Cancer Chemother Pharmacol (1993) 32: 134–136

Cancer Chemotherapy and Pharmacology

Phase II study of a 72-h concurrent continuous infusion of cisplatin and etoposide in advanced non-small-cell lung cancer

Hiroshi Saito[1]*, Kaoru Shimokata[2], Masashi Yamamoto[3], Hideo Saka[2], Shuzo Sakai[4], Hidehiko Saito[2]

[1] Department of Medicine, Chubu National Hospital, Obu, Aichi, Japan
[2] First Department of Internal Medicine, Nagoya University School of Medicine, Nagoya, Japan
[3] Department of Medicine, Nagoya Ekisaikai Hospital, Nagoya, Japan
[4] Department of Medicine, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan

Received 9 August 1992/Accepted 20 January 1993

Abstract. We conducted a phase II study to evaluate the antitumor activity and safety of concurrent continuous infusion of cisplatin and etoposide in advanced non-small-cell lung cancer (NSCLC). Cisplatin (30 mg/m^2 daily) and etoposide (80 mg/m^2 daily) were given as a 24-h continuous infusion for 72 h to 48 patients with previously untreated advanced NSCLC. Of the 46 evaluable patients, 9 achieved a partial response, for an overall response rate of 20% (95% confidence interval, 9.4%–33.9%). The median duration of response was 23 weeks. The median duration of survival for all patients was 34.4 weeks. The major toxicity was hematologic. Leukopenia (WHO grade ≥ 3) was observed in 22 patients (48%) and thrombocytopenia (WHO grade ≥ 3), in 13 patients (28%). In all, 20 patients (43%) experienced severe anemia (WHO grade ≥ 3). Nonhematologic toxicity mainly consisted of moderate to severe alopecia in 33 patients (72%) and moderate to severe nausea and vomiting in 25 patients (54%). No significant nephrotoxicity was seen. We conclude that a 72-h concurrent continuous infuson of cisplatin and etoposide does not appear to be active against advanced NSCLC.

Introduction

Non-small-cell lung cancer (NSCLC) is one of the most chemotherapy-resistant solid tumors, and its prognosis is dismal. Although several promising chemotherapeutic agents are under investigation, the number of currently available drugs is limited. One approach to improving the therapeutic efficacy in NSCLC is to identify an optimal administration method for currently available agents. As single agents, cisplatin and etoposide produce response rates of greater than 10% in NSCLC [1]. The combination of cisplatin and etoposide has been reported to be synergistic in animal models and in some clinical studies [14, 15]. The combination of cisplatin and etoposide given as a short-term infusion is one of the most widely used regimens for the treatment of advanced NSCLC, producing a response rate of 32% [9]. The major toxicity of this combination is myelosuppression [10]. The rationale for giving etoposide as a continuous infusion is based on pharmacokinetic considerations and the schedule dependency that has been demonstrated in experimental tumors and in clinical trials [3, 13, 16]. Prolonged exposure to cisplatin has been demonstrated to be more tumoricidal than short-term exposure in in vitro tumor models [5], and total exposure to filterable platinum has been shown to increase when cisplatin is given by continuous infusion [2, 6]. However, the limited number of continuous-infusion trials has made it difficult to draw any firm conclusions regarding the advantages of this type of administration. For this reason we conducted a phase II study to evaluate the antitumor activity and safety of concurrent continuous infusion of cisplatin and etoposide in patients with advanced NSCLC.

Patients and methods

Patients with histologically confirmed unresectable NSCLC were eligible for this study. Other eligibility criteria for entry into this study included no prior chemotherapy or radiotherapy; no evidence of brain metastases; the presence of measurable or evaluable disease; an age of <80 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; a leukocyte count of $\geq 4{,}000/\text{mm}^3$ and a platelet count of $\geq 100{,}000/\text{mm}^3$; a blood urea nitrogen (BUN) value of <25 mg/dl; a serum creatinine level of ≤ 1.5 mg/dl; and a bilirubin value of ≤ 2.0 mg/dl. Informed consent was obtained from all patients.

The treatment schedule was as follows: cisplatin (30 mg/m^2) and etoposide (80 mg/m^2) were concurrently given as a 24-h continuous infusion over 3 days. Cisplatin (15 mg/m^2) and etoposide (40 mg/m^2) were diluted in 500 ml normal saline and in 500 ml 5% dextrose water, respectively, and were infused over 12 h. Alternatively, the same doses

* Current address: Hiroshi Saito, Division of Clinical Pharmacology, The Johns Hopkins University School of Medicine, 600 North Wolfe Street/Osler 527, Baltimore, MD 21209, USA

Correspondence to: Kaoru Shimokata, First Department of Internal Medicine, Nagoya University School of Medicine, 65 Tsurumai, Showa-ku, Nagoya 466, Japan

Table 1. Patients' characteristics

Characteristics	Number of patients
Eligible/evaluable	48/46
Median age in years (range)	63 (34–79)
Sex:	
M	31
F	15
Performance status (ECOG):	
0	14
1	25
2	7
Stage:	
IIIb	17
IV	29
Histology:	
Adenocarcinoma	27
Squamous-cell carcinoma	10
Large-cell carcinoma	9

of both drugs were admixed in 500 ml normal saline and were infused over 12 h. Nausea and vomiting were controlled by continuous infusion of metoclopramide and of dexamethasone with or without oral lorazepam. Therapy was repeated every 4 weeks according to the hematologic status unless there was evidence of disease progression or unacceptable toxicity. Patients were taken off the study if an objective response was not obtained after the second course of chemotherapy. Patients were considered to be evaluable if they completed at least one course of chemotherapy.

