PROGNOSTIC ANALYSIS OF JAPANESE MEN WITH METASTATIC GERM CELL TUMORS SHOWING FAVORABLE RESPONSE TO BLEOMYCIN, ETOPOSIDE AND CISPLATIN AS FIRST-LINE CHEMOTHERAPY

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The objective of this study was to evaluate the efficacy of first-line bleomycin, etoposide and cisplatin (BEP) chemotherapy in Japanese patients with metastatic germ cell tumors (GCTs). Between 1996 and 2006, 88 male patients with metastatic GCTs were treated with first-line BEP at our institution. Of these 88, 47 (16, seminoma; 31, nonseminoma), who did not receive high-dose chemotherapy following BEP because of the normalization of serum tumor markers, were included in this study. The primary site was the testis in 42 patients, retroperitoneum in 3, and mediastinum in 2. The full-dose regimen used for BEP consisted of cisplatin 20 mg/m^2 on days 1 to 5, etoposide 100 mg/m^2 on days 1 to 5, and bleomycin on days 2, 9 and 16. Therapeutic outcome was assessed according to several clinicopathological parameters. Following 2 to 4 cycles of BEP (median, 4 cycles), α-fetoprotein, β-human chorionic gonadotropin and lactate dehydrogenase were normalized in all 47 patients. Eighteen patients (38.3%) achieved a complete response (CR) after BEP alone, while BEP resulted in a partial response and stable disease in the remaining 23 (48.9%) and 6 (12.8%), respectively. In addition, surgical resection of the residual tumors following BEP was performed in 15 patients, of whom 12 (80.0%) and 3 (20.0%) achieved pathological and surgical CR, respectively. At a median follow-up of 27 months, all patients were alive; however, disease recurrence occurred in 5 (seminoma, 1; nonseminoma, 4), and all these 5 were subsequently treated with high-dose chemotherapy as salvage therapy. In this series, 1-, 3- and 5-year recurrence-free survival rates were 95.0, 91.4 and 79.2%, respectively, and, there was no significant difference in recurrence-free survival between patients with seminoma and those with nonseminoma. These findings suggested that patients with metastatic GCTs, regardless of histological subtype (*i.e.*, seminoma or nonseminoma), who showed favorable response to first-line BEP chemotherapy, could achieve an excellent prognostic outcome.

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Key words : BEP chemotherapy, Germ cell tumor, Recurrence, Metastasis

INTRODUCTION

Although germ cell tumors (GCTs) are relatively rare, accounting for only 1% of all malignancies in men, they are medically and economically important diseases since they represent the most common solid tumor in men between 15 and 35 years of age, suggesting the potential for loss of productive years. The introduction of cisplatin-based combination chemotherapy regimens, however, has resulted in the conversion of metastatic GCTs with an extremely poor prognosis into the paradigm of a curable solid malignancy. Among several regimens available, BEP, which consists of bleomycin, etoposide and cisplatin, has proved to be highly efficacious against metastatic GCTs, and is currently the most widely used regimen as a first-line therapy for metastatic GCTs[1]. For example, Saxman et al. reported that 118 patients with minimal- or moderate-stage disseminated GCTs who received either three or four cycles of BEP achieved 5-year recurrence-free survival greater than 80%[2]. At our institution as well, since 1996, BEP has been administered as a first-line chemotherapy following orchiectomy for patients with metastatic GCTs.

Despite advances in the treatment for men with metastatic GCTs, there remains a small but significant group of patients, even those with lower-risk GCTs, who will develop recurrent diseases after BEP therapy[2]. Recently, a variety of efforts have been made to improve therapeutic outcomes for men with intermediate- or high-risk GCTs, such as the introduction of novel chemotherapeutic agents and high-dose chemotherapy combined with peripheral blood stem cell transplantation[3–5]. However, the appropriateness of first-line chemotherapy regimens used for metastatic GCT patients with comparatively favorable characteristics has not been intensively investigated, particularly in Japanese patients. Considering these issues, we retrospec-

tively analyzed the clinical outcomes of BEP chemotherapy performed for 47 Japanese patients who did not receive the high-dose chemotherapy regimen usually applied if the tumor marker remains high following 2–3 courses of BEP.

