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Original

High-dose Chemotherapy with Peripheral Blood Stem Cell Transplantation for Patients with Poor Prognosis Advanced Germ Cell Tumor

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SUMMARY

About one half of all advanced germ cell tumor (GCT) patients with poor prognosis defined by the International Germ Cell Cancer Collaborative Group (IGCCCG) die of cancer. We evaluated salvage high-dose chemotherapy (HDCT) with peripheral blood stem cell transplantation (PBSCT) for patients with poor prognosis advanced GCT in Dokkyo Medical University. Three patients with poor prognosis advanced GCT were treated with HDCT as salvage chemotherapy. Two patients had primary testicular GCT and one patient had primary mediastinal GCT. Treatment responses were pathological complete remission (CR) in one, surgical CR in one and partial remission (PR) in one. Effectiveness and side effects of HDCT with PBSCT for poor prognosis cases with advanced GCT were shown in this study. However, further accumulation of these studies is needed.

Key Words : Advanced germ cell tumor, Poor prognosis, High dose chemotherapy, Peripheral blood stem cell transplantation

INTRODUCTION

Germ cell tumor (GCT) account for only 1% of all cancers in men[1], but are the most common solid tumor in males between 15 and 35 years of age, a population in whom all cancers are rare[2]. Approximately 95% of malignant tumors arising in the testis are GCTs, with other testicular neoplasms occurring more rarely. Approximately 5-7% of GCT arises in extragonadal sites[3]. Extragonadal GCTs most commonly arise in the midline of the body, particularly in the retroperitoneum and the mediastinum.

GCT has attracted major interest from medical oncologists because of its uniquely good response to combination chemotherapy. During the last three decades, GCT has become the most curable type of solid tumor even at an advanced stage. Seventy to 80% of patients with metastatic GCTs can be cured with cisplatin-based combination chemotherapy with or without surgical excision of post-chemotherapy residual masses[4]. The remaining 20% to 30% of metastatic GCTs become candidates for salvage chemotherapy, either because of incomplete response to primary chemotherapy or because of relapse after complete remission (CR)[4,5]. Various strategies have been utilized as sec-

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Table 1 Patient's characteristics

	Age	Pathology	Tumor marker				Metastases
			α-FP	HCG	β-HCG	LDH	
			(ng/ml)	(IU/l)	(ng/ml)	(mU/ml)	
(1)	40	IT, MT, E, Y	10400	10900	210	1928	RPLN, Lung
(2)	24	S, E, Y	33100	740	7.1	2904	RPLN, Lung
(3)	21 (mediastinal primary)	IT	88800	(not evaluated)		507	LN

IT ; Immature Teratoma, MT ; Mature teratoma, E ; Embryonal carcinoma, Y ; Yolk sac tumor, S ; Seminoma, RPLN ; Retro-peritoneal lymph node, LN ; lymph node
α-FP ; alpha fetoprotein, HCG ; human chorionic gonadotropin,
β-HCG ; beta human chorionic gonadotropin, LDH ; lactate dehydrogenase

ond-line chemotherapy after failure to cure with primary cisplatin-based combination chemotherapy. This includes standard-dose regimens with cisplatin plus ifosfamide plus either etoposide[6] or paclitaxel[7] or HDCT with peripheral blood stem cell transplantation (PBSCT)[8]. There are no randomized studies proving the superiority of one approach compared with another. However, for patients who are refractory to standard dose cisplatin-based combination chemotherapy, HDCT has been the logical approach offering a distinct possibility for long-term survival and cure[9].

Prognostic factor studies in advanced GCT have led to the definition of risk groups suitable for different treatment strategies ; most recently, the International Germ Cell Cancer Collaborative Group (IGCCCG) has produced a widely accepted classification system for advanced GCTs[10]. The patient population is divided into 3 groups defined as good, intermediate and poor prognosis groups respectively. These groups comprise 60%, 26% and 14% of advanced GCT patients, with corresponding cure rates of approximately 90%, 80% and 50%[10]. Since about one half of all patients with poor prognosis advanced GCT die of cancer, current clinical investigations seeking to improve survival in these patients have focused on developing more effective chemotherapy treatments. One of the important strategies for poor prognosis advanced GCT patients has been based on the use of more intensive chemotherapy. It is very important to report the evaluation of the treatment experience of advanced GCT with poor prognosis, in order to share useful knowledge of these few and valuable cases. Hasumi et al. reported the original article of HDCT with PBSCT for 5 patients with poor risk advanced GCT (poor prognosis of IGCCCG or advanced extent of Indiana University stage)[11]. In this report, we evaluated our HDCT with PBSCT for patients with poor prognosis advanced GCT.

