Irinotecan Plus Cisplatin Has Substantial Antitumor Effect As Salvage Chemotherapy Against Germ Cell Tumors

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BACKGROUND. Only 20–30% of patients with refractory or recurrent germ cell tumors (GCT) are cured by salvage chemotherapy. Irinotecan, a new derivative of camptothecin, is a potent anticancer agent against a variety of solid cancers. The current pilot study investigated the efficacy of salvage chemotherapy with irinotecan in combination with cisplatin (CDDP) or nedaplatin (NDP), a derivative of cisplatin, for GCT.

METHODS. The combination chemotherapy consisted of 100–150 mg/m^2 irinotecan on Days 1 and 15 or 200–300 mg/m^2 on Day 1 in combination with 20 mg/m^2 CDDP on Days 1–5 or 100 mg/m^2 NDP on Day 1 every 4 weeks. Patients with refractory GCT, ranging in age from 17 to 43 years, received 2–11 cycles of the combination chemotherapy. The median duration of follow-up is 28 months (8–140 months).

RESULTS. Twenty patients entered this study, 18 of whom were assessed for response and toxicity. The response rate was 50 % (two complete responses and seven partial responses). Nine patients remain alive without disease. However, six patients died of the disease and one patient died of a brain glioma. The 5-year survival rate was approximately 53%. Myelosuppression was the major toxicity, but was manageable.

CONCLUSIONS. This pilot study demonstrates that the chemotherapy with irinotecan in combination with CDDP or NDP showed significant anticancer activity for patients with refractory GCT, without serious side effects. Although this study comprised only a few patients, these findings suggest that the combination chemotherapy may be one of the options of salvage chemotherapy for patients with refractory GCT. ***Cancer* 2002;95:1879–85.** *© 2002 American Cancer Society.*
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KEYWORDS: irinotecan, cisplatin, nedaplatin, salvage chemotherapy, germ cell tumor.

The overall response rate of patients with germ cell tumors (GCT) to combination chemotherapy including cisplatin (CDDP) has improved.[1]Despite the high cure rate for patients with GCT, between 20–30% of patients with disseminated disease failed to achieve a durable complete response (CR) to primary CDDP-based chemotherapy.[1,2] Several clinical trials were directed at improving treatment efficacy for the poor-risk patients. For example, ifosfamide and CDDP in combination with vinblastine or etoposide achieved CRs in approximately 50% of the patients as second-line therapy.[3,4] However, only one half of these CRs remain durable. In addition, high-dose carboplatin and etoposide with autologous bone marrow transplant cures a small population of patients as third-line therapy.[5,6] New potent

anticancer agents have been developed and are used to treat patients with GCT, GCT being resistant to CDDP-based chemotherapy. Monotherapy and combination chemotherapy including paclitaxel demonstrate good therapeutic results as salvage chemotherapy.[7–9] Gemcitabine is also used to treat patients with refractory GCT.[10,11] However, the efficacy is not satisfactory. Therefore, new effective therapeutic modalities are necessary to treat patients with the drug-resistant GCT.

Irinotecan is a semisynthetic antineoplastic drug with the skeleton of camptothecin. Its antitumor activity is exerted through the inhibition of Type I DNA topoisomerase. Although irinotecan is very effective against a variety of solid cancers,[12,13] there is no report on its effectiveness against GCT. We have demonstrated that irinotecan in combination with CDDP or nedaplatin (NDP), a platinum analog, exerts more significant antitumor activity against human GCT xenografts in nude mice than irinotecan or CDDP alone.[14,15] In addition, the antitumor effect of irinotecan in combination with CDDP or NDP is superior to that of irinotecan in combination with carboplatin or DWA-2114R, other platinum analogs. This laboratory study also showed that CDDP combination therapy with irinotecan is more effective without serious toxicity than with vinblastine or etoposide. Although combination chemotherapy with CDDP and vinblastine induced the toxic death of some mice, a combination of irinotecan and CDDP did not. Another study also demonstrated that a combination of irinotecan and CDDP resulted in synergistic cytotoxicity, but irinotecan in combination with etoposide had only an additive cytotoxic effect.[16] The current pilot study investigated the antitumor effect of combination chemotherapy with irinotecan in combination with CDDP or NDP as salvage therapy for patients with refractory GCT.

