Feasibility and usefulness of high-dose chemotherapy (high-dose ifosfamide, carboplatin and etoposide) combined with peripheral blood stem cell transplantation for male germ cell tumor: a single-institute experience

Isao Hara[a], Hideaki Miyake[a], Yuji Yamada[a], Kazuki Yamanaka[b], Junya Furukawa[a], Masafumi Kumano[a], Atsuhi Takenaka[a] and Masato Fujisawa[a]

Although the usefulness of high-dose chemotherapy with peripheral blood stem cell transplantation for advanced germ cell tumor is still under evaluation in phase III randomized controlled studies, this approach is currently used as one treatment option for relapsed or advanced male germ cell tumor. Clinical outcomes of high-dose chemotherapy for a single institute from Japan are presented herein. We administered 63 courses of high-dose ifosfamide, carboplatin and etoposide chemotherapy (1250 mg/m^2 carboplatin; 1500 mg/m^2 etoposide; 7.5 g/m^2 ifosfamide) to 34 men with germ cell tumors. Of these, 27 patients underwent high-dose ifosfamide, carboplatin and etoposide as first-line therapy after 2–3 courses of conventional bleomycin, etoposide and cisplatin chemotherapy, and seven patients underwent high-dose ifosfamide, carboplatin and etoposide for relapsed germ cell tumor. Peripheral blood stem cells were harvested during previous chemotherapy and sufficient CD34$^+$ cells were harvested for transplantation. Although all patients experienced grade 4 hemotoxicity, leukocyte counts recovered to above 1000/μl within 8–11 days after peripheral blood stem cell transplantation. No treatment-related deaths occurred. After a mean follow-up of 45 months (range 12–118 months), 23 of 34 patients (67.6%) remained disease-free. High-dose ifosfamide, carboplatin and etoposide could be performed safely, and could offer an effective means of treating advanced or refractory germ cell tumors in men. *Anti-Cancer Drugs* 17:1057–1066 © 2006 Lippincott Williams & Wilkins.

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[a]Division of Urology, Kobe University Graduate School of Medicine, Kobe and [b]Department of Urology, Hyogo Medical Center for Adults, Akashi, Japan.

Correspondence to I. Hara, Division of Urology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki Cho, Chuo Ku, Kobe City 650-0017, Japan.
Tel: +81 78 382 6155; fax +81 78 382 6169;
e-mail: hara@med.kobe-u.ac.jp

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Introduction

Treatment outcomes for metastatic testicular cancer have dramatically improved since the introduction of *cis*-platinum (CDDP)-based chemotherapy [1]. Although chemotherapy comprising CDDP, vinblastine and bleomycin has been widely used, bleomycin, etoposide and CDDP (BEP) chemotherapy has now gained wider use due to better disease-free survival and reduced neuromuscular toxicity, as proven in a randomized controlled trial (RCT) [2]. Currently, 3–4 cycles of BEP represents standard therapy for metastatic germ cell tumor (GCT). Approximately 20–30% of these patients, however, do not experience durable complete remission, and only 25% of these patients who do not experience remission may be cured using CDDP and ifosfamide-based salvage chemotherapies such as etoposide, ifosfamide and CDDP (VIP) with or without surgical resection [3].

At present, two strategies are being tried for CDDP-refractory GCT. The first is the introduction of novel anticancer drugs such as paclitaxel, gemcitabine, oxaliplatin and irinotecan. Combination protocols including these drugs display substantial antitumor effects for advanced or relapsed GCT [4–6]. The second strategy involves dose-intensified chemotherapy. As GCTs are highly sensitive to chemotherapeutic agents, dose intensification represents a promising strategy for the treatment of poor-risk or refractory GCTs. High-dose chemotherapy (HDCT) was originally applied to heavily pretreated patients, but clinical outcomes were not good and toxicity was not negligible [7]. Motzer *et al.* [8] showed that HDCT as a second-line chemotherapy offers significantly better response rates and toxicity outcomes compared with HDCT as third-line chemotherapy. This finding has suggested the use of HDCT in earlier settings, such as first-line therapy immediately after conventional chemotherapy [9–12]. Peripheral blood stem cell (PBSC) transplantation (PBSCT) is now widely performed as a supportive therapy for HDCT rather than bone marrow transplantation, because of reduced invasiveness and earlier hematological recovery [13]. Numerous papers support the usefulness of HDCT and

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the relative merits of the approach are currently under investigation in phase III trials. We have applied high-dose ifosfamide, carboplatin and etoposide chemotherapy (ICE) with PBSCT for advanced or relapsed male GCT patients in our institute. Initial experiences with high-dose ICE were presented in 1999 [14]. The present study examined the feasibility and usefulness of high-dose ICE with more patients and a longer follow-up period. We recently changed the HDCT regimen from high-dose ICE to high-dose ICE + paclitaxel (T-ICE) (175 mg/m^2 paclitaxel on day 1, total dose of 1250 mg/m^2 carboplatin, 1500 mg/m^2 etoposide and 7.5 g/m^2 ifosfamide, administered in five divided doses on days 1–5) to improve clinical outcomes. Although the number of patients was small ($n = 5$) and duration of follow-up was short (range, 7–15.5 months), four of five patients showed no recurrence of disease [15].

