Clinical Results of High-Dose Chemotherapy Followed by Autologous Peripheral Blood Stem Cell Transplantation in Children with Advanced Stage Rhabdomyosarcoma

Regardless of improvement in cure of Rhabdomyosarcoma (RMS), the results in treatment of advanced stage of RMS in children are still dismal. Recently, high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (HDC/APBSCT) has been tried to manage the advanced high-risk RMS patients. We investigated the effectiveness of HDC/APBSCT by reviewing the clinical records of high-risk pediatric RMS patients in single institute database. Over twenty years, 37 patients were diagnosed as RMS with high-risk at the time of first diagnosis. These patients were classified as two groups according to treatment method. The first group was HDC/APBSCT and the other was conventional multi-agent chemotherapy group. Differences of clinical results between the two groups were analyzed. The median age of patients was 5 yr, ranging from 6 months to 15 yr. The 5-yr event free survival rate (EFS) of all patients was 24.8%± 4.8%. HDC/APBSCT group and conventional multi-agent chemotherapy group were 41.3%± 17.8% and 16.7% ± 7.6% for 5-yr EFS, respectively (\(P = 0.023\)). There was a significant difference in the result of HDC/APBSCT between complete remission or very good partial response group and poor response group (50%± 20.4% vs 37.5%± 28.6%, \(P = 0.018\)). HDC/APBSCT can be a promising treatment modality in high-risk RMS patients.

Key Words: Rhabdomyosarcoma; Children; Chemotherapy; Bone Marrow Transplantation

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common type of soft-tissue sarcoma occurring in childhood and adolescence in Korea. In spite of its highly malignant characteristics, cure rate of RMS has been improved during past 40 yr from approximately 20% in 1970 to higher than 70% currently (1-3). Since 1972, Intergroup Rhabdomyosarcoma Study (IRS) committee has conducted various treatment strategies for pediatric soft tissue sarcoma patients. With contemporary multimodal therapy, much more children and adolescents with this disease are cured (3).

However, high risk disease such as clinical group III or IV and alveolar type RMS have shown dismal results until now. The IRS has used therapeutic window studies to confirm the predictive nature of preclinical xenograft models and to identify several newly developed agents and combinations of agents with activity in high-risk patient group (4). Despite these efforts, the outcome for these high-risk patients has not improved (5). Recently, high dose chemotherapy followed by autologous peripheral blood stem cell transplantation (HDC/APBSCT) has tried for these clinical group III or IV high-risk patients by some institutes.

However, the result seems controversial up until these days (6, 7).

Multimodal therapy including surgery, radiation, and multi-agent combination chemotherapy was performed during over two decades in our institution. In the current years, some patients with high-risk features have been treated with HDC/APBSCT. We reviewed the clinical records of pediatric high-risk RMS over twenty years in a single institute and explored the clinical implication of HDC/APBSCT in these patients.

MATERIALS AND METHODS

This study was performed by retrospective review of medical records for patients with RMS in a single institute. Between 1982 and 2006, 37 patients who have been diagnosed as RMS high-risk group and treated in Severance Hospital, Seoul, Korea were reviewed. All patients have been classified by Tumor-Node-Metastasis (TNM) staging system and clinical group stage system employed in IRS. The treatment results were reviewed to compare the patients who have undergone HDC/APBSCT and the patients treated with conventional multi-agent chemotherapy alone. The patients reviewed in this study have not been includ-
ed in any other published reports.

The chemotherapeutic regimen composed with ifosfamide, carboplatin and etoposide (ICE) was used for hematopoietic stem cell mobilization in the patients with HDC/APBSCT. Serial subcutaneous injections of recombinant granulocyte colony stimulating factor (G-CSF) were given until recovery phase of chemotherapy. The peripheral blood stem cells were collected by continuous flow apheresis.

Criteria for high-risk RMS were as follows; Group III or IV patients at diagnosis by IRS clinical group stage system, and Stage III or IV disease by TNM staging. Especially, the patients with Group IV or Stage IV patients regardless of tumor site and size, embryonal histology over 10 yr old or all alveolar histology were classified to very high-risk group (8).

