Clinical Features and Treatment Outcomes in Patients with Extragonadal Germ Cell Tumors: A Single-center Experience

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Abstract. *Background: The prognosis for non-seminomatous extragonadal germ cell tumors (EGCTs), especially mediastinal, has been shown to be worse than for seminomatous EGCTs. Patients and Methods: Fourteen patients with EGCT (seven pure seminomas and seven non-seminomas) were treated at the Kanazawa University Hospital between 1992 and 2014; the primary tumor sites were mediastinum in nine patients and retroperitoneum in five patients. All patients were treated with cisplatin-based combination chemotherapeutic regimens followed by a multimodal strategy that included high-dose chemotherapy (HDCT), aggressive surgery, and early salvage chemotherapy. Results: Although all patients with seminomatous EGCT achieved long-term survival, almost all patients with non-seminomatous EGCT had elevated serum tumor markers and high mortality rates. However, we experienced that patients with mediastinal non-seminomatous EGCT achieved long-term cancer-free survival with HDCT. The 5-year overall survival of patients with seminomatous and non-seminomatous EGCT was 100% and 44%, respectively. Conclusion: Herein we describe the treatment outcomes of patients with EGCT at our Institute and propose HDCT reconsideration for poor-risk patients.*

Although male germ cell tumors (GCTs) typically arise in the testis, approximately 2%-5% are of extragonadal origin, with the most common sites being in the midline, particularly the mediastinum and the retroperitoneum. Primary extragonadal GCTs (EGCTs) are classified by the staging system of the International Germ Cell Cancer Collaborative Group (IGCCCG) and treated with cisplatin-based combination chemotherapeutic regimens, similar to primary gonadal GCTs. According to the IGCCCG classification, the prognosis of non-seminomatous GCT is generally worse than that of seminomatous GCT (2). Similarly, the overall survival (OS) differs between the seminomatous and non-seminomatous EGCT. Bokemeyer *et al*. reported that OS of patients with seminomatous EGCT was 88%, whereas those of patients with retroperitoneal and mediastinal non-seminomatous EGCT were 62% and 45%, respectively (3). The aim of the present study was to describe the clinical features and treatment outcomes of patients with retroperitoneal and mediastinal EGCTs at the Kanazawa University Hospital.

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Key Words: Extragonadal germ cell tumor, high-dose chemotherapy, salvage therapy.

Patients and Methods

A series of 14 patients with EGCT treated at the Kanazawa University between 1992 and 2014 were retrospectively reviewed. The EGCT diagnosis was made on the basis of GCTs arising in the mediastinum, retroperitoneum, or other extragonadal sites, without demonstrable testicular abnormalities, as determined by physical examination and testicular ultrasonography. High orchiectomy was performed in patients with abnormalities detected by palpation or testicular ultrasonography. All patients were categorized into prognostic groups according to the IGCCCG classification on the basis of histology, location of the metastasis, and levels of the following serum tumor markers at the time of diagnosis: alpha-fetoprotein (AFP), human chorionic gonadotrophin (HCG), lactate dehydrogenase (LDH). Tumor response was classified as follows: complete remission (CR) was defined as the complete disappearance of all clinical target lesions with normalization of tumor markers, whereas pCR was defined as the absence of tumor lesions by histology and CRs was defined as the survival of tumor lesion by histology despite complete excision. A partial response (PR) was defined as a decrease of ≥50% in the sum of the products of the perpendicular diameters of measurable tumor lesions without the appearance of new lesions. In addition, when serum tumor markers were positive or negative, the cases were denoted as PRm+ or PRm, respectively. Progressive disease (PD) was defined as either the increase in tumor size of ≥25% or occurrence of new lesions.

Death due to any reason was used as the end-point for OS determination. Actuarial survival curves were calculated according to the Kaplan-Meier method, and comparisons were accomplished using the log-rank test.

Results

Patients' characteristics are summarized in Table I. Fourteen patients, including seven patients with pure seminomatous EGCT and six patients with non-seminomatous EGCT, were identified from our records. One patient with retroperitoneal primary EGCT had undergone high orchiectomy; however, due to the pathologically suspicious "burned-out" or regressed tumor, and the initially high serum AFP levels, this case was clinically considered as non-seminomatous EGCT despite the lack of histological confirmation (case 9). The primary sites of non-seminomatous EGCT were the mediastinum in nine patients and the retroperitoneum in five patients. According to the IGCCCG classification, nine patients belonged to the good- or intermediate-risk group, and five patients to the poor-risk group.

