Cancer Chemother Pharmacol (1992) 31: 187–192

Cancer Chemotherapy and Pharmacology

Phase II study of *cis*-diammine(glycolato)platinum, 254-S, in patients with advanced germ-cell testicular cancer, prostatic cancer, and transitional-cell carcinoma of the urinary tract

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Received 27 February 1992/Accepted 10 August 1992

Summary. A multicenter cooperative study was conducted to evaluate the clinical efficacy and safety of *cis*-diammine(glycolato)platinum (254-S), a second-generation anticancer platinum complex, in the treatment of genitourinary cancers. 254-S was given i.v. at 100 mg/m^2 at 4-week intervals. As a result, 2 complete responses (CRs) and 8 partial responses (PRs) were obtained in 35 patients with transitional-cell carcinoma (TCC) of the urinary bladder or pyeloureter, 3 PRs were obtained in 16 subjects with prostatic cancer, and 6 CRs and 6 PRs were obtained in 15 patients with testicular cancer, generating objective response rates of 28.6% [95% confidence interval (CI), 14.6%–46.3%], 18.8% (95% CI, 4.0%–45.6%), and 80.0% (95% CI, 51.9%–95.7%), respectively. Bone marrow suppression was the dose-limiting toxicity, although it was reversible. Although no hydration was performed in approx. 40% of the patients, the incidence of nephrotoxic effects was low and most of those encountered were mild, the exception being one patient who showed severe renal insufficiency after the first treatment. Nausea and vomiting occurred in approx. 70% of the patients, but most gastrointestinal toxicities were controlled without antiemetic treatment. In addition, liver-function impairment was rarely observed. We conclude that 254-S is a promising cisplatin analogue for the treatment of genitourinary cancers and is worthy of further investigation in large-scale, randomized comparative studies with other platinum derivatives in both single-agent and combination regimens.

Introduction

Malignancies in urogenital organs show various sensitivities to anticancer chemotherapy. For example, cisplatin-based combination chemotherapy shows very strong antitumor activity against testicular cancer and produces an obvious effect on the survival of patients afflicted with this cancer [3]. This type of chemotherapy is partially effective against transitional-cell carcinoma (TCC) of the urinary tract [12] but does not produce a favorable antitumor effect in patients with prostatic cancer [1]. In addition, cisplatin's nephrotoxicity and gastrointestinal toxicity reduce its clinical utility in combination chemotherapy. Thus, for the purpose of improving the efficacy and safety of chemotherapy for urological malignancies, a high priority has been placed on the development of a new anticancer agent.

cis-Diammine(glycolato)platinum (254-S; NSC375101D), a second-generation platinum complex synthesized by Shionogi & Co., Ltd. (Osaka, Japan) [11], has shown higher water solubility and superior antitumor activity and has produced less nephro- and gastrointestinal toxicity as compared with cisplatin in nonclinical studies [11, 13, 14]. In the phase I clinical study, bone marrow suppression (thrombocytopenia and leukopenia, in particular) was regarded as the major dose-limiting factor, although no significant nephrotoxicity was found, and the optimal dose for phase II study was determined to be 100 mg/m^2, given at 4-week intervals [9, 10]. On the basis of the favorable results obtained in the phase I clinical study, we conducted a phase II clinical study of 254-S in the treatment of urological malignancies, including TCC of the urinary tract, prostatic cancer, and testicular cancer.

Patients and methods

Between June 1987 and August 1991, 42 patients with TCC of the urinary tract, 24 individuals with prostatic cancer, and 16 patients with testicular cancer were treated with 254-S alone at the institutions comprising the 254-S Urological Cancer Study Group (Table 1).