The patients treated with HDC/APBSCT were categorized as good response group and poor response group according to radiographic measurement of disease after conventional multi-agent chemotherapy. Patients with complete resolution of disease (complete resolution, CR) or decrease maximum perpendicular diameter of mass more than 50% (partial response, PR) were defined as good response group. Patients with increased diameter of mass or decreased diameter less than 50% were considered as poor response group.

All of these 37 patients were classified as high-risk RMS. Medical records of these high-risk patients were closely reviewed to analyze the relationship between treatment modality and outcome, retrospectively. We compared the effect of HDC/APBSCT between good response group and poor response group, also. Kaplan-Meier curve was generated to compare the 5-yr event free survival rate (EFS) of each group. The differences between

| Patient number | Age (yr) | Sex | Primary site | Histologic type | Stage | Group | PBSCT | Operation | Radiation Therapy | Outcome | OS (yr) |
|----------------|---------|-----|--------------|----------------|-------|-------|-------|-----------|-------------------|---------|---------|
| 1              | 3       | F   | GU           | Embryonal      | 3     | 3     | -     | +         | +                 | Dead    | 1       |
| 2              | 5       | M   | H&N          | Others         | 3     | 3     | -     | -         | +                 | Alive   | 25.2    |
| 3              | 2       | F   | PM           | Embryonal      | 4     | 4     | -     | -         | +                 | Dead    | 0.75    |
| 4              | 11      | M   | H&N          | Alveolar       | 3     | 3     | -     | -         | +                 | Dead    | 3.42    |
| 5              | 4       | M   | GU           | Embryonal      | 3     | 3     | -     | -         | +                 | Alive   | 19      |
| 6              | 9       | M   | Ext          | Alveolar       | 4     | 4     | -     | +         | +                 | Dead    | 2.3     |
| 7              | 3       | F   | H&N          | Alveolar       | 4     | 4     | -     | -         | -                 | Dead    | 0.8     |
| 8              | 1       | F   | GU           | Others         | 3     | 3     | -     | -         | +                 | Dead    | 1.25    |
| 9              | 4       | F   | GU           | Embryonal      | 3     | 3     | -     | +         | +                 | Dead    | 1.34    |
| 10             | 5       | M   | GU           | Embryonal      | 3     | 3     | -     | -         | +                 | Dead    | 2       |
| 11             | 3       | F   | H&N          | Embryonal      | 3     | 3     | -     | -         | +                 | Dead    | 1.92    |
| 12             | 2       | M   | GU           | Others         | 3     | 3     | -     | -         | +                 | Dead    | 1.4     |
| 13             | 5       | F   | H&N          | Embryonal      | 3     | 3     | -     | -         | -                 | Alive   | 19.2    |
| 14             | 1       | F   | T            | Alveolar       | 4     | 4     | -     | -         | +                 | Dead    | 0.08    |
| 15             | 15      | F   | T            | Embryonal      | 4     | 4     | -     | -         | +                 | Dead    | 0.4     |
| 16             | 1       | M   | GU           | Others         | 3     | 3     | -     | -         | +                 | Dead    | 1       |
| 17             | 12      | M   | T            | Others         | 4     | 4     | -     | -         | -                 | Dead    | 1.5     |
| 18             | 4       | M   | GU           | Embryonal      | 3     | 3     | -     | +         | +                 | Alive   | 9.8     |
| 19             | 4       | M   | PM           | Embryonal      | 3     | 3     | -     | -         | -                 | Dead    | 0.6     |
| 20             | 10      | M   | PM           | Alveolar       | 3     | 3     | -     | -         | -                 | Dead    | 1.2     |
| 21             | 12      | F   | GU           | Alveolar       | 4     | 4     | -     | -         | -                 | Dead    | 0.5     |
| 22             | 1       | M   | GU           | Alveolar       | 3     | 3     | -     | -         | +                 | Dead    | 4       |
| 23             | 12      | M   | PM           | Alveolar       | 4     | 4     | -     | +         | +                 | Dead    | 0.7     |
| 24             | 1       | M   | T            | Others         | 4     | 4     | -     | -         | -                 | Dead    | 0.45    |
| 25             | 15      | M   | Ext          | Alveolar       | 2     | 4     | +     | +         | +                 | Dead    | 2.84    |
| 26             | 2       | M   | Ext          | Alveolar       | 2     | 4     | -     | +         | +                 | Dead    | 4.25    |
| 27             | 7       | M   | H&N          | Alveolar       | 4     | 4     | +     | -         | -                 | Alive   | 9.55    |
| 28             | 15      | F   | T            | Alveolar       | 4     | 4     | +     | -         | +                 | Dead    | 1       |
| 29             | 3       | M   | H&N          | Embryonal      | 3     | 3     | +     | +         | +                 | Alive   | 4.37    |
| 30             | 2       | F   | H&N          | Alveolar       | 4     | 4     | +     | -         | -                 | Alive   | 5.1     |
| 31             | 6       | M   | PM           | Embryonal      | 4     | 4     | +     | -         | +                 | Alive   | 4.2     |
| 32             | 1       | F   | T            | Alveolar       | 4     | 4     | +     | -         | +                 | Dead    | 2       |
| 33             | 11      | F   | T            | Embryonal      | 4     | 4     | +     | +         | +                 | Dead    | 1.8     |
| 34             | 14      | F   | T            | Alveolar       | 4     | 4     | +     | -         | +                 | Dead    | 1       |
| 35             | 6       | F   | T            | Alveolar       | 4     | 4     | +     | +         | +                 | Alive   | 1.7     |
| 36             | 14      | M   | Ext          | Embryonal      | 4     | 4     | +     | +         | +                 | Alive   | 2.5     |
| 37             | 12      | F   | Ext          | Alveolar       | 4     | 4     | +     | +         | +                 | Alive   | 1       |

