Improved Outcome of Central Nervous System Germ Cell Tumors: Implications for the Role of Risk-adapted Intensive Chemotherapy

To determine the impact of treatment protocols on the outcome of central nervous system germ cell tumors (CNS-GCTs), we reviewed the medical records of 53 patients who received front-line chemotherapy from September 1997 to September 2006. Pure germinoma, normal alpha-fetoprotein level and beta-human chorionic gonadotropin level <50 mIU/mL were regarded as low-risk features and the others as high-risk. Patients from different time periods were divided into 3 groups according to the chemotherapy protocols. Group 1 (n=19) received 4 cycles of chemotherapy comprising cisplatin, etoposide and bleomycin. Group 2 (n=16) and group 3 (n=18) received 4 cycles of chemotherapy with cisplatin, etoposide, cyclophosphamide and vincristine in the former and with carboplatin, etoposide, cyclophosphamide and bleomycin in the latter. In group 2 and group 3, high-risk patients received double doses of cisplatin, carboplatin and cyclophosphamide. Radiotherapy was given after chemotherapy according to the clinical requirements. The event-free survivals of groups 1, 2, and 3 were 67.0%, 93.8%, and 100%, respectively (group 1 vs. 2, *P*=0.06; group 2 vs. 3, *P*=0.29; group 1 vs. 3, *P*=0.02). Our data suggest that risk-adapted intensive chemotherapy may improve the outcome of patients with malignant CNS-GCTs.

Key Words : *Neoplasms, Germ Cell and Embryonal; Central Nervous System; Drug Therapy; Survival*

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INTRODUCTION

Primary central nervous system origin germ cell tumors (CNS-GCTs) are rare. The incidence of CNS-GCTs is relatively higher in Korea as well as Japan and Taiwan (1-3). In the past, radiation therapy was used as a single modality for the treatment of CNS-GCTs (4-12). Although 40 to 60 Gy of local irradiation with variable doses of craniospinal irradiation has been very effective in pure germinonas, the survival rates of patients with nongerminonatous GCTs have been relatively poor with the cure rate around 50%. In the 1980s, investigators began to report the effectiveness of systemic chemotherapy especially for nongerminomatous CNS-GCTs (13-15). Until recently, a number of chemotherapeutic agents have been used in various combinations, among which cisplatin has been most frequently used. However, the optimal therapeutic strategy for CNS-GCTs is not established yet.

Since September 1997, we have used front-line chemotherapy followed by radiotherapy for pure germinomas as well as nongerminomatous GCTs. The early treatment strategy for these patients was to use uniform doses of chemotherapy regardless of the differences in pathology and tumor marker status, which was unsatisfactory. Thereafter, we tried to begin risk-adapted strategy, which used higher doses of cytotoxic agents with high-dose cisplatin-based intensified regimen for high-risk patients. Unfortunately, we found, despite the excellent response rate, unexpectedly high incidence of ototoxicity in patients who received high-dose cisplatin, which urged us to revise the treatment protocol to a less ototoxic carboplatin-based one.

In here, we report our single center experience using different treatment protocols that have been evolved according to the clinical requirements, and the impact of the change in treatment policy on the outcomes of patients with malignant CNS-GCTs.

