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Phase II study of (glycolate-*O,O'*) diammineplatinum(II), a novel platinum complex, in the treatment of non-small-cell lung cancer*

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Summary. A total of 68 patients with non-small-cell lung cancer who either had not previously been treated (38) or had undergone prior therapy (30) were treated in a phase II study of (glycolate-*O,O'*) diammineplatinum(II) (NSC 375101D; 254-S), a new platinum complex. The drug was given as a single intravenous infusion at a dose of 100 mg/m^2 every 4 weeks. All 68 patients could be evaluated for response and 62, for toxicity. Objective responses were seen in 10 of 68 cases (14.7%; 95% confidence interval, 7.3%–25.4%), and the median duration of response was 15 weeks (range, 8–23 weeks). The response rates were similar for previously untreated and treated patients (13% and 17%, respectively), including three previously treated with cisplatin. Myelosuppression was the dose-limiting toxicity. Thrombocytopenia (<100,000 platelets/mm^3) and leukocytopenia (<3,000 WBC/mm^3) were observed in 22 (35%) and 18 (29%) patients, respectively. Mild to moderate nausea and vomiting occurred in 45 cases (73%). No significant renal or neurotoxicity was observed. We conclude that as a single agent, 254-S is well tolerated but appears to have marginal activity against non-small-cell lung cancer.

Introduction

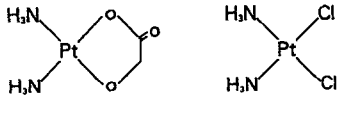
Although a number of agents have been demonstrated to be active against non-small-cell lung cancer (NSCLC), mainly as part of combination chemotherapy, the impact of such treatment on the survival and quality of life of patients with NSCLC remains controversial [1, 6, 11]. Because of the limitations of conventional therapy, the development of new anticancer agents is considered a high priority.

(Glycolate-*O,O'*) diammineplatinum(II) (NSC 375101D; 254-S) is a second-generation platinum complex that was developed by Shionogi Pharmaceutical Company (Osaka, Japan) [16] (Fig. 1). Preclinical studies have demonstrated that 254-S has high activity against rodent solid tumors and both lower renal toxicity and higher aqueous solubility than cisplatin [16–18]. A phase I study by the 254-S Study Group demonstrated that 254-S was well tolerated, producing acceptable toxicity at the maximally tolerated dose of 120 mg/m^2. The dose-limiting toxicity was thombocytopenia. No significant renal toxicity was found, in contrast with previous studies using cisplatin [2].

In an attempt to evaluate the activity and toxicity of 254-S in the treatment of NSCLC, a phase II study was conducted at the National Cancer Center Hospital, Tokyo.

Patients and methods

Cytological or histological proof of NSCLC (adenocarcinoma, squamous-cell carcinoma, large-cell carcinoma, or adenosquamous carcinoma) was required for all patients entering this study. Only those with a predicted life expectancy of ≥ 2 months, an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 3, measurable or evaluable disease, and no malignancy at other sites were eligible. Patients had to be <80 years old and could not have received anticancer agents for at least 4 weeks. Subjects who had previously received cisplatin (CDDP) were included in the study to evaluate whether 254-S would exhibit non-cross-resistance to CDDP. Patients had to demonstrate: (1) normal



254-S Cisplatin

Fig. 1. Chemical structures of 254-S and cisplatin

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Table 1. Patient characteristics

Total number of patients	68
Evaluable patients	68
Mean age (range) in years	63 (29–79)
Men	42
Women	26
ECOG performance score:	
0	2
1	52
2	9
3	5
Stage:	
Limited disease	16
Disseminated disease	52
Histology:	
Adenocarcinoma	52
Squamous-cell carcinoma	9
Large-cell carcinoma	5
Adenosquamous carcinoma	2
Prior chemotherapy:	
(–)	38
(+) with CDDP	16
(+) without CDDP	14

Table 2. Antitumor effect of 254-S against non-small-cell lung cancer

Prior treatment	Number of patients	Response			Response rate (%)
		PR	NC	PD	
No	38	5	17	16	13.2
Yes	30	5	19	6	16.7
CDDP(+)	16	3	10	3	
CDDP(–)	14	2	9	3	

Table 3. Response rate according to histological subtype

Histological type	Number of patients	Response		
		PR	NC	PD
Squamous-cell carcinoma	9	4	1	4
Adenocarcinoma	52	5	30	17
Large-cell carcinoma	5	0	4	1
Adenosquamous carcinoma	2	1	1	0

bone marrow function (WBC, $\geq 3{,}000/mm^3$; platelet $\geq 100{,}000/mm^3$; hemoglobin, ≥ 9.0 g/dl); (2) normal renal function (serum creatinine values of ≤ 1.4 mg/dl and/or creatinine clearance of ≥ 60 ml/min); (3) other laboratory data of ≤ 2 times the normal limit (although patients with liver dysfunction due to liver metastases were permitted in this study); and (4) no evidence of apparent cardiovascular disease, serious active infection, or hemorrhagic disorders. Prior to study entry, informed consent was obtained from all patients.

