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Therapy for poor-risk patients with small-cell lung cancer using bolus ifosfamide and oral etoposide

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Summary. A total of 47 poor-risk small-cell lung cancer patients (elderly, poor performance status, recent myocardial infarction, or extensive-stage disease with biochemical abnormalities) were treated with a regimen of bolus ifosfamide at 1.5 g/m^2 with equidose mesna as a 30-min infusion, followed by 100 mg oral etoposide daily for 8 days. Therapy was repeated every 3 weeks. The overall response rate was 60% (75% for limited-stage and 48% for extensive-stage disease), and the overall median survival was 7 months. Patients' performance status significantly improved with therapy (P <0.0001). Despite the poor-risk factors, the Manchester prognostic score was applied and verified. The median survival was 8 months for patients with a good prognosis, 6 months for those with an intermediate prognosis and 2.5 months for poor-prognosis patients (P = 0.0002). Therapy was well tolerated. The median WHO grade of haematological toxicity was 2 (range, 0–4). Only 10/226 (4%) courses were delayed due to leukopenia. Blood transfusions followed 18/226 (8%) courses. Intravenous antibiotics were given following 15/226 (7%) courses. No patient required platelet support. Poor-risk patients who have a good or intermediate Manchester prognostic score may benefit from this low-toxicity regimen.

Introduction

Patients with small-cell lung cancer treated with combination chemotherapy have a median life expectancy of about 51 weeks for limited-stage disease and 33 weeks for extensive-stage disease [7]. Patients aged over 70 years, those who have cardiac failure or have had a recent myocardial infarction, or those who have extensive disease with biochemical abnormalities are often considered to be unsuitable for chemotherapy studies.

Single-agent ifosfamide and etoposide have shown response rates of 50% and 40%, respectively [2, 4]. When these two agents were used in combination with a 24-h infusion of 5 g/m^2 ifosfamide and etoposide at 120 mg/m^2 given i.v. on days 1 and 2 and at 240 mg/m^2 given orally on day 3, the response rate was 90% for limited-stage disease and the updated 2-year actual survival was 22% for these patients [12].

A low-toxicity regimen was devised using ifosfamide as a short infusion given over 30 min followed by oral etoposide for 8 days. The rationale for this therapy is that bolus ifosfamide has little toxicity when given at a dose of 5 g/m^2 with equidose mesna [11], and etoposide has been shown to be more effective when given in fractionated doses over 3–5 days [5]. This regimen involved either an inpatient admission for 1 day or treatment as a day case.

Materials and methods

A total of 47 patients with histologically proven small-cell lung cancer were entered into the study. Staging investigations included a full blood count, a biochemical profile and liver function tests (gamma GT, LDH, ALT). Chest radiographs were done prior to each cycle of therapy. Radionucleotide and ultrasound scans were carried out to confirm clinical and biochemical abnormalities that suggested metastatic disease. The Karnofsky performance status (KP) [6] has been shown to be an important prognostic factor in our patients [3] and was documented in all patients together with the respiratory score [9] prior to each course of chemotherapy. A nadir full blood count was done routinely.

Limited-stage (LS) disease was defined as an inoperable tumour confined to one hemithorax but including mediastinal extension, ipsilateral supraclavicular lymphadenopathy, and ipsilateral pleural effusions. Patients with tumours beyond LS were classified as having extensive-stage (ES) disease.

Patients received 1.5 g/m^2 ifosfamide with 1.5 g/m^2 mesna as an i.v. infusion over 30 min. Oral etoposide at 100 mg was given daily for 8 days, commencing on the same day as the ifosfamide infusion. Patients also received 200 mg oral mesna 4 and 8 h after ifosfamide. The aim was to repeat the therapy at 3-week intervals for a maximum of six cycles. If the leukocyte count was <3.0 × 10^9/l and/or the platelet count was <100 × 10^9/l when chemotherapy was due, treatment was delayed by

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Table 1. Reasons for poor-risk classification

KP <50	6	KP <50 + liver metastases	4
Age >70 years	10	KP <50 + bone metastases	4
Liver metastases	5	KP <50 + cardiac history	1
Bone metastases	5	KP <50 + other[a]	2
Cardiac history	3	KP <50 + liver + bone	2
		KP <50 + liver + age >70 years	1
		Liver + cardiac history	1
		Liver + bone metastases	2
		Liver + age >70 years	1
Totals	29		18

[a] 1 extensive bilateral pulmonary metastases, 1 extensive lymphadenopathy >5 cm
KP, Karnofsky performance status

Table 2. Patient characteristics at entry

	Number (%)
Total	47
Men	31 (66)
Women	16 (34)
Median age	62 years
range	45–74 years
Limited stage	20 (42)
Extensive stage	27 (57)
Haemoptysis	19 (40)
Chest pain	20 (43)
Dyspnoea	41 (87)
Weight loss	29 (62)
Dysphagia	4 (9)
Hoarseness	9 (19)
Superior vena caval obstruction	5 (11)
Stridor	4 (9)
Hyponatraemia (NA ≤ 128 mmol/l)	9 (19)
Elevated LDH	20 (43)
Elevated Alk Phos	15 (32)
Median Karnofsky performance status	60 (range, 40–80)
Median respiratory score[a]	3 (range, 1–5)
Median number of therapy cycles	6 (range, 1–6)

