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Specialist Interest Articles

Prospective Study of Etoposide Scheduling in Combination Chemotherapy for Limited Disease Small Cell Lung Carcinoma

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78 patients with limited disease small cell lung carcinoma (SCLC) were entered into a prospective randomised study of two combination regimens (AVE-5 and AVE-1) that differed only in the scheduling of etoposide. Patients in the AVE-5 arm received etoposide intravenously 60 mg/m² on day 1 and orally 120 mg/m² on days 2–5 of each cycle. Patients in the AVE-1 arm received etoposide 300 mg/m² intravenously on day 1. Patients in both arms received doxorubicin and vincristine on day 1 of each cycle. The complete (53% vs. 26%) and the overall (75% vs. 52%) response rates were significantly higher in the AVE-5 arm. Median survival was also increased from 11 to 14 months in this arm. Toxicity was low and similar in both groups. The daily administration of etoposide in low toxicity combination therapy for SCLC is important. This can be conveniently achieved by using etoposide orally.
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INTRODUCTION

ETOPOSIDE HAS the highest tumour response rate (45%) of all the single agents used for small cell lung cancer (SCLC) [1] and is the only single agent reported to be curative in a patient with SCLC [2]. The activity of single-agent etoposide in SCLC is schedule-dependent and improved results are obtained with repeated daily administrations compared with single-day infusion [3]. Etoposide scheduling in combination chemotherapy has only been evaluated in one study, in which it was administered with doxorubicin and cyclophosphamide from day 3 of each cycle in patients with extensive disease [4]. No advantage with daily etoposide was found.

Standard chemotherapy for SCLC (cyclophosphamide, doxorubicin and vincristine [CAV]), results in an overall response rate in patients with limited disease of 75%, a median survival of 12 months and a fatal sepsis rate of 3.9% [5]. CAV is based on single agents with a response rate of 20–30% [1].

At our hospital the AVE-5 regimen was devised in which cyclophosphamide in CAV was replaced by etoposide [6]. Etoposide was given intravenously on day 1 and orally on the next 4 days of each cycle and was therefore convenient to administer on an outpatient basis. The use of oral etoposide is based on the finding that its bioavailability is approximately 50% of that from the intravenous route, although this is variable [7]. The use of a similar regimen that used etoposide intravenously only at a large single dose on day 1 of each cycle (AVE-1) has also been reported [8]. These regimens differed only in the scheduling of etoposide and were therefore studied in a prospective randomised trial.

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PATIENTS AND METHODS

Eligibility and staging

Patients referred to the combined lung cancer clinic at Groote Schuur Hospital, Cape Town, Provincial Hospital, Port Elizbeth, and Frere Hospital, East London, between August 1986 and July 1989, were eligible. Patients had SCLC diagnosed either histologically or by fine-needle aspiration biopsy.

Staging consisted of complete blood count, serum liver enzymes, chest radiograph, liver ultrasound (or isotope scan) and a bone scan. We did not routinely do bone marrow trephines and aspirations in view of the low yield in patients with negative biochemistry and bone scans at our institutions. Patients were considered to have limited disease if their disease was confined to the hemithorax, mediastinum and ipsilateral supraclavicular nodes.

The study was approved by the ethics committees of the contributing hospitals and informed written consent was obtained from all patients.

Treatment and evaluation

Randomisation between the two regimens was by selection from a large pool of sealed envelopes. Patients in the AVE-5

Table 1. Patient's characteristics

	AVE-5	AVE-1
Patients	40	38
Age (yr) (median, range)	58 (35–71)	59 (33–72)
M/F	26 (65%) 14 (35%)	24 (63%) 14 (37%)
Performance status		
0	2 (5%)	3 (8%)
1	23 (58%)	21 (55%)
2	11 (28%)	10 (26%)
3	4 (10%)	4 (11%)

Table 2. Response rate and survival

	AVE-5	AVE-1
Response		
Complete response	21 (53%)	10 (26%)
Partial response	9 (23%)	10 (26%)
Overall response	30 (75%)	20 (53%)
Survival		
1 year	22 (55%)	16 (43%)
2 year*	3 (21%)	2 (11%)
Median (mo)	14	11

*2 year survival is provisional since minimum follow-up in surviving patients is not yet 2 years.

arm received etoposide intravenously 60 mg/m^2 on day 1 and orally 120 mg/m^2 on days 2–5 of each cycle. Patients in the AVE-1 arm received etoposide 300 mg/m^2 intravenously on day 1. Patients in both arms received doxorubicin 40 mg/m^2 and vincristine 2 mg on day 1 of each cycle of chemotherapy. The aim was to administer 6 cycles of chemotherapy every 3 weeks but treatment was discontinued after 4 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 μl.

Patients with a maintained response received a course of chest irradiation 2 weeks after completing chemotherapy if their lung function was adequate. The dose was 50 Gy in 2.5 Gy fractions with four fractions per week given to the tumour bed and mediastinum with a minimum 2 cm margin. Radiation therapy had been used at a lower dose in the previous report of AVE-5 and was not used with AVE-1.

Patients who responded to chemotherapy and who relapsed while off-therapy were re-treated 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. Performance status was evaluated for all patients with the Eastern Co-operative Oncology Group scale. Response to chemotherapy (evaluated before radiation) and toxicity were measured with WHO recommendations. Responses were assessed by a multidisciplinary panel, which at Groote Schuur Hospital included a radiologist. Survival rates were determined by the Kaplan–Meier method; response rates were compared with the χ^2 test and survival with Gehan's Wilcoxon test [9].

