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Ifosfamide, Doxorubicin and Etoposide in Small Cell Lung Cancer Patients with Poor Prognosis

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61 patients with small cell lung cancer in a poor prognosis group were treated with chemotherapy and with thoracic radiotherapy if they had 'limited stage' disease. No prophylactic cranial irradiation was given. Chemotherapy comprised doxorubicin 50 mg/m^2 and ifosfamide 5 g/m^2 with mesna on day 1, and etoposide 120 mg/m^2 intravenously on days 1 and 2 and 240 mg/m^2 orally on day 3. Treatment was repeated every 3 weeks for a maximum of six courses and no dosage reductions were allowed. Complete response rate in limited stage patients was 55% and 16% in extensive stage patients. The partial responses were 38% and 66% respectively. Overall median survival was 10.5 months with 2-year survival of 14%. The corresponding values for limited stage disease were 13 months and 16% and for extensive stage disease 8 months and 13%. Despite the addition of doxorubicin at a somewhat higher dosage than usual in this type of regimen and a policy of no dose reduction, toxicity was generally mild. There was, however, a 19% relapse rate in complete responders in the brain, apparently as the sole site of disease.
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INTRODUCTION

COMBINATION CHEMOTHERAPY is the accepted treatment for small cell lung cancer and a small proportion of treated patients now survive 2 years or more. Etoposide has been substituted for vincristine in the cyclophosphamide/doxorubicin/vincristine (CAV) regimen or added as a fourth drug [1–5]. The overall response rate in these etoposide combinations was over 80% with a complete response (CR) rate of 50% or more in limited stage (LS) disease. There was a significant improvement in response duration and survival with CEV (cyclophosphamide/etoposide/vincristine) in patients with extensive disease and a trend favouring CEV in LS disease compared with CAV [6]. The latest results with doxorubicin/cyclophosphamide/etoposide (ACE) [3,7] show CR rates of 65% in limited disease and median survival of 15 months with about 20% of patients live at 3 years. In extensive stage (ES) disease, the CR rate was about 40% with median survival of 8–9 months. Attempts to improve these results with alternating chemotherapy or prolonged etoposide infusions have not been successful [8].

The use of ifosfamide and etoposide in patients with small cell lung cancer has also produced good overall response rates of 90% in LS disease and over 60% in ES disease; median survival for LS was 11 months and 8 months for ES [9]. In an updated analysis 23% of LS patients were alive at 2 years or more. The toxicity of the combination was not severe. Ifosfamide is probably more active and less myelosuppressive than cyclophosphamide [10,11]. Therefore, we decided to substitute ifosfamide for cyclophosphamide in combination with doxorubicin and etoposide.

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PATIENTS AND METHODS

61 patients with previously untreated small cell carcinoma of the bronchus, histologically proven, were studied. Routine examination was done and Karnofsky and respiratory scores [12], complete blood count, creatinine, urine, electrolytes, liver function and bone marrow aspirate and trephine samples were assessed. Radionuclide and ultrasound scans were done to confirm metastatic disease. Patients were excluded if there was evidence of brain metastases (routine computerised tomography [CT] was not used), if the Karnofsky score was 30 or less or if the patients were more than 70 years old. LS disease (29 patients) was defined as inoperable tumour confined to a hemithorax but including mediastinal extension, ipsilateral supraclavicular lymphadenopathy and pleural effusions. The remaining 32 patients had metastatic tumour beyond LS and were classified as ES. The median age was 54 years (range 38–70). There were 34 males and 27 females (Tables 1 and 2). Prognosis was defined as poor if the patient had two or more of the following elevation of lactate dehydrogenase alkaline phosphatase, hyponatraemia, ES disease, Karnofsky score below 60 and low bicarbonate [13].