Dose modification was made according to hematologic toxicity. If a neutrophil nadir was <500/mm^3 or a platelet nadir was <50,000/mm^3 in the first cycle, the etoposide dose was decreased by 25% in the second cycle. If the above-mentioned myelotoxicity was observed in the second cycle, the cisplatin dose was decreased by 33% in the third cycle.

Standard criteria were used for response assessment [18]. A complete response was defined as the disappearance of all evidence of tumor for at least 4 weeks and a partial response, in 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 evaluable disease, a partial response was defined as an estimated decrease in tumor size of $\geq$50% for at least 4 weeks. No change was defined as a reduction of <50% or an increase of <25% in the size of the tumor. Progressive disease was defined as the appearance of new tumor lesions or an increase in tumor size of >25% in measurable or evaluable disease. Toxicity was evaluated using WHO criteria [18]. Durations of response and survival were measured from the 1st day of treatment. The survival curve was calculated by the method of Kaplan and Meier [8].

Results

A total of 48 patients were entered in the study from May 1989 through September 1990. Two patients were inevaluable because of an overdose of chemotherapeutic agents. The characteristics of the 46 evaluable patients are shown in Table 1. The median age of the patients was 63 years, and 41% of them were older than 65 years. Most patients (85%) had an ECOG performance status of 0 or 1. Adenocarcinoma was the dominant histology (59%). Patients received a median of two treatment cycles, with the range being one to six. Nine partial responses were obtained, for an overall response rate of 20% (95% confidence interval, 9.4%–33.9%). The median duration of partial response was 23 weeks (range, 7–95 weeks). The median duration of survival for all patients was 34.4 weeks. A total of 16 (35%) patients survived for more than 1 year.

Table 2. Maximal toxicity encountered in 46 patients

	Number of patients WHO grade				
	0	1	2	3	4
Leukopenia	1	11	12	22	0
Thrombocytopenia	21	6	6	12	1
Anemia	4	11	11	17	3
Nausea/vomiting	11	10	16	7	2
Alopecia	4	9	27	5	1
Nephrotoxicity	36	10	0	0	0

The toxicity of the regimen was evaluated in 46 evaluable patients and is summarized in Table 2. Hematologic toxicity was the principal toxicity of the regimen. Leukopenia (WHO grade $\geq$3) was observed in 22 patients (48%); the median leukocyte nadir was 2,100/mm^3 (range, 1,000–4,400/mm^3). Thrombocytopenia (WHO grade $\geq$3) was observed in 13 patients (28%); the median platelet nadir was 92,000/mm^3 (range, 24,000–300,000/mm^3). WHO grade $\geq$3 anemia was observed in 20 patients (43%), 3 of whom had a hemoglobin level of <6.5 g/dl. Nonhematologic toxicity mainly consisted of moderate to severe alopecia in 33 patients (72%) and moderate to severe nausea and vomiting in 25 patients (54%). Nephrotoxicity, however, was mild in this regimen, and the maximal creatinine elevation of 2.0 mg/dl was seen in only 4 patients (9%). There was no treatment-related death.

Discussion

We conducted this phase II study to examine the potential advantages of continuous-infusion schedules of cisplatin and etoposide [2, 6, 13, 16] in the treatment of advanced NSCLC. However, we obtained only a 20% response rate (95% confidence interval, 9.4%–33.9%), which was lower than the 32% that has been reported for a short-term infusion schedule of the same two agents [9]. Two groups of workers investigating concurrent continuous infusion have also reported response rates higher than those we obtained [11, 12]. This difference might be partly explained by differences in the doses and schedules of infusion of cisplatin and etoposide and in patient selection. Furthermore, the number of patients involved in the latter two studies was small. In contrast, the North Central Cancer Treatment Group has recently conducted a phase III randomized study comparing a bolus infusion of cisplatin and etoposide with a continuous infusion of the same two drugs and has reported that a continuous-infusion regimen did not offer any therapeutic advantages as compared with a bolus-infusion regimen [7]. The authors also observed that infusion therapy was associated with a greater degree of myelosuppression and with higher treatment-related mortality. Although we did not encounter any treatment-related death,

the major toxicity was also myelosuppression in our study. On the basis of the results of both our study and the North Central Cancer Treatment Group study, it is unlikely that continuous infusion of cisplatin and etoposide improves therapeutic efficacy in advanced NSCLC.