Materials and methods

Patients

Between November 1994 and October 2003, a total of 34 men with advanced or relapsed GCT underwent high-dose ICE combined with PBSCT. All study protocols were approved by the institutional review board of the Kobe University Graduate School of Medicine. A summary of patient characteristics is shown in Table 1. High-dose ICE was performed as first-line therapy followed by conventional chemotherapy in 27 patients, and was performed as salvage therapy in seven relapsed patients. Primary tumors were gonadal in 28 patients (82.4%) and extragonadal in six patients (17.6%). Most patients (94.1%) displayed non-seminomatous GCTs. Risk criteria were stratified according to a modification of the International Germ Cell Consensus Classification (IGCCC). As free β-human chorionic gonadotropin (β-hCG) is usually measured rather than intact or total β-hCG in Japan, free β-hCG was stratified into low (<100 ng/ml; $n = 20$), intermediate (100–1000 ng/ml; $n = 7$) and high (>1000 ng/ml; $n = 7$) values. Other criteria such as concentrations of α-fetoprotein (AFP) and lactate dehydrogenase (LDH), primary site, histology (seminoma or nonseminoma) and presence of visceral metastases were identical to those in the IGCCC. Details of patients who underwent high-dose ICE as first-line or salvage therapy are presented in Tables 2 and 3, respectively.

Table 1 Patient characteristics

Characteristics	First line ($n=27$)	Relapsed ($n=7$)
Age		
median	32.8	42.7
range	17–49	30–61
Primary site		
testis	22	6
EGGCT	5	1
Histology		
seminoma	1	1
nonseminoma	26	6
Number of metastatic sites		
0	3 (EGGCT)	1 (marker elevation)
1	2	4
2	13	0
3 or more	9	2
Sites of metastasis		
lung	18	3
RPLN	25	3
MLN	10	0
PLN–ILN	0	2
liver	5	0
brain	0	1
bone	1	1
Serum tumor markers		
β-hCG: <100 ng/ml	14	6
β-hCG: 100–1000 ng/ml	7	0
β-hCG: >1000 ng/ml	6	1
AFP: <1000 ng/ml	16	6
AFP: 1000–10 000 ng/ml	7	1
AFP: >10 000 ng/ml	4	0
LDH: <300 IU/l	6	2
LDH: 300–2000 IU/l	16	3
LDH: <2000 IU/l	5	2
Risk (modified IGCCC)		
good	0	
intermediate	14	
poor	13	

EGGCT, extra gonadal germ cell tumor; RPLN, retroperitoneal lymph node; MLN, mediastinal lymph node; PLN, pelvic lymph node; ILN, inguinal lymph node; β-hCG, beta-human chorionic gonadotropin; AFP, alpha feto protein; LDH, lactate dehydrogenase; IGCCC, international germ cell consensus classification.

Eligibility

High-dose ifosfamide, carboplatin and etoposide as first-line therapy

Patients diagnosed with intermediate or poor risk received 2–3 courses of conventional BEP therapy (CDDP 20 mg/m^2, days 1–5; etoposide 100 mg/m^2, days 1–5; bleomycin 30 mg/body, days 2, 9 and 16) (Table 2). PBSC harvest was performed during second or third BEP therapies. After 2–3 courses of BEP, serum markers (AFP, β-hCG, LDH) and results of radiography were evaluated. If levels of tumor markers decreased to within normal limits, an additional two courses of BEP therapy were performed, whereas high-dose ICE was applied if tumor markers remained high at this point. During the course of the study, 45 patients were diagnosed with intermediate or poor risk and underwent initial BEP therapy. High-dose ICE was administered to 27 of the 45 patients (60%). The remaining 18 patients were treated using a total of 4–5 courses of BEP therapy.

High-dose ifosfamide, carboplatin and etoposide for relapsed patients

At the time of recurrence, BEP or VIP therapy was performed to assess the response to CDDP and to harvest PBSCs (Table 3). High-dose ICE was used as adjuvant in three of seven patients (Re-1, Re-3, Re-7), because resected specimens contained viable cancer. The other four patients underwent high-dose ICE because tumor marker levels did not decrease to within normal ranges after previous salvage chemotherapy.