MATERIALS AND METHODS

Patients and treatments

From September 1997 to September 2006, 55 patients with

newly diagnosed malignant CNS-GCTs received front-line chemotherapy at our institution. Fifty-three patients were analyzed and data from 2 patients were not included due to early loss to follow-up against medical advice before completion of chemotherapy. When histologic confirmation was not done, typical magnetic resonance imaging (MRI) scan findings along with elevated tumor marker(s) such as alpha-fetoprotein (AFP) and/or beta-human chorionic gonadotropin (bHCG) were used for diagnosis. Evaluations using brain MRI, whole spine MRI, cerebrospinal fluid (CSF) cytology, and tumor marker levels in serum and CSF were performed in all patients prior to the initiation of chemotherapy. Patients were divided into either low-risk or high-risk groups. The low-risk criteria were defined as follows; 1) pure germinoma confirmed by histology, 2) normal AFP level, and 3) low serum and CSF bHCG level (<50 mIU/mL). All the others who did not meet any of the low-risk criteria were regarded as high-risk considering that some patients with histologically proven germinoma have elevated AFP and high bHCG levels, which suggest they actually possess nongerminomatous components in their unbiopsied sites. For the analysis of treatment outcome, patients from different time periods were divided into 3 groups according to the differences in chemotherapy protocols. Group 1 (from Septmeber 1997 to September 2002; n=19) received 4 cycles of chemotherapy (cisplatin 100 mg/m^2 on day 0, etoposide 100 mg/m^2 from day 0 to 4, bleomycin 15 mg/m^2 on day 0) named "PEB" every 3 weeks irrespective of their risk status. For group 2 (from October 2002 to July 2004; n=16) and group 3 (from August 2004 to September 2006; n=18), risk-adapted chemotherapies were given with cisplatin, etoposide, cyclophosphamide and vincristine (CECO) in the former and with carboplatin, etoposide, cyclophosphamide and bleomycin (CECB) in the latter-high-risk patients received double doses of cisplatin, carboplatin and cyclophosphamide. In addition, bleomycin was added to the high-risk patients in group 3. Details of risk-adapted chemotherapy are illustrated in Fig. 1. The CECO or CECB regimens were composed of 2 different schedules alternating every 3 week intervals and were completed after 4 cycles. All radiotherapy was given after chemotherapy and was individualized according to the clinical requirements (Table 1). The radiotherapy was delivered to the local field with or without craniospinal irradiation. The protocols used were approved by the Institutional Review Board of Samsung Medical Center (2008-11-056, 2009-02-050) and informed consent was obtained from the patients and/or guardians before starting treatments.

Evaluation for response and toxicity of chemotherapy

Response to chemotherapy was determined by MRI and tumor marker measurements. The radiologic response was defined as follows: complete response (CR), no radiographic evidence of residual tumor and normal tumor marker(s); partial response (PR), more than 50% reduction in tumor volume with at least 50% reduction of tumor marker(s); stable disease (SD), less than 50% reduction in tumor volume or less than 25% increase in any measurable tumor area without an substantial increase in tumor marker(s); progressive disease (PD), more than 25% increase in measureable tumor size and/or substantial elevation of tumor marker(s). Considering that a significant proportion of GCTs remain remnant lesion despite complete regression of viable tumors, we regarded a non-secreting remnant visible tumor without any increase in size for at least 2 yr after a completion of treatment as a clinical CR. When a significantly large tumor removed after chemotherapy and before radiotherpay revealed no viable tumor cells, it was also regarded as a clinical CR. Hematologic and non-hematologic toxicities were assessed by blood tests, clinical symptoms or signs, and specific tests if needed. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 3.0.

Supportive care

Patients receiving cisplatin were adequately hydrated with intravenous fluids. When diabetes insipidus was present, oral

CECO

Course [a]

Day	0	1	2	3	4
CDDP	▲	▲	▲	▲	▲
VP-16	▲	▲	▲	▲	▲

| CDDP | 20 (40*) mg/m²/day |
| VP-16 | 100 mg/m²/day |

Course [b]

Day	0	1	...	7	...	14
VCR	▲			▲		▲
CPM	▲	▲				

| VCR | 1.5 mg/m²/day |
| CPM | 1 (2*) g/m²/day |

CECB

Course [a]

Day	0	1	2
CBDCA	▲	▲*	
VP-16	▲	▲	▲
Bleo			▲*

CBDCA	450 mg/m²/day
VP-16	150 mg/m²/day
Bleo	15 mg/m²/day

Course [b]

Day	0	1	2
VP-16	▲	▲	▲
CPM	▲	▲	
Bleo			▲*

VP-16	150 mg/m²/day
CPM	1(2*) g/m²/day
Bleo	15 mg/m²/day

Fig. 1. Risk-adapted chemotherapy. CECO regimen is for group 2 and CECB regimen for group 3. In each regimen, course [a] and course [b] were administered alternatively as '[a]-[b]-[a]-[b]' every 3 week intervals and were completed after 4 cycles in total.
*For high-risk patients.
CDDP, cisplatin; VP-16, etoposide; VCR, vincristine; CPM, cyclophosphamide; CBDCA, carboplatin; Bleo, bleomycin.

