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Effective New Low Toxicity Chemotherapy with Carboplatin, Vinblastine and Methotrexate for Small Cell Lung Cancer: a Randomised Trial against Doxorubicin, Cyclophosphamide and Etoposide

A.L. Jones, J. Holborn, S. Ashley and I.E. Smith

Carboplatin has been incorporated into a new low toxicity combination chemotherapy regimen with methotrexate and vinblastine (CVM) against small cell lung cancer (SCLC). We have compared CVM (carboplatin 300 mg/m², vinblastine 6 mg/m², methotrexate 30 mg/m², all intravenously every 4 weeks) with ACE (doxorubicin 40 mg/m², cyclophosphamide 600 mg/m², etoposide 100 mg/m² all intravenously day 1–3, every 3 weeks) in a randomised trial. 36/54 evaluable patients treated with CVM achieved an objective response (67%) (95% confidence limits [CL] 54–79%) compared with 44/50 treated with ACE (88%) (95% CL 80–97%, $P = 0.06$). For patients with limited disease treated with CVM, 14/17 (83%) (95% CL 64–100%) had an objective response compared with 14/15 (93%) (95% CL 81–100%) treated with ACE (not significant). Overall median survival was 8 months for CVM and 7 months for ACE. Haematological toxicity was significantly lower for CVM than ACE and consequently dose reduction/delay and infection were less with CVM. Subjective toxicity was low and alopecia was significantly less for CVM than ACE. CVM is an active, well tolerated new chemotherapy regimen for SCLC.
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INTRODUCTION

COMBINATION CHEMOTHERAPY for small cell lung cancer (SCLC) achieves useful palliation for the majority of patients and has been shown in several randomised studies to prolong median survival [1, 2]. However, long-term survival and cure is rare, occurring in only 5–10% of patients [3]. Intensive chemotherapy regimens and high-dose chemotherapy with or without autologous bone marrow rescue have resulted in higher response rates but have failed to achieve any significant improvement in overall survival and are often associated with considerable treatment-related morbidity [4–6]. In this context an intensive carboplatin-based regimen given in combination with ifosfamide and etoposide was recently shown by our unit to achieve a high response rate but only marginal survival benefit, at the expense of considerable toxicity [7].

An important aim should therefore be to design palliative regimens of low subjective toxicity appropriate for treating the majority of patients with SCLC. As part of this aim, we wished to develop a treatment regimen that did not cause alopecia. Carboplatin, an active agent at conventional dose in SCLC [8], was a suitable candidate in this respect, but it proved difficult to identify others. Initially we piloted a regimen using carboplatin with methotrexate and vincristine which both have useful single agent activity in SCLC [9, 10]. This achieved an overall response rate of 70% in the first 17 patients: 5 complete response (CR) and 7 partial response (PR) but toxicity was high for a palliative therapy, including significant alopecia, neuropathy and constipation. Vinblastine was therefore substituted for vincristine on the

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basis that it avoided these toxicities and could be presumed to have similar activity.

We have therefore compared a new combination of modified dose carboplatin (300 mg/m^2), vinblastine and methotrexate (CVM) with a standard conventional regimen of doxorubicin, cyclophosphamide and etoposide (ACE) as first-line treatment in unselected patients with SCLC. This regimen has been reported to produce response rates of 75–90% depending on stage and prognostic features [11–13].

PATIENTS AND METHODS

104 previously untreated patients with histologically or cytologically confirmed SCLC were entered into this trial between August 1987 and April 1990. During part of this time period patients with limited disease and performance status 0 or 1 were eligible for intensive therapy with other protocols. Patients for this study were selected on the basis of unsuitability for intensive therapy (based on performance status, age or concomitant medical disease) or unwillingness to have such therapy. Details of patients' characteristics are given in Table 1. 54 patients were randomised to CVM (see below) and 50 patients to ACE (see below). The median age was 67 (range 33–79) years for CVM and 64 (47–75) years for ACE. The distribution of performance status (WHO classification) was similar for both groups and patients with poor performance status (grades 3 and 4) were included. 32 patients had limited disease (LD), of whom 17 were randomised to CVM and 15 were given ACE. 72 patients had extensive disease (ED) and of these 37 were randomised to CVM and 35 to ACE.

