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Clinical study

Clinical outcome of high-dose chemotherapy combined with peripheral blood stem cell transplantation for male germ cell tumors

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Peripheral blood stem cell transplantation (PBSCT) is widely performed currently instead of bone marrow transplantation (BMT) because bone marrow reconstruction is better and the procedure is less invasive. We applied 26 courses of high-dose chemotherapy (1250 mg/m^2 of carboplatin, 1500 mg/m^2 of etoposide and 7.5 g/m^2 of ifosfamide) to 14 male patients with germ cell tumors. Eleven patients underwent high-dose chemotherapy as induction after two to three courses of conventional BEP therapy. The remaining three patients had recurrent disease after conventional chemotherapies. Peripheral blood stem cells were harvested during previous chemotherapy and sufficient CD34$^+$ cells were harvested for transplantation. Although all patients had grade 4 hematotoxicity, the white blood cell count recovered to more than 1000/μl within 8–11 days after PBSCT. No treatment-related death was found. Nine of 14 patients (64.3%) remain disease free at 18 months of median follow up time (range 12–60). We conclude that high-dose chemotherapy is a safe and effective means of treating advanced or refractory germ cell tumors in male patients. [© 1999 Lippincott Williams & Wilkins.]

Key words: Germ cell tumor, peripheral blood stem cell transplantation, super high-dose chemotherapy.

Introduction

The treatment outcome of advanced testicular cancer has been dramatically improved since the introduction of cisplatin-based chemotherapy and the surgical resection of residual masses.[1,2] However, approximately 20–30% of these patients do not have durable, complete remission after these strategies and their prognosis is not satisfactory even after salvage chemotherapy.[3,4] Indeed high-dose chemotherapy with bone marrow transplantation (BMT) has afforded long-term remission in 15–20% of these refractory or relapsed patients, but heavier hematologic toxicity was evident in patients who had already undergone several courses of conventional chemotherapy.[5–7] Although high-dose chemotherapy should be introduced earlier to patients with advanced disease to improve clinical outcome and decrease toxicity, BMT requires general anesthesia to harvest bone marrow cells and treatment-related death is mostly associated with bone marrow suppression in 10% of patients who undergo high-dose chemotherapy with BMT.[5,6]

Peripheral blood stem cell harvest (PBSCH) means to collect stem cells from peripheral blood at the time of bone marrow recovery after conventional chemotherapy and to store them at −80°C. After high-dose chemotherapy, these stem cells are reinfused to reconstruct bone marrow. Peripheral blood stem cell transplantation (PBSCT) has been frequently applied for bone marrow rescue, because of its low invasiveness and early hematologic recovery after high-dose chemotherapy.[8,9] As PBSCT is more widely performed, earlier introduction of high-dose chemotherapy is becoming more feasible. Moreover, we showed that a sufficient amount of stem cells for transplantation could be harvested during two to three courses of bleomycin, etoposide and cisplatin (BEP) therapy, which is a standard first-line chemotherapy for germ cell tumors.[10] This report shows the clinical outcomes of high-dose chemotherapy as induction for poor-risk patients or as salvage chemotherapy for relapsed patients.

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Materials and methods

Patients

Between November 1994 and May 1999, 14 patients with advanced non-seminomatous germ cell tumor underwent high-dose chemotherapy combined with PBSCT. Primary tumors were gonadal in 12 (85.7%) and extragonadal in two (14.3%). Extragonadal manifestation was in the mediastinum and in the retroperitoneum. The characteristics of these patients are listed in Table 1. Their median age was 29 years (range 19–51). According to the Indiana classification, 11 patients (78.6%) had advanced disease, two (14.3%) had moderate disease and one (7.1%) had minimal disease. Histology of the primary tumors, metastatic sites, and the values of α-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) are listed in Table 1.

Eleven patients (In 1–11) underwent high-dose induction chemotherapy followed by two to three courses of standard BEP therapy, since serum markers did not fall within normal value or huge metastatic lesions remained after BEP therapies. The remaining three patients (Sal 1–3) had recurrent disease.

