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NEÜ YAYINEVİ

Autologous Hematopoietic Stem Cell Transplantation in Pediatric Malignant Diseases: 12 Years of Experience

Pediatrik Malign Hastalıklarda Otolog Hematopoietik Kök Hücre Nakli-12 Yıllık Deneyim

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Öz

Amaç: Bu çalışmada yüksek riskli pediatrik solid tümör hastalarında uyguladığımız otolog hematopoietik kök hücre tedavisinin (OHKHT) etkinlik ve güvenilirliğini 12 yıllık tecrübemizle paylaşmayı amaçladık.
Hastalar ve Yöntem: Ocak 2009-Temmuz 2021 tarihleri arasında Çocuk Kemik İliği Nakil Ünitesi'nde 18 yaş altı OHKHT yapılan pediatrik maligniteli hastaların verileri retrospektif olarak değerlendirildi.
Bulgular: Ortanca yaşı 7,8 (0,5-18) yıl olan 51 hasta (24 kız, 27 erkek) çalışmaya dahil edildi: sırasıyla nöroblastom, ewing sarkomu, hodgkin lenfoması, hodgkin dışı lenfoma, germ hücreli tümör ve yumuşak doku sarkomu olan 20, 15, 8, 4, 2 ve 2 hasta vardı. Hastaların nötrofil ve trombosit engraftman ortanca süreleri sırasıyla 11 (8-45) gün ve 16 (4-62) gün ve ortanca hastanede kalış süresi 38 (17-67) gün idi. Tüm hastalarda ortanca takip süresi 2.83 (0.12-10.81) yıl ve genel sağkalım %51.3±10.3; Ewing sarkomu ve nöroblastom olgularının ortanca takip süreleri ve sağkalım oranları sırasıyla 2,63 (0,12-10,55) yıl ve % 64,2 ±14,9 ve 2,81 (0,31-7,91) yıl ve %42,8±12 idi. Nöroblastom hastalarında; karboplatin, etoposid, melfalan (CEM) hazırlık rejimi olarak alan 4 hastanın tümü ölürken, hazırlık rejimi olarak busulfan ve melfalan (Bu/Mel) rejimi alan 16 hastanın 6'sı öldü: Bu/Mel grubunun ortanca takip süresi 3.08 (0.32-7.91) yıl ve genel sağkalım %55,1±13,8 idi (p:0,001).
Sonuç: Hasta sayımızın sınırlı olmasına rağmen, kliniğimizde Ewing sarkomu ve nöroblastom olgularımızda elde edilen verilerde ve literatürde OHKHT'nin yapılmayan hastalara göre daha iyi sağkalım sağladığı görülmektedir.

Anahtar Kelimeler: Otolog hematopoietik kök hücre nakli, nöroblastom, Ewing sarkomu, pediatri, onkoloji.

Abstract

Aim: In this study, we discuss the efficacy and safety of autologous hematopoietic stem cell transplantation (AHSCT) for high-risk pediatric solid-tumor patients based on 12 years of experience.
Patients and Methods: The data of patients aged < 18 years with pediatric malignancies who underwent AHSCT between January 2009 and July 2021 at the Pediatric Bone Marrow Transplant Unit were evaluated retrospectively.
Results: Fifty-one patients (24 girls and 27 boys; median age, 7.8 years; range: 0.5–18 years) were enrolled in the study; 20, 15, 8, 4, 2, and 2 patients had diagnoses of neuroblastoma, Ewing's sarcoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, germ cell tumor, and soft tissue sarcoma, respectively. The median neutrophil and platelet engraftment times were 11 (8–45) and 16 (4–62) days, respectively, and the median hospital stay was 38 (17–67) days. The median follow-up time was 2.83 (0.12–10.81) years and the overall survival (OS) rate was 51.3 ± 10.3% for all patients; the median follow-up times and survival rates for the Ewing's sarcoma and neuroblastoma cases were 2.63 (0.12–10.55) years and 64.2 ± 14.9%, and 2.81 (0.31–7.91) years and 42.8 ± 12%, respectively. All four patients who received the conditioning regimen of carboplatin, etoposide, and melphalan (CEM) died; 6 of 16 neuroblastoma patients who received the busulfan and melphalan (Bu/Mel) regimen as a conditioning regimen died: the median follow-up period of the Bu/Mel neuroblastoma patients was 3.08 (0.32–7.91) years and the OS rate was 55.1 ± 13.8%.
Conclusion: Although the number of patients in this study was limited, AHSCT resulted in better survival for Ewing's sarcoma and neuroblastoma cases than reported for those who did not undergo AHSCT in our clinic.

