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Phase II study of cisplatin as a 5-day continuous infusion with vindesine plus recombinant human granulocyte-colony-stimulating factor in the treatment of advanced non-small-cell lung cancer

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Summary. A total of 36 patients with advanced non-small-cell lung cancer (NSCLC) were treated with a combination of 5-day continuous i.v. infusion of cisplatin (25 mg/m^2 daily), bolus infusion of vindesine (3 mg/m^2) on days 1 and 8, and s.c. injection of recombinant human granulocyte-colony-stimulating factor (2 μg/kg daily) on days 6–21. Treatment was repeated every 3–4 weeks. Responding patients with stage IIIA or IIIB disease received chest radiation therapy (50–60 Gy) after this treatment. One complete response and 23 partial responses were observed, for an overall response rate of 66.7% (24/36; 95% confidence limits, 51.3%–82.1%). The median duration of response was 5.7 months and the median overall survival was 10.1 months. WHO grade 3 or 4 leukopenia and neutropenia occurred in 22 (61%) and 27 (75%) patients, respectively, but the mean duration of leukopenia (<2,000/mm^3) and neutropenia (<1,000/mm^3) was 3.4 and 3.5 days, respectively, and there was no instance of life-threatening infection. Thrombocytopenia and anemia of grade 3 or 4 occurred in 28% and 36% of our subjects, respectively. Grade 2 nausea and vomiting occurred in 47% of the patients. Elevated serum creatinine levels (>1.5 mg/dl) were observed in 3 (8%) of the 36 patients. One patient died of acute renal faialure induced by hemorrhage of a gastric ulcer. This regimen is effective in the treatment of NSCLC and further studies of this combination are warranted.

Introduction

Cisplatin (CDDP) is one of the most effective agents against non-small-cell lung cancer (NSCLC), and combination chemotherapy containing CDDP has been widely used in the treatment of inoperable NSCLC [2]. In recent years, however, both the response rate and the survival of patients appear to have reached their limits. To push these limits further, new and more effective anticancer agents are obviously needed; in the meantime, it is important that the optimal therapeutic schedule for the administration of existing drugs be determined.

In clinical trials, the most common method of CDDP administration is short-term bolus infusion. However, the optimal therapeutic schedule for the administration of CDDP has not yet been established. In vitro studies by Drewinko et al. [5] and Matsushima et al. [13] show that CDDP cytotoxicity is enhanced by prolonged exposure to low doses of this drug. Belliveau et al. [1] report that the area under the concentration-time curve (AUC) achieved for non-protein-bound CDDP was twice as high after 5-day continuous infusion than that observed when an equivalent dose of CDDP was given by short-term bolus infusion. These findings suggest that continuous infusion of CDDP might improve the therapeutic efficacy as compared with that resulting from conventional short-term bolus infusion. To determine the effectiveness of continuous infusion of CDDP, we performed a phase II study of 5-day continuous infusion of CDDP as a single agent against advanced NSCLC and obtained an AUC value similar to that reported by Belliveau et al. [1] and an encouraging response rate of 40%, which was associated with low toxicity [17].

Vindesine (VDS) has also been identified as an active single agent in the treatment of NSCLC [19]. Gralla et al. [9] have reported a 43% rate of response to VDS given in combination with CDDP by short-term bolus infusion to 81 patients with NSCLC. On the basis of these findings, we performed a pilot phase II study of 5-day continuous infusion of CDDP plus VDS in 30 patients with advanced NSCLC and obtained a response rate of 50% [15]. However, grade 3 or 4 leukopenia was observed in 60% of the patients, and treatment delays occurred in 20% of cases because of incomplete recovery from leukopenia [15].

Eguchi et al. [6] have reported that recombinant human granulocyte-colony-stimulating factor (rhG-CSF) shortens the duration of leukopenia following intensive chemotherapy. Fukuoka et al. [8] have studied the effect of rhG-CSF

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in NSCLC patients receiving a combination of mitomycin C, VDS, and CDDP (MVP regimen) and have shown that s.c. injection of rhG-CSF at a dose of 2 μg/kg daily on days 2–21 makes it possible to give the MVP regimen safely every 3 weeks.

We therefore conducted a new phase II study in which rhG-CSF (Chugai) was added to continuous infusion of CDDP plus VDS to increase the dose intensity of CDDP and VDS by preventing treatment delays due to leukopenia. The purpose of this study was to evaluate the activity of continuous-infusion CDDP plus VDS against NSCLC as measured by the response rate and overall survival resulting from an increase in the dose intensity of CDDP and VDS.