Other criteria

Other requirements for HDCT were as follows: histological diagnosis of GCT; Karnofsky performance status

Table 2 **Patient characteristics (first line)**

Pt no.	Age (years)	Side	Histology	Stage[a]	Number of metastasis	Lung meta size (cm) × no.	RPLN size (cm)	Other metastasis	Initial AFP (ng/ml)	Initial β-HCG (ng/ml)	LDH (IU/l)	Modified 'IGCCC	First line	No of HDCT	Post HDCT AFP	Post HDCT HCG β	Treatment after HDCT	Clinical response of HDCT	Follow-up period (months)	Outcome
In-1	32	lt	E,Y	3C (liver)	4	2 × 5	8	liver, MLN	95	48.74	12 385	poor	BEP (3)	1	WNL	WNL	RPLND (pCR)	pCR	117.9	NED
In-2	29	lt	E,S	3B2	2	3 × >10	3	none	11	WNL	1402	intermediate	BEP (2)	2	WNL	WNL	RPLND (pCR)	pCR	16.7	DOD
In-3	41	rt	T,E,Y	3A	2	0	5.2	MLN	7933	95	1052	intermediate	BEP (2)	1	WNL	WNL	RPLND (sCR T)	sCR	108.7	NED
In-4	24	lt	E	3B2	2	8 × 5	3	none	3690	1.22	1311	intermediate	BEP (2)	1	WNL	WNL	RPLND (sCR T) + lung (pCR)	sCR	81.4	NED
In-5	30	EG (med)	Y	EG	0	0	0	MLN	28 000	WNL	1241	poor	BEP (3)	2	12	WNL	MLND (pCR)	pCR	79.6	NED
In-6	23	lt	Y	3B2	3	3.5 × >20	8	MLN	483	470	270	intermediate	BEP (3)	3	WNL	WNL	RPLND (sCR E) + salvage chemotherapy (PD)	sCR (E)	13.5	DOD
In-7	25	rt	T (post-chemo)	3B2	2	1 × >10	>20	none	5855	21	2301	poor	BEP (3)	1	WNL	WNL	RPLND (incomplete T) + salvage chemotherapy (PD)	PR	21.2	DOD
In-8	48	EG (retro)	necrosis only	EG	2	5 × >20	7	none	WNL	441	225	intermediate	BEP (3)	2	WNL	0.29	salvage chemotherapy (PD)	PR	25.4	DOD
In-9	45	rt	E, S	3C (liver)	3	5.6 × >10	11.8	liver	WNL	1653	195	poor	BEP (2)	1	WNL	0.84	salvage chemotherapy (PR)	PR	75.1	NED
In-10	33	rt	Y, E, T, S	3B2	2	3.5 × >10	10	none	18 522	482	205	poor	BEP (2)	3	WNL	WNL	RPLND (sCR T) + lung (pCR)	sCR	74.7	NED
In-11	19	lt	E, T	3C (liver)	2	0	10.4	liver	1300	35.6	1265	poor	BEP (2)	2	WNL	WNL	RPLND (sCR T) + Liver (pCR)	sCR	73.5	NED
In-12	25	lt	C, T	3C (liver)	3	3 × >20	10	liver	WNL	25759	490	poor	BEP (2)	3	WNL	1.01	salvage chemotherapy (PR)	PR	60.2	NED
In-13	41	lt	S	3C (bone)	3	6.5 × 1	12	bone	WNL	5.5	2576	intermediate	BEP (4)	1	WNL	WNL	radiation (Bone)	CR	63.3	NED
In-14	46	lt	S, E, C	3B2	2	2.7 × >20	12.3	none	15 442	9373.2	3504	poor	BEP (2)	3	WNL	0.14	salvage chemotherapy (PD)	PR	22.0	DOD
In-15	47	lt	C	3B2	2	3 × >20	9	none	WNL	21 599	902	poor	BEP (2)	3	WNL	0.35	salvage chemotherapy (PD)	PR	18.9	DOD
In-16	17	EG (med)	?	EG	0	0	0	MLN	4396	0.22	162	poor	BEP (2)	1	WNL	WNL	MLND (pCR)	pCR	49.9	NED
In-17	23	Lt	burned out	RPLN	1	0	5	none	12.4	100	409	intermediate	PEB (3)	1	WNL	WNL	RPLND (refused)	PR	48.9	DOD
In-18	31	rt	T (post-chemo)	3C (liver)	3	2.5 × 8	6.5	liver	205	1400	600	poor	BEP (3)	3	10	0.4	salvage chemotherapy (PR) + RPLND (sCR) + liver (pCR)	PR	34.2	NED
In-19	34	EG (retro)	?	EG	0	0	15	none	17139	WNL	413	poor	BEP (3)	1	WNL	WNL	RPLND (pCR)	pCR	36.6	NED

Table 2 (Continued)