PATIENTS AND METHODS

Between 1996 and 2006, there were 88 male patients diagnosed as having metastatic GCTs who were treated with BEP as first-line chemotherapy at our institution. Of these 88, 41 whose tumor markers remained high after 2–3 courses of BEP subsequently received high-dose chemotherapy[6]; therefore, this study included the remaining 47 who did not receive high-dose chemotherapy following BEP because of the normalization of tumor markers. The characteristics of these 47 are summarized in Table 1 according to histological subtype (seminoma, 16; nonseminoma, 31). Clinicopathological staging and response were determined based on the General Rules for Clinical and Pathological Studies on Testicular Tumors[7] and risk criteria were stratified according to the International Germ Cell Consensus Classification (IGCCC)[8].

As a rule, BEP therapy was repeated at 3-week intervals for a total of 2 to 4 cycles (median, 4 cycles). The regimens of BEP were as follows: etoposide 100 mg/m^2 administered on days 1 to 5 of each cycle, cisplatin 20 mg/m^2 on days 1 to 5 of each cycle, and bleomycin 30 mg on day 2, 9 and 16 during cycles 1 through 2.

Surgical resection was performed on patients who showed evidence of residual tumor mass following BEP therapy with one exception; that is, surgery was not recommended in patients with seminoma who have a residual mass smaller than 3 cm after BEP according to previous studies[9,10]. In this series, complete response was subdivided into the three groups as follows: patients in whom the metastatic tumors disappeared completely and whose tumor markers became normal were judged to have achieved clinical complete response (cCR), while pathological complete response (pCR) and surgical complete response (sCR) were defined as complete resection of either necrosis, fibrosis or mature teratoma with no viable residual disease and the complete excision of all viable tumors, respectively.

All statistical analyses were performed using Statview 5.0 software (Abacus Concepts, Inc., Berkeley, CA, USA). The period of recurrence-free survival was measured from the initiation of chemotherapy to the appearance of recurrent disease or the date of last follow-

Table 1. Patients characteristics

	Seminoma (n=16)	Nonseminoma (n=31)	Over all (n=47)
Median age (years, range)	36 (19–67)	29 (21–50)	31 (19–67)
Site of primary tumor (%)			
Testis	14 (87.4)	28 (90.3)	42 (89.4)
Retroperitoneum	1 (6.3)	2 (6.5)	3 (6.4)
Mediastinum	1 (6.3)	1 (3.2)	2 (4.2)
Clinical stage (%)			
II	8 (50.0)	13 (41.9)	21 (44.6)
III	6 (37.5)	15 (48.4)	21 (44.6)
Extragonadal	2 (12.5)	3 (9.7)	5 (10.8)
Pretreatment AFP (ng/ml)			
No. elevated (>10)	0 (0.0)	27 (87.1)	27 (57.5)
Median elevated value	—	276.3	276.3
Median range	—	12.1–27,521.1	12.1–27,521.1
Pretreatment β HCG (nglml)			
No. elevated (>0.1)	12 (75.0)	22 (71.0)	34 (72.4)
Median elevated value	0.9	1.6	1.1
Median range	0.2–22.4	0.2–779.8	0.2–779.8
Pretreatment LDH (UIL)			
No. elevated (>220)	9 (56.2)	25 (80.1)	34 (72.4)
Median elevated value	778.2	674.9	726.3
Median range	380.4–4,112.6	222.8–2,609.3	222.8–4,112.6
IGCCCG classification (%)			
Good	10 (62.5)	7 (22.5)	17 (36.2)
Intermediate	6 (37.5)	15 (48.4)	21 (44.6)
Poof	—	6 (19.4)	6 (12.8)
Not Classifiable	0 (0.0)	3 (9.7)	3 (6.4)

AFP, α-fetoproten, β-hCG, β-human chorionic gonadotropin, LDH, lactate dehydrogenase; IGCCCG, Intematlonal Germ Cell Cancer Collaboratlve Group.

up. Recurrence-free survival rates of patients were analyzed by the Kaplan-Meier method, and differences were determined by log-rank test. Probability (p) values less than 0.05 were considered significant.

