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Original Paper

A Limited Role for VEEP (Vincristine, Etoposide, Epirubicin, Prednisolone) Chemotherapy in Childhood Hodgkin's Disease

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The VEEP regimen (vincristine, etoposide, epirubicin, prednisolone), with or without involved field radiotherapy, has been shown to be an effective treatment in adult Hodgkin's disease. In an attempt to avoid the late sequelae of both alkylating agents and radiotherapy this regimen has been studied in a series of 54 children and young adults. Early analysis suggested that the relapse rate was higher with VEEP than with standard alkylating agent-based regimens. Sufficient follow-up has now been achieved to evaluate the likelihood of sustained remission following second-line treatment and therefore the overall long term survival with this treatment approach. The 5-year Overall Survival (OS) and 5-year Progression Free Survival (PFS) for patients with stage I–III disease was 93% and 82% respectively. However, the 5-year OS and PFS for stage IV patients was only 44% and 50%, respectively. Of 13 patients who were initial treatment failures on VEEP, 7 of whom had advanced disease, only 6 were salvaged with second-line therapy. 8 of 33 who attained a complete response (CR) relapsed and there were 2 relapses in those achieving a partial response (PR) ($n = 8$). All those relapsing from CR/PR were salvaged by second-line alkylating agent chemotherapy ± radiotherapy, ± high dose chemotherapy. In conclusion, patients with stage I–IIIA, non-bulky disease, the moderately high relapse rate did not adversely affect the overall high cure rate, although VEEP failures were subjected to a high total treatment burden. VEEP alone is inadequate in patients with stage IV disease, bulky mediastinal disease in/or those with B symptoms in whom there is a high primary failure rate and relatively poor results with second line therapy.

Key words: VEEP, bulky mediastinal disease, primary non-responses, stage IV
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INTRODUCTION

COMBINATION CHEMOTHERAPY has an established role in childhood Hodgkin's disease and in most studies is given with involved field radiotherapy. In stage IA cervical disease, radiotherapy alone, as currently used by the United Kingdom Children's Cancer Study Group (UKCCSG) may be effective and the salvage rate of these patients with chemotherapy in the event of relapse results in a very high overall cure rate [1, 2].

The chemotherapy regimens generally used are similar to those in the treatment of adult Hodgkin's disease and most involve the use of alkylating agents. The MOPP regimen (mustine, vincristine, prednisolone and procarbazine) is the gold standard against which all regimens are compared. Although the results with MOPP or hybrid regimens in children are excellent [3–5] this outcome has to be balanced against early and late adverse effects. Significant myelosuppression is common and gonadal failure is inevitable in the young adult male [6, 7]. ChlVPP (chlorambucil, vinblastine, procarbazine and prednisolone) was developed to reduce acute toxicity and produces comparable results. Late sequelae such as second malignancy and sterility are similar to MOPP and there is also a recent suggestion that ovarian dysfunction may be common in girls [8, 9]. The risk of second malignancy varies with the total doses given, use of radiotherapy and age at diagnosis but it has been estimated that with combined modality treatment the actuarial risk of

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all secondary cancers may even be as high as 20% at 20 years from diagnosis [10].

Most current chemotherapy regimens in Europe and the U.S.A. contain multiple drugs e.g. MOPP–ABVD hybrid combined with involved field radiotherapy [3, 5]. The use of a hybrid regimen, though containing only 3–4 courses of MOPP, is still likely to be accompanied by a significant risk of male sterility.

The advantage of anthracycline-based regimens such as ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) is comparable efficacy with high response rate and few relapses. However, there are other long-term sequelae associated with the doxorubicin and bleomycin such as cardiomyopathy and lung fibrosis, respectively. The VEEP regimen consists of vincristine, epirubicin, etoposide and prednisolone. Epirubicin was chosen because of its lesser cardiotoxic effects [11] and etoposide because of its efficacy [12] and lack of sterilising effect. The omission of bleomycin avoids pulmonary toxicity, especially if mediastinal irradiation is given. Experience in adults has confirmed the lack of significant cardiac toxicity and persisting fertility in adult males using the VEEP regimen [13].

The results of a pilot study using VEEP in children have been reported in which, despite encouraging response rates in relapsed Hodgkin's disease, the event-free survival in newly diagnosed patients appeared to be poorer than with standard regimens [14]. In the present study, this group and a cohort of subsequently treated children have been followed up to examine the likelihood of long-term survival in relapsed patients due to second-line therapy.