254-S was supplied by Shionogi Pharmaceutical Company (Osaka, Japan) as a lyophilized powder in a 100-mg, single-use vial. The drug was diluted in 300 ml 5% xylitol solution immediately prior to injection and was given as an intravenous drip infusion over 60 min. No additional hydration was given except to 16 patients who had received intensive prior chemotherapy that included CDDP. Antiemetic agents were not given during the first course of treatment. Six patients received radiation therapy in brain and bone metastases for clinical relief and were excluded for evaluation of toxicity.

Courses were repeated every 4 weeks, depending on the hematological status. If the WBC and platelet counts were $<3{,}000/mm^3$ and $<100{,}000/mm^3$, respectively, on the planned day of treatment, therapy was postponed until recovery. The dose was reduced by 25% if grade 4 myelotoxicity was observed. Patients were taken off study if evidence of disease progression was observed during any course or if an objective response was not obtained after the second course. Treatment was discontinued if unacceptable toxicity developed. Responding patients continued to receive 254-S until either disease progression or the development of severe toxicity. Patients were considered to be evaluable for response if they completed at least one course of treatment.

Prior to treatment the following data were obtained: complete history and physical examination; determination of performance status; complete blood counts; blood chemistry, including renal and hepatic functions; urinalysis; chest X-ray; ECG; computerized tomographic (CT) chest scan; abdominal CT scan or echography; brain CT scan; and bone scintigraphy. The physical examination, complete blood counts, blood chemistry, and chest X-ray were repeated at least once a week.

Standard World Health Organization (WHO) response criteria were used to evaluate the antitumor effect of the drug [8]. A complete response (CR) was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks. A partial response (PR) was defined as a reduction by at least 50% of the product of the largest perpendicular diameters of one or more clearly measurable lesions or a reduction of >50% in evaluable disease lasting >4 weeks. No change (NC) included a regression of indicator lesions insufficient to meet the criteria for response, an increase of <25% in any measurable lesion, and the absence of new lesions. Progressive disease (PD) indicated an increase in any measurable lesion by >25% or a new area of malignant disease. Duration of response was measured from the initial day of treatment until the date of the first observation of progressive disease. Toxicity was also evaluated according to WHO criteria [21].

Results

Patient characteristics

A total of 68 patients with NSCLC were entered in this study between December 1987 and February 1990. In all, 68 patients were evaluable for response and 62, for toxicity; 6 subjects who received palliative irradiation were excluded for evaluation of toxicity. The characteristics of the patients are shown in Table 1. The median age of the 68 patients was 63 years (range, 20–79 years); 42 were men and 26, women. The majority of patients (54/68) had a performance status of 0 or 1, and 76% (52/68) had stage IV disease. The histological type of the tumor was adenocarcinoma in 52 patients, squamous-cell carcinoma in 9 cases, large-cell carcinoma in 5 subjects, and adenosquamous carcinoma in 2 patients. In all, 30 patients had received prior chemotherapy, 16 of whom had undergone intensive chemotherapy with CDDP. The median number of 254-S courses given was 2.2 (range, 1–5).

Response

The response rate for this study is shown in Table 2. No CR was obtained, but 10 PRs were observed. The duration of response ranged from 8 to 23 weeks (median, 15 weeks). The overall response rate was 14.7%, with a 95% confi-

Table 4. Hematological toxicity

	Count	Number of patients		
		No prior treatment	Prior treatment	Total
Leukocytes (/mm³)	≥4,000	15	13	28
	3,000–3,900	9	7	16
	2,000–2,900	9	6	15
	1,000–1,900	1	1	2
	<1,000	0	1	1
Hemoglobin (g/dl)	≥11.0	13	15	28
	9.5–10.9	14	5	19
	8 – 9.4	6	5	11
	6.5– 7.9	1	1	2
	< 6.5	0	2	2
Platelets (× 10⁴/mm³)	≥10.0	23	17	40
	7.5– 9.9	5	2	7
	5 – 7.4	4	4	8
	2.5– 4.9	2	1	3
	< 2.5	0	4	4

Table 5. Nonhematological toxicity

Toxicity	Incidence (%)	WHO grade			
		1	2	3	4
Nausea/vomiting	72.5	10	25	10	0
Diarrhea	12.9	6	2	0	0
Fever	24.2	15	1	0	0
Alopecia	17.7	6	5	0	0
Peripheral neuropathy	6.5	6	1	0	0
Allergy	6.2	2	0	0	2
Renal:					
Elevation of BUN	1.6	1	0	0	0
Elevation of creatinine	6.5	4	0	0	0
Hepatic:					
Elevation of GOT	17.7	9	1	1	0
Elevation of GPT	17.7	8	2	1	0

dence interval of 7.3%–25.4%. The response rate for previously untreated patients was 13.2% (5/38), with a 95% confidence interval of 4.4%–28.2%. There were five responders among previously treated patients, three of whom had received prior chemotherapy that included CDDP. One patient with squamous-cell carcinoma had previously responded, but the disease subsequently progressed after this subject had undergone seven courses of a regimen containing CDDP. Another subject with adenosquamous carcinoma had developed stable disease after receiving three courses of CDDP and vindesine. The other patient, who had adenocarcinoma, had undergone three courses of CDDP and vindesine as adjuvant chemotherapy after surgical resection. The duration of response in these three patients was 12, 14, and >11 weeks, respectively. Table 3 shows the response rate according to histological subtype. Overall, 4 of 9 cases of squamous-cell carcinoma, 5 of 52 patients with adenocarcinoma, and 1 of 2 subjects with adenosquamous carcinoma responded to 254-S. None of the five patients with large-cell carcinoma showed a response.

