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Treatment at an Inexperienced Center Suggests Worse Prognosis of Metastatic Germ Cell Tumors

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Abstract. *Background/Aim: We evaluated the clinical outcomes of patients with metastatic germ cell tumors (GCT) treated at our hospital, which belongs to a regional cancer center. Patients and Methods: Data pertaining to patients with metastatic GCT were obtained between April 2007-October 2017 and was retrospectively analyzed. Key outcome measures included objective response rates and survival rates.Results: All 42 patients received chemotherapy [complete response: eight (19.0%); partial response: 21 (50.0%); stable disease (SD): nine (21.4%); progressive disease: four patients (9.5%)]. Post-chemotherapeutic surgery was performed for seven out of 21 cases of partial response and two out of nine of stable disease. The 5-year survival rates of patients with good, intermediate and poor prognosis (International Germ Cell Consensus Classification) were 100%, 100%, and 71.4%, respectively. Patients who received induction chemotherapy at other hospitals had significantly poorer prognosis than those at our hospital (p=0.0043). Conclusion: Patients with metastatic GCT should preferably receive chemotherapy at an experienced institution.*

Since the 1970s, surgical resection of residual tumor mass following chemotherapy has been a critical component in the care of patients with testicular germ cell tumors (GCTs) (1). At least one-third of patients with disseminated disease will have a residual mass requiring surgery (2).

Recent therapeutic advances have helped improve the prognosis of patients with advanced GCTs, even for those with initial poor prognosis as per the International Germ Cell Consensus Classification (IGCCC) (3). Similarly, a Japanese multicenter cohort study revealed improved outcomes in patients classified in the IGCCC poor-prognosis category (4).

However, there are still some intractable cases even in this era. The establishment of a management strategy for advanced GCT based on treatment results is a crucial imperative. The incidence of testicular GCT in Japan is much lower than that in Western countries (5, 6). Kawai *et al*. pointed out that most patients with advanced testicular cancer in Japan are treated at university hospitals or regional cancer center-based urological oncology units, not in highly specialized centers (7).

Therefore, in this study, we evaluated the clinical outcomes of patients with metastatic GCT treated at our hospital, which belongs to a regional cancer center.

Patients and Methods

In this retrospective study, we evaluated the medical records of patients diagnosed with metastatic GCT at our hospital between April 2007 and October 2017. The study protocol was approved by the Ethics Committee of the Kanazawa University Graduate School of Medical Science (approval number 2786). Data pertaining to the following variables were extracted: Age at the initiation of induction chemotherapy; site of primary disease; histological type; IGCCC prognostic category; the number of treatment lines; antitumor agents per treatment line; and the type of institute where induction chemotherapy was administered.

The key outcome measures were overall survival (OS) and the presence/absence of post-chemotherapeutic surgery. In this study, OS was defined as the duration of time from the induction of chemotherapy. The GraphPad Prism 8 software (GraphPad Software Inc., San Diego, CA, USA) was used for data analysis and graphical

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Key Words: Metastatic germ cell tumor, non-seminoma, chemotherapy, post-chemotherapeutic surgery, IGCCC prognosis.

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Table I. *Clinical characteristics of the study population (N=42).*

Characteristic		Value
Age, years		
Median (range)		35 (14-69)
Site of primary disease, n (%)		
Gonadal		33 (78.6)
Mediastinal		6 (14.3)
Retroperitoneal		3 (7.1)
Histological type, n (%)		
Seminoma		16 (38.1)
Non-seminoma		25 (59.5)
*Unknown		1 (2.4)
IGCCC prognostic classification, n (%)		
Good		21 (50.0)
Intermediate		12 (28.6)
Poor		7 (16.7)
Total number of therapeutic lines, n (%)		
1		24 (57.1)
2		12 (28.6)
3		2 (4.8)
≥4		4 (9.5)
Anti-tumor agents per treatment line, n (%)		
1st	BEP	42 (100)
2nd	VelP	13 (31.0)
	VIP	3 (7.1)
	TIP	1 (2.4)
	HDCT	1 (2.4)
3rd	TIP	3 (7.1)
	VIP	1 (2.4)
	GEM	1 (2.4)
4th	CDGP+CPT-11	1 (2.4)
	GEMOX	1 (2.4)
	Pazopanib	1 (2.4)
	TIN	1 (2.4)
Institution administering induction chemotherapy, n (%)		
Our institution		34 (81.0)
Other		8 (19.0)

IGCCC: International Germ Cell Consensus Criteria (3); BEP: bleomycin, etoposide, and cisplatin; VelP: vinblastine, ifosfamide, and cisplatin; VIP: etoposide, ifosfamide, and cisplatin; TIP: paclitaxel, ifosfamide, and cisplatin; HDCT: high-dose chemotherapy; GEM: gemcitabine; TIN: paclitaxel, ifosfamide, and nedaplatin; GEMOX: gemcitabine and oxaliplatin. *This case was suspected of having so-called 'burned-out tumor' which had regressed and viable cells were not recognized structurally in the primary site.

illustration. Kaplan–Meier curves were used to compare survival time. Between-group differences concerning survival were assessed using the log-rank test. *p*-Values less than 0.05 were considered indicative of statistical significance.