The drug was given at a dose of 100 mg/m^2 by i.v. infusion over 60 min after being dissolved in 300 ml 5% xylitol; dose modification within 15% deviation (85–115 mg/m^2) was allowed, depending on the patient's condition. In principle, the treatment with 254-S was repeated every 4 weeks at least two times; patients who showed a complete response (CR), a partial response (PR), or disease progression (PD) after

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Table 1. The 254-S Urological Cancer Study Group

Department of Urology:	
Hokkaido University	T. Koyanagi
Tohoku University	S. Orikasa
University of Chiba	J. Shimazaki
University of Tokyo	Y. Aso (Co-chairman)
Keio University	H. Tazaki
Nippon Medical College	M. Akimoto
Jikei University School of Medicine	T. Machida
Cancer Institute Hospital	T. Kawai
Kanazawa University	H. Hisazumi
Nagoya City University	K Otaguro
Kyoto University	O. Yoshida (Co-chairman)
Osaka University	T. Sonoda and A. Okuyama
Center for Adult Diseases, Osaka	T. Kotake
Kobe University	S. Kamidono
Okayama University	H. Ohmori
Hiroshima University	T. Usui

the first treatment were accepted for the antitumor-effect analysis by the study committee, even if the second treatment was not carried out.

When deemed necessary by the investigator, i. v. hydration was performed to maintain daily urinary excretion of >1,500 ml during the 5 days after drug administration, taking into account the patient's condition. If WBC and platelet counts had not recovered to values of 3,000/mm^3 and 100,000/mm^3, respectively, by the 4th week after administration, the next treatment was postponed until such recovery was noted. If these WBC and platelet values had not been obtained by week 6 after drug administration, the next dose was reduced or treatment was discontinued according to the following criteria: 70,000/mm^3 $\leq$ platelet <100,000/mm^3 and WBC $\geq$3,000/mm^3 [25% dose reduction (75 mg/m^2)]; 50,000/mm^3 $\leq$ platelet <70,000/mm^3 or 2,000/mm^3 $\leq$ WBC <3,000/mm^3 [50% dose reduction (50 mg/m^2)]; and platelet <50,000/mm^3 or WBC <2,000/mm^3 (treatment discontinued).

All evaluable patients had histologically confirmed and bidimensionally measurable disease. They had an estimated life expectancy of >8 weeks, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–3, a WBC of >3,000/mm^3, a platelet count of >100,000/mm^3, a hemoglobin level of >9.0 g/dl, a serum creatinine value of <2.0 mg/dl, creatinine clearance of $\geq$60 ml/min, or other laboratory data of $\leq$2 times the normal limit. In addition, they showed no evidence of apparent cardiovascular disease, serious active infections, or other serious complications. None of the patients had received myelosuppressive chemotherapy within 4 weeks prior to treatment with 254-S. All of the patients with prostatic cancer had previously undergone conventional endocrine therapy and had become endocrine-insensitive.

Prior to study entry, informed consent was obtained from all patients. Prior to the initiation of 254-S treatment, patients were assessed by means of ultrasound examinations, computerized axial tomographic scans, bone scintigraphy, X-ray examinations, and serum marker assays such as those for α-fetoprotein and β-human chorionic gonadotropin (for testicular cancer) as well as radioimmunoassays for prostatic acid phosphatase (PAP, for prostatic cancer). Tumor response to the chemotherapy was assessed by repeat examinations and was evaluated according to the criteria of the Japanese Urological Association [6], which are almost equivalent to the WHO criteria [15].

Results

Patients' characteristics

Of the 42 patients with TCC of the urinary tract, 35 were evaluable for tumor response (21 with bladder cancer and 14 with pyeloureteral cancer) and 38 were evaluable for safety. Of the 24 patients with prostatic cancer, 16 were evaluable for tumor response and 20, for safety. Of the 16 patients with testicular cancer, 15 were evaluable for both tumor response and safety (2 seminomas and 13 nonseminomas). Characteristics of the 66 patients who were evaluable for tumor response are shown in Table 2. In all, 16 patients were excluded from the antitumor-effect analysis by the Study Committee; the reasons for their exclusion, the 254-S doses and numbers of courses given, and the tumor response obtained are summarized in Table 3.