MATERIALS AND METHODS

Patients

This study was conducted at the Departments of Urology at Kyoto Prefectural University of Medicine, Osaka University Medical School, and Osaka Medical Center for Cancer and Cardiovascular Diseases from 1988 to 2000. This treatment protocol was approved by the Institutional Review Board at each institute. We explained the objectives and contents of the study and the meaning of participating in the study to the patients. Their informed consent was obtained before the study.

Eligibility criteria included histopathologically documented gonadal or extragonadal GCT that was refractory to first-line or second-line CDDP-based chemotherapy, performance status of less than 2, and an interval of at least 2 weeks between the most recent CDDP-containing therapy and entry into this study. Anticipated life expectancy was required to be at least 12 weeks. Patients were also required to have normal end-organ function, including a granulocyte count of 1000/mL or higher, a platelet count of 80,000/mL or higher, a glomerular filtration rate of 60 mL/min or higher, and a serum creatinine level less than or equal to 1.5 times the upper level of the institutional norm.

Study Protocol

Eligible patients received irinotecan at a starting dose of 100 mg/m^2 on Days 1 and 15 or 200 mg/m^2 on Day 1 every 4 weeks. CDDP, 20 mg/m^2, on Days 1–5 (11 patients) or NDP, 100 mg/m,^{2}, on Day 1 (7 patients) was also given every 4 weeks. For patients not experiencing any Grade 3 or higher toxicity during the first course of the therapy, the dose of irinotecan was increased to 150 mg/m^2 on Days 1 and 15 or to 300 mg/m^2 on Day 1.Doses were reduced based on hematologic toxicity. The selection of CDDP or NDP was dependent on the patients' physicians.However, NDP was used for all cases after 1999 because NDP caused less nephrotoxicity than CDDP. After 1992, "Hangeshashinto," a Chinese medicine preparation containing baicalin, was given at 7.5 g per day for 7 days every 2 weeks to prevent diarrhea due to irinotecan. Patients with myelosuppression were administered granulocyte–colony-stimulating factor (G-CSF). When the white blood cell count (WBC) in patients was less than 2000 or the neutrophil count was less than 1000, G-CSF was administered. The administration of G-CSF was continued until the WBC was higher than 5000.

Evaluation Procedures

In follow-up studies, tumor markers were evaluated, including α-fetoprotein (AFP), β-human chorionic gonadotropin (β-Hcg), and lactate dehydrogenase (LDH), as well as complete blood cell counts and serum biochemistry. Tumor measurements made by chest X-ray and computed tomographic scan were repeated every two courses of therapy. A CR was defined as the disappearance of all evidence of disease for at least 6 weeks when documented by imaging and all tumor markers. A partial response (PR) was defined as at least a 50% reduction in the product of the perpendicular diameters of each indicator lesion. Progressive disease (PD) was defined as a 25% increase in the product from any lesion or the appearance of any new lesions. No change (NC) was defined as that which did not meet any of the above criteria.

TABLE 1
Patient Characteristics

Patient no.	Age	Stage[a]	Site of disease	Pathology	Previous therapy
1	29	III	B + L + RPLN	S + E + T	PVB + EP + VIP + BX + LX + RPLND + R
2	43	II	RPLN	C	PVB + EP
3	31	III	L + RPLN	S + E	PVB + EP
4	28	III	L	C	PVB + BEP
5	28	III	MLN + RPLN	S	PVB + BEP + R
6	27	III	L + RPLN	T	BEP + LX + RPLND
7	40	III	L	E + T	BEP
8	32	III	L + RPLN	E + T	BEP + HD
9	34	III	RPLN + L	S	BEP + VIP + RPLND
10	40	—[b]	CLN	S	BEP + VIP + HD + R
11	28	II	RPLN	S + C + T	PVB + BEP + VIP
12	28	III	L	C	BEP + HD
13	19	III	L + RPLN	E + C + T	BEP + HD
14	22	III	L + RPLN	E + T	BEP + VIP + RPLND
15	17	II	RPLN	S + C	BEP
16	27	—[b]	MLN + RPLN	E	BEP
17	34	III	L + Li + RPLN	E	BEP + VIP
18	30	III	L + MLN + RPLN	E	BEP + VIP

