Long-Term Side Effects of Hematopoietic Stem Cell Transplantation in Children: A Single Center Experience

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has the potention to provide curative therapy for selected benign and malignant disorders. In patients undergoing allo-HSCT in childhood, long term side effects are increased as with the prolonged survival time. Fifty-one patients underwent allo-HSCT between 2001-2014 and survived for at least two years were enrolled in this study. Clinical evaluation with detailed physical examination and required laboratory tests were done routinely to determine long term side effects. Mean follow-up period after allo-HSCT was 68.3±31.4 months (range: 24-141 months), patients' age average was 9.3 ± 4.9 years (range: 6 moths-17 years), 56.9% of them were male, and 92.2 % (n= 47) of donors were match family donors. We determined long term side effects in 56.8% of patients. Most of the long term side effects were endocrine complications with 17.6%. Oculary long term side effects were found in 15.7% and associated with haploidentical and match unrelated donor (MUD) transplantations (p= 0.002). We found that chronic graft versus host disease (GVHD) rate was increased with MUD transplantation (p=0.003) and acute liver GVHD (p= 0.002). Osteoporosis frequency was positively correlated with follow-up time (p= 0.002) and found much more in malign disorders than benign ones (p=0.002). Osteoporosis was rarely found in conditioning regimens included cyclophosphamide (p= 0.004). Long-term side effect risk was higher in patients underwent allo-HSCT in older age (p= 0.003). Patients need to be monitored routinely for a long time after allo-HSCT. Haploidentical and MUD transplantation increase long term side effects. Future wide-spread studies are necessary to determine long term side effects of allo-HSCT-received children.

Keywords: Hematopoietic Stem Cell Transplantation, Long-Term Side Effects, Child

ÖZET

Hematopoetik Kök Hücre Nakli Yapılan Çocuklarda Geç Yan Etkiler: Tek Merkez Deneyimi

Allojeneik Kök Hücre Transplantasyonu (KHT) bazı malign ve benign hastalıkların küratif tedavisinde umut vericidir. Allojeneik KHT yapılan çocuklarda yaşam sürelerinin uzaması ile birlikte geç dönem yan etkilerde de artış olmaktadır. 2001-2014 yılları arasında allojeneik KHT yapılan ve en az 2 yıl süreyle takip edilen 51 çocuk hasta çalışmaya dahil edildi. Geç dönem yan etkilerin tespiti için ayrıntılı fizik muayene ve gerekli laboratuvar analizleri periyodik olarak yapıldı. Allojeneik KHT sonrası ortalama 68.3±31.4 ay (24-141 ay) süreyle izlenen hastaların yaş ortalaması 9.3±4.9 yıl (6 ay-17 yıl) idi.

Hastaların %56.9'u erkek olup, %92.2'sine (n= 47) aile içi uygun donörden KHT uygulanmıştı. Geç dönem yan etki görülme oranı %56.8, en sık görülen geç yan etki ise %17.6 ile endokrin komplikasyonlardı. Hastaların %15.7'sinde oküler geç yan etki saptandı. Oküler geç yan etkilerin haploidentik ve akraba dışı uygun vericiden KHT yapılması ile ilişkili olduğu tespit edildi (p= 0.002). Akraba dışı uygun transplantasyon ve akut karaciğer graft versus host hastalığın (GVHD)'nın kronik GVHD görülme sıklığını artırdığını saptadık (p=0.003). Osteoporoz gelişimi, izlem süresiyle (p= 0.002) ve malign hastalıklarla pozitif korelasyon göstermekteydi (p= 0.002). Siklofosfamid içeren hazırlama rejimleri ile tedavi edilen hastalarda osteoporoz daha nadir olarak saptandı (p= 0.004). Allojeneik KHT yapılan hastalar transplantasyon sonrasında uzun dönemde düzenli olarak izlenmelidir. Haploidentik ve akraba dışı uygun vericiden yapılan KHT'da daha sık geç yan etki görülmektedir. Allojeneik KHT tedavisi alan çocuklarda geç dönem yan etkilerin ortaya konabilmesi için daha geniş çaplı araştırmalara ihtiyaç bulunmaktadır.