Table 2. Characteristics of the patients evaluated for tumor response

	TCC of the urinary tract	Prostate cancer	Testicular cancer
Evaluable patients (*n*)	35	16	15
Mean age (years)	65.2 (range, 37–79)	67.3 (range, 54–80)	33.5 (range, 20–61)
Sex:			
M	26	16	15
F	9	0	0
ECOG performance status:			
0	11	4	11
1	12	6	2
2	7	1	2
3	4	4	0
4	1	1	0
Metastasis:			
No	9	3	0
Yes	26	13	15
Prior chemotherapy:			
No	22	7	13
Yes, with CDDP	9	2	2
Yes, without CDDP	4	7	0
Dose (mg/m^2):			
85– 95	4	0	1
85–105	29	16	12
85–115	2	0	2
Hydration:			
No	16	5	5
Yes	19	11	10

Two patients with a PS of 4 were judged to be eligible as subjects in this study since their PS levels were regarded as false PS 4 scores resulting from bone metastasis. A total of 24 patients (36.4%) had undergone prior chemotherapy, including 13 who had (26.5%) been treated with cisplatin-based regimens. In all, 9 patients (13.6%), including 6 with TCC and 3 with testicular cancer, were treated at modified doses with $\pm$5%–$\pm$15% deviation. Hydration was performed in 60.6% of the patients.

Tumor response

The tumor responses obtained in the 66 evaluable patients are summarized in Table 4. Of the 35 patients with TCC of the urinary tract, 2 with bladder cancer achieved a CR and 2 with pyeloureteral cancer as well as 6 with bladder cancer showed a PR, resulting in a 28.6% response rate (14.3% for pyeloureteral cancer and 38.1% for bladder cancer) with a

Table 3. Summary of the patients excluded from evaluation

Disease	Reasons for exclusion	Number of patients	254-S administration [dose (mg/m^2) × number of courses]	Tumor response
TCC of the urinary tract	Anemia	1	70 × 1	NC
	Prior chemotherapy within 4 weeks	1	96 × 1	NC
	Inadequate evaluation	2	99 × 1	NE
			101 × 1	NE
	Inadequate dose of 265-S	2	60 × 2	NC
			82 × 3	PR
	Insufficient administration of 254-S	1	102 × 1	NC
Prostatic cancer	Age above the higher limit (84 years)	1	102 × 1	PD
	No histological diagnosis	1	100 × 3	PD
	Inadequate evaluation	1	102 × 1	NC
	Inadequate dose of 254-S	2	70 × 3	NC
			68 × 2	PD
	Discontinuation of treatment due to adverse effects	3	85 × 1	NE
			99 × 1	NE
			101 × 1	NE
Testicular cancer	Insufficient renal function (serum creatinine, >2.0 mg/dl)	1	103 × 1	NC

NE, Not evaluable

Table 4. Overall tumor response

Disease	Number of patients	Tumor response				Response rate[a] (CR+PR)
		CR	PR	NC	PD	
TCC of the urinary tract	35	2	8	16	9	28.6% (14.6%–46.3%)
Pyeloureter	14		2	7	5	14.3% (1.8%–42.8%)
Bladder	21	2	6	9	4	38.1% (18.1%–61.6%)
Prostatic cancer	16		3	7	6	18.8% (4.0%–45.6%)
Testicular cancer	15	6	6		3	80.0% (51.9%–95.7%)
Seminoma	2		1		1	50.0% (1.3%–98.7%)
Non-seminoma	13	6	5		2	84.6% (54.6%–98.1%)
Totals	66	8	17	23	18	37.9% (26.2%–50.7%)

[a] Values in parentheses represent 95% confidence intervals

95% confidence interval (CI) of 14.6%–46.3%. Of the 16 patients with prostatic cancer, 3 showed a PR, for an 18.8% response rate (95% CI, 4.0%–45.6%). All of the patients with prostatic cancer had adenocarcinoma and had been resistant to conventional endocrine therapy. Of the 15 patients with testicular cancer, 6 with nonseminomatous cancer achieved a CR and 1 with seminoma as well as 5 with non-seminoma showed a PR, presenting an 80% response rate (95% CI, 51.9%–95.7%). Among the three patients with testicular cancer who were treated with modified doses of 254-S, a CR was obtained in the one who received 106 mg/m^2 and a PR was obtained in one who was given 86 mg/m^2 and in the one who was treated at 107 mg/m^2.

