ity. Although there was a decrease in response rate, the number of patients was too small and they were not randomly assigned to the two different doses, to allow any conclusion on the presence of a dose-response curve of teniposide in this combination in NSCLC.

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Phase II Study with Mitomycin, Ifosfamide and Carboplatin in Inoperable Non-small Cell Lung Cancer

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In a phase II study of non-small cell lung cancer a new chemotherapy combination of mitomycin 6 mg/m² intravenously on day 1, carboplatin 400 mg/m² intravenously on day 1 and ifosfamide with mesna 5 g/m² intravenously over 24 hours on day 1 was evaluated. A maximum of four chemotherapy cycles was given at intervals of 4 weeks to 34 patients with progressive, inoperable disease. 1 complete and 10 partial remissions were documented, the overall response rate being 32.4%. In a further 13 patients (38.2%) the previously progressing tumours remained stable for at least 6 weeks. The median time to progression for responding patients was 184 days. The median survival time for the whole group has not yet been reached at 293 days. A considerable but easily manageable myelosuppression was the principal toxicity despite a "no dose reduction" policy. Indeed, the dose intensity of the chemotherapy actually given was extremely close (97%) to that intended on protocol. In conclusion, the regimen is active in patients with advanced non-small cell lung cancer but requires regular haematological monitoring to prevent morbidity resulting from myelotoxicity.
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INTRODUCTION

CISPLATIN-BASED combination regimens have the highest and most reproducible response rates (30–35%) in the treatment of advanced non-small cell lung cancer (NSCLC) [1, 2]. The dosage of cisplatin is limited by nephrotoxicity, neurotoxicity and ototoxicity and lung cancer patients are often elderly and have other systemic medical problems. Carboplatin, a cisplatin analogue, lacks many of the toxicities of the parent compound and has activity in NSCLC [3].

Among the other more active drugs in the treatment of NSCLC are mitomycin and ifosfamide. Combinations of these two agents with cisplatin have produced response rates of 40% or greater [4–6]. The main toxicity of carboplatin is myelosuppression whereas this is generally mild for mitomycin and ifosfamide. We therefore combined these three agents in a phase II study for patients with inoperable NSCLC.

PATIENTS AND METHODS

Patients

Between May and November 1989, 34 patients (21 males, 13 females) with progressive, histologically proven non-small cell lung cancer were entered into the study. 27 patients had squamous cell carcinomas, 6 adenocarcinomas and 1 undifferentiated NSCLC. 5 patients had received previous radiotherapy. There were 12 stage IIIB and 22 stage IV patients. Distant metastatic sites included lung/pleura (12 patients), liver (5 patients), bone

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(4 patients) and other sites (5 patients). Elevated hepatic enzymes were present in 23 patients. The median age was 58 years (range 42–68). 8 patients had a Karnofsky score of 40–60, 13 a score of 70 and the other 13 a score of 80 or more. Routine investigations, staging, Karnofsky and respiratory scores were performed as previously described [7].

Treatment

Chemotherapy consisted of mitomycin 6 mg/m^2 intravenously on day 1, carboplatin 400 mg/m^2 intravenously on day 1, and ifosfamide with mesna 5 g/m^2 intravenously over the first 24 hours (mesna 2.5 g/m^2 was given orally for another 12 hours). This treatment, given on an inpatient basis (hospitalisation for 24 hours), was repeated every 4 weeks for a maximum of four cycles. If the white blood cell count was less than 3 × 10^9/l and/or the platelets less than 100 × 10^9/l, therapy was delayed by 1 week or until recovery to above these levels. No dosage reductions were made.

Standard UICC criteria [8] were used to evaluate response and toxicity after each cycle and monthly after the last cycle.

RESULTS

All 34 patients entered into the study were evaluable for response and toxicity. 21 patients were given the maximum number of four treatment courses, 3 additional patients received three courses, 5 additional patients receive two courses, and in 5 patients, treatment was discontinued after the first course because of progressive disease or death. A total of 108 treatment cycles has been administered.

Table 1. Karnofsky performance score and respiratory score: pretreatment data and changes during chemotherapy

	CR and PR (n = 11)	Stable disease (n = 13)	Progressive disease (n = 3)
Karnofsky score			
Pretreatment score			
Median	80	70	50
Range	70–100	40–90	50–60
Changes			
Improvement			
+10 points	5	1	0
+20 points	1	2	0
+30 points	0	1	0
No change	3	4	1
Deterioration			
−10 points	2	4	0
−20 points	0	1	0
−30 points	0	0	2
Respiratory score			
Pretreatment score			
Median	2	2	4
Range	1–5	1–5	3–5
Changes			
Improvement			
+1 point	3	0	0
+2 points	2	1	0
+3 points	1	0	0
No change	4	9	3
Deterioration			
−1 point	1	3	0

CR = complete remission, PR = partial remission.