Patients and methods

From July 1989 to December 1990, 36 patients with advanced NSCLC were entered in this phase II protocol. Eligibility criteria included histologically proven NSCLC; stage III A, III B, or IV disease [stage III A disease only if it was incurable by surgery because of (1) gross mediastinal involvement by primary tumor extension or mediastinal nodal involvement as observed on plain chest roentgenograms or computed tomograms, (2) proximal bronchial extension, or (3) extensive invasion of the chest wall, or a combination of some or all of these factors]; measurable lesions; an age of <80 years; an Eastern Cooperative Oncology Group (ECOG) performance score of ≦3; a WBC of ≧4,000/mm^3; a platelet count of ≧100,000/mm^3; a total bilirubin level of <2 mg/dl; SGOT and SGPT values of less than twice the normal range; a serum creatinine level of <1.5 mg/dl; creatinine clearance of >40 ml/min; no history of prior chemotherapy or surgery; the absence of concurrent active malignancies; and informed consent of the patients. Prior radiotherapy was permitted only if CNS metastasis was present at the time of diagnosis. Radiation was given to treat documented brain metastasis before the initiation of chemotherapy.

Pretreatment evaluation included a complete medical history, physical examination, and complete blood count (CBC), determination of urinary creatinine clearance, relevant laboratory tests, a chest roentgenogram, an ECG, complete urinalysis, and a bone marrow examination. All patients underwent bronchofiberscopy, a radionuclide bone scan, a computerized tomographic (CT) scan of the brain and thorax, and an abdominal ultrasound examination or CT scan. Physical examinations, CBC and differential counts (determined three to four times per week during neutropenia), and chest roentgenography were performed weekly, as were biochemical tests and serum electrolyte determinations. Chest CT scans and determinations of creatinine clearance were done before each course of CDDP. Staging procedures were those of the tumor-node-metastasis system, and the terms stage III A and stage III B were the same as those used in the International Panel Staging System [16].

CDDP was reconstituted in 0.9% NaCl solution immediately before its use and was infused by constant pump infusion for 5 consecutive days (on days 1–5) at a dose of 25 mg/m^2 daily. In practice, one-third of the daily dose was infused continuously every 8 h with 20 mEq KCl and 1 mg/kg metoclopramide in 800 ml 0.9% NaCl solution. Moreover, for nausea and vomiting, methylprednisolone (125 mg) was given i.v. over 30 min simultaneously with the beginning of CDDP administration and thereafter every 8 h for 5 consecutive days. VDS was given at 3 mg/m^2 on days 1 and 8 as a bolus injection. rhG-CSF was injected s.c. at 2 μg/kg daily on days 6–21. Chemotherapy was repeated every 3–4 weeks.

Patients were evaluated for response after the completion of one or two cycles. A complete response (CR) was defined as the complete disappearance of all known disease as indicated by examinations carried out at least 4 weeks apart. A partial response (PR) was defined as a reduction of ≧50% in the product of the longest perpendicular diameters of all measurable lesions for ≧4 weeks in the absence of new lesions. Stable disease (SD) was defined as either a reduction of <50% or an increase of <25% in the product of the longest perpendicular diameters of the measurable lesions for ≧4 weeks in the absence of new lesions. Progressive disease (PD) was defined as an increase of ≧25% in the tumor area or the appearance of new lesions. The duration of response was defined as the time from the initiation of chemotherapy until the appearance of the first sign of progressive disease. The toxicity criteria used were those recommended by the World Health Organization (WHO) [14]. The responses and drug toxicities were evaluated during regular meetings of the group, which consisted of members and extramural observers. Survival curves from day 1 of treatment until death were calculated by the method of Kaplan and Meier [10], and statistical differences between survival curves were computed by the log-rank test [12].

Therapy was discontinued if disease progression occurred after the first course of treatment or if SD was observed after the second course. In patients showing a CR or PR, treatment was continued for a total of four courses (4 months). Responding patients with stage III A or III B disease received chest radiation therapy (RT; 50–60 Gy) after this treatment. Four patients who had CNS metastases received cranial irradiation (40–50 Gy) immediately before the initiation of chemotherapy. Patients whose cancer was resistant to chemotherapy or who experienced a relapse were given carboplatin i.v. at 275–300 mg/m^2 on day 1 and etoposide i.v. at 100 mg/m^2 on days 1–3 every 4 weeks as second-line chemotherapy, depending on the patient's clinical condition.