Results

The clinical characteristics of the study population are summarized in Table I. A total of 42 patients were included in the analysis [median age at diagnosis: 35 years (range, 14-69)]; of these, most patients had gonadal GCT, and non-seminoma; one was of unknown histological type. According to the IGCCC risk stratification, 21 patients were classified as having a good prognosis, and seven patients were classified with poor prognosis. The most frequent total number of therapeutic lines was one, and only four patients had four or more lines. All 42 patients received induction chemotherapy with a combination regimen of bleomycin, etoposide, and cisplatin (BEP). The most frequent salvage chemotherapy regimen used as a second-line treatment was vinblastine, ifosfamide, and cisplatin (VeIP); followed by etoposide, ifosfamide, and cisplatin; paclitaxel, ifosfamide, and cisplatin; and high-dose chemotherapy. Nineteen percent of patients were administered induction chemotherapy at other hospitals.

Table II. *Therapeutic effects according to RECIST v1.1*

	N (%)
CR	8 (19.0)
PR	21 (50.0)
Post-chemotherapeutic surgery	7
Post-pubertal-type teratoma	2
No viable cells	5
SD	9 (21.4)
Post-chemotherapeutic surgery*	2
Post-pubertal-type teratoma	2
PD	4 (9.5)
Death	4
Died of primary disease	3
Died of cause unrelated to treatment	1

CR: Complete response; PD: progressive disease; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease. *Includes surgery performed at other institutions.

Table II shows the therapeutic effects according to the Response Evaluation Criteria in Solid Tumors v1.1 (8). During the observation period of this study (median=63 months), eight (19.0%) patients achieved complete response, 21 (50.0%) achieved partial response (PR), nine (21.4%) showed stable disease (SD), and four (9.5%) patients developed progressive disease. Of the 21 PR cases, seven non-seminomatous cases underwent post-chemotherapeutic surgery. Pathological findings showed post-pubertal-type teratoma in two patients, while no viable cells were observed in five patients. Of the nine SD cases, two non-seminomatous cases underwent surgery because of suspected growing teratoma syndrome; pathological examination showed post-pubertal-type teratoma. None of these patients received additional chemotherapy and nine were followed by surveillance.

Disease progression occurred in four patients (9.5%), and death occurred in four (9.5%) patients. One patient died of acute leukemia which was unrelated to the treatment for GCT, while three patients died of their primary disease. All

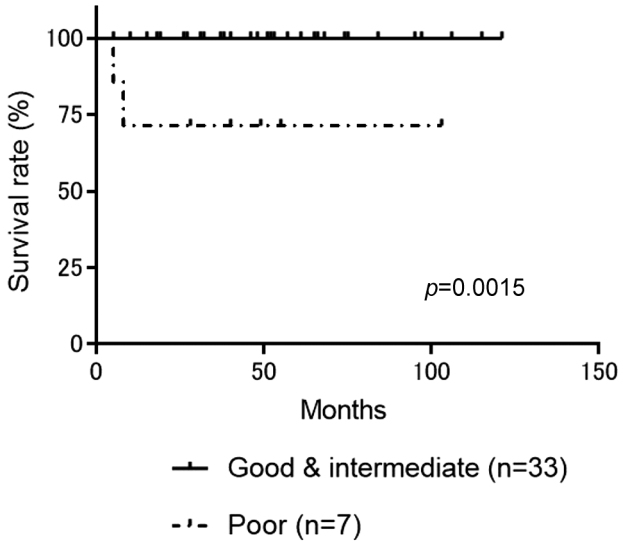

Figure 1. *Kaplan–Meier curves showing the overall survival of patients according to International Germ Cell Consensus Criteria prognostic category (3).*

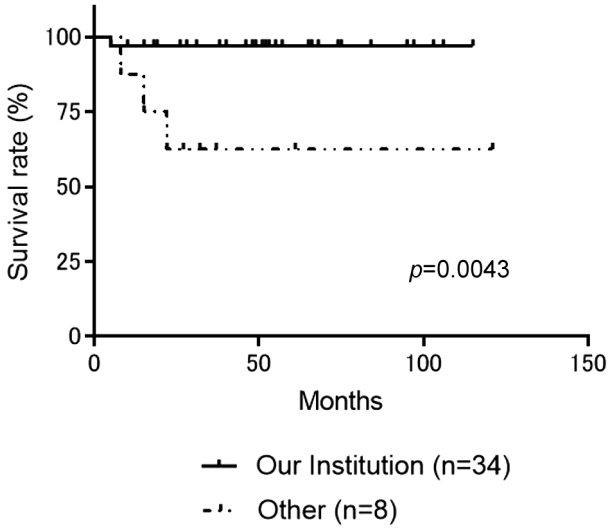

Figure 2. *Kaplan–Meier curves showing overall survival of patients according to the institution where induction chemotherapy was administered. Patients who received induction chemotherapy at other institutions showed significantly poorer prognosis as compared to those treated at our Institution.*