Pt no.	Age (years)	Side	Histology	Stage[a]	Number of metastasis	Lung meta size (cm) × No.	RPLN size (cm)	Other metastasis	Initial AFP (ng/ml)	Initial β-HCG (ng/ml)	LDH (IU/l)	Modified ' IGCCC	First line	No of HDCT	Post HDCT AFP	Post HDCT HCG β	Treatment after HDCT	Clinical response of HDCT	Follow-up period (months)	Outcome
In-20	21	lt	E	3B2	3	1.5 × >20	>20	MLN	WNL	WNL	643	intermediate	BEP (3)	2	WNL	WNL	none	CR	35.4	NED
In-21	32	rt	S	2B	1	0	8	none	277	0.7	383	intermediate	BEP (2)	1	WNL	WNL	RPLND (sCR T)	sCR	32.5	NED
In-22	36	rt	C, Y, S, mature T	3A	2	0	2	MLN	233	157	652	intermediate	BEP (3)	3	WNL	0.2	salvage chemotherapy (PD)	PR	14.1	DOD
In-23	49	rt	E, Y, T	3B2	2	1.8 × >10	8.5	none	5635.9	2.2	799	intermediate	BEP (3)	1	WNL	WNL	RPLND (sCR T) + lung (pCR)	sCR	31.3	NED
In-24	28	rt	Y, E, immature T	3B2	2	2.6 × 9	5.2	none	512	440	358	intermediate	BEP (3)	1	WNL	WNL	RPLND (pCR) + lung (pCR)	pCR	29.2	NED
In-25	46	rt.	C	3B2	3	4.8 × >20	7.8	MLN	WNL	10 000	5190	poor	BEP (2)	3	WNL	1.7	salvage chemotherapy (PD)	NC	15.8	DOD
In-26	33	lt	S, T, E	3A	2	0	>10	MLN	1424	5.4	238	intermediate	BEP (2)	1	35	WNL	MLND (sCR T) + RPLND (sCR T)	sCR	23.3	NED
In-27	23	EG (Retro)	E	EG	3	3 × >20	>10	MLN	104	560	1701	intermediate	BEP (2)	6	WNL	WNL	RPLND (sCR T)	sCR	17.5	NED

EG, extragonadal; med, mediastinum; retro, retroperitoneum; E, embryonal carcinoma; Y, yolk sac tumor; S, seminoma; T, teratoma; C, choriocarcinoma; RPLN, retroperitoneal lymph node; MLN, mediastinal lymph node; AFP, α-fetoprotein; HCG, human chorionic gonadotropin; WNL, within normal limit; LDH, lactate dehydrogenase; IGCCC, International Germ Cell Consensus Classification; HDCT, high-dose chemotherapy; RPLND, retroperitoneal lymph node dissection; pCR, pathological complete response; sCR, surgical complete response; MLND, mediastinal lymph node dissection; PD, progressive disease; PR, partial response; NED, no evidence of disease; DOD, dead of disease.

[a]Clinical stage was classified according to the 'General rule for clinical and pathological studies on testicular tumors' of the Japanese Urological Association.

$\geq 60\%$; adequate renal function (serum creatinine levels ≤ 1.5 mg/dl; creatinine clearance > 70 ml/min), liver function [total bilirubin ≤ 2.0 mg/dl, aspartate aminotransferase and alanine aminotransferase ≤ 100 IU/l] and hematological parameters (leukocyte count $\geq 3000/\mu l$, hemoglobin ≥ 10 g/dl, platelet count $\geq 10 \times 10^4/\mu l$); and provision of written informed consent. Exclusion criteria were as follows: serious infectious disease; serious mental disorder; double cancer; liver cirrhosis; or positive results for hepatitis B antigen or hepatitis C antibody.

Pretreatment evaluation

Before therapy and again before high-dose ICE, patients were examined to determine the extent of disease. Evaluation included complete history; physical examination; chest radiography; computed tomography of the abdomen, chest and brain; creatinine clearance, baseline blood biochemistry, blood cell counts, and AFP, LDH and β-hCG levels.

Treatment protocol

High-dose ifosfamide, carboplatin and etoposide as first-line therapy

Patients diagnosed with advanced disease (In1-27) received 2–3 courses of conventional BEP therapy (CDDP 20 mg/m^2, days 1–5; etoposide 100 mg/m^2, days 1–5; bleomycin 30 mg/body, days 2, 9 and 16) before high-dose ICE to assess tumor responsiveness and to harvest stem cells (Table 2). As previously described, patients with tumor marker levels that remained high after 2–3 courses of BEP therapy were subsequently treated with high-dose ICE. Otherwise, patients received an additional two courses of BEP therapy. High-dose ICE was performed after harvesting sufficient CD34 + cells during BEP therapy for transplantation. The high-dose ICE regimen comprised total doses of 1250 mg/m^2 carboplatin, 1500 mg/m^2 etoposide and 7.5 g/m^2 ifosfamide, administered in five divided doses on days 1–5. Carboplatin was administered over 2 h in 500 ml of 5% glucose. Undiluted etoposide was administered through a central venous line over 3 h. Ifosfamide was dissolved in 100 ml of normal saline and given over 1 h. Cytostatic drug administration was accompanied by forced alkali diuresis on days 1–6. Granisetron hydrochloride (3 mg) and hydrocortisone sodium succinate (250 mg) were administered 30 min before carboplatin for antiemesis. Mesna (300 mg/m^2) was administered after the end of ifosfamide and repeated 4 and 8 h later.

In principle, high-dose ICE was repeated until levels of tumor markers normalized, as long as tumor marker levels continued to decrease and sufficient numbers of CD34$^+$ cells were available.

