Tandem High-Dose Chemotherapy and Autologous Stem Cell Transplantation in Young Children with Atypical Teratoid/Rhabdoid Tumor of the Central Nervous System

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INTRODUCTION

Central nervous system (CNS) atypical teratoid/rhabdoid tumor (ATRT) is highly malignant. ATRT accounts for 2%-3% of childhood CNS tumors, but up to 20% of malignant CNS tumors in patients younger than 3 yr of age with atypical teratoid/rhabdoid tumors (ATRT). The prognosis of ATRT is extremely poor because these tumors often rapidly relapse or progress despite aggressive surgery, conventional chemotherapy, and/or irradiation (3, 4). Since Hilden et al. (1) created a registry for ATRT, the efficacy of many different treatments has been explored to improve the survival of ATRT patients (5-7). However, there has been no consensus as to the proper treatment strategy for ATRT. The very poor prognosis of ATRT in infants and young children may be related to both the lower tolerance of younger patients for surgical procedures and to delays in diagnosis. Poor prognosis may be also related to the limited use of radiotherapy (RT) in very young children due to the risks of functional impairment of the developing brain and late adverse effects including global reduction in IQ, cognitive deficits, and neuroendocrine dysfunctions (8-11).

The feasibility and effectiveness of tandem high-dose chemotherapy and autologous stem cell transplantation (HDCT/autoSCT) were evaluated in children younger than 3 yr of age with atypical teratoid/rhabdoid tumors (ATRT). Tandem HDCT/autoSCT was administered following six cycles of induction chemotherapy. Radiotherapy (RT) was administered if the tumor relapsed or progressed, otherwise, it was administered after 3 yr of age. Tumors relapsed or progressed during induction chemotherapy in 5 of 9 patients enrolled; 3 of these 5 received tandem HDCT/autoSCT as a salvage treatment. One patient died from sepsis during induction chemotherapy. The remaining 3 patients proceeded to tandem HDCT/autoSCT; however, 2 of these patients showed tumor relapse/progression after tandem HDCT/autoSCT. All 7 relapses/progressions occurred at primary sites even in patients with leptomeningeal seeding. Toxicities during tandem HDCT/autoSCT were manageable. A total of 5 patients were alive with a median follow-up of 20 (range 16-70) months from diagnosis. Four of 5 patients who received RT after relapse/progression are alive. The probability of overall survival at 3 yr from diagnosis was 53.3% ± 17.3%. Our tandem HDCT/autoSCT is feasible; however, early administration of RT prior to tandem HDCT/autoSCT should be considered to improve the outcome after tandem HDCT/autoSCT.

Key Words: Rhabdoid Tumor; Central Nervous System; Drug Therapy; Stem Cell Transplantation; Radiotherapy; Child
of high-risk pediatric solid tumors such as high-risk neuroblastoma and high-risk embryonal brain tumors (12-14). The results of clinical trials using HDCT/autoSCT for infants and young children with malignant brain tumors also showed that it is possible to avoid or defer RT until 3 yr of age while maintaining or improving survival rates (15, 16). Recently, a few smaller studies suggested that tandem HDCT/autoSCT might be feasible for treating recurrent or high-risk brain tumors and might further improve outcomes (17, 18). In the present study, we evaluated the feasibility and effectiveness of tandem HDCT/autoSCT in children younger than 3 yr of age with ATRT. Our new treatment strategy aimed both to improve survival and to reduce risks for significant late adverse effects of RT.

**MATERIALS AND METHODS**

**Patients**

From July 2005, a phase I/II prospective study using tandem HDCT/autoSCT for very young children with malignant brain tumors was initiated by Korean Society of Pediatric Neuro-Oncology. Children younger than 3 yr of age at diagnosis who were newly diagnosed with malignant brain tumors including ATRT were eligible for inclusion in the study. Low grade brain tumors including stem glioma were excluded from the study. The primary goal of the present study was to evaluate the feasibility of tandem HDCT/autoSCT in very young children with malignant brain tumors and the secondary goal was to evaluate whether tandem HDCT/autoSCT might improve survival of very young children with malignant brain tumors. The present study analyzed only patients with ATRT because ATRT has unique characteristics compared to other brain tumors.