RESULTS

Patients' characteristics

78 patients were entered; 53 (68%) of the patients came from Groote Schuur Hospital (Table 1). The patients' characteristics were similar between the two groups.

In the AVE-5 and AVE-1 groups, respectively, the mean number of cycles of first line chemotherapy was 5.6 and 5.4 in responding patients (complete or partial), and 3.7 and 3.3 in patients who failed to respond. Radiation was administered to responding patients in 19 (63%) and 13 (65%) of patients in the AVE-5 and AVE-1 arms, respectively.

Response and survival

The response rate and survival are shown in Table 2. The minimum follow-up in surviving patients was longer than the median survival for both treatment arms. The median follow-up in 8 (20%) surviving patients treated with AVE-5 was 19 months (range 14–29 months) and, in 6 (16%) surviving patients treated with AVE-1, 22.5 months (14–39).

There was a significantly higher complete response rate (53% vs. 26%, $P = 0.023$, χ^2) and overall response rate (75% vs. 53%, $P = 0.04$) in the AVE-5 group. The median duration of response was 10 months in both groups.

Progressive disease occurred in responding patients in 90% (27/30) of patients treated with AVE-5 and 80% (16/20) treated with AVE-1. The first site of progression in responding patients treated with AVE-5 and AVE-1, respectively, were cerebral metastases in 30% and 25%, the lung in the primary site in 27% and 25% and lung metastases in 17% and 20%.

Survival was significantly higher in the AVE-5 group (14 vs. 11 months, $P = 0.03$, Gehan's Wilcoxon test).

Toxicity

Nausea was controlled with standard anti-emetics in all except 4 patients (grade 3 nausea in Table 3), who required admission for management. Alopecia was common.

There were no episodes of grade 4 leukopenia (white blood cells under 1000/μl) in either group. The frequency of other complications, including grade 3 leukopenia (white cells under 2000/μl) and neurotoxicity, was similar in both groups. Paraesthesiae were reversible in all cases after discontinuation of vincristine. There was 1 death from chemotherapy which necropsy revealed was because of necrotising enterocolitis. This

Table 3. Toxicity

	AVE-5	AVE-1
Leukopenia grade 3	4 (10%)	5 (13%)
Paraesthesiae grade 1	6 (15%)	5 (13%)
Nausea grade 3	1	3 (8%)
Bonchospasm	2 (5%)	2 (5%)
Diarrhoea grade 3	1	0
Enterocolitis (fatal)	0	1

was not associated with leukopenia and occurred after the first infusion of AVE-1. 1 patient had severe diarrhoea after AVE-5 and required admission for rehydration.

DISCUSSION

The AVE-1 and AVE-5 regimens is derived from CAV with the replacement of cyclophosphamide by etoposide. Similarly derived regimens that include etoposide are CEV (10) in which doxorubicin is replaced, ACE (11) in which vincristine is replaced and VACE (12) in which etoposide is added and no drugs replaced.

In the previous reports of patients with limited disease treated with AVE-5 and AVE-1, median survival was 12 and 7 months, respectively. The results in these studies cannot, however, be directly compared since they refer to patients treated at a different institution and from a different population. The regimens were considered by their institutions to be as effective as more intensive combination regimens.

The different dose schedules used in AVE-1 and AVE-5 arose from difficulties in interpreting early studies of etoposide scheduling. Etoposide has been reported as requiring administration over 3–5 days for optimal effect [13]. These data have been criticised because patients treated in divided doses had increased myelotoxicity [8]. The dose scheduling of single-agent etoposide was subsequently studied in 40 previously untreated patients with extensive disease [3]. Daily etoposide administration over 5 days per cycle was compared with single-day infusion. Survival was significantly higher (10 vs. 6.3 months) and the frequency of grade 4 leukopenia lower (0 vs. 15%) in the patients receiving daily etoposide.

Our study extends this finding to combination therapy. A significantly higher response rate and survival were found with AVE-5 compared with AVE-1 in the doses used, which resulted in low toxicity with both regimens. The use of etoposide with vincristine did not result in increased neurotoxicity, independent of etoposide scheduling.

Etoposide scheduling in combination chemotherapy has only been previously evaluated in one study, of patients with extensive disease [4]. These patients were treated with doxorubicin 50 mg/m^2 plus cyclophosphamide 600 mg/m^2 and etoposide 500 mg/m^2, which was administered orally either on day 3 or in divided doses from days 3 to 7. No difference was found between the two regimens. There may be cross-resistance when etoposide is used in combination therapy [3]. If so, an advantage with daily etoposide may still be discernible with low toxicity combinations, as used in the present study. An alternative explanation for the finding of similar efficacy in the earlier study is that etoposide may act synergistically in combination chemotherapy, which may be prejudiced by its administration on day 3.

AVE-5 has greater antitumour activity than AVE-1 and similar toxicity. Antitumour activity in SCLC is independent of toxicity [9, 10]. The different regimens should be evaluated in prospective studies. AVE-5 and CEV contain two myelotoxic drugs and will be less myelotoxic than regimens which contain cyclophosphamide, doxorubicin and etoposide. The outcome of a comparison of AVE-5 and CEV will depend on the toxicity and tumoricidal synergism between etoposide and doxorubicin at the low dose of 40 mg/m^2 or etoposide and cyclophosphamide at 1000 mg/m^2, as used in the regimens.

Further studies of more protracted administration of oral etoposide, both as a single agent and in combination therapy, are underway [3, 14]. The present study shows the importance of daily administration of etoposide in low toxicity combination therapy for SCLC, and also that this can be conveniently achieved by using the drug orally.

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