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Responses and adverse effects of carboplatin-based chemotherapy for pediatric intracranial germ cell tumors

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Purpose: Cisplatin-based chemotherapy has been commonly used for the treatment of intracranial germ cell tumors (IC-GCTs). However, this treatment exhibits some adverse effects such as renal problems and hearing difficulty. Carboplatin-based chemotherapy was administered to pediatric patients with IC-GCTs from August 2004 at the Samsung Medical Center. In this study, we assessed the responses and adverse effects of carboplatin-based chemotherapy in pediatric IC-GCTs patients according to the risk group, and compared the results with those of the previous cisplatin-based chemotherapy.

Methods: We examined 35 patients (27 men and 8 women) diagnosed with IC-GCTs between August 2004 and April 2008 and received risk-adapted carboplatin-based chemotherapy at the Samsung Medical Center. Patients were divided into either low-risk (LR) or high-risk (HR) groups and a retrospective analysis was performed using information from the medical records.

Results: Although hematological complications were common, hearing difficulties or grade 3 or 4 creatinine level elevation were not observed in patients who underwent carboplatin-based chemotherapy. The frequency of febrile neutropenia did not differ between the risk groups. The overall survival was 100% and event-free survival (EFS) was 95.7 %. The EFS rate was 100% in the LR group and 90% in the HR group, respectively.

Conclusion: Despite their common occurrence in high-risk patients, no lethal hematological complications were associated with carboplatin-based treatment. The current carboplatin-based chemotherapy protocol is safe and effective for the treatment of pediatric patients with IC-GCTs.

Key words: Intracranial germ cell tumor, Carboplatin, Adverse effects

Introduction

Intracranial germ cell tumors (IC-GCTs) are lesions that develop in patients of all ages. They vary in their geographic incidence and in Japan and the Far East, the incidence of germ cell tumors is five to eightfold greater than that in Western societies[1]. In 2002, Cho et al.[2] reported that the frequency of IC-GCTs was 11.2% in 677 Korean pediatric patients with brain tumors and in 2009, Goodwin et al.[3] reported that the incidence was 2.6 per million in the Asian population. The age distribution of affected patients is unimodal; there is an abrupt surge in frequency during the early pubertal years; 68% of patients are diagnosed between 10 and 21 years of age[4]. Cisplatin-based chemotherapy has been commonly used for the treatment of IC-GCTs[5,6]. However, in 2005, You et al.[7] reported the results of cisplatin-based chemotherapy in patients with IC-GCTs diagnosed at the Samsung Medical Center from October 2002 to December 2003 and the limitations of cisplatin-based chemotherapy. For preventing cisplatin-associated toxicities, carboplatin-based chemotherapy has been used for pediatric patients with IC-GCTs from August 2004 at our center. In 2010, Yoo et al.[8] reported the effectiveness of risk adapted carboplatin-based chemotherapy for patients with malignant central nervous system-GCT. Some experts have recommended that more intensive chemotherapy is more beneficial for high-risk patients[9]. However, there are no studies on the responses and toxicities of carboplatin-based chemotherapy in Korea, and no analysis of toxicity associated with risk groups. Therefore, in this study, the responses to carboplatin-based chemotherapy were assessed and the toxicities according to risk group were evaluated.

Materials and methods

1. Patients

Thirty-five patients who were diagnosed with IC-GCTs from August 2004 to April 2008 and received chemotherapy at Samsung Medical Center were included in this study. All patients except one had a surgical biopsy before chemotherapy was started. When histological confirmation was not done before the chemotherapy, magnetic resonance imaging (MRI) findings along with elevated tumor marker(s) such as α-fetoprotein (AFP) and/or β-human chorionic gonadotropin (β-HCG) were used for the diagnosis. Evaluations using brain MRI, whole spine MRI, cerebrospinal fluid (CSF) cytology, and tumor marker levels in the serum and CSF were performed in all patients prior to the initiation of chemotherapy. The patients were divided into either low-risk (LR) or high-risk (HR) groups. The LR criteria were defined as follows: 1) pure germinoma confirmed by histology, 2) normal AFP level, and 3) a low serum and CSF β-HCG level (<50 mIU/mL). All of the others that did not meet any of the LR criteria were regarded as HR; some patients with a histologically proven germinoma had an elevated AFP and high β-HCG levels, which suggested they actually had nongerminomatous components at sites that were not biopsied.