three of the patients who died of primary disease were administered induction chemotherapy at other hospitals. Two of these, patients were lost to follow-up at the previous hospital. The 5-year OS for our cohort was 92.6% (data not shown). The 5-year OS rates of patients in IGCCC good, intermediate, and poor prognosis categories were 100%, 100%, and 71.4%, respectively (Figure 1). We performed a subgroup analysis based on the institution where induction chemotherapy was administered. The 5-year OS rate of patients who received induction chemotherapy at our hospital (97.0%) was significantly longer than that of patients who were treated at other hospitals (62.5%; p=0.0043) (Figure 2).

Discussion

In a large cohort study of patients with metastatic GCT (n=704), conducted at a high-volume institute (Indiana University Hospital), the 5-year OS of patients in IGCCC good, intermediate, and poor prognosis categories were 97%, 92%, and 73%, respectively (9). Our results are comparable to the results at that institution, despite the low number of cases in our cohort. A study based on the American National Cancer Database investigated the clinical outcomes of 33,417 patients with testicular GCT. Compared to high-volume hospitals, patients treated at low-volume hospitals were found to have a worse survival rate (10). This indicates that patients with metastatic GCT should be administered chemotherapy at high-volume centers in the earliest stage of the disease.

Once chemotherapy achieves a marked response, post-chemotherapy resection of the residual mass helps eradicate any residual teratoma or viable GCT. Several reports have recommended surgical resection for tumors with a high propensity for chemoresistance (such as teratoma, those with somatic transformation, and cisplatin-refractory disease) (10-14). Shah *et al*. underlined the need to refer patients to an experienced tertiary care center before deeming their disease as 'unresectable'; this is because surgical resection can be critical for oncological control (15). For our cohort, we performed post-chemotherapeutic surgery for seven non-seminomatous cases in the PR group and nine non-seminomatous cases in the SD group. Histopathological findings of these patients showed post-pubertal-type teratoma or absence of viable cells that required additional treatment.

According to a recent study of 82 patients who received chemotherapy for non-seminomatous testicular GCT, the level of serum *miRNA 371a-3p* was found to predict viable disease with 100% sensitivity and 100% negative predictive value (16). Additionally, the miRNA level was also positively correlated with treatment failure and relapse (17). Since no viable cells were observed in the five patients with PR in our cohort, unnecessary post-chemotherapeutic surgery might be avoided for such patients using this technique in the future.

Sharma *et al*. investigated 30 cases of GCT with somatic transformation; the 5-year OS was 87.5% (18). In our cohort, one patient had an extragonadal mediastinal GCT with sarcomatous components; the multiple lung metastases showed

good response to pazopanib. The patient is still alive as of 6 years despite somatic transformation after BEP, vinblastine, ifosfamide and cisplatin, and combination chemotherapy (19). Although GCT with sarcomatous components is associated with a poorer prognosis than basic GCT (20), we were able to control metastatic disease and achieved long-term survival for this patient. As demonstrated in our study, treatment administered at an institution experienced in the treatment of metastatic GCT can help achieve long-term survival.

The lower survival rate of patients in the present cohort who received induction chemotherapy at other institutions is attributable to the inclusion of all three patients who died of their primary disease. One patient received only two courses of BEP combination chemotherapy as induction chemotherapy, despite being in the IGCCC poor prognosis category. The other two patients were lost to follow-up, and eventually visited our Department with severely advanced disease. These facts underline the need for appropriate induction chemotherapy in patients with metastatic GCT. Additionally, primary patient education in institutions with abundant treatment experience is required in order to avoid loss to follow-up. As mentioned above, there are no high-volume centers in Japan with respect to treatment of GCTs; however, our institution has shown the efficacy of pegfilgrastim in the BEP combination chemotherapy regimen for GCT (21). In addition, our Institution has also demonstrated the utility of panolosetron as supportive therapy in BEP combination chemotherapy (22). The total number of 42 patients in 10 years, or four patients per year, is not high. However, we are contributing as a referral facility for the region.

In conclusion, patients with metastatic GCT should preferably receive induction chemotherapy at an experienced institution. Moreover, the education of patients to achieve treatment compliance is a key imperative.

Conflicts of Interest

The Authors declare no conflicts of interest associated with this article.

Authors' Contributions

HY and KI designed the study, and HY wrote the initial draft of the article. HY, SK and HI contributed to the analysis and interpretation of data and assisted in preparing the article. All other Authors contributed to data collection and interpretation, and critically reviewed the article. All Authors approved the final version of the article and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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