Table 1. Radiotherapy (RT) in each group of patients

RT	Group 1 (n=19)			Group 2 (n=16)			Group 3 (n=18)		
	High-risk	Low-risk	Total	High-risk	Low-risk	Total	High-risk	Low-risk	Total
No. of patients: RT not done*	1	1	2	1	0	1	1	0	1
No. of patients: RT done	8	9	17	9	6	15	6	11	17
Median RT dose, Gy (range)									
Craniospinal	15	0	0	36	19.5	19.5	21.5	19.5	19.5
	(0-36)	(0-23.4)	(0-36)	(19.5-39)	(0-19.5)	(0-39)[†]	(19.5-36)	(0-24)[†]	(0-36)[†]
Local	19	30	20	18	19.8	18	13.5	19.8	16.2
	(10-40)	(10-40)	(10-40)	(10-20)	(10.8-30)	(10-30)	(10.8-18)	(10.8-30.6)	(10.8-30.6)
Tumor bed in total	45	30	30	54	34.8	39.3	35	39.3	39.3
	(30-56)	(30-41.4)	(30-56)	(30-57)	(30-39.3)	(30-57)	(30.3-54)	(28.8-41.4)	(28.8-54)
Mean RT dose, Gy									
Craniospinal	16.6	2.6	9.2	30.2	13.0	23.3	25.7	17.4	20.3
Local	19.3	25.3	22.5	16.7	21.7	18.7	14.1	19.0	17.3
Tumor bed in total	43.8	32.4	37.8	47.0	34.7	42.5	39.8	36.4	37.6

*Four patients did not receive radiation therapy due to premature death (2 in group 1), progression after second-look surgery (1 in group 2), or morbidity by tumor bleeding (1 in group 3); [†]P value <0.05 when compared with corresponding values of group 1.

desmopression was used to maintain the input/output balance. When the neutrophil count fell below 0.5×10^9/L, patients received granulocyte colony-stimulating factor (G-CSF) daily until it reached above 1.0×10^9/L. Irradiated (25 Gy) red blood cells or platelet concentrates were transfused to maintain the hemoglobin level above 8.0 g/dL and the platelet count above 20×10^9/L.

Statistical analysis

Fisher's exact test or chi-square test and Mann-Whitney U-test were used for a comparison of frequencies and observed values between groups. A P value <0.05 was considered as significant. The Kaplan-Meier estimates of overall survival (OS) and event-free survival (EFS) were used throughout the analysis and were calculated from the date of diagnosis to the date of last follow-up or event. An event was defined as disease recurrence, progression, or death from any cause. Survival curves were compared by the log-rank test. Statistical analysis was performed with the SPSS software version 12.0.

RESULTS

Patient characteristics

The median age at diagnosis was 13.8 yr (range, 6.4-22.4) and the male to female ratio was 2.8:1. Clinicopathologic characteristics are detailed in Table 2. Histologic diagnosis was obtained in 51 patients by endoscopic (n=28), stereotactic (n=12), open (n=10), or transsphenoidal (n=1) biopsy. No tumors were totally removed before chemotherapy. Two patients were diagnosed with a typical MRI finding and tumor marker elevation without a tissue diagnosis. On histologic

examination, 40 patients had germinomas and 11 were proven to have nongerminomatous GCTs. Two patients without a tissue diagnosis had significantly elevated tumor markers. In addition to 11 patients with biopsy-proven nongerminomatous GCTs, 2 patients having secreting tumors (bHCG levels 3 887 and 123 mIU/mL in CSF, respectively) without histologic comfirmation and 13 patients with biopsy-proven germinoma but having elevated AFP and/or bHCG ≥50 mIU/mL were also regarded as high-risk. Accordingly, 26 patients (49.1%) were allocated to the high-risk category. The demographic composition of each group is shown in Table 3. The frequency of high-risk patients in each group was not statistically different (group 1 vs. 2, P=0.37; group 1 vs. 3, P=0.60; group 2 vs. 3, P=0.20). The most common site of tumor involvement was pineal gland and almost a half of patients (45.3%) had diabetes insipidus at initial presentation. AFP and/or bHCG were significantly elevated in 45.3% of patients. CSF cytology revealed negative in all cases.