Table 2. Haematological toxicity, blood transfusions, antibiotics and platelet transfusions

	Cycle			
	1	2	3	4
Haemoglobin nadir (g%)				
Median	10.9	9.0	7.9	7.5
Range	6.7–12.6	6.8–12.6	5.0–11.7	5.9–11.0
Blood transfusions				
None	30/34	20/29	12/24	4/21
1–3 units	2/34	6/29	5/24	10/21
≥ 4 units	1/34	2/29	6/24	7/21
WBC nadir (× 10^9/l)				
Median	1.7	1.0	1.1	0.6
Range	0.5–6.2	0.4–3.7	0.4–3.6	0.1–2.4
Antibiotics				
None	15/34	14/29	9/24	5/21
Oral	6/34	1/29	2/24	1/21
Intravenous	12/34	13/29	12/24	15/21
Platelet nadir (× 10^9/l)				
Median	42	31	19	13
Range	11–302	9–188	10–221	5–160
Platelet transfusions				
None	27/34	20/29	9/24	4/21
≥ 4 units	6/34	8/29	14/24	17/21

Response

Of the 34 patients entered into the study, 10 patients were documented as partial responders and 1 patient as a complete responder, the objective response rate being 32.4% (95% confidence limits: 17.4%–50.5%). In an additional 13 patients (38.2%, 95% confidence limits: 22.2%–56.4%), the previously progressive tumour remained stable for at least 6 weeks. Amongst the 11 responders, 8 had squamous cell carcinomas and 3 had adenocarcinomas. No responses were seen in previously irradiated patients, and 61.5% of all objective responses occurred in the first two treatment cycles. 8 responders had limited (stage IIIB) disease and 3 extensive (metastatic) disease.

The median time to progression was 184 days for responders (range 147–265 days) and 147 days for patients with stable disease (range 40–231 days).

Comparing the Karnofsky and respiratory scores before and after chemotherapy, we found a trend towards an improvement of both scores in patients with objective tumour response, whereas neither score showed gross change in patients with stable disease (see Table 1).

Survival

The median survival time for the whole group of 34 patients entered into the study, as well as for the responding patients, has not yet been reached at 293 days (> 9.8 months).

Toxicity

Bone marrow depression was the main toxicity, and a cumulative effect with increasing courses of chemotherapy was evident (see Table 2). Nadir counts taken at weekly intervals between chemotherapy courses were available after 104 out of 108 administered treatment cycles. Based on the worst nadir count, grade 3 leucopenia was seen after 31% of cycles and grade 4 after 45% of cycles. Grade 3 and 4 thrombocytopenia occurred

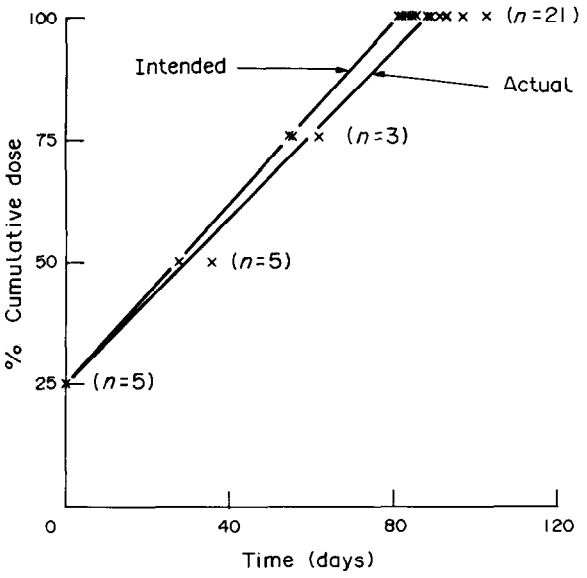

Fig. 1. Intended and actual dose intensity. The actual cumulative percentage dose given to each patient is plotted vs. the time since start of treatment.

on 20% and 50% of cycles and anaemia on 27% and 5% of cycles, respectively. Despite severe leucopenia and a policy of "no dose reduction", the frequency of serious infections was low. Treatment delay was infrequent, and all delays but two (9 days and 14 days) amounted to less than 1 week. The administered dose intensity was 97% of the intended protocol dose intensity (see Fig. 1). Antibiotics were given liberally and often prophylactically. There was 1 infection death, probably related to chemotherapy, although the nadir white blood cell count was only 2×10^9 cells/l. Patients received prophylactic platelet transfusions if the count was 20×10^9/l or less.

Vomiting was moderate or severe (grade 3 or 4) on 23.1% of all courses. Stomatitis and diarrhoea were very rare, and there was no case of cystitis. Transient lethargy occurred after 12.9% of all courses lasting usually less than 1–2 days. After 3 cycles (2.8%), a mild and reversible rise in serum creatinine was observed; 1 patient did develop acute anuric renal failure after the fourth chemotherapy cycle and died 14 days later.

DISCUSSION

The results of the current study demonstrate that the mitomycin/ifosfamide/carboplatin regimen is active in advanced NSCLC. The efficacy is comparable to other regimens including "standard" cisplatin-based combination chemotherapies, but the current results are arguably better when the relatively poor prognostic factors of our patient population (low performance status, extrathoracic metastases, previous radiotherapy) are taken into account.

In three other studies with cisplatin, mitomycin and ifosfamide [4–6] the remission rates were 69%, 56% and 40%, respectively, i.e. somewhat higher than in the current study, but the median survival times were shorter (9.5, 9.2 and 5.5 months, respectively). Furthermore, our patients were all known to have progressing tumours prior to the start of the treatment.

As was to be expected, the dose-limiting toxicity of the regimen was myelosuppression. This toxicity, recorded from the worst of the nadir counts, was well manageable. The incidence of significant infections was low, and the dose intensity actually delivered was very close to that intended (97%). Although nausea and vomiting occurred in about one quarter of all patients, the study was not conducted with the use of the newer 5-HT antagonist antiemetics, but with metoclopramide and prochlorperazine.

In agreement with Cullen *et al.* [5] we found a clinical improvement in about half the responding patients, the Karnofsky and respiratory scores being better at the end of the treatment as compared to the assessment before chemotherapy. Patients whose tumours were only stabilised by the chemotherapy, however, experienced no significant changes in these parameters. We conclude that a reduction of the tumour burden is needed to result in an improvement of clinical symptoms and performance status.

The tolerance of the mitomycin/ifosfamide/carboplatin regimen might be improved further with haematological growth factor support and allow further increase in dose intensity.

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