PATIENTS AND METHODS

Patients were diagnosed and treated at various paediatric oncology centres in the U.K. and the Republic of Ireland. Since 1990 patients given this regimen were predominantly male, in whom fertility was a major concern and from a single centre. All were previously untreated with chemotherapy.

Patients were staged according to the Ann Arbor System [16]. Staging procedures included clinical history, physical examination, chest X-ray, computed tomography of chest and abdomen and/or ultrasound of abdomen and pelvis. Staging laparotomy was not performed routinely. Biopsy specimens were classified as per the Rye Criteria [15] namely, lymphocyte predominant (LP), nodular sclerosing (NS), mixed cellularity (MC) and lymphocyte depleted (LD).

Relapse was documented where possible by biopsy if peripheral nodes or bone marrow were involved. In cases where this was not possible, unequivocal new radiological lesions were accepted as proof of relapse in the absence of another reasonable explanation. Overall survival (OS) and progression-free survival (PFS) curves were calculated using the method of Kaplan and Meier [17].

Patients were treated with up to eight courses of combination chemotherapy comprising vincristine, epirubicin, prednisolone and etoposide, administered at 21-day intervals. Before 1992, etoposide was given orally at a dose of 200 mg/m^2 D_{1-4} and epirubicin 40 mg/m^2 as an intravenous infusion over 30 min. In 1992, because of concern about efficacy and the reliability of oral etoposide in children the regimen was modified and was administered in the following schedule: vincristine 1.5 mg/m^2 days 1 and 8, epirubicin 50 mg/m^2 intravenous (i.v.) infusion, over 6 hours on day 1, etoposide 100 mg/m^2 i.v. infusion over 1 h days 1–5 and prednisolone 60 mg/m^2 orally (P.O.) days 1–8. Dose adjustments for toxicity were at the discretion of individual physicians. The total number of courses depended on the timing of achieving complete remission (usually CR + 2 courses). Those who failed to achieve CR or had progression while on treatment were changed after 2–6 cycles to ChlVPP. Consolidation with radiotherapy (XRT), (30–35 Gy) was considered for children with bulky mediastinal disease at diagnosis defined as disease exceeding one-third of the chest diameter on a posterior anterior chest X-ray at the level of T_5 vertebra and/or with localised abnormalities either clinical or radiological, characteristic of residual disease on completion of VEEP chemotherapy. This was not compulsory and was at the discretion of individual physicians. High-dose gallium and magnetic resonance imaging (MRI) were used in some patients but were not standard. Similarly, in some cases residual disease was biopsied.

RESULTS

54 patients were treated between 1987 and 1995; the median follow-up at the time of analysis was 5.5 years. Ages ranged from 2–19 years with a median of 10 years, M:F ratio was 2.4:1.

Stage distribution and the histological subtypes are shown in Table 1. 38 patients had mediastinal disease at presentation, of whom 18 patients had bulky mediastinal disease. 27 patients had B symptoms at diagnosis. NS was the predominant histological subtype 40/54 (74%) followed by MC-13/54 (24%). There was 1 patient with LP subtype, 4 patients had had involved field radiotherapy for stage 1A high cervical disease and were treated with VEEP at the time of first relapse. One patient had a local recurrence, 2 in the abdomen and one in the abdomen and thorax.

All patients ($n = 54$) have been evaluated for response and have been categorised into three groups. (Table 1) Responses according to risk factors are shown in Table 2.

Complete response

33 patients (61%) attained complete response (CR) to VEEP chemotherapy, of whom 4 had bulky mediastinal disease and 11 had B symptoms at diagnosis. 4 received radiotherapy as consolidation treatment after completion of VEEP

Table 1. *Responses to VEEP according to stage and histology*

	Stage			Histology				Bulky mediastinal disease
	I	II	III	IV	NS	MC	LP	
Complete responses	2	21	8	2	22	10	1	4
Partial responses	1	4	1	2	8	0	0	4
Progressive disease		6	3	4	10	3	0	10

Table 2. *Initial response and outcome following VEEP according to risk factors at diagnosis*

	B-Symptoms	Bulky mediastinum	Advanced stage (III/IV)
CR/PR ($n = 41$)	17	8	13
Initial PD ($n = 13$)	10	10	7
Relapses ($n = 10$)	5	4	5

CR, complete response; PR, partial response; PD, progressive disease.