High-dose ifosfamide, carboplatin and etoposide for relapsed patients

The remaining seven patients (Re-1–7) had been treated in other institutes and experienced disease recurrence (Table 3). Initial treatment, sites of recurrence and duration from initial treatment to recurrence are listed in Table 3. These patients underwent salvage chemotherapy and CD34$^+$ cells were collected. As three of these patients (Re-1, Re-3 and Re-7) also underwent resection of recurrent retroperitoneal lymph nodes and pathological findings revealed viable cancer cells, high-dose adjuvant chemotherapy was performed. The schedule of high-dose ICE was the same as for first-line therapy.

Stem cell transplantation

PBSCs were collected during bone marrow regeneration after conventional BEP therapy. We have previously reported the efficacy of BEP therapy for PBSC mobilization in patients with germ cell cancer [16]. Briefly, recombinant human granulocyte colony-stimulating factor was administered from the first day leukocyte count decreased to $< 2000/\mu l$ and was continued until PBSC harvest. Median number of granulocyte colony-stimulating factor administrations was 8 (range 1–20). Leukoapheresis was performed once or twice during each cycle of chemotherapy. PBSCs were collected by leukoapheresis, using a Cobe Spectra continuous flow cell separator (Cobe Laboratories, Lakewood, Colorado, USA), when leukocyte and platelet counts reached $\geq 10\,000$ and $\geq 50\,000/\mu l$, respectively. We have previously reported the details of PBSC harvest, and shown that the number of previous chemotherapies and the percentage of immature leukocytes represent independent predictors for the number of harvested CD34$^+$ cells [17]. Cryopreservation in liquid nitrogen, thawing and transfusion proceeded according to standard procedures. PBSCT ($> 5 \times 10^6$/kg CD34$^+$ cells) was performed 72 h after last administration of chemotherapeutic agents (day 8). Haptoglobin was administered > 2 h before PBSCT to prevent renal dysfunction because of hemolysis.

Supportive treatment

Patients received subcutaneous injection of recombinant human granulocyte colony-stimulating factor at a dose of 5 μg/kg from day 2 of PBSCT, and were isolated in a private room from day 7 until leukocyte count recovered to $> 1500/\mu l$. Vancomycin (1.5 g) and amphotericin B (12 ml) were orally administered for total decontamination of intestinal bacterial flora. Fluconazole (100 mg) was administered intravenously once daily. When fever was present ($> 38^\circ$C), blood, urine, throat and stool cultures were examined, and empirical antibiotics were started. Carbapenem and γ-globulin (2.5 g for 3 days) were also administered. Red blood cell concentrates were transfused to maintain hemoglobin levels > 8.0 g/dl. Platelet concentrates were also transfused to maintain platelet levels at $> 20\,000/\mu l$.

Table 3 Patients characteristics (relapse)

Pt no.	Age (years)	Side	His	Stage[a]	Initial tumor site	Initial treatment	Period from initial treatment to recurrence (months)	Tumor sites at recurrence	AFP (ng/ml)	β-HCG (ng/ml)	LDH (IU/l)	Treatment before HDCT	No. of HDCT	Post-HDCT AFP	Post-HDCT β-HCG	Clinical response of HDCT	Treatment after HDCT	Follow-up period (months)	Outcome
Re-1	30	rt	E	2B→2B	RPLN	VAB6 (3) + RPLND (sCR T)	5.2	RPLN	3030	WNL	409	BEP (3) + VIP(3) + tumorectomy	1	WNL	WNL	CR	radiation	107	NED
Re-2	62	rt	E, Y	3B2→ 3C	RPLN lung	VAB6 (3) + RPLND (pCR)	128.3	lung	WNL	3110	2649	EP (2)	1	WNL	3.56	NC	salvage chemotherapy (PD)	12.4	DOD
Re-3	42	lt	Y, T, S	2A→2A	RPLN	VAB6 (1) + BEP (2) + RPLND (sCR E) + BEP (2)	6.0	RPLN	WNL	WNL	363	RPLND + VIP (1)	2	WNL	WNL	NC	radiation	70.1	NED
Re-4	43	lt	S	1→3B →2B	none	lung meta: BEP (2) CR	16.5	inguinal LN	WNL	0.63	553	BEP (2)	1	WNL	WNL	pCR	inguinal LND (pCR)	56.1	NED
Re-5	35	EG (retro)	?	EG	RPLN	BEP (3) + RPLND	46.5	elevation of AFP	29	WNL	128	BEP (1)	1	58	WNL	PD	radiation	53.1	AWD
Re-6	52	rt	S, E, Y, immature T	1→3C	none	observation	39.8	pelvic LN, lung, bone	WNL	WNL	3301	BEP (2)	3	WNL	WNL	PD	salvage chemotherapy (PD)	6.3	DOD
Re-7	29	rt	E, Y, immature T	1→3B2	none	observation	56.7	RPLN, lung, brain	25	0.2	295	BEP (4) + RPLND + resection of brain tumor + brain radiation	1	WNL	WNL	PD (rt kidney, RPLN)	op + salvage chemotherapy (CR)	5.5	NED

EG, extragonadal; retro, retroperitoneum; E, embryonal carcinoma; Y, yolk sac tumor; T, teratoma; S, seminoma; RPLN, retroperitoneal lymph node; RPLND, retroperitoneal lymph node dissection; sCR, surgical complete response; pCR, pathological complete response; AFP, α-fetoprotein; WNL, within normal limit; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; HDCT, high-dose chemotherapy; NC, no change; NED, no evidence of disease; DOD, dead of disease; AWD, alive with disease.

