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IS THE MVP REGIMEN LESS ACTIVE THAN PREVIOUSLY DESCRIBED?

Results of a phase II study in advanced non-small cell lung cancer

DOMENICO FERRIGNO and GIANFRANCO BUCCHERI

Combination chemotherapy with anti-proliferative agents is often used in patients with advanced non-small cell lung cancer (NSCLC) in good performance status. The mitomycin C, vinblastine and cisplatin (MVP) regimen has been the Eastern Cooperative Oncology Group (ECOG) standard for several years because of high response rates in spite of significant toxicity. In a phase II study, we observed 55 consecutive patients treated with MVP chemotherapy using the same dosage, schedule, and precautions as used by the ECOG group. The dose intensity reached for each drug was 85% of the projected dose. Fifty-one patients were assessable for response and toxicity, while all subjects were evaluable for survival. There was no complete remissions, 8 partial (15%), 34 stable (66%) and 9 progressive (17%) in patients. The median survival rate was 34 weeks (95% confidence interval 28–37 weeks). There were no treatment-related deaths and no grade 4 toxicity. Alopecia and emesis were the most significant adverse effects. Haematological toxicity was minimal. Other side-effects, such as neuropathy and nephrotoxicity, were also rare. Hence, response rates and toxic complications were lower than previously reported. We conclude that the MVP regimen has to be re-evaluated.

Lung cancer is the leading cause of cancer deaths among men and women in the United States. In 1994 it was estimated that 172 000 new cases would be identified and 80% (138 000) of these individuals would have non-small cell lung carcinomas (NSCLC) (1). Only 30% of lung cancer patients have localized disease, amenable for resection with curative intent (2). The 5-year survival rate of the patients with regional or distant spread is poor (2). For these patients, the role of chemotherapy remains controversial, and constitutes an inexhaustible source of debate among lung cancer specialists (3–5). Since 1988, 9 clinical trials have been conducted to compare combination chemotherapy with the best supportive care: all showed a trend towards a prolonged survival in patients receiving chemotherapy, with a statistically significant difference in 4 studies (6). Two recent meta-analyses (7, 8), confirmed statistically the reduction in mortality rate after chemotherapy and this suggests that combination chemotherapy does have a role in patients with non-resectable NSCLC. A variety of combination chemotherapy regimens have shown activity in advance NSCLC patients (9). The ECOG conducted 3 sequential phase III trials evaluating multiple drug regimens that had produced >30% response rates in earlier phase II studies (10–12). The combination of mitomycin, vinblastine, and cisplatin (MVP) produced the highest response rate in 2 consecutive trials, despite a significant toxicity (11, 12). We started the present investigation with the idea of confirming the activity and toxicity of the MVP regimen in a phase II study, before comparing this regimen with a non-platinum combination, the MACC regimen (13), in a subsequent ran-

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From the Department of Respiratory Medicine, A. Carle Hospital, Cuneo, Italy.
Correspondence to: Dr. Domenico Ferrigno, Dept. of Respiratory Medicine, A. Carle Hospital, I-12100 Cuneo, Italy. Tel.: +39.171.441.777/733; fax: +39.171.611.597.
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domized phase III trial. This part of the study is currently open to accrual. Herein, we report the results of the phase II study.

Material and Methods

Eligibility

Patients were eligible if they had cytologic or histologic proof of NSCLC (mixed histology with small cell features was not acceptable) (14). None of the patients had received prior chemotherapy. Other eligibility criteria were: locally advanced, metastatic (stage IIIa-b/IV) (15), or recurrent disease; Karnofsky performance status (16) $\geqslant 50$, normal blood cell count; normal hepatic and renal function (bilirubin <2 mg/dl and creatinine <1.5 mg/dl). All patients had measurable or assessable sites of disease. Neither prior surgery nor radiation therapy was considered as an exclusion criterion, provided the recurrence had been documented pathologically and at least 4 weeks had elapsed after an exploratory intervention. Patients with active cardiac diseases or serious intercurrent medical illnesses were ineligible. Patients with a single small inoperable lesion (maximum diameter <4 cm) were also ineligible if they were suitable for small-field radical radiation therapy. Patients were assessed with clinical history and physical examination, complete blood cell count, serum chemistry, bronchoscopic examination, chest x-rays and tomograms, computed tomography of the thorax, brain and upper abdomen. In the absence of other inoperability criteria, any radiological finding equivocal for nodal mediastinal involvement was considered an indication to mediastinoscopy. Informed verbal consent was obtained from all patients, and the protocol was approved by the ethical committee of our institution.