Table 3. Characteristics of patients with progressive disease

Stage	Histology	Site of disease	Bulky mediastinal disease	Second-line treatment	Status
IIA	NS	Cervical nodes, mediastinum	Yes	ChlVPP + Med XRT	Alive
IIA	NS	Cervical nodes, mediastinum	Yes	ChlVPP + Med XRT	Alive
IIB	NS	B/L cervical nodes	No	ChlVPP	Alive
IIB	NS	B/L cervical nodes, mediastinum	Yes	ChlVPP + HD melphalan + ABMT	Alive
IIIB	MC	Cervical and para-aortic nodes	No	ChlVPP + involved field XRT	Alive
IIIB	MC	Mediastinum, para-aortic nodes	Yes	ChlVPP + BEAM + ABMT + Med XRT	Alive
IIA	NS	Cervical nodes, mediastinum	Yes	ChlVPP + Med XRT 2×BEAM + ABMT	Died
IIB	NS	B/L cervical nodes, mediastinum	Yes	ChlVPP + Med XRT	Died
IIIB	MC	Cervical, para-aortic nodes and spleen	No	None	Died
IVB	NS	Cervical nodes, mediastinum, bone and bone marrow	Yes	CCNU, chlorambucil and prednisolone	Died
IVB	NS	Mediastinum, lung	Yes	ChlVPP + mantle XRT	Died
IVB	NS	Mediastinum, bone, cervical nodes	Yes	ChlVPP + methyl prednisolone + mantle + inverted Y XRT	Died
IVB	NS	Mediastinum, lungs	Yes	ChlVPP	Died

ABMT, autologous bone marrow transplantation; Med, mediastinum; BEAM, BCNU, etoposide, cytosine arabinoside, melphalan; HD, high-dose; XRT, radiotherapy; ChlVPP, chlorambucil, vinblastine, prednisolone, procarbazine; NS, nodular sclerosing; MC, mixed cellularity; B/L, bilateral.

because of the presence of bulky mediastinal disease at presentation. 2 received mediastinal radiation alone while the other 2 had standard mantle radiation.

Partial response

8 patients (15%) achieved a partial response (PR). PR was documented after 6 or more courses of VEEP in 5 patients and between 3 and 5 courses of VEEP in 3 patients. All eventually achieved CR, 5 with radiotherapy and 3 with further chemotherapy—ChlVPP. Radiation treatment consisted of standard mantle ($n = 2$), mediastinal and neck radiation ($n = 2$) and involved field radiation to neck alone ($n = 1$). Biopsy of the suspected lesions was not done in any of these patients.

Progressive disease

13 patients (24%) had progressive disease on VEEP, of whom 10 had bulky mediastinal disease at presentation, 7/13 had advanced disease at diagnosis—3 stage III, 4 stage IV. 10 had B symptoms (Table 3).

Relapses

8/33 (24%) who attained CR, relapsed, of whom 2 had bulky mediastinal disease. All except 1 relapsed within 18 months of diagnosis and 6 relapsed at the site of original disease. There were 2 relapses in those with PR at completion of VEEP and both had bulky mediastinal disease. Both relapsed after having received radiotherapy after completion of VEEP. One child relapsed at the site of original mediastinal disease and the second relapsed in the abdomen (Table 4).

Salvage treatment

Of the 10 patients who relapsed from CR/PR, all remain in second remission after alternative non-cross-resistant chemotherapy ChlVPP ($n = 3$), ChlVPP/ABVD ($n = 2$), ChlVPP + XRT ($n = 3$), ChlVPP + high-dose melphalan + autologous bone marrow transplantation (ABMT) ($n = 2$). 4 patients with progressive disease were salvaged with second-line chemotherapy, ChlVPP, with or without radiotherapy and 2 also received high-dose chemotherapy with ABMT rescue.

Survival

Five years progression-free survival (PFS) for stages I, II and III is 82% and for stage IV is 50% (Figure 1). Overall 5-year survival for stages I, II and III is 93% and for stage IV is 44% (Figure 2) ($P < 0.005$). 7 patients died, all from progressive disease with no response to subsequent treatment. 4 had stage IV disease and all had B symptoms at diagnosis. 6 had bulky mediastinal disease at diagnosis (Figure 3).

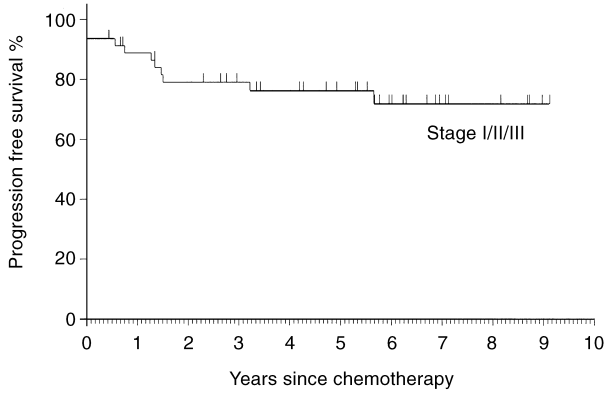

Figure 1. 5-year progression-free survival (PFS) after VEEP for patients with stage I–III Hodgkin's disease.

