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Phase II study of carboplatin, cisplatin, and vindesine in advanced non-small-cell lung cancer

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Abstract. Cisplatin in combination with vindesine has been widely used for the treatment of advanced non-small-cell lung cancer (NSCLC), producing an overall response rate of 32%. We conducted a phase II study to examine whether the addition of carboplatin to the combination of cisplatin and vindesine would improve the antitumor activity of the two platinum agents in advanced NSCLC without increasing their toxicity. Carboplatin (240 mg/m^2) and vindesine (3 mg/m^2) were given intravenously on day 1 and cisplatin (60 mg/m^2) and vindesine (3 mg/m^2), on day 8. Of the 40 evaluable patients with advanced NSCLC, 12 showed a partial response, for an overall response rate of 30% (95% confidence interval, 17%–47%). The median duration of response was 12 weeks, and the median survival duration for all patients was 38 weeks. The major toxicity was hematologic: leukopenia (WHO grade ≥ 3) was observed in 21 patients (53%) and anemia (WHO grade ≥ 3), in 13 patients (33%). However, thrombocytopenia was mild and WHO grade 3 toxicity was observed in only 4 patients (10%). Nonhematologic toxicities consisted mainly of WHO grade ≥ 2 nausea and vomiting in 16 patients (40%) and WHO grade ≥ 2 alopecia in 11 patients (28%). No significant nephrotoxicity or neurotoxicity was seen. Our findings indicate that the addition of carboplatin to the combination of cisplatin and vindesine does not improve antitumor activity in patients with advanced NSCLC.

Introduction

Despite recent advances in chemotherapy, non-small-cell lung cancer (NSCLC) remains one of the most common malignancies, resulting in high mortality. The platinum compound cisplatin is among the most active chemotherapeutic agents against NSCLC [1] and is widely used as a primary component of combined regimens for the treatment of advanced NSCLC [3]. Gandara and co-workers [7] obtained a 36% response rate with high-dose cisplatin (200 mg/m^2) alone in NSCLC. Donnadieu et al. [5] revealed that higher-dose cisplatin (≥ 100 mg/m^2) was associated with better response rates than lower-dose cisplatin (≤ 70 mg/m^2) by a meta-analysis. Although a dose-response effect for cisplatin in NSCLC has not been clearly defined, these studies have suggested a possible dose-response effect for cisplatin in the treatment of NSCLC. However, higher-dose cisplatin (120–200 mg/m^2) has produced significant levels of nephrotoxicity, neurotoxicity, and ototoxicity [8, 15, 16, 18].

Carboplatin, an analogue of cisplatin, has moderate activity (10% response rate) against NSCLC [4]. This compound is far less nephrotoxic, neurotoxic, and ototoxic than cisplatin, and its limiting toxicity is myelosuppression [9, 20]. Therefore, one approach for increasing the dose intensity of platinum compounds without increasing the overall toxicity is to use a combination of cisplatin and carboplatin. This approach appears to be promising in the chemotherapy of ovarian cancer [12, 17]. When given in combination with vindesine, cisplatin has yielded a 32% response rate in advanced NSCLC [3]. We therefore conducted a phase II study to evaluate the antitumor activity and safety of adding carboplatin to the combination regimen of cisplatin and vindesine for the treatment of advanced NSCLC. We used carboplatin at 240 mg/m^2 and cisplatin at 60 mg/m^2 in an attempt to give a total dose equivalent to 120 mg/m^2 cisplatin, assuming a 4:1 potency ratio for cisplatin to carboplatin on a milligram basis [13].

Patients and methods

Patients with histologically confirmed, unresectable NSCLC were eligible for this study. Other eligibility criteria included: no prior chemotherapy or radiotherapy; no evidence of brain metastasis; measurable or

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evaluable disease; an age of between 18 and 75 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; a leukocyte count of $\geq$3,500/mm^3; a platelet count of $\geq$100,000/mm^3; a serum creatinine level of $\leq$1.5 mg/dl; and a bilirubin value of $\leq$2.0 mg/dl. Informed consent was obtained from all patients.