Treatment

Patients were treated every 3 weeks with ifosfamide, etoposide and doxorubicin for a maximum of six courses. Each course consisted of ifosfamide 5 g/m^2 with mesna at the same dose in 2 l 0.9% saline as a 24 h intravenous infusion on day 1. A further infusion of mesna 3 g/m^2 in 1 l of saline was continued over the next 12 h. Etoposide 120 mg/m^2 was given intravenously on days 1 and 2 and 240 mg/m^2 orally on day 3. Doxorubicin 50 mg/m^2 was also given on day 1. Lorazepam 1 mg intravenously was administered before chemotherapy and repeated every 8 h for 24 h, metoclopropramide was given as necessary for nausea and vomiting. 3 weeks after the last course of chemotherapy, thoracic radiotherapy (4 MeV) was given to LS patients. The pre-chemotherapy volume was irradiated in complete responders or with a margin of at least 2 cm around any residual disease. In

*Table 1. Clinical features**

	LS (n=29)	ES (n=32)	Total (n=61)
Interval from symptoms to diagnosis (mo)			
<1–3	59	53	56
>3–6	38	47	43
Unknown	3	0	1
Interval from diagnosis to treatment (mo)			
<1	83	69	76
1–2	14	22	18
>2	3	9	6
Superior vena claval obstruction	21	6	14
Weight loss (>10% over 6 mo)	41	44	43
Lymphadenopathy			
Hilar	66	53	60
Mediastinal	34	47	41
Ipsilateral SCF	0	19	10
Contralateral SCF	0	19	10
Cervical	0	13	7
Axillary	0	13	7
Pleural effusion	31	16	24
Marrow involvement	0	12	6
Liver	0	35	16
Bone	0	54	23
Soft tissue		12	5
Other metastases	0	8	7
Hyponatraemia	6	8	7
Low bicarbonate	10	22	16
Normal enzymes	24	34	30
Raised enzymes			
Alkaline phosphate	55	41	48
Lactate dehydrogenase	31	50	41
ALT	0	7	3
GGT	31	44	38

*All figures are percentages.
ALT = alanine aminotransferase and GGT = glutamyl transpeptidase.
SCF = Supraclavicular fossa.

patients with complete radiological response the field was centred on the site of the original thoracic tumour. Two treatment schemes were used. Most patients received a single fraction of 12.5 Gy with a 360° rotation technique and others, in whom rotation was not technically feasible received a 27.5 Gy midline dose in eight fractions over 10 days with a parallel opposed pair. Prophylactic cranial irradiation was not given.

Before each course, patients were assessed by routine examination, Kanofsky and respiratory scores, repeat biochemistry, haematology and chest radiography. If the white cell count was less than 3×10^9/l and/or the platelet count was less than 100×10^9/l therapy was delayed a week until recovery (blood count was checked weekly). No dosage reductions were made. Patients were advised to contact the hospital if they felt unwell between courses and appropriate investigations were then undertaken. If disease progressed treatment was discontinued and symptomatic measures started.

Follow-up

At the end of treatment patients were seen montly for 4 months and then every 3 months for a year and every 6 months thereafter. Routine investigations and chest radiography were repeated at each visit; additional investigations were done if clinically indicated. Objective response was assessed at first follow-up by standard WHO criteria [14]. Repeat bronchoscopy was done in LS patients when possible. Toxicity, Karnofsky and respiratory scores were recorded after each course of treatment and 1 month after the end of treatment. No patient has been excluded from analysis because of incomplete treatment, early death or toxicity.

Table 2. Karnofsky and respiratory scores (percentage of patients)

	Pretreatment		After course 2		After course 4		1 mo after treatment	
Score	LS	ES	LS	ES	LS	ES	LS	ES
Karnofsky								
<50*	0	0	7	3	17	6	17	13
50–70	72	72	38	38	21	19	10	9
80–100	28	28	55	59	62	75	73	78
Respiratory†								
1–2	14	19	48	34	66	75	55	63
3–4	86	72	52	53	17	22	28	28
5*	0	9	0	13	17	3	17	9

*Includes patients who died.
†1–2 = climb hills, stairs, walk any distance on the flat at normal pace without dyspnoea; 3–4 = walk more than 108 m at own speed without dyspnoea, dyspnoea on walking 108 m or less and 5 = dyspnoea on mild exertion, e.g. undressing (dying patients included).

RESULTS

LS patients

Response. 55% (95% CI 36–74%) of the 29 patients achieved a complete response (CR) when assessed clinically and radiologically 1 month after the end of chemotherapy. 15 showed CR by the third course of chemotherapy and the other attained CR 1 month after radiotherapy. 13 of the 16 patients underwent repeat bronchoscopy; 12 had neither macroscopic nor microscopic evidence of tumour. 11 patients (38%, CI 21–58%) were partial responders, 8 of whom (73%) achieved partial response (PR) by the end of the third course. The remaining 2 patients were non-responders. The median duration of CR was 13.5 months (range 7–19) and of PR 7 months (1–23).