B: brain; L: lung; Li: liver; CLN: cervical lymph node; MLN: mediastinal lymph node; RPLN: retroperitoneal lymph node; C: choriocarcinoma; E: embryonal carcinoma; S: seminoma; T: teratoma; BEP: bleomycin, etoposide, cisplatin; EP: etoposide, cisplatin; HD: high-dose chemotherapy; PVB: cisplatin, vinblastine, bleomycin; VIP: etoposide, ifosfamide, cisplatin; BX: resection of brain metastasis; LX: resection of lung metastasis; RPLND: retroperitoneal lymph node dissection; R: radiation.

[a] Data from Bosl and Motzer.[1]

[b] Extragonadal tumor.

Statistical Analysis

Disease-specific survival was determined by the Kaplan–Meier method. Confidence interval (95% CI) was assessed using Simon's method.[17]

RESULTS

Patient Characteristics

Twenty patients with refractory GCT entered this study. Refractory disease was defined as GCT that was resistant to first-line or second-line CDDP-based chemotherapy. Two patients were ineligible, leaving 18 patients enrolled in the study. They ranged in age from 17 to 43 years (median, 29 years; Table 1). Histologically, 3 patients had pure seminomatous GCT and 15 had nonseminomatous GCT. In addition, 16 patients had testicular GCT and 2 had extragonadal GCT. All patients had at least one elevated tumor marker (AFP, β-Hcg, LDH) before irinotecan-containing salvage chemotherapy. Only one patient had brain metastasis.

Antitumor Effect

A median of five cycles of irinotecan-containing salvage chemotherapy was administered (2–11 cycles). Eleven and seven patients received irinotecan in combination with CDDP and NDP, respectively. All 18 patients were examined and the outcome data are shown in Tables 2–4 and Figure 1. An impressive response rate of 50% was obtained, with two CRs and seven PRs. Six of the seven patients with PRs achieved marker-negative status (Table 2). In addition, the remaining patients experienced NC and none of them experienced PD. In 11 patients who were treated with irinotecan and CDDP, a response rate of 45% was achieved (CR, 1; marker-negative PR, 4; NC, 6). The response rate for seven patients treated with irinotecan and NDP was 57% (CR, one; marker-negative PR, two; marker-positive PR, one; NC, three). Therefore, the response to a combination of irinotecan and NDP was similar to that to a combination of irinotecan and CDDP.

Two patients showed high serum levels of AFP before salvage chemotherapy (Table 3). The serum levels decreased after chemotherapy, but were higher than the normal range. Thirteen patients had high levels of serum β-Hcg. The high serum β-Hcg levels in seven patients became less than the sensitivity of examination after combination chemotherapy. In contrast, serum β-Hcg levels in two patients increased after salvage chemotherapy. Three patients with seminoma demonstrated high serum LDH levels. The serum LDH level in one patient decreased to normal range after chemotherapy, but the levels in the other two patients increased.

TABLE 2
Outcome Data

Outcome	No. of patients (n = 18) (%:95% CI)	No. of patients treated with CDDP (n = 11) (%:95% CI)	No. of patients treated with NDP (n = 7) (%:95% CI)
Complete response	2 (11.1:0.0–26.6)	1 (9.1:0.0–26.1)	1 (14.2:0.0–40.4)
Partial response	7 (38.9:16.4–61.4)	4 (36.4:8.0–64.8)	3 (42.9:6.2–79.6)
Marker-negative	6	4	2
Marker-positive	1	0	1
No change	9 (50.0:26.9–73.1)	6 (54.5:25.1–83.9)	3 (42.9:6.2–79.6)
Overall response rate (%)	50.0	45.0	57.0
95% CI	26.9–73.1	15.6–74.4	23.7–90.3

CDDP: cisplatin; NDP: nedaplatin; CI: confidence interval.