Anhtar Kelimler: Hematopoetik Kök Hücre Transplantasyonu, Uzun dönem yan etki, Çocuk

INTRODUCTION

Allogeneic haemopoietic stem cell transplantation (allo-HSCT) has the potential to provide curative therapy for selected benign and malignant disorders. Allo-HSCT has become an available treatment option for increasing number of patients and diseases, recently.[1] Particularly in patients undergoing allo-HSCT treatment in childhood, long-term complications are increased as major problems with the prolonged life expectancy following allo-HSCT. The most common long-term side effects include chronic graft-versus-host disease (cGVHD), hypothyroidism, osteoporosis, cataracts, and so on. Total body irradiation (TBI) and cGVHD are well known risk factors of long-term complications.[1,2]

In the present study, we aimed to analyze the long-term complications and associated risk factors of 51 children received HSCT treatment for benign or malign disorders and followed without relapse at least 2 years.[2]

PATIENTS AND METHODS

Study was approved by the Ethical Committee of Gulhane Military Medical Academy.

Data were collected to 2014 from all patients who underwent allo-HSCT for between 2001 and 2014 at Gulhane Military Medical Faculty Department of Pediatric Hematology and Oncology Transplantation Unit. All of the data were obtained retrospectively from hospital records. Patients surviving for at least two years without relapse after transplantation were included in the study as long time survivors. Patients who relapsed or died within two years of transplant were excluded from the study.

Cardiovasculary risk factor evaluation and routine clinical assessment were performed for all participants at 1 year and yearly thereafter.[3] Cardiac and vasculary functions were assessed by using echocardiography (HD11 XE Ultrasound System, Philips Medical Systems Bothell, WA, USA). Echocardiographic shortening fraction (ESF) below 30% was considered as cardiovasculary dysfunction.[4] The diagnosis of hypertension was defined as blood pressure levels above the 95th percentile.[5]

Clinical evaluations were done routinely to determine the pulmonary complications for all patients at 6 months, 1 year and yearly thereafter.[3] Pulmonary functions were measured by spirometry (MiniSpir MIR Spirometer, Roma, Italy) according to the standards of American Thorasic Society/European Respiratory Society.[6] Forced vital capacity (FVC), forced expiratory volume in one second (FEV1), the ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC), and forced expiratory flow rates (FEF25%, FEF50%, FEF75%, and FEF25%-75%) were measured. FVC less than 80% of predicted value was considered as restrictive dysfunction, FEV1 values under 80% of predicted value was defined as obstructive dysfunction, whereas mean expiratory flow 25 (MEF) rates <25% of predicted were defined as bronchiolitis obliterans.[4] Where necessary, radiological imaging (X-ray, CT) was performed.

In order to assess the renal functions, glomerulary filtration rates were (GFR) calculated by 24-hour creatinine clearance for patients capable of collecting the 24-hour urine sample and by Schwartz formula for other patients (GFR, ml/second per

1.73m^2)¼k_height (cm)/creatinine (mg/dl), where "k" is an age-dependant factor (patient <1 year: k¼0.45; patient >1 year: k¼0.55). Chronic renal impairment was defined as GFR <90 ml/second per 1.73 m^2 over 3 months, at least a year after HSCT. Of the 6th month onwards after transplantation, all patients underwent renal ultrasound every 6 months.

Screening dual photon densitometry was performed to determine skeletal complications at 1 year after transplantation, annually.[3] A bone mineral density (BMD) Z-score between -1 and -2.5 was considered as osteopenia, and BMD Z-score under -2.5 was defined as osteoporosis.[7]

For monitoring the endocrinological long term side effects; all anthropometric measurements were performed in the morning while children were wearing only underclothes without shoes. Height and weight were measured at 2 different occasions throughout the interview, and averages of these 2 values were used for analyses. Height was measured using a standard stadiometer and approximated to the nearest 0.1 cm. Children were weighed twice by a portable digital scale, and these values were also approximated to nearest 0.1 kg. Body mass index (BMI) was calculated as kg/m^2. All subjects had a BMI above 95 percentile for their age and gender; and therefore were classified as obese. To assess the effects on the hormonal axis between hypothalamus, pituitary and gonads, we measured serum levels of thyroid stimulating hormone (TSH), thyroid hormones (total and free T4, T3), adrenocorticotropic hormone (ACTH), cortisol, insulin-like growth factor I (IGF-I), insulin-like growth factor binding protein 3 (IGFBP-3), luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol in girls and testosterone in boys.[4]

Ocular complications were evaluated at 6 months, 12 months and yearly thereafter for all patients. Detailed ocular examination including visual acuity and biomicroscobic fundus examination were done by an expert ophthalmologist, and Schirmer's test was performed to diagnose sicca syndrome.

All of the patients received a complete oral and dental evaluation by an expert pediatric dentist at 1 year after HSCT and yearly thereafter. Further radiological examinations and dental treatments were performed in appropriate cases.

Serum levels of direct/total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine transaminase (ALT) were measured every 3 months for the first year and then every 6 months thereafter. Ferritin levels were measured at patients received erythrocyte transfusions. Additional diagnostic examinations such as magnetic resonance imaging (MRI) and liver biopsy were performed for patients with suspected iron overload to determine the liver functions.

Detailed neurological examination and electroencephalography (EEG) were performed in all patients before and after the HSCT. Neurological evaluation was done at 12 months after transplantation and yearly thereafter by a pediatric neurologist. Additional diagnostic tests such as MRI, electromyography, nerve conduction studies were performed in selected cases with symptoms or signs of neurologic or cognitive dysfunction.

To diagnose and monitor the GVHD scoring suggested by Filipovic et al was used.[8]

Statistical Analyses

All statistical analyses were performed with SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA). Number, percentage, mean, median, minimum, maximum and standard deviation values were used to identify the data as appropriate. Conformity of the normal distribution of continuous variables was assessed by Kolmogorov-Smirnov test. During comparisons between groups, continuous variables were assessed and compared by using Mann–Whitney U test, and the χ^2 test was used for categorical variables. P-values < 0.05 were considered statistically significant.

RESULTS

Fifty-one patients who have undergone allo-HSCT between 2001-2014 and survived for at least two years were enrolled in the study. All allo-HSCTs performed during the study period were the first transplantations. Patients were followed-up for long-term complications after HSCT. Mean fol-

Table 1. Demographic characteristics of the patients

Follow up time	68.3 ± 31.4 months (range:24-141 months)
Median age at transplantation	9.3 ± 4.9 years (range: 6 months-17 years)
Gender (%)	
Male	29 (56.9)
Female	22 (43.1)
Malign Diseases (%)	
AML	11 (21.6)
ALL	8 (15.7)
NHL	6 (11.8)
CML	3 (5.9)
Others	4 (7.8)
Non-malign Diseases (%)	
Thalassemia major	12 (23.5)
Fanconi	3 (5.9)
SCID	2 (3.9)
Others	2 (3.9)
Type of donor (%)	
MSD	47 (92.2)
Haploidentical	3 (5.9)
MUD	1 (2)
Source of stem cells (%)	
Bone marrow	43 (84.3)
PBSC	7 (13.7)
Cord blood + Bone marrow	1 (2)
Conditioning regimen (%)	
Busulfan, cyclophosphamide	22 (43.1)
TBI, cyclophosphamide	8 (15.7)
TBI, Etoposide	5 (9.8)
Busulfan, ATG, fludarabine	3 (5.9)
Others	13 (25.5)
Acute GVHD (%)	
Grade 0–I	7 (13.7)
Grade II-IIII	4 (7.8)
Chronic GVHD (%)	
None	44 (86.2)
Limited	5 (9.8)
Extensive	2 (3.9)

Abbreviations: AML= acute myeloid leukemia; ALL= acute lymphoblastic leukemia; NHL= non-Hodgkin's lymphoma; CML= chronic myeloid leukemia; SCID = Severe combined immunodeficiency; MSD= matched sibling donor; MUD= matched unrelated donor; PBSC= peripheral blood stem cell; TBI= total body irradiation; ATG= antithymocyte globulin; GVHD= graft-versus-host disease.

Table 2. Long-term side effects of the patients

	n	%
Endocrine system	9	17.6
Growth retardation	4	7.8
Hypogonadism	4	7.8
Hypothyroidism	1	2
Oculary system	8	15.7
Sicca sydrome	5	9.8
Cataracts	1	2
Hypertensive retinopathy	1	2
Chorioretinal atrophy	1	2
Graft versus host disease	7	13.7
Musculoskeletal and soft tissue	6	11.8
Osteoporosis	6	11.8
Respiratory tract	5	9.8
Bronchiolitis obliterans	2	3.9
Asthma bronchiale	2	3.9
Pneumothorax	1	2
Mucocutaneous	5	9.8
Cutaneous sclerosis	4	7.8
Alopesi areata	1	2
Gastrointestinal tract and Hepatobiliary tract	4	7.8
Hepatitis B infection	3	5.8
Hepatitis B carrier	1	2
Renal	3	5.9
Chronic renal failure	2	3.9
Nephrolithiasis	1	2
Oral cavity	3	5.9
Sicca sydrome	3	5.9
Nervous system	2	3.9
Encephalopathy	1	2
Transverse myelitis	1	2
Cardiovasculary system	1	2
Hypertension	1	2

low-up period after HSCT was 68.3 ± 31.4 months (range: 24-141 months), patients' average age was 9.3 ± 4.9 years (range: 6 months-17 years), 56.9% of them were male (n= 29), and 92.2% (n= 47) were match family donors.

Demographic characteristics of the patients are summarized in Table 1. All long term side effects determined were shown in Table 2.

Of the 51 patients, 9 (17.6%) had long-term endocrinological complications. These were short stature (n= 4), hypogonadism (n= 4), hypothyroidism and on thyroid replacement therapy (n=

1), respectively. None of the patients with adrenal insufficiency was detected in this study. Oculary long term side effects including sicca syndrome (n= 5), cataracts (n= 1), hypertensive retinopathy (n= 1), and chorioretinal atrophy (n= 1) were found in 15.7% (8/51) of patients. Long-term ocular complications were increased in haploidentical matched unrelated donor (MUD) transplantations (p= 0.002). Furthermore ocular long term side effects were correlated with age, (p= 0.003) serum ferritin levels, (p= 0.004) and mean corpuscular volume (p= 0.003) positively.

Chronic graft versus host disease was observed in 7 of 51 patients (13.7%) as a long-term side effect related to immunity and infections. We found that cGVHD rates were statistically significantly higher in patients with MUD transplantation and with prior acute liver GVHD (p= 0.003 and p= 0.002, respectively). Six of the patients (11.8%) had osteoporosis as the long-term side effect affecting musculoskelatal and soft tissues. Osteoporosis frequency was positively correlated with follow-up time (p= 0.002) and found much more in malign disorders than benign ones (p= 0.002). We couldn't find any difference among conditioning regimens as regard of long term side effects. However, osteoporosis was rarely found in conditioning regimens included cyclophosphamide (p= 0.004). Long term side effects related to respiratory tract were determined in 5 of 51 patients (9.8%), such as asthma (n= 2), pneumothorax (n= 1), and bronchiolitis obliterans (n= 2). Mucocutaneous long term side effects such as cutaneous sclerosis (n= 4), and alopesi areata (n= 1) were found in 9.8% (5 of 51).

When the patients were evaluated in terms of long term side effects of gastrointestinal tract and hepatobiliary tract, it was diagnosed chronic hepatitis B infection in 3 patients and hepatitis B carriage in a patient. Renal long term side effects were chronic renal failure (n= 2) and urolithiasis (n= 1). Sicca syndrome, which is a long term side effect of oral cavity, were determined in 3 of 51 patients (5.8%). Neurological examination revealed long term nervous system side effects in 2 patients (3.9%); one had encephalopathy and the other had transverse myelitis. Hypertension was detected in only one patient in the examinations for long term side effect associated with cardiovasculary system.

DISCUSSION

Approximately 50,000 bone marrow transplantations are performed annually in the world.[3] As the success rates of HSCT increased parallel to the technological developments, long survival was provided and the frequency of long term side effects increased accordingly. Long term side effects include different clinical pictures affecting endocrinological, renal, pulmonary, cardiovasculary, musculoskeletal, gastrointestinal, immunological, neurological, mucosa and cutaneous systems.[3,9] Secondary cancer development may also be added to this list. Therefore, regular monitoring of these patients is very important. All patients are periodically monitored for systemic functions according to a protocol before and after transplantation.[3] Patients were scanned with a detailed evaluation of complications and organ functions at the 6th month and the 12th month post-transplant, and the scans were repeated every year. After the 2nd year of tranplantation any detectable dysfunctions associated with allo-HSCT were considered as long term side effects.

Gifford et al.[1] reported chronical health problems in 91% of 99 patients treated with allo-HSCT. In another study 66.4% of the patients with autologous and/or allogeneic HSCT had chronic health problems.[10] In our study we determined long term side effects affecting any system in 56.8% (29/51) of patients with allo-HSCT.

Growth retardation, hypothyroidism, hypoadrenalism and hypogonadism have been reported as endocrinological long term side effects.[3] In our study, we detected any endocrinological long term side effects in 17.6% of the patients. Künkele et al.[4] has determined short stature in 25% of 39 patients. Ferry et al.[2] reported short stature requiring growth hormone therapy in 25 of 105 patients treated with allo-HSCT due to malignant causes. We determine short stature requiring growth hormone therapy in 4 patients (7.8%). Growth hormone deficiency rates were lower in our study compared with the literature data. Fertility may be affected after HSCT, in different degrees depending on gonadal damage. We found hypogonadism in 4 of our cases (7.8%), this rate was lower than the literature[2] data since the average age of our patients was only 9.3±4.9 years.

Ferry et al.[2] determined the frequency of hypothyroidism as 36% in the 10-year follow up after HSCT and showed that it was particularly associated with TBI. Künkele et al.[4] reported that they detected hypothyroidism according to the laboratory tests in 6.7% of patients after transplantation. In this study we found hypothyroidism requiring thyroid replacement therapy in 2% of patients. We didn't find any statistical significant relationship between conditioning regimen and the development of hypothyrodism.

Cataract, sicca syndrome and microvasculary retinopathy are probable oculary long term side effects.[3] Gifford et al.[1] reported long term oculary side effects in 40 of 99 patients, in that 20 of them had cataracts. In a study conducted in patients with leukemia[11], they reported that 44.6% of the patients had oculary long term side effects, and the most common amongst them was cataract (36.4%). In the present study, we found any oculary long term side effects in 15.7% of the patients. While sicca syndrome was detected in 5 of our patients (9.8%) only one of the 51 patients had bilateral cataract. Since the frequency of cataract is lower in our patients, this may be associated with fact that 37.2% of patients included in this study had benign diseases and they were not given any steroid treatment.

In our study, there was statistically significant difference between the patients with and without oculary long term side effects in terms of donor types (p= 0.002). 97.7% of the patients without any oculary long term side effects were treated with HSCT from full match sibling donors; on the other hand 2.3% of them were treated with HSCT from haploidentical or matched unrelated donors. We determined significant difference in terms of age between the patients with and without oculary long term side effects. We also found that oculary complications accrued with the increasing age and correlated with serum ferritin levels, (p= 0.004) and mean corpuscular volume (p= 0.003) positively.

cGVHD and immune-deficiency related to GVHD are the leading post-transplant mortality reasons after marrow grafting.[12] GVHD is a major complication of allo-HSCT, and may affect as much as 40–60% of allo-HSCT patients.[13] In our study, cGVHD was observed in 7 of 51 (13.7%) patients. We found statistically significant difference between the patients with and without cGVHD in terms of donor type (p= 0.003). In this study we determined that MUD-HSCT increased the likelihood of cGVHD. We found that cGVHD rate was increased with MUD transplantation and acute liver GVHD.

Decrease in bone mineral density is a well-known complication of HSCT. In a study conducted in patients with leukemia, Baker et al.[11] reported the osteoporosis rate as 13.7%. In our study, we found the osteoporosis rate as 11.8% (6/51) and osteoporosis frequency was positively correlated with follow-up time (p= 0.002) and found much more in malign disorders than benign ones (p= 0.002). Since the incidence of osteoporosis was higher in patients with malign diseases, we think this may be due to high dose steroids prior to HSCT in malignant patients. We found a significant difference between the patients with and without osteoporosis in terms of conditioning regimens. In cyclophosphamide-containing regimens, osteoporosis was less likely to. According to this data, giving priority to conditioning regimens containing cyclophosphamide before HSCT can be considered to be protective from the development of osteoporosis.

Long term pulmonary side effects may be detectable at 15-40% of patients after HSCT.[13] In a study, with a follow-up after allo-HSCT, 31 of 69 patients were determined abnormalities in pulmonary function tests, and 12 of them were symptomatic.[14] In a prospective study, cumulative incidence of lung impairment was 35% by pulmonary function. Most of them were asymptomatic and cGVHD was the major risk factor for reduced lung function.[15] We have determined long term respiratory side effects in 9.8% of the patients. Bronchial asthma, pneumothorax and bronchiolitis obliterans (BO) were detected in 3.9%, 2%, and 3.9%, respectively.

