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Phase II trial of carboplatin in patients with advanced germ-cell testicular tumors and transitional cell carcinomas of the urinary tract

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Summary. Carboplatin, an analog of cisplatin, was evaluated in a phase II study involving 25 patients with advanced testicular tumor and 45 with transitional cell carcinoma (TCC) of the urinary tract; 21 and 38 cases, respectively, were evaluable for response. Prior treatment with cisplatin-based chemotherapy had occurred in 7 of the testicular cancer patients and in 11 with TCC. The response rate (complete + partial response) in testicular tumors was 47.6%. The best response rate was observed in seminomas (70.0%), whereas the response rate in nonseminomas was 27.3%. The seminoma patients had mainly stage IIIA or less than IIIA disease, with metastatic lesions restricted to the lymph nodes. Three responses were seen in patients previously treated with cisplatin. In TCC, the response rate was 18.4%. Good-risk patients were treated with a dose of 400 mg/m^2 every 4 weeks, whereas poor-risk patients received a lower dose of 300 mg/m^2. The response rates for good-risk patients were 50.0% in testicular lesions and 26.1% in TCC. For poor-risk patients, the response rates were 40.0% and 6.7%, respectively. Carboplatin was well tolerated, with no significant renal impairment or ototoxicity detected. Nausea and vomiting were experienced by 51.7% of patients, but the severity was low; half of these patients demonstrated WHO grade I toxicity. However, myelosuppression was severe. In conclusion, carboplatin demonstrated activity in both testicular tumors and TCC and is worthy of further study, especially in combination with other active drugs.

Cisplatin plays a major role in various combinations of chemotherapy in patients with advanced germ-cell testicular tumors (testicular tumors) and patients with advanced transitional cell carcinoma of the bladder, pelvis, and ureter (TCC of the urinary tract) [2, 9]. However, it is an extremely toxic drug, causing severe nausea and vomiting as well as renal and auditory impairments. Carboplatin is a second-generation cisplatin analog with a different toxicity profile. A phase I study carried out on carboplatin in Japan [5] showed that the major dose-limiting factors were thrombocytopenia and granulocytopenia. Gastrointestinal toxicities such as nausea and vomiting were tolerable, and no significant renal impairment was obseved without hydration. The optimal dose for phase II trials was recommended to be 300 mg/m^2 every 4 weeks in poor-risk patients and 400 mg/m^2 in good-risk patients. On the basis of the results of the phase I study, we conducted a phase II study on urological malignancies. The results of a single-drug administration of carboplatin to patients with advanced testicular cancer and TCC of the urinary tract are reported.

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Patients and methods

Between January 1986 and December 1987, 25 patients with advanced testicular tumors (mean age, 29.9 years) and 45 patients with TCC of the urinary tract (mean age, 67.1 years) were treated with carboplatin alone at the institutions comprising the Carboplatin Study Group (Table 1). The drug was given at a dose of 400 mg/m^2 every 4 weeks for patients whose performance status (PS) was 0–1, and 300 mg/m^2 was given every 4 weeks to patients whose PS

Table 1. The Carboplatin Study Group on Urological Cancer (Chairmen: T. Niijima and H. Tazaki)

Departments of Urology:	
Hokkaido University	(T. Koyanagi)
Tohoku University	(S. Orikasa)
Yamagata University	(K. Suzuki)
University of Tsukuba	(K. Koiso)
Tochigi Cancer Center Hospital	(M. Hagiwara)
Saitama Cancer Center Hospital	(K. Tari)
National Cancer Center Hospital	(T. Kakizoe)
The Jikei University School of Medicine	(T. Machida)
National Medical Center Hospital	(K. Fujita)
Keio University	(H. Tazaki)
Tokyo Medical and Dental University	(H. Oshima)
University of Tokyo	(Y. Aso)
Nihon Medical College	(M. Akimoto)
National Second Tokyo Hospital	(S. Kimura)
Cancer Institute Hospital	(T. Kawai)
Yokosuka Municipal Hospital	(Y. Satomi)
Niigata Prefectural Cancer Center Hospital	(Y. Sakata)
Hamamatsu University School of Medicine	(K. Kawabe)
Nagoya Memorial Hospital	(T. Fujita)
Kyoto University	(O. Yoshida)
Osaka University	(T. Sonoda)
The Center for Adult Diseases, Osaka	(T. Kotake)
Okayama University	(H. Ohmori)
Kyushu University	(J. Kumazawa)

was 2–3. The drug was given for at least two cycles unless the disease was progressive.