Response to chemotherapy

Radiologic responses and clinical CR rates are listed in Table 4. Among the 24 patients who had significantly elevated tumor marker(s) at initial diagnosis, 22 (91.7%) showed complete normalization of the tumor marker(s), and it was 100% in both group 2 and 3. The majority of patients responded to chemotherapy and no patients showed disease progression during chemotherapy. Two patients in group 1 were not evaluable for radiologic response due to a premature death during chemotherapy. The high-risk patients in group 3 showed better clinical CR rate when compared with those in group 1 (85.7% vs. 22.2%, P=0.04).

Table 2. Clinical characteristics of subjected patients (n=53)

Characteristics	No. of patients (%)
Sex	
Male	39 (73.6)
Female	14 (26.4)
Symptoms or signs	
Visual dysfunction	32 (60.4)
Headache	31 (58.5)
Vomiting	25 (47.2)
Diabetes insipidus	24 (45.3)
Motor disturbance	15 (28.3)
Obtundation	4 (7.5)
Precocious puberty	4 (7.5)
Short stature	3 (5.7)
Tumor markers	
AFP elevation+bHCG <50 mIU/mL	5 (9.4)
AFP elevation+bHCG ≥50 mIU/mL	7 (13.2)
bHCG ≥50 mIU/mL+normal AFP	12 (22.6)
bHCG <50 mIU/mL+normal AFP	29 (54.7)
Tumor location	
Pineal (P)	19 (35.8)
Sellar or suprasellar (S)	13 (24.5)
Thalamus (T) or basal ganglia (BG)	7 (13.2)
Ventricle (V)	1 (1.9)
S+BG	1 (1.9)
P+S	7 (13.2)
P+V	1 (1.9)
Multiple	4 (7.5)
Histology	
Germinoma (G)	40 (75.5)
Endodermal sinus tumor (EST)	1 (1.9)
Choriocarcinoma (CC)	2 (3.8)
Immature teratoma (IT)	2 (3.8)
Embryonal carcinoma (EC)	0 (0)
G+EST	2 (3.8)
G+IT	1 (1.9)
IT+EST	2 (3.8)
EC+EST	1 (1.9)
Unknown (biopsy not performed)	2 (3.8)
Risk group	
High-risk	26 (49.1)
Low-risk	27 (50.9)

AFP, alpha-fetoprotein; bHCG, beta-human chorionic gonadotropin.

Second-look operation

Second-look surgery was performed in 4 high-risk patients (1 in group 1, 2 in group 2, 1 in group 3) who had a significantly large residual tumor after chemotherapy, which revealed no viable tumor cells in 2 patients; one from choriocarcinoma to mature teratoma, and the other from immature teratoma to mature teratoma. The other 2 patients (1 in group 1, 1 in group 2) having viable malignant cells eventually died despite post-surgery irradiation and high-dose chemotherapy, one from disease progression and the other from treatment-related toxicities.

Table 3. Number of patients by tumor marker, histology, and risk

Parameters	No. of patients		
	Group 1 (n=19)	Group 2 (n=16)	Group 3 (n=18)
Tumor marker elevation*			
Yes	9	9	6
No	10	8	12
Histology			
Germinoma	16	9	15
Nongerminomatous	3	5	3
Unknown	0	2	0
Risk group			
High-risk	9	10	7
Low-risk	10	6	11

*AFP elevation and/or bHCG ≥50 mIU/m.

Toxicities of chemotherapy

Most patients (96.2%) developed grade 4 neutropenia and 41 patients (77.4%) required hospitalization due to neutropenic fever at least once. The incidence of neutropenic fever defined as 'total episodes of neutropenic fever per total number of chemotherapy cycles' was significantly higher in group 2 (66.1%) and group 3 (51.4%) when compared with group 1 (21.9%). The relative risk of neutropenic fever in group 2 over group 1 was 2.67 ([95% CI, 1.79-3.99], $P<0.001$), group 3 over group 1 was 1.84 ([95% CI, 1.33-2.52], $P=0.001$), and group 2 over group 3 was 1.40 ([95% CI, 0.94-2.01], $P=0.08$), respectively. All the episodes of neutropenic fever were manageable without significant complications except in one episode which was associated with mortality in group 1. The incidence of grade 3 or 4 thrombocytopenia was also higher in group 2 (87.5%) and group 3 (88.9%) than that of group 1 (31.6%). Four high-risk patients in group 2 who received 2 cycles of high-dose cisplatin (200 mg/m^2/cycle) developed high-frequency sensorineural hearing loss, 3 of whom had diabetes insipidus. One patient with choriocarcinoma in group 3 became in bed-ridden state due to massive tumor bleeding which happened during chemotherapy, but showing normal bHCG level and no evidence of tumor progression at 44 months after diagnosis.