Response rates as a function of the site of disease

Table 5 summarizes the response rates as a function of the location of the disease. In patients with TCC, the primary tumor (40.0%) and lung metastases (37.5%) responded well as compared with the other metastatic sites. In patients with prostatic cancer, lung metastases showed the most favorable response (50%), whereas seven bone metastases failed to show any positive response. Of the 16 patients with prostatic cancer who had evaluable lesions, 10 showed an elevated serum PAP level prior to treatment, and only 1 patient showed a decrease of ≥50% in PAP (PR) after treatment. In patients with testicular cancer, metastases in the lung and lymph node responded well; however, two liver metastases did not respond at all.

Response rates in relation to prior cisplatin-based combination chemotherapy

Table 6 summarizes the response rates as a function of prior chemotherapy. Of the 13 patients who had previously undergone cisplatin-based treatment, only 1 with TCC showed a favorable response (PR), generating a 7.7% response rate (95% CI, 0.2%–36.0%). On the other hand, of the 53 patients who had not previously received cisplatin (no prior chemotherapy or prior non-cisplatin-based chemotherapy), 24 responded to 254-S, for a 45.3% response

Table 5. Tumor responses as a function of the site of disease

Disease site	Number of patients	Tumor response				Response rate[a] (CR+PR)
		CR	PR	NC	PD	
TCC of the urinary tract:						
Primary	15		6	7	2	40.0% (16.3%–67.7%)
Lung	8	2	1	3	2	37.5% (8.5%–75.5%)
Liver	2			1	1	–
Bone	5		1	3	1	20.0% (0.5%–71.6%)
Lymph node	12	1	1	7	3	16.7% (2.1%–48.4%)
Prostatic cancer:						
Primary	14		4	10		28.6% (8.4%–58.1%)
Lung	2	1			1	50.0% (1.3%–98.7%)
Bone	6			4	2	–
Lymph node	3	1		2		33.3% (0.8%–90.6%)
Prostatic acid phosphatase	10		1	4	5	10.0% (0.3%–44.5%)
Testicular cancer:						
Lung	8	3	3		2	75.0% (34.9%–96.8%)
Liver	2				2	–
Lymph node	9	2	5	2		77.8% (40.0%–97.2%)

[a] Values in parentheses represent 95% confidence intervals

Table 6. Tumor responses as a function of prior chemotherapy

Disease	Prior chemotherapy	Number of patients	Tumor response				Response rate[a] (CR+PR)
			CR	PR	NC	PD	
TCC of the urinary tract	No	22		7	12	3	31.8% (13.9%–54.9%)
	Yes, with CDDP	9		1	3	5	11.1% (0.3%–48.3%)
	Yes, without CDDP	4	2		1	1	50.0% (6.8%–93.2%)
Prostatic cancer	No	7		1	2	4	14.3% (0.4%–57.9%)
	Yes, with CDDP	2		2	2		
	Yes, without CDDP	7		2	3	2	28.6% (3.7%–71.0%)
Testicular cancer	No	13	6	6		1	92.3% (64.0%–99.8%)
	Yes, with CDDP	2				2	–
	Yes, without CDDP	–					–
Totals	Prior CDDP treatment	13		1	5	7	7.7% (0.2%–36.0%)
	No prior CDDP treatment	53	8	16	18	11	45.3% (31.6%–59.6%)

[a] Values of parentheses represent 95% confidence intervals

rate (95% CI, 31.6%–59.6%), including 7 PRs in TCC patients who had not received prior chemotherapy and 2 CRs in those who had previously undergone non-cisplatin-based chemotherapy, 1 PR in a patient with prostatic cancer who had not received prior chemotherapy and 2 PRs in patients with prostatic cancer who had previously undergone cisplatin-based chemotherapy, and 6 CRs and 6 PRs in patients with testicular cancer who had not received prior chemotherapy.