Eligibility

Patients were eligible for this study if they fulfilled the following requirements: histological diagnosis of germ cell tumor; diagnosed as advanced disease by Indiana classification and serum markers did not fall within normal values or huge metastatic lesions remained after two to three courses of BEP therapy; viable cancer cells found by surgical resection after salvage chemotherapy in recurred patient; a Karnofsky performance status of at least 60%; adequate renal (serum creatinine level ≤ 1.5 mg/dl, Ccr > 70 ml/min), liver (bilirubin level ≤ 2.0 mg/dl, GOT, GPT ≤ 100) and hematologic (leucocyte count $\geq 3000/\mu l$, hemoglobin ≥ 10 g/dl, platelet count $\geq 10 \times 10^4/\mu l$) function; and provision of written informed consent. Exclusion criteria were as follows: serious infectious disease; serious mental disorder; double cancer; liver cirrhosis; positive hepatitis B antigen or hepatitis C antibody.

Pretreatment evaluation

Before therapy and again before high-dose chemotherapy, patients were examined to determine the extent of disease. Evaluation included complete history; chest X-ray; computed tomography of the abdomen, chest and brain; creatinine clearance, baseline blood chemistry, blood cell counts, AFP and β-HCG.

Treatment protocol

High-dose chemotherapy as induction (Table 2). The patients (In 1–11) diagnosed as having advanced disease by the Indiana classification received two to three courses of conventional BEP therapy (cisplatinum 20 mg/m^2, day 1–5, etoposide 100 mg/m^2; day 1–5, bleomycin 30 mg/body; day 2, 9 and 16) before high-dose chemotherapy to assess tumor responsiveness and to harvest stem cells. In eight out of these patients (In 3, 4, 5, 6, 8, 9, 10 and 11), serum markers (AFP or β-HCG) did not fall within normal limits. Although three patients (In 1, 2 and 7) showed normal values of serum markers after BEP therapy, radiology revealed a large mass. Since one of these patients (In 2) showed normal values of serum markers before orchiectomy, further high-dose chemotherapy was needed. From all 11 patients, enough CD34$^+$ cells were harvested during BEP therapy for transportation, then they underwent high-dose chemotherapy. The high-dose chemotherapy regimen consisted of total doses of 1250 mg/m^2 of carboplatin, 1500 mg/m^2 of etoposide and 7.5 g/m^2 of ifosfamide. They were 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 with 3 l on days 1–6. Granisetron hydrochloride (3 mg) and hydrocortisone sodium succinate (250 mg) were administered 30 min before carboplatin as anti-emetics. Mesna (300 mg/m^2) was administered after the end of ifosfamide, and repeated 4 and 8 h later.

High-dose chemotherapy as a salvage therapy (Table 3). Three patients (Sal 1–3) were treated in other institutes and their diseases recurred. The initial treatment and sites of recurrence are listed in Table 3. These patients had undergone salvage chemotherapy and CD34$^+$ cells were collected. Since two of them (Sal 1 and 3) also had resection of recurrent retroperitoneal lymph nodes and pathological findings revealed the viable cancer cells, high-dose adjuvant chemotherapy was performed. The schedule of high-dose chemotherapy was the same as that for induction therapy.

