Cancer Chemother Pharmacol (1987) 19: 172–174

Cancer Chemotherapy and Pharmacology

Extensive stage small cell carcinoma of the bronchus

A randomised study of etoposide given orally by one-day or five-day schedule together with intravenous adriamycin and cyclophosphamide

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Summary. Fifty-four patients whose disease had been staged as extensive small cell carcinoma of the bronchus were randomised to receive either CAV[1] (cyclophosphamide 600 mg m^{-2} i.v., adriamycin 50 mg m^{-2} i.v., given on day 1, and etoposide 500 mg m^{-2} p.o. given on day 3) or CAV[5] (cyclophosphamide and adriamycin given as for CAV[1], etoposide 500 mg m^{-2} given in divided dose over days 3–7) on a 21-day schedule. The two regimens proved comparable (CR+PR 55% vs 56%), and the survival curves were virtually superimposable (median survival: CAV[1], 8 months; CAV[5], 9 months). Only five patients are still alive. The toxicity of the two treatments was similar. The scheduling of etoposide over 1 or 5 days seemed clinically unimportant in this study, perhaps because of concurrent use of other effective chemotherapy drugs.

Introduction

Small cell carcinoma of the bronchus (SCBC) comprises approximately 20% of cases of lung cancer. Extensive disease is frequent at diagnosis, being found in 50%–75% of cases, with metastases commonly involving lymph nodes, liver, bone and bone marrow and the CNS [3, 12].

Cyclophosphamide and adriamycin have an established role in the treatment of this disease, and both drugs are usually given i.v. Etoposide, an epipodophyllotoxin derivative, is also highly active and in widespread use [13, 14]. Animal data [7] and limited human data [4, 13, 14, 15] suggest a high degree of schedule dependency for this drug, which is therefore commonly given i.v. daily over 3–5 days. Recently an oral preparation has become available, providing a convenient alternative. Although gastrointestinal absorption is somewhat erratic between patients it is unaffected by food or concurrent chemotherapy [8], and approximately 50% of the drug is absorbed [8, 11, 16].

We thought it unlikely that the described schedule dependency would be clinically important when etoposide was used in combination with other drugs. We decided to test this by randomising patients with extensive SCBC to etoposide given either by 1- or 5-day schedule and report our results.

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Materials and methods

Between December 1981 and August 1985 all patients aged less than 70 years presenting to the Wessex Medical Oncology Unit with extensive stage small cell carcinoma of the bronchus were considered eligible for this study.

A diagnosis of small cell carcinoma was accepted on cytology or biopsy material once confirmed by our review pathologist (Dr A. Herbert). Routine staging of disease for all patients with this diagnosis involved full physical examination, chest X-ray, peripheral blood count, biochemical profile, abdominal ultrasound, radionuclide bone scanning and bone marrow aspiration. Extensive disease was diagnosed in patients with pleural disease, extrathoracic disease at any site (except ipsilateral supraclavicular nodes) or spread to the contralateral lung or lymph nodes.

Following diagnosis patients were considered for randomisation in our clinical trial. The inclusion criteria were broad; however, patients aged >69 years, patients with a Karnofsky Performance status (KPS) <5 and those with severe cardiac, renal or metal impairment unrelated to tumour were excluded from study.

Patients were randomised to receive oral etoposide (100-mg capsules) at a total dose of 500 mg m^{-2} either as a divided dose on day 3 (CAV[1]), or as a divided dose over days 3–7 (CAV[5]). No specific instructions were given to the patients as to the timing, during the day, of the capsules. In addition, all study patients were treated on day 1 with cyclophosphamide 600 mg m^{-2} i.v. and adriamycin 50 mg m^{-2} i.v. All drugs were given at 21-day intervals.

The following dose modification criteria were used; total WBC $>3.5\times10^9$/l, total platelets $>150\times10^9$/l, 100% doses; WBC $3–3.5\times10^9$/l and/or platelets $100–150\times10^9$/l, 75% doses of all drugs; WBC <3.0 and/or platelets $<100\times10^9$/l, delay treatment by 1 week. Adriamycin doses were reduced in the presence of an elevated serum bilirubin as follows; serum bilirubin <20 μmol/l 100%, 20–50 μmol/l 50%, >50 μmol/l 25% doses. Empirical dose reductions were made in any patients developing severe mucositis or requiring i.v. antibiotics for neutropenic fever.

Follow-up studies included routine physical examination, blood count, biochemical profile and chest X-ray. All patients received at least three treatment cycles unless progressive disease was documented. Patients in whom no response had occurred by the end of the third cycle were designated non-responders (NR), withdrawn from the study,

and treated symptomatically on an individual basis, usually with radiotherapy.