Response rates as a function of PS

As shown in Table 7, all patients with prostatic cancer who responded to 254-S belonged to the good-risk group (PS 0 or 1), generating a 30.0% response rate (95% CI, 6.7%–65.3%). However, in patients with TCC and testicular cancer, favorable response rates were also obtained in the poor-risk (PS 2 or 3) group [TCC: 4 PRs/12, 33.3% (95% CI, 9.9%–65.1%); testicular cancer: 1 PR/2, 50.0% (95% CI, 1.3%–98.7%)].

Toxicity

Details of the side effects observed during the treatment are summarized in Table 8. Toxicity was graded according to the WHO grading system [15].

Bone marrow suppression seemed to be a major dose-limiting factor. Among 73 patients who were evaluable for toxicity, leukopenia occurred in 46 (63.0%); thrombocytopenia, in 51 (69.9%); and anemia, in 40 (54.8%). The incidence of grade 3 or 4 bone marrow toxicity was 23.3% for leukopenia, 37.0% for thrombocytopenia, and 23.3% for anemia.

Table 7. Tumor responses as a function of PS

Disease		PS	Number patients	Tumor response				Response rate[a] (CR+PR)
				CR	PR	NC	PD	
TCC of the urinary tract	Good risk	0–1	23	2	4	12	5	26.1% (10.2%–48.4%)
	Poor risk	2–3	12		4	4	4	33.3% (9.9%–65.1%)
Prostatic cancer	Good risk	0–1	10		3	4	3	30.0% (6.7%–65.3%)
	Poor risk	2–3	6			3	3	–
Testicular cancer	Good risk	0–1	13	6	5		2	84.6% (54.6%–98.1%)
	Poor risk	2–3	2		1		1	50.0% (1.3%–98.7%)

[a] Values in parentheses represent 95% confidence intervals

Table 8. Summary of the adverse effects observed during the present study

Adverse effects	Number of patients evaluated for toxicity	Number of patients experiencing toxicity	Incidence	WHO grade			
				1	2	3	4
Leukopenia	73	46	63.0%	13	16	15	2
Thrombocytopenia	73	51	69.9%	11	12	10	18
Anemia	73	40	54.8%	10	13	16	1
GOT ↑	73	10	13.7%	9	1	0	0
GPT ↑	73	14	19.2%	11	3	0	0
Serum creatinine ↑	73	11	15.1%	5	5	0	1
BUN ↑	73	13	17.8%	8	2	0	3
Nausea and vomiting	73	56	76.7%	15	30	11	0
Anorexia	73	58	79.5%	22	23	13	0
Diarrhea	73	3	4.1%	1	2	0	0
Hearing disorder	73	9	12.3%	9	0	0	0
Alopecia	73	10	13.7%	7	3	0	0
Malaise	73	5	6.8%	1	2	2	0

Although no hydration was performed in approx. 40% of the patients, nephrotoxicity was minimal and reversible in most cases, the exception being one patient who showed irreversible, severe renal insufficiency; this patient (72 years old, TCC, PS 3), who had previously been treated with cisplatin, died of severe renal insufficiency 7 days after the initial administration of 254-S at a dose of 150 mg (100 mg/m^2) without hydration.

Hepatotoxicity was encountered in a very limited number of patients. Nausea and vomiting occurred in 76.7% of the patients, although the incidence of a toxicity of WHO grade 3 was only 15.1%. Anorexia was observed in 79.5% of the patients. A hearing disturbance of WHO grade 1 was found in 12.3% of the patients. No allergic reaction was observed in this study.