The treatment and outcome profiles of patients are summarized in Table II. The median follow-up duration was 30 months (range=3-67 months). The 5-year OS of patients with seminomatous and non-seminomatous EGCT was 100% and 44%, respectively (p=0.29) (Figure 1). The 5-year OS of good- or intermediate-risk and poor-risk group patients was 100% and 40%, respectively (p=0.18) (Figure 2). All patients received three to four courses of standard bleomycin, etoposide, cisplatin (BEP) regimen. A total of seven patients underwent surgical resection after chemotherapy (cases 1, 2, 5, 7, 8, 9, and 12). Retroperitoneal surgery was performed on two patients, and mediastinal surgery on five patients. Three patients (cases 1, 8, and 12) had immature teratomas, one patient (case 5) had a teratoma with malignant transformation. In three patients (cases 2, 7, and 9), either necrosis or fibrosis was observed in tumors. Twelve patients were alive at the end of the follow-up duration, and three achieved CR. Two patients with primary mediastinal non-seminomatous GCT (PMNSGCT) died during follow-up: one patient died from acute megakaryocytic leukemia approximately 7 months after diagnosis (case 8), and one patient died from the progression of primary disease (case 1).

Table I. *Patients' characteristics*.

Number of patients	14
Median age (year old)	27.5 (18-49)
Follow-up (months)	Median 30.0 (3-67)
Histology	
Seminoma	7
Non-seminoma	6
Unknown (*)	1
Gender	
Male/Female	14/0
Primary tumor site	
Mediastinum	9
Retroperitoneum	5
Site of metastasis	
Lung	2
Lymph node	3
Tumor marker at pretreatment	
AFP (ng/mL)	
Median (range)	3055 (<1-188530)
hCG-β (IU/L)	
Median (range)	2.68 (<0.1-74.2)
LDH (IU/L)	
Median (range)	323 (115-750)
IGCCC prognosis	
Good/Intermediate	7/2
Poor	5
Type of treatment	
Chemotherapy	7
Chemotherapy + surgery	7

(*) Patient with retroperitoneal primary extragonadal germ cell tumor underwent high orchiectomy; however, pathology indicated "burned-out" tumor.

Discussion

An international analysis of 635 patients with EGCT by Bokemeyer *et al*. revealed that the 5-year OS of patients with seminomatous EGCT was 88%, with no differences between patients with retroperitoneal and mediastinal location, while the 5-year OS of patients with retroperitoneal and mediastinal non-seminomatous EGCT was 62% and 45%, respectively (3). Thus, seminomatous EGCT is associated with good prognosis irrespective of the primary site, while PMNSGCT shows the worst prognosis. Furthermore, the 5-year OS of poor-risk patients was 48% in the IGCCCG study (2). In our series, the 5-year OS of patients with seminomatous and non-seminomatous EGCT was 100% and 43%, respectively, and the 5-year OS of patients classified as poor-risk group by the IGCCCG classification was 40%. Accordingly, the prognosis of EGCT in our study appears to be very similar to that reported previously.

Mazumdar *et al*. described that the rate of serum tumor marker declines during chemotherapy and has prognostic value that is independent of risk (4). In addition, we previously showed that prolonged half-life of tumor markers predicted a poor response to standard chemotherapeutic regimens (5). Moreover, Ebi *et al*. reported that the assessment of serum tumor markers 7 days after the initiation of chemotherapy might be a useful prognostic factor with regard to OS (6). Due to the very small number of patients in our study, we could not confirm the statistical difference in OS between patients with short- and long-life of tumor markers or those with decreasing and increasing tumor markers levels on day seven. Consequently, in our series, most patients with unsatisfactory declines in serum tumor markers tended to undergo a form of second-line or salvage chemotherapy.

