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Short communication

Phase II study of Mitomycin C, etoposide and vindesine in metastatic stage IV non-small-cell lung cancer

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Summary. A total of 72 patients with metastatic stage IV non-small-cell lung cancer (NSCLC) were treated with combination chemotherapy comprising the MEV regimen (mitomycin C, 8 mg/m^2 given i.v. on day 1; etoposide, 100 mg/m^2 given i.v. on days 1–3; and vindesine, 3 mg/m^2 given i.v. on day 1; treatment repeated every 3 weeks). In 65 evaluable patients, the objective response rate was 37% (complete responses, 4.7%; partial responses, 32.3%). The median survival was 7.6 months for all patients. The treatment was very well tolerated. MEV proved to be an active and non-toxic regimen for the treatment of metastatic NSCLC.

Introduction

Non-small-cell lung cancer (NSCLC) includes a group of poorly drug-responsive tumors. The most active regimens for its treatment include cisplatin combined with etoposide (VP-16) or vinca alkaloids, which produce response rates ranging from 30% to 33% [3, 9, 11]. The best results seem to be achieved by the addition of mitomycin C (MMC) to cisplatin (CDDP) and vindesine (VDS) or vinblastine (VLB), but at the cost of a considerable increase in toxicity [7, 12]. MMC plus VDS is one of the most active non-cisplatin-based regimens; it results in objective response (OR) rates of 29%–34%.

The aim of the present study was to evaluate a new regimen in which VP-16 was added to MMC and VDS in an attempt to improve the antitumor activity without producing a significant increase in toxicity. The goal was to develop an effective regimen for the treatment of advanced NSCLC that would exhibit antitumor activity similar to that of CDDP-based combinations but would result in significantly less toxicity.

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Patients and methods

The study was open to patients aged <70 years who exhibited histologically or cytologically confirmed NSCLC, stage IV disease and an Eastern Cooperative Oncology Group (ECOG) performance status of <3. No prior exposure to chemotherapy was permitted; previous radiotherapy was not considered to be an exclusion criterion. Normal renal, hepatic and bone marrow function was required.

From March 1988 to March 1990, 72 patients entered the trial; of these, 65 were evaluable for response and toxicity. Table 1 summarizes the characteristics of our patients. All subjects received combination chemotherapy consisting of 8 mg/m^2 MMC given i.v. on day 1, 100 mg/m^2 VP-16 given i.v. on days 1–3 and 3 mg/m^2 VDS given i.v. on day 1; treatment was repeated every 3 weeks (MEV regimen). Therapy was continued for a maximum of six cycles in patients who achieved an OR and in those who exhibited stable disease (SD) in the absence of severe toxicity. No dose reduction was planned, but cycles were delayed until recovery in cases of toxicity. Reevaluation was done after three cycles of chemotherapy for assessment of response. Response and toxicity were graded according to WHO criteria [16]. Survival was estimated by the Kaplan and Meier method [8].

Results

The response rate in the 65 evaluable patients was as follows: 24 (37%) ORs (95% confidence limits, 25%–49%) consisting of 3 (4.7%) complete responses (CRs) and 21 (32.3%) partial responses (PRs). In all, 22 (33.8%) subjects exhibited SD and 19 (29.2%) developed progressive disease. The CRs lasted 2, 17+ and 19+ months, respectively. The median duration of response for PRs was 4 months (range, 1–12+ months) and that for SD was 4.5 months (range, 3–13 months). A statistically significant correlation was observed between ORs and female gender ($P = 0.02$). A higher OR rate was observed in patients who had not previously undergone radiotherapy and in subjects in whom lymph nodes were the only metastatic site; however, both of these correlations did not reached statistical significance. The possible relationship between the female gender and the OR rate is difficult to explain; some differences between men and women were noted in the patient population: the histological diagnosis

Table 1. Characteristics of patients

Number of patients	65
Sex:	
M	52
F	13
Age:	
Median	60.5 years
Range	33–70 years
ECOG performance status:	
1	37
2	28
Histotype	
Epidermoid	39
Adenocarcinoma	25
Large-cell	1
Pretreatment:	
Chemotherapy	0
Radiotherapy	16
Sites of Metastases:	
Lymph nodes	13
Contralateral lung	16
Bone	16
Adrenal gland	4
Liver	9
Multiple	7

Table 2. Toxicity of the present regimen

Toxicity	WHO grade	Patients (*n*)
Leucopenia	1	25 (38.4%)
	2	6 (9.2%)
	3	4 (6.1%)
	4	0 (0)
Thrombocytopenia	1	2 (3%)
	2	1 (1.5%)
	3	9 (0)
	4	0 (0)
Anemia	1	3 (4.6%)
	2	4 (6.1%)
	3	0 (0)
	4	0 (0)
Nausea/vomiting	1	31 (47.6%)
	2	12 (18.4%)
	3	0 (0)
	4	0 (0)
Neurological	1	3 (4.6%)
	2	1 (1.5%)
	3	0 (0)
	4	0 (0)
Alopecia	1	4 (4.6%)
	2	31 (47.6%)
	3	18 (27.6%)
	4	0 (0)

in women more frequently involved adenocarcinoma ($P = 0.002$), and the women were younger than the men ($P = 0.03$). A chance effect of sub-group analysis cannot be excluded.