After four treatment cycles all metastatic sites (except bone) were re-evaluated. The patients (in CR or PR) were then treated with a further two to five courses (to give a total of six to nine courses) in a flexible fashion, with the aim of giving two cycles of chemotherapy after CR, or stable partial remission (i.e. unchanging disease parameters) as judged by sequential restaging procedures.

Complete remission (CR) was defined as complete return to normality of all pre-existing disease sites, partial remission (PR) as a >50% reduction in diameter of tumour masses, and no response (NR) as <50% regression of tumour. Patients who were non-evaluable (NE) for response were those who had died prior to completing four treatment cycles. These patients were included in survival analysis only.

At this point, consenting patients were randomised again to receive either maintenance therapy for 1 year with oral etoposide 100 mg daily for 5 days and cyclophosphamide 200 mg doses for 5 days at 4-weekly intervals or no further therapy. In addition, patients who achieved CR were treated with prophylactic cranial irradiation (2400r in 10 fractions over 2 weeks) after completion of induction chemotherapy and prior to maintenance (if given).

Following completion of treatment patients were reviewed initially monthly, then 2-monthly. Relapsing disease was not treated with further chemotherapy, but with radiotherapy to symptomatic sites. The major end-point of this study was survival. This was analysed using a proportional hazards model [5] with the aid of the BMDP, computer package [6]. The two groups were compared directly and with allowance made for confounding variables (age, sex, KPS).

Results

During the period of this study a total of 83 patients with extensive stage small cell carcinoma were seen, 21 of whom were ineligible for randomisation for the following reasons; age (12), low KPS (4), disabling CNS disease (2), mental status (2), deep jaundice (1). A further 8 patients (CAV^1, 2; CAV^5, 6) were randomised but later withdrawn from the study for the following reasons; limited disease (5), age >70 years (2), review histology at relapse showed non-Hodgkin's lymphoma (1).

Thus, 54 patients form the subject of this analysis. Follow up is available on all these patients, and since survival was regarded as the major end-point of the study, no second party review of response evaluation was undertaken.

The clinical characteristics of our patients are shown in Table 1. Age and sex distributions were comparable in both arms of the trial. More patients proved to have a low KPS in the CAV^1 group. However, when allowance was made for this in our statistical analysis it did not affect the comparison between the two groups. Differences were also apparent in the number, and sites of metastases (e.g. marrow, involved in 2/29 CAV^1 vs 10/25 CAV^5). These differences tended to favour the CAV^1 group, but since their prognostic significance is ill defined, they were not included in the statistical analysis.

Both treatment groups received between one and nine CAV treatment cycles (mean 4.5 CAV^1 and 4.7 CAV^5). CR and CR + PR rates were: CAV^1 27.5% and 55%, CAV^5 20% and 56%. The same number (five) of patients in each arm of the study was randomised to receive maintenance chemotherapy, but the numbers were too small for meaningful analysis of any effect of this treatment on survival.

The survival curves were very similar (Fig. 1). Median survival in both arms of the study was similar at 8 months (CAV^1) and 9 months (CAV^5). Similarly, 2-year survival rates were comparable (respectively 8% and 9%). From the proportional hazards model the increase in hazard for CAV^5 compared with CAV^1 was 1.01 (95% C.I. 0.55–1.86). Five patients (CAV^1, 2; CAV^5, 3) are still alive at 7, 7, 12, 15 and 42 months. Only three of these patients, however, are at present disease free; CAV^1 15+ months, CAV^5 7+ and 42+ months.

Table 1. Patient characteristics

	CAV^1	CAV^5
No. of patients	29	25
Age range (median) (years)	35–69 (62)	47–68 (61)
Sex:		
Male	18	14
Female	11	11
Performance status (Karnofsky):		
5–6	4	1
7–8	18	15
9–10	7	9
Sites of metastases:		
Lymph node	9	13
Bone	12	13
Bone marrow	2	10
Liver	12	12
Pleura	4	–
Other	3	2
No. of sites of metastasis:		
1	17	10
2	9	7
3	2	4
>3	–	4