[a]Clinical stage was classified according to the 'General rule for clinical and pathological studies on testicular tumors' of the Japanese Urological Association.

Results

Response

High-dose ifosfamide, carboplatin and etoposide as first-line therapy

The 27 patients underwent a mean of 2.1 courses of high-dose ICE (range, 1–6) as first-line therapy, followed by 2–3 courses of BEP therapy (Table 2). A summary of clinical outcomes is presented in Table 4. Tumor markers reduced to within normal ranges in 17 of the 27 patients (63.0%). The two patients (In-13, In-20) who showed clinical CR did not require surgery and showed no evidence of disease. One patient who refused to undergo retroperitoneal lymph node dissection for residual tumor subsequently developed recurrence and eventually died of the disease. The remaining 14 patients underwent surgical resection for residual tumor, but complete resection was abandoned in one patient (In-7) owing to growing teratoma syndrome. No evidence of disease has yet been identified in five patients with only necrosis (pathological CR) and seven patients who only displayed teratoma elements. One patient with a resected specimen containing viable cancer cells experienced recurrence and died of the disease despite salvage chemotherapy. As of the time of writing, 14 of the 17 patients (82.3%) who showed normalization of tumor markers with high-dose ICE have survived.

Meanwhile, 10 patients (37.0%) did not show normalization of tumor marker levels. Salvage chemotherapy including the use of novel anticancer drugs such as paclitaxel or gemcitabine was typically performed for patients who still show elevation of β-hCG after high-dose ICE. Prognosis for these patients was, however, quite poor and five of the eight patients who received salvage chemotherapy (62.5%) died of the disease. Conversely, we performed surgery if the patient displayed high AFP levels with only lymph node involvement. We have previously reported that salvage surgery is useful in such patients [18] and several reports support this finding [19,20]. No evidence of disease was found in the two patients (In-5, In-26) who underwent lymph node dissection according to this strategy.

Mean duration of follow-up was 45.2 months (range 13.5–117.9 months) and 18 of the 27 patients (66.7%) survived without disease. Although disease-specific survival curves were compared according to our risk criteria, no differences were found between intermediate and poor prognosis groups (Fig. 1; $P = 0.636$ log-rank test).

High-dose ifosfamide, carboplatin and etoposide for relapsed patients

High-dose ICE was used as salvage therapy in seven relapsed patients (Table 3). Recurrence developed in five patients (Re-1, Re-2, Re-3, Re-4, Re-5) despite previous CDDP-containing chemotherapy. One patient (Re-5) appeared absolutely refractory to BEP therapy. In the other two patients (Re-6, Re-7), extent of disease was markedly severe despite first recurrence. A summary of clinical outcomes is presented in Table 4. Two patients (Re-1, Re-3) who showed clinical and pathological CR have survived without recurrence so far. Three patients, however, presented with progressive disease despite high-dose ICE. One patient (Re-6) died of the disease despite three courses of high-dose ICE and another patient (Re-5) remains alive but with disease.

Mean duration of follow-up was 44.4 months (range 12.4–107.0 months). As of the time of writing, four of seven patients (57.1%) remain alive without disease and one patient is alive with disease.

Comparison of clinical outcomes according to tumor origin (gonadal vs. extragonadal)

In this study, 22 patients displayed tumors of gonadal origin, while extragonadal origin was identified in six patients. Patient characteristics and clinical outcomes were compared for each group (Table 5). No significant differences were identified in any characteristics between gonadal and extragonadal origins.

Hematological toxicity and recovery

The 34 patients underwent a total of 63 courses of high-dose ICE. Although all patients experienced grade 4 hemotoxicity, leukocyte count recovered within 11 days after PBSCT in all cases (mean, 8.8 days) (Table 6). Mean nadir for platelet count was $1.6 \times 10^4/\mu l$ and recovery to $\geq 5 \times 10^4/\mu l$ took a mean of 12.9 days after PBSCT (range 11–27 days). Mean nadir of hemoglobin was 7.1 g/dl. Hematological toxicity and recovery were compared according to number of high-dose chemotherapies, but no significant differences were found. This suggests that hematological recovery was stable if sufficient $CD34^+$ cells were transplanted.