The treatment schedule was as follows: carboplatin at 240 mg/m^2 and vindesine at 3 mg/m^2 were given intravenously on day 1 and cisplatin at 60 mg/m^2 and vindesine at 3 mg/m^2, on day 8. Carboplatin was reconstituted in 500 ml of 5% dextrose in water and was infused over 90 min. Vindesine was infused over 15 min. Cisplatin was dissolved in 100 ml of normal saline and infused over 30 min with adequate hydration. Mannitol and furosemide were given for diuresis; nausea and vomiting were controlled with metoclopramide and dexamethasone. Therapy was repeated every 4 weeks unless there was evidence of disease progression or unacceptable toxicity.

Dose modifications were made in response to any myelosuppression that occurred. If a leukocyte count of <2,000/mm^3 or a platelet count of <50,000/mm^3 was obtained on day 8, both cisplatin and vindesine were withheld. If a leukocyte count of 2,000–3,000/mm^3 or a platelet count of 50,000–75,000/mm^3 was obtained on day 8, only vindesine was withheld. If a leukocyte nadir count of <1,000/mm^3 or a platelet nadir count of <50,000/mm^3 was observed or if neutropenic fever developed during the first course of treatment, the carboplatin and vindesine doses were decreased by 25% in the second course; if one of the latter three toxicities occurred during the second course, the carboplatin and vindesine doses in the third course were decreased by 50% from the initial doses and the cisplatin dose was decreased by 25%.

Standard criteria were used for response assessment [21]. A complete response was defined as the disappearance of all evidence of tumor for at least 4 weeks; a partial response, in terms of measurable disease, was defined as a reduction of >50% in the sum of the products of the two greatest perpendicular diameters of all measurable lesions for at least 4 weeks. In terms of evaluable disease, a partial response was defined as an estimated decrease in the tumor size of $\geq$50% for at least 4 weeks. Stable disease was defined as a reduction of <50% and an increase of <25% in measurable or evaluable disease. Progressive disease was defined as the appearance of new tumor lesions or an increase in the tumor size by >25% in measurable or evaluable disease.

Patients were considered to be evaluable for assessment of response and toxicity if they completed at least one course of chemotherapy. Toxicity was evaluated according to WHO criteria [21]. Durations of response and survival were measured from the 1st day of treatment, and the survival curve was calculated by the method of Kaplan and Meier [10].

Results

Between February 1991 and May 1992, 41 patients were entered into this phase II study. Only one patient was inevaluable after registration because of refusal of chemotherapy. The median age of the patients was 66 years (range, 38–73 years). Most patients (83%) had an ECOG performance status of 0 or 1 (Table 1). Adenocarcinoma was the dominant histology (65%).

Patients received a median of two treatment courses, with the range being one to nine courses. Four patients received only one course of chemotherapy; three had progressive disease after the first course of chemotherapy, and one refused further chemotherapy because of nausea and vomiting. A total of 92 courses were given during the first 3 cycles and dose modifications were made in 12 courses (13%). Vindesine on day 8 was withheld in nine courses. The doses of carboplatin and vindesine were reduced on day 1 in one of the second courses. In one third course, the doses of carboplatin and vindesine were reduced on day 1, and vindesine on day 8 was withheld. One patient could not receive cisplatin and vindesine on day 8 in the second course because of hepatic failure.

Table 1. Patients characteristics

Characteristics	Number of patients
Eligible/evaluable	41/40
Sex:	
M	26 (65%)
F	14 (35%)
Performance status (ECOG):	
0	10 (25%)
1	23 (58%)
2	7 (18%)
Stage:	
IIIb	18 (45%)
IV	22 (55%)
Histology:	
Adenocarcinoma	26 (65%)
Squamous-cell carcinoma	7 (18%)
Large-cell carcinoma	7 (18%)

Table 2. Maximal toxicity observed in 40 NSCLC patients

	WHO grade			
	1	2	3	4
Leukopenia	4 (10%)	12 (30%)	18 (45%)	3 (8%)
Thrombocytopenia	3 (8%)	4 (10%)	4 (10%)	0
Anemia	7 (18%)	16 (40%)	11 (28%)	2 (5%)
Nausea/vomiting	17 (43%)	10 (25%)	6 (15%)	0
Alopecia	18 (45%)	10 (25%)	1 (3%)	0
Nephrotoxicity	4 (10%)	0	0	0
Neurotoxicity	2 (5%)	2 (5%)	0	0