Table 1. Patient characteristics

Purpose of SHD	Patient no.	Age	Side	His[a]	Stage[b]	Indiana classification	Lung (size) (cm)	Lung (no.)	RPLN (size) (cm)	Other metastases (size)	AFP (ng/ml)	β-HCG (ng/ml)
Induction	In 1	31	left	E, Y	3C (liver)	advanced, 9	2	5	8	liver, Virchow	95	48.74
	In 2	29	left	E, S	3B2	moderate, 6	3	>10	3	none	11	WNL
	In 3	41	right	T, E, Y	3A	advanced, 8	0	0	5.2	Virchow	7933	95
	In 4	24	left	E	3B2	advanced, 7	8	5	3	none	3690	1.22
	In 5	30	EGCT	Y	mediastinum	advanced, 7	0	0	0	MLN (23 cm)	28000	WNL
	In 6	22	left	Y	3B2	advanced, 8	3.5	>20	8	none	483	470
	In 7	25	right	T	3B2	advanced, 8	1	>10	>20	none	5855	21
	In 8	48	EGCT	necrosis	RPLN, lung	advanced, 8	5	>20	7	none	WNL	441
	In 9	45	right	E, S	3C (liver)	advanced, 9	5.6	>10	11.8	liver	WNL	1653
	In 10	33	right	Y, E, T, S	3B2	advanced, 8	3.5	>10	10	none	18522	482
	In 11	19	left	E, T	3C (liver)	advanced, 9	0	0	10.4	liver	940	21.5
Salvage	Sal 1	28	right	E	2B	moderate, 5	0	0	>5	none	633	160
	Sal 2	51	right	E, Y	3B2	advanced, 8	3	>10	>5	none	315	10.8
	Sal 3	41	left	Y, T, S	2A	minimal, 3	0	0	>5	none	1126	WNL

[a]E, embryonal carcinoma, Y, yolk sac tumor. S, seminoma; T, teratoma; C, choriocarcinoma.
[b]Stage classified according to general rules for clinical pathological studies on testicular tumors.
WNL, within normal limits; MLN, mediastinal lymph node.

Table 2. Induction BEP therapy

Patient no.	AFP pre-BEP (ng/ml)	β-HCG pre-BEP (ng/ml)	First-line chemotherapy (no. of courses)	AFP half-life (days)	β-HCG half-life (days)	AFP post-BEP (ng/ml)	β-HCG post-BEP (ng/ml)	Effect marker	Effect tumor size
In 1	95	48.74	BEP (3)	13	6.8	WNL	WNL	CR	PR
In 2	WNL	WNL	BEP (2)			WNL	WNL	NE	PR
In 3	7933	95	BEP (2)	7.3	6	12	0.11	PR	PR
In 4	3690	1.22	BEP (2)	8.3	11.1	16	WNL	PR	PR
In 5	28000	WNL	BEP (3)	16.2	9.1	46	WNL	PR	PR
In 6	483	470	BEP (3)	8.3	7.5	WNL	0.26	PR	PR
In 7	5855	21	BEP (3)	7.6	8.6	WNL	WNL	CR	NC
In 8	WNL	441	BEP (3)		14	WNL	1.99	PR	PR
In 9	WNL	1653	BEP (2)		8.7	WNL	3.48	PR	PR
In 10	18522	482	BEP (2)	6.1	6.4	50	2.82	PR	PR
In 11	940	21.5	BEP (2)	12.3	10.9	22	0.45	PR	NC

WNL, within normal limits; CR, complete response; PR, partial response; NE, not evaluated; NC, no change.

Table 3. Salvage SHD therapy

Patient no.	Induction chemotherapy (no. of courses) Surgical resection (history) Adjuvant chemotherapy (no. of courses)	Recurrence (time to recurrence)	Treatment for recurrence	AFP before HDC (ng/ml)	β-HCG before HDC (ng/ml)
Sal 1	VAB6 (3) RPLND (teratoma) None	marker elevation, RPLN (6 months)	BEP (3) VIP (3) tumorectomy (RPLN)	546	WNL
Sal 2	VAB6 (3) RPLND (necrosis) VAB6 (1)	lung (10 years)	PE (2)	WNL	8.3
Sal 3	VAB6 (1)+BEP (2) RPLND (viable cell) BEP (2)	RPLN (6 months)	tumorectomy (RPLN) VIP (1)	WNL	WNL

VAB6, cyclophosphamide+vinblastine+actinomycin D+bleomycin+cisplatin; WNL, within normal limits. RPLN, retroperitoneal lymph node; BEP, bleomycin+etoposide+cisplatin; WNL, within normal limits; RPLND, retroperitoneal lymph node dissection; VIP, cisplatin+etoposide+ifosfamide; PE, cisplatin+etoposide.