Survival. The median survival for all patients was 13 months; 25% of the group were alive at 18 months after the start of chemotherapy and 16% at 24 months or more (Fig. 1).

Toxicity. 67% of all patients completed treatment. A total of 142 courses (or 82% of the possible maximum) was given. Of these, 11 courses (8%) were delayed because of toxicity. Grade 3 leucopenia occurred in five courses and grade 4 in four courses. Intravenous antibiotics were administered on 13 occasions and orally on 19 occasions for suspected or confirmed infection. There was 1 death due to septicaemia and leucopenia. 22 transfusions were given. Grade 3 thrombocytopenia (no grade 4) was noted on four courses. Moderate or severe nausea and vomiting was observed in 18 courses but on 89% of courses it was mild or absent. 1 patient developed transient ifosfamide encephalopathy. A further patient had temporary grade 2 renal toxicity on the sixth course of treatment. Improvement in Karnofsky status occurred in most patients after the second course; the score was normal or near normal in 21 patients 1

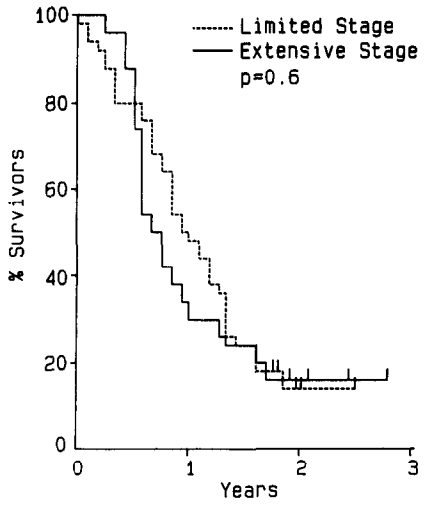

Fig. 1. Survival.

month after treatment compared with 12 patients before treatment (Table 2). 25 of the 29 patients had a respiratory score of 3 or more, indicating moderate or severe breathlessness at the beginning of the chemotherapy but after the last course, 18 patients had a score of two or less indicating little or no breathlessness (Table 2).

Relapse. 6 of the 16 CR patients have relapsed and 9 of the 11 partial responders have progressed. 3 of the 6 in the CR group relapsed in the brain, 2 had local thoracic relapse and 1 relapsed in both the liver and brain. 5 of the 9 partial responders relapsed in the brain. 2 had local thoracic relapse and 1 relapsed in bone; the other patient relapsed both locally in the thorax and also in the brain. 1 patient with local relapse was given further chemotherapy.

ES patients

Response. The CR rate for 32 extensive stage patients was 16% (CI 5–33%) 4 of these 5 patients attained CR after the second course and the other patient achieved CR after all six courses. 21 other patients (66%, CI 47–81%) were classed as partial responders. 17 responded by the third course of chemotherapy. In 4 of the 5 complete responders, macroscopic and microscopic absence of tumour was confirmed by repeat bronchoscopy. 6 patients failed to respond. The median duration of CR was 10 months (range 7–28) and of PR 7 months (4–25).

Survival. The median survival for all 32 patients was 8 months, 22% survived more than 18 months and 13% survived 24 months or more (Fig. 1). The median duration of survival for the partial and complete responders was 7 and 8 months, respectively.

Toxicity. For the 32 patients, 146 courses of chemotherapy (76% of the possible maximum) were given; 62% of the patients received all six courses. Chemotherapy was delayed on 13 courses (9%) due to low blood counts. Grade 3 leucopenia occurred on 11 occasions and grade 4 leucopenia on 4 occasions. Grade 3 thrombocytopenia was noted after four courses and grade 4 on two courses, which required platelet transfusions. Blood transfusion was given on 34 occasions. Antibiotics were administered for probable infection after 20 courses (with 4 episodes of life-threatening septicaemia) and on 12 further occasions oral antibiotics were given. There were 37 episodes of moderate or severe nausea and vomiting. 2 patients developed transient ifosfamide-related encephalopathy and a further patient had grade 2 renal toxicity. Improvement in Karnofsky score and respiratory score also occurred with treatment (Table 2).