TABLE 3
Marker Status

	AFP (ng/mL)		β-Hcg (ng/mL)		LDH (IU/L)	
Patient no.	Pre	Post	Pre	Post	Pre	Post
1	N	N	0.3	0.2	N	N
2	N	N	11.3	N	N	N
3	538	107	N	N	N	N
4	N	N	56.0	N	N	N
5	N	N	5.0	2.4	690	N
6	N	N	5.1	40.3	N	N
7	N	N	0.3	N	N	N
8	108	54	N	N	N	N
9	N	N	N	N	595	2274
10	N	N	N	N	521	2344
11	N	N	1.3	N	N	N
12	N	N	6.1	N	N	N
13	N	N	91.0	0.6	N	N
14	N	N	0.2	N	N	N
15	N	N	1.0	N	N	N
16	N	N	0.6	0.7	N	N
17	N	N	97.0	1.4	N	N
18	N	N	0.6	N	N	N

N: within normal limit; AFP: α-fetoprotein; β-Hcg; β-human chorionic gonadotropin; LDH: lactate dehydrogenase; Pre: previous chemotherapy; Post: postchemotherapy.

Of 18 patients, 10 underwent operation for residual tumors (Table 4). There were seven PRs (marker-negative PR, six; marker-positive PR, one) and three NCs. Salvage surgery was performed for four patients (one PR, three NCs) with positive markers. Two patients had disease recurrence after the salvage surgery. Pathologic examination demonstrated six necroses, three mature teratomas, and one viable malignant tumor (choriocarcinoma). The serum levels of tumor markers in the patient who had viable cancer in residual tumor were within the normal range before the operation.

The median duration of follow-up is 28 months (range, 8–140 months; Table 4). The median time to response was 2.5 months. Nine patients are currently alive and free of progressive GCT, one patient is alive with PD, and eight have died of disease. The 3- and 5-year survival rates were approximately 64% and 53%, respectively (Fig. 1). One patient died of glioma 10 years after receiving this irinotecan-containing combination chemotherapy. However, this death might not be related to the chemotherapy.

Adverse Effects

Table 5 lists the adverse events according to World Health Organization criteria.[18] Neutropenia was significant in all patients and five patients had neutropenia with fever. Fifteen patients received G-CSF, the median duration of which was 6 days (3–12 days) per one cycle. Similarly, Grade 2–4 thrombocytopenia/anemia was reported in all patients. Seven patients received platelet transfusions during the therapy. Patients received a median of 28 U (3–95 U) of platelet transfusion per one cycle. Discontinuity of chemotherapy was not necessary for these hematologic toxicities.

Other common side effects were alopecia and nausea/vomiting. Diarrhea was also common, but not universal. The mild diarrhea experienced may have been the result of the administration of Hange-shashinto. Initially, two patients who could not use this agent suffered from severe diarrhea. No toxicity-related deaths were caused by this combination chemotherapy.

DISCUSSION

There are several reports on combination chemotherapy with irinotecan and CDDP against some cancers. Experimental studies demonstrated that the combination of irinotecan and CDDP resulted in enhanced

TABLE 4
Results

Patient no.	Administered platin compound	Response	Time to response (mos)	Duration of response (mos)	Surgery after chemotherapy	Pathology at surgery	Present status	Overall survival (mos)
1	CDDP	NC	NA	NA	Yes	Necrosis	Dead	120
2	CDDP	PRm−	5	140	Yes	Necrosis	NED	140
3	NDP	NC	NA	NA	No	NA	Dead	25
4	CDDP	PRm−	2	124	Yes	Choriocarcinoma	NED	124
5	CDDP	NC	NA	NA	Yes	Necrosis	Dead	39
6	CDDP	NC	NA	NA	No	NA	Dead	30
7	CDDP	PRm−	2	75	Yes	Necrosis	NED	75
8	NDP	PR	2	45	Yes	Teratoma	NED	45
9	CDDP	NC	NA	NA	No	NA	Dead	24
10	CDDP	NC	NA	NA	No	NA	Dead	25
11	NDP	CR	3	34	No	NA	NED	34
12	CDDP	PRm−	3	32	Yes	Necrosis	NED	32
13	CDDP	NC	NA	NA	Yes	Teratoma	Dead	21
14	CDDP	CR	2	28	No	NA	NED	28
15	NDP	PRm−	8	14	Yes	Teratoma	NED	14
16	NDP	NC	NA	NA	No	NA	Dead	10
17	NDP	NC	NA	NA	No	NA	AWD	8
18	NDP	PRm−	2	12	Yes	Necrosis	NED	12