Key words: Autologous hematopoietic stem cell transplantation, neuroblastoma, Ewing's sarcoma, pediatrics, oncology

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INTRODUCTION

The prognosis of pediatric solid tumors has improved greatly due to the use of multi-agent chemotherapy, aggressive surgery, and targeted radiation therapy. However, patients with metastatic, refractory, or recurrent disease still have a poor prognosis and are candidates for aggressive treatments, such as autologous hematopoietic stem cell transplantation (AHSCT) (1-3). High-dose chemotherapy with AHSCT is a potentially curative treatment, particularly in patients with chemotherapy-sensitive malignancies; it can eliminate minimal residual disease and is suitable for children with high-risk solid tumors for whom conventional multimodal therapy may not be sufficient (1-3).

AHSCT is suitable for high-risk pediatric patients with solid tumors who respond to chemotherapy, and have harvestable stem cells and a clinical condition suitable for this aggressive treatment (4). AHSCT allows doses of chemotherapeutic agents to be increased above those used in the context of myeloablation. Therefore, most preparative regimens consist of combinations of chemotherapeutic agents administered at high dosages to maximize antitumor cytotoxicity (4). Transplant-related mortality has decreased with advances in supportive care, the use of growth factors, and good infection management. Disease recurrence remains the most common cause of treatment failure in patients undergoing AHSCT (5).

In this study, we discuss the efficacy and safety of AHSCT treatment for high-risk pediatric solid tumor patients based on 12 years of experience.

PATIENTS AND METHODS

Patients

Pediatric patients aged < 18 years with malignancy, and who were scheduled for AHSCT at the Pediatric Bone Marrow Transplant Unit between January 2009 and July 2021, were included in the study. Eligibility criteria, other than the indication for transplantation, included a Lansky's performance status of 0.70%, left ventricular ejection fraction of 0.50%, and normal liver and kidney function. Written informed consent was obtained from the parents or legal guardians in all cases involving high-dose chemotherapy, AHSCT therapy, or peripheral blood stem cell (PBSC) mobilization and collection. Ethics committee approval was obtained for the study (KAEK No: 2022/256).

Peripheral blood stem cell mobilization and collection

PBSCs mobilized with granulocyte colony-stimulating factor (G-CSF; filgrastim) were administered for 4 days before starting the subcutaneous (SC) collection (6, 7). PBSCs were collected using the Spectra Optia apheresis device through a double-lumen central venous catheter. G-CSF (filgrastim) was administered subcutaneously for 4 days in patients who failed the PBSC collection. Then, the stem cells were collected from the bone marrow under operating room conditions (7).

Conditioning regimen and supportive treatment

The busulfan/melphalan (Bu/Mel) regimen consisted of 12.8 mg/kg Bu, provided as 6-hourly doses over 4 days (between days −6 and −3 before transplant); 140 mg/m^2 Mel was administered by intravenous (IV) infusion on day −2 (8, 9). IV levetiracetam was given from day 1 of Bu to the last day of infusion to prevent Bu-related neurologic toxicity. The carboplatin, etoposide, melphalan (CEM) protocol consisted of carboplatin at a dose of 300 mg/m^2/day and etoposide at a dose of 200 mg/m^2/day between days −5 and −2, and Mel at a dose of 45 mg/m^2 on days −8, −7, −6, and −5 (10, 11). The carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioning regimen consisted of carmustine at a dose of 300 mg/m^2/day on day −7, 300 mg/m^2/day etoposide in two doses, and 400 mg/m^2/day cytarabine in two doses on days −6 to −3, and 140 mg/m^2 Mel on day −2 IV (12, 13). Transplants were performed in reverse barrier isolation rooms. Cryopreserved PBSCs were infused after rapid thawing at 37°C on day 0. Diphenhydramine (1 mg/kg) and methylprednisolone (2 mg/kg) were administered to prevent dimethylsulfoxide toxicity. All patients received G-CSF (10 mg/kg/day) from day 1 until neutrophil engraftment. Oral antibiotic therapy was started empirically and IV antibiotic therapy was started in cases of fever. Irradiated blood products devoid of leukocytes were used to maintain a hemoglobin level > 8 g/l and platelet count > 10 × 109/l.

