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Original Paper

A Prospective Randomised Study in Limited Disease Small Cell Carcinoma—Doxorubicin and Vincristine plus Either Cyclophosphamide or Etoposide

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A prospective randomised study was undertaken in patients with limited disease small cell carcinoma of the lung (SCCL), which compared doxorubicin, 50 mg/m², and vincristine, 2 mg i.v. (intravenously) on day 1, with either cyclophosphamide, 800 mg/m² on day 1 (CAV) or etoposide, 60 mg/m² i.v. on day 1 and 120 mg/m² orally on days 2–5 (AVE). Responding patients were to receive six cycles of chemotherapy at 3 weekly intervals followed after 2 weeks by mediastinal irradiation. Response rates and toxicity were evaluated by the chi square or Fisher's exact test and survival by the logrank test. 81 patients were entered into the study, 38 of whom received CAV and 43 received AVE. In the patients treated with CAV and AVE, the overall response rate was 61% (confidence limit (CL), 45–71%) and 74% (CL, 61–87%) respectively, the complete response rate was 32% (CL, 17–47%) and 51% (CL, 36–66%), respectively ($P = 0.07$) and the median survival was 12 and 14.5 months, respectively ($P = 0.15$). In the patients treated with CAV and AVE, the incidence of grade 3 and 4 leucopenia was 29% (CL, 15–43%) and 9% (CL, 0–18%), respectively ($P = 0.025$). No patient developed doxorubicin cardiomyopathy. These findings support the role of etoposide in first line chemotherapy for SCCL. AVE is among the more efficacious regimens for SCCL and also has a relatively low toxicity.

Key words: small cell lung cancer, chemotherapy, etoposide
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INTRODUCTION

THE COMBINATION of cyclophosphamide, doxorubicin and vincristine (CAV) has been widely regarded as one of the standard chemotherapy regimens for the treatment of patients with small cell carcinoma of the lung (SCCL). In untreated patients with limited disease (LD) SCCL, CAV prolonged survival from 3 months to 12 months; CAV resulted in a complete response rate of 41%, an overall response rate of 75%, WHO grade 4 leukaemia in 26.5% and a fatal sepsis rate of 3.8% [1].

Etoposide was subsequently reported to be the most active single agent in SCCL [2] and also the only single agent to result in cure in SCCL [3]. Attempts were made to modify the CAV regimen to include etoposide. These have included the replacement of either cyclophosphamide, doxorubicin or vincristine in CAV by etoposide to form the AVE [5, 6], CEV [4] or CAE [7] regimens. Etoposide has also been added to CAV to form the CAVE regimen [8].

The aim of this prospective study was to compare CAV and an AVE regimen in which etoposide was administered over 5 days.

PATIENTS AND METHODS

Patients referred to the combined lung cancer clinic at Groote Schuur Hospital, Provincial Hospital, Port Elizabeth, South Africa and Frere Hospital in East London, South Africa between March 1990 and August 1993 were eligible for entry into this study. The study was approved by the ethics committees of the contributing hospitals. Informed written consent was obtained from all patients. Patients had SCCL diagnosed either histologically or by fine needle aspiration biopsy. Eligible patients had no prior history of congestive cardiac failure.

Staging investigation consisted of complete blood count,

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serum liver functions, chest radiograph, liver ultrasound (or scan) and a bone scan. Patients were considered to have limited disease if their disease was limited to the hemithorax, mediastinum and ipsilateral supraclavicular nodes.

Patients in both arms of the study received doxorubicin (50 mg/m^2) and vincristine (2 mg) intravenously (i.v.) on day 1 of each cycle of chemotherapy. Patients in the CAV arm received cyclophosphamide (800 mg/m^2) i.v. on day 1. Patients in the AVE arm received etoposide (60 mg/m^2) i.v. on day 1 and (120 mg/m^2) orally on days 2–5 of each cycle. The aim was to administer six cycles of chemotherapy 3 weeks apart, but treatment was discontinued after four cycles if there had been no response. Chemotherapy was given at full dosage and treatment was, therefore, delayed to allow haematological recovery in patients with a white blood cell count of less than 3000/mm^3.

