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Ifosfamide and Mitomycin in Combination for the Treatment of Patients with Progressive Advanced Non-small Cell Lung Cancer

Howard Gurney, Edson Sydney de Campos, David Dodwell, Arvind Kamthan and Nicholas Thatcher

42 patients with progressive and advanced non-small cell lung cancer received chemotherapy comprising ifosfamide 1.5 g/m², mesna 1.5 g/m² and mitomycin 1.2 mg/m² daily for 5 days. Only those patients with symptoms and progressive disease were selected for treatment. Partial response was achieved in 10/42 patients (23.8%) and stable disease in 25/42 (59.5%). The Karnofsky performance status (KP) improved in 10/42 patients (23.8%) and a subjective respiratory symptom score improved in 12 patients (28.6%). In addition 27 patients (64.3%) had stabilisation of both the KP and respiratory score following chemotherapy. These results indicate that the ifosfamide and mitomycin combination is active in non-small cell lung cancer in this selected group of patients with antitumour and symptom control activity.
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INTRODUCTION

PATIENTS WITH advanced non-small cell lung cancer have a median survival of less than 12 months with or without chemotherapy [1]. Ifosfamide has been found to be one of the more active agents in this tumour with response rates of 10–30% when used as a single agent [2]. Mitomycin induces a similar response rate in these patients [3]. The policy at this institution is to treat with chemotherapy only those patients with advanced non-small cell lung cancer who have progressive and symptomatic disease. It was in a group of such patients that we assessed a combination of ifosfamide and mitomycin for palliative and antitumour effect.

PATIENTS AND METHODS

Patient characteristics are listed in Table 1. To be eligible, patients were required to have progressive (asssessed by monthly tumour evaluation) and symptomatic disease, be aged 70 years or less, have adequate bone marrow function as assessed by a white cell count (WCC) $\geq 3.0 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l, and have a creatinine clearance >50 ml/min. Karnofsky performance status and the Medical Research Council (MRC) respiratory score [4, 5] were assessed prior to each chemotherapy and 1 month after completion of all treatment. The relationship of disease stage to breathlessness assessed by

Correspondence to E.S. de Campos.
The authors are at the Cancer Research Campaign Department of Medical Oncology, Christie Hospital and Holt Radium Institute, Manchester M20 9BX, U.K.
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Table 1. Patients' characteristics

Characteristics	No. of patients (total 42)
Median age in years (range)	61 (36–78)
Sex	
Males	37
Females	5
Performance status	
90–80	12
70–60	19
50–40	11
Respiratory score	
1–2	12
3	14
4–5	16
Histology	
Adenocarcinoma	12
Squamous cell carcinoma	24
Large cell carcinoma	6
Sites of metastases	
Mediastinal nodes	29
Ipsilateral pleura	9
Other nodes	
Axillary	3
Ipsilateral neck	3
Contralateral neck	1
Both sides of neck	3
Contralateral lung	8
Liver	3
Bone	5
Subcutaneous	2
Other (i.e. soft tissue and adrenal)	3
Stage	
III B	20 (4 patients received previous XRT).
IV	22 (2 patients received previous XRT).

XRT = X-ray therapy.

Table 2. Disease stage and respiratory score

	Stage	
Respiratory score*	III B	IV
1, 2 = "Mild"	4(+1)	7
3 = "Moderate"	9(+1)	4
4, 5 = "Severe"	3(+2)	9(+2)

Patients who had received previous thoracic radiotherapy are in parentheses.

*Medical Research Council respiratory score: grade 1 = climbs hills and stairs without dyspnoea; grade 2 = walks any distance at normal pace on flat without dyspnoea; grade 3 = walks > 100 yards at own speed without dyspnoea; grade 4 = dyspnoea if walks 100 yards or less; grade 5 = dyspnoea on mild exertion e.g. undressing.

the respiratory score is given in Table 2. WHO criteria were used to assess tumour response and toxicity [6]. Patients who had received radiotherapy but not chemotherapy were eligible. Patients with central nervous system metastases were not eligible but computed tomography (CT) was only performed to confirm clinical suspicion of intracranial metastatic disease. Patients with stable or asymptomatic disease were observed and treatment was not commenced until progression of disease or symptoms developed. The median observation interval was 2 months for this study group of patients.

Chemotherapy regimen

Treatment consisted of intravenous infusion ifosfamide 1.5 grams/m^2 and mesna 1.5 g/m^2 1 l litre of normal saline daily over 1 h for 5 days, followed by mesna 1.5 g/m^2 in 1 l of normal saline over 12 h. Mitomycin 1.2 mg/m^2 was given as a bolus intravenous injection daily for 5 days. A maximum of four courses of treatment were given in the absence of progression, each at an interval of 21 days providing the WCC was $>3.0\times10^9$/l, platelets $>100\times10^9$/l and creatinine clearance >50 ml/min on the day of chemotherapy. No dose reduction of chemotherapy was undertaken, but treatment was delayed weekly to allow blood counts or creatinine clearances to recover. Nadir blood counts were performed 10–14 days after each chemotherapy cycle.

RESULTS

Of the 42 patients, 4 received 1 cycle, 4 received 2, 7 received 3 and 27 received 4 cycles of chemotherapy. The median follow-up was 13 months (maximum 24 months). 4 patients had a treatment delay of 1 week each. There were no dose reductions, nor complete remissions. 2 patients died on treatment of progressive disease. 10 patients out of 42 (23.8%, confidence limits 12%–39%), achieved a partial response; 25 patients had stable disease (59.5%, confidence limits 43%–74%); and in 5 patients disease continued to progress while on treatment. Median response duration for patients achieving a partial response was 5.5 months (range 2–16 months).

