVPP is a low toxicity, low cost regimen which is eminently suitable for general use. Subsets of patients (particularly those without B symptoms) have an excellent prognosis with this regimen. An exciting phase of development of Hodgkin's disease treatment is now beginning. The evolution of autologous bone marrow transplantation as an effective salvage treatment modality with acceptable toxicity may change our concepts of management, allowing use of a low toxicity regimen as initial therapy, reserving toxic therapy for those threatened by a relapse.

In conclusion, our results confirm that ChlVPP is effective first line treatment for advanced HD, particularly in patients with good prognostic features.

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