Toxicity

Details of the side effects observed during this treatment are summarized in Tables 4 and 5. Myelosuppression was the dose-limiting toxicity, with a median WBC nadir of 4,150/mm³ (range, 900–14,000/mm³) and a median platelet nadir of 125,000/mm³ (range, 8,000–263,000/mm³). Leukocytopenia of <3,000 WBC/mm³ and thrombocytopenia of <100,000 platelets/mm³ were observed in 18 (29%) and 22 cases (35%), respectively. Anemia (hemoglobin, <9.0 g/dl) was observed in 12 patients (19%). As expected, more severe myelosuppression was observed in patients who had received prior chemotherapy (Table 4).

Nausea and vomiting were observed in 73% of patients but were mild to moderate as compared with that seen during treatment with CDDP. In all, >85% of our patients complained of late emesis and anorexia; however, emesis induced by 254-S was controllable with antiemetic agents such as metoclopromide.

Renal toxicity was minimal and reversible. Diarrhea, fever, alopecia, and peripheral neuropathy were observed in 12.9%, 24.2%, 17.7%, and 6.5% of patients, respectively. Temporary elevations in GOT and GPT values were observed in 17.7% and 17.7% of cases, respectively.

Allergic reactions were observed in four patients; two of them had only urticaria, but anaphylactic shock occurred in the other two. Both of the patients with anaphylaxis had received their first course of treatment with no trouble, but in the second course they suddenly developed anaphylaxis during drug administration.

Discussion

CDDP has been used for the treatment of a wide variety of malignancies. It is one of the most active agents in non-small-cell lung cancer (NSCLC), with a single-agent response rate of approximately 15% [8]. We have previously reported a response rate of 14% for CDDP given as a single agent [4]. However, its serious side effects, including nephrotoxicity and gastrointestinal toxicity, require frequent modifications of treatment. Several platinum complexes have been synthesized and screened throughout the world in an attempt to develop analogs with antitumor activity equal to or greater than that of CDDP that produce lower toxicity.

254-S is a second-generation platinum complex that was introduced into clinical trial because it had higher antitumor activity and lower toxicity in mice as compared with CDDP [16]. We have reported that 254-S showed in vitro antitumor activity equivalent to that of CDDP against lung cancer cell lines [13].

In the present study 254-S showed antitumor activity against NSCLC that was similar to that of CDDP. Howev-

er, in patients who had not received prior chemotherapy, the response rate of 13.2% was unexpectedly low. Furuse et al. [5] reported that the response rate to 254-S was 19% (7/37) in patients with NSCLC and 25% in previously untreated patients. Their results are close to the predicted upper limit of the confidence interval for our trial. In their study, responses were observed in 1 of 23 patients with adenocarcinoma and in 6 of 14 patients with squamous-cell carcinoma. In the present study a similar pattern was observed, with responders including 5 of 52 patients with adenocarcinoma, 4 of 9 cases of squamous-cell carcinoma, and 1 of 2 patients with adenosquamous carcinoma. Response rates by histological subtype were almost the same in their study as in ours. In the case of CDDP, response rates were 17% for squamous-cell carcinoma, 15% for adenocarcinoma, and 4% for large-cell carcinoma [8]. Although the numbers of patients were small, 254-S may have a different response rate by histology when compared with CDDP.

Three responders had previously been treated with CDDP. In gynecological malignancies and head and neck cancers, 254-S has been reported to have activity against tumors refractory to CDDP [7, 12]. Nishimura et al. [12] and Inuyama et al. [7] have suggested that 254-S may be partially non-cross-resistant to CDDP, and our results are consistent with that hypotheses.

Myelosuppression was dose-limiting and occurred at a high incidence and degree of severity in patients who had received prior treatment with CDDP. Sasaki et al. [14] reported that the degree of thrombocytopenia was inversely correlated with the creatinine clearance rate in patients who received 254-S and suggested that the drug should be given carefully to patients with impaired renal function. We did not see significant renal toxicity. Other toxicities were mild to moderate and controllable, with the exception of anaphylaxis. It has previously been reported that allergic reactions occur following the administration of several platinum complexes [3, 9, 15, 19, 20]; these adverse reactions might be prevented by premedication with diphenhydramine [15, 20].

Clinical comparison of an analog with its parent compound is very complicated [10]. Our study did not address the question as to whether 254-S has an advantage over CDDP in the treatment of NSCLC. One option would be to perform a randomized comparison of the single agents; instead, we have chosen to conduct a trial of vindesine/CDDP vs vindesine/254-S in patients with advanced NSCLC.

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