Cancer Chemother Pharmacol (1992) 30: 212–214

Cancer Chemotherapy and Pharmacology

Short communication

Mitomycin C plus vindesine or cisplatin plus epirubicin in previously treated patients with symptomatic advanced non-small-cell lung cancer

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Received 1 December 1991/Accepted 16 March 1992

Summary. A total of 40 previously treated patients with symptomatic advanced non-small-cell lung cancer (NSCLC) were subjected to second-line chemotherapy with mitomycin C plus vindesine (MV) or cisplatin plus epirubicin (PE). The 12 patients treated with the MV regimen showed no objective response (OR) or symptom palliation. In the 28 patients who received the PE regimen, we obtained a 25% partial response rate, with amelioration of tumor-related symptoms occurring in 35.7% of cases and improvement in the performance status being noted in 25% of subjects. Both regimens were well tolerated. These data show that the administration of cisplatin-based second-line chemotherapy to patients with symptomatic advanced NSCLC may be useful.

Introduction

Non-samll-cell lung cancer (NSCLC) includes a group of poorly drug-responsive tumors. To date, no evidence has been provided that chemotherapy improves the survival of patients with advanced disease [4, 14, 15]. However, cytotoxic treatment is widely used for palliation in such patients. The aim of the present study was to evaluate the usefulness of two second-line chemotherapy regimens in patients with symptomatic advanced (stage IIIB–IV) NSCLC who had previously been treated with an active first-line chemotherapy regimen.

Patients and methods

To be eligible for entry into the present study patients were required to be <70 years of age, to have symptomatic stage IIIB–IV NSCLC, to show an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of <3, to have previously undergone chemotherapy, and to display normal renal, hepatic, and bonemarrow function was required. From July 1988 to July 1991, 40 patients were entered in the trial; all subjects were evaluable for response and toxicity. A total of 12 individuals who had been pretreated with the same cisplatin (CDDP) – based PEV regimen [CDDP + epirubicin (EDX) + etoposide (VP-16)] were subjected to second-line chemotherapy with the MV regimen, consisting of 10 mg/m^2 mitomycin C (MMC) given i.v. on day 1 and 3 mg/m^2 vindesine (VDS) given i.v. on day 1, with treatment being repeated every 4 weeks). The other 28 patients, who had been pretreated with our non-CDDP-based MEV regimen (MMC+VP-16+VDS) [6], underwent second-line chemotherapy with the PE regimen, consisting of 70 mg/m^2 CDDP given i.v. on day 1 and 60 mg/m^2 EDX given i.v. on day 1, with treatment being repeated every 4 weeks. All patients received first-line chemotherapy (PEV or MEV) in two independent nonrandomized phase II studies. Table 1 summarizes the characteristics of our patients. Therapy was continued for a maximum of six cycles in patients who achieved an objective response (OR).

Response and toxicity were graded according to WHO criteria [13]. The assessment of tumor-related symptoms was done by physicians and patients together using the following categories: free of symptoms, diminished symptoms, unchanged symptoms, or increased symptoms. An improvement in symptoms was considered to have occurred when a patient was either symptom-free or showed a diminution of tumor-related symptoms at two consecutive evaluations.

Results

Among the 12 patients treated with the MV regimen, we observed no OR, 4 cases of stable disease (SD) and 8 cases of progressive disease (PD). An improvement in symptoms (dyspnea and coughing) was noted in 1 patient (8.3%), but no subject showed an improvement in PS. The median survival from the beginning of first-line and second-line chemotherapy was 9.5 (range, 4–13) and 5 (range, 2–9) months, respectively. Among the 28 patients treated with the PE regimen, we noted 7 (25%) partial responses (PR), 6 (21.4%) cases of SD, and 15 (53.6%) cases of PD. Two responses occurred in two subjects who had previously responded to first-line MEV chemotherapy. The median duration of response was 4 months (range, 2–14 months). The median survival from the beginning of first-line and second-line chemotherapy was 12 (range, 1–18+) and 6 (range, 5–32) months, respectively. In all, 10 patients

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Table 1. Characteristics of patients