Stem cell transplantation

Peripheral blood stem cells (PBSCs) were collected during bone marrow regeneration after conventional BEP therapy. We previously reported the efficacy of BEP therapy for PBSC mobilization in patients with germ cell cancer.[10] Briefly, recombinant human granulocyte colony stimulating factor (rhG-CSF) was administered from the day when the leukocyte count had decreased to below 2000/μl and was continued until PBSC harvest. Leukoapheresis was performed once or twice during each cycle of chemotherapy. PBSCs were collected by means of leukoapheresis, using a Cobe Spectra continuous flow cell separator (Cobe Laboratories, Lakewood, CO), when leukocyte and platelet counts reached at least 10 000 and 50 000/μl, respectively. Cryopreservation in liquid nitrogen, thawing and transfusion proceeded according to standard procedures. PBSC were transplanted (PBSCT) 72 h after the last administration of chemotherapeutic agents (day 8). Haptoglobin was administered over 2 h before PBSCT to prevent renal dysfunction due to hemolysis.

Supportive treatment

The patients received rhG-CSF at a dose of 5 μg/kg as a s.c. injection from the second day of PBSCT and they were isolated in a private room from day 7 until the leukocyte count recovered to more than 1500/μl. Vancomycin (1.5 g) and amphotericin B (12 ml) were orally administered for total decontamination of intestinal bacterial flora. Fluconazol (100 mg) was i.v. administered once each day. When fever was presented (higher than 38°C), blood, urine, throat and

stool cultures were examined, and empirical antibiotics were started. Carbapenem and γ-globulin (2.5 g for 3 days) which has a high titration against cytomegalovirus were also administered. Red blood cell concentrates were transfused to maintain hemoglobin levels above 8.0 g/dl. Platelet concentrates were also transfused to maintain platelet levels more than 20 000/μl.

Results

Response

High-dose chemotherapy as induction (Table 4). Eleven patients (In 1-11) underwent one or two courses of high-dose chemotherapy as induction followed by two or three courses of BEP therapy. AFP and β-HCG became normalized in nine patients (In 1-7, 10 and 11). Residual tumors in these patients were surgically resected. Necrosis only (pathological CR) in four patients and teratoma (surgical CR) in three patients was identified by histological examination of the resected specimens. Residual cancer was found in one patient (In 6) and one extra course of high-dose chemotherapy was administered. However, this patient died of recurrent disease 16 months after initial therapy. Although only a teratomatous element was found in the remaining one patient (In 7), the abdominal mass was so large that complete tumor resection was impossible. Thus the response rate including CR and PR was 63.6%. Serum markers did not normalize in two patients (In 8 and 9), so they were further treated with taxol. Although β-HCG was increased in patient In 8 by taxol therapy, β-HCG became normalized after high-dose chemotherapy. In the other patient (In 9), β-HCG fell within normal limits. This patient refused RPLND and has survived without recurrence. The median follow up period was 20 months (12-60 months) and seven out of 11

Table 4. Induction of HDC therapy

Patient no.	Times of HDC (% dose)	AFP	β-HCG	Surgical resection (histology)	Effect	Following treatment	Recurrence	Treatment for recurrence	Follow up (months)	Status of disease
In 1	1 (60%)	WNL	WNL	RPLND (necrosis)	pCR	none	none		60	NED
In 2	2 (80%)	WNL	WNL	RPLND (necrosis)	pCR	none	lung (2 months)	HDC (100%) × 2	20	DOD
In 3	1 (100%)	WNL	WNL	RPLND (teratoma)	sCR	none	none		47	NED
In 4	1 (100%)	WNL	WNL	RPLND (teratoma) lung (necrosis)	sCR	none	none		47	NED
In 5	2 (100%)	WNL	WNL	MLND (teratoma) lung (necrosis)	pCR	none	none		41	NED
In 6	2 (100%)	WNL	WNL	RPLND (embryonal carcinoma)	PR	HDC (100%)	lung, RPLN (7 months)	BEP (100%) × 3	16	DOD
In 7	1 (70%)	WNL	WNL	RPLND (incomplete resection of teratoma)	NC	5-FU p.o.	RPLN	BEP (100%) × 1	23	AWD
In 8	2 (80%)	WNL	0.29		NC	taxol+HDC (100%) × 2	refractory		16	AWD
In 9	1 (100%)	WNL	0.84		NC	semi-high-dose PE+taxol	none		15	NED
In 10	3 (100%)	WNL	WNL	RPLND (necrosis) lung (necrosis)	pCR	none	none		13	NED
In 11	2 (100%)	WNL	WNL	PRLND (immature teratoma)	sCR	none	none		12	NED