Overall survival is illustrated in Fig. 1. The median survival was 7 months with 10% survival beyond 18 months. Toxicity of this combination was manageable. Grade 1 or 2 nausea and vomiting occurred as the maximum gastrointestinal toxicity in 21 patients, grade 3 in 17 patients and grade 4 in 2 patients. No patient experienced encephalopathy and only 1 had cystitis (non-haemorrhagic) which settled with continued intravenous hydration. Significant myelotoxicity occurred in 21% of patients,

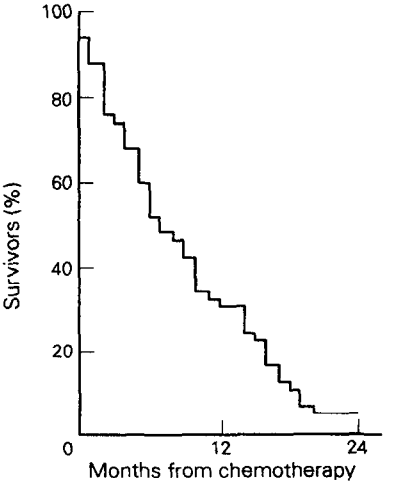

Fig. 1. Overall survival for all patients (n = 42).

with grade 3 and 4 leucopenia occurring in 6 and 3 patients respectively, but no patient had significant thrombocytopenia. There were 3 episodes of infection during leucopenia requiring intravenous antibiotics. There was no other significant toxicity, and there were no treatment related deaths.

The ifosfamide and mitomycin combination had a positive effect on the patients' symptoms and performance. An improvement in Karnofsky performance status was noted in 10 patients (23.8%) and in 27 (64.3%) the score remained stable throughout the course of treatment and at a month after the last course of chemotherapy. 5 patients experienced a deterioration in Karnofsky score. The respiratory score improved in 12 patients (28.6%) and remained stable in 27 (64.3%). Only 3 patients noted a deterioration in their respiratory symptoms whilst on chemotherapy. There was no correlation between inital Karnofsky performance score, tumour histology type, and stage of disease extension (extensive vs. limited disease) and response. However, there was statistical correlation between partial responders and good respiratory score before treatment (χ^2 = analysis for trend $P = 0.0035$).

DISCUSSION

Combination chemotherapy, at best, causes only a modest improvement in survival for patients with advanced non-small cell lung cancer [1]. Survival at 2 years is less than 20% regardless of treatment [7, 8] despite response rates as high as 67% in some studies [9]. At least three studies have failed to show a significant difference in the survival of patients randomised between chemotherapy or no chemotherapy treatment arms [10–12]. Since currently available treatment does not significantly affect duration of life, palliation of symptoms and quality of life are other important factors that should be addressed.

Based on these considerations, the policy for this study was to treat only those patients who had symptomatic and progressive disease. The general condition of this group of patients was therefore inferior to most other reported series, with 30 of 42 patients (71.4%) having a Karnofsky performance score of 70% or less. The patients' general poor performance score (due to constitutional effects of their cancer, lethargy, anaemia, weight loss etc.) was a reason for not giving immediate thoracic radiotherapy. All of the patients were life-long cigarette smokers with various degrees of chronic obstructive airways disease and it was thought that palliative thoracic radiotherapy was unlikely to help their breathlessness. Half of the patients had extensive stage disease and 12 patients with moderate or severe breathlessness had unirradiated limited stage disease, some of these having pleural effusion or contralateral neck nodes. Nevertheless patients were considered for radiotherapy initially, during and at the end of chemotherapy. 7 patients received palliative thoracic radiotherapy after chemotherapy had been started. 70% of patients had moderate breathlessness attributable to their tumour (and chronic obstructive airways disease) as indicated by a respiratory score of 3 or more. In contrast, 60–80% of patients in recently reported studies using chemotherapy in this tumour have had a Karnofsky performance score of 80% or more [1, 6, 8, 9, 12]. Performance status has been shown to be one, if not the major, determinant of survival for advanced non-small cell lung cancer [13–15]. However, it was not possible in this study to find statistical correlation between Karnofsky performance score and rate of response. It is however important to note that in our study a good respiratory score predicted better treatment response.

Despite the fact that these patients had progressive disease before chemotherapy, the ifosfamide and mitomycin combination produced a stabilisation or an improvement in the performance status in 88% of patients. In addition, over 90% had stabilisation or an improvement in their respiratory score when measured before and 1 month after completion of chemotherapy. This was achieved with acceptable toxicity and with 27 of 42 patients (64.3%) completing all four courses of chemotherapy. The fractionation of the treatment over 5 days rather than the more conventional short-term administration may have contributed to this relatively low level of side-effects [8, 9, 13].

An objective response rate of 24% is lower than the majority of other studies using ifosfamide in combination with other agents [2]. However, the patients in the current study had a relatively poor performance status as a group, and all had progressive disease prior to entry. In relation to this, almost 60% of patients had stabilisation of disease in addition to the 23% of those who developed a partial response, confirming the activity of this combination in non-small cell lung cancer.

In conclusion, this combination of ifosfamide and mitomycin has activity in a selected group of poor prognosis patients with non-small cell lung cancer and is capable of alleviating breathlessness and improving performance status. Future studies using currently available cytotoxic agents should concentrate on determining methods to select patients likely to benefit from these agents, and should examine the effect of chemotherapy on patients' symptoms and quality of life rather than tumour response and survival alone.

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