Of 18 patients with stage IIIb disease, 5 (28%) achieved a partial response, as did 7 of 22 patients (32%) with stage IV disease, for an overall response rate of 30% (95% confidence interval, 17%–47%). There was no complete response. The median duration of partial response was 12 weeks (range, 7–51 weeks), and the median survival duration for all patients was 38 weeks.

Hematologic toxicity was the major toxicity of this regimen (Table 2). The median leukocyte count nadir was 1,850/mm^3 (range, 800–5,400/mm^3), and 3 patients (8%) had a leukocyte count of <1,000/mm^3. WHO grade $\geq$3 anemia was observed in 13 patients (33%); 2 patients had a hemoglobin level of <6.5 g/dl. In contrast, thrombocytopenia was mild; the median platelet count nadir was 122,000/mm^3 (range, 29,000–292,000/mm^3), and no patient had a platelet count of <25,000/mm^3. Non-hematologic toxicities consisted mainly of nausea and vomiting and alopecia. Nephrotoxicity was minimal, and a creatinine level of >2 mg/ml was seen in only one patient. Neurotoxicity was also minimal with this regimen. One patient died of hepatic failure (due to exacerbation of chronic hepatitis C) after the administration of carboplatin and vindesine in the second course. Cerebral infarction developed in one patient, and phlebitis and right femoral artererial occlusion developed in another patient.

Discussion

The combination of carboplatin and cisplatin in advanced NSCLC has been evaluated by several groups of investigators. Kreisman and co-workers [11] gave 350 mg/m^2 carboplatin and 50 mg/m^2 cisplatin to patients with advanced NSCLC and reported a 13% response rate; this result led them to conclude that the combination of carboplatin and cisplatin does not produce a better response in NSCLC than that produced by carboplatin alone. In contrast, Niitani et al. [14] used 300 mg/m^2 carboplatin and 80 mg/m^2 cisplatin and obtained a 42% response rate, although the number of the patients studied was small. It is interesting that Sculier and colleagues [19] compared the combination of moderate doses of carboplatin (200 mg/m^2) and cisplatin (60 mg/m^2) with high-dose cisplatin alone (120 mg/m^2) and reported that the combination chemotherapy was as active in NSCLC as high-dose cisplatin (24% response rate in both cases). In the present phase II study, we examined whether the addition of carboplatin to the widely employed combination of cisplatin and vindesine would improve the antitumor activity of the latter drugs against advanced NSCLC. The doses of carboplatin and cisplatin given in our study were almost equivalent to those used by Sculier et al. [19]. However, the 30% response rate we achieved is comparable with that reported for the combination of cisplatin and vindesine [3], indicating no benefit for the addition of carboplatin to this combination therapy in advanced NSCLC.

The dose-limiting toxic effect of carboplatin is myelosuppression, particularly thrombocytopenia [9, 20]. Therefore, dosing of carboplatin based on renal function has been recommended to avoid unacceptable thrombocytopenia [6]. This pharmacodynamically based method of dosing of carboplatin has been validated in a combination chemotherapy [2]. We gave carboplatin at a fixed dose of 240 mg/m^2 in the present study and observed a relatively low incidence and only a mild degree of thrombocytopenia. This finding might be explained in part by our use of a moderate dose of carboplatin. The minimal nephrotoxicity that we observed is consistent with the observation of Sculier et al. [19], who have reported that the combination of carboplatin and cisplatin is less nephrotoxic than high-dose cisplatin alone.

In summary, the combination of carboplatin, cisplatin, and vindesine is active against advanced NSCLC and produces acceptable levels of toxicity. However, the addition of carboplatin to the combination of cisplatin and vindesine does not improve the response rate. Further evaluation of this three-drug combination at the doses and schedule used in this study is not warranted in advanced NSCLC.

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