Nonhematological toxicity

Nonhematological toxicities were classified according to National Cancer Institute Common Toxicity Criteria and are shown in Fig. 2. Vomiting and diarrhea represent common toxicities, and grade 3 toxicity was observed in 3.4% for vomiting and 8.6% for diarrhea. Although fever is also frequently observed in association with neutropenia, only one case of grade 3 fever was observed. Toxicities were compared according to the number of courses of HDCT. No significant differences according to number of HDCT courses were found however. None of these effects were life-threatening and no treatment-related deaths were identified.

Discussion

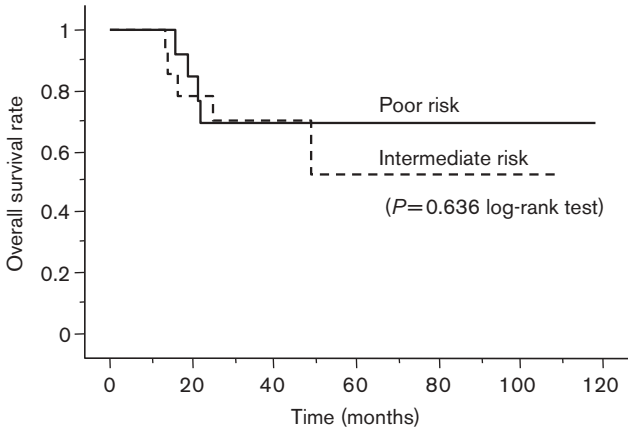
We have been performing high-dose ICE since 1994, since PBSCT was introduced as a bone marrow support therapy in the early 1990s, making HDCT safer and more

Table 4 Clinical outcome according to the tumor marker level after HDCT

(a) HDCT as first-line therapy		
Tumor markers fell down within normal range after HDCT		
	No. of patients	Dead of disease
clinical CR	2	0
pathological CR	5	0
surgical CR (T)	7	0
surgical CR (E)	1	1
incomplete resection	1	1
refusal of RPLND	1	1
total	17	3 (17.6%)
Tumor markers did not fall down within normal range after HDCT		
	No. of patients	Dead of disease
AFP positive – operation	2	0
β-hCG positive – other chemotherapy	8	5
total	10	5 (50%)
(b) HDCT for relapsed patients		
	No of patients	Dead of disease
clinical CR	1	0
pathological CR	1	0
NC	2	1
PD	3	1
total	7	2 (28.6%)

HDCT, high-dose chemotherapy; CR, complete response; T, teratoma; E, embryonal carcinoma; RPLND, retroperitoneal lymph node dissection; AFP, α-fetoprotein; hCG, human chorionic gonadotropin; NC, no change; PD, progressive disease.

Fig. 1



Overall survival rate according to our modification of the International Germ Cell Consensus Classification.

feasible. Until that time, HDCT had been performed using autologous bone marrow transplantation for heavily pretreated patients. Toxicity was, however, severe and clinical outcomes were not as good as expected for such clinical applications [7]. Introduction of PBSCT enabled safer repetition of HDCT cycles at an earlier time. Bhatia *et al.* [21] used two cycles of high-dose CE (carboplatin 2100 mg/m^2; etoposide 2250 mg/m^2) as initial salvage chemotherapy, with a resultant durable cancer-free rate of

Table 5 Comparison of gonadal origin and extragonadal origin

Characteristics	Gonadal origin (n=28)	Extragonadal origin (n=6)	P-value
Indication of HDCT			
induction	22	5	0.64[a]
salvage	6	1	
Histology			
seminoma	2	0	0.67[a]
nonseminoma	26	6	
Risk (modified IGCCC)			
intermediate	12	2	0.46[a]
poor	10	3	
Clinical response			
CR	18	3	0.51[b]
pathological CR	25	3	
surgical CR	10	0	
PR	0	2	
NC	5	0	
PD	0	1	
Outcome			
NED	16	6	0.65[a]
DOD	7	1	(NED vs. others)
AWD	4	0	

IGCCC, International Germ Cell Consensus Classification; CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NED, no evidence of disease; DOD, dead of disease; AWD, alive with disease.
[a]χ^2-square test.
[b]Mann–Whitney's U-test.

57% with no treatment-related deaths. Similarly, Margolin *et al.* [22] showed that in 20 GCT patients who were unlikely to be cured by standard-dose chemotherapy (SDCT), two cycles of high-dose ICE (carboplatin 1200 mg/m^2; etoposide 60 mg/kg; IFM 6–9 g/m^2) resulted in nine patients (45%) displaying no evidence of disease after a median follow-up period of 45 months. Beyer *et al.* [23] recently compared HDCT and SDCT as first salvage chemotherapy using matched-pair analysis. Although this was a retrospective study, patient HDCT and SDCT backgrounds were strictly adjusted using several important factors, and HDCT was found to improve 2-year disease-specific survival by 6–12%.