Table 1. Patients' characteristics and therapeutic response

Characteristic	Number of patients	Number of responders
Total/evaluable patients	36/35	24[a]
Median age (years)	63 (range, 35–75)	
Sex:		
M	31	21[a]
F	5	3
ECOG performance status:		
0	12	9
1	12	11
2	7	3[a]
3	5	1
Stage:		
III A	1	1[a]
III B	11	9
IV	24	14
Weight loss (≧10% body weight)		
Yes	10	6
No	26	18[a]
Histology:		
Squamous-cell carcinoma	20	13[a]
Adenocarcinoma	15	11
Large-cell carcinoma	1	0

[a] Including one patient who achieved a CR

Results

Of the 36 patients entered into this study, 35 were considered to be evaluable for both response and toxic effects; 1 patient died of acute renal failure induced by hemorrhage of a gastric ulcer before the response could be assessed and was included only in the toxicity analysis. The pretreatment characteristics of the patients and their therapeutic responses are summarized in Table 1. Patients received a median of 3 treatment cycles (range, 1–4 cycles).

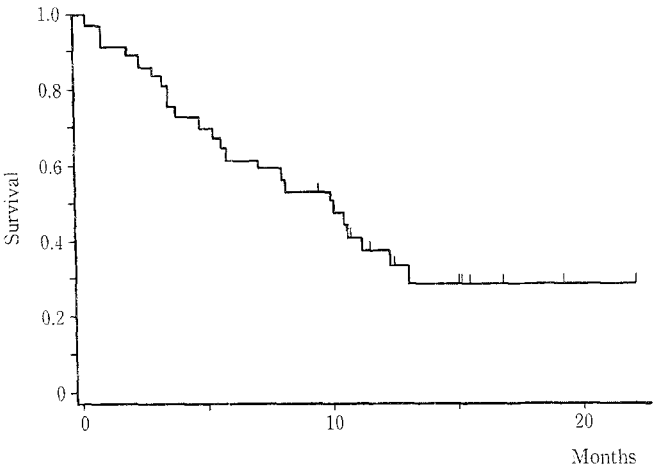

Fig. 1. Actuarial survival curve generated for 36 patients with NSCLC who were treated with cisplatin as a 5-day continuous infusion plus vindesine plus recombinant human granulocyte-colony-stimulating factor

Table 2. Toxicity encountered

	Maximal toxicity according to WHO grade				
	0	1	2	3	4
Leukopenia	4	1	9	10	12
Neutropenia	4	0	5	6	21
Thrombocytopenia	12	9	5	8	2
Anemia	2	3	18	12	1
Fever[a]	15	11	10	0	0
Fatigue	2	5	16	13	0
Nausea, vomiting	6	13	17	0	0
Diarrhea	26	10	0	0	0
Alopecia	6	5	17	8	0
Neurotoxicity (peripheral)	17	16	3	0	0
Elevated SGOT/SGPT	25	4	6	1	0
Elevated serum creatinine	33	2	0	1	0

Data represent the number of patients affected
[a] Fever with neutropenia

Among the 35 completely evaluable patients, 1 achieved a CR (squamous-cell carcinoma) and 23 showed a PR, for a response rate of 68.6% (24/35; 95% confidence limits, 52.3%–84.0%) and an overall response rate of 66.7% (24/36; 95% confidence limits, 51.3%–82.1%). PRs were achieved by 12 of 20 patients with squamous-cell carcinoma and by 11 of 15 patients with adenocarcinoma. Patients showing an ECOG performance status of 0 or 1 responded significantly better than did those whose score was 2 or 3 (83% vs 33%; $P < 0.001$). Patients with stage III disease responded better than did those with stage IV disease (83% vs 58%), but this difference was not statistically significant. In all, 7 patients developed SD and 4 PD. The median duration of response was 5.7 months (range, 1.8–15.3 + months) for PRs and 9.6 months for the CR. The median overall survival (36 patients) was 10.1 months (Fig. 1). Patients with stage IIIA or stage IIIB disease survived statistically significantly longer than did those with stage IV disease (10.7 vs 5.0 months; $P < 0.05$, log-rank test). Patients showing an ECOG performance status of 0 or 1 survived significantly longer than those whose score was 2 or 3 (10.3 vs 4.5 months; $P < 0.05$), and patients who had shown a loss of <10% of their body weight survived longer than those who had lost more weight in the previous 6 months (10.6 vs 5.0 months; $P < 0.01$). Overall, six patients received chest RT. In all, 1 of 11 patients who had failed to respond to the present regimen received second-line chemotherapy with carboplatin plus etoposide, but this patient did not respond. Of the 24 responding patients, 19 experienced relapses; 5 of the latter received second-line chemotherapy, and a PR was noted in only 1 patient. The sites of relapse that occurred in areas of former disease were the lung ($n = 9$ patients), mediastinal lymph nodes ($n = 2$), and bone ($n = 1$). The sites of relapse that occurred in new areas were the lung ($n = 3$ patients), pleura ($n = 2$), brain ($n = 1$), and chest wall ($n = 1$).