[a] MRC respiratory score

Table 3. Response to therapy

	Overall (%)	LS (%)	ES (%)
Complete remission	10 (21)	7 (35)	3 (11)
Partial remission	18 (38)	8 (40)	10 (37)
Stable disease	2 (4)	0	2 (7)
Progressive disease	13 (28)	4 (20)	9 (33)
Deaths	4 (9)	1 (5)	3 (11)
Totals	47	20	27

1 week. The first cycle of therapy was given on an inpatient basis, and subsequent therapy could be given on an outpatient basis if it was well tolerated. Response status was assessed 1 month after the last cycle of therapy unless tumour progression occurred, in which case therapy was discontinued. Treatment response and toxicity were classified according to standard criteria [8], and survival was assessed from the date of commencement of chemotherapy.

LS patients who had achieved a complete or partial remission with chemotherapy were considered for mediastinal radiotherapy. This was given either as a single fraction of 12.5 Gy using a 360° rotation technique to exclude the spinal cord from the high-dose volume or in eight fractions over 10 days using a parallel, opposed pair [12].

Results

All 47 patients were considered to be of poor risk, i.e. elderly, >70 years old, with a poor performance status, a KP of ≤ 50, cardiac failure or a myocardial infarction within the previous 3 months, or extensive liver or bone disease (Table 1). The median duration of follow-up was 19 months. Patient characteristics are shown in Table 2. In all, 27 patients had ES disease, including lymphadenopathy (1), bilateral intrapulmonary metastases (1), or metastases to bone (9), liver (12) or liver and bone (4).

Response to therapy

Overall, 10 (21%) patients achieved a complete remission and 18 (38%) achieved a partial remission. The overall response rate was 28/47 (60%). The response rate for LS was 75%, and that for ES disease was 48% (Table 3). Of the responders, 70% did so following the first cycle of therapy, and there were no further responses after two cycles of therapy. A total of 13 patients who had a good response to chemotherapy subsequently received thoracic irradiation. Patients' performance status significantly improved with chemotherapy (P <0.0001). The median KP was 60 before and 80 after therapy.

Toxicity

Toxicity is summarised in Table 4. A total of 226 courses of therapy were given; the treatment was well tolerated. Of 47 patients, 26 (55%) had some evidence of haematological toxicity. The median WHO grade was 2 (range, 0–4). Only 10 (4%) courses were delayed due to leukopenia at the time at which therapy was due.

Two patients died of infection and cancer, one of whom developed bacterial endocarditis and pneumonia with cerebral infarction. A non-haemolytic *Streptococcus* grew from the valve vegetations. This patient had bone marrow and liver metastases and died after the first course of chemotherapy. Another patient, who was not neutropenic, died suddenly of *Pseudomonas* septicaemia after the first course of chemotherapy.

Intravenous antibiotics were given for infection that followed 15 (7%) courses of therapy in 14 (30%) patients. No patient required platelet transfusion. Blood transfusions were given to 16 (34%) patients following 18 (8%) courses of therapy.

Most patients developed reversible, total alopecia. Excluding alopecia, the median WHO grade of non-haematological toxicity was 1 (range, 0–5). Vomiting or nausea followed 172 (76%) of 226 courses of therapy and was the chief cause of non-haematological toxicity. Only three patients developed mild cystitis.

Table 4. Toxicity of therapy

Course	1	2	3	4	5	6
Patients (*n*)	47	44	38	35	32	30
Hb pre-treatment	12.8	12.2	11.9	11.6	11.8	11.7
nadir (g/l)	12.0	10.7	11.1	11.1	11.2	11.5
WBC pre-treatment	9.1	6.1	6.6	5.8	5.5	5.5
nadir ($\times 10^9$/l)	5.7	6.3	6.0	5.9	6.7	4.7
Platelets pretreatment	388	382	338	327	307	323
nadir ($\times 10^9$/l)	309	330	367	325	335	317
Blood transfusions (*n*)	2	3	6	1	2	4
Infection:						
WHO grade 0	35	35	34	33	28	29
1	4	6	3	2	1	1
2	6	2	1	0	3	0
3	0	1	0	0	0	0
Deaths	2	0	0	0	0	0
Antibiotics:						
i.v.	6	4	1	1	2	1
oral	8	4	1	1	2	0