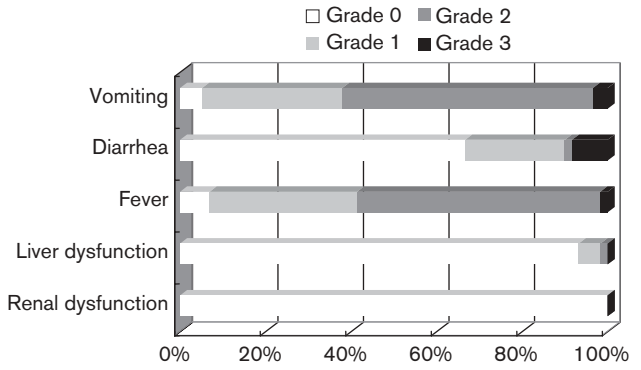
Although these results were obtained from studies treating relapsed patients, the kinds of patients who cannot be managed using standard chemotherapies can be predicted to some extent. The most recent risk criteria were established by the International Germ Cell Cancer Collaborative Group [24]. Patients with advanced GCT were divided into three categories of good, intermediate and poor prognosis, with 5-year survival rates for these three groups of 91, 79 and 48%, respectively, when treated using SDCT. Considering that HDCT should be introduced in the earlier setting, performing HDCT as a first-line chemotherapeutic approach appears to be a sound rationale for patients with poor prognosis. In fact, Motzer *et al.* [11] administered two cycles of high-dose CE (carboplatin 1500 mg/m^2; etoposide 1200 mg/m^2) in 22 patients who showed incomplete response to first-line chemotherapy, achieving a durable cancer-free rate of 36%. German groups have also used one cycle of VIP followed by multiple cycles of

Table 6 Hematological toxicity according to number of HDCT

	WBC nadir (/μl)	WBC >1000 (days after PBSCT)	Plt nadir ($\times 10^4$/μl)	Plt $>5 \times 10^4$ (days after PBSCT)	Hb nadir (g/dl)
First course ($n=34$)	212±132	8.9±1.2	1.6±0.5	12.8±2.9	7.0±1.4
Second course ($n=15$)	250±221	8.7±1.8	1.6±0.7	13.1±2.3	6.9±1.2
Third course ($n=9$)	270±231	8.3±0.9	1.6±0.7	12.9±5.3	7.9±1.5

HDCT, high-dose chemotherapy; WBC, white blood cell; PBSCT, peripheral blood stem cell transplantation; Plt, platelet; Hb, hemoglobin.

Fig. 2



Nonhematological toxicity of high-dose ifosfamide, carboplatin and etoposide. Toxicity was classified according to National Cancer Institute Common Toxicity Criteria.

high-dose VIP with PBSCT [9,10,12], achieving durable cancer-free rates of 72–73% with low rates of treatment-related deaths (4–9%). Bokemeyer *et al.* [9] also compared clinical outcomes between first-line HDCT and SDCT using matched-pair analysis. In that report, HDCT data from 147 patients and SDCT data from 309 patients were used. On the basis of IGCCC, 146 of the 147 HDCT patients were fully matched to SDCT patients and 2-year progression-free survival was significantly prolonged with HDCT compared to SDCT (75 vs. 59%, respectively; $P=0.0056$). Although this was not an RCT, the study statistically confirmed the supremacy of HDCT over SDCT for first-line chemotherapy. The present study obtained similar clinical outcomes using HDCT as first-line therapy. The 3-year overall survival rate was 66.7% and no treatment-related deaths were observed. No significant differences were, however, found between poor and intermediate groups in disease-specific survival after high-dose ICE according to our modified IGCCC. The most plausible reason for this finding is that our modification was not entirely appropriate. As only β-hCG data were available in our patients, we should try to establish risk classification according to β-hCG by ourselves in Japan.

Despite these encouraging results, phase III RCTs are definitely needed to confirm the clinical usefulness of HDCT. The most recent phase III RCT was reported in 2005 [25] from a European group. They compared four cycles of VIP with three such cycles followed by one cycle of high-dose carboplatin, etoposide and cyclophosphamide (CarboPEC) using hematopoietic stem cell support for relapsed GCT patients. No significant improvements with CarboPEC were observed in either 3-year event-free survival (35 vs. 42%, respectively; $P=0.16$) or overall survival (53 vs. 53%). Treatment-related deaths occurred in 3% of SDCT patients and 7% of HDCT patients. The conclusion was that a single cycle of HDCT after three cycles of SDCT exerts no effects on treatment outcomes. Although the message from that study is clear, we must await the results of RCTs dealing with multiple cycles of HDCT. In fact, most investigators believe that one cycle of HDCT is insufficient, and multiple cycles of HDCT are typically used. Rates of treatment-related death from multiple cycles of HDCT are usually below 5%. In fact, two RCTs are ongoing in patients with poor-to-intermediate prognosis, one in the US and the other in Europe. Both studies are treating untreated poor-prognosis male GCT patients using a standard arm of four cycles of BEP. As the high-dose arm, the US trial is performing two cycles of BEP followed by two cycles of high-dose CEC, while the European trial is performing one cycle of VIP followed by three cycles of high-dose VIP. To the best of our knowledge, no conclusions have yet been presented. We hope that these trials will clarify the role of HDCT for men with GCT.

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