WNL, within normal limit; RPLND, retroperitoneal lymph node dissection; pCR, pathological complete response; NED, no evidence of disease; DOD, died of disease; sCR, surgical complete response; AWD, alive with disease.

patients (63.6%) survived without disease. Two patients (18%) with recurrent lung tumors after 2 (In 2) and 7 (In 6) months, died despite of additional chemotherapies.

High-dose chemotherapy as salvage (Table 5). Three patients (Sal 1-3) had initial treatment in other institutes, then their tumors recurred. Two of them (Sal 1 and 3) had high-dose chemotherapy after resection of recurrent sites. Although one patient (Sal 1) had elevated serum markers before high-dose chemotherapy, these values became normal after high-dose chemotherapy. The other patient (Sal 3) recurred in retroperitoneal lymph nodes after 6 months of initial treatment including RPLND and two adjuvant courses of BEP therapy. This patient underwent RPLND first, since serum markers did not rise and growing teratoma syndrome was suspected. However, the tumor invaded to the mesocolon and histological findings of the tumor revealed a yolk sac tumor with severe lymphatic and venous invasion. This patient was judged to be cisplatin resistant and underwent one course of etoposide, ifosfamide and cisplatin (VIP) therapy as salvage. During VIP therapy, PBSCH was performed and two courses of high-dose chemotherapy followed. Both of them lived without disease 12 and 42 months after high-dose chemotherapy. The other patient (Sal 2) could not undergo multicycles of high-dose chemotherapy due to myocardial infarction. He died 12 months after one cycle of high-dose chemotherapy.

Hematologic toxicity and recovery (Table 6)

Fourteen patients underwent 26 courses of high-dose chemotherapy in total. The median number of $CD34^+$ cells transfused was 5×10^6 cells/kg (range 2.7-16). The median period of rh-GCSF administration was 10 days (range 8-17). Although all patients experienced grade 4 hematotoxicity, leukocyte count all recovered within 11 days after PBSCT. The median platelet nadir was $1.7 \times 10^4/\mu l$ (range 0.6-3.1) and platelet recovery to $5 \times 10^4/\mu l$ or more took a median of 12 days (range 9-16) after PBSCT. The median Hb nadir was 6.9 g/dl (range 5.7-10.8) and red blood cells (RBC) were transfused in 15 out of 26 courses (57.7%). No side effects of PBSCT were apparent.

Non-hematologic toxicity (Figure 1)

Non-hematologic toxicity was classified according to the 'Grading of toxicity' by the Japan Clinical Oncology Group and is listed in Figure 1. Pharyngitis and stomatitis was observed in 30 and 54% of the patients, respectively. Only one patient had grade 1 renal dysfunction. Liver dysfunction and diarrhea were observed in 39%. None of these effects was life threatening and no treatment-related death was evident.

Table 6. Hematological recovery

		Median	Range
WBC nadir	(/μl)	200	0–400
WBC > 1000	(days after PBSCT)	9	8–11
Plt nadir	(/μl)	1.7	0.6–3.1
Plt > $5 \times 10^4 \mu l$	(days after PBSCT)	12	9–16
Infused Plt	(U)	40	20–100
Hb nadir	(g/dl)	6.9	5.7–10.8
Infused RBC	(U)	2	0–6

WBC, white blood cell; PBSCT, peripheral blood stem cell transplantation; Plt, platelet; Hb, hemoglobin; RBC, red blood cell.