A pediatric neuropathologist who had no information about the children's clinical courses, reviewed all cases. Loss of nuclear expression of INI1 was confirmed by immunohistochemical staining. Disease extent at diagnosis was assessed using brain and spinal magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) cytology.

**Induction treatment prior to HDCT/autoSCT**

Surgery was the primary treatment for all resectable tumors. Six cycles of conventional chemotherapy were administered prior to tandem HDCT/autoSCT. Alternating CECV regimens (cisplatin 3 mg/kg once daily i.v. on day 0; etoposide 2.5 mg/kg once daily i.v. on days 0, 1, and 2; cyclophosphamide 50 mg/kg once daily i.v. on days 1 and 2; vincristine 0.05 mg/kg once daily i.v. on days 0 and 7) and CEIV regimens (carboplatin 10 mg/kg once daily i.v. on days 0 and 1; etoposide 2.5 mg/kg once daily i.v. for 5 consecutive days from day 0; ifosfamide 50 mg/kg once daily i.v. for 5 consecutive days from day 0; vincristine 0.05 mg/kg once daily i.v. on days 0 and 7) were used. Induction chemotherapy cycles were scheduled to start 28 days apart, but some delays were permitted to allow absolute neutrophil count (ANC) and platelet count to recover to 1,000/μL and 100,000/μL, respectively. Peripheral blood stem cells (PBSCs) were collected during the recovery phase of the first chemotherapy cycle.

**Salvage treatment after relapse/progression during induction chemotherapy**

If the tumor relapsed or progressed during induction chemotherapy, second-look surgery was performed whenever possible. RT was also administered whenever second-look surgery was not possible or when a large residual tumor remained after second-look surgery. Otherwise, RT was administered after tandem HDCT/autoSCT. Tandem HDCT/autoSCT was given if the tumor remained progression free during salvage treatment after first relapse/progression.

**Tandem HDCT/autoSCT**

The CTE regimen (carboplatin 500 mg/m² once daily i.v. on days -8, -7, and -6; thiotepa 300 mg/m² once daily i.v. on days -5, -4, and -3; etoposide 250 mg/m² once daily i.v. on days -5, -4, and -3) and CM regimen (cyclophosphamide 1,500 mg/m² once daily i.v. on days -8, -7, -6, and -5; melphalan 60 mg/m² once daily i.v. on days -4, -3, and -2) were employed for the first and second HDCT/autoSCT, respectively. We allowed a 12-16 week interval between the first and second HDCT/autoSCT to prevent toxic death in the second HDCT/autoSCT. Roughly half of the PBSCs collected during a single leukapheresis round were infused for marrow rescue at each HDCT/autoSCT session. In patients who remained in complete response after tandem HDCT/autoSCT, RT was deferred until 3 yr of age unless the tumor relapsed.

**Response and toxicity criteria**

Disease response was evaluated by MRI and CSF cytology. Evaluations were repeated every two or three chemotherapy cycles prior to the first HDCT/autoSCT, between the first and second HDCT/autoSCT, every three months for the first year after the tandem HDCT/autoSCT, every four months for the second year after tandem HDCT/autoSCT, and then every six months thereafter. Tumor responses were categorized according to the Response Evaluation Criteria in Solid Tumors (RECIST) (19). Toxicities during HDCT/autoSCT were graded using the National Cancer Institute’s Common Toxicity Criteria (version 2.0).

**Statistics**

Survival rates and event-free survival rate ± standard errors from diagnosis were estimated using the Kaplan-Meier method. An event was defined as the occurrence of a relapse, progression, or treatment-related death. Survival rates and progression-free survival rate ± standard errors from HDCT1 and RT were estimated using the Kaplan-Meier method. Progressive disease was defined as greater than a 25% increase in tumor size or the ap-
pearance of a new area of tumor.

Ethics statement
The institutional review board of Keimyung University Hospital approved this study (IRB No.2005-12-009). All parents/guardians gave their informed consent for this study.