The median survival was 7.6 months for all patients. The survival curve is shown in Fig. 1. The treatment was well tolerated. Only 4 (6.1%) subjects developed grade 3 leucopenia that did not require a delay of chemotherapy. None of the patients exhibited thrombocytopenia or nausea and vomiting that was more severe than grade 2. Table 2 summarizes the toxicity data.

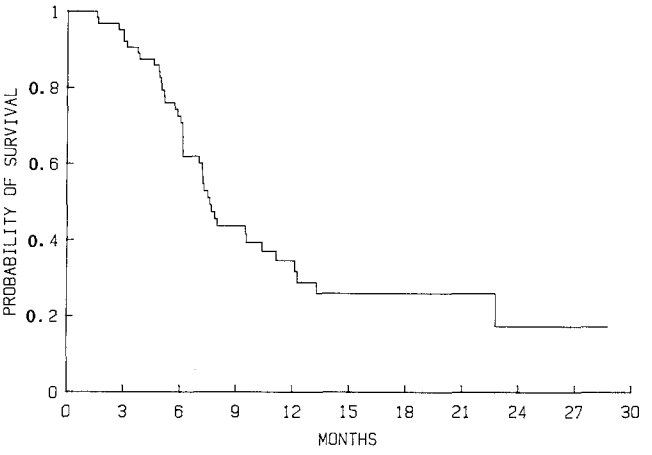

Fig. 1. Survival curve for all evaluable patients

Discussion

CDDP-based chemotherapy regimens are widely used in advanced NSCLC. Combinations containing CDDP, MMC and VDS or VLB are reported to yield the highest response rates. Kris et al. [12] used CDDP, MMC and VDS in stage III–IV NSCLC and reported a 60% OR rate (CRs, 7%). Gralla et al. [7] treated 100 patients, 50% of whom exhibited stage IIIA–IIIB disease, and obtained a 67% OR rate. A few randomized trials have failed to confirm these data, reporting lower response rates [6, 13, 21]; in all of these studies, CDDP was given at a dose of 80–120 mg/m^2 and produced marked toxicity. Some investigators have used CDDP at a dose of 40 mg/m^2 in an attempt to reduce toxicity, but these authors also reported lower response rates of 31% and 20% [2, 19].

MMC plus VDS is one of the most active regimens that do not include cisplatin. Kris et al. [10] have reported a 29% OR rate, and Luedke et al. [14] have obtained a 34% OR rate (CRs 4.4%); both of these studies involved patients exhibiting stage III–IV disease. In some large, randomized trials, the activity of the MMC and VDS combination was no lower than that observed for CDDP-based regimens [5, 15]. Some authors have added hexamethylmelamine [1] or 5-fluorouracil [17] to MMC and VDS but failed to achieve improved results. Shroeder et al. [20] and Pawel and co-workers [18] have added ifosfamide to MMC and VDS and obtained a response rate that was comparable with hat found for CDDP-containing regimens; however, they also noted considerable toxicity.

In the present study we decided to add VP-16, which shows activity against NSCLC [4], to MMC and VDS in an attempt to improve the therapeutic index of the combination and to develope an alternative regimen that produces less toxicity than does CDDP-containing chemotherapy. This combination had not been used previously. Our re-

sults, which included a 37% OR rate (CRs, 4.7%) and two CRs that lasted for >17 and >19 months, respectively are interesting because they were obtained in patients who exhibited metastatic disease. To date, the highest response rates reported in the literature for CDDP-containing regimens [7, 12] as well as those reported for MMC plus VDS by Kris et al. [10] and Luedke et al [14] have been obtained in studies that included patients exhibiting stage IIIB or IIIA disease. Apart from its efficacy, MEV chemotherapy was well tolerated and produced low toxicity, resulting in a good quality of life for treated patients. MEV also proved to be less toxic than the MMC plus VDS regimen [10, 14], despite the addition of VP-16. A possible explanation may be that MMC was used at a low dose and that VDS was given only on day 1 of each cycle. In conclusion we believe that MEV might be a reasonable alternative either to a "no treatment" policy or to more toxic CDDP-based chemotherapy regimens. A randomized trial comparing MEV with one of the most active CDDP-containing combinations is currently in progress.

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