Table 2 shows the toxicity observed. The main side effect encountered was myelosuppression. Leukopenia and neutropenia of grade 3 or 4 occurred in 22 (61%) and 27 (75%) patients, respectively. However, there was no instance of life-threatening infection. The mean duration of leukopenia (<2,000/mm^3) and neutropenia (<1,000/mm^3) was 3.4 ± 1.7 days (range, 1–7 days) and 3.5 ± 1.5 days (range, 1–7 days), respectively, and recovery from them was always complete by day 21. In all, 10 patients (27%) experienced grade 3 or 4 thrombocytopenia, and 2 of them required platelet transfusions; 13 patients (36%) developed grade 3 or 4 anemia and were given blood transfusions. Four patients who received cranial radiation did not show such excessive hematologic toxicity. Grade 2 fever with neutropenia occurred in 10 patients (28%), and the mean duration of fever (grade 2) was 2.6 ± 1.1 days (range, 1–5 days). Grade 2 or 3 fatigue was frequently encountered, but it disappeared within 1 week after drug administration. In all, 36% of the patients complained of nausea, and transient vomiting occurred in 47%; 17% of the patients experienced no nausea or vomiting. Alopecia occurred in 83% of the patients; neurotoxicity, in 53%; and transient elevations of SGOT/SGTP, in 31%. Only one patient experienced a grade 3 elevation of serum creatinine; on day 12 of the first cycle, this patient died of acute renal failure induced by hemorrhage of a gastric ulcer, which was presumably a treatment-related toxicity. There was no treatment delay, reduction of the chemotherapy dose, or refusal of further treatment because of toxicity.

Discussion

There has been major interest in combination chemotherapy consisting of CDDP plus vinca alkaloid in NSCLC since the initial report of Gralla et al. [9]. Combinations of CDDP plus VDS have been extensively used in the treatment of NSCLC during this decade [2]. These combinations, in which CDDP is given by short-term infusion, have been reported to produce response rates of 27%–43% [3, 4, 7, 9, 11, 18, 20] and median survival periods of 6–10 months [3, 4, 7, 11, 18, 20]. In comparison with these studies, the present regimen yielded a considerably better

response rate (66.7%). Our therapeutic schedule, which involved 5-day continuous infusion of CDDP, might have been responsible for this promising response rate. The median duration of survival (10.1 months) for all patients in this study was also longer than that previously obtained using VDS and short-term bolus infusion of CDDP. Although the duration of response and survival for six patients who received consolidative RT may have been related to the RT, these results suggest that CDDP is a schedule-dependent drug and that 5-day continuous infusion is an effective method of CDDP administration in the treatment of NSCLC.

The major toxicity encountered was hematologic, mainly involving leukopenia and neutropenia. As compared with data obtained in previous studies of CDDP given as a short-term infusion in combination with VDS [3, 4, 7, 9, 11, 18, 20], the incidence of hematologic toxicity during the present study was high. In particular, leukopenia and neutropenia of grade 3 or 4 was observed in 61% and 75% of all patients, respectively. However, the mean duration of leukopenia (<2,000/mm^3) and neutropenia (<1,000/mm^3) was 3.4 days and 3.5 days, respectively, and recovery from them was always complete within 3 weeks. Therefore, in this study, no severe infection such as pneumonia or sepsis occurred and no treatment delay was required because of neutropenia. The injection of rhG-CSF might have shortened the duration of leukopenia and neutropenia in the present study; in our pilot phase II trial of 5-day continuous infusion of CDDP and VDS in the absence of rhG-CSF, the mean duration of leukopenia (<2,000/mm^3) and neutropenia (1,000/mm^3) was 6.0 $\pm$ 2.6 days (range, 2–9 days) and 11.3 $\pm$ 1.9 days (range, 8–14 days), respectively [15]. In the present study as compared with our previously reported phase II trial [15], the incidence of fever (grade 2) with neutropenia was reduced (28% vs 40%) and the duration of fever was shortened (2.6 vs 6.1 days). In spite of the high CDDP dose given in the present study (125 mg/m^2), vomiting occurred in only 47% of patients, and in all cases it was grade 2. Elevated serum creatinine levels were observed in only 3 patients (8%). In comparison with data obtained in studies of CDDP given at virtually the same dose (120 mg/m^2) by short-term bolus infusion [4, 7, 9, 11, 20], the incidence of vomiting and elevated serum creatinine in the present study was low.

In conclusion, this treatment modality produced an encouraging response rate in association with relatively low toxicity. The question as to whether this treatment might be better than the conventional approach of bolus CDDP infusion can be answered only in a randomized phase III trial.

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