All evaluable patients had histologically confirmed and bidimensionally measurable disease. They had an estimated life expectancy of >12 weeks, a performance status of 0–3, a WBC count >4,000/mm^3, a platelet count >100,000/mm^3, hemoglobin >11 g/dl, and serum creatinine <1.2 mg/dl or creatinine clearance >60 ml/min. None of the patients had received myelosuppressive chemotherapy within the 4 weeks preceding the use of carboplatin.

Prior to chemotherapy, the patients were assessed by means of ultrasonographic examinations, computerized axial tomography (CAT) scans, lymphography, and serum marker assays such as those for α-fetoprotein and β-human chorionic gonadotropin. The response to chemotherapy was assessed by repeating the examinations and evaluated according to the Japanese evaluation criteria proposed by the Koyama-Saito Study Group [3], which are equivalent to the WHO criteria [12].

Results

Of the 25 patients with testicular cancer, 21 (84%) were evaluable for response (10 seminoma and 11 nonseminoma) and toxicity. Of the 45 patients with TCC of the urinary tract, 38 (84%) (27 bladder, 4 bladder plus renal pelvis and/or ureter, 6 renal pelvis and/or ureter, and one urethra) were evaluable for response and 39 (85%) were evaluable for toxicity. The reasons for exclusion from the evaluation are summarized in Table 2.

Response of testicular tumor

Of the patients with testicular cancer, one showed a complete response (CR); nine, partial responses (PRs); three, minor responses (MRs); four, no change (NCs); and four, progressive disease (PDs). The response rate (CR+PR) was 47.6%. As shown in Table 3, the patients with seminoma showed a favorable response rate compared with those with nonseminoma (70.0% vs 27.3%). This may partially depend on the difference in the extent of the disease; that is, 8 of 10 seminoma were restricted to the lymph nodes, whereas 9 of 11 nonseminoma included pulmonary or liver metastases (Table 4).

Table 2. Summary of the patients excluded from evaluation

Patient group	Excluded from evaluation of response
Testicular tumor	1. combined with other chemotherapy 2. age, 6 years 3. no bidimensional lesion 4. no bidimensional lesion
TCC of the urinary tract	1. combined with other chemotherapy 2. PS 4 3. active triple cancer 4. combined with radiation therapy 5. no bidimensional lesion 6. no bidimensional lesion 7. no bidimensional lesion

Response of TCC of the urinary tract

Of the patients with TCC of the urinary tract, 1 showed a CR; 6, PRs; 3, MRs; 14, NCs; and 14, PDs. The response rate (CR+PR) was 18.4%. In Table 5, the responses at each organ site are summarized. There was no difference in the response rate as a function of the site of the primary tumor, although bladder tumors were most frequently observed.

Response rates as a function of the location of the disease

The response rates as a function of the location of the disease are summarized in Table 6. In the testicular tumors, lymph node metastases responded better than pulmonary metastases. In TCC of the urinary tract, lymph node and pulmonary metastases showed favorable responses to carboplatin treatment, whereas other sites of involvement, such as liver and bone metastases as well as primary tumors, showed a very poor response.

Response rates in relation to prior cisplatin-based combination chemotherapy

Table 7 summarizes the response rates as a function of prior cisplatin-based chemotherapy. Of the 21 testicular tumor cases, 7 had received prior cisplatin-based combination chemotherapy: cisplatin + etoposide + peplomycin in 2 cases (1 NC and 1 PR), cisplatin + vinblastin + bleomycin in 2 cases (2 PRs), cisplatin + etoposide + bleomycin in 1 case (NC), cisplatin + vinblastin + peplomycin in 1 case (PR), and cisplatin + adriamycin + ifosphamide in 1 case (PR). Of these 7, 3 cases achieved PR with the present carboplatin treatment. In TCC of the urinary tract, 11 cases had received prior cisplatin-based combination chemotherapy, and none achieved PR with carboplatin.

Response rates as a function of PS

As shown in Table 8, in both malignancies a majority of the good responders belonged to the good-risk patient group, with a PS of 0 or 1. CR was achieved in only 1 of 15 cases with TCC of the urinary tract b belonging to the poor-risk patient group, with a PS of 2 or 3.