CDDP: cisplatin; NDP: nedaplatin; AWD: alive with disease; NA: not applicable; NED: no evidence of disease; PRm−: marker-negative partial response.

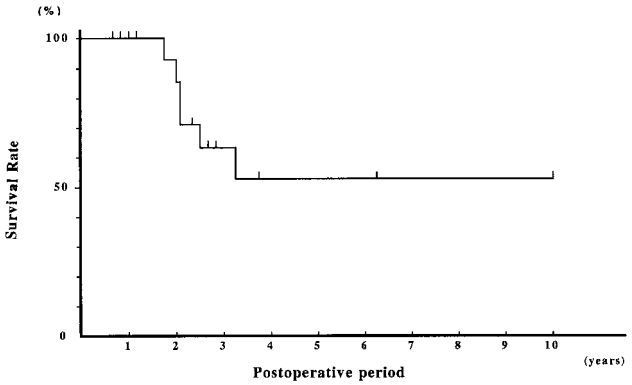

FIGURE 1. Disease-specific survival of germ cell tumor patients treated with irinotecan in combination with cisplatin or nedaplatin as salvage chemotherapy. Disease-specific survival rate was determined by the Kaplan–Meier method.

TABLE 5
Adverse Events

	Grade				
Adverse events	0	1	2	3	4
Neutropenia	0	0	0	3	15
Thrombocytopenia	0	0	1	7	10
Anemia	0	0	4	6	8
Mucositis	11	6	1	0	0
Nausea/vomiting	0	1	9	8	0
Diarrhea	2	3	8	4	1
Renal toxicity	12	3	3	0	0
Alopecia	1	0	17	0	0
Skin	16	1	1	0	0
Fever	7	4	6	0	1

antitumor efficacy.[16,19] Phase I and II studies also showed the promising antitumor activity of the combination chemotherapy.[20,21] These reports have shown that simultaneous exposure or sequencing of CDDP before irinotecan appears optimal. However, the exact mechanisms for the enhanced antitumor activity observed between irinotecan and CDDP are not well understood. The mechanisms await further investigations.

This is the first preliminary study to evaluate the efficacy of irinotecan in combination with CDDP or NDP in patients with refractory or recurrent GCT. This combination chemotherapy achieved an impressive 50% response rate, with NC in another 50% of patients. Approximately 64% of patients were alive at 3 years, with a median follow-up of 28 months. Because this study was a single-arm design, we cannot compare the efficacy of chemotherapy of irinotecan plus CDDP with that of other salvage chemotherapy regimens. However, these results suggest that this irinotecan-containing combination chemotherapy may be associated with a relatively high proportion of patients who achieved CR/PR as salvage chemotherapy. The toxicity of this regimen was substantial, but not critical. Hematologic toxicity was universal, but was manageable. This may be due to the extensive use of G-CSF. Although platelet transfusions were required in

some patients, there was no evidence of cumulative thrombocytopenia. Furthermore, no patient was removed from this study because of hematologic side effects. Diarrhea was one of the dose-limiting factors for irinotecan. However, patients experiencing severe diarrhea were relieved by the administration of Hange-shashinto, a Chinese medicine preparation containing baicalin (TJ-14). These findings suggest that this combination chemotherapy was relatively well tolerated with a high response rate compared with other salvage chemotherapies.[8,9]