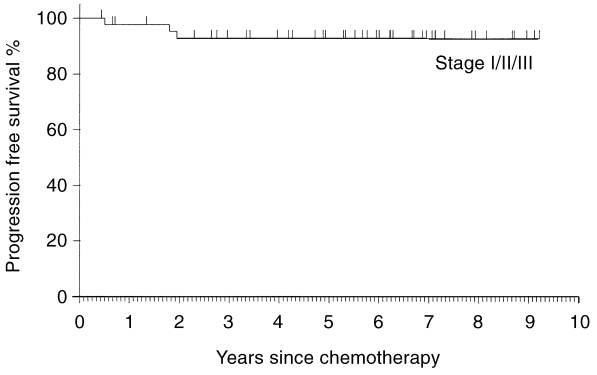

Figure 2. 5-year overall survival (OS) after VEEP for patients with stage I–III Hodgkin's disease.

Table 4. Characteristics of relapsed patients

Stage	Sex	Histology	Sites of disease	Site of relapse	Bulky med disease	Response to VEEP	No. of courses VEEP	Tx at relapse	Status
1A	M	MC	Cervical nodes	Mediastinum	No	CR	6	ChlVPP×5	Alive NED 87 months
IVB	F	NS	Cervical, mediastinal para-aortic bone deposits	Cervical node para-aortic	Yes	CR	8	ChlVPP×3/ ABVD×3	Alive NED 60 months
III	M	MC	Cervical	Para-aortic	No	CR	8	ChlVPP×4 HD melphalan ABMT	Alive NED 67 months
IIB	M	NS	Cervical mediastinum	Cervical nodes mediastinum	Yes	PR	8	ChlVPP×5 HD melphalan ABMT	Alive Alive 72 months
IVB	M	NS	Cervical axillary bone deposits	Para-aortic spleen	No	CR	7	ChlVPP×4/ ABVD×3	Alive NED 68 months
IIIA	M	NS	Cervical spleen para-aortic nodes mediastinum	Cervical nodes	Yes	CR	8	ChlVPP×6	Alive NED 32 months
IB	M	NS	Mediastinum	Mediastinum para-aortic	Yes	PR	6	ChlVPP×6 plus ABD XRT	Alive NED 72 months
IVB	M	NS	Cervical mediastinum lungs para-aortic	Para-aortic supraclacvular	No	CR	6	ChlVPP×6	Alive NED 12 months
IIA	F	MC	Cervical mediastinum	Para-aortic iliac	No	CR	6	ChlVPP×5 plus ABD XRT	Alive NED 79 months
IIA	M	NS	B/L cervical nodes	Cervical node	No	CR	6	ChlVPP×6 plus neck XRT	Alive NED 10 months

ABMT, autologous bone marrow transplantation; ABD XRT, abdominal radiation; HD, high-dose; Tx, treatment; NED, no evidence of disease; CR, complete response; PR, partial response. All other abbreviations as in Table 3.

Follow-up data on late effects were available for only half the patients. There was no clinically evident cardiac toxicity during treatment or in the follow-up period Echocardiographic evaluation to assess left ventricular function was performed in 24 patients after completion of VEEP chemotherapy and was normal in 22. One patient had mildly reduced left ventricular contractility and the other child had reduced left ventricular posterior wall thickness. The age group of this cohort of patients precluded assessment of their fertility status.

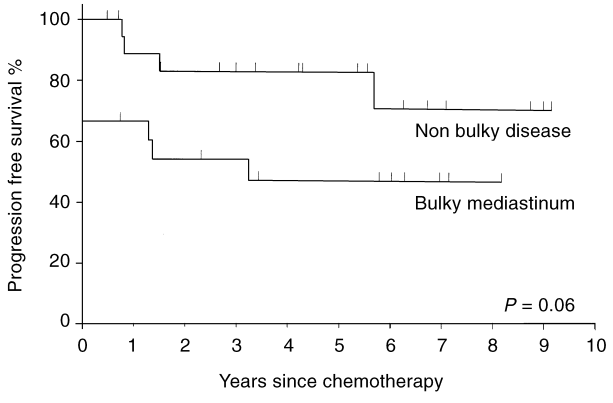

Figure 3. 5-year progression-free survival according to presence of bulky mediastinal disease.