RESULTS

Patient characteristics at diagnosis
Nine patients with ATRT were enrolled between September 2005 and March 2010 from 5 institutions. Patient characteristics are listed in Table 1. The median age at diagnosis was 12 (range 4-28) months. The tumor was located at the posterior fossa in five patients, supratentorially in three, and at the spinal cord in one. Four patients had significant residual tumors (> 1.5 cm²) after initial surgery and six patients had leptomeningeal seeding.

Treatment prior to HDCT/autoSCT
Treatments and responses are listed in Table 1. Three patients (Patients 1, 5, and 9) proceeded to HDCT/autoSCT as scheduled without relapse/progression during induction chemotherapy (1 complete response and 2 partial responses). Tumor relapse or progression during induction chemotherapy was seen in five patients (Patients 2, 3, 4, 6, and 7). All relapses/progressions occurred at the primary tumor sites even in patients with leptomeningeal seeding. As salvage treatment, second-look surgery and/or RT were performed in four of the patients; the remaining patient (Patient 6) died due to tumor progression before initiation of salvage treatment. Three of 4 patients who received salvage treatment remained progression free during salvage treatment and could proceed to HDCT/autoSCT; however, the remaining patient (Patient 2) died due to tumor progression despite second-look surgery and RT. One patient (Patient 8) died due to sepsis during induction chemotherapy. Otherwise, toxicities during induction chemotherapy were manageable without significant organ dysfunction. The median number of CD34⁺ cells collected during a median of 3 (range 1-4) leukapheresis events was 52.1 (range 11.1-205.1) × 10⁶ cells/kg.

Tandem HDCT/autoSCT
A total of 6 patients (three without relapse/progression and three after relapse/progression) proceeded to HDCT/autoSCT (Table 1). Tumor status prior to the first HDCT/autoSCT was complete response in two patients and partial response in four. The median age at the first HDCT/autoSCT was 20 (range 10-35) months. The median time from the first infusion of PBSCs to the initia-

Table 1. Patient characteristics

| No. | Sex/Age at Dx | Location | Residual tumor > 1.5 cm² | M stage | Summary of treatment | Tumor status at HDCT1 | RT CSI/LRT (Gy) | Age at RT | Final outcome (follow-up from Dx) |
|-----|--------------|----------|-------------------------|---------|----------------------|-----------------------|----------------|----------|----------------------------------|
| 1   | F/4 m        | PF       | No                      | 3       | Sg – CTx6 – HDCT1 – HDCT2 – (PRG) | PR                   | ND           | ND       | 15 m (Dead), PRG at 13 m         |
| 2   | F/6 m        | Spine    | Yes                     | 3       | Sg – CTx6 – (PRG) – Sg – RT    | -                     | 0/54.0       | 12 m     | 7 m (Dead), PRG at 4 m          |
| 3   | F/0 m        | PF       | Yes                     | 3       | Sg – CTx6 – (PRG) – Sg – HDCT1 – HDCT2 – RT | PR                    | 23.4/30.6    | 25 m     | 16 m+ (DF), PRG at 8 m          |
| 4   | M/11 m       | PF       | No                      | 0       | Sg – CTx6 – (RL) – Sg – RT – HDCT1 – HDCT2 | CR                    | 0/30.0       | 20 m     | 50 m+ (DF), RL at 6 m           |
| 5   | F/12 m       | PF       | No                      | 0       | Sg – CTx6 – HDCT1 – HDCT2 – (RL) – Sg – CTx – RT | CR                    | 23.4/32.4    | 36 m     | 70 m+ (DF), RL at 21 m          |
| 6   | M/13 m       | ST       | No                      | 1       | Sg – CTx4 – (PRG) – Sg – RT – HDCT1 – HDCT2 – (PRG) – CTx | PR                    | 19.8/21.6    | 19 m     | 19 m+ (AWD), PRG at 4 m         |
| 7   | F/16 m       | ST       | Yes                     | 0       | Sg – CTx1                   | -                     | ND           | ND       | 2 m, TRM (Sepsis)               |
| 8   | F/28 m       | ST       | Yes                     | 3       | Sg – CTx6 – HDCT1 – HDCT2 – RT | PR                    | 23.4/30.6    | 40 m     | 20 m+ (DF)                      |