Staging investigations

Before treatment all patients had a clinical examination including documentation of measurable tumour masses, a peripheral full blood count, plasma urea and electrolytes, serum creatinine, serum liver function tests, chest X-ray and ultrasound of liver and upper abdomen. Skeletal surveys, isotopic bone scans and computed tomography (CT) of thorax and/or abdomen were carried out when indicated, either clinically or by abnormal serum biochemistry or liver function tests.

Patients had a nadir full blood count at day 14 of the first course of treatment. In the absence of severe haematological toxicity, this nadir count was omitted on subsequent courses.

Before each course of treatment, patients were assessed by clinical examination, full blood count, plasma biochemistry, serum creatinine and liver function tests and chest X-ray. Other investigations were repeated when clinically indicated to assess tumour response or to investigate toxicity. Staging investigations were repeated after completion of treatment to document response but repeat bronchoscopy was not carried out unless clinically indicated.

Table 1. Patients' characteristics

	CVM	ACE
Patients	54	50
Median age (range)	67 (33–79)	64 (47–75)
Male : female	31 : 23	30 : 20
Performance status		
0	4	3
1	25	19
2	17	18
3	6	8
4	2	2
Limited disease	17	15
Extensive disease	37	35

Randomisation and treatment

Patients were stratified according to whether they had limited or extensive disease and randomised using a random number series to receive CVM or ACE. The first course was usually given as an inpatient and subsequent courses were given as an outpatient if the first course was well tolerated.

The chemotherapy regimens were as follows. CVM patients received carboplatin 300 mg/m^2 in 500 ml of 5% dextrose over 60 minutes on day 1, vinblastine 6 mg/m^2 (maximum 10 mg) on day 1 and methotrexate 30 mg/m^2 (maximum 50 mg) on day 1, all intravenously, repeating every 28 days. Folinic acid rescue, 15 mg orally every 6 hours for 6 doses, was given starting 24 hours after methotrexate. ACE patients received doxorubicin 40 mg/m^2 on day 1, cyclophosphamide 600 mg/m^2 on day 1, both intravenously and etoposide 100 mg/m^2 on days 1–3, intravenously (200 mg/m^2 orally was substituted on days 2 and 3 if outpatient treatment was given), repeating every 21 days.

Treatment costs. For a patient with surface area 1.7 m^2 the current cost of a course of CVM is £375 and £323 for ACE.

Antiemetic cover. Patients were given dexamethasone 8 mg and metoclopramide 20 mg, both intravenously, before chemotherapy and dexamethasone 4 mg and metoclopramide 10–20 mg, both orally, every 4 hours for 48 hours after chemotherapy. This regimen was subsequently modifed according to need.

Dose modification

For initial treatment, or for any subsequent course, a carboplatin dose reduction was made based on impaired renal function as follows: for serum creatinine $\leq$ 130 μmol/l (WHO grade 0), carboplatin dose 300 mg/m^2; serum creatinine 131–265 μmol/l (grade 1), 200 mg/m^2; serum creatinine 266–530 μmol/l (grade 3), 100 mg/m^2; serum creatinine $\geq$ 531 μmol/l (grade 4), omit carboplatin.

If the white blood cell (WBC) count failed to recover to $\geq 3.0 \times 10^9$/l or the platelet count to $\geq 100 \times 10^9$/l when the next cycle of treatment was due, then treatment was delayed by 1 week to allow recovery of the blood count. After two delays, the dose of all drugs was reduced by 25% for subsequent courses. If patients developed WHO grade 3 haematological toxicity (haemoglobin $\leq$ 7.9 g/dl; WBC $\leq 1.9 \times 10^9$/l; platelets $\leq 50 \times 10^9$/l), then the dose of all drugs was reduced by 25% for subsequent courses.

Treatment duration and crossover

Patients who achieved an objective response (see below) continued to a maximum of 6 courses of chemotherapy. Treatment was discontinued after one course if there was clear evidence of disease progression or after 2 courses if the disease remained unchanged. Patients who failed to respond to initial chemotherapy or who relapsed following initial chemotherapy were crossed over to the alternative combination when clinically appropriate.

Radiotherapy

Patients presenting with limited disease who achieved complete or partial remission after completion of 6 courses of chemotherapy received thoracic irradiation, 50 Gy tumour dose in 20 fractions over 4 weeks.

Table 2. Response (%)

	CVM	ACE	
Patients	54	50	
Overall response			
CR	7 (13)	6 (12)	
PR	29 (54)	38 (76)	} $P = 0.06$
Total	36 (67)	44 (88)	
Limited disease	17	15	
CR	4 (24)	4 (27)	
PR	10 (58)	10 (67)	} NS
Total	14 (83)	14 (93)	
Extensive disease	37	35	
CR	3 (8)	2 (6)	
PR	19 (51)	28 (80)	} $P < 0.05$
Total	22 (59)	30 (86)	

NS = not significant.