As described above, the prognosis of seminomaous EGCT is promising regardless of its location (*i.e*., mediastinum or retroperitoneum), whereas the prognosis of non-

Table II. *Clinical features and treatment outcomes*

Case no.	Age	Year of 1st treatment	Primary site	Histology (biopsy)	Histology (resection)	IGCCC	Chemotherapy	AFP (ng/mL)	hCG-β (ng/mL)	hCG (IU/L)	LDH (IU/L)	Course	Observation period (months)	Outcome
1	20	1997	Mediastinum	IT+Y	IT+Y	Poor	BEP(8), VIP(4), HDCT(2), TIP(2), CPT-11/N(3)	1254	74.2		<230	Elevation of hCG-β	61	Dead
2	19	2000	Mediastinum	S	Viable cell(–)	Good	BEP(2), HDCT(1)	<10	<0.1		329	pCR	53	NED
3	31	2004	Mediastinum	Y	n.d	Poor	BEP(4), HDCT(2)	188530	<0.1		<230	PRm-	67	NED
4	29	2008	Mediastinum	n.d	S	Good	BEP(3)	<10	<0.1		129	CR	4	NED
5	38	2008	Retroperitoneum	EC	T with malignant	Inter mediate	BEP(2), TIP(2), VIP(3)	3055	4.8		740	PRm-	37	AD
6	45	2008	Retroperitoneum	n.d	S	Good	BEP(3)	5.4	<0.1		115	CR	62	NED
7	27	2009	Mediastinum	S	Viable cell(–)	Good	BEP(3)	<10	0.6		269	pCR	57	NED
8	18	2009	Mediastinum	Y+T with malignant	IT	Poor	BEP(4)	3307	2.81		391	CR	6	Dead
9	20	2009	Retroperitoneum	n.d	Viable cell(–)	Poor	BEP(4), VeIP(2)	10922	0.72		343	pCR	54	NED
10	49	2012	Retroperitoneum	S	Testis; burned-out tumor s/o	Good	BEP(3), VeIP(1)	<1	0.41		316	PRm-	22	AD
11	41	2013	Retroperitoneum	IT	n.d	Inter mediate	BEP(4), VeIP(4)	7603	4.1		335	PRm+	9	AD
12	19	2013	Mediastinum	Y	IT	Poor	BEP(4), VeIP(1), TIP(3)	879	6.09	1720	750	PD	9	AD
13	28	2013	Mediastinum	S	n.d	Good	BEP(4)	<1	1.86	54.1	280	PRm-	7	AD
14	18	2013	Mediastinum	S	n.d	Good	BEP(3)	4	2.54	45.6	296	PRm-	3	AD

M: Mediastinum; R: retroperitoneum; S: seminoma; IT: immature teratoma; T: teratoma; Y: yolk sac tumor; EC: embryonal carcinoma; ND: not done; NED: no evidence of disease, and AD: alive with disease; BEP: bleomycin, etoposide, cisplatin; VIP: etoposide, ifosphamide, cisplatin; VeIP: vinblastin, ifosphamide, cisplatin; TIP: paclitaxel, ifosphamide, cisplatin; CPT-11/N: irinotecan, nedaplatin; and HDCT: high-dose chemothepapy.

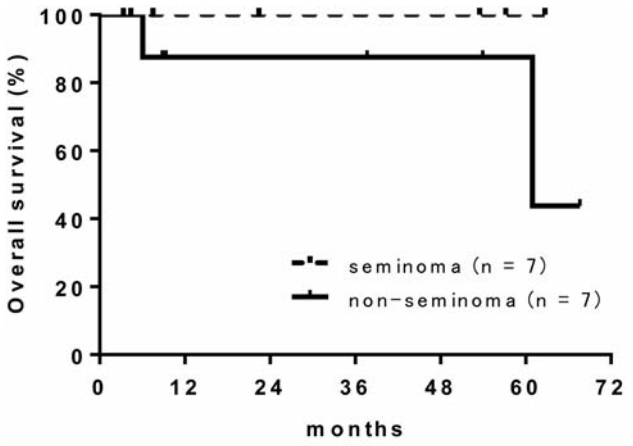

Figure 1. *Overall survival of patients with extragonadal germ cell tumors according to histology.*

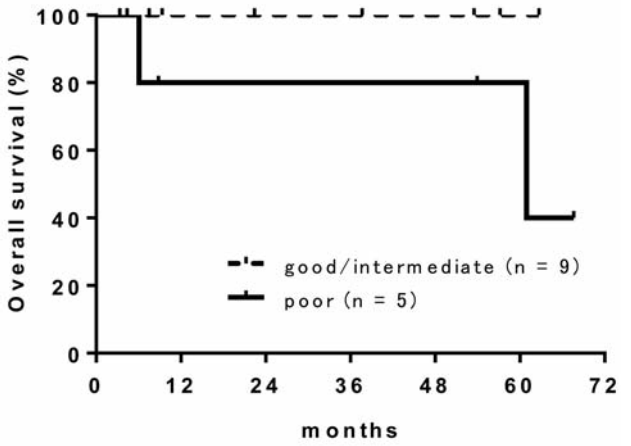

Figure 2. *Overall survival of patients with extragonadal germ cell tumors according to the International Germ Cell Cancer Collaborative Group classification.*

