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Combination Chemotherapy with Vincristine, Epirubicin and Cyclophosphamide in Small Cell Lung Carcinoma

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The aim of this prospective study was to assess the activity of a combination of vincristine, epirubicin and cyclosphosphamide (VEC) in previously untreated patients with limited small cell lung carcinoma (SCLC) and to delineate the feasibility of dose escalation for epirubicin in this regimen. The chemotherapy schedule included cyclophosphamide, 1000 mg/m², vincristine, 1 mg/m² and escalating doses of epirubicin: 50 mg/m², 70 mg/m² and 90 mg/m²; respectively in three consecutive groups of patients. Drug cycles were repeated every 3 weeks. 118 patients from eight institutions were enrolled in this study between February 1986 and March 1989. Objective tumour response was observed in 81 of 116 evaluable patients (70%) including 25 patients (22%) who achieved a complete remission. Responding patients received thoracic radiation after the fourth cycle of chemotherapy. The median duration of response was 30 weeks and the median duration of survival was 52 weeks. There were no significant differences in treatment results between the consecutive groups of patients. The regimen was well tolerated for all doses of epirubicin. The main toxicities included alopecia (96%), nausea and vomiting (81%) and leukopenia (44%). Grade 4 haematological toxicity was observed in 3 patients (2.6%). No significant epirubicin dose-dependent side effects, except for mucositis were observed.
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INTRODUCTION

IN SPITE of the high sensitivity of small cell lung carcinoma (SCLC) to both cytostatic agents and chemotherapy, cure is still a rare endpoint in treatment of this tumour. Most patients experience a relapse within 2 years as a result of the emergence of drug-resistant cancer cells during chemotherapy. A large number of different cytostatic agents have been demonstrated to be active in SCLC, but there is no regimen considered to be optimal. The combination of vincristine, doxorubicin and cyclophosphamide (VAC) has been one of the most commonly used within the last decade [1]. Doxorubicin is one of the most active agents in SCLC and has probably significant impact on complete response rate and survival [2–4]. The utility of this drug in VAC combination is limited, however, due to its dose-related cardiac toxicity. It has been suggested that epirubicin, a derivative of doxorubicin, is a drug of similar activity but of less cardiotoxicity than its parent compound [5, 6]. The activity of epirubicin given as a single drug in a dose of 100–120 mg/m² was also demonstrated in SCLC [7–11]. Data pooled from these five studies on a total of 177 chemotherapy-naive SCLC patients showed a 46% remission frequency, one of the highest reported for single-agent chemotherapy of this tumour. As the mainstay of the SCLC management is multidrug chemotherapy, we have undertaken a prospective multicentre phase II study in which doxorubicin in VAC regimen was replaced by epirubicin. The purpose of this trial was to evaluate the activity of a combination

of cyclophosphamide, epirubicin and vincristine (VEC) and to delineate the feasibility of dose escalation for epirubicin in this regimen.

PATIENTS AND METHODS

Eligibility criteria for this study included histological or cytological diagnosis of SCLC, measurable or evaluable limited disease, ECOG performance status 0 to 3, white blood cell (WBC) count of more than 4.0×10^9/l, platelet count of more than 100×10^9/l, total serum bilirubin less than 25 μmol/l, serum creatinine less than 130 μmol/l, no recent myocardial infarction and no controlled arrythmia. No prior chemotherapy or radiotherapy was permitted. Patients had to give informed consent in accordance with institutional practice.

Pretreatment evaluation included physical examination, electrocardiogram, left ventricular ejection fraction (LVEF) measurement (not obligatory), chest radiograph and tomography, fibre-optic bronchoscopy, complete blood count and biochemistry. Extrathoracic spread was ruled out by abdominal CT scanning or ultrasonography and bone marrow bilateral biopsy. Bone scans or radiological survey were done in patients suspected of having bone metastases. Screening for brain metastases was not done routinely, but patients with suspicious symptoms were evaluated by brain computed tomography (CT). Limited disease was defined as tumour confined to one hemithorax, the mediastinum and supraclavicular lymph nodes.