Study design

Treatment began within one day of registration. As originally described (17), the MVP regimen consisted of mitomycin C (10 mg/m^2 intravenously (i.v.)), vinblastine (6 mg/m^2 i.v.) and cisplatin (40 mg/m^2 i.v.) administered together on day 1 and repeated every 21 days. Standard intravenous pre- and posttreatment hydration was given with cisplatin. Patients received prophylactic antiemetic therapy with a 5-HT3 antagonist (granisetron, SmithKline Beecham). Doses were adjusted based on the day-of-treatment count, according to predefined haematological criteria. If leukocytes and/or thrombocytes fell below 4 000/mm^3 and 100 000/mm^3 respectively, 50% of the projected dose of each drug was given. If leukocytes were less than 2 000 and/or platelets less than 50 000/mm^3, treatment was delayed until the blood cell count became normal again. Doses of single cytotoxic agents were reduced by 50% or withheld if cardiac, hepatic, renal, gastrointestinal, and oral toxic effects occurred. Patients were maintained on chemotherapy until disease progression, unacceptable toxicity, no compliance with the protocol requirements or treatment refusal. After cessation of the MVP regimen, no second-line chemotherapy was given.

Table 1

Patients' characteristics (n = 55 patients)

Male/female	53/2
Median age, years (range)	65 (38–73)
Median Karnofsky performance status (range)	80 (50–100)
ECOG performance status	
0	2
1	22
2	28
3	3
Median percent weight loss in 6 months (range)	4% (0–20%)
Histology	
Squamous cell types	28
Adenocarcinomas	15
Large cell anaplastic carcinomas	3
Mixed or unclassified carcinomas	9
Stage of disease	
IIIa	10
IIIb	23
IV	20
Recurrent disease	2
Sites of metastases	
Lung	6
Adrenal glands	3
Bones	3
Brain	1
Liver	1
Skin	1
Multiple sites	5
Prior treatment	
None	53
Surgery	2

ECOG: Eastern Cooperative Oncology Group

End point of study

The evaluation of tumour response required at least a complete physical examination including blood chemistry and chest x-rays. This was done after a minimum of two courses of chemotherapy, and then at 3-week intervals, just before the next cycle of MVP. CT scans and other diagnostic tests, which were initially abnormal, were repeated every 2 months or more frequently, if clinically indicated. Rebronchoscopy was not a requirement for the assessment of response. Irradiated sites were not considered in the evaluation of tumour response. Standard definitions of complete response (CR), partial response (PR), no change (NC) and progressive disease (PD) were used (18). A tumour volume reduction, which did not fulfil the criteria of at least PR, was declared a minor regression (MR), and defined as between a 50%–25% reduction in the product (sum of the products) of the longest perpendicular diame-

Table 2

Delivery of chemotherapy

Total no. of courses given	144
Median no. of courses for patient (range)	4 (1–9)
Total no. of courses given with reduced doses	27
Total no. of courses delayed	16
Weeks of delay/total weeks of treatment	55/436
Median DI% of three drugs*	
Mitomycin C	86
Vinblastine	85
Cisplatin	86

* Average for the whole group of patients; DI% = Percentage of the projected dose intensity

ters of the indicator lesion (lesions). CR, PR and MR had to be proved on at least two consecutive evaluations, 3 weeks apart.

Drug toxicity was graded (18) before each chemotherapy cycle. The dose intensity (DI) is defined as the total amount of the drug given, divided by body surface and the time taken to administer it. This definition implies that both dose reductions and treatment delays affect the calculated DI. Actual and projected DIs for each drug in the MVP regimen were calculated following the examples given by Longo et al. (19). In this study, DIs were referred to the entire duration of treatment and reported as mean percentages of the intended DI (DI%) for the whole population.

Statistical analysis

The BMDP package (Statistical Software, Los Angeles, California, USA) was used for data processing (20). Survival time was measured from the beginning of therapy until death or to the last follow-up visit, and progression-free survival from the beginning of therapy to the date of disease progression. Time to progression and survival analyses were based on the Kaplan-Meier product-limit estimates (21).

Results

Between October 1992 and October 1994, 55 consecutive NSCLC patients were enrolled in the trail. The clinical characteristics of the patients are summarized in Table 1. Two of the 55 patients who were assigned to the chemotherapy died within 7 weeks after initiation of chemotherapy (massive haemoptysis in one case and unexplained sudden death in the other). In both cases no postmortem examination was performed. Before receiving the second course of MVP, another 2 patients refused the allocated therapy, or were no longer compliant with protocol requirements. Thus, 51 patients were assessable for reponse and toxicity, while all 55 were evaluated for survival.

The median number of cycles of chemotherapy received by our patients was 4 (range 1–9). Forty-one patients had at least 2 cycles and 14 completed a minimum of 6 courses. Details of the treatment are presented in Table 2. The toxic effects are summarized in Table 3. There were no treatment-related deaths and no grade 4 toxicity. Haematological toxicity was minimal; only 8 (16%) patients developed grade 2 anaemia, and only 2 (4%) patients developed grade 2/3 neutropenia with 3 episodes of bacterial infections. The most significant adverse effect was alopecia, and emesis. Other side-effects were rare. There were no complete responses and 8 partial responses, giving an overall response rate on 'intent to treat basis' of 16%. Seventeen patients (33%) achieved a tumour volume reduction that did not fulfil the partial response criteria. Another 17 (33%) subjects had stable disease, while 9 (18%) progressed at their first evaluation. Median survival for the whole group was 34 weeks (95% confidence interval 28–37 weeks) (Fig. 1). Median time to progression was 14 weeks (95% confidence interval 12–15 weeks).

