

## Incidence and Risk Factors for Early-Onset Hypertension after Allogeneic Hematopoietic Stem Cell Transplantation in Children

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**Background and Objectives:** Survivors of pediatric hematopoietic stem cell transplantation (HSCT) are at risk for developing hypertension. The objectives of this study are to evaluate the prevalence and risk factors of early onset hypertension during the engraftment period after HSCT.

**Subjects and Methods:** This is a retrospective study of 157 consecutive patients (mean age at HSCT:  $9.1 \pm 5.1$  years) who underwent HSCT for acute myeloid leukemia ( $n=47$ ), acute lymphoblastic leukemia ( $n=43$ ), severe aplastic anemia ( $n=41$ ), and other reasons ( $n=26$ ). Blood pressure data were collected at five time points: 0, 7, 14, 21, and 28 days after HSCT. Hypertension was defined as having systolic and/or diastolic blood pressure  $\geq 95$ th percentile according to age, gender, and height. To analyze the risk factors related to hypertension, data, including patients' demographic and transplant characteristics, were reviewed.

**Results:** Hypertension developed in 59 patients (38%), among whom 12 (7.6%) required long term therapy. Thirty-two (54%) patients had systolic and diastolic, 8 (14%) had only systolic, and 19 (32%) had only diastolic hypertension. Younger age, acute graft-versus-host disease, sinusoidal obstruction syndrome, treatment with antifungal agent, and greater increase in serum creatinine (Cr) levels were associated with hypertension. Multivariate analysis showed that younger age at HSCT and greater increase in serum Cr level were independent risk factors for hypertension.

**Conclusion:** Prevalence of hypertension during immediate post-HSCT period is high, especially in younger children. A greater increase in Cr after HSCT was significantly associated with hypertension. Further study is needed to elucidate long-term cardiovascular complications in pediatric HSCT survivors. (**Korean Circ J 2013;43:804-810**)

**KEY WORDS:** Hematopoietic stem cell transplantation; Child; Incidence; Blood pressure; Hypertension.

### Introduction

Hypertension frequently occurs among pediatric patients who have received allogeneic hematopoietic stem cell transplantation

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(HSCT). In a previous cohort study, hypertension was 2.06 times {95% confidence interval (CI): 1.39-3.04} more likely to occur in allogeneic transplant recipients than healthy sibling controls.<sup>1)</sup> Although most cases of hypertension are not life-threatening, they can contribute to transplantation morbidity and are potential risk factors for the development of late-onset cardiovascular complications.<sup>2)3)</sup> However, specific risk factors for hypertension in the pediatric allogeneic HSCT population have not been well-defined.

Children are less likely than adult patients to have pre-transplant hypertension, diabetes, a smoking history, or other high-risk factors that may predispose them to hypertension. Hence, hypertension in children during the early post-transplantation period is most likely the result of the conditioning regimen and the medications used for supportive care and post-transplantation complication treatment.<sup>2)5-10)</sup> Although several previous studies have shown that factors such as acute kidney injury and the use of immuno-

suppressants may lead to late-onset hypertension, little is known about the risk factors for hypertension during the early post-transplantation period, which includes the time period from actual transplant to full hematopoietic engraftment.<sup>11)12)</sup> Numerous post-transplant complications, such as acute graft-versus-host disease (GVHD) and sinusoidal obstruction syndrome (SOS), occur during this period, and an understanding of the risk factors for hypertension may help to predict and lower other early transplant-related morbidities and mortality. This study defines the incidence of and risk factors for hypertension during the early period after transplant for a cohort of children who received allogeneic HSCT.

## Subjects and Methods

### Study population

A retrospective study was done on 157 children (<18 years, 89 males) who received allogeneic HSCT from April 2009 to June 2012 at the Seoul St. Mary's Hospital. Patients who received a diagnosis of hypertension or predisposing conditions for the development of hypertension, such as chronic renal disease, diabetes, or cardiovascular problems before HSCT were excluded from this study. The underlying diagnoses were acute myeloid leukemia (n=47), acute lymphoblastic leukemia (n=43), aplastic anemia (n=41), and others (n=26). One hundred five patients had malignant conditions (67%) and 52 had non-malignant conditions (33%). The mean age at HSCT was 9.1±5.1 (range, 4 months-17.9 years). Patients' demographic and transