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Single-Center Outcomes of Autologous Hematopoietic Stem Cell Transplantation Accompanied by High-Dose Chemotherapy in Patients with Solid Organ Tumors

Solid Organ Tümörlü Hastalarda Yüksek Doz Kemoterapi Eşliğinde Otolog Hematopoietik Kök Hücre Naklinin Tek Merkez Sonuçları

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ABSTRACT

Aim: In contrast to hematologic diseases, the use of hematopoietic stem cell transplantation (HCT) for solid organ tumors is limited, with recommendations available only for certain selected diagnoses and cases.
Methods: Data from 16 adult patients who underwent HCT with a diagnosis of solid organ tumor between 2006-2023 were analyzed.
Results: The median age of the patients was 36.5 years (21–46), and 13 (81.2%) were male. Seven patients (43.7%) had testicular germ cell tumors (GCT), four (25%) had Ewing sarcoma, and five (31.3%) had other solid organ tumors. Autologous HCT was performed in 14 patients (87.5%) due to relapsed/refractory disease, and only five patients (31.3%) achieved a complete response to salvage therapy prior to transplantation. Post-transplant relapse occurred in 92.8% of patients, with a median progression-free survival (PFS) of 6.5 (2-32) months. Fourteen patients (87.5%) died, including two during transplantation, with a median overall survival (OS) of 53.0 (9–213) months. Although the median PFS for testicular GCT patients after autologous HCT was longer than that of other patients (12.0 vs. 4.5 months; p=0.04), the median OS was similar (90.0 vs. 46.0 months; p=0.52).
Conclusion: The literature regarding the role of HCT in solid organ tumors is generally based on retrospective data and periods when older treatment approaches are employed. With the current use of immunotherapy and targeted therapies, both the necessity and stage at which HCT should be performed should be further investigated, and new studies are needed to address this issue.

Keywords: Solid organ tumors, Germ cell tumors, Ewing sarcoma, Autologous hematopoietic stem cell transplantation

ÖZ

Amaç: Hematopoetik kök hücre naklinin (HCT), hematolojik hastalıkların aksine, solid organ tümörlerinde kullanımı sınırlı olup, öneriler bazı seçilmiş tanılarda ve seçilmiş olgularda mevcuttur.
Yöntem: Solid organ tümörü tanısıyla, 2006-2023 yılları arasında HCT yapılan 16 erişkin hastanın verisi analiz edildi.
Bulgular: Hastaların ortanca yaşı 36.5 (21-46) olup, 13'ü (%81.2) erkekti. Hastaların 7'sinde (%43.7) testis kaynaklı germ hücreli tümör (GCT), 4'ünde (%25) Ewing sarkomu ve 5'inde ise diğer (%31.3) solid organ tümörü tanısı vardı. Otolog HCT, 14 (%87,5) hastaya relaps/refrakter hastalık nedeni ile uygulandı ve sadece 5 (%31.3) hasta nakil öncesi kurtarma tedavisine tam yanıtlıydı. Nakil sonrası relaps %92.8 hastada görülürken, ortanca progresyonsuz sağkalım süresi (PFS) süresi 6.5 (2-32) aydı. Hastalardan, 2'si nakilde olmak üzere, 14'ü (%87.5) öldü ve hastaların ortanca genel sağkalım süresi (OS) süresi 53.0 (9–213) aydı. Testis GCT hastalarının otolog HCT sonrası ortanca PFS'si diğerlerine göre daha uzun olsa da (12.0 ve 4.5 ay; p=0.04), ortanca OS'si benzerdi (90.0 ve 46.0 ay; p=0.52).
Sonuç: Solid organ tümörlerinde HCT'nin yerine dair literatür bilgileri genellikle eski tedavi yaklaşımların uygulandığı döneme ve retrospektif verilere dayanmaktadır. Günümüzde kullanımları ön plana çıkan immunoterapi ve hedefe yönelik tedavilerle birlikte, HCT'nin hem gerekliliği hem de hangi aşamada yapılmasının daha fazla sorgulanmalıdır ve bu yönde yeni çalışmalar gerekmektedir.

Keywords: Solid organ tümörleri, Germ hücreli tümör, Ewing sarkomu, Otolog hematopoietik kök hücre nakli

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Introduction

Hematopoietic stem cell transplantation (HCT) is a process in which hematopoietic stem cells of any donor type and from any source are administered to a recipient to replace (autologous) or change (allogeneic) the hematopoietic system after intensive chemotherapy, which is also considered beneficial for the disease. Hematologic malignancies such as bone marrow-derived cancers and lymphoproliferative diseases, some hematologic and non-hematologic benign diseases, and some solid organ malignancies benefit from this treatment method at different stages of the treatment process, depending on the disease [1]. In the 1990s, with some successful outcomes obtained from the use of high-dose chemotherapy combined with autologous HCT (auto-HCT) in certain solid organ tumors, interest in this approach increased [2]. However, in the early 2000s, in addition to the possible exception of breast carcinoma, the benefit of this treatment approach for solid tumors remains uncertain, and many oncologists believe that it should be discontinued [3]. Failure to successfully complete prospective randomized trials in this direction and HCT-related toxicity have led to a decline in interest in this approach, although there is evidence suggesting that it may improve tumor response rates and/or possibly progression-free survival (PFS), especially in some selected patient subgroups. [4]. During the same period, HCT administered in combination with high-dose chemotherapy in adult patients was reported to have largely equivocal results in solid tumors other than breast carcinoma and germ cell tumors (GCTs) [5]. Based on current knowledge, the use of HCT in solid organ tumors is limited, and recommendations are available for selected diagnoses and cases [1,6].

In the 2015 guidelines, HCT was generally not recommended, except for solid tumors such as GCTs, neuroblastoma, medulloblastoma, selected breast cancer, and sarcoma, which were generally reiterated in the 2022 recommendations with very few changes. Although the primary diagnoses for HCT in the pediatric age group (neuroblastoma, medulloblastoma, and Ewing's sarcoma) and the adult age group (primarily GCTs and, to a lesser extent, Ewing's sarcoma and breast and ovarian cancers in selected cases) vary, there are recommendations for only auto-HCT in adult patients and allogeneic HCT (allo-HCT) in addition to auto-HCT in pediatric patients at the selected case level [1,6].

Based on the current knowledge, the use of HCT in solid organ tumors is limited, with recommendations available only for certain selected diagnoses and specific cases. In this retrospective study, we aimed to evaluate patients with solid organ tumors who underwent HCT with high-dose chemotherapy in light of the literature.

Materials and Methods

Patients over the age of 18 years who were diagnosed with solid organ tumors and underwent HCT between 2006 and 2023 in the adult HCT unit of Akdeniz University Faculty of Medicine Hospital were included in the study. Data were collected from written patient files, an electronic hospital database, clinical records from the hematology and oncology departments, hospital central laboratory records, and the national death notification system. Information on sex, age, Eastern Cooperative Oncology Group (ECOG) performance score, comorbidities, date of diagnosis, initial treatment and response to this treatment, mobilization methods, transplant dates, preparation regimens, number of stem cells administered, engraftment status, post-transplant infectious processes, tandem transplantation status, relapsed disease and subsequent treatments, last visit dates, and survival status were recorded.

The post-transplant PFS status of the patients was evaluated. Post-transplant PFS was defined as the time from the date of transplantation to the date of disease progression, the date of the last follow-up if the patient was alive, or the date of death due to any cause. Overall survival (OS) was defined as the time from the date of diagnosis to the date of death from any cause or the date of the last follow-up.

Statistical analysis

IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Descriptive statistics were used to analyze the data. Categorical data were

presented as numbers and ratios, and numerical data were presented as medians, minima, and maxima. Comparisons between independent groups were conducted using the Mann-Whitney U test, which is appropriate for non-normally distributed continuous variables. Kaplan-Meier survival analysis was applied for OS and PFS, and log-rank tests were used to examine the factors affecting survival.

Results

Between 2006 and 2023, 19 patients with solid organ tumors who underwent HCT were identified, but 3 were excluded from the study because of insufficient data. The analysis included 16 patients with a median age of 36.5 years (21–46), 13 (81.2%) of whom were male. All the patients had an ECOG performance score of 0–1. Regarding additional comorbidities, one patient each had chronic renal failure, hypertension, and asthma. Seven patients had testicular GCT, four had Ewing sarcoma, two had gestational trophoblastic tumors (one choriocarcinoma), two had soft tissue sarcomas (one rhabdomyosarcoma and one synovial sarcoma), and one had osteosarcoma. In the first-line treatment after diagnosis, six patients received BEP (bleomycin, etoposide, cisplatin), three received IMA (ifosfamide, mesna, and adriamycin), two received IMA+HD-MTX (high-dose methotrexate), and one each received VAC-IE (vincristine, adriamycin, cyclophosphamide-ifosfamide, etoposide) and MTX. The treatment protocols for the 3 patients were not accessible. Patients received a median of three cycles (2–4) as first-line therapy. Fourteen out of 16 patients had relapsed/refractory disease prior to transplantation, including seven patients with primary refractoriness, and received a median of four (2–8) additional cycles of chemotherapy. Five of 11 patients achieved a complete response (CR), 3 had a partial response (PR), 2 had stable disease (SD), and 1 had progressive disease. All transplants were auto-HCTs; 10 patients were mobilized with chemotherapy+granulocyte colony-stimulating factor (G-CSF) and the others were mobilized with G-CSF alone. The time from diagnosis to transplantation was 6 months in 2 patients who underwent consolidative auto-HCT as first-line treatment, whereas the median time from diagnosis to transplantation was 29.5 (6–187) months in 14 patients who experienced relapse/refractory disease. Eleven patients received carboplatin+etoposide, four patients received high-dose (HD)-ICE (ifosfamide, carboplatin, etoposide), and one patient received busulfan+melphalan. After the preparation regimen, patients received a median of 4.7x106 (3.4–8.7) CD34+ stem cell infusions per kilogram. Two patients died in the first month post-transplant, one from neurological and cardiac complications, and the other from Klebsiella-induced sepsis, while still in the neutropenic period. The median neutrophil engraftment time for the other 14 patients was 10 (8–12) days, and the median platelet engraftment duration was 13 (11–27) days. The most common post-transplant complications were diarrhea and mucositis, which developed in all the patients.

A second auto-HCT (non-tandem) was performed in three patients (two with testicular GCT and one with gestational trophoblastic tumor). Prior to the second transplant, all three patients had progressive disease and received carboplatin+etoposide as the conditioning regimen. None of the patients experienced engraftment issues and no mortality related to the second transplant was observed. Among the three patients who underwent a second transplant, 13 of the 14 patients (92.8%) developed disease relapse after auto-HCT. The posttransplant PFS of these patients is a median of 6.5 (2–32 months). Due to relapsed/refractory disease, all patients received additional chemotherapy, with a median of three cycles (2–4) of different chemotherapy protocols. The OS for two patients (one with osteosarcoma who remained in remission after auto-HCT and another with testicular GCT who received chemotherapy following relapse after auto-HCT) was 46 and 39 months, respectively. All the other patients died. Two of the deaths occurred due to causes other than an active malignancy. During follow-up, only one patient developed secondary myelodysplastic syndrome (MDS). The median number of treatment lines administered to all patients, including transplant patients, was six (3–14) months, with a median OS of 53.0 (9–213) months. The demographic characteristics, treatments, response status, and survival outcomes of the patients are presented in Table 1.

Table 1. Demographic characteristics, treatments, response, and survival status of the patients.

Parameters		Patients (n=16)
Age (Median, years)		36.5 (21–46)
Gender	Male	13 (81.2%)
	Woman	3 (18.8%)
Comorbidity	Hypertension	1 (6.2%)
	Asthma	1 (6.2%)
ECOG	0–1	16 (100%)
Solid Organ Tumor	Testicular GCT	7 (43.7%)
	Ewing sarcoma	4 (25%)
	Gestational trophoblastic tumor	2 (12.5%)
	Soft tissue sarcoma	2 (12.5%)
	Osteosarcoma	1 (6.2%)
RR disease before auto-HCT		14 (87.5%)
Mobilization	Chemotherapy+G-CSF	10 (62.5%)
	G-CSF	6 (37.5%)
Time from diagnosis to auto-HCT (Median, months)		29.5 (6-187)
Response prior to auto-HCT	Complete response	5 (31.3%)
	Partial response	3 (18.8%)
	Stable disease	2 (12.5%)
	Progressive disease	1 (6.2%)
	Uncertain	5 (31.2%)
Conditioning regimen	Carboplatin+Etoposide	11 (68.7%)
	HD-ICE	4 (25%)
	Busulfan+Melphalan	1 (6.2%)
Given CD34+ cells (Median, cells/kg)		4.7x10^6 (3.4–8.7)
Engraftment time (Median, days)	Neutrophil	10 (8–12)
	Thrombocyte	13 (11–27)
Insufficient engraftment		2 (12.5%)
Auto-HCT related mortality		2 (12.5%)
Relapse after auto-HCT	Exist	13 (81.2%)
	None	1 (6.2%)
Latest status	Alive	2 (12.5%)
	Death	14 (87.5)

Auto-HCT; Autologous hematopoietic stem cell transplantation, ECOG; Eastern Cooperative Oncology Group (ECOG) performance score, GCT; Germ cell tumor, G-CSF; Granulocyte colony stimulating factor, HD-ICE; High-dose ifosfamide, carboplatin, etoposide,RR; relapsed and refractory

Patients with testicular GCT were compared with other patients (Table 2). There was no difference between the two groups in terms of median age, time from diagnosis to auto-HCT, or the total number of treatment lines, including auto-HCT. While PFS was significantly longer after auto-HCT in testicular GCT patients than in patients with other solid tumors, the OS in both groups was similar.

Table 2. Comparison of testicular germ cell tumor and other solid organ tumors.

	Testicular GCT (n=7)	Other solid tumors (n=8)	P value
Age (Median, years)	41	36.5	0.71
Time from diagnosis to auto-HCT (Median, months)	86.2	69.6	0.42
Total number of treatment lines (Median)	5.5	6	0.17
PFS after auto-HCT (Median, months)	12	4.5	0.04
OS (Median, months)	90	46	0.52

Auto-HCT; Autologous hematopoietic stem cell transplantation, GCT; Germ cell tumor, OS; Overall survival, PFS; Progression-free survival

Discussion

We present the outcomes of 16 adult patients who underwent auto-HCT, 43.7% of whom were diagnosed with GCT, 25% with Ewing sarcoma, and 31.3% with other solid organ tumors. Relapse occurred in 92.8% of patients post-transplant, with a median PFS of 6.5 (2-32) months. A total of 14 patients (87.5%) died, including 2 at the time of transplantation, and the median OS duration for these patients was 53.0 (9–213) months.

Randomized controlled studies are infrequent, and information on the role of HCT in solid organ tumors is generally based on retrospective data. The most comprehensive data and information are available from the European Society for Blood and Marrow Transplantation (EBMT) registry, which reported that by the end of 2022, 65,586 transplants (97% auto-HCT and 3% allo-HCT) were performed in 47,221 patients with solid organ tumors, 52% of whom were women and 58% of whom were in the adult age group (≥18 years). One of the striking points here is that, while auto-HCT was primarily performed in the adult age group before the 2000s, it has been preferred in the pediatric age group at a similar

or higher rate since then. The primary reason for this shift appears to be the documented success of auto-HCT in treating different diagnoses across age groups over time [7]. Currently, auto-HCT is predominantly used in pediatric cases of diseases such as neuroblastoma, medulloblastoma, and Ewing sarcoma [8,9]. In adults, it is primarily applied in GCT, with less frequent use in Ewing sarcoma, other sarcomas, breast cancer, and ovarian cancer [7].

Although HCT emerged as a potential option for adult solid organ tumors after the 1990s, the lack of randomized trials designed to either validate or refute its efficacy has resulted in most of the current knowledge being based on nearly 30 years of retrospective experience [7]. In recent years, particular focus has been placed on its effectiveness in high-risk advanced-stage breast cancer in adults. Studies have demonstrated that auto-HCT, when used as an adjuvant treatment, prolongs PFS and improves OS in certain subgroups [10,11]. However, according to the results of 15 randomized controlled trials conducted until 2011, auto-HCT significantly improved PFS and was reported to have no impact on OS [12]. In a 2020 study presenting updated data with 20 years of follow-up, compared with standard adjuvant chemotherapy, auto-HCT significantly improved OS only in very high-risk patients (with involvement of ≥10 axillary lymph nodes) [13]. However, considering that the patients in this study were also treated with the same treatment strategies and agents for breast cancer 20 years ago, and the significant increase in OS and PFS provided by targeted therapies in current approaches (trastuzumab, humoral therapies, drug-antibody conjugates, and immune checkpoint inhibitors) [14], auto-HCT no longer seems to be a treatment strategy in this patient group. Since breast cancer patients are now treated with current oncological approaches, no patients have been diagnosed with breast cancer who underwent auto-HCT in our clinic.

Unlike other solid organ tumors treated with chemotherapy alone, GCT is a curable cancer, even in advanced stages, with a 5-year OS rate of over 95%, especially with cisplatin-based treatment. However, an estimated 20–30% of patients either have refractory disease or experience disease recurrence [15]. Unlike the non-standardized and less effective salvage treatments before 1990, over the past 20–25 years, high-dose chemotherapy combined with auto-HCT has shown longer PFS and OS advantages in relapsed/refractory patients than classical salvage chemotherapy [16]. Studies have highlighted that conditioning regimens with carboplatin and etoposide are particularly effective in this patient group, with 5-year PFS and OS rates reported to be approximately 50% with auto-HSCT [17]. Experience has been obtained primarily from male and testicular cancer patients with GCTs. The number of female patients with relapsed/refractory GCT, mostly of ovarian origin, who underwent auto-HCT with intensive chemotherapy was very low. Nevertheless, the recommendations for GCT in female patients are similar [18]. Previous studies have shown that age ≥ 40 years, which is an unfavorable prognostic indicator in addition to metastatic disease and histological subtype, is not an unfavorable prognostic factor when auto-HCT is combined with intensive chemotherapy. In addition, it has been reported that this treatment approach has similar toxicity and safety in patients aged ≥ 40 years and those aged < 40 years; therefore, it can be applied to patients aged ≥ 40 years who are suitable for treatment [19]. In contrast to gonadal GCTs, non-gonadal GCTs, which are rarer, have worse responses to both first-line and salvage therapies. These patients have OS rates of 40–50%, whereas the OS rate in relapsed patients is approximately 10% [20,21]. In summary, auto-HCT with high-dose chemotherapy (carboplatin+etoposide) is recommended as a standard approach for patients with GCTs, primarily those refractory to platinum-based chemotherapy or those who have relapsed, rather than first-line treatment [6,17,22]. In our study, 3 out of 5 patients ≥ 40 years of age (40–46) were GCTs patients, and all GCTs occurred in men, originated from the testis, and were of non-seminoma histological subtype. The carboplatin+etoposide regimen was used as the conditioning regimen in all our GCTs patients, except for one who received the HD-ICE regimen. Compared with other solid organ tumors, auto-HCT in testicular GCT patients provided a PFS advantage, but no OS advantage.

However, studies on other solid organ malignancies are limited. Although data on different histological

subtypes are limited, there is no strong evidence supporting the efficacy of auto-HCT in soft tissue sarcomas [22]. In a study conducted on patients with advanced-stage ovarian cancer and those with limited or extensive small cell lung cancer, high-dose chemotherapy as first-line treatment did not provide any additional advantage in terms of PFS or OS [3]. Data on auto-HCT in adult patients with other chemosensitive cancers, including Ewing/PNET (primitive neuroectodermal tumors) and certain CNS tumors, are limited, and this approach cannot be recommended as a standard [6]. However, based on studies in pediatric age groups with solid tumors such as Ewing sarcoma and medulloblastoma, high-dose chemotherapy and auto-HCT may be potential clinical options in selected adult and adult young adolescent (AYA) patients [23,24]. In our study, the most common patient group to receive auto-HCT after GCTs was the AYA (adolescent and young adult) group with Ewing sarcoma (26% of patients).

Although interest in tandem transplantation is increasing due to the advantageous results provided by HCT in some pediatric and adult patient groups, studies in adult patients with adult breast cancer have not shown any additional benefits compared to single HCT. In pediatric patients, no additional benefit has been shown, except for the potential benefit in selected neuroblastoma and Ewing sarcoma patients with a poor prognosis [7,11,13]. The information and experience regarding allo-HCT is much weaker than that regarding auto-HCT. Checkpoint inhibitors, such as nivolumab/pembrolizumab (PD-1/PD-L1) and ipilimumab (CTLA-4), which have achieved successful results through T-cell cytotoxicity in cancer immunotherapy [25], led to the idea that similar outcomes could be obtained with donor-derived healthy T cells following allo-HCT. However, contrary to expectations, allo-HCT has been nearly abandoned, particularly in the adult patient group, owing to both transplant-related toxicity and the success achieved with molecularly targeted therapies. Therefore, allo-HCT is now recommended only within the scope of clinical trials [7,26]. In our clinic, no patients with solid organ tumors underwent allo-HCT.

One of the most critical aspects of this treatment option is treatment-related mortality (TRM), as we unfortunately lost two patients due to sepsis caused by engraftment failure/delay. In fact, the exclusion of total body irradiation (TBI), which does not provide a treatment advantage and leads to late complications, along with the use of peripheral stem cells, has significantly reduced the TRM over time to approximately 1%. Another important point is the HCT recommendations according to the response status or relapse time of patients. In selecting patients and diseases in which auto-HCT is planned in the first-line setting (primarily pediatric patients), HCT is recommended for patients with CR, very good partial response (VGPR), and PR to induction therapy, whereas auto-HCT is recommended for patients with SD or minimal response (MR) (<50%) in early phase studies. HCT is not recommended for this patient group because the life expectancy of unresponsive/refractory and progressive patients is very short, even after transplantation. The recommendation for HCT in patients with relapsed disease is limited to those who have not previously received HCT, respond to previous treatment, and experience relapse 12 months after diagnosis [7]. In our study, 14 patients (87.5%) underwent auto-HCT for relapsed/refractory disease, and only five (31.2%) achieved CR.

Conclusion

The literature recommendations are primarily based on retrospective data, usually from past treatment algorithm periods. In the era of immunotherapy and targeted therapies, which has become prominent in current treatment algorithms, there is a need for updated randomized controlled trials or well-designed registry studies to provide information on the necessity of HCT and the optimal timing for its administration.

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