LIMITATION OF CONVENTIONAL CISPLATIN- BASED COMBINATION CHEMOTHERAPY FOR DISSEMINATED GERM CELL TUMOR : — IMPLICATION FOR INTRODUCTION OF AGGRESSIVE TREATMENT AS AN INITIAL CHEMOTHERAPY —

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Abstract : To assess the limitation of standard cisplatin-based combination chemotherapy for metastatic germ cell tumor, clinical records of 37 patients with metastatic testicular cancer and extragonadal germ cell tumor treated with primary chemotherapy were reviewed. Thirteen patients of 37 had limitation of the treatment. We categorized the mode of treatment limitation into 5 criteria according to the response of tumor marker levels and radiographic findings, and recurrence. Tumor volume was strongly associated with the limitation of the treatment. Indiana University Staging System, not Royal Marsden Hospital's classification clearly discriminated the patient with limitation of standard cisplatin-based combination chemotherapy. High dose chemotherapy was effective for patients to whom the initial chemotherapy with standard cisplatin-based regimen was effective. It did not offer any benefit to patients with refractory tumor. We conclude that it is important to introduce more aggressive chemotherapy regimens as an initial chemotherapy to patients with large volume tumor.

Key words : Germ cell tumor, Cisplatin-based chemotherapy
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INTRODUCTION

Cisplatin-based combination chemotherapy is very effective for germ cell tumor. PV¹⁾, PEB²⁾, or VAB-6³⁾ therapy is considered as a standard regimen for its efficacy. However, the management of patients with far advanced stage germ cell tumor is still difficult. Treatment results for such patients are not satisfied, even though high dose chemotherapy is conducted^{4,5)}. In this study, we present clinical characteristics of patients to whom standard cisplatin-based combina-

tion chemotherapy was not effective. Furthermore, we discuss the indication of high-dose chemotherapy for disseminated testicular cancer and extragonadal germ cell tumor on the basis of our limited experience of high-dose chemotherapy.

PATIENTS AND METHODS

From January, 1986 to March, 1997, total 103 patients with testicular tumor and 2 patients with extragonadal germ cell tumor (EGGCT) were treated at Gunma University Hospital. Pathological findings

and stage distributions were shown at table. 1. One patient with mediastinal seminoma underwent primary median sternotomy followed by PEB therapy for microscopic residual cancer. The other patients with EGGCT and 36 patients with metastatic testicular cancer were treated with primary chemotherapy consisting of 3 to 4 courses of PVB or PEB therapy. We reviewed the clinical records of these 37 patients, and analyzed the characteristics of patients to whom primary PVB or PEB therapy was not effective. We classified the limitation of primary chemotherapy as five criteria as shown in Table. 2, on the basis of radiographic response (R response), tumor marker response (TM response), and recurrence.

Stage distribution was classified according to Royal Marsden Hospital's (RMH) classification (Table. 3) and Indiana University Staging System (Table. 4).

Table 1 Pathological findings and stage distribution

Testicular tumor			
Germ cell tumor			
Seminoma		Non-seminoma	
I	43		19
IM	1		3
IIA	3		3
IIB	1		2
IIC	4		4
III	0		4
IV	0		11
Malignant lymphoma			
I			3
IIE			1
Epidermoid cyst			
			1
Extragenital germ cell tumor			
Seminoma			1
Embryonal ca			1

Stage distribution : Royal Marsden Hospital classification

Table 2 Criteria of limitation of chemotherapy

(A) progressive disease (PD) of both R response and TM response.
(B) partial response (PR) of both R response and TM response.
(C) recurrence after any R response, complete response (CR) of TM, and salvage surgery.
(D) recurrence after radiographic PR and CR of TM.
(E) recurrence after CR of both R response and TM response.

Table 3 Extent of metastatic tumor : Indiana University Staging System.

Minimal extent
1. Elevated markers only.
2. Cervical nodes ($\pm$ nonpalpable retroperitoneal nodes).
3. Unresectable nonpalpable retroperitoneal disease.
4. Fewer than 5 pulmonary metastasis per lung field and largest < 2 cm ($\pm$ nonpalpable retroperitoneal nodes).
Moderate extent
5. Palpable abdominal mass only (no supradiaphragmatic disease).
6. Moderate pulmonary metastasis : 5-10 per lung field and largest < 3 cm, or solitary pulmonary metastasis of any size > 2 cm ($\pm$ nonpalpable retroperitoneal disease).
Advanced extent
7. Advanced pulmonary metastases : primary mediastinal germ-cell-tumor or > 10 metastases per lung field or multiple pulmonary metastases with largest > 3 cm ($\pm$ nonpalpable retroperitoneal disease).
8. Palpable abdominal mass plus supradiaphragmatic disease.
9. Liver, bone, or central nervous system metastasis.