Statistical analysis

Median and range values were calculated for numerical parameters, and frequencies and percentages for categorical parameters. Patient age, sex, diagnosis, transplant type, stem cell source, priming regimen, and transplantation-related adverse event data were summarized. Survival analyses were performed with the Kaplan-Meier method and survival curves were drawn. The log-rank test was used to compare survival between subgroups in the

survival analyses. A p-value < 0.05 was considered significant. All statistical analyses were performed using SPSS software (ver. 22.0; IBM Corp., Armonk, NY, USA) software. Event-free survival (EFS) was defined as the time from day 0 (day of transplant) to disease progression or relapse, or death from any cause. Overall survival (OS) was defined as the time from day 0 (day of transplant) to last contact with the healthcare team or death.

RESULTS

Fifty-one malignant pediatric patients with an indication who received AHSCT were included in the study. The median age of the patients was 7.8 (0.5–18) years; there were 24 females and 27 males. The characteristics of the patients and transplantations are given in Table 1. The median follow-up period after transplantation was 2.83 (0.12–10.81) years.

Hematopoietic recovery

The median number of CD34 cells infused was 3.25 × 106/kg (0.3–26). All patients experienced severe myelosuppression. Hematopoietic recovery was defined as achieving an absolute neutrophil count > 0.5 × 109/l and unsupported platelet count > 20 × 109/l for at least 3 days. These values were calculated after a median of 11 (8–45) and 16 (4–62) days, respectively. The median number of days with fever was 5 (1–15 days), and the median number of IV antibiotic days was 14 (5–25 days). The patients were hospitalized for a median of 38 (17–67) days from the day of the stem cell infusion until discharge.

Non-hematological toxicities

All patients experienced moderate nausea and vomiting during the conditioning regimen. A short-term generalized convulsion was observed in one patient. During the myelosuppression period, 21 patients had gastrointestinal complaints, manifested as mucositis and diarrhea, which required pain relief. Twelve patients needed total parenteral nutrition (TPN), which was applied to the patients for a median of 7 (2–27) days. Grade I and II acute graft-versus-host disease with skin involvement was observed in two patients. Five patients developed hepatic veno-occlusive disease, which was severe in one case. Acinetobacter baumannii growth was detected in the catheter of one patient. No transplantation-related deaths were recorded.

Survival

As of May 2022, 32 patients were alive and disease-free, one is living with relapsed disease, and 18 have died. No transplantation-related deaths were reported; relapse and progressive disease were the only causes of death. The median relapse time after transplantation was 8.93 (1.41–94.94) months. The

Table 1. Characteristics of patients and transplantation

Characteristics	Value
Age (years) (median)	7,8 (0,5-18)
Gender	
Female	24 (% 47)
Male	27 (% 53)
Diseases	
Neuroblastoma	20 (% 39)
Ewing Sarcoma	15 (% 29)
Hodgkin Lymphoma	8 (% 16)
Non-Hodgkin lymphoma	4 (% 8)
Soft tissue sarcoma	2 (% 4)
Germ Cell Tumor	2 (% 4)
Stem cell source	
Peripheral blood	49 (% 96)
Bone marrow	2 (% 4)
Conditioning Regime	
Busulfan/Melphalan (Bu/Mel)	33 (% 64)
Carmustine/Cyt/Eto/Mel (BEAM)	8 (% 16)
Carboplatin/Eto/Mel (CEM)	6 (% 12)
Others(Bu/Cyc, Bu/Eto/Cyc, Cyc/Eto/carbo)	4 (% 8)
Neutrophil engraftment time (median days)	11 (8-45)
Platelet engraftment time (median days)	16 (4-62)
Hospitalization period (median days)	38 (17-67)

Abbreviations
Cyc: Cyclophosphamide, Cyt: Cytarabine, Eto: Etoposide, , carbo: Carboplatin.

Table 2. Comparison of Neuroblastoma Conditioning Regimes

	Total Patient	Dead patient	Alive patient
BU/MEL	16	6	10 (%62,50)
CEM	4	4	0 (%0,00)
Total	20	10	10 (%50,00)