Patients with limited disease who achieved complete remission after completion of 6 courses of chemotherapy were offered entry into a randomised UK multicentre trial comparing prophylactic cranial irradiation (PCI) 36 Gy in 18 daily fractions, PCI 24 Gy in 12 daily fractions and no PCI. Details of this trial will be reported separately.

Response, toxicity and survival

Tumour response was defined according to standard WHO criteria. CR was defined as disappearance of clinical, radiological and biochemical evidence of disease for at least 2 months and PR was defined as a reduction in the product of 2 diameters of measurable disease by at least 50% for at least 1 month [14].

Toxicity was likewise graded according to standard WHO criteria [14] except that nausea and vomiting were separately graded as follows (since patients were given prophylactic antiemetics): grade 1, nausea alone; grade 2, transient vomiting, fewer than 4 episodes; grade 3, more than 4 episodes of vomiting; and grade 4, intractable vomiting requiring intravenous fluids to prevent dehydration.

Groups were compared using the χ^2 test and Mann–Whitney test for trend. Response duration and survival were both calculated from the data of first treatment using a standard life-table method and compared using the log-rank statistic [15].

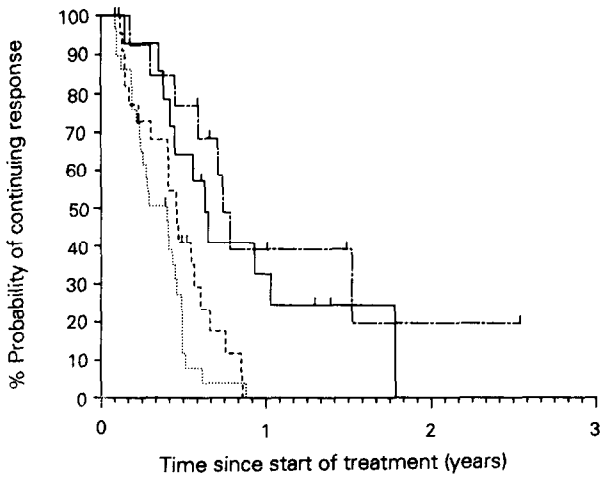

Fig. 1. Duration of response. ACE (LD) —·—·—, CVM (LD) ———, ACE (ED) ·····, CVM (ED) ----------.

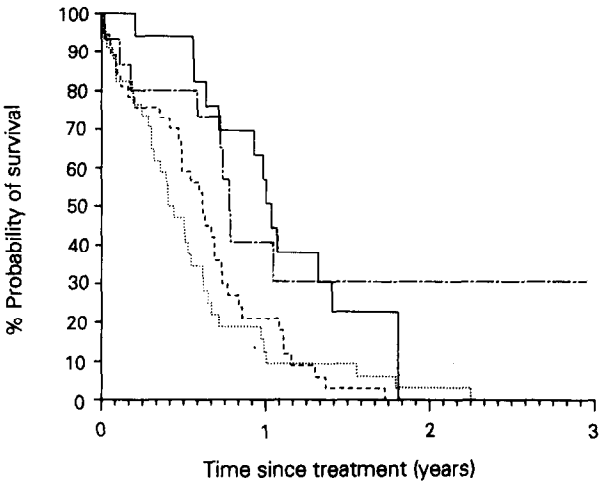

Fig. 2. Survival. ACE (LD) —·—·—, CVM (LD) ———, ACE (ED) ·····, CVM (ED) ----------.

Ethics

This protocol was approved by the Royal Marsden Hospital's ethics committee and witnessed informed consent was obtained from all patients according to current guidelines laid down by the committee.

RESULTS

Response

Details of response by stage are given in Table 2. The overall response rate was 67% for CVM and 88% for ACE; this difference was not quite significant ($P = 0.06$). For patients with limited disease there was no difference in the overall response rate (CVM 83%, ACE 93%) or CR rate (CVM 24%, ACE 27%). For patients with extensive disease the response rate was significantly lower for CVM (59%) than for ACE (86%) ($P = < 0.05$) although there was no difference in the CR rate (8% for CVM and 6% for ACE).

Response duration is shown in Fig. 1. There was no difference in median response duration for all patients given CVM (6 months: 95% CL 5–8 months) compared with ACE (5 months: 95% CL 3–6 months).