The schedule of etoposide administration is worth mentioning. Time dependency of etoposide administration has been experimentally and clinically documented [3, 13, 16]. However, Chatelut et al. [4] have reported no difference in the pharmacokinetic parameters of etoposide between a 72-h continuous-infusion schedule and a short-term infusion schedule, suggesting that no additional benefit is provided by a 72-h continuous infusion. Both our study and the North Central Cancer Treatment Group study support this suggestion. In contrast, Waits et al. [17] have obtained a 23% response rate in NSCLC by giving etoposide alone orally for 21 consecutive days. Chronic administration of etoposide, either orally or parenterally, might be promising. Therefore, the search for an optimal administration schedule of etoposide should be continued to improve therapeutic efficacy in the treatment of advanced NSCLC.

References

1. Bakowski MT, Crouch JC (1983) Chemotherapy of non-small cell lung cancer: a reappraisal and a look to the future. Cancer Treat Rev 10: 159
2. Belliveau JF, Posner MR, Ferrari L, Crabtree GW, Cummings FJ, Wiemann MC, O'Leary GP Jr, Griffin H, Phaneuf MA, O'Rourke A, Calabresi P (1986) Cisplatin administered as a continuous 5-day infusion: plasma platinum levels and urine platinum excretion. Cancer Treat Rep 70: 1215
3. Cavalli F, Sonntag RW, Jungi F, Senn HJ, Brunner KW (1978) VP-16-213 monotherapy for remission induction of small cell lung cancer: a randomized trial using three dosage schedules. Cancer Treat Rep 62: 474
4. Chatelut E, Chevreau C, Blancy E, Lequellec A, Canal P, Roche H, Houin G, Bugat R (1990) Pharmacokinetics and toxicity of two modalities of etoposide infusion in metastatic non-small-cell lung carcinoma. Cancer Chemother Pharmacol 26: 365
5. Drewinko B, Brown BW, Gottlieb JA (1973) The effect of *cis*-diamminedichloroplatinum(II) on cultured human lymphoma cells and its therapeutic implications. Cancer Res 33: 3091
6. Forastiere AA, Belliveau JF, Goren MP, Vogel WC, Posner MR, O'Leary GP Jr (1988) Pharmacokinetic and toxicity evaluation of five-day continuous infusion versus intermittent bolus *cis*-diamminedichloroplatinum(II) in head and neck cancer patients. Cancer Res 48: 3869
7. Goldberg RM, Jett JR, Therneau TM, Johnson PS, Tschetter LK, Krook JE, Veeder MH, Owen D, Etzell PS, Andres DF (1990) Bolus versus infusion regimens of etoposide and cisplatin in treatment of non-small cell lung cancer: a study of the North Central Cancer Treatment Group. J Natl Cancer Inst 82: 1899
8. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. Am Stat Assoc J 53: 457
9. Klastersky J (1986) Therapy with cisplatin and etoposide for non-small-cell lung cancer. Semin Oncol 13 [Suppl]: 104
10. Klastersky J, Sculier JP, Ravez P, Libert P, Michel J, Vandermoten G, Rocmans P, Bonduelle Y, Mairesse M, Michiels T, Thiriaux J, Mommen P, Dalesio O, the EORTC Lung Cancer Working Party (1986) A randomized study comparing a high and a standard dose of cisplatin in combination with etoposide in the treatment of advanced non-small-cell lung carcinoma. J Clin Oncol 4: 1780
11. Krook JE, Jett JR, Little C (1989) A phase I–II study of sequential infusion of VP-16 and cisplatin therapy in advanced lung cancer. Am J Clin Oncol 12: 114
12. Marechal F, Berthiot G, Cattan A (1990) Five-day continuous infusion of cisplatin and etoposide in non-small cell lung cancer. A phase II trial. Acta Oncol 29: 989
13. Matsushima Y, Kanzawa F, Hoshi A, Shimizu E, Nomori H, Sasaki Y, Saijo N (1985) Time-schedule dependency of the inhibiting activity of various anticancer drugs in the clonogenic assay. Cancer Chemother Pharmacol 14: 104
14. Schabel FM Jr, Trader MW, Laster WR Jr, Corbett TH, Griswold DP Jr (1979) *cis*-Dichlorodiammineplatinum(II): combination chemotherapy and cross-resistance studies with tumors of mice. Cancer Treat Rep 63: 1459
15. Sierocki JS, Hilaris BS, Hopfan S, Martini N, Barton D, Golbey RB, Wittes RE (1979) *cis*-Dichlorodiammineplatinum(II) and VP-16-213: an active induction regimen for small cell carcinoma of the lung. Cancer Treat Rep 63: 1593
16. Slevin ML, Clark PI, Joel SP, Malik S, Osborne RJ, Gregory WM, Lowe DG, Reznek RH, Wrigley PFM (1989) A randomized trial to evaluate the effect of schedule on the activity of etoposide in small-cell lung cancer. J Clin Oncol 7: 1333
17. Waits TM, Johnson DH, Hainsworth JD, Hande KR, Thomas M, Greco FA (1992) Prolonged administration of oral etoposide in non-small-cell lung cancer: a phase II trial. J Clin Oncol 10: 292
18. World Health Organization (1979) Handbook for reporting results of cancer treatment. WHO Offset Publication 48, World Health Organization, Geneva