Table 5. Outcome of salvage SHD therapy

Patient no.	Metastatic site before HDC	AFP before HDC	β-HCG before HDC	No. of HDC (% dose)	AFP	β-HCG	Additional treatment	Follow up (months)	Status of disease
Sal 1	RPLN (Y, E)	546	WNL	1 (80%)	WNL	WNL	RT	42	NED
Sal 2	Lung	WNL	8.3	1 (80%)	WNL	3.56	PE (2), NC+MAC (1)+VP 16 p.o	12	DOD
Sal 3	RPLN (Y) invasion of mesocolon	WNL	WNL	2 (80%)	WNL	WNL	RT	12	NED

RPLN, retroperitoneal lymph node; Y, yolk sac tumor; E, embryonal carcinoma; WNL, within normal limits; RT, radiation; NED, no evidence of disease; DOD, died of disease.

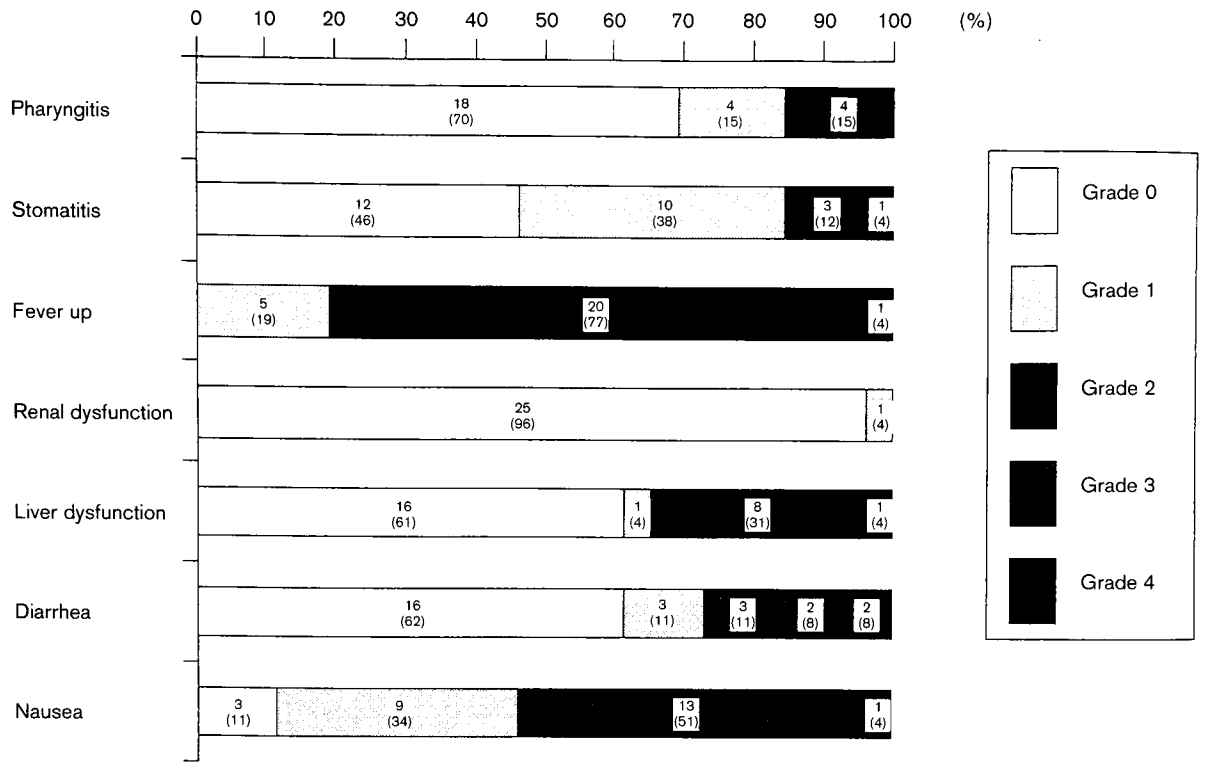

Figure 1. Non-hematological toxicity of high-dose chemotherapy. Toxicity was classified according to 'Grading of toxicity' by the Japan Clinical Oncology Group. Numbers in parentheses represent percentage of patients.