Abbreviations:
BU/MEL: Busulfan/Melphalan, CEM: Carboplatin/Etoposide/Melphalan

EFS rate for the entire group was 57.4 ± 7.9% at 2 years. The EFS rate at 2 years was 64.2% ± 14.9% for the Ewing's sarcoma patients, 40.8% ± 12.5% for the neuroblastoma patients, 87.5 ± 11.7% for the Hodgkin's lymphoma patients, and 87.5 ± 11.7% for the non-Hodgkin's lymphoma patients. The OS rate was 51.3 ± 10.3% for the entire group, with a median follow-up of 2.83 (0.12–10.81) years. The OS rate for Ewing's sarcoma was 64.2 ± 14.9%, with a median follow-up duration of 2.63 (0.12–10.55) years. The OS rate for neuroblastoma was 42.8 ± 12%, with a median follow-up time of 2.81 (0.31–7.91) years. The OS rate for Hodgkin's lymphoma was 58.3 ± 25.1%, with a median follow-up of 6.42 (0.5–10.81) years. The OS rate for non-Hodgkin's lymphoma was 75 ± 21.7%, with a median follow-up of 3.49 (0.25–6.23) years (Figure 1). The OS rate was 55.1 ± 13.8% for the neuroblastoma patients using the Bu/Mel regimen, in respect to the receiving CEM that no living rest, with a median follow-up of 3.08 (0.32–7.91) years (p = 0.001) (Table 2 and Figure 2).

DISCUSSION

Although childhood cancer accounts for only a small proportion of the global cancer burden, it remains one of the leading causes of death in children and adolescents (14). OS has improved in recent years, due to remarkable progress in the diagnosis and treatment of childhood cancers. According to 2014 statistics from the American Cancer Society, 5-year survival rates for pediatric cancer exceed 80% in developed countries (14).

The prognosis of relapsed/progressed childhood cancers remains unfavorable, particularly for certain solid tumors such as neuroblastoma, and bone and soft tissue sarcomas (15). Numerous attempts have been made to improve the prognosis, and high-dose chemotherapy and AHSCT have played an important

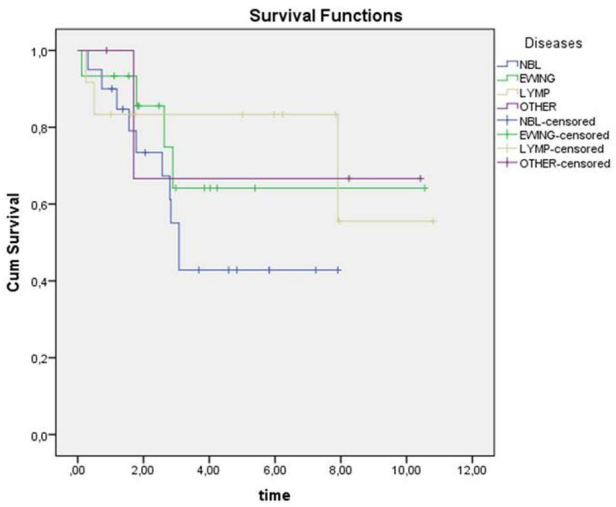

Figure 1. Overall survival curve of patients undergoing autologous hematopoietic stem cell transplantation

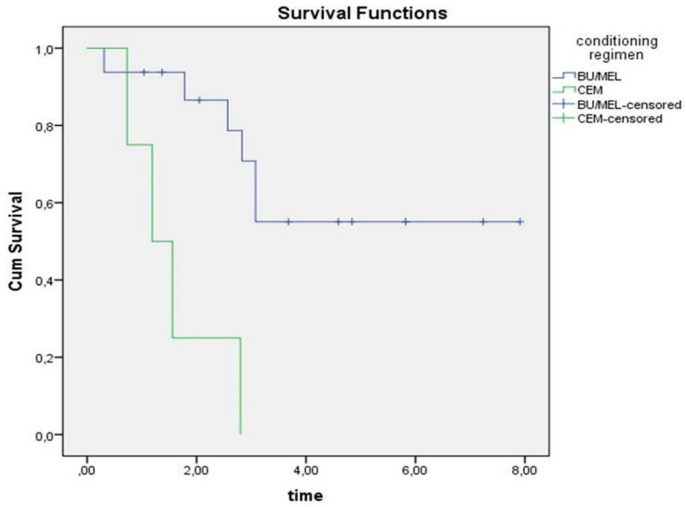

Figure 2. Comparison of the overall survival curve of neuroblastoma patients treated with the BU/MEL and CEM conditioning regimens

role in some cases (3, 4). However, survival rates for most relapsed/progressed solid tumors have generally been stable for almost 30 years (16).

The ability to safely collect, store, and reinfuse the patient's hematopoietic stem cells has led to bone marrow tolerance of cytotoxic therapy, allowing for more intensive treatment of some malignancies (17). Improvements in supportive care, the use of growth factors, and improved management of infectious complications have reduced mortality due to cytotoxic regimens. Unfortunately, disease recurrence remains the most common cause of treatment failure in patients undergoing AHSCT (5).