Patients with a maintained response received a course of chest irradiation 2 weeks after completing chemotherapy if their lung functions were adequate. The dose of radiation administered was 50 Gy in 2.5 Gy fractions with four fractions per week which was given to the tumour bed and mediastinum with a minimum 2 cm margin.

Patients who responded to chemotherapy and who relapsed while off therapy, were retreated with the same regimen they had initially received. Patients who relapsed while on treatment or who failed to respond were treated on an *ad hoc* basis, most often with irradiation.

Randomisation between the two treatment regimens was by selection from a large surplus of sealed envelopes. The performance status was evaluated for all patients according to the WHO scale. Toxicity was graded according to the WHO scale and was measured at the time of the following cycle of chemotherapy. Response to chemotherapy (evaluated prior to radiation) was evaluated according to WHO recommendations. Survival rates were determined by the Kaplan–Meier method. Response rates and toxicity were compared using chi square or Fisher's exact test, and survival by the logrank method.

RESULTS

81 patients were entered into this study. All patients were evaluated for response and toxicity. The patient characteristics are shown in Table 1 and are similar between the two groups. In the CAV and AVE groups, the mean number of cycles of first line chemotherapy was 5.3 and 5.4 in responding patients (complete or partial), respectively, and 3.5 and 3.4 in patients who failed to respond. Up to 50 Gy of radiation was administered to responding patients in 61 and 63% of patients in the CAV and AVE arms, respectively.

Table 1. Patient characteristics

	CAV	AVE
Patients	38	43
Age		
Median	60	59
Range	48–73	42–71
Sex ratio M:F	27:11	28:15
	71%:29%	65%:35%
Performance status		
0	2 (5%)	3 (7%)
1	19 (50%)	23 (53%)
2	15 (39%)	12 (28%)
3	2 (5%)	5 (12%)

Table 2. Results of treatment

	CAV	AVE	
Response rates			
Complete response	12 (32%)	22 (51%)	(P = 0.07)
Partial response	11 (29%)	10 (23%)	
No change	9 (24%)	7 (16%)	
Progressive disease	6 (16%)	4 (9%)	
Median duration of response	9 months	10 months	
Median survival	12 months	14.5 months	(P = 0.15)
Survival rates			
1 year	50%	72%	
2 year	15%*	14%*	

*The 2 year survival rate is provisional as the minimum follow-up is more than the median survival but less than 2 years.

The results of treatment are described in Table 2 and survival is shown in Figure 1. The minimum follow-up is longer than the median follow-up in both groups. The difference in the complete response rate, 32% (CL (confidence limits), 17–47%) with CAV compared with 51% (CL, 36–66%) with AVE, approached statistical significance (P = 0.07). The median and 1 year survival were also higher in the AVE group (P = 0.15) but the 2 year survival rates in the two groups were similar.

Progressive disease developed in responding patients in 20 of 23 patients (87%) treated with CAV and in 29 of 32 (91%) patients treated with AVE. The first site of failure in responding patients for the CAV and AVE patients was in the brain in 30 and 41%, local disease in 35 and 31%, lung in 30 and 28% and the liver in 5 and 0%, respectively.

Nausea was controlled with metoclopramide in all except 10 patients who either required admission or 5-HT$_3$ antagonists. Alopecia was common in both groups. Other toxicity is described in Table 3. The incidence of grade 3 and 4 leucopenia was 29% (CL, 15–43%) in patients treated with CAV which was statistically significantly higher than the 9% (CL, 0–18%) incidence seen in patients treated with AVE (P = 0.025, Fisher's exact test). There were, however, no episodes of fatal sepsis. Cardiomyopathy from doxorubicin use was not observed.