Table 3. Response rates in testicular tumor patients

	No. of patients	Response[a]					Response rate (%) (CR+PR)
		CR	PR	MR	NC	PD	
Seminoma	10	0	7	2	1	0	70.0
Nonseminoma	11	1	2	1	3	4	27.3
Total	21	1	9	3	4	4	47.6

[a] CR, complete response; PR, partial response; MR, minor response; NC, no change; PD, progressive disease

Effects on serum tumor markers in testicular tumor cases

Each of 14 patients with a testicular tumor showed an elevated serum α-fetoprotein (AFP) value before the administration of carboplatin. In three of them the AFP level returned to normal, in six cases there was an improvement of ≥50%, and in three the AFP either improved by <50% or showed an elevation of <25%. Thus, 64.3% (9 of 14) showed an improvement in AFP value of ≥50% of the pretreatment value.

In addition, 14 of the testicular tumor patients showed an elevated serum β-human chorionic gonadotropin (HCG-β) value. Three patients showed a complete reduction of HCG-β after treatment with carboplatin, whereas in seven the HCG-β value improved by ≥50%. In three cases this value increased by >25%. Thus, 71.4% (10 of 14) showed an improvement in HCG-β value of ≥50%. Nine patients showed simultaneous elevations in both markers before carboplatin treatment; of these, six showed an improvement in both markers of ≥50%.

Table 4. Clinical stages of testicular tumor patients

Stage[a]	IIA	IIB	IIIA	IIIB	IIIC
Seminoma	2	3	3	2	
Nonseminoma			2	8	1

[a] IIA, regional lymph nodes <5 cm in maximal diameter; IIB, regional lymph nodes >5 cm in maximal diameter; IIIA, extraregional lymph nodes; IIIB; pulmonary metastases; IIIC, distant metastases other than pulmonary (cited from the general rules for clinical and pathological studies on testicular tumors, proposed by the Japanese Urological Association and the Japanese Pathological Society in 1984)

Adverse effects

Table 9 summarizes the adverse effects of carboplatin treatment. Myelosuppression was the major toxic effect. Of 31 cases of leukopenia, 11 (35.5%) were rated as WHO

Table 5. Response rates in patients with TCC of the urinary tract

Site of TCC	No. of patients	Response					Response rate (%) (CR+PR)
		CR	PR	MR	NC	PD	
Bladder tumor	27	1	4	2	10	10	18.5
Bladder and renal pelvis and/or ureter	4	0	1	1	1	1	
Renal pelvis and/or ureter	6	0	1	0	3	2	16.7
Urethra	1	0	0	0	0	1	
Total	38	1	6	3	14	14	18.4

Table 6. Response rates as a function of the location of disease

	No. of patients	Response					Response rate (%) (CR+PR)
		CR	PR	MR	NC	PD	
Testicular tumor							
pulmonary metastases	11	2	1	1	4	3	27.3
lymph node metastases	14	1	7	2	2	2	57.1
TCC							
primary	19	0	1	0	11	7	5.3
pulmonary metastases	12	0	3	1	5	3	25.0
liver metastases	3	0	0	1	1	1	0
bone metastases	5	0	0	0	2	3	0
lymph node metastases	10	3	0	1	2	4	30.0

Table 7. Response rates as a function of prior cisplatin-based chemotherapy

	No. of patients	Response					Response rate (%) (CR+PR)
		CR	PR	MR	NC	PD	
Testicular tumor							
prior cisplatin-based combination chemotherapy	(−) 14	1	6	2	2	3	50.0
	(+) 7	0	3	1	2	1	42.9
TCC							
prior cisplatin-based combination chemotherapy	(−) 27	1	6	3	7	10	25.9
	(+) 11	0	0	0	7	4	0

Table 8. Response rates as a function of performance status

	No. of patients	Response					Response rate (%) (CR+PR)
		CR	PR	MR	NC	PD	
Testicular tumor							
good risk (PS 0–1)	16	1	7	3	4	1	50.0
poor risk (PS 2–3)	5	0	2	0	0	3	40.0
TCC							
good risk (PS 0–1)	23	0	6	2	7	8	26.1
poor risk (PS 2–3)	15	1	0	1	7	6	6.7

Table 9. Toxicity of carboplatin (testicular tumor + TCC)

	No. of patients	Incidence (%)	WHO grade			
			1	2	3	4
Leukopenia	31	51.7	3	17	10	1
Thrombocytopenia	32	54.2	9	8	6	9
Anemia	18	30.0	3	2	11	2
Elevation of						
GOT	9	15.3	7	2	0	0
GPT	10	16.9	8	2	0	0
Elevation of serum creatinine	1	1.7	1	0	0	0
Nausea and vomiting	31	51.7	15	14	2	0
Diarrhea	2	3.3	1	1	0	0
Alopecia	1	1.6	0	1	0	0

grade 3 or 4, whereas 15 (46.9%) of 32 cases of thrombocytopenia were WHO grade 3 or 4.

