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Ifosfamide, mitomycin and radiotherapy in non-small-cell lung cancer

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Summary. Ifosfamide and mitomycin C are two of the more active single agents in non-small-cell lung cancer (NSCLC). This study evaluates these drugs in combination followed by radiotherapy. A total of 33 ambulatory patients with inoperable NSCLC were treated with 5 g/m^2 ifosfamide as a 24-h infusion, with the concurrent administration of sodium 2-mercaptoethane sulphonate (mesna; 160% of the ifosfamide dose) and 6 mg/m^2 mitomycin C given as an i.v. bolus injection on the 2nd day. The median age of the patients was 61 years. In all, 20 patients had limited disease and 13, extensive disease. A total of 30 were assessable for response to chemotherapy, 8 of whom achieved a partial response (PR) and 5, a complete response (CR) (2 were verified bronchoscopically). The overall response rate was thus 43%. All but one response (a PR) were in patients with limited disease (LD). A total of 21 patients, including 13 responders, received thoracic irradiation (30 Gy in 8 fractions over 10 days) following chemotherapy. One PR was converted to a radiological CR. In all, 17 (55%) of the patients were alive at 1 year. All patients suffered chemotherapy-induced alopecia (WHO grade 3), but there were no treatment modifications due to myelosuppression, haemorrhagic cystitis or other toxicity. WHO grade 3 nausea and vomiting were seen in all patients. There was one treatment-related death. Combination therapy using ifosfamide and mitomycin C has useful activity in NSCLC.

Introduction

Chemotherapy has questionable value in non-small lung cancer NSCLC). Due to poor response rates, lack of survival benefit and the toxicity associated with the treatment, chemotherapy is mostly offered to patients in clinical trials to establish the usefulness of individual drugs or combinations. From the data that are emerging, ifosfamide clearly appears to be an active agent [2, 5, 10, 11], with a mean response rate from all published data of 26% [1]. Mitomycin C has shown single-agent response rates of 20% in previous studies [11, 12] and, in combination with vindesine in a recent study [8], has shown activity in over 50% of patients. The object of this study was to evaluate the role of these two active drugs in combination chemotherapy followed by thoracic irradiation.

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Patients and methods

Between October 1983 and June 1984, 33 patients with histologically confirmed, inoperable NSCLC were entered in the study. All patients were below the age of 70, with ambulatory performance status (WHO grade 0, 1 or 2). No patient had received previous chemotherapy or radiotherapy, and all had normal blood counts and renal function. Isotopic bone and liver scans were done as a part of the staging procedure.

All patients in the study had radiologically measurable intrathoracic disease. In all, 20 patients had stage III intrathoracic disease with no metastases, and 13 had extensive disease – 8 with contralateral or bilateral neck nodes and 5 with abnormal bone or liver scans. One patient in the limited disease (LD) group had had >10% weight loss in the preceding 6 months, and ten patients in the extensive disease group had had significant weight loss.

Chemotherapy consisted of 5 g/m^2 ifosfamide and 5 g/m^2 sodium 2-mercaptoethane sulphonate (mesna) given as a 24-h infusion in 3 l normal saline on day 1, preceded by 1 l normal saline infused in 2 h as prehydration. Mesna (1 g/m^2) was given at 28, 32 and 36 h (total mesna dose, 160% of the ifosfamide dose). On day 2 6 mg/m^2 mitomycin C was given as a bolus i.v. injection. Cycles were repeated every 3 weeks if the white blood cell count exceeded 3.5×10^9 cells/l and platelets exceeded 100×10^9/l.

Union International Contra le Cancrum (International Union Against Cancer; UICC) criteria were used to assess the intrathoracic disease response. All patients had clearly identifiable intrathoracic tumour volume without any major pulmonary atelectasis or pleural effusion. Patients who showed complete disappearance of radiological disease at the end of the chemotherapy were considered for repeat bronchoscopy.

Radiotherapy was given at the end of four courses (earlier in the case of patients with progressive disease). Patients were treated on a cobalt teletherapy unit and received 30 Gy mid-plane dose in 8 daily fractions over 10 days. Parallel opposed pairs were used, with a maximal mid-plane field size of 120 cm^2. In partial and complete responders an attempt was made to cover the previously observed primary disease.