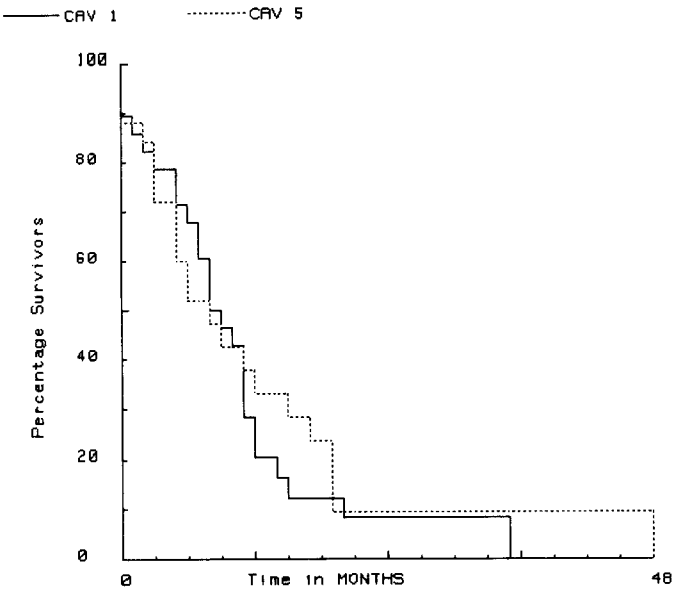

Fig. 1. Survival from into trial of patients treated with CAV^1 or CAV^5

Table 2. Therapy and response

	CAV[1]	CAV[5]
No. of treatment cycles		
Range (mean)	1–9 (4.5)	1–9 (4.7)
Response[a] (%):		
CR	8 (27.5)	5 (20)
PR	8 (27.5)	9 (36)
NR	6 (21)	6 (24)
NE	7 (24)	5 (20)
Maintenance:		
No. randomised	8	9
Randomised to maintenance	5	5
Toxicity:		
Neutropenic fever	8	6
Treatment delay (low counts)	6	7
Possible toxic death	3	2
Alive (duration in months)	2 (12, 15)	3 (7, 7, 32)

[a] CR, complete remission; PR, partial remission; NR, no response; NE, not evaluable

A comparable number of patients in each group had neutropenic fever or a delay in treatment (Table 2). Five patients, all with active disease, died unexpectedly between treatment courses. These cases were all recorded as toxic deaths, though in none was this adequately documented (Table 2).

Discussion

Etoposide is a widely used and highly active chemotherapeutic drug [13, 14]. Dombernowsky, using the L1210 leukaemia model [7], demonstrated that frequent administration of etoposide in divided dose was advantageous. This was to some extent confirmed by Cavalli et al. [4] in small cell carconoma of the bronchus. Sixty patients (45 previously untreated) were randomised to receive single-agent etoposide 250 mg m^{-2} i.v. weekly, 500 mg m^{-2} p.o. divided over 3 days weekly, or 850 mg m^{-2} p.o. divided over 5 days at 3-weekly intervals. The second regimen (500 mg m^{-2} p.o. over 3 days weekly) produced the highest response rate. However, the numbers of patients in the study were small. In a recent study conducted in patients with newly diagnosed, extensive stage SCBC, Slevin et al. [15] compared etoposide 500 mg m^{-2} by 24-h i.v. infusion with the same drug given at a dose of 100 mg m^{-2} i.v. over 2 h each day for 5 days. A marked difference in response rate (10% vs 78% PR) in favour of daily administration was noted. As a result of this and previous studies [13, 14], etoposide is generally administered i.v. over 3–5 days.

The absorption of oral etoposide may also be dose-limited. A recent study [9] suggests that absorption of the drug at doses in excess of 400 mg is severely limited. Our patients were not instructed to adhere to a strict divided dose schedule, and this factor tends to favour the group randomised to CAV[5]. The potential influence of variable oral absorption in our negative study, when compared with those described above, using the i.v. route, is difficult to ascertain. We assume that the lack of schedule dependency demonstrated reflected the use of etoposide with two other drugs known to be highly active in SCBC. Our regimens (CAV[1] or CAV[5]) were both well tolerated and our treatment results, following a limited number of courses of chemotherapy administered in a flexible fashion, were comparable to others in the literature [1, 2, 10].

We conclude that the schedule for administration of etoposide – p.o. for 1 vs 5 days – was unimportant in the clinical setting of this trial. Further studies in other diseases (e.g. non-Hodgkin's lymphoma) would be needed to confirm that this result is generally applicable. Both CAV regimens produced results comparable to those obtained with more intensive or prolonged therapy.

Acknowledgements. We would like to thank Bridget Stone and Toto Gronlund for help collecting and processing our data, Sally Smith for typing the manuscript and Dr M. J. Campbell for statistical help.

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Received July 6, 1986/Accepted October 27, 1986