2. Treatments

After biopsy, four cycles of chemotherapy were administered, followed by radiotherapy (RT). A risk-adapted carboplatin-based regimen (carboplatin, etoposide, cyclophosphamide, bleomycin) was implemented and bleomycin was used only in the HR patient group. In addition, in the high risk group, a double-dose carboplatin was used (LR group 450 mg/m^2/day for 1 day, HR group 450 mg/m2/day for 2 days). The regimens were composed of two different schedules alternating every three weeks and were completed after four cycles (Fig. 1). All patients received RT. A radiological oncologist individualized the RT dose for each patient before RT.

3. Methods

A retrospective review of the patient medical records including age, gender, weight loss, symptoms (fever, nausea, vomiting, auditory symptoms), blood tests (nadirs of leukocyte/absolute neutrophil count (ANC)/hemoglobin/platelet/albumin, peak levels of total bilirubin/aspartate aminotransferase (AST)/alanine aminotransferase (ALT)/creatinine), numbers of red blood cell and platelet transfusion, primary site of the tumor, and the histological findings were recorded. Pure tone audiometry and speech audiometry were used for hearing examinations. The toxicities were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC version 3.0)[10].

4. Statistics

Fisher's exact test and the Chi-square test were used for a com-

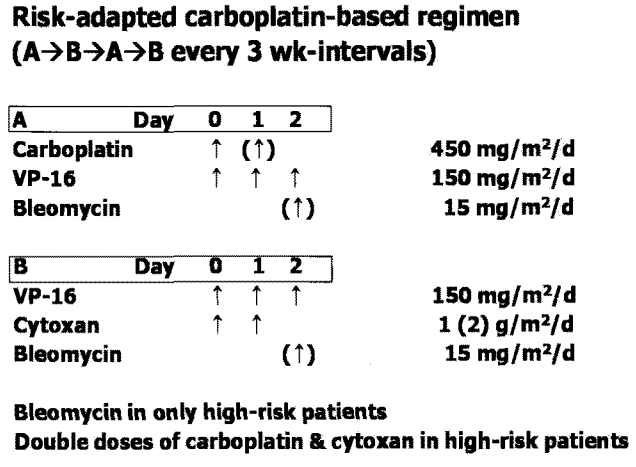

Fig. 1. Risk-adapted carboplatin-based regimen.

parison of the frequencies and observed values between the study groups. The Mann-Whitney U-test and Kruskal-Wallis test were used for non-parametric statistical analysis to evaluate the difference between the groups. For the survival analysis, Kaplan-Meier analysis was used. The data were analyzed using SPSS (version 12.0, SPSS Inc, Chicago, IL, USA) and a *P*-value less than 0.05 was considered significant.

Results

The patients' clinical/pathological characteristics are detailed in Table 1. The median patient age was 15.5 years (range, 6.4–26.2 years) and the median follow up period was 23 months (range, 4–49 months). The hematological toxicities were the most common. The overall frequency of grade 3 or 4 hematological toxicity was in the following order: neutropenia (100%), thrombocytopenia (91.4%), and anemia (54.3%). However, there was no significant difference in the hematological toxicities except for anemia between the LR group and the HR group. A Grade 3 or 4 anemia was 33.3% in the LR group and 85.7% in the HR group ($P<0.01$).

Febrile neutropenia (85.7%) was the third most common in patients treated with carboplatin-based chemotherapy. There was no difference in the frequency of febrile neutropenia between the LR group and the HR group. The frequency of microbiologically documented infection (MDI) was five in the HR group ($P<0.01$). However, there was no mortality associated with a MDI. Grade 3 or 4 creatinine elevation was not present in any of the patients. Pure tone audiometry and speech audiometry after 4 cycles of chemotherapy was assessed in seven patients and all seven patients had normal findings. Hearing difficulty was not found in any of the patients who received carboplatin-based chemotherapy (Table 2).

In an analysis of continuous variables associated with toxicity, hematological parameters such as nadirs of leukocyte/hemoglobin/ANC/platelet showed lower values in the HR group. The patients in the HR group had longer chemotherapy intervals than the patients in the LR group ($P<0.01$). The nadir of albumin and peak levels of total bilirubin/AST/ALT/and creatinine were not different between the LR group and the HR group. However, the patients in the HR group had more weight loss during the treatment period. The mean percentage of weight loss in the LR group was 4.8±4.9%, and in the HR group it was 12.1±8.7% ($P<0.01$). Red blood cell and platelet transfusions were more frequent in the HR group ($P<0.01$). The overall survival (OS) rate was 100% and the event free survival (EFS) rate was 95.7% (Fig. 2). The EFS rate was 100% in the LR group, and 90% in the