The incidence of BO after HSCT varies between 0-48%.[16] The risk factors associated with the development of late onset pulmonary complications were identified as cGVHD and advanced stage disease.[17] We detected BO in 3.9% of our patients. These patients had severe cGVHD consistent with the literature. Pneumothorax is a rare long term

side effect after HSCT. This sitiuation usually develops on the basis of BO and GVHD.[18] We found only one pneumothorax of our 51 cases. It was consistent with the literature data that the patient had severe GVHD and BO.

Chronic obstructive pulmonary disease may occur in approximately 20% of long term survivors after HSCT.[12] cGVHD is the most important factor claimed in the pathogenesis.[12] Khan et al.[19] suggested that patients who are non-allergic might have allergic status after allo-HSCT from allergic donors. After the second year of HSCT we determined astma in 2 patients who had not any pulmonary disease before the treatment.

Skin is affected in approximately 70% of patients who had cGVHD.[3] Gifford et al.[1] found cutaneous sclerosis in 4% of 99 patients. We found cutaneous sclerosis and alopesia areata in 7.8% and 2%, respectively. All of these patients with skin complications had also cGVHD.

A recent prospective study showed that the prevalence of serum hepatitis B surface antigen (HBsAg) and HCV-RNA-positive HSCT patients were 3.1% and 6.0%, respectively.[20] In our study we found long term liver side efect in 7.8% of patients. All of them were associated with hepatitis B virus; 5.8% had hepatitis B infection, whereas 2% were hepatitis B carriers.

Renal dysfunctions were reported in patients with HSCT as rates of 5-65%.[3] Chronic kidney disease is reported as a complication particularly after allo-HSCT.[21] In a study performed on 66 patients with allo-HSCT, chronic renal failure frequency was 11% at the first year.[22] We also found 5.9% (3/51) of long term renal side effects in the present study.

In a study by Hoffmeister et al.[23], nephrolithiasis rate in HSCT patients was reported as 4.7%. In that study the authors suggested that rate of nephrolithiasis increases proportionally with follow-up time and age. In the present study we determined nephrolithiasis in 2% of patients. However, we predicted that frequency of nephrolithiasis would be increased if the patients were followed by a longer time period.

Sicca syndrome characterized with xerostomia and hyposalivation is the leading oral complication of HSCT.[3] Daikeler et al.[24] reported the frequency of oral sicca syndrome as 20% in HSCT patients. We've detected oral sicca syndrome in 5.9% (3 of 51) cases. Consistent with the literature data, all of the patients diagnosed sicca syndromes were also with cGVHD.

Neurological complications after HSCT are generally secondary to infections, drugs and metabolic disorders.[3] P. Barba et al.[25] reported the neurological complication rate as 14% in 191 allo-HSCT patients. In another study by Azik et al.[26], neurological complication frequency of 89 allo-HSCT children was reported as 11%. We found neurological complication in 2 of 51 children (3.9%); one had encephalopathy and the other one had transverse myelitis secondary to varicella infection. P. Woodard et al.[27] informed that 6.4% (26 of 405) of children performed allo-HSCT had encephalopathy and 3 of them were medication-related. The patient detected encephalopathy in our study was also medication-related. In a study conducted in allo-HSCT patients[25], authors found peripheral neuropathy in 8 of 191 patients (4.1%), and one of them was secondary to HHV-6 infection. In the present study we found one patient (1 of 51) with transverse myelitis secondary to Varicella Zoster Virus infection.

In comparison to other systemic complications, cardiovasculary complications occur relatively infrequently. Cardiac toxicity is claimed to be responsible for mortality in 2% autologous and 3% of allogeneic HSCT recipients.[3] In a study on 689 HSCT-received children, 120 (17%) patients were diagnosed with hypertension.[28] In a study by Tichelli et al.[29] conducted in 265 allo-HSCT patients, the incidence of cardiovasculary complications were reported as 1.5% at 5 years, whereas 22.1% at 25 years follow-up period. We detected hypertension in only one patient. Since the development of cardiovasculary long term complications may last for decades, so the rates of cardiovasculary complications increase within long time.

In conclusion, we determined long term side effects in 56.8% of patients. None of them had secondary cancers. Long term complication rates were higher in patients underwent HSCT in older ages. Patients need to be monitored routinely for a long time af-

ter HSCT, due to the probability of high rates of long term side effects. Future wide-spread studies are necessary to determine long term side effects of HSCT-received children.

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