H&N, Head and neck; PM, Parameningeal; GU, Genitourinary; Ext, Extremity; T, Trunk; OS, overall survival.
groups were analyzed using univariate analysis with the log-rank test. The differences of the mean between the two groups were analyzed by Student’s t-test. A P value less than 0.05 was regarded as statistically significant. Toxicities were reviewed by the Eastern Cooperative Oncology Group (ECOG) common toxicity criteria for all patients.

Ethics statement
Retrospective review of database in this study was approved by the institutional review board of the Yonsei University Health System, Severance Hospital (Approval No., 4-2011-0655). The informed consent was exempted by the board.

RESULTS

Patient characteristics
The clinical characteristics of the patients are summarized in Table 1. All the thirty-seven patients were diagnosed as RMS clinical group III or IV. The median age of patients was 5 yr (range; 6 months-15 yr). Seventeen patients were female and other 20 patients were male. Twenty four patients were treated with the conventional multi-agent chemotherapy while other thirteen patients were treated with HDC/APBSCT. Local treatment of disease included operation or radiation therapy. Eleven patients have undergone cytoreductive surgery as a local treatment, and 28 patients received radiotherapy as a local treatment. The modality of local treatment was chosen by clinical situation of each patient.

The differences of clinical manifestation between conventional multi-agent chemotherapy group and HDC/APBSCT group are shown in Table 2. The age of patients in each group was 5.9±4.3 yr and 8.7±5.3 yr which was not statistically different (P=0.084). The most frequent primary site was genitourinary area. The proportion of patients according to primary site at diagnosis and histological findings are shown in Table 3. Fifteen patients were embryonal type (41%) and sixteen patients were alveolar type (43%). The patients with embryonal type were usually clinical group III. On the contrary, the patients with alveolar type were mainly clinical group IV patients. The proportion of alveolar type in this study was more than generally reported proportion of overall RMS patients (9). Other histology included undifferentiated and pleomorphic types. There was no botryoidal type.

The clinical characteristics of the patients undergone HDC/APBSCT are summarized in Table 4. Thirteen patients were treated with HDC/APBSCT, and the clinical group of patients at the time of diagnosis was group IV, except 1 patient (patient number 25).
ber 29). Nine patients had showed very good partial response or complete remission before HDC/APBSCT. The patients with relapse after HDC/APBSCT undergone salvage treatment consisted with radiation therapy and ICE based chemotherapy. The conditioning regimens for HDC/APBSCT varied as shown in Table 4.