Patients were treated in a prospective three-step trial. Chemotherapy regimen consisted of cyclophosphamide, 1000 mg/m^2, vincristine, 1 mg/m^2 and escalating doses of epirubicin: 50, 70 and 90 mg/m^2, respectively in three consecutive groups of patients, all drugs administered intravenously every 3 weeks. Standard antiemetic therapy was applied in most cases. Treatment schedule included chest irradiation (10–20 MeV or ^{60}Co) which was started 2 weeks after the 4th cycle of chemotherapy. The initial tumour area was irradiated in complete responders or with a margin of at least 2 cm around any residual disease. The target dose was either 30 Gy in 10 fractions over 12 days or 40 Gy in 20 fractions over 26 days with a parallel opposed pair. Prophylactic cranial irradiation was not given.

Before each cycle patients were assessed by physical examination, WHO performance status, electrocardiogram and laboratory tests. Drug application was delayed a week if the WBC count was less than 3.5×10^9/l and/or platelet count was less than 100×10^9/l. If postponement of chemotherapy was necessary for more than 3 weeks, the patient was taken off the study. No dosage reductions were made. Chest X-ray was repeated every second cycle. After the 4th and the 9th cycle complete restaging was done. Clinical complete remission had to be confirmed by bronchoscopy and cytology. Chemotherapy was continued up to a total number of nine cycles unless progression or excessive toxicity occurred earlier. Complete responders were then randomly allocated to either six cycles of maintenance chemotherapy of cyclophosphamide, vincristine and methotrexate or to follow up. The impact of maintenance chemotherapy on treatment results will be the subject of another report. Patients who achieved partial remission and those with stable disease were given maintenance chemotherapy until progression occurred. Patients who relapsed during chemotherapy were treated according to the institutional practice. A combination of etoposide and cisplatin was recommended as a salvage chemotherapy regimen. Patients who responded to chemotherapy and who relapsed while off-therapy were retreated with VEC combination or were given second-line regimens.

Table 1. Patients' characteristics

	Dose of epirubicin (mg/m^2)			
	50	70	90	Total
Number	36	58	24	118
Sex				
Females	6	9	2	17
Males	30	49	22	101
Age				
Mean	53.1	56.0	57.9	55.5
Range	(34–64)	(28–70)	(50–67)	(28–70)
Performance status				
0	8	27	7	42
1	19	19	11	49
2	9	11	6	26
3	0	1	0	1

Response to chemotherapy (evaluated before radiotherapy) followed standard WHO criteria [12]. Drug toxicity was graded according to the WHO five-point scale [13]. Survival was computed from the first day of treatment. Statistical methods included χ^2 test for comparison of proportions and log rank test [14] for analysing survival data. A value of $P < 0.05$ was regarded as significant.

RESULTS

Between February 1986 and March 1989 a total of 118 patients from eight institutions were entered in this trial. The median number of chemotherapy cycles per patient was 6, range 1–15. 42 patients received the planned nine chemotherapy cycles. 95 patients were given thoracic irradiation. 2 patients were not evaluable for response: 1 as a result of early death not related to tumour progression and 1 for treatment refusal after the first cycle. No major differences in pretreatment characteristics were present between three consecutive groups of patients given epirubicin in a dose of 50 mg/m^2, 70 mg/m^2 and 90 mg/m^2 (Table 1). Complete tumour remission was seen in 25 patients (22%) and a partial remission in 56 patients (48%). The response rate did not relate to the dose of epirubicin (Table 2). Remission was seen in 66, 73 and 67% of patients given epirubicin in a dose of 50, 70 and 90 mg/m^2, respectively. The median duration of response for all patients was 30 weeks. No significant differences were seen in relation to the dose of epirubicin (Fig. 1). The median duration of survival for the whole group was 52 weeks and there were no significant differences in either of the treatment groups (Fig. 2). 2-year survival rate for the whole group was 12%.