Events and survival

In group 1, four patients relapsed, one prematurely died due to uncontrolled increased intracranial pressure, and another died from infectious complications. In group 2, the one and only event was tumor recurrence. The patient eventually died from disease progression after high-dose chemotherapy and autologous stem cell rescue. There was no event in group 3. The 5-yr OS and EFS of 53 patients were 90.6% and 85.5%, respectively, with a median follow-up of 59 months (range, 22-124) from the diagnosis (Fig. 2A). The low-

Table 4. Number of patients by response after treatment

| Parameters | No. patients (%) | | | | | | | | |
| | Group 1 | | | Group 2 | | | Group 3 | | |
	High-risk (n=9)	Low-risk (n=10)	Total (n=19)	High-risk (n=9)	Low-risk (n=10)	Total (n=19)	High-risk (n=9)	Low-risk (n=10)	Total (n=19)
Tumor marker*									
Normalized	7 (77.8)	–	7 (77.8)	9 (100)	–	9 (100)	6 (100)	–	6 (100)
Partially decreased	1 (11.1)	–	1 (11.1)	0 (0)	–	0 (0)	0 (0)	–	0 (0)
Increased	0 (0)	–	0 (0)	0 (0)	–	0 (0)	0 (0)	–	0 (0)
Not evaluable	1 (11.1)	–	1 (11.1)	0 (0)	–	0 (0)	0 (0)	–	0 (0)
Radiologic response									
CR	0 (0)	2 (20)	2 (10.5)	4 (40)	1 (16.7)	5 (31.3)	2 (28.6)	5 (45.5)	7 (38.9)
PR	5 (55.6)	8 (80)	13 (68.4)	5 (50)	5 (83.3)	10 (62.5)	4 (57.1)	6 (54.5)	10 (55.6)
SD	2 (22.2)	0 (0)	2 (10.5)	1 (10)	0 (0)	1 (6.3)	1 (14.3)	0 (0)	1 (5.6)
PD	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Not evaluable	2 (22.2)	0 (0)	2 (10.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Clinical CR	2 (22.2)	6 (60)	8 (42.1)	7 (70)	2 (33.3)	9 (56.3)	6 (85.7)	10 (90.9)	16 (88.9)
P value[†]	–	–	–	0.07	0.6	0.4	0.04	0.15	0.005

*Of 24 patients (9 in group 1, 9 in group 2, 6 in group 3) whose tumor marker(s) at initial diagnosis were significantly elevated (AFP elevation and/or bHCG ≥50 mIU/mL); [†]Values when compared with each risk group and total patients in group 1.
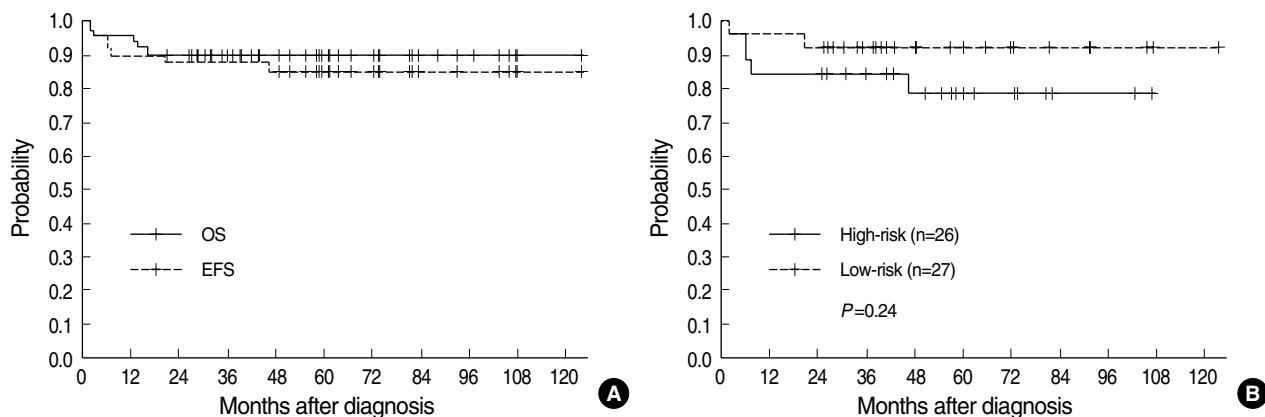CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Fig. 2. The Kaplan-Meier estimate of survival. The 5-yr overall survival (OS) and event-free survival (EFS) of 53 patients were 90.6% and 85.5%, respectively (A). Low-risk patients show better EFS than high-risk patients (92.6% vs. 79.3%, P=0.24) without a statistical significance (B).