Hematopoietic stem cell-assisted high-dose chemotherapy was evaluated in a randomized clinical trial of patients with Ewing's sarcoma (European Ewing Tumor Working Initiative of National Groups [Euro-EWING] 99 and EWING 2008). In that study, 287 patients with isolated pulmonary (lung or pleural) metastatic disease received six courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) and one course of vincristine, dactinomycin, and ifosfamide (VAI). Next, the patients were randomly assigned to groups receiving one course of Bu plus Mel high-dose chemotherapy followed by autologous stem cell rescue, or seven cycles of conventional chemotherapy with VAI followed by whole-lung irradiation. During a median follow-up of approximately 8 years, no significant difference in the 8-year EFS rates was detected between the two groups (53% vs. 43%). The 8-year OS rates were 54% vs. 55%, respectively. In addition, infection rates, as well as gastrointestinal and liver toxicities, were higher in the high-dose chemotherapy and AHSCT groups; there were four deaths in this group, and none in the conventional chemotherapy group (18).

In an open-label phase III study (Ewing 2008R3), 109 patients with metastatic Ewing's sarcoma (excluding those with pulmonary metastases only) received six cycles of VIDE and eight cycles of consolidation therapy with vincristine, actinomycin D, and cyclophosphamide. Patients were then randomly assigned to groups receiving treosulfan plus Mel followed by hematopoietic stem cell support or no other treatment. After a median follow-up of almost 3.5 years, the addition of hematopoietic stem cell support and high-dose chemotherapy did not improve 3-year EFS (21% vs. 19%). However, posthoc analysis of a subset of 41 patients aged < 14 years of age demonstrated a potential benefit of this approach for 3-year EFS (39% vs. 9%) (19).

In a thesis study that evaluated 71 patients with Ewing's sarcoma, which was completed in 2022 at our institution, the OS rate was 43.4 ± 0.65%. AHSCT was applied in 19 of 71 cases (26.7%). The OS of the patients who did not undergo AHSCT (n = 52; 73.2%) was 36.2% ± 0.69%, and the OS of the patients who underwent AHSCT was 66.7 ± 1.61% ($p < 0.05$) (20). In our study, the EFS rate of patients with Ewing's sarcoma (metastatic, undergoing inadequate surgery, tumor volume > 200 ml) was 64.2% ± 14.9% at 2 years. The OS rate was relatively high for Ewing's sarcoma compared to the literature, at 64.2 ± 14.9%. The median follow-up was 2.63 (0.12–10.55) years. No transplantation-related deaths were recorded.

Consolidation therapy with stem cell salvage improves EFS, but not OS, according to a Cochrane review of three randomized trials of 739 children with high-risk neuroblastoma. In that analysis, high-dose chemotherapy and hematopoietic stem cell transplantation improved EFS and tended to improve OS in two studies compared with conventional therapy, although the results were not significant. No difference in secondary malignant disease or treatment-related deaths was observed between the two treatment groups, but significantly higher rates of treatment-related toxicities, such as renal damage, interstitial pneumonia, and veno-occlusive disease, were seen in those treated with stem cell transplantation compared with those treated with conventional chemotherapy (21).

The clinical features and prognoses of 458 children with high-risk neuroblastoma were assessed at a single center. The 5-year EFS rate was 31.2 ± 2.6% and the 5-year OS rate was 43.9 ± 3.2%. The 5-year EFS and OS rates in 142 AHSCT patients with bone marrow metastases (38.1 ± 5.5% and 35.7 ± 4.7%, respectively) were better than those of 196 patients with bone marrow metastases who did not undergo transplantation (26.5 ± 4.5% and 25.1 ± 3.6%, respectively) ($p = 0.001$). The EFS and OS rates of patients with bone metastases who underwent AHSCT were significantly better than those of patients who did not (22).

The results of the Turkish Pediatric Oncology Group (TPOG) national protocol were evaluated in a study that included 272 high-risk neuroblastoma patients. The EFS and OS rates were 28% and 36% at 5 years, respectively. The EFS rate after induction was 41% (n = 138) in the conventional chemotherapy arm and 29% in the AHSCT group (n = 47) ($p = 0.042$); the OS rates were 45% and 39%, respectively (p =

0.05) (10). The OS rate was 54.5%, and the EFS rate was 39%, at a median follow-up of 20.7 (7.8–105.6) months in a study conducted by Yılmaz et al., in which 11 patients with a diagnosis of refractory/ultra-high-risk neuroblastoma underwent tandem MIBG scans and AHSCT (23).