Discussion

Cisplatin has been recognized to be one of the most useful anticancer agents in the treatment of many malignancies and has been used as a main component of various regimens in combination chemotherapy for genitourinary cancers [1, 3, 12]. However, serious side effects of cisplatin, including nephrotoxicity and gastrointestinal toxicity, require unfavorable modifications of the treatment with this agent. Carboplatin, a cisplatin analogue, has produced improved toxicity and favorable antitumor effects, resulting in response rates of 18.4% for TCC of the urinary tract and 47.6% for testicular cancer in a phase II trial in Japan [2], but has failed to produce positive responses in patients with prostatic cancer [8].

254-S, a second-generation platinum complex, has shown higher antitumor activity and lower toxicity as compared with cisplatin in nonclinical studies [11, 13, 14]. In the present phase II clinical study in genitourinary cancers, including TCC of the urinary tract, prostatic cancer, and testicular cancer, the compound produced favorable antitumor effects. High rates of tumor response were obtained in patients who had not received prior chemotherapy (31.8% for TCC and 92.3% for testicular cancer), and two CRs (TCC) and two PRs (prostatic cancer) were also observed in patients who had previously undergone non-cisplatin-based chemotherapy. On the other hand, there was only one responder among the patients who had received prior cisplatin-based chemotherapy; thus, we could not confirm the results of other studies in which 254-S produced excellent antitumor effects, even in such patients, indicating a lack of complete cross-resistance between cisplatin and 254-S [4, 5].

Although it has been demonstrated that cisplatin-based chemotherapy is highly effective in the treatment of testic-

ular cancer, we thought that the use of 254-S as monotherapy in patients with testicular who had not previously received cisplatin was justified for the following reasons:

1. 254-S is a cisplatin analogue that has shown a similar spectrum of equivalent or higher antitumor activity in comparison with cisplatin in nonclinical and clinical studies. Therefore, it was also expected to produce comparable or superior antitumor effects against testicular cancer and to cause less toxicity in comparison with the parent drug.

2. Additionally, since this product is a cisplatin analogue, a limited tumor response was expected in patients who had undergone prior cisplatin-based chemotherapy due to presumed cross-resistance. Therefore, we deemed it necessary to conduct the study in patients who had not previously received cisplatin so as to confirm the efficacy of 254-S against testicular cancer.

3. Moreover, the protocol also stated that treatment with 254-S could be changed to cisplatin-based chemotherapy if the patient failed to respond to 254-S. Among 13 patients with testicular cancer who had not previously undergone chemotherapy, only 1 developed PD; a CR was subsequently obtained by changing the 254-S treatment to a 5-drug combination regimen containing cisplatin.

In the assessment of tumor response as a function of PS, response rates were high in the good-risk group (PS 0 or 1). However, four PRs and one PR were obtained in patients with TCC and testicular cancer, respectively, even in the poor-risk group (PS 2 or 3); these results may have been related to the low toxicity of 254-S, which enabled the administration of this compound at doses high enough to produce a PR, even in patients with such low PS scores.

As judged from the results of this study, the nephrotoxicity induced by 254-S seemed to be milder and to occur less frequently than that caused by cisplatin; similar findings have also been obtained in other clinical studies of this compound [4, 5, 7]. However, due to the death of one patient in the course of the present study, we suggest that during treatment with 254-S, careful monitoring be required for patients with low PS scores who have previously undergone cisplatin therapy. Other toxic effects, including gastrointestinal toxicity, were mild to moderate and tolerable.

Thus, we conclude that 254-S is a promising cisplatin analogue for the treatment of TCC of the urinary tract, prostatic cancer, and testicular cancer and that it warrants further investigation in large-scale, randomized comparative studies with other platinum derivatives in both single-agent and combination regimens.

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