RESULTS

Following 2–4 cycles of BEP (median, 4 cycles), α-fetoprotein (AFP), β-human chorionic gonadotropin (β-hCG) and lactate dehydrogenase (LDH) were normalized in all 47 patients. As shown in Table 2, 18 (38.3%) achieved cCR, while BEP resulted in partial response and stable disease in the remaining 23 (48.9%) and 6 (12.8%), respectively. Of 29 patients with residual tumor mass after BEP therapy, 15 underwent surgical resection of residual tumor, and 12 and 3 were diagnosed with pCR and sCR, respectively. Of 3 patients who achieved sCR, 2 received either high-dose ICE (ifosfamide, carboplatin, etoposide) or conventional VIP (etoposide, ifosfamide, cisplatin) therapy, while the remaining 1 refused to undergo further treatment. Despite the presence of residual mass following BEP, 14 patients did not undergo subsequent surgical resection; that is, 7 refused to undergo surgical resection, and surgery was not recommended for the remaining 7 patients with seminoma because the residual tumor was smaller than 3 cm.

At a median follow-up of 27 months (range, 2–133 months), all 47 patients were alive; however, 5 (10.7%; seminoma, 1; nonseminoma, 4) developed recurrent diseases during the median recurrence-free period of 20

Table 2. Treatment outcomes

	Seminoma (n=16)	Nonseminoma (n=31)	Over all (n=47)
Median cycles of BEP (range)	4 (2–4)	4 (2–4)	4 (2–4)
Resection of residual tumor after BEP (%)	1 (6.3)	14 (45.2)	15 (31.9)
Response (%)			
cCR	8 (50.0)	10 (32.3)	18 (38.3)
pCR	1 (6.2)	11 (35.5)	12 (25.5)
sCR	0 (0)	3 (9.7)	3 (6.4)
PR	6 (37.6)	6 (19.3)	12 (25.5)
SD	1 (6.2)	1 (3.2)	2 (4.3)
Disease recurrence after BEP (%)	1 (6.3)	4 (12.9)	5 (10.6)
Current status			
No evldence of disease	16	29	45
Alive with disease	0	2	2
Died of disease	0	0	0

BEP, bleomycin, etoposide, cisplatin, cCR, clinical complete response; pCR, pathological complete response; sCR, surgical complete response; PR, padial response; SD, stable disease.

Table 3. Patients characteristics and clinical outcomes of relapse cases

Case No.	Age (years)	Primary site	Histological diagnosis	Site of metastasis	Pretreatment AFP (ng/ml)	Pretreatment β-HCG (ng/ml)	Pretreatment LDH (IU/L)	IGCCCG classification
#1	40	Testis	S	Lung	5	0.63	595	Good
#2	31	Retroperitoneum	E	None	1,600	0.6	1,100	Intermediate
#3	31	Testis	Y	Lung, RPLN	3,165	293	1,566	Intermediate
#4	31	Testis	E, Y	Lung, RPLN	4,430	104	1,771	Intermediate
#5	36	Testis	S, C	RPLN	4	2	281	Intermediate

Case No.	Cycles of BEP	Postchemotherapy surgery		Response	Recurrence-free interval (months)	Salvage treatment	Current status
		Resected site	Histological diagnosis				
#1	2	—	—	cCR	20	HDCT	Disease-free
#2	3	RPLN	Necrosis	pCR	48	HDCT+TIP	Alive wlth disease
#3	4	—	—	PR	48	HDCT	Alive with disease
#4	4	RPLN	E	sCR	4	HDCT+Surgery	Disease-free
#5	5	—	—	PR	2	HDCT+Surgery	Disease-free

AFP, α-fetoprotein; β-hCG, β-human chorionic gonadotropin; LDH, lactate dehydrogenase; IGCCCG: International Germ Cell Cancer Collaborative Group; S, seminoma; E, embryonal carcinoma; Y, yolk sac tumor; C, choriocarcinoma; RPLN: retroperitoneal lymph node; BEP, bleomycin, etoposide, cisplatin; cCR: clinical complete response; pCR: pathological complete response; sCR: surgical complete response; PR: partial response; HDCT: high dose chemotherapy; TIP: paclitaxel, ifosfamide, cisplatin.