risk patients showed better EFS than the high-risk patients although it was not statistically significant (Fig. 2B). In group 1, the high-risk patients showed inferior EFS compared to the low-risk patients without a statistical significance (Fig. 3A). In group 2 and group 3, even the high-risk patients showed excellent EFS (Fig. 3B, C). The event-free survival of group 1, group 2, and group 3 were 67.0%, 93.8%, and 100%, respectively (group 1 vs. 2, P=0.06; group 2 vs. 3, P=0.29; group 1 vs. 3, P=0.02) (Fig. 3D). All patients in group 3 are alive event-free with a median follow-up of 36 months (range, 26-51).

DISCUSSION

Malignant CNS-GCTs have been classified as germinomas vs. nongerminomatous GCTs or secreting vs. non-secreting tumors. However, such classifications have limitations since biopsy-proven germinomas can have nongerminomatous elements among the unbiopsied sites and non-secreting tumors can also have nongerminomatous components such as immature teratoma with less favorable prognosis (16). It is well-known that both nongerminonatous and secreting GCTs have worse prognosis. Therefore, we regarded those as high-risk either having nongerminomatous components or having elevated AFP or bHCG ≥50 mIU/mL. Considering that ger-
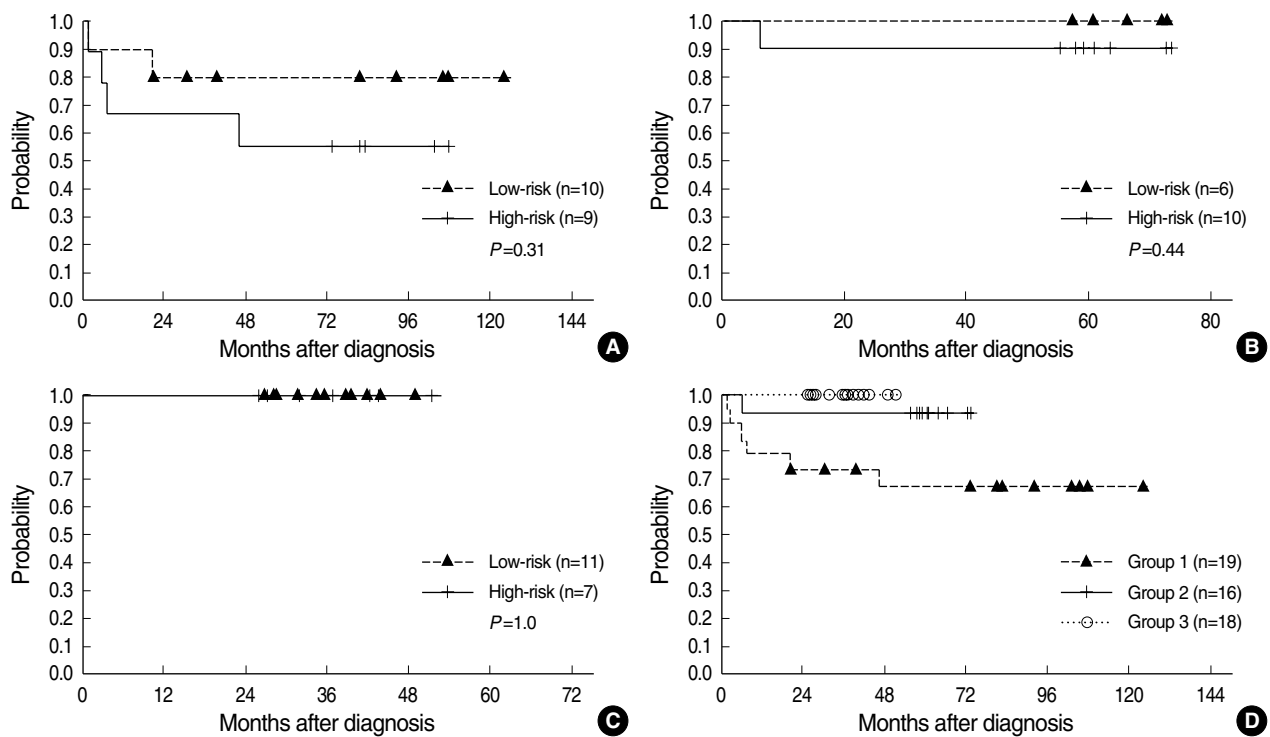
Fig. 3. The Kaplan-Meier estimate of event-free survival (EFS). In group 1, the high-risk patients show inferior EFS compared to the low-risk patients without a statistical significance (A). In group 2 (B) and group 3 (C), even the high-risk patients show excellent EFS. The EFS of group 3 is superior to that of group 1 (P=0.02), while the difference between group 1 and group 2 (P=0.06) as well as group 2 and group 3 (P=0.29) do not show a statistical significance (D).