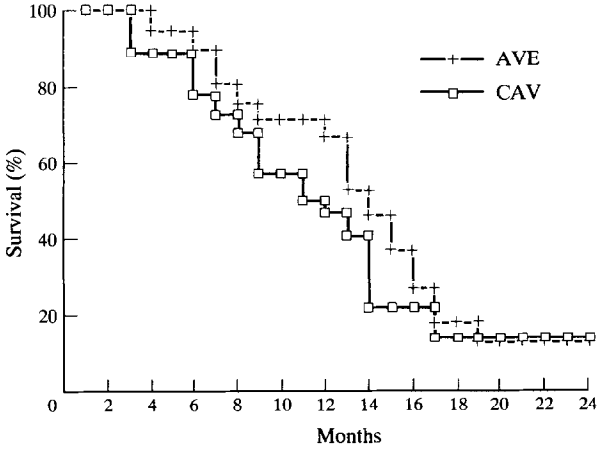

Figure 1. Survival rates in patients treated with CAV and AVE.

Table 3. Toxicity of treatment

	CAV	AVE
Leucopenia		
Grade 3	7 (18%)	3 (7%)
Grade 4	4 (11%)	1 (2%)
Thrombocytopenia		
Grade 3	3 (8%)	2 (5%)
Paraesthesia	9 (24%)	10 (23%)
Diarrhoea	—	1 (2%)
Bronchospasm	—	2 (5%)
Nausea		
Grade 3	7 (18%)	4 (9%)

DISCUSSION

AVE was developed as a safe, effective and convenient regimen for SCCL. AVE is relatively safe in that one of the myelotoxic agents in CAV, cyclophosphamide, has been replaced by etoposide. In the initial studies of AVE [5, 9], the dose of doxorubicin was 40 mg/m^2 and this was increased in this study to 50 mg/m^2 in view of the low toxicity previously observed. AVE is convenient in that etoposide is given in a fractionated schedule, i.v. on day 1 and orally on days 2–5. AVE was shown to improve survival and response rates in a prior prospective randomised study with a similar combination chemotherapy regimen [6], in which the etoposide was administered i.v. on day 1 only. This is similar to the findings with single agent etoposide chemotherapy [11].

AVE is a preferred regimen to CAV in that it had a higher response rate, in particular a higher complete response rate which approached statistical significance ($P = 0.07$), and also a higher median duration of survival, which was not, however, statistically significant. In addition, AVE had a lower incidence of grade 3 and grade 4 leucopenia, which was statistically significant. No cardiomyopathy was observed with AVE—the total dose of doxorubicin administered was 300 mg/m^2 in patients receiving six cycles of chemotherapy, and patients with a past history of congestive cardiac failure were excluded from this study. It should be noted that the cost of etoposide is considerably higher than that of cyclophosphamide, although this might be partly offset by reduced complications.

Other etoposide-containing regimens derived from CAV have been evaluated. In CEV [6], etoposide is used in combination with cyclophosphamide (1000 mg/m^2) and vincristine and it, therefore, contains two myelotoxic agents, like AVE. CEV was compared in a prospective study with the combination of high dose cyclophosphamide (2000 mg/m^2) and vincristine (CV) and also the CAV regimen [4]. In 116 LD patients who were treated with the CV, CAV and CEV regimens, median survivals were 10, 13 and 14 months, respectively, which were not statistically significantly different. In 237 patients with extensive disease treated with CV, CAV and CEV regimens, the median survivals were 7, 8 and 10 months, which were statistically significant. The incidence of WHO grade 4 leucopenia after the first cycle of chemotherapy in patients treated with CV, CAV and CEV regimens were 42, 21 and 25%, respectively.

A prospective study of AVE and CEV would be necessary to determine whether doxorubicin or cyclophosphamide is preferable for use in combination with etoposide. However, when these regimens were compared to CAV (using different doses of cyclophosphamide as above), the AVE regimen had decreased myelotoxicity which was not shown in the CEV study.

The regimens which have used etoposide in combination with both cyclophosphamide and doxorubicin (CAE) [7] or have added etoposide to CAV (CAVE) [8, 10] so as to include three myelotoxic agents would be expected to be more myelotoxic than either CAV, CEV or AVE. An additional regimen that is currently widely used is the combination of etoposide plus cisplatin although its superiority to CAV has not been conclusively proven [12, 13]. It would be beyond the scope of this report to review these results, which has recently been done elsewhere [14, 15].

These findings support the role of etoposide in first line chemotherapy for SCCL. AVE is among the more efficacious regimens for SCCL and also has a relatively low toxicity.

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