months (range, 2 to 48 months). Table 3 summarizes the characteristics of 5 patients with disease recurrence. Following the diagnosis of disease recurrence, high-dose ICE was administered in all 5 patients as salvage therapy. Of these 5, 3 are currently alive disease-free after salvage therapy, and the remaining 2 are alive with disease. As presented in Table 3, one (case #2) developed disease recurrence again after high-dose ICE, which continued to progress despite additional chemotherapies, and is currently being followed without any treatment, while another (case #3) is now receiving high-dose ICE for recurrent disease following BEP. In this series, 1-, 3- and 5-year recurrence-free survival rates were 95.0, 91.4 and 79.2%, respectively (Fig. 1), and there was no significant difference in the recurrence-free survival between patients with seminoma and those with nonseminoma (Fig. 2).

DISCUSSION

Accumulated evidence clearly demonstrated that BEP, currently regarded as the most effective regimen as first-line therapy for metastatic GCT, could achieve

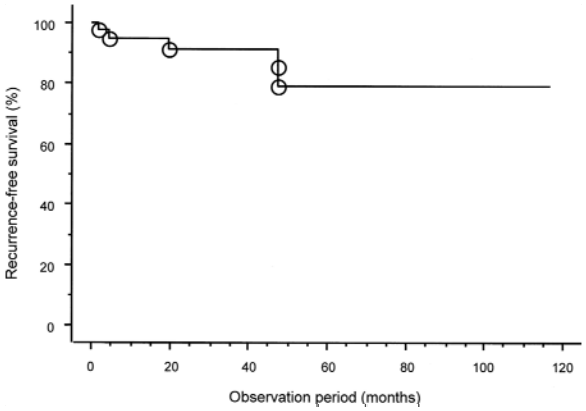

Fig. 1. Recurrence-free survival in 47 patients with metastatic germ cell tumors who were treated with bleomycin, etoposide and cisplatin chemotherapy.

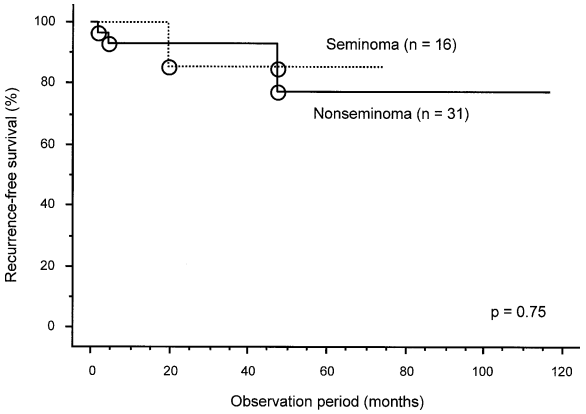

Fig. 2. Comparison of recurrence-free survival between 16 patients with seminoma and 31 with nonseminoma who were treated with bleomycin, etoposide and cisplatin chemotherapy.

recurrence-free survival rates greater than 80% for patients with comparatively favorable characteristics[1,2]. Several studies, however, have identified a subgroup of patients who are less likely to be cured with conventional chemotherapeutic regimens, including BEP. This subgroup is characterized by certain clinical risk factors (*i.e.*, markedly elevated tumor markers, nonpulmonary visceral metastases and primary mediastinal nonseminomatous germ cell tumors)[11,12]. In addition, various novel modalities to further improve the survival of patients with metastatic GCTs have been explored, such as the addition or substitution of novel agents and the introduction of myeloablative high-dose chemotherapy with peripheral stem cell rescue, and the outcomes of these approaches seem to be promising[3–5,13]. Considering these findings, it would be important to evaluate the significance of BEP chemotherapy as the first-line regimen for patients with metastatic GCTs in order to reconstruct the therapeutic strategy for such patients.