GCT patients who do not have a CR with first-line chemotherapy or who have disease recurrence after CR have often been treated with ifosfamide plus CDDP-containing therapy as salvage chemotherapy.[1,3,4] High-dose chemotherapy with stem cell rescue is another treatment choice for refractory or recurrent GCT.[1,5,6] A multicenter joint study for high-dose chemotherapy is now in progress in Japan.[22] However, both of the above treatments as salvage chemotherapy cure approximately 20–25% of patients with GCT. Because this cure rate is not satisfactory, the use of new potent anticancer agents is an option to improve the therapeutic results. Paclitaxel is one of the new anticancer chemotherapeutic agents that promotes microtubular assembly, which blocks mitosis.[23,24] Monotherapy with paclitaxel is effective against GCT, which is resistant to CDDP-based chemotherapy.[7,25–27] However, the response rate of the paclitaxel monotherapy for refractory GCT was not good, ranging from 11% to 26%. Various paclitaxel doses, schedules, and eligibility criteria were used in these studies. An in vitro study demonstrated that there was a synergistic cytotoxic effect of paclitaxel and CDDP against resistant GCT.[28] Combination chemotherapy including paclitaxel shows good therapeutic results (response rate, 68–71%) as salvage chemotherapy.[8,9] Gemcitabine is a new synthetic nucleotide derivative that inhibits pyrimidine synthesis. Gemcitabine is also used against refractory GCT, but the response rate (15–19%) was not satisfactory.[10,11] These reports have demonstrated that gemcitabine has some antitumor effects as salvage chemotherapy against GCT. Compared with these results, combination chemotherapy containing irinotecan may play a important role in salvage chemotherapy for refractory GCT. However, further studies are necessary to evaluate whether these new anticancer agents including irinotecan are effective against recurrent or CDDP-refractory GCT.

The response rate of 18 patients with refractory GCT was 50%. In 11 patients treated with irinotecan and CDDP, the response rate was 45%. The response rate in seven patients who received irinotecan and NDP was 57%. These findings suggest that the response of refractory GCT to a combination of irinotecan and NDP is similar to that of irinotecan in combination with CDDP.

The clinical use of CDDP is sometimes limited due to its nephrotoxicity. NDP is a second-generation platinum complex with reduced nephrotoxicity that exerts its antitumor activity against various cancers including testicular, gynecologic, and lung carcinomas.[29,30] An in vitro study has demonstrated that the combination of irinotecan and NDP showed a marked synergistic interaction, which was produced by concurrent exposure.[31] The mechanism responsible for the synergy is the enhancement of the irinotecan-induced topoisomerase I inhibitory effect by NDP. These results and our data suggest that irinotecan plus NDP might demonstrate significant anticancer effect with low nephrotoxicity.

Several studies have demonstrated that patients with a primary testis tumor site, a previous CR to CDDP-based chemotherapy, and a low-volume metastasis are more likely to be cured with CDDP plus ifosfamide-containing chemotherapy.[1,32] In contrast, patients with primary mediastinal nonseminoma or resistant tumor to first-line chemotherapy rarely achieve long-term response to conventional-dose CDDP-based chemotherapy. The identification of prognostic factors for irinotecan-containing chemotherapy is needed and may be used to select patients for a favorable treatment outcome.

The prognosis of extragonadal GCT patients is poor. In the current study, two patients with extragonadal GCT were treated with four to five cycles of irinotecan in combination with CDDP or NDP. These GCTs were refractory to combination chemotherapy of CDDP plus etoposide with bleomycin or ifosfamide, as well as to high-dose chemotherapy (carboplatin, ifosfamide, and etoposide). The responses were classified as NC. Further studies are required to determine whether the chemotherapy of irinotecan in combination with CDDP or NDP is effective against extragonadal GCT.

The median duration of follow-up is 28 months (range, 8–140 months) in this study. The number of GCT cases in Japan is relatively lower than that in the United States. In addition, most of the 18 patients with GCT in this study were enrolled recently. Therefore, the median duration of follow-up is not long, although some patients were observed for more than 10 years.

The data presented here confirm that chemotherapy with irinotecan in combination with CDDP or NDP has substantial antitumor activity without significant adverse reactions as salvage chemotherapy against GCT. Ongoing studies are now attempting to determine how best to combine irinotecan with CDDP, paclitaxel, and other agents with demonstrable

activity against GCT. This possibility awaits further investigations.

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