Table 2 Status before HDCT

Prior chemotherapy	Pre-HDCT		
	α-FP	β-HCG	LDH
	(ng/ml)	(ng/ml)	(mU/ml)
(1) VIP (2 cycles)	71	0.5	474
(2) BEP (2 cycles)	347	0.1	396
(3) EP (3 cycles), VIP (1 cycle)	44400	2.5	371

VIP ;
Etoposide 100 mg/m^2/day (day 1～day 5)
Ifosfamide 1.2 g/m^2/day (day 1～day 5)
Cisplatin 20 mg/m^2/day (day 1～day 5)
BEP ;
Bleomycin 30 mg/day (day 1, day 8, day 15)
Etoposide 100 mg/m^2/day (day 1～day 5)
Cisplatin 20 mg/m^2/day (day 1～day 5)
EP ;
Etoposide 100 mg/m^2/day (day 1～day 5)
Cisplatin 20 mg/m^2/day (day 1～day 5)

Patients

We treated three patients with poor prognosis advanced GCT between April 1995 and January 2006. All three patients were treated with HDCT as salvage chemotherapy. Patient characteristics and patient status before HDCT are summarized in Tables 1 and 2. All patients were male with an average age of 28.3 years (range 21-40). Two patients had primary testic-

ular GCTs and one patient had primary mediastinal GCT. Both patients with testicular GCT underwent radical orchiectomy. One patient with mediastinal primary GCT underwent partial resection of the mediastinal tumor. Histological types of GCT were non-seminomas in two and mixed type of seminoma and non-seminoma in one. Follow-up periods for these patients were 105 months, 148 months and 11 months, respectively.

Treatment

Treatment consisted of standard dose cisplatin-based combination chemotherapy plus granulocyte-colony stimulating factor (G-CSF) followed by peripheral blood stem cell (PBSC) collection and subsequently HDCT with PBSCT. It was planned to separate sufficient numbers of PBSC in order to support each course of HDCT with approximately 2×10^6 $CD34^+$ cells/kg body weight. HDCT consisted of etoposide 400 mg/m^2, ifosfamide 2.0 g/m^2 and carboplatin 300 mg/m^2 given intravenously on days −6, −5, −4 and −3 during each cycle of therapy. The day of PBSCT was designated as day 0 ; the days before are indicated as minus and the days following are indicated as plus. All patients were scheduled to receive autologous PBSC support with$>2\times10^6$ $CD34^+$ cells/kg body weight retransfused on day 0 of each HDCT cycle. All patients received G-CSF, 5 mg/kg/day starting on day 0 and continuing until blood cell count recovery. If all abnormally elevated serum tumor marker values returned to normal, residual tumor was resected when it seemed to be including viable tumor cells.

Evaluation of response

Patients with complete disappearance of all tumor lesions including marker normalization with chemotherapy alone were classified as achieving complete remission (CR). If patients became free of disease only after additional resection of necrosis or mature teratoma, they were considered to have achieved 'pathological complete remission' (pCR) and if viable undifferentiated tumor elements could be demonstrated, they were considered to have achieved 'surgical complete remission' (sCR). Partial remission (PR) was defined as a>50% reduction in the sum of the products of the longest perpendicular diameters of measurable lesions, and normal tumor markers were considered PRm− ; PRm+required a decline of tumor markers without normalization post-HDCT. No change (NC) was defined as no objective decrease in the tumor measurements qualifying as PR and no objective increase qualifying as progressive disease (PD) ; and PD was defined as greater than 25% increase in the product of the longest perpendicular diameters of any measurable lesion or the appearance of new lesions or an increase in serum markers. Patients with normalization of tumor markers and complete resection of all residual masses were considered to have "no evidence of disease" (NED). Toxicity was evaluated according to the National Cancer Institute-Common Terminology Criteria for Adverse Event version 3.0 (NCI-CTCAE v3.0) classification.

RESULTS

Therapeutic results

Therapeutic results and current status for each patient are summarized in Tables 3 and 4. Two patients are currently alive. One patient died of progressive disease after completion of therapy. Treatment responses were one pCR, one sCR and one PRm+.

