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Short communication

Ifosfamide, cisplatin, vinblastine combination chemotherapy in the treatment of advanced non-small-cell lung cancer

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Summary. A total of 42 evaluable patients with previously untreated advanced non-small-cell lung cancer were treated with a combination of cisplatin (80 mg/m^2, day 1), vinblastine (5 mg/m^2, days 1 and 15), and ifosfamide (1.2 g/m^2, days 1–3). In all, 1 complete response and 15 partial responses were obtained, for an overall response rate of 38% (95% confidence limits, 23.6%–54.4%). The median duration of response was 15 weeks, and the median overall survival was 56 weeks. Toxicity mainly consisted of moderate to severe alopecia in 28 patients (67%), moderate to severe nausea and vomiting in 27 subjects (64%), and leukopenia comprising <1,000 leukocytes/mm^3 in 6 cases (14%). In all, 16 patients (38%) had microscopic hematuria (WHO grade 1), but no hemorrhagic cystitis was documented. Although this three-drug combination appears to have moderate antitumor activity against non-small-cell lung cancer, the addition of ifosfamide to the combination of cisplatin and vinblastine did not seem to improve the response rate.

Introduction

Ifosfamide, an oxazaphosphorine, is one of the most active agents against non-small-cell lung cancer (NSCLC); a mean response rate of 26% has been reported [1], and its dose-limiting factors are uro- and neurotoxicity rather than myelotoxicity. However, its role in combination chemotherapy in NSCLC remains unclear. Currently, the combination of cisplatin with either vinca alkaloids (vinblastine or vindesine) or etoposide is widely used in the treatment of advanced NSCLC and has resulted in a 40% response rate [2]. In an attempt to improve the response rate, we added ifosfamide to the combination of cisplatin and vinblastine in this phase II study in advanced NSCLC.

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Patients and methods

Patients with histologically confirmed unresectable NSCLC were eligible for this study. Further eligibility criteria for entry in this study included: no prior history of malignancy, no prior chemotherapy or radiotherapy, no evidence of brain metastases, measurable or evaluable disease, an age of <80 years, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, a leukocyte count of ≥4,000/mm^3, a platelet count of ≥100,000/mm^3, a blood urea nitrogen (BUN) level of ≤25 mg/dl, a serum creatinine value of ≤1.5 mg/dl, and a bilirubin level of ≤1.5 mg/dl. The treatment schedule was as follows: 80 mg/m^2 cisplatin on day 1, 5 mg/m^2 vinblastine on days 1 and 15, and 1.2 g/m^2 ifosfamide on days 1–3. On day 1, cisplatin was infused over ≥30 min, followed by ifosfamide, which was infused over 60 min; vinblastine was given by i. v. bolus. Mannitol and furosemide were given for diuresis. On days 2 and 3, only ifosfamide was given. Uroprotection with mesna or *N*-acetylcysteine was not done. Metoclopramide and methylprednisolone were given to prevent nausea and vomiting.

Therapy was repeated every 4 weeks according to the hematologic status unless there was evidence of disease progression or unacceptable toxicity. Vinblastine treatment was withheld on day 15 when the leukocyte count was <2,000/mm^3 or the platelet count was <80,000/mm^3. Standard criteria were used for response assessment [12]. The survival curve was calculated using the method of Kaplan and Meier [6].

Results

Between August 1986 and February 1989, 43 patients were entered in the study. Only 1 patients was inevaluable because of an overdose of chemotherapeutic agents. The characteristics of the 42 evaluable patients are shown in Table 1. Patients received a median of two treatment cycles, with a range of one to seven being given. In all, 8 patients received only one cycle of chemotherapy; 4 of these showed disease progression, 3 refused further chemotherapy because of side effects, and 1 developed cerebral infarction. In all, 1 complete response and 15 partial responses were obtained, for an overall response rate of 38% (95% confidence limits, 23.6%–54.4%). The duration of complete response in 1 case was 64+ weeks. The median duration of partial response was 14 weeks (range, 7–95 weeks). The median overall survival was 56 weeks.

Table 1. Patient characteristics

Characteristics	Number of patients
Eligible/evaluable	43/42
Median age in years (range)	64.5 (39–78)
Sex:	
M	32
F	10
Performance status:	
0	17
1	22
2	3
Stage:	
IIIa	9
IIIb	12
IV	21
Histology:	
Adenocarcinoma	17
Squamous-cell carcinoma	17
Large-cell carcinoma	8

Table 2. Hematologic toxicity

WHO grade	Hematologic parameter	Number of patients (%)
Leukocytes ($\times 10^3/mm^3$):		
0	≥4	1 (2.4)
1	3–3.9	3 (7.1)
2	2–2.9	9 (21.4)
3	1–1.9	23 (54.8)
4	<1	6 (14.3)
Platelets ($\times 10^3/mm^3$)		
0	≥100	28 (66.7)
1	75–99	3 (7.1)
2	50–74	6 (14.3)
3	25–49	5 (11.9)
4	<25	0

The toxicity of the regimen was mainly hematologic (Table 2). Overall, 6 patients (14%) had leukocyte counts of <1,000/mm^3; 2 subjects (4.7%) developed severe anemia and 1 of these developed cerebral infarction after one course. Nonhematologic toxicity consisted mainly of moderate to severe nausea and vomiting in 27 patients (64%) and moderate to severe alopecia in 28 cases (67%). Of 5 patients (12%) who showed a rise in serum creatinine to >2 mg/dl, 1 developed nonoliguric renal failure. In all, 16 patients (38%) had microscopic hematuria (WHO grade 1); no hemorrhagic cystitis was documented. Only 1 subject developed adynamic ileus. There was no treatment-related death.

Discussion

Thus far, two phase II studies have evaluated ifosfamide in combination with cisplatin and vinca alkaloids (vindesine was used in these two studies), and the response rates were inconsistent (17.5% and 62%, respectively) [8, 10]. In the present phase II study, we obtained a 38% response rate by combining ifosfamide with cisplatin and vinblastine. Although this three-drug combination chemotherapy has moderate activity against NSCLC, the addition of ifosfamide did not seem to improve the response rate as compared with previous trials evaluating the combination of cisplatin and vinblastine [7, 11]. In a randomized study evaluating the addition of either ifosfamide or mitomycin C to the combination of cisplatin and vindesine, neither the response rates (20% vs 26%) nor the median survival were reported to be significantly different [9]. However, promising results have been obtained by the addition of ifosfamide to the combination of cisplatin and mitomycin C [3–5], and future phase III studies are necessary to clarify the role of ifosfamide in the treatment of NSCLC.

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