Dx, diagnosis; HDCT1, first high-dose chemotherapy; HDCT2, second HDCT; CSI, craniospinal irradiation; LRT, local radiation therapy; PF, posterior fossa; ST, supratentorial; Sg, surgery; PRG, progression; RL, relapse; CR, complete response; PR, partial response; ND, not done; TRM, treatment-related mortality; AWD, alive with disease; DF, disease free.

Table 2. Type of grade 3 and 4 toxicity of tandem HDCT/autoSCT

| Parameters                                      | HDCT1 (n = 6) | HDCT2 (n = 6) |
|------------------------------------------------|---------------|---------------|
| Hematologic toxicity                           |               |               |
| CD34⁺ cells (× 10⁶/kg)                         | 23.1 (5-42.6) | 14.0 (3.4-47.8) |
| Time (days) to reach an ANC 500/µL             | 9 (8-13)      | 10 (9-12)     |
| Time (days) to reach a PLT count 20,000/µL     | 16 (10-35)    | 26 (12-64)    |
| Presence of high fever ≥ 38.5°C                | 3             | 2             |
| Days of high fever ≥ 38.5°C                    | 2 (0-2)       | 0 (0-5)       |
| Documented infection                           | 1             | 3             |
| Non-hematologic toxicity                       |               |               |
| Stomatitis                                     | 5             | 2             |
| Vomiting                                       | 1             | 0             |
| Diarrhea                                       | 0             | 0             |
| Elevation of liver enzyme                      | 2             | 0             |
| Hepatic veno-occlusive disease                 | 1             | 0             |
| Renal failure                                  | 0             | 1             |
| Hypokalemia                                    | 1             | 1             |
| Hypoalbuminemia                                | 0             | 0             |
| Hyperkalemia                                   | 0             | 0             |
| Seizures                                       | 0             | 0             |
| Multi-organ failure                            | 0             | 0             |
| Toxic death                                    | 0             | 0             |

°Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0); †Median (range); ‡The first day when ANC exceeded 500/µL for 3 consecutive days; §The first day when PLT count exceeded 20,000/µL without transfusion for 7 days; HDCT1, first high-dose chemotherapy; HDCT2, second HDCT; ANC, absolute neutrophil count; PLT, platelet.
tion of the second HDCT was 95 (range 82-116) days. The characteristics of tandem HDCT/autoSCT are shown in Table 2. Time to obtain ANC > 500/μL in each HDCT was 9 (8-13) days and 10 (9-12) days and time to platelet > 20,000/μL was 16 (10-35) days and 26 (12-24) days, respectively. Frequent grade 3/4 toxicities during tandem HDCT/autoSCT were stomatitis and fever. Frequencies of grade 3/4 toxicities were not higher in the second HDCT/autoSCT compared to the first HDCT/autoSCT. Toxicities were manageable and there was no treatment-related death during tandem HDCT/autoSCT.

**Radiation therapy**

In summary, 6 patients received RT (Table 1). Only one received RT after HDCT/autoSCT as planned and 5 received RT as salvage treatment after relapse/progression. The median age at initiation of RT was 22 (range 12-40) months and 5 patients received RT before 3 yr of age and 2 of whom are alive with disease free. Radiation dosage of these two patients was craniospinal 23.4 Gy/local 30.6 Gy, and local 30 Gy only. Four patients received both craniospinal and local RT, and 2 patients received local RT alone. Neuro-cognitive functions of lived patients were not yet evaluated.