Table 4 Royal Marsden Hospital staging classification

Stage	Definition
IM	Rising postorchidectomy markers only
II	Abdominal lymphadenopathy
A	< 2 cm
B	2-5cm
C	> 5 cm
III	Supradiaphragmatic lymphadenopathy
O	No abdominal disease
ABC	Abdominal node size as in stage II
IV	Extralymphatic metastases
L1	< 3 lung metastases
L2	> 3 lung metastases all < 2 cm diameter
L3	> 3 lung metastases 1 or more < 2 cm
H+	Liver involvement

RESULTS

Table. 5 shows the clinical characteristics of patients with limitation of primary chemotherapy. Total 13 patient of 37 had limitation of the treatment.

In pattern A, tumors progressed during 3 or 4 courses of PEB therapy. High dose chemotherapy (HDCT) with autologous bone marrow transplantation (ABMT) had no effect. In pattern B, tumor marker response was PR. PE therapy after primary PVB therapy was effective in one patient. In two patients with stage IIIA tumor and primary mediastinal tumor were treated with standard dose PE therapy followed by HDCT with ABMT. They got CR after surgical resection of residual tumors. Two patients were treated with PEB therapy followed by VAB6 therapy. One of them whose tumor marker level did not get normal range died of disease. In pattern C, recurrence occurred in patients who underwent surgi-

Table 5 Clinical characteristics of patients with limitation of primary chemotherapy

Pattern	Response to initial chemotherapy		Age	Pathology	Clinical Stage		PVB/PEB	Salvage chemotherapy	Response to salvage chemotherapy		Salvage surgery	Recurrence	Prognosis
	RAD	TM			RMH	IUS			RAD	TM			
A	PD	PD	17	C	IV	AD	PEB	HDCT	PD	PD	—	—	Dead
			34	C	IV	AD	PEB	HDCT	PD	PD	—	—	Dead
			25	T+E+S	IV	MIN	PVB	PE	PR	CR	+	—	NED
			20	T+Y	III	AD	PVB	PE-HDCT	PR	CR	+	—	NED
B	PR	PR	21	E	EGGCT*	AD	PVB	PE-HDCT	PR	CR	+	—	NED
			17	T	IIB	MOD	PEB	VAB6	PR	CR	+	—	NED
			32	C+E	IIB	MOD	PEB	VAB6	PR	PR	—	+	Dead
			19	C+T+E	IV	AD	PEB	—	—	—	+	+	Dead
C	PD	CR	37	T	IIA	MIN	PEB	—	—	—	+	+	NED
			21	T	III	AD	PEB	—	—	—	+	+	NED
D	PR	PR	30	T+E+Y	IV	AD	PVB	—	—	—	—	+	Dead
			31	T+E	IV	AD	PEB	—	—	—	—	+	Dead
E	CR	CR	21	E	IIA	MIN	PEB	—	—	—	—	+	Dead

RAD: radiographic response, TM: tumor marker response

NED: no evidence of disease

CR: complete response, PR: partial response, PD: progressive disease

HDCT: high dose chemotherapy, PVB: cisplatin+vinblastine+bleomycin

PE(B): cisplatin+etoposide(+bleomycin), VAB6: vinblastine+actinomycin-D+cyclophosphamide+cisplatin+bleomycin

*: HDCT was performed after recurrence.