Overall survival is shown in Fig. 2. There was no difference in overall survival for CVM (8 months: 95% CL 7–10 months) and ACE (7 months: 95% CL 4–9 months). For patients with LD, median survival was 12 (95% CL 7–17) months for CVM and 9 (95% CL 2–>13) months for ACE. For patients with extensive disease, the survival was 7 (95% CL 6–9) months for CVM and 5 (95% CL 4–7) months for ACE.

17 patients receiving CVM and 19 patients receiving ACE were also given thoracic irradiation. This is in excess of the number of responses for patients with limited disease and reflects the fact that some patients who did not achieve a partial response were also irradiated. 8 patients receiving CVM and 11 patients receiving ACE also received PCI.

Crossover responses

36 patients have been crossed over and are evaluable for response to second-line chemotherapy (Table 3). Only 2 out of

Table 3. Response to second-line chemotherapy (%)

	Patients	CR	PR	Total	
CVM	11	–	2 (18)	2 (18)	$P < 0.05$
ACE	25	1 (4)	13 (52)	14 (56)	

Table 4. Haematological toxicity: frequency (%) based on worst toxicity for any course of treatment for 201 courses of CVM and 223 courses of ACE

	1	2	3	4	Total	
WBC						
CVM	19	9	15	5	48	$P < 0.005$
ACE	4	8	33	47	92	
Platelets						
CVM	5	2	2	–	9	$P = 0.01$
ACE	8	8	12	–	28	
Haemoglobin						
CVM	28	26	–	–	54	$P < 0.05$
ACE	27	37	8	–	72	

11 patients (18%) who received CVM as second-line therapy responded compared with 14 out of 25 patients (56%) receiving ACE ($P < 0.05$). The median duration of response to second-line therapy with ACE was 4.5 months; the durations of response to second-line CVM were 2 and 5 months.

Toxicity

Haematological toxicity was greater with ACE than with CVM. Details are given in Table 4. Leukopenia occurred in 92% of patients on ACE compared with 48% of patients on CVM, including grade 3/4 toxicity in 80% of patients on ACE and only 20% of patients on CVM ($P < 0.005$). This difference was reflected in the incidence of infection (Table 5) which occurred in 59% of courses of ACE compared with 24% of courses of CVM, including grade 3–4 neutropenic infection in 35% of patients on ACE compared with 6% of patients on CVM ($P < 0.001$).

Thrombocytopenia was seen in 28% of patients on ACE and 9% of patients of CVM with severe thrombocytopenia ($\leq 50 \times 10^9$/l) in 12% of patients on ACE and 2% of patients on CVM ($P = 0.01$). However, there were no bleeding complications related to thrombocytopenia.

Details of non-haematological toxicity are given in Table 5. There was a significant difference in alopecia with 68% of patients on ACE developing grade 3–4 alopecia (requiring a wig) compared with only 2% of patients on CVM. There was no significant difference in the incidence of nausea and vomiting with 20% of patients experiencing grade 3–4 nausea/vomiting on ACE and 16% on CVM (patients received prophylactic antiemetics as described previously). No other severe toxicities including nephrotoxicity were seen.

Table 5. Other toxicity: frequency (%) based on worst toxicity for any course of treatment for 201 courses of CVM and 223 courses of ACE

	1	2	3	4	Total	
Infection						
CVM	6	12	6	–	24	$P < 0.001$
ACE	9	15	26	9	59	
Nausea/vomiting						
CVM	28	40	14	2	84	NS
ACE	30	20	20	–	70	
Mucositis						
CVM	18	8	6	–	32	NS
ACE	26	15	2	–	43	
Diarrhoea						
CVM	12	2	–	–	14	NS
ACE	20	6	2	–	28	
Alopecia						
CVM	20	2	2	–	24	$P < 0.001$
ACE	6	17	59	9	91	
Neuropathy						
CVM	8	2	–	–	10	NS
ACE	15	4	–	–	19	
Constipation						
CVM	20	8	4	–	32	NS
ACE	22	6	–	–	28	
Rash						
CVM	6	–	2	–	8	NS
ACE	4	–	–	–	4	

Dose reduction

Dose reduction was more common with ACE than with CVM reflecting the greater myelosuppression seen with ACE. 40% of patients on ACE required a dose reduction of up to 25% and 10% a dose reduction of up to 50% compared with 11% of patients on CVM requiring a dose reduction of up to 25%, and 4% requiring a dose reduction of up to 50%.