Table 1. Characteristics of Intracranial Germ Cell Tumor Patients

Variables	Patients	
	Number	%
Sex		
Male	27	77.1
Female	8	22.9
Risk group		
Low	21	60.0
High	14	40.0
Tumor location		
Pineal (P)	12	34.3
Sellar or Suprasellar (S)	10	28.6
Thalamus (T) or basal ganglia (BG)	6	17.1
Ventricle (V)	1	2.8
P+S	3	8.6
Multiple	3	8.6
Histology		
Germinoma (G)	29	82.8
Choriocarcinoma (CC)	1	2.9
Immature Teratoma (IT)	1	2.9
Mature Teratoma (MT)	1	2.9
G+IT	2	5.6
Unknown (biopsy not performed)*	1	2.9

*Unknown one patient had typical magnetic resonance imaging scan findings along with elevated CSF α-fetoprotein level (695 ng/mL, normal level <20 ng/mL)

Table 2. Grade 3 or 4 Toxicities of Intracranial Germ Cell Tumor Patients

Toxicities	Patients No. (%)			
	Total	Low Risk	High Risk	*P*-value
Hematologic				
Leukocyte	35 (100)	21 (100)	14 (100)	NS
ANC	35 (100)	21 (100)	14 (100)	NS
Platelet	32 (91.4)	18 (85.7)	14 (100)	NS
Hemoglobin	19 (54.3)	7 (33.3)	12 (85.7)	0.005
Infection				
Febrile neutropenia	30 (85.7)	18 (85.7)	12 (85.7)	NS
MDI*	5 (14.3)	0 (0)	5 (35.7)	0.006
Gastrointestinal				
Nausea	6 (17.1)	2 (9.5)	4 (28.6)	NS
Vomiting	5 (14.3)	2 (9.5)	3 (21.4)	NS
Weight loss	3 (8.6)	1 (4.8)	2 (14.3)	NS
Hepatobiliary				
AST	2 (5.7)	1 (4.8)	1 (7.1)	NS
ALT	3 (8.6)	2 (9.5)	1 (7.1)	NS
Hypoalbuminemia	0 (0)	0 (0)	0 (0)	NS
Hyperbilirubinemia	0 (0)	0 (0)	0 (0)	NS
Renal				
Cystitis	0 (0)	0 (0)	0 (0)	NS
Creatinine	0 (0)	0 (0)	0 (0)	NS
Ototoxicity				
Hearing loss	0 (0)	0 (0)	0 (0)	NS

Abbreviations: No., number; ANC, absolute neutrophil count; MDI, microbiologically documented infection; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NS, nonspecific.

*Identified organisms: *Candida tropicalis, Candida glabrata, Klebsiella pneumoniae, Staphylococcus aureus, Escherichia coli, Enterococcus gallinarum, Streptococcus viridians*

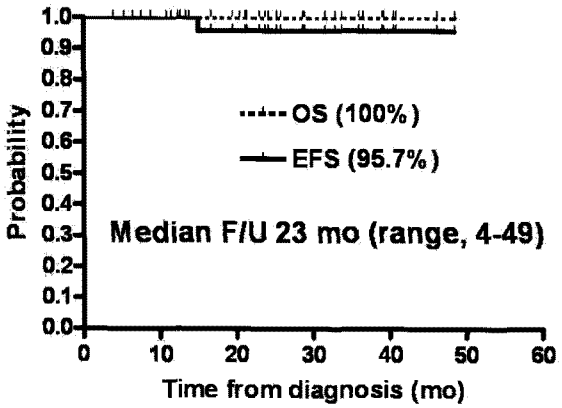

Fig. 2. The 5-year overall survival (OS) (100%) and event-free survival (EFS) (95.7%) of 35 patients.

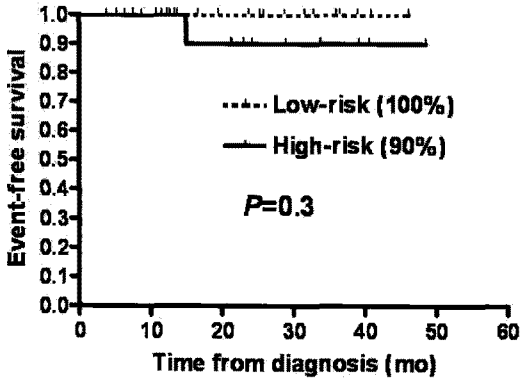

Fig. 3. Event-free survival (EFS) rate for LR group (100%) and for HR group (90%) (P>0.05).