A thesis study of neuroblastoma patients evaluated at our institution in 2017 reported that the 5-year OS and EFS rates were 52% and 34%, respectively, in 33 patients treated according to the TPOG 2009 neuroblastoma protocol. AHSCT was performed in 10 of 22 stage 4 patients. The 3-year OS rate was 71.1%, and the 5-year OS rate was 35.6%, in patients who underwent AHSCT. The 3-year OS rate was 37.5% in patients who did not undergo AHSCT. No significant difference in OS was detected between patients who received and did not receive AHSCT (p = 0.164). However, the OS of patients who underwent AHSCT was better (24). In this study, the 2-year EFS was 40.8 ± 12.5%, the OS was 42.8 ± 12%, and the median follow-up was 2.81 (0.31–7.91) years for 20 neuroblastoma patients who underwent AHSCT.

Bu/Mel improved EFS, and caused fewer serious adverse events, than CEM in an international, randomized, multi-arm, open-label phase III study (HR-NBL1/SIOPEN) comparing CEM vs. Bu/Mel as high-dose chemotherapy in high-risk neuroblastoma. The median follow-up time was 7.2 (5.3–9.2) years. At 3 years, 146 of 296 patients in the Bu/Mel group and 188 of 302 in the CEM group had an event. The 3-year EFS rates were 50% and 38% (p = 0.0005) (25). In our study, the OS rate for neuroblastoma patients who underwent the Bu/Mel regimen was 55.1 ± 13.8%, which was better than the OS rate of all neuroblastoma patients (42.8 ± 12%). Despite the limited number of cases, the OS of patients transplanted with Bu/Mel was better than that of CEM protocol and non-transplanted patients, and transplantation with Bu/Mel significantly contributed to survival.

Second-line chemotherapy followed by high-dose chemotherapy and AHSCT is the regimen of choice for patients with Hodgkin's lymphoma who develop refractory disease during treatment or relapse < 1 year after completing treatment (26, 27). A study of 82 patients with refractory Hodgkin's lymphoma reported that, after aggressive second-line therapy (high-dose chemoradiotherapy), AHSCT resulted in a 49% 5-year OS rate (28). In another study, the 10-year EFS and OS rates were 41% and 51%, respectively, for primary refractory Hodgkin's lymphoma patients treated with chemotherapy plus radiation therapy (29). In a Turkish study by Hazar et al., in which patients with recurrent or refractory pediatric Hodgkin's lymphoma who underwent AHSCT with a median follow-up period of 39 months were evaluated, the 5-year OS and EFS rates were 63.1% and 54.3%, respectively (12). In another study from Turkey, the 3-year OS rates for patients with Hodgkin's lymphoma and an indication for AHSCT were 100% for late relapse (relapsed 1 year after treatment completion) and for early relapse (relapsed 3–12 months after completing the treatment); the respective rates for those with resistant disease were 83.3% and 57.6% (p = 0.003) (30). Autologous and allogeneic hematopoietic stem cell therapy can be applied in patients with non-Hodgkin's lymphoma, and long-term remission can be achieved in relapsed patients (31). In our study, the 2-year EFS rate was 87.5 ± 11.7% for Hodgkin's lymphoma and 75 ± 21.7% for non-Hodgkin's lymphoma. The OS rate was 58.3 ± 25.1% for Hodgkin's lymphoma with a median follow-up of 6.42 (0.5–10.81) years, and 75 ± 21.7% for non-Hodgkin's lymphoma with a median follow-up of 3.49 (0.25–6.23) years. Although the survival rates of our patients were high, it was not possible to draw any definitive conclusions due to the low number of cases.

This study had several limitations, including the single-institution retrospective design and small sample size. Also, the different therapeutic protocols used during the study period may have affected the treatment results, particularly the comparison between neuroblastoma patients who received Bu/Mel and those who did not. However, all of the protocols were based on various combinations of the same induction chemotherapeutic agents used today; therefore, differences between protocols are unlikely to affect our findings over the long term.

CONCLUSION

The efficacy and toxicity of AHSCT combined with multi-agent chemotherapy, radiation, and surgery for solid tumors remain controversial. Our study involved a small number of patients. Although the use of AHSCT in children and adolescents with high-risk solid tumors has shown promising results, disease recurrence remains a major challenge. AHSCT should be used in specific subsets of patients, along with post-transplant immunomodulatory maintenance or vaccine, cytokine, or antibody therapies. Prospective randomized multicenter clinical trials of pediatric patients with solid tumors should be conducted.

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