In contrast only 8 patients (16%) receiving ACE had treatment delayed because of haematological toxicity indicating rapid recovery of blood counts by the time of next treatment. No patients receiving CVM had their treatment delayed.

DISCUSSION

This trial confirms that CVM is an active and well tolerated new chemotherapy regimen for small cell lung cancer. Although vinblastine has not been proven effective as a single agent in SCLC in phase II trials, our response rate with CVM was similar to the 70% response rate obtained in our pilot study when vincristine was used instead of vinblastine. Our results suggest that CVM is slightly less active than ACE in terms of response rate (although a significant difference was seen only in extensive disease patients and there was no difference in survival). Although the number of patients in this study might permit a type II error in terms of response and survival the main aim was to produce a low toxicity regimen and the slight reduction in activity must be balanced against significantly less haematological toxicity, infections and alopecia with CVM. Indeed, to our knowledge, this is the first effective combination regimen described for SCLC that does not cause alopecia. This benefit would of course be lost if PCI was of proven benefit in SCLC but at present the role of PCI remains controversial, even in patients with a relatively good prognosis [16].

In terms of response duration and survival, CVM was as effective as ACE. To some extent this is attributable to more than 50% of patients initially treated with CVM subsequently achieving a second-line response to ACE, indicating that the two regimens are non-crossresistant. In terms of clinical practice, this gives the opportunity of offering a low toxicity CVM regimen without alopecia as first-line treatment, with the possibility of falling back on a more toxic conventional ACE regimen if required at a later date.

Our overall response rate and complete response rate for ACE were comparable with the overall response rates of 56–80% and complete response rates of 20% for patients with limited disease reported elsewhere in the literature using similar regimens [12, 13]. One group has reported a higher CR rate (50%) using a 5 day schedule of etoposide [12]. It must be acknowledged that

our overall median response duration and survival are relatively short. This, at least in part, reflects a selection policy in which fit patients suitable for trials of intensive treatment were generally excluded from this trial. However, our overall median survival is still comparable with the 8–9 months reported by Mead *et al.* [12]. An additional factor which might affect response and survival with ACE was probably our policy of dose reduction to avoid haematological toxicity in this group of patients for whom palliation was a major aim of treatment. In this context, the haematological toxicity with CVM was unexpectedly low even for a regimen designed for palliation. It may well be possible therefore to increase the carboplatin dose to 400 mg/m^2 in this regimen and thereby possibly increase efficacy without losing the benefit of low toxicity. Although the cost of carboplatin as a single agent is high, the total costs of a course of each regimen are comparable making CVM an attractive outpatient-based regimen for the many patients with SCLC for whom intensive therapy is considered inappropriate.

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Stage II Melanoma in the West of Scotland, 1976–1985: Prognostic Factors for Survival

David M. Tillman, Tom Aitchison, Douglas C. Watt and Rona M. MacKie

The outcome of 142 patients undergoing therapeutic lymphadenectomy for clinical stage II malignant melanoma was retrospectively assessed. 5 year survival was 26%, and survival was not altered in the 25 patients who received two courses of adjuvant combination chemotherapy after lymphadenectomy. On univariate analysis, the most significant determinants of survival were the number of malignant nodes removed at lymphadenectomy ($P = 0.00004$), the age of the patient ($P = 0.009$) and the disease-free interval between primary and stage II disease ($P = 0.01$). The following features were not significantly related to survival: sex, site, histogenetic type of primary tumour, tumour thickness and level of invasion. The number of malignant lymph-nodes was confirmed on multivariate analysis as the single most useful and significant predictor of survival, with the patient's age providing an additional significant contribution. In future adjuvant trials in stage II melanoma after therapeutic lymphadenectomy, patients should be stratified for both age and number of malignant nodes.
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INTRODUCTION

PATIENTS WITH stage IIb melanoma (clinically detectable metastatic disease in regional lymph-nodes) have a poor prognosis. Reported 5 year survival figures range between 13–38% and 10 year survivors are uncommon. In most previous series, the study populations included both patients undergoing elective (clinical stage I, pathological stage II) and therapeutic (clinical stage II, pathological stage II) lymphadenectomy [1–8]. In such series, although survival figures were often presented for clinical stage II disease separately (Table 1), the prognostic indicators for survival were usually determined for the whole stage II study population [1–8]. Few studies have dealt exclusively with clinical