Relapse. 1 of the 5 complete responders has relapsed in the brain. 16 of 21 partial responders have progressed. Of these 16, 6 relapsed in the brain, 3 in the liver, 3 in bones, 1 locally in thorax, 2 in abdominal nodes and 1 relapsed locally in the thorax and in the liver.

DISCUSSION

Our study of ifosfamide, doxorubicin and etoposide showed (in a total group of 61 patients) a median survival of 10.5 months, with 44% and 14% of patients alive at 1 and 2 years, respectively. In a retrospective analysis of a subset of patients (in the same poor prognostic group as in the current study) who were treated with ifosfamide and etoposide only, median survival was 7.5 months with 1 and 2 year survivals of 14% and 2% [9,13]. Such a comparison should be cautiously interpreted, although the known prognostic factors have been taken into consideration. Nevertheless the addition of doxorubicin to ifosfamide and etoposide possibly improved survival in this poor prognostic group. Although our study included LS disease these patients had other features (e.g. elevated alkaline phosphatase and lactate dehydrogenase) that were predictive of an unfavourable outcome [13].

Our results were generally similar to those obtained with other ACE-type regimens [2–4,9,15,16] even though we did not use sophisticated radiological investigations for staging purposes and the fact that our patients were in a poor prognosis group. Indeed we saw a median survival of 13 months in LS and the 2 year survival of 16% of patients who were not intensively staged. Again, these results are similar to other combinations involving cyclophosphamide, vincristine, etoposide and doxorubicin.

The doxorubicin dose in several ACE-type regimens has usually been 40 or 45 mg/m^2 rather than the somewhat higher dose we used of 50 mg/m^2 (also our policy was no dosage reduction although treatment was deferred weekly until blood count recovery). Despite this protocol and the fact that most of the patients (72%) had a poor performance status before treatment, there was only 1 case of transient encephalopathy and 1 treatment-related death from septicaemia. Chemotherapy was delayed for 8% of the courses and intravenous antibiotics were required only on 9% of courses. Performance status improved after the second course of chemotherapy and breathlessness assessed by the respiratory score improved quickly following treatment. These symptomatic benefits are important in patients with a poor prognosis.

In our study there was a low percentage of courses in which grades 3 or 4 leucopenia or thrombocytopenia occurred but nadir blood counts were not routinely measured. However, antibiotics were immediately introduced in patients suspected of having infection, which partly accounts for the high number of presumed infective episodes. 6 patients relapsed in the brain and 4 other patients in the CR group relapsed with the brain as at the apparent sole site of disease. This brain relapse rate of 19% suggests that prophylactic brain irradiation may have a role in patients even with poor prognostic features. Our regimen produced rapid tumour response with improvement in symptoms without severe toxicity. The policy of no dosage reduction and the addition of doxorubicin may have contributed to this result.

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Proto-oncogene Expression in Differentiating and Non-differentiating Chronic Myelogenous Leukaemia Cells

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Despite the profound differences between the chronic and blastic phases of chronic myelogenous leukaemia, no differences between chronic and blastic phase cells have been described at the molecular level. Differences have been found in the levels of expression of c-myc, c-myb and p53, which fell when chronic phase cells were cultured, while the levels of expression of the genes were stable when blastic crisis cells were cultured. In contrast c-fms expression increased and MRS expression decreased after culture of chronic or blastic phase cells. The data suggest that the regulation of expression of some genes in blastic crisis cells is unaltered while that of others is disrupted. It is not known whether the failure of c-myc, c-myb and p53 expression to fall during the culture of blastic phase cells is the cause of or a reflection of the failure of these cells to differentiate.
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INTRODUCTION

CHRONIC myelogenous leukaemia (CML) invariably evolves into an acute or blastic phase. During the initial phase, myeloid differentiation is intact while impaired maturation is the hallmark of the blastic phase. Why myeloid maturation fails during the blastic phase is not known. We have established a suspension culture system in which chronic and blastic phase cells behave *in vitro* similarly to their behaviour *in vivo*. The immature cells