Hb, hemoglobin

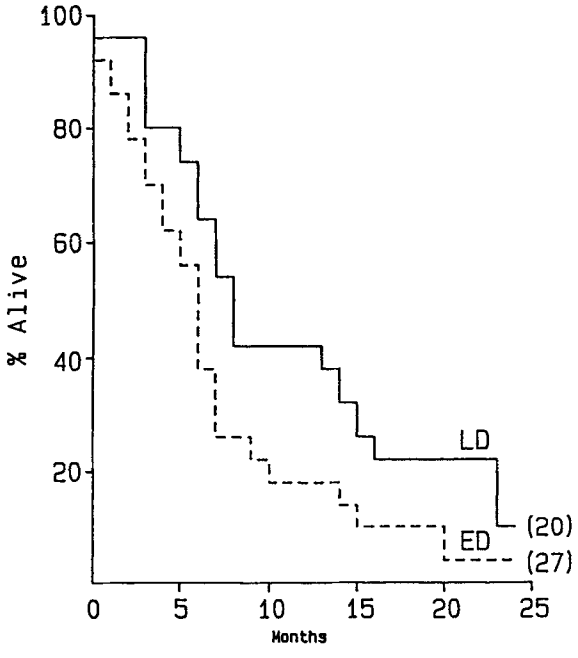

Fig. 1. Survival of patients according to stage. *LD*, limited-stage disease; *ED*, extensive-stage disease

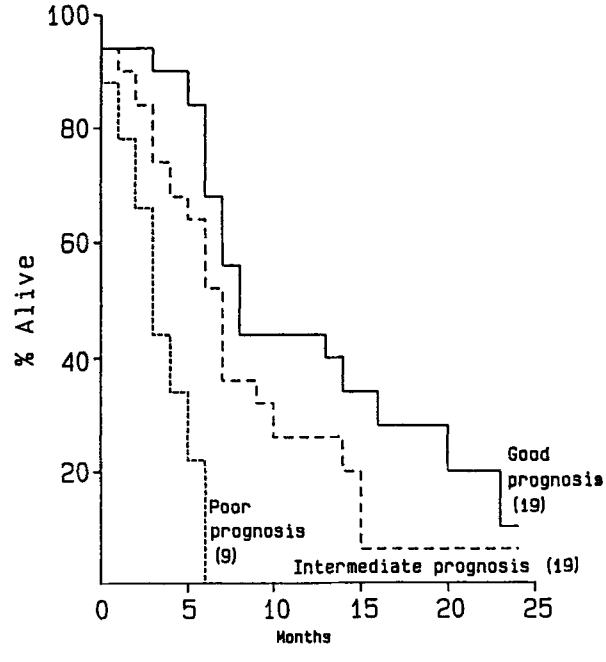

Fig. 2. Survival of patients according to the Manchester score

Current status

Currently, two patients are alive and disease-free (at 17 and 22 months) and two are alive with cancer (at 24 months each). One patient was lost to follow-up, having gone to Australia at 4 months of follow-up. Of the 42 who have succumbed, 39 died of cancer, 1 had an intercurrent death (at home the day after discharging himself from the hospital; he had been receiving i.v. antibiotics after three cycles of therapy and was not neutropenic), and 2 died of infection after the first course of chemotherapy. The overall median survival was 7 months: 8 months for patients with LS disease, and 5.5 months for those with ES disease (Fig. 1).

The Manchester score of prognostic factors was derived from retrospective data and showed that six pre-therapy variables had a significant effect on survival in small-cell lung cancer: performance status, disease stage, serum sodium, alkaline phosphatase, lactic dehydrogenase and serum bicarbonate [3]. The survival according to the Manchester score is shown in Fig. 2: 8 months for a good prognosis, 6 months for an intermediate prognosis, and only 2.5 months for poor-prognosis patients ($P < 0.0002$).

Discussion

Therapy with bolus ifosfamide and 8 days of oral etoposide was well tolerated. The regimen was associated with an overall response rate of 60%. In the subgroup of patients with LS disease, the response rate was 75%, although the median survival was only 8 months. This therapy is less effective than more intensive therapies for which these poor-risk patients would not have been considered suitable.

The treatment was associated with an overall significant improvement in performance status. All responses occurred after the first or second cycle of therapy. This regimen can be used to palliate disease in poor-risk patients who have distressing symptoms that cannot be controlled by other means; it can be stopped after two courses if no response occurs.

Analysis of this prospective group of patients according to the Manchester score confirms our previous retrospective analysis for prognostic factors [3]. Other investigators have reported the results of studies aimed at low-toxicity therapy for poor-risk patients. Allan et al. [1] used vindesine and etoposide, achieving a 72% response rate in 43 evaluable patients; the response rate was 86% for LS and 66% for ES disease. Although the response rate was superior to that seen in the present study, survival was similar at 8 months.

The next logical step could be to use single-agent therapy alone. Slevin et al. [10] reported the use of i.v. etoposide and showed a 72%–80% response rate, and we are now evaluating an oral etoposide regimen.

In conclusion, this regimen has activity in small-cell lung cancer and could be used in poor-risk patients not considered fit enough to undergo more intensive chemotherapy. Poor-risk patients in the good and intermediate Manchester prognostic score groups would be likely to benefit from this treatment.

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