Table 1. Patient characteristics ($n = 33$)

Age:	
Range	38–69 years
Median	61 years
Men: Women	31:2
Limited disease	20
Extensive disease	13
WHO performance status	
0 and 1	20
2	13
Histology	
Squamous	20
Adeno	7
Large cell anaplastic	5
Other	1

Table 2. Toxicity ($n = 33$)

	WHO grade				
	0	1	2	3	4
Alopecia (after 4 courses, $n = 22$)	0	0	0	22	0
Leucopenia (day 21 counts)	28	5	0	0	0
Thrombocytopenia (day 21 counts)	33	0	0	0	0
Anaemia (day 21 counts)	25	4	4	0	0
Nausea, vomiting	0	0	0	33	0
Haematuria	32	1	0	0	0
Raised serum creatinine	32	1	0	0	0

Results

The characteristics of the patients are given in Table 1. A total of 30 patients were assessable for response to chemotherapy. Two died due to autopsy-confirmed myocardial infarction after two courses, and there was one death due to septicaemia after two courses. Five CRs were verified in two patients by repeat bronchoscopy and biopsy. Eight patients achieved a radiological PR. The overall response rate was thus 43%. All but one response (a PR) were achieved LD patients. In all 13 responding patients, the radiological response was seen after two courses.

Of the 17 non-responders, 9 patients with static disease went on to receive four courses in view of symptomatic improvement, which varied from non-specific symptoms such as weight gain and feeling of well-being to reduction in troublesome chest symptoms such as cough and chest pain. Similar subjective improvement was seen in all responders. Chemotherapy was stopped after two courses in patients with progressive disease. A total of 21 patients, including the 13 responders, received thoracic irradiation. One PR was converted to a radiological CR.

The overall median survival (33 patients) was 347 days (Fig. 1); 17 patients were alive at 12 months and 2, at 24 months. The median duration of response from the start of treatment was 396 days. All but two relapses were intrathoracic. All patients suffered chemotherapy-induced alopecia (WHO grade 3), but there were no treatment modifications due to myelosuppression, haemorrhagic cystitis or other toxicity. WHO grade 3 nausea and vomiting were seen in all patients. One patient with extrathoracic disease and tumour progression after two courses died of leucopenia and septicaemia (Table 2).

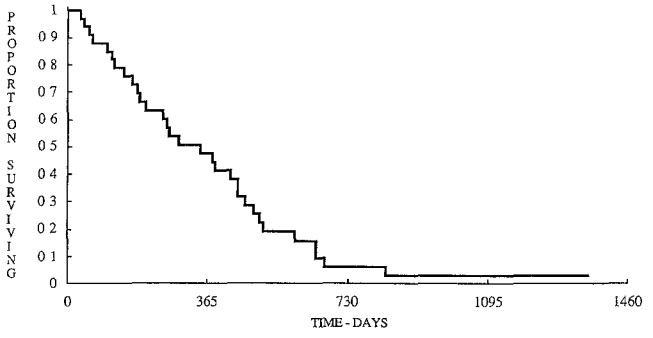

Fig. 1. Overall survival

Discussion

The anti-tumour effect of the combination of ifosfamide and mitomycin C was confirmed in this study, with 43% of 30 evaluable patients achieving objective response, which is similar to some of the best results achieved with other combinations in NSCLC [6]. Combinations including ifosfamide and mitomycin C, which are two of the most active agents, are increasingly being used in NSCLC, and major responses in over 30% of patients can be achieved without unacceptable toxicity [7]. Higher response rates might possibly be achieved by the introduction of other proven, active agents such as cisplatin [4] to combinations containing ifosfamide; such a study has recently been completed in our department [3]. With 11 of 13 responders in the present study developing primary intrathoracic relapse, the effect of a higher dose of radiation might also be worth studying. Both of these approaches will invariably increase the toxicity of treatment, and selection of patients who are likely to benefit would be of paramount importance.

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