**Toxicity**

There was no patient who died of toxicity directly related to HDC/APBSCT. However, every patient had grade III or IV hematologic complications such as thrombo-cytopenia or neutropenia. These hematologic complications were shown in either conventional chemotherapy or HDC/APBSCT without difference. There was one case of treatment related mortality in the conventional chemotherapy group. A 12 yr-old male patient (patient number 23) was treated with multi-agent chemotherapy of ICE. After 6-cycles of scheduled chemotherapy, the patient failed to recover from myelosuppression and died due to invasive bacterial infection.

**Survival and outcomes**

The overall survival rate of all patients reviewed in this study is shown in Fig. 1A. The 5-yr EFS was 24.8% ± 4.8%. The patients with HDC/APBSCT showed higher EFS than conventional chemotherapy group. The 5-yr EFS of each group were 41.3% ± 17.8% and 16.7% ± 7.6%, respectively. As shown in Fig. 1B, P value was 0.023 and median follow-up duration was 7.3 yr. Fig. 1C shows the difference of EFS that had been in complete remission or very good partial response versus partial response, which means poor response to conventional multi-agent chemotherapy. The 5-yr EFS was better in the patients who had achieved complete remission or very good partial response (50.0% ± 20.4%) than in patients with partial response or disease progression (37.5% ± 28.6%) at the time of HDC/APBSCT. The 5-yr EFS difference was statistically significantly between two groups (P = 0.018). The 5-yr EFS according to treatment method in very high-risk group are shown in Fig. 1D. In this group, the difference of survival rate between HDC/APBSCT group (12 patients) and conventional chemotherapy group (9 patients) was statistically significant (P < 0.001). The 5-yr EFS was 32.3% ± 18.4% for HDC/

![Fig. 1. Event-free survival rates. Patients with advanced rhabdomyosarcoma (A). Patients with high risk rhabdomyosarcoma, according to high dose chemotherapy and autologous peripheral blood stem cell transplantation or not (B) the status at the time of hematopoietic stem cell transplantation (C) high dose chemotherapy and autologous peripheral blood stem cell transplantation or not (D).](http://dx.doi.org/10.3346/jkms.2012.27.9.1066)
APBSCT group and 0% for conventional chemotherapy group.

DISCUSSION

Chemotherapy plays critical role in treatment of advanced stage RMS, because RMS is chemosensitive. Until now, several effective multi-agent chemotherapies were studied (10, 11). Van Winkle and his coworkers reported the Children’s Cancer Group (CCG) experience of combination chemotherapy regimen consisted with ICE (12). The overall response rate of 97 enrolled patients was 51% (27% complete response). After that report, conventional multi-agent chemotherapy in RMS was well established and considered as standard therapy. Finding and investigating the most effective combination of multi-agent chemotherapeutic agent is still the main stream to improve survival rate of high-risk RMS patients. However, poor treatment results for these patients were reported until now (4, 5). Therefore, HDC/APBSCT, a new treatment option for these patients has been in controversy effect and safety (6, 7). This study was performed to clarify the issue of safety of HDC/APBSCT.

The 5-yr EFS of all 37 patients was 24.8% ± 4.8%. It means that the patients reviewed in this study were classified as poor prognosis group. However, the patients undergone HDC/APBSCT had shown better prognosis than the other group. The EFS of these patients was 41.3% ± 17.8%. One of the important factors to decide whether to do HDC/APBSCT is the response to conventional multi-agent chemotherapy before HDC/APBSCT. The patients with complete remission or very good partial response had better prognosis than patients with poor response to conventional multi-agent chemotherapy before HDC/APBSCT. As mentioned, the high-risk patients with good response to conventional chemotherapy had much more longer survival rate than poor response patients (5-yr EFS was 50.0% ± 20.4%). All the patients included in this study showed various pathologic types, and they were divided into patients who received surgery and those who did not. Considering all these factors, we performed a multivariate analysis. However, because the number of patients were too small, the results were not statistically significant.