HR group (Fig. 3). One patient in the high risk group had tumor recurrence and he is under treatment again.

Discussion

Platinum-based chemotherapy is commonly used in patients with IC-GCTs. The leading platinum compounds used in cancer chemotherapy are cisplatin, carboplatin and oxaliplatin. They share some structural similarities. However, there are marked differences among them in therapeutic use, pharmacokinetics and adverse effect profiles. Cisplatin is the most highly protein bound, followed by oxaliplatin and carboplatin; the degree of protein binding is related to adverse responses[11]. It appears to be superior to carboplatin in terms of therapeutic effectiveness (germ cell tumors, bladder cancer, and head and neck cancer)[12, 13], however, it has some severe associated toxicity such as ototoxicity and nephrotoxicity.

In 1994, Allen et al.[14] reported the effect of carboplatin in patients with newly diagnosed germinomas of the central nervous system. In 2002, Stern et al.[15] suggested carboplatin could be used to substitute for cisplatin during the treatment of pediatric germ cell tumors and in 2005, You et al.[7] reported results of a cisplatin-based treatment of pediatric patients with IC-GCTs at the Samsung Medical Center and the limitations of cisplatin-based chemotherapy. The EFS rate in the LR group treated with cisplatin-based chemotherapy was 100% and for the HR group it was 88.9%. The EFS rates were similar to the results of current study. However, four of nine patients in the high risk group had hearing difficulty and had a diagnosis of sensorineural hearing loss. In this study, seven patients had pure tone audiometry and speech audiometry by otology experts; none of the patients treated with carboplatin-based chemotherapy had sensorineural hearing loss. And grade 3 or 4 creatinine elevation was not found in patients treated with carboplatin-based chemotherapy, even in HR group patients who received double-dose carboplatin-based chemotherapy. In addition, there was no significant cystitis identified in any of the patients treated with carboplatin-based chemotherapy. And Yoo et al.[8] recommended carboplatin-based chemotherapy in patients with central nervous system-GCTs because many patients may have signs of diabetes insipidus. Cisplatin may not be appropriate for patients with diabetes insipidus because they must be managed by strict input/output measurements along with adequate hydration and desmopressin replacement. Considering the immature renal and hearing function of pediatric patients, carboplatin can be the useful agent for pediatric patients with IC-GCTs.

In contrast to cisplatin, myelotoxicity represents the most prominent adverse effect of carboplatin. Carboplatin induced myelosuppresion is dose-related and results in thrombocytopenia and neutropenia[11]. In this study, the HR group patients received a double-dose carboplatin and needed more frequent RBC and platelet transfusions. The neutrophil recovery was also delayed in HR group patients. Myelosuppression is closely related to infection, which is a major cause of morbidity and mortality in cancer patients[16]. The probability of developing MDI, when a child presents with fever and therapy-induced neutropenia, ranges from 10 to 40%[17-20]. However, cisplatin can also induce myelosuppression and febrile neutropenia. You et al.[7] reported that the frequency of grade 4 neutropenia associated with cisplatin-based chemotherapy was 100% and the frequency of grade 3 or 4 infectious complication was 80% in the LR group, 100% in the HR group. In 2007, Okamoto et al.[21] compared the effects of carboplatin and cisplatin in patients with small cell lung cancer. They reported a high percentage of neutropenia in the carboplatin group (95%) and cisplatin group (90%). However, there was no difference in infection prevalence between the carboplatin group and cisplatin group (P=0.78). In this study, grade 3 or 4 neutropenia was 100% and grade 3 or 4 febrile neutropenia was 85.7%. In addition, five patients in the HR group

had a MDI. However, all infections were controlled by antibiotic treatment and supportive care with no sequelae. No complication or mortality associated with infection occurred in patients treated with carboplatin-based chemotherapy.

In conclusion, carboplatin-based chemotherapy used for the treatment of IC-GCTs is safer and more effective than we expected for the treatment of pediatric patients with IC-GCTs. There was no significant nephrotoxicity and ototoxicity in the patients treated with carboplatin-based chemotherapy. Although hematological toxicities were frequent in the HR group of patients, there were no lethal complications associated with the carboplatin-based treatment. A multicenter prospective, multivariate study is required to determine the long-term efficacy and feasibility of the current protocol.

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