Clinical staging: RMH; Royal Marsden Hospital classification, EGGCT; extragonadal germ cell tumor

IUS; Indiana University Staging system, AD; advanced, MOD; moderate, MIN; minimal

Pathology: T; teratoma, E; embryonal ca, C; chorioca, Y; yolk sac tumor, S; seminoma

Table 6 Limitation of primary chemotherapy and clinical stage according to RMH classification

Stage	NS	S
IM	3(0)	1(0)
IIA	3(2,1)	3(0)
IIB	2(0)	1(0)
IIC	4(2,1)	4(0)
III	4(2,0)	0
IV	11(6,5)	0
EGGCT	1(1,0)	0

RMH classification: Royal Marsden Hospital classification

EGGCT: extragonadal germ cell tumor

cal resection of postchemotherapeutic residual tumors. One patient had viable embryonal carcinoma in his resected retroperitoneal lymph node and had recurrence 1 mo after surgery. He died of aortoduodenal fistula. Other 2 patient had pure teratoma and had no evidence of disease after surgical resection. In pattern D, surgical resection of residual mass was not performed. Their tumor had teratomatous element. They died of disease after recurrence. In one patient, HDCT with ABMT was performed. But it did not stabilize the disease. In pattern E, small paraaortic metastatic lymph node disappeared after primary chemotherapy. However, scheduled administration of chemotherapy drugs was not possible for his severe liver dysfunction.

Clinical stage distribution of patients with metastasis and with limitation of the primary chemotherapy

Table 7 Limitation of primary chemotherapy and extent of disease according to Indiana University Staging System

Extent	NS	S
Minimal	13(3,1)	7(0)
Moderately	5(2,1)	2(0)
Advanced	10(8,5)	0

*(a, b): a; number of patients with limitation

b; number of dead patients

NS: non-seminoma, S: seminoma

was shown in table 6 and 7. Patients with metastatic seminoma were successfully treated with primary chemotherapy. According to the Royal Marsden Hospital Classification, 54 % of patients with stage IV tumor and 37.5% of patients with less than IV tumor had the limitation of the treatment. However, 80% of patients with advanced extent disease and 38.5% of patients with minimal or moderately extent disease had the limitation, according to the Indiana University Staging System.

HDCT with ABMT was performed to 5 five patients. Two patients in pattern B was successfully treated with HDCT and they have no evidence of disease. HDCT was not effective for two patients in pattern A and one in pattern D.

DISCUSSION

PVB, PEB, or VAB-6 therapy is considered as a standard regimen for metastatic testicular cancer.

However, its limitation for far-advanced stage was reported. We reported the clinical characteristics of patients with metastatic testicular germ cell tumor with special reference to postchemotherapeutic surgery⁶⁾. This study described the relationship between pathological findings of both primary and metastatic tumor in patients to whom chemotherapy was successful. In this study, we analyzed the clinical characteristics of patients to whom the conventional cisplatin- containing chemotherapy was not effective.

We classified the limitation of the primary chemotherapy as five criteria as described above. Prognosis of patients with absolute refractory status as pattern A is miserable. HDCT after several courses of PEB therapy did not offer any benefit to patients. Pattern B is good indication for salvage chemotherapy. After obtaining PR in both radiographic and tumor marker levels, other chemotherapy regimens should be considered. HDCT was effective for two patients. In pattern C, tumor recurrence occurred after CR. Two patients with adult type pure teratoma was successfully treated with extended surgery for metastatic lesions. In pattern D, treatment was stopped by several reasons. Tumor recurrence occurred soon after the treatment. HDCT in recurrent status was not effective. Clinical course of a patient in pattern E was unusual one. We speculate his liver dysfunction to be the cause of unusual course in this patient.

These patients had large metastatic tumor volume. As shown in table 4 and 5, Indiana University Staging System, not RMH classification, clearly discriminate the patients with limitation of conventional dose cisplatin-based combination chemotherapy.

HDCT did not offer any benefit to patients with refractory state, pattern A and recurrent state in pattern D. On the contrary, two patients with PR by initial chemotherapy had good prognosis by conducting HDCT and postchemotherapeutic surgery. Introduction in responded phase is thought to be a key to get benefits from HDCT^{7,8)}. Recent advance in hematological technique enables us to store peripheral blood stem cells at the recovery phase of white blood cells during chemotherapy. Scheduled harvest of peripheral blood stem cells and scheduled introduction of HDCT during responded phase will be ideal treatment strategy for far-advanced stage germ cell cancer.

This analysis of limitation of PEB or PVB therapy drive us to undertake the introduction of VeIP therapy, which is considered as a 3rd line chemotherapy, as an initial chemotherapy to patients with far-advanced stage. In the future, combination with VeIP induction therapy and HDCT with peripheral blood stem cells transplantation should be tried to patients with far-advanced stage.

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