DISCUSSION

The VEEP regimen has been claimed in adults to be comparable in effectiveness to ChlVPP but with fewer late sequelae [13]. In that study a significant percentage of patients received local radiotherapy either electively or for residual imageable disease following initial chemotherapy. Similarly, most series of the non-alkylating regimen ABVD have combined the chemotherapy with radiation. There are a few exceptions to this, such as the small series reported by Behrendt in which 17 patients were treated with an overall relapse-free survival of 71% [18].

In the present study, the initial failure rate with VEEP was high, with only 33 (61%) patients achieving CR and 8 (15%) PR, an overall response rate of only 76%. Furthermore, only

25 (46%) patients, maintained sustained remission on VEEP alone. These results compare poorly with other published paediatric Hodgkin's disease studies [3–5, 27]. It is of note that the 13 patients who had progressive disease during VEEP had either bulky mediastinal disease, B symptoms, extra nodal disease or a combination of these (see Table 3). Stage IV patients whose disease was refractory to VEEP or who had only a short-lived response to second-line chemotherapy eventually died of progressive disease. Out of 331 patients in the UKCCSG HD1 study treated with ChlVPP, there were no instances of disease progression on treatment, even of those with bulky mediastinal or stage IV disease. In general, irrespective of treatment, patients whose disease is primarily refractory to first-line chemotherapy have a poor prognosis with a reported long-term survival of less than 20% with conventional dose salvage therapy [19, 20]. A number of prognostic factors have been described that may influence the outcome of salvage therapy in Hodgkin's disease—B symptoms, nodal disease at presentation or relapse, response to initial chemotherapy, bulky disease and duration of previous remission [21, 22]. High-dose chemotherapy with autologous stem cell rescue is now increasingly used in poor risk patients who have failed conventional chemotherapy [23, 24].

In the present study, radiotherapy (30–35 Gy) was used to consolidate CR in some of those who had had bulky mediastinal disease or for the treatment of presumed residual disease after response to VEEP. This was probably unnecessary in many cases and the use of standard dose XRT (35 Gy) was probably excessive, as the dose of XRT needed to eradicate microscopic disease after CR is achieved is less than required to sterilise clinically apparent disease [25]. In the current UKCCSG study HD2, those who achieve CR with ChlVPP chemotherapy are not electively irradiated, irrespective of initial tumour bulk, and those with residual disease on imaging must have biopsy to prove active tumour before proceeding to radiotherapy.

Relapse did not inevitably lead to a poor outcome in our patients. All those who relapsed after CR/PR were subsequently salvaged with alternative combination chemotherapy with or without radiotherapy and in 2 patients with high-dose chemotherapy with ABMT rescue. However, more than 50% of patients received total treatment in excess compared with other paediatric Hodgkin's disease studies of planned combined modality treatment [3–5].

In early stage disease the overall survival is comparable with ChlVPP. In the UKCCSG Hodgkin's study I, 5 year overall survival for stage II was 97% and for stage III I 78%. However, the results for stage IV patients with VEEP were very poor (5 year OS 44% versus 5 year OS 80% with ChlVPP). It seems unlikely that the dose of etoposide, particularly in this schedule, will carry a significant risk of secondary leukaemia [26] and to date there has been no clinically evident cardiac toxicity though two patients had echocardiographic evidence of mild left ventricular dysfunction. With longer follow-up late treatment-related complications cannot be excluded, but as most patients did not receive irradiation it can be assumed that the incidence of late cardiac toxicity will be similar to or slightly less than that now extensively reported in children with acute lymphoblastic leukaemia (ALL) or solid tumours who have received 250–300 mg/m^2 of anthracycline.

In conclusion, although effective in localised disease, VEEP alone is inappropriate for stage IV, bulky mediastinal stage II or III and those with B symptoms (Figure 3). The latter require either a more intensive alkylating agent-based regimen or combination chemotherapy and radiotherapy. The best results in stage IV disease are those of the German–Austrian Paediatric Study Group using the OPPA/COPP regimen in which alkylating agents are combined with multiple site radiotherapy. This has produced event-free survival in excess of 80% [27]. In these patients late sequelae may be justified in order to achieve a high cure rate.

The results of our study suggest that the VEEP regimen, in the absence of local irradiation, is less efficacious in children than either MOPP or ChlVPP and has a limited role in the treatment of childhood Hodgkin's disease perhaps restricted to boys with stage I to IIIA non-bulky disease. Whether it has any advantages over short duration MOPP/ABVD hybrid and low-dose involved field irradiation is debatable and depends on what precisely the late sequelae of these regimens will prove to be when clearly defined.

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