Discussion

Locally advanced and metastatic NSCLC constitutes a therapeutic dilemma. A large number of studies have been

Table 3

Worst toxicity experienced (toxicity grades according to Miller and colleagues, (18))

No. of patients with toxicity	0	1	2	3	4	Total %
Haematological						
Haemoglobin	27	16	8	0	0	47
Leukocytes	42	7	1	1	0	18
Platelets	45	5	1	0	0	12
Gastrointestinal						
Oral	40	8	3	0	0	21
Nausea/Vomiting	22	13	14	2	0	57
Renal						
Creatinine	41	8	2	0	0	20
Hair	23	7	19	2	0	55
Neurologic	42	6	3	0	0	18

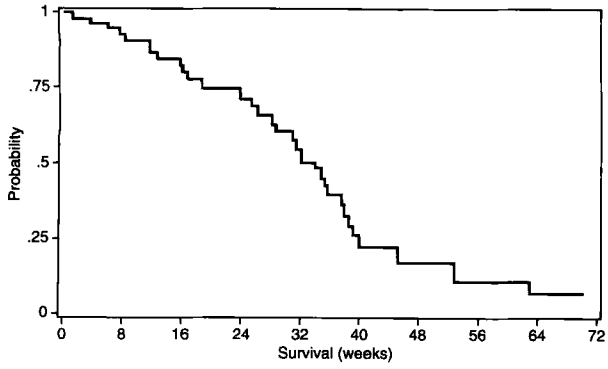

Figure. Survival probability for all 55 patients. Median survival 34 weeks (95% C.I. 28–37); dead, n = 34; censored, n = 21.

conducted to evaluate the impact of chemotherapy in this group of patients. The most active single agents, with cumulative response rates exceeding 15%, are vinblastine, vindesine, ifosfamide, mitomycin C, and cisplatin (22). The majority of responses are partial, while complete remissions are rare, occurring in less than 5% of the patients treated. It is generally accepted that combination therapy is more active than single agent treatment in NSCLC. Although recent studies (7, 8, 23–25) have supported the opinion that chemotherapy offers a modest but real survival advantage to patients with unresectable NSCLC, the question remains as to whether chemotherapy is really worthwhile for such patients (3–5). Although regimens containing cisplatin probably have the highest response rates (26, 27), several studies suggest a lack of correlation between response and survival (28). We have previously speculated that platinum-based regimens might be unable to increase the survival duration, because of their toxicity, and that regimens with modest anti-tumour activity and mild to moderate toxicity are not necessarily inferior to more active and toxic regimens (29). In our experience, the MACC regimen was able to ensure a significant life prolongation (30), despite a disappointing response rate of 8% (31). Very few clinical trials, directly comparing platinum and non-platinum based regimens, are available.

The MVP regimen was originally reported to give a 53% response rate by Mason & Catalano (17). The ECOG selected this regimen as the reference one in their randomized trials. Ruckdeschel et al. (11, 12) confirmed the high response rate to MVP in 2 consecutive studies. In the first study of 104 advanced NSCLC patients, this regimen produced a response rate of 26% with a 5% CR rate, and a median survival of 23.7 weeks, the the expense of 1 respiratory death (11). The second randomized trial was designed to compare the 4 most active regimens of metastatic NSCLC patients (12). It was reported that MVP had the highest overall response rate (31%) with a median survival of 22 weeks. These results, however, were weighed down by a significant toxicity with 7 (6%) treatment-related deaths (12). A subsequent trial conducted by Bonomi et al. (32) again showed the highest response rate (CR 1 + PR 35, 20%) for the MVP regimen. Survival analysis, paradoxically, showed that MVP-treated patients had a trend toward a reduced rate of survival. Seven (4%) treatment-related deaths occurred. In our experience, the MVP regimen was neither as active nor as toxic as previously described. Median survival (34 weeks) was within the expected range for this patient sample. Another recent study seems to confirm our results. Ellis et al. (33) used a partially modified MVP schedule, emphasizing the symptom relief and the toxicity. They achieved a 32% objective response rate, with one CR and 37 PR, and a median survival of 5 months. The schedule was well tolerated. Only 19% of patients developed grade 3/4 nausea/vomiting, 3% showed significant alopecia, and other toxicities were minimal. Moreover, in 69% of the symptomatic patients there was a complete disappearance or improvement in at least one tumour-related symptom.

We conclude that the MVP should be tested in a comparative setting and such a randomized phase III study has been initiated.

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