minomas can secrete small amount of bHCG, a relatively low bHCG level (<50 mIU/mL) was not included in the high-risk criteria.

Our risk-adapted chemotherapy strategy produced very high clinical CR rate when we included those having a radiological remnant tumor into the complete responders provided that it was considered nonevolving. Assessing the response of GCTs is frequently confusing because treated GCTs tend to remain as remnant fibrotic, calcified, cystic or fully differentiated mass but actually containing no viable tumor cells. Therefore, we also regarded those as clinical complete responders who had a small residual lesion with normal tumor marker levels at the end of chemotherapy, provided that the lesion did not show any increase in size without any elevation of tumor markers for more than 2 yr after a completion of irradiation. In fact, 2 of 4 patients in this study who underwent second-look surgery after chemotherapy had no viable tumor cells despite a significantly large residual tumor size after chemotherapy.

Because of the rarity of these tumors and a lack of large prospective studies, the optimal therapeutic strategy for malignant CNS-GCTs remains unsettled. An early study by Rich et al. (5) suggested that nongerminomatous or secreting tumors were relatively resistant to radiotherapy. After the chemotherapy was introduced as a treatment modality for gonadal GCTs, the efficacy of chemotherapy for CNS-GCTs has been tested

by many investigators. In 1995, Itoyama et al. (17) showed the effectiveness of multidisciplinary treatment including combination chemotherapy in treating AFP-producing CNS-GCTs. In the next year, the International Central Nervous System Germ Cell Tumor Study Group reported the results of an international cooperative trial using chemotherapy without irradiation, which showed 78% of CR rate (84% for germinoma, 78% for nongerminomatous GCTs) (18). However, 49% of the complete responders in their study eventually relapsed, which implicates the indispensible role of radiotherapy. The importance of radiotherapy was confirmed again in a study, in which patients with secreting CNS-GCTs were treated with chemotherapy alone, but unfortunately 12 of the 13 non-irradiated patients eventually relapsed (19). On the other hand, a study by Robertson et al. (20) using 'sandwich' therapy (chemotherapy-radiation-chemotherapy) showed 67% of 4-yr EFS among 18 nongerminomatous GCT patients and they concluded that the multi-modality adjuvant therapy approach appeared to dramatically improve the prognosis of these tumors. More recently, clinical trials using systemic chemotherapy combined with radiotherapy showed clear benefits over the strategy using radiotherapy alone especially for nongerminomatous GCTs. Matsutani et al. (21) conducted a multiinstitutional phase II study to establish a postsurgical combined chemotherapy and radiotherapy, and concluded that their protocols were effective for patients with germi-