Subsequent therapy and survival

Case 1 underwent retro-peritoneal lymph node dissection (RPLND) and thoracotomy after HDCT, and histological examination proved that the masses were mature teratoma and embryonal carcinoma (sCR). Adjuvant chemotherapy (paclitaxel, gemcitabine and nedaplatin ; TGP) was performed, and his status has remained NED for 94 months. Case 2 underwent RPLND after HDCT, and histological examination proved the mass to be necrotic tissue (pCR). Thereafter, he developed adrenal metastasis and lymph node of Virchow metastasis, and TGP chemotherapy was performed. Adrenalectomy and lymph node dissection were performed because all abnormally elevated serum tumor marker values returned to normal. Histological examination proved the mass of the adrenal gland to be yolk sac tumor and that of the lymph node of Virchow to be seminoma. Adjuvant chemotherapy (TGP) was performed, and he has remained NED for 52 months. One patient could not continue HDCT after two cycles of HDCT because of poor tolerance due to

Table 3 Therapeutic results

HDCT	Post HDCT			Radiological response	Surgery for residual tumor		Pathology
	α-FP (ng/ml)	β-HCG (ng/ml)	LDH (mU/ml)				
(1) 2 cycles	5	0.1	288	PR	RPLND	→	MT
					Thoracotomy	→	E
(2) 2 cycles	5	0.1	207	PR	RPLND	→	viable cell (−)
(3) 2 cycles	332	1.8	132	PR	(−)		

HDCT ; High dose chemotherapy
Etoposide : 400 mg/m^2/day (day −6～day −3)
Ifosfamide 2.0 g/m^2/day (day −6～day −3)
Carboplatin 300 mg/m^2/day (day −6～day −3)
PR ; Partial remission, RPLND ; Retro-peritoneal lymph node dissection

Table 4 Current status of patients

	Prognosis	Additional treatment
(1)	Surgical CR	TGP (3 cycles) (NED : more than 94 months)
(2)	Pathological CR → Relapse (Adrenal gland and LN of Virchow)	TGP (7 cycles) Adrenalectomy → Y LND → S (NED : more than 52 months)
(3)	PR m (+) → PD (Dead)	VIP (3 cycles)

CR ; Complete remission, NED ; No evidence of disease,
LND ; lymph node dissection
TGP ;
Paclitaxel 160 mg/m^2/day (day 1, day 8)
Gemcitabine 1000 mg/m^2/day (day 1, day 8)
Nedaplatin 100 mg/m^2/day (day 2)

severe toxicities despite a response to HDCT. The patient underwent standard dose VIP chemotherapy after two cycles of HDCT, but died of progressive disease 5 months after HDCT.

Treatment side effects

Toxicities are summarized in Table 5. As expected all patients experienced severe hematological toxicities, but all showed complete hematological recovery after stem cell re-infusion. There were no deaths, and none of the patient required hemodialysis or developed chronic renal insufficiency. Apart from hematological toxicity, side effects consisted mainly of gastrointestinal events and infectious complications. Gastrointestinal side effects were mostly manageable by supportive measures such as antiemetic therapy.

DISCUSSION

Remarkable progress has been made in the medical treatment of metastatic GCTs, achieving a substantial increase in cure rates from approximately 25% in the mid-1970s to nearly 80% today[5]. The successful management of advanced GCTs with cisplatin-based combination chemotherapy with or without surgical excision of post-chemotherapy residual masses stands as a milestone in medical oncology. Improved treatment outcome for metastatic GCTs was observed in a randomized trial of a combination with bleomycin, etoposide and cisplatin (BEP) as standard treatment[2]. For advanced GCT, drug resistance is the major cause of treatment failure. The development of drug resistance is dose-related and one important component of cura-

Table 5 Side effects

	NCI-CTCAE v3.0 grade				
	0	1	2	3	4
Leukopenia					3 cases
Thrombocytopenia				1 case	2 cases
Fever		1 case	2 cases		
Nausea				3 cases	
Anorexia			1 case	2 cases	
Renal dysfunction	3 cases				

NCI-CTCAE v3.0 ; National Cancer Institute-Common Terminology Criteria for Adverse Event version 3.0

tive experimental drug schedules is the use of a combination of cytotoxic agents at their maximum tolerated doses (MTDs). It may be clear that resistance to chemotherapy must be overcome by the introduction of non-cross resistant drugs and drug dose increment. Although less toxic treatment is being investigated for patients with good prognosis advanced GCT, one of the important strategies for patients with poor prognosis advanced GCT has been the use of more intensive chemotherapy.

There is no consensus as to whether HDCT should be given to any defined subset of advanced GCT patients. At Memorial Sloan-Kettering Cancer Center[12], all patients with advanced GCT were treated with two cycles of standard dose cisplatin-based combination chemotherapy. Serum tumor markers were determined weekly (days 6, 14, 21) during each cycle of chemotherapy. Before administration of the third cycle of chemotherapy, half-lives of serum tumor markers were calculated starting from the day 6 value and used to direct further therapy. If the serum tumor markers were rising or the half-life was prolonged (unsatisfactory marker decline), therapy was changed to HDCT (two cycles of HDCT) with PBSCT. If the serum tumor markers showed a decline in their respective half-lives (satisfactory marker decline), the patient was considered an early responder and received additional cycles of standard dose cisplatin-based combination chemotherapy. In the present study, two patients received HDCT as second line chemotherapy. In both patients, the half-lives of serum tumor markers were prolonged before administration of the third cycle of chemotherapy. Therefore, the treatment strategy was changed, and HDCT was performed. Case 3 received HDCT as third line chemotherapy, because the patient was referred to our hospital after first line chemotherapy without collecting PBSC. Although the half-lives of serum tumor makers were prolonged in this patient, he received standard dose cisplatin-based combination chemotherapy as second-line chemotherapy in order to collect PBSC.