Discussion

After the success of cisplatin-based chemotherapy for treating germ cell tumors, an important issue is to develop the most effective therapy for patients who are refractory to or who have relapsed from conventional chemotherapy. These numbers are estimated at 20% of advanced germ cell tumors. Salvage chemotherapy consisting of VIP has been widely applied to such patients. The response rate and durable complete remission rates are 25 and 15%, respectively, which are unsatisfactory.[11] Therefore, a dose-intensified regimen has been introduced after conventional salvage chemotherapy. Nichols *et al.* reported that five of 38 patients (13%) who had undergone initial BEP and subsequent VIP therapy went into continuous complete remission over a minimal follow-up of 1 year.[6] Since most high-dose chemotherapy regimens consist of carboplatin (up to 1500 mg/m^2), etoposide (1200-1500 mg/m^2) and ifosfamide (7.5 g/m^2)/cyclophosphamide (90-150 mg/kg), which is essentially the same as VIP therapy, high-dose chemotherapy was introduced as an initial salvage strategy instead of VIP when the safety of high-dose chemotherapy could be secured. In fact, Motzer *et al.* reported that the early use of high-dose chemotherapy reduced toxic hematologic effects compared with after multicycles of chemotherapy.[7] Recently, they reported the efficacy and safety of high-dose chemotherapy as a first-line strategy for patients with poor-risk germ cell tumors.[12] Thus, high-dose chemotherapy has been starting earlier. The main reason for this is safety. As supportive therapy improved, the rate of treatment-related death in high-dose chemotherapy decreased. Nichols reported a 13% rate of treatment-related death in 1992,[6] but recently this has dropped to 0 to 4%.[12,13]

Most clinicians performing high-dose chemotherapy adopt autologous bone marrow transplantation (ABMT) as a bone marrow rescue. PBSCT is currently replacing ABMT. Indeed, PBSCT is superior in several ways to ABMT. For example, ABMT requires general anesthesia for harvest, whereas PBSCT does not. PBSCT is performed during scheduled conventional chemotherapy, whereas ABMT needs time. Hematologic recovery is more rapid after PBSCT than ABMT. Beyer *et al.* demonstrated the earlier recovery of neutrophils and platelets after PBSCT than by a prospective randomized trial.[14] In our present study, neutrophils recovered to over 1000/μl within 11 days after PBSCT in all patients and no one died of

treatment-related causes. We also applied ABMT before the introduction of PBSCT and we believe it to be safer and more convenient than ABMT.

Ten out of 15 patients (67%) who underwent high-dose chemotherapy remain disease-free and five of them were followed up for over 24 months. Although we assume that this clinical outcome is much better than that before the introduction of high-dose chemotherapy, we cannot draw any conclusions since this was not a prospective randomized study. Randomized trials should be performed to prove the efficacy of the therapy. It is certain that randomized trials should be performed to prove the efficacy of the therapy. However, testicular cancer patients are rare and young. It seems impossible to conduct randomized trials in a single institute. In fact, only one randomized trial failed to show a therapeutic benefit.[15] However, limitations of this trial have been pointed out.[16] Another randomized trial comparing four cycles of BEP therapy versus two cycles of BEP therapy followed by two cycles of high-dose chemotherapy is now ongoing by the US Inter group. In Japan, multicenter clinical trials of high-dose chemotherapy combined with PBSCT are ongoing. These studies will disclose the effect and limitation of high-dose chemotherapy. In our study, we showed the safety of high-dose chemotherapy combined with PBSCT and demonstrated fairly good clinical outcomes. We will accumulate more cases and follow up these patients for longer periods to precisely evaluate high-dose chemotherapy.

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