At the time of diagnosis, far advanced patients who were classified to very high-risk patient may have no treatment option except systemic multi-agent chemotherapy. For these patients, HDC/APBSCT might be an only chance to cure. Because our study was not prospective, double blinded and controlled, our data may have selection bias. Therefore, to make a more worthy information, prospective controlled study will be needed. However, depending on these data, we can conclude that HDC/APBSCT must be considered in very high-risk or far advanced RMS patients to cure their disease. For very high-risk patients, effective and powerful local treatment methods such as radiation or operation cannot be performed. Therefore, HDC/APBSCT will be an important treatment option. However, preference towards HDC/APBSCT may lead to over treatment. The long-term complication and quality of life of patients who have undergone HDC/APBSCT is not confirmed yet. We must decide to treat with HDC/APBSCT under careful consideration. Patient who are eligible for multi-modality of treatment must be treated with multi-modal therapy before being considered as a candidate for HDC/APBSCT.

In spite of establishment of effective conventional multi-agent chemotherapy, many advanced stage high-risk RMS show poor response to usual dose chemotherapy. Children with metastatic disease at presentation, those older than 10-yr old or bone and bone marrow metastasis, had poorer outcome. This may show that high-dose chemotherapy may have a key role in these patients (13). Therefore, not only patients with good response to usual dosage multi-agent chemotherapy but also patients with poor response to conventional chemotherapy can be a candidate for HDC/APBSCT. In our study, EFS in HDC/APBSCT group was higher than that of conventional multi-agent chemotherapy group.

Several previous studies have shown the clinical effectiveness and survival advantages in advanced high risk RMS patients with HDC/APBSCT (13-18). It is very important to decide whether RMS patient will undergo HDC/APBSCT or not. Matsubara and his colleagues reported a single institute experience about HDC/APBSCT in high risk RMS patients. They emphasized that high-risk RMS patients who had good response to multi-agent combination chemotherapy will have a good treatment result with HDC/APBSCT (14). On the contrary, RMS patients with refractory to conventional chemotherapy would show response to HDC/APBSCT. There was a case report on a 17 yr-old girl with refractory RMS after conventional chemotherapy who achieved partial remission after HDC/APBSCT (15). In our study, about 25% of patients with poor response to conventional multi-agent chemotherapy showed efficacy to HDC/APBSCT. It means that HDC/APBSCT can be a treatment option in these extremely hopeless patients.

The patients with good response to conventional chemotherapy may be considered as a candidate for HDC/APBSCT group. However, the patients with relatively poor response to conventional multi-agent chemotherapy may not be considered as a candidate for treatment because of the high cost and uncertain effect of HDC/APBSCT. Some decades ago, HDC/APBSCT had relatively high treatment related mortalities. This was because, there were not enough conservative treatment methods that were available, such as G-CSF. However, currently, vast methods in conservative management has improved, which resulted in a relatively safer environment for HDC/APBSCT. Therefore, HDC/APBSCT in patients refractory to conventional multi-agent chemotherapy may be possible, therefore it is necessary to conduct a randomized-controlled prospective trial in this group of patients.
However, HDC/APBSCT is not always effective and safe. As the dose of chemotherapeutic agent increase, the effectiveness and toxicity are elevated together (17, 18). Therefore, regimen related toxicity must be considered to patients when planning HDC/APBSCT. Cancer cell contamination or resistance to high-dose chemotherapy can be a problem for HDC/APBSCT. Some patients with stage IV alveolar RMS who have experienced relapse were reported to have poor response to HDC/APBSCT (19).

It must be considered to the high-risk RMS patient that regimen related toxicity, pre-transplantation conditioning regimen, stem cell source, cancer cell contamination for the autologous stem cell transplantation. Studies in management of long term complication and quality of life in patient with HDC/APBSCT will be needed.

Recently, other target therapy for high-risk RMS has been investigated. Topoisomerase-I and monoclonal antibody such as 8H9 will be a new window of opportunity for treatment of RMS (8, 20). It is important not only to treat RMS and reach complete remission, but also to prevent recurrence of the disease. There are some known methods which may prevent metastasis and recurrence of the disease. All-trans retinoic acid is known to be blocker of tumor recurrence and metastasis (21).

HDC/APBSCT seems to achieve prolonged remission in pediatric high-risk RMS. It may be considered as a treatment option in high-risk RMS patients who are in complete remission or who show very good partial response following conventional chemotherapy. In conclusion, HDC/APBSCT will be a promising treatment modality in high-risk RMS patients for its tolerable treatment related toxicity and effectiveness.

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