Einhorn et al. reported that advanced GCT is potentially curable by HDCT, even when this regimen is used as second-line, third-line or later therapy[13]. A randomized trial of three cycles of standard dose cisplatin-based combination chemotherapy plus one cycle of HDCT compared with four cycles of conventional dose cisplatin-based combination chemotherapy did not show any survival benefit[14]. It may be that multiple cycles of HDCT are necessary to achieve a favorable outcome, and therefore, the single cycle of HDCT given in that trial may not have significantly affected the outcome. Motzer et al. pointed out that dose-intensive therapy for patients with a poor-risk advanced GCT who have had minimal prior therapy is preferred over treatment of heavily pretreated patients because chemotherapy-related myelotoxicity is cumulative[15]. Non-randomized studies of first line sequential HDCT (one cycle of standard dose cisplatin-based combination chemotherapy followed by three to four sequential cycles of HDCT) for patients with a poor-risk advanced GCT demonstrated preliminary results that compared favorably to historical data[16,17].

Recently, treatment programs have incorporated primary HDCT in the treatment strategy for previously untreated patients with a poor-risk advanced GCT. Droz et al. did not support the use of primary HDCT

for patients with a poor-risk (high-volume metastatic non-seminomatous GCT), because a randomized trial of two cycles of standard dose cisplatin-based combination chemotherapy plus two cycles of HDCT compared with four cycles of standard dose cisplatin-based combination chemotherapy showed no survival benefit[18]. However, all results must be interpreted with caution because of the small patient numbers that characterized the randomized phase 2 trial. Heidenrich commented that a currently ongoing trial on primary HDCT will further elucidate its role in the management of advanced GCT patients with a poor-risk[19]. In fact, he pointed out that matched-pair analysis and the ongoing prospective randomized clinical phase 3 trial of primary HDCT suggest a 20% improvement in cancer-specific survival. Mozter et al. concluded that the routine inclusion of primary HDCT for patients with a poor-risk advanced GCT (intermediate and poor prognosis according to the IGCCCG) did not improve treatment outcome in the randomized phase 3 trial[20]. They reported that the 1-year durable CR rate and overall survival at 2 years did not differ between standard dose chemotherapy group (four cycles of cisplatin-based combination chemotherapy) and HDCT group (two cycles of standard dose cisplatin-based combination chemotherapy plus two cycles of HDCT). However, for patients with unsatisfactory marker decline after two cycles of standard dose cisplatin-based combination chemotherapy, the 1-year durable CR rate was 34% for the standard dose chemotherapy group and 61% for the HDCT group ($P=0.03$). This raises the possibility that patients with a poor-risk advanced GCT who have an unsatisfactory marker decline during the first two cycles of standard dose chemotherapy such as our three cases may benefit from switching to HDCT.

In the present study, all patients received further chemotherapy after HDCT. Identifying new treatment options with significant antitumor activity in patients who have received HDCT remains a priority. Nicolai et al. investigated the long-term results of a combination of paclitaxel, cisplatin and gemcitabine for salvage chemotherapy as a third-line or further chemotherapy in 22 patients with advanced GCTs[21]. The response rate was 36% including 4 patients who were long-term disease-free survivors after more than 80, 81, 94 and 99 months. Furthermore, Einhorn et al. suggested that long-term disease-free survival is possible with paclitaxel plus gemcitabine in the patient population that progressed after HDCT, and had not previously received paclitaxel or gemcitabine[22]. In this phase II study, they reported that the overall response rate and CR rate were 31% and 12.5% in thirty-two patients. In our study, 2 patients were treated with paclitaxel, gemcitabine and nedaplatine (TGP) after HDCT, and sCR was achieved in one and NC in one and these two have remained disease-free survivors for more than 52 and 94 months, respectively. Ongoing research in this area may not only improve the treatment of patients with refractory disease but also facilitate further insight into the mechanisms of drug resistance. It is hoped that increased knowledge of the molecular mechanisms underlying GCT will lead to the development of further new therapeutic options.

Conclusion

In the present study, HDCT with PBSCT can be used in poor prognosis GCTs with acceptable toxicity, and represents an effective salvage treatment. However, data from more patients should be accumulated in order to describe final conclusions regarding the effectiveness of HDCT with PBSCT for poor prognosis advanced GCTs.

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