Treatment toxicity was evaluated in 116 patients. The combination was well tolerated in all treatment groups. The main toxicities included alopecia, nausea and vomiting, leukopenia and neurotoxicity (Table 3). Grade 4 haematological toxicity

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Table 2. Response to treatment

	Dose of epirubicin (mg/m²)			
	50	70	90	Total
Complete remission	6(17)	14(25)	5(21)	25(22)
Partial remission	17(49)	28(49)	11(46)	56(48)
Stabilisation	7(20)	11(19)	6(25)	24(21)
Progression	5(14)	4 (7)	2 (8)	11 (9)

No.(%)

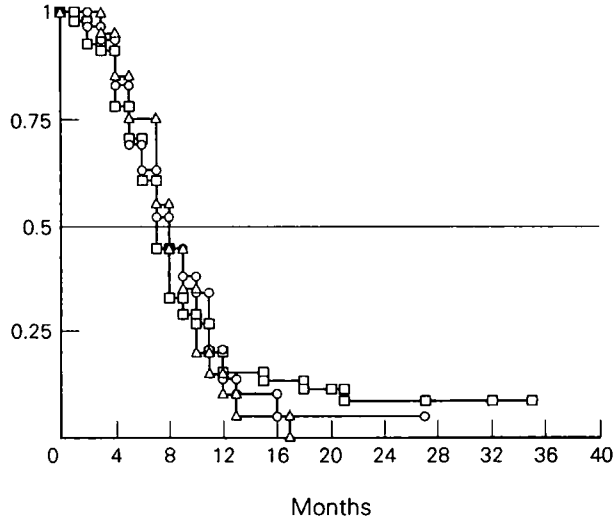

Fig. 1. Duration of remission in relation to epirubicin dose: ○—○ 50 mg/m²; □—□ 70 mg/m²; △—△ 90 mg/m².

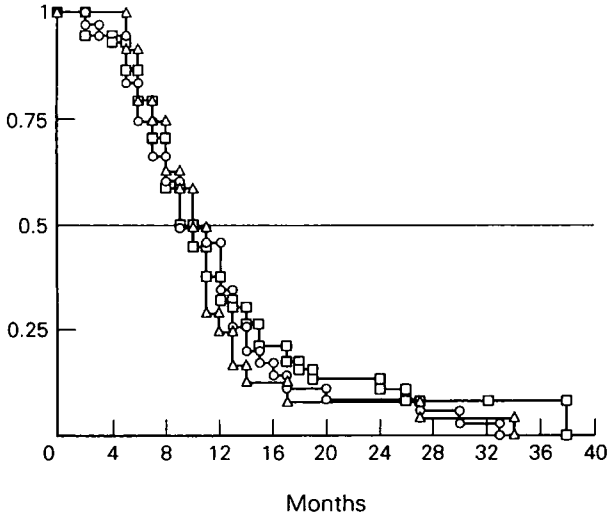

Fig. 2. Duration of survival in relation to epirubicin dose: ○—○ 50 mg/m²; □—□ 70 mg/m²; △—△ 90 mg/m².

Table 3. Treatment toxicity

Toxicity	Dose of epirubicin (mg/m²)			Total	Grades 3 and 4
	50	70	90		
Leukopenia	17(49)	22(39)	12 (50)	51(44)	9 (8)
Thrombocytopenia	2 (6)	4 (7)	1 (4)	7 (6)	1 (1)
Alopecia	34(97)	53(93)	24(100)	111(96)	55(47)
Nausea/vomiting	27(77)	47(82)	20 (83)	94(81)	17(15)
Diarrhoea	2 (6)	4 (7)	3 (13)	9 (8)	3 (3)
Mucositis	—	4 (7)	8 (33)	12(10)	2 (2)
Nephrotoxicity	1 (3)	1 (2)	2 (8)	4 (3)	—
Cardiotoxicity	3 (9)	7(12)	3 (13)	13(11)	2 (2)
Neurotoxicity	6(17)	14(25)	8 (33)	28(24)	1 (1)
Constipation	6(17)	17(30)	6 (25)	29(25)	5 (4)
Other	4(11)	14(25)	5 (21)	23(20)	—