**Survival**

Tumors relapsed or progressed in seven patients (five during induction chemotherapy and two after tandem HDCT/autoSCT). Four of the seven patients are still alive after salvage treatment. One patient died from sepsis during induction chemotherapy. Only one patient remained progression free after diagnosis. Therefore, a total of five patients are alive with a median follow-up of 20 (range 16-70) months from diagnosis. The probabilities of overall survival and event-free survival at 3 yr from diagnosis were 53.3% ± 17.3% and 0%, respectively (Fig. 1A). Five of six patients who received tandem HDCT/autoSCT are alive with a median follow-up of 13 (range 7-64) months from the first HDCT/autoSCT. The probabilities of overall survival and progression-free survival at 3 yr from the first HDCT/autoSCT were 80.0% ± 17.9% and 31.2% ± 24.5%, respectively (Fig. 1B). Five of 6 patients who received RT are alive with a median follow-up of 14 (range 2-46) months from the initiation of RT. The probabilities of overall survival and progression-free survival at 3 yr from the initiation of RT were 80% ± 17.9% and 53.3% ± 24.8%, respectively (Fig. 1C).

**DISCUSSION**

Unacceptable adverse effects of RT, particularly craniospinal RT, for very young children with brain tumors has led a number of institutions and national groups to adopt chemotherapy-based strategies designed to avoid or delay RT (20-22). Actually cure has been documented in several cases even in the absence of RT (1, 23). In a phase I study using novel chemotherapy regimen including thiopeta, carboplatin, and carmustine for recurrent brain tumor in children, two patients with relapsed ATRT were reported to remain alive longer than 7 yr after HDCT/autoSCT (24). These data suggested that HDCT has significant activity.
against ATRT. In the present study, we evaluated the feasibility and effectiveness of tandem HDCT/autoSCT in very young children with ATRT, aiming to improve survival and to avoid or defer RT until after the most radiosensitive neurodevelopmental mileposts. To our knowledge, the present study is the first trial employing the tandem HDCT/autoSCT strategy for very young children with ATRT.

ATRT was very rare and previously misdiagnosed as other CNS embryonal tumors such as primitive neuro-ectodermal tumor or germ cell tumor. However, recently diagnostic confirm was possible using diverse immunohistochemical staining and detecting INI1 gene loss. The major of rhabdoid tumor arises as a result of homozygous inactivating deletions or mutations of the INI1 gene located in chromosome band 22q11.2 (25).

In our small cohort, tumors progressed or relapsed in seven of nine patients. Interestingly, all relapses/progressions occurred at primary sites even in patients with leptomeningeal seeding. However, four of five patients who received RT after relapse/progression are still alive. Recent studies have showed that RT might be more efficacious than chemotherapy for ATRT patients, even for very young children (3, 26). Chi et al. (27) recently reported encouraging results of a single arm trial for newly diagnosed ATRT patients, in which local RT was administered during the early treatment period irrespective of age. Taken together, these findings suggest that RT is effective in ATRT and that early administration of RT, at least local RT, might prevent early relapse/progression during induction chemotherapy, resulting in improved outcomes.

In our study, only 3 patients completed induction chemotherapy and could proceed to tandem HDCT/autoSCT as scheduled without relapse/progression. These findings suggest that our induction chemotherapy regimen might be ineffective for preventing tumor relapse/progression. A few investigators have described long-term survivors who had received RT and chemotherapy which had been used for the treatment of rhabdomyosarcoma patients (6, 7, 27). Taken together, a novel chemotherapy regimen as well as early administration of RT is needed to improve outcomes in the treatment of ATRT.

Recently, Rosenfeld et al. (28) reported the feasibility of tandem HDCT/autoSCT in patients with brain tumors. They used the same tandem HDCT regimen (CTE/CM) as ours. Two of 19 patients who received the first HDCT/autoSCT and 4 of 11 patients who received the second HDCT/autoSCT died of toxicity. The authors concluded that the CTE/CM regimen is not feasible for preventing tumor relapse/progression. A few investigators have described long-term survivors who had received RT and chemotherapy which had been used for the treatment of rhabdomyosarcoma patients (6, 7, 27). Taken together, a novel chemotherapy regimen as well as early administration of RT is needed to improve outcomes in the treatment of ATRT.

In summary, our tandem HDCT/autoSCT is feasible; however, early administration of RT prior to tandem HDCT/autoSCT should be considered to improve the outcome after tandem HDCT/autoSCT even in very young patients.

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