As described above, high-dose chemotherapy (high-dose ICE) is routinely performed at our institution for patients whose serum tumor markers did not normalize following BEP; therefore, this study included a total of 47 who did not receive high-dose chemotherapy following several courses of BEP because of the normalization of serum tumor markers. Of these 47, cCR was achieved in only 18 patients. In addition to these 18, 7 seminoma patients with residual tumors smaller than 3 cm were not candidates for surgical resection according to the criteria described in previous studies[9,10]. Accordingly, further surgical management should have been considered for the remaining 22 patients; however, 7 of these 22 refused to undergo surgical resection, and surgery was consequently performed for the remaining 15. Despite the lack of a significant difference, the incidence of disease recurrence in patients who refused surgery (28.6%) was greater than that in those who underwent surgery (13.3%). The outcome of the present series is supported by previous studies showing that approximately 15% of the patients with residual tumor following first-line chemotherapy have viable malignant cells[14,15]. Collectively, these findings confirm the importance of post-chemotherapy surgery for patients with residual metastatic tumor masses.

The 5-year recurrence-free survival rate of this series was 79.2%, and only 10.6% of these patients developed disease recurrence, which is consistent with several previous studies[1,2], while disease recurrence occurred in 34.1% of the patients who received high-dose chemotherapy following BEP as an induction therapy. These findings suggest that it is well associated with the prognostic outcome in patients with metastatic germ cell tumors whether favorable response to BEP therapy could be achieved or not. However, once disease has recurred in patients showing a favorable response to BEP therapy, it becomes difficult to control; that is, approximately

30% of such patients achieve a complete cure[16]. Accordingly, it would be potentially important to perform effective salvage therapy to improve survival in patients developing relapsed disease after first-line chemotherapy. To date, several approaches have been investigated as salvage therapy for controlling recurrent disease, and at our institution, high-dose chemotherapy was applied as the primary salvage therapy for patients with recurrent metastatic GCTs. In this series, except for one patient receiving high-dose ICE, 3 of the 4 patients with recurrent GCTs were treated with high-dose ICE combined with surgery and remains alive with no evidence of disease. Although it would be difficult to draw a definitive conclusion based on the data of such a small number of patients, these findings suggest that high-dose chemotherapy could be one of the attractive approaches when metastatic GCTs relapsed after conventional cisplatin-based combination chemotherapy.

In conclusion, patients with metastatic GCTs showing favorable response to BEP as first-line chemotherapy could achieve excellent prognostic outcome. However, it is necessary to combine other therapeutic modalities in addition to BEP to further improve the prognosis of such patients; that is, surgical resection should be performed in patients with residual tumor mass after BEP, and intensive salvage therapy, such as high-dose chemotherapy, should be considered in patients who subsequently develop disease recurrence after BEP.

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和文抄録

初期治療としてのブレオマイシン，エトポシドおよびシスプラチン併用化学療法に対して良好な反応を示した転移性胚細胞腫瘍の予後解析

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1996年から2006年の間に初回化学療法としてブレオマイシン，エトポシドおよびシスプラチン併用化学療法（BEP 療法）を施行した転移性胚細胞腫瘍88例中，BEP 療法に対して良好な反応を示したため，引き続き大量化学療法を施行しなかった47例を対象に，その治療成績を検討した．47例の組織型はセミノーマおよび非セミノーマが，それぞれ16および31例で，原発部位は精巣，後腹膜および縦隔が，それぞれ42，3および2例であった．BEP 療法を2～4コース（中央値，4コース）施行後，AFP，β-HCG および LDH は全例において正常化し，18，23および6例を，それぞれ CR，PR および SD と診断した．残存病巣を有する29例中15例に対して外科切除を施行し，12および3例が，それぞれ病理学的および外科的 CR と診断された．経過観察期間の中央値は27カ月で全例が生存中であるが，5例に再発を認めた．再発症例には，救済化学療法として大量化学療法を全例に施行した．47例の1，3および5年非再発率は，それぞれ95.0，91.4および79.2％であり，セミノーマおよび非セミノーマ症例の非再発率に有意差を認めなかった．以上より，初回化学療法としての BEP 療法に良好な反応を示した転移性胚細胞腫瘍症例に対しては，必要に応じて外科療法および強力な救済化学療法を追加することで，優れた治療成績を挙げることが可能であるものと考えられた．

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