	Regimen	
	MV	PE
Number of patients	12	28
Sex:		
M	10	24
F	2	4
Age (years):		
Median	58	62
Range	42–67	33–70
Stage:		
IIIB	6	11
IV	6	17
PS:		
1	1	10
2	11	18
Histology:		
Epidermoid	8	16
Adenocarcinoma	4	10
Large-cell	0	2
Previous response to chemotherapy	4	9
Tumor-related symptoms:		
Dyspnea	2	4
Cough	3	7
Pain	3	6
Hemoptysis	1	2
More than one symptom	3	9

Table 2. Relationship between response and changes in tumor-related symptoms

Group	Symptoms	Response			All patients
		PR	SD	PD	
MV	Symptom-free	0	0	0	0
	Imporved	0	1	0	1
	Unchanged after 3 months	0	1	0	1
	Worse	0	2	8	10
	Total	0	4	8	12
PE	Symptom-free	3	0	0	3
	Improved	4	3	0	7
	Unchanged after 3 months	0	1	0	1
	Worse	0	2	15	17
	Total	7	6	15	28

(35.7%) reported amelioration of symptoms (dyspnea in 1 case, coughing in 2 cases, pain in 3 cases, dyspnea and coughing in 2 cases, and dyspnea and pain in 2 cases), with 3 of these subjects being symptom-free (dyspnea in 2 cases and coughing in 1 case); 7 patients (25%) showed an improvement in PS.

Table 2 shows the relationship between response and changes in tumor-related symptoms for both regimens; Table 3 shows the relationship between response and performance status. Both regimens were well tolerated. MV caused grade 3 leukopenia in 4 (33.3%) subjects, grade 3 anemia in 1 (8.3%) case, and grade 3 peripheral neurotoxicity in 1 (8.3%) patient. PE caused grade 3 leukopenia in 2 (7.1%) subjects, no thrombocytopenia or anemia exceeding grade 2, and grade 3 nausea and vomiting in 3 (10.7%) patients.

Table 3. Relationship between response and performance status

Group	PS	Response			All patients
		PR	SD	PD	
MV	Improved	0	0	0	0
	Unchanged after 3 months	0	2	0	2
	Worse	0	2	8	10
	Total	0	4	8	12
PE	Improved	4	2	0	6
	Unchanged after 3 months	3	2	2	7
	Worse	0	2	13	15
	Total	7	6	15	28

Discussion

NSCLC is a complex of drug-resistant tumors. The most active regimens used against this disease have included CDDP + VP-16 (OR rates, 30%–33%) [2, 7, 10]. These results seem to be improved by the addition of MMC to CDDP and VDS or vinblastine, but at the cost of a considerable increase in toxicity [5, 11]. MMC plus VDS constitutes one of the most active non-CDDP-based regimens (OR rates, 29%–34%) [9, 12].

Chemotherapy is widely used in NSCLC for palliation of tumor-related symptoms (e.g., dyspnea, coughing, pain, and hemoptysis). The indication for second-line chemotherapy in this group of neoplasms is debatable at present, but it may be useful in symptomatic patients showing a good PS. The data in the literature on salvage chemotherapy are limited and the results have been poor. Klastersky et al. [8] used MMC+VDS in 12 pretreated patients with NSCLC and obtained only 1 PR. In 41 patients who had received prior CDDP-based chemotherapy, Eagan et al. [3] used MMC plus methotrexate plus lomustine and obtained on OR rate of 22%. Albain et al. [1] used CDDP plus VDS plus VP-16 in 22 patients who had previously been treated with a non-CDDP-containing regimen and reported no OR.

The present trial represents the first attempt to evaluate the interrelationships between response, tumor-related symptoms, and PS in NSCLC. Our failure to obtain a response or symptom palliation in patients who were treated with MMC plus VDS after they had undergone first-line CDDP-based chemotherapy is in accordance with the data of Klastersky et al. [8]. In contrast, in patients who were given CDDP plus EDX after they had received first-line MEV chemotherapy, we obtained on OR rate of 25%, observing alleviation of symptoms in 35.7% of cases and an improvement in PS in 25% of our subjects. We conclude that the administration of CDDP-based second-line chemotherapy to patients with symptomatic advanced

NSCLC may be useful and that the MEV regimen [6] may be a reasonable choice for the first-line treatment of such patients due to its efficacy (37% OR, including a 4.7% complete response rate in stage IV disease) and mild toxicity and to the possibility for the successful treatment of such pretreated patients with second-line CDDP-based chemotherapy.

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