No.(%)

occurred in 3 patients (2.6%) and grade 4 cardiac toxicity—in one patient (0.9%). Chemotherapy was delayed due to myelotoxicity for 9% of the cycles. Peripheral neurotoxicity was common but reversible in all cases after discontinuation of vincristine. No major differences in the rate of side effects were observed between the treatment groups except for mucositis which was dose-related ($P < 0.001$).

DISCUSSION

Since the late 1970s no significant progress in the overall results of treatment of SCLC has been achieved [15]. As only a few new, more effective antineoplastic agents have been developed, the analogues of the currently available drugs have been tested in an attempt to decrease treatment toxicity. Our study was initiated in 1986, i.e. at the time the VAC regimen was considered a standard chemotherapy combination. This regimen resulted in patients with limited disease in an overall response rate of 70% and a median survival of 12 months [16]. We decided to substitute doxorubicin in VAC combination for its potentially less cardiotoxic analogue, epirubicin.

The results of this study demonstrated antitumour activity of the regimen. The response rate observed here proved to be similar to those reported for VAC combination [16]. A randomised study comparing VAC and VEC chemotherapy in SCLC demonstrated similar activity and toxicity of both regimens except for less myelosuppression after the first cycle of VEC [17].

The probable advantage of epirubicin over its parent compound is the possibility of administering higher cumulative doses with acceptable risk of congestive heart failure [5]. Dose-related response rate in SCLC patients has been suggested by some authors [3, 18], but questioned by others [15]. Previous phase II studies demonstrated a high activity and acceptable toxicity of epirubicin given alone at 100–200 mg/m² [7–11]. This study aimed at determining the possibility of escalation of epirubicin dose in standard combination chemotherapy. Since at the time this study was initiated no data on high-dose epirubicin chemotherapy were available, we selected a starting epirubicin dose of 50 mg/m², similar to that used for doxorubicin in VAC combination. When, after including the first 35 patients no serious toxicity was observed, this dose was increased to 70 mg/m² and, finally, to 90 mg/m². Although good tolerance for epirubicin up to 90 mg/m² per cycle was demonstrated, no

significant dose-related differences in reponse rates and survival were found. These results should be considered with caution, however, due to the limited number of patients in the consecutive treatment groups and due to the non-random method of patient allocation. It is also possible that the maximum tolerated dose (MTD) of epirubicin was not reached in this study. Phase I studies conducted on patients with non-small cell lung cancer and breast cancer concluded that the MTD for this drug as a single agent is 150–165 mg/m^2 [19, 20]. A recent study by the South–East European Oncology Group suggested that epirubicin at a dose of 120 mg/m^2 can be combined safely with cyclophosphamide or cisplatin in patients with extensive SCLC [21].

According to the common practice at the time this study was designed, we chose nine cycles of induction chemotherapy. Based on the experience of more recent randomised studies of short-versus long-duration chemotherapy [22] it is possible that similar results might have been achieved with 5–6 chemotherapy cycles. In our successive study only five cycles of epirubicin-containing combination chemotherapy were administered. Short duration chemotherapy, aiming at a better quality of survival and at diminishing the cost of therapy, may also reduce the possible risk of cumulative cardiotoxicity if higher single doses of epirubicin were to be applied.

As expected, the principle toxicity with VEC regimen was alopecia. Nadir blood counts were not routinely measured, but evaluation performed before each cycle suggests that haematological toxicity was acceptable and was not dose-limiting. Despite the lack of impressive response duration and median survival with the VEC combination, the mild toxicity of the regimen prompted us to continue studies with this anthracycline. In our next study, including patients with both limited and extensive disease, vincristine in VEC combination was replaced with etoposide. Early results of this trial suggest significant improvement in treatment results still with an acceptable toxicity [23].

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