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Short communication

Mitomycin, ifosfamide and cisplatin in non-small-cell lung cancer*

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Summary. Chemotherapy with mitomycin C, ifosfamide and cisplatin (MIC) is reported to produce responses of 56% and 69% in inoperable non-small-cell lung cancer (NSCLC) [1,2]. We evaluated the regimen in 45 similar patients who received up to six courses of 6 mg/m^2 mitomycin C, 3 g/m^2 ifosfamide, and 50 mg/m^2 cisplatin every 3 weeks. In all, 18 patients had limited disease (LD) and 27 had extensive disease (ED). A total of 18 patients responded (40%), 9/18 with LD and 9/27 with ED; there were 4 complete responders. The median duration of response was 25 weeks, and median survival was 32 weeks (range, 2–96 weeks). Toxicity was moderate. Nausea and vomiting were controlled with i.v. dexamethasone and high-dose metoclopramide. Other toxicities included myelosuppression and alopecia. This study confirms that MIC is one of the most active regimens for treatment of NSCLC, with acceptable toxicity.

Introduction

There is a great need for effective chemotherapeutic regimens for non-small-cell lung cancer (NSCLC). In large-scale studies in metastatic disease, most regimens produce responses in 22%–26% of patients [4]. A recent study by Cullen et al. [2] of MIC in 74 patients with inoperable NSCLC recorded an overall response rate of 56% [95% confidence interval (CI), 44%–68%] in 60 evaluable patients. The median duration of response was 8.8 months. A similar response rate (69%) was reported in 32 NSCLC patients treated with MIC [3]. These are among the best response rates thus far achieved in NSCLC. The present study reports further experience with MIC in patients with NSCLC.

Patients and methods

Ambulatory patients aged ≤70 years, with inoperable, histologically proven NSCLC that was clinically and/or radiologically evaluable, were eligible for this phase II study. The treatment schedule consisted of mitomycin C (6 mg/m^2, i.v. bolus), ifosfamide (3 g/m^2, i.v. infusion over 3 h) and cisplatin (50 mg/m^2, i.v. infusion over 1 h). Mesna (sodium 2-mercaptoethane sulfonate, 1 g/m^2) provided cover against urinary tract toxicity from the ifosfamide infusion, followed by 500 mg/m^2 mesna at 7 and 9 h after the ifosfamide. Chemotherapy was repeated every 3 weeks for a usual maximum of four courses unless there was evidence of disease progression, no response after two treatments, or unacceptable side effects. Four responding patients received up to six courses. Chemotherapy was delayed by 1 week if the white cell count (WCC) on the planned day of treatment was $<3.0\times10^9$/l or if the platelet count was $<100\times10^9$/l. doses of all drugs were reduced to 75% if subsequent delays occurred. Nausea and vomiting were controlled by i.v. lorazepam, dexamethasone and high-dose metoclopramide [2]. After each course, response was assessed clinically and radiographically using WHO criteria [5].

Results

Between January 1987 and June 1988, 45 patients entered the study; pre-treatment characteristics are shown in Table 1. The overall response rate to chemotherapy was 18/45 patients, i.e. 40% (CI, 25%–55%). In all, 4 patients achieved a complete response and 14, a partial response. In the patients with limited disease (LD), the response rate

Table 1. Patient characteristics

Total (*n*)		45
Male/female		34/11
Age range (median)		29–67 (61) years
WHO performance status:	0	12
	1	26
	2	7
Histological type:	Squamous carcinoma	23
	Adenocarcinoma	10
	Large-cell carcinoma	12
Limited/extensive disease		18/27
Previous treatment:	Surgery + radiotherapy	1
	Radiotherapy alone	3
	Chemotherapy + radiotherapy	2

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was 9/18 and in those with extensive disease (ED) it was 9/27. The response rates for the different cell types were: squamous carcinoma 11/23; adenocarcinoma 2/10; and large-cell carcinoma 5/12. Two of the six previously treated patients responded, both having received only prior radiotherapy. The median duration of response was 25 weeks (range, 12–96 weeks). The median survival for responders was 44 weeks (range, 23–96 weeks) and that for non-responders was 22 weeks (range, 2–78 weeks). Of 42 patients with full toxicity data available, 13 suffered WHO grade 3 nausea and vomiting and 1 suffered intractable vomiting (grade 4).

The WCC was $<3.0 \times 10^9$/l on seven occasions, leading to treatment delay. Nadir WCCs were $<3.0 \times 10^9$/l on 27 occasions (39%). Significant thrombocytopaenia (platelet count of $<100 \times 10^9$/l) occurred on six occasions during the nadir phase. One patient who received six courses of chemotherapy subsequently developed a microangiopathic haemolytic anaemia. One patient developed transient cystitis not associated with haematuria, and another patient developed mild haematuria after chemotherapy. There were no significant increases in serum creatinine. All patients who received two or more courses of chemotherapy developed grade 3 alopecia. A total of 21 patients subsequently received radiotherapy, including 13 who were treated in remission following MIC and 8 who did not respond to chemotherapy.

Discussion

Mitomycin C, ifosfamide and cisplatin are among the most active single agents in NSCLC [1]. Our response rate of 40% for MIC (95% CI, 25%–55%) was lower than those previously reported by Cullen et al. [2] (56%; 95% CI, 44%–68%) and Giron et al. [3] (68%; 95% CI, 59%–78%), but the confidence intervals overlap. In the present study, survival was 5.5 months longer for responders than for non-responders. This approximates to the response duration, which was 6.25 months.

This study confirms that MIC is an active regimen for treatment of NSCLC and that its toxicity is manageable. In the majority of cases each course was given during a single overnight admission. MIC is sufficiently active to be used in controlled trials compared with supportive care in patients with metastatic disease and in trials of adjuvent chemotherapy in patients with limited but inoperable disease who are being treated with radiotherapy.

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