seminomatous EGCT, especially PMNSGCT, is indisputably unfavorable. According to the IGCCCG classification, seminomatous EGCT without non-pulmonary visceral metastasis belongs to the good-risk group, while non-seminomatous EGCT is categorized as intermediate- or poor-risk group. Additionally, almost all patients with non-seminomatous EGCT are classified as poor risk due to primary tumor location, tumor dissemination, and elevated serum tumor markers. For poor-risk patients, standard induction treatment consists of four cycles of BEP chemotherapy (7). Motzer *et al*. investigated high-dose chemotherapy (HDCT) and autologous hematopoietic stem cell rescue as first-line approaches in the only randomized phase III trial, comparing four cycles of BEP with two cycles of BEP followed by two cycles of HDCT (8). This study concluded that routine inclusion of HDCT in first-line treatment for intermediate- and poor-risk patients did not improve treatment outcomes. At present, four cycles of BEP chemotherapy are considered to be appropriate as first-line treatment for poor-risk patients. Moreover, surgical resection is also recommended for patients with any visible residual mass and serum tumor markers normalization following the first-line chemotherapy (7).

Conversely, it is difficult to determine the optimal approach for salvage treatment of relapsed or refractory disease in poor-risk patients. The regimens of choice as conventional-dose chemotherapy (CDCT) are etoposide, ifosphamide, and cisplatin; vinblastin, ifosphamide, and cisplatin; or paclitaxel, ifosphamide, and cisplatin; however, the response rate to CDCT is unsatisfactory. While Sarkaria *et al*. reported that normalization or decrease in tumor markers after chemotherapy and/or before surgical treatment is the strongest independent predictor of improved survival in a cohort of PMNSGCT (9), surgical resection in the presence of increasing tumor markers after chemotherapy has remained controversial. However, Radaideh *et al*. suggested that extensive surgical approach by an experienced surgeon could result in long-term survival even in patients with PMNSGCT with increasing serum tumor markers (10).

In our report, there were four patients with PMNSGCT (cases 1, 3, 8, and 12), two of whom died during follow-up. However, the other two patients survived: in fact, one of them underwent HDCT as salvage chemotherapy and was alive with no evidence of disease at the end of the follow-up duration with 67 months. The routine inclusion of HDCT as first-line chemotherapy for poor-risk patients was denied in the only phase III randomized trial (8); however, the results of secondary analysis in this study demonstrated that patients with early chemotherapy resistance, evidenced by an unsatisfactory decline in serum tumor markers during the first two cycles of BEP, experienced a higher durable CR when treatment was changed to HDCT. Furthermore, Lorch *et al*. retrospectively compared HDCT with CDCT using a large international database of patients with relapsed or refractory metastatic GCTs and demonstrated a benefit from HDCT given as intensification of first salvage treatment. Due to the limitations inherent in the retrospective design, this analysis by Lorch *et al*. does not prove the superiority of HDCT over CDCT; rather, these findings emphasize the need for another prospective randomized trial comparing CDCT with HDCT in poor-risk patient populations (11). Therefore, there may be room to reconsider HDCT as a first salvage treatment for poor-risk patients such as those with PMNSGCT. Furthermore, a more aggressive chemotherapy should also be investigated in these patients. In contrast, the prognosis of seminomatous EGCT is promising regardless of

the primary site, while the prognosis of retroperitoneal non-seminomatous GCT is also favorable, albeit to an extent, with appropriate therapeutic modalities.

In conclusion, as expected, the treatment outcomes in our report were heterogeneous and comparable with the existing literature. Retroperitoneal and mediastinal seminomatous EGCTs are associated with good prognosis. In addition, while retroperitoneal non-seminomatous EGCTs also have a relatively good prognosis, PMNSGCT do not. However, one PMNSGCT case in our cohort experienced long-term cancer-free survival with HDCT as salvage chemotherapy. Thus, it is necessary to establish an optimal regimen as salvage chemotherapy and to re-evaluate the utility of HDCT in patients with PMNSGCT through evaluation of additional cases in future clinical studies.

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Received October 5, 2015
Revised November 11, 2015
Accepted December 3, 2015