The median number of days to the nadir of the leukocyte count (2,300/mm^3; range, 500–3,200) and thrombocyte count (55,000/mm^3; range, 4,000–92,000) were 17 (range, 2–30) and 19 (range, 13–35), respectively. Recovery from the nadir required 10 (range, 3–26) and 7 days (range, 1–21), respectively.

There was a slight elevation in transaminase levels. As for renal toxicity, only one case showed grade 1 serum creatinine elevation, which returned to normal during the continuous carboplatin therapy. Nausea and vomiting were observed in 31 patients (51.7%); however, 29 (93.5%) were WHO grade 1 or 2. Diarrhea occurred in two patients and alopecia in one.

Discussion

The high response rates currently obtained with cisplatin-based combination chemotherapy of testicular tumors [2] and TCC of the urinary tract [9] cause strategic problems in the investigation of new drugs in previously nontreated patients. If the drug is an analog with a high likelihood of cross-resistance and single-agent phase-II investigation is contemplated, the problem becomes more difficult. Because the expected response rate may be lower than that established for combination chemotherapy, the number of cases studied in phase-II trials must be decreased.

At present, the Ministry of Health and Welfare of Japan generally recommends studying over 30 cases in a disease-oriented phase II study, if the results are to be included in the application for a product license. This number was determined on the basis of an assumption of a response rate of about 20% [11]. In this context, 38 cases of TCC of the urinary tract is an appropriate number for evaluating the effectiveness of carboplatin, which had a response rate of 18.4%; with these numbers, the 95% confidence limit ranged from 7.7% to 34.3%. On the other hand, the testicular tumor cases responded well to carboplatin, showing a 47.6% response rate; the 95% confidence limit ranged from 25.7% to 70.2%, although the number of cases tested was less than 30. Thus, from a regulatory perspective in Japan, the results obtained from the present phase-II study are considered to be sufficient to certify the effectiveness of carboplatin in treating both of these diseases.

Mainly because of the above-mentioned reasons, there have been few reports of phase II studies on the single-drug administration of carboplatin for testicular tumors. Motzer et al. [4] obtained 2 PRs from a total of 20 evaluable patients treated with carboplatin alone. All patients entered in the trial were refractory to cisplatin-based chemotherapy, and toxicity was mild and tolerable. The initial dose of carboplatin was 250–350 mg/m^2, and this was escalated up to 500 mg/m^2. Peckham et al. [8] treated testicular tumor patients who had relapsed after cisplatin-based chemotherapy. Only one PR was obtained from a total of seven patients. These authors pointed out the ethical problems of studying nontreated patients who have a high probability of cure with an established combination chemotherapy. They proposed a strategy for investigating carboplatin for the treatment of testicular tumors, mainly involving a combination chemotherapy alternating cisplatin and carboplatin.

Trump et al. [10] also carried out a phase II study on single-agent carboplatin in previously treated testicular tumors. All patients had responded well to the previous treatment, but only one case showed a CR (95% confidence limit, 0.1%–22.8%).

Oliver et al. [6] treated previously nontreated cases of measurable, metastatic TCC with carboplatin as a part of MRC phase II trials. The dose was 400 mg/m^2 and they obtained 2 PRs from a total of 20 patients. Canetta et al. [1] have summarized all the available data concerning phase II studies on carboplatin. In testicular tumors, 37% of 46 patients were evaluated as responders (CRs + PRs), whereas in bladder tumors, 19% of 26 patients responded. In testicular tumors, the percentage of responders among previously nontreated patients was 75%–91%, whereas cases previously treated with cisplatin-based chemotherapy showed a range of 0–33%. The same tendency was observed for TCC of the bladder: 21% vs 14%. In our study, partially incomplete cross-resistance was also observed.

For both diseases in the present study, the higher dose (400 mg/m^2) was given to good-risk patients, and poor-risk patients received the lower dose (300 mg/m^2). A majority of the good responders were observed among the good-risk patient group. Investigations are needed to determine whether the higher dose of carboplatin has a more beneficial activity [7] or if the high response rate was due to the good PS of the patients.

Carboplatin was well tolerated in our study, with little nonhematologic toxicity. Most of the patients did not require medication for gastrointestinal symptoms. Myelosuppression was the major toxicity, but none of the patients required specific treatment, such as a blood transfusion. Thus, carboplatin, a drug that can be used in outpatient clinics, is considered to be useful in treating testicular tumors and TCC of the urinary tract. Further studies on its use in combination chemotherapy are needed.

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