nomas and those with an intermediate prognosis. A multi-institutional retrospective analysis by Ogawa et al. (22) reported a higher 5-yr survival rate in chemotherapy group than that in non-chemotherapy group (84% vs. 44%). According to the Children's Oncology Group report in 2007 on the efficacy of pre-radiation chemotherapy with response-based radiation therapy in children with CNS-GCTs, although the number of patients was small (n=26), 3-yr OS was 100% for germinomas and 79% for nongerminomatous GCTs (23).

In the current study, authors demonstrated an improvement in the survival rate of our patients using risk-adapted intensive chemotherapy in conjunction with subsequent radiotherapy. Our early treatment outcomes using 4 cycles of PEB regimen prior to radiotherapy had resulted in unsatisfactory outcome, which showed 67% of 5-yr EFS. Therefore we changed the chemotherapy strategy to more intensive risk-adapted cisplatin-based regimens. Although this change in treatment strategy showed excellent survival outcomes (1 relapse occurred among 16 patients), an unexpected high incidence of ototoxicity in high-risk patients who received high-dose cisplatin (200 mg/m^2/cycle, 2 cycles) put us into a major protocol revision. Thereafter, we have been using a carboplatin-based regimen, with which no ototoxicity has occurred. Carboplatin is known to be less nephrotoxic or ototoxic than cisplatin (24, 25). Considering the high incidence of diabetes insipidus among patients with CNS-GCTs, cisplatin may not be appropriate for those having diabetes insipidus because they should be controlled with strict input/output balance along with adequate hydration and desmopressin replacement, which is often very difficult. Almost a half (45.3%) of our patients had diabetes insipidus before treatment and ototoxicity occurred in 4 of 10 patients who received high-dose cisplatin. Notably, 3 of 5 patients (60%) who received high-dose cisplatin and also had diabetes insipidus ultimately developed ototoxicity. Since our current protocol using carboplatin-based regimen not only gave rise to excellent survival rate but also were more tolerable without ototoxicity, we believe that our current carboplatin-based chemotherapy protocol is highly effective for malignant CNS-GCTs.

One of the major limitations of our study is that the radiation guideline was not consistent. Patients in group 2 and group 3 generally received higher dose of craniospinal irradiation as compared with group 1, although a statistically significant difference was found only between the low-risk patients of group 1 and group 3 when matched with each corresponding risk group (Table 1). At any rate, the radiation dose in our cohort was not any higher than usual doses applied in other studies-only 10 patients (18.5%) receiving more than 30 Gy of craniospinal irradiation or more than 50 Gy to the tumor bed (data not shown). Wolden et al. (9) applied 45 to 54 Gy to the tumor bed with or without craniospinal irradiation, which produced approximately 70% of 5-yr disease-free survival rate, but is still inferior to our results. In a report by Ogawa et al. (22), the median radiation dose was 50 Gy to the primary site and 30 Gy to the whole brain and whole spine, which is also higher than that used in our patients.

Despite our excellent results for both low-risk and high-risk patients, we cannot conclude that our current strategy is also advantageous for low-risk patients because studies using radiotherapy as a single treatment modality generally have shown excellent outcomes in pure germinoma. However, we believe that further reduction of radiation dose might be possible in selected patients with our current chemotherapy protocols.

Although intensive chemotherapy led to a high incidence of severe myelosuppression and infection, all infectious episodes following risk-adapted intensive chemotherapy were manageable with broad-spectrum antibiotics and G-CSF supports and there were no infection-related major complications. Because of the rarity of CNS-GCTs, nationwide or multicenter clinical trial is required to determine the efficacy of current strategy.

In conclusion, our strategy using short course of risk-adapted intensive systemic chemotherapy prior to radiotherapy shows excellent results even in high-risk patients with malignant CNS-GCTs. However, high-dose cisplatin in high-risk patients causes a high incidence of ototoxicity, especially in the presence of diabetes insipidus, which favors the use of the carboplatin-based regimen in that it has lower toxicity profiles without the expense of efficacy as shown in our study.

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