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Short Communication

Bolus Versus 5-Day Continuous Infusion of Cisplatin with Mitomycin and Vindesine in the Treatment of Advanced Non-Small Cell Lung Cancer (NSCLC): a Phase III Prospective Randomised Trial of the Italian Oncology Group for Clinical Research (GOIRC)

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The aim of this randomised trial was to compare the efficacy of bolus versus continuous infusion cisplatin combined with mitomycin C and vindesine (MVP) for chemotherapy-naive patients with stage IIIB–IV non-small cell lung cancer (NSCLC). 97 patients (49 given bolus cisplatin—arm A and 48 given continuous infusion cisplatin—arm B) were evaluable for response. In arm A, 2 patients achieved a complete response (CR), 21 achieved a partial response (PR), whilst in arm B, 14 patients achieved a PR (29%) ($P = 0.07$). Median survival was 8 months in both arms. Myelosuppression was the most frequent and severe toxicity, with a higher incidence of grade 3–4 leucopenia in arm A when compared with arm B (44% versus 25%). In conclusion, there is no advantage for a cisplatin 5 day infusion in the MVP regimen. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: cisplatin, continuous infusion, MVP, non-small cell lung cancer, randomised phase III study
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INTRODUCTION

THE COMBINATION of mitomycin C, vindesine and cisplatin (MVP) is considered to be one of the most active regimens in non-small cell lung cancer (NSCLC), with objective response rates ranging from 30 to 60% in advanced disease [1, 2].

Since the 1970s, one of the attempts to reduce the toxic effects of cisplatin has been based on administering it as a prolonged continuous infusion, for 4–5 days. Using this schedule in the treatment of different kinds of tumours, a significant decrease in renal and neurological toxicity has been reported, together with a maintained efficacy [3–7]. Moreover, some *in vitro* studies have suggested that prolonged exposure to cisplatin might increase its cytotoxic effects, in comparison with short exposure [8, 9].

On the basis of this rationale, we designed a prospective randomised trial comparing the standard cisplatin intravenous (i.v.) infusion with a 5 day continuous infusion schedule in patients with advanced NSCLC treated with an MVP regimen. The objectives were to compare response rate, time to progression, survival and to evaluate the toxicity of the two treatment modalities.

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PATIENTS AND METHODS

From June 1992 to January 1996, 100 consecutive chemotherapy-naive patients with histologically proven NSCLC, stage IIIB–IV and measurable disease, entered the study (Figure 1). Their characteristics are reported in Table 1. Patients with symptomatic brain metastases were excluded. All eligible patients were stratified by stage (IIIB versus IV), performance status (0–1 versus 2–3) and weight loss in the last 6 months (< 10% versus ≥ 10%). The chemotherapy regimens were as follows: arm A, mitomycin 8 mg/m^2, i.v. bolus, day 1 on courses 1, 2, 4 and 6, vindesine 3 mg/m^2, i.v. bolus, weekly for 4 weeks for cycle 1, then days 1 and 15 on cycles 2–6, and cisplatin 125 mg/m^2 i.v. day 1, with concomitant hydration

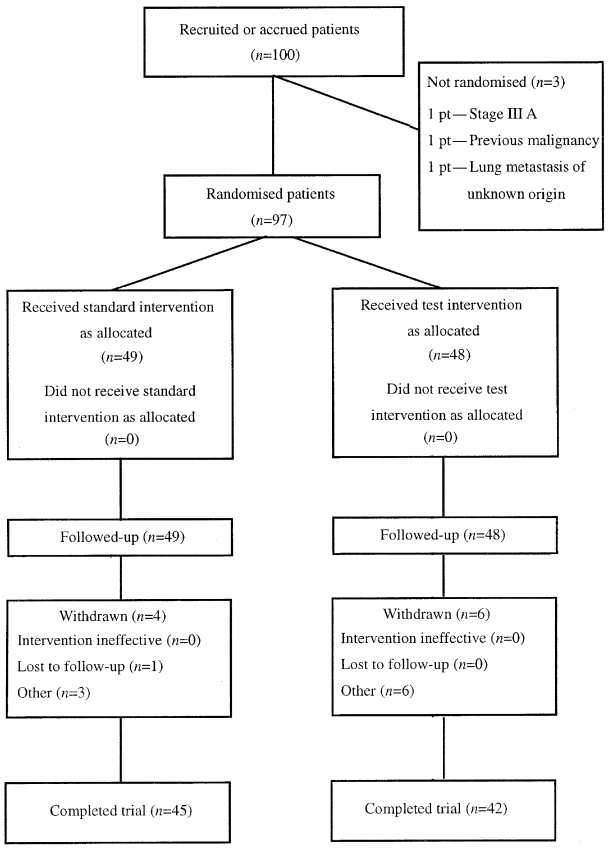

Figure 1. Flow chart of the progress of patients through the trial. (Adapted from Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996, 276, 637–639).

and mannitol. Arm B, the same as for arm A, with cisplatin administered in a continuous i.v. infusion over 120 h at the dose of 125 mg/m^2, starting on day 1, diluted daily in 3000 ml of normal saline with KCl 40 mEq and $MgSO_4$ 2 g. Courses were repeated every 28 days and continued until progression or up to a maximum of six cycles. Chemotherapy was stopped if at least an objective improvement was not achieved after three cycles.

A local regional treatment, mostly radiation therapy, was allowed for responding patients in stage IIIB, after the third cycle, at the discretion of the investigator.

Response to treatment was evaluated after three and six cycles of chemotherapy; patients whose disease progressed after completion of the treatment were treated subsequently at the discretion of the investigator and monitored for survival.

A study sample size of 240 patients was calculated in order to detect a 20% difference in objective response (from 40 to 60%). A planned interim analysis was performed after the first 100 patients to evaluate the toxicity and the compliance to the treatment; due to the low compliance, an evaluation of activity was also performed.

An absence of any advantage and even a negative trend was observed for the experimental arm, and for this reason the study was closed.

RESULTS

All eligible patients were evaluable for response, on an intention to treat analysis. In both arms, the best response,

Table 1. *Patient characteristics*

	Arm A no.	Arm B no.
Entered	50	50
Not eligible	1	2
Sex		
Male	44	39
Female	5	9
Age (years)		
Median	63	61
Range	39–75	44–74
Performance status		
0–1	44	44
2–3	5	4
Stage		
IIIB	18	20
IV	31	28
Disease sites in stage IV		
Lung	27	27
Nodes	17	17
Bone	14	13
Liver	4	6
Pleura	4	2
Other	12	12

complete (CR) or partial (PR), was achieved after three cycles of chemotherapy and no improvement in the percentage and in the quality of the response was observed increasing the number of the cycles beyond the third. A maximum of six cycles was allowed.

Overall, 309 cycles (177 in arm A and 132 in arm B) were given to 97 patients, with a mean number of cycles of 3.2, with 73% of patients receiving at least three cycles. In arm A, 2 patients achieved a CR (4%) and 21 achieved a PR (43%), whilst in arm B, 14 patients achieved a PR (29%), with an overall response of 47% (95% confidence interval (CI) 34–60%) and 29% (95% CI 16–41%), respectively ($P = 0.07$). No significant difference in objective response rates (44% and 40%) was noted for stage IIIB. In stage IV patients, a significantly higher response rate of 48% was observed in arm A (95% CI 32–63%) versus 21% in arm B (95% CI 6–35%) ($P = 0.03$). 10 patients were considered non-responders and were withdrawn from the study for the following reasons: in arm A, 1 patient was withdrawn for peritonism after one cycle, 1 for early death due to intestinal infarction after one cycle, 1 for early death due to unknown reasons 20 days after the beginning of the first cycle (probable toxic death), and 1 because lost to follow-up after the first cycle; in arm B, 1 patient discontinued the treatment after the third cycle for paroxysmal supraventricular tachycardias, 2 patients were withdrawn for refusal after the first and the third cycle, 1 died from pulmonary embolism after the first cycle, 1 patient interrupted the treatment because of a stroke after the first cycle and 1 for toxic death due to febrile neutropenia after the first cycle. In both arms, 8 patients were considered to have stable disease (16% and 17%, respectively).

In arms A and B the responses by histological subtype were, respectively, 59% and 35% in squamous cell carcinoma, and 35% and 36% in adenocarcinoma. All randomised patients were included in the evaluation of time to progression and of survival, according to an intention to treat analysis. The minimum follow-up for the trial was 30

Table 2. WHO toxicity (%)

	Arm A				Arm B			
	1	2	3	4	1	2	3	4
Leucopenia	18	22	32	12	28	21	17	8
Thrombocytopenia	22	12	6	6	13	4	13	2
Anaemia	16	54	18	0	36	43	8	2
Mucositis	8	2	8	0	2	0	0	0
Renal	36	2	6	2	25	0	0	0
Neurological	18	22	12	0	25	7	8	0

months, with a maximum of 73 months. In July 1998, 7 patients were still alive, 2 in arm A and 5 in arm B.

The median time to progression and the median survival were, respectively, 5 and 8 months in arm A and 4 and 8 months in arm B, with no significant difference ($P = 0.96$). In arms A and B, the 1 and 2 year survival rates were 27% and 30%, and 8% and 10%, respectively.

Toxicity is reported in Table 2, according to WHO criteria, as the worse grade experienced for number of patients. Myelosuppression was the most frequent and severe toxicity in both arms, with no statistically significant difference.

2 patients died during the first cycle, 1 in arm A for unknown reasons with grade 2 leucopenia, and 1 in arm B, a toxic death due to febrile neutropenia, as mentioned above.

DISCUSSION

The main objective of this study was to compare two regimens with the same drugs and the same dose intensity, with the schedule of cisplatin (continuous infusion versus bolus) being the only difference.

We observed, in the continuous infusion arm, a trend in the reduction of grade 3–4 toxic effects, with a lower incidence of leucopenia, anaemia and neurotoxicity, and an absence of mucositis and renal toxicity. However, in terms of activity, the results were disappointing, with a negative trend in objective responses (46% in arm A and 29% in arm B) the difference significantly detrimental in stage IV patients, 48% versus 21% ($P = 0.03$). Time to progression and survival were comparable in the two arms. These results led to the early closure of this study after the planned interim analysis. In fact, the experimental infusion arm, although possibly less toxic, had other problems, including major complications, the hospitalisation costs incurred and lower compliance.

These data suggest that the modification of the pharmacokinetics of cisplatin, with a lower plasma peak concentration, consequent to a continuous infusion schedule, can correlate to a reduction in toxicity, but also to lower activity in NSCLC. Considering another recent negative report in patients with head and neck cancer [10], there are, in our opinion, no favourable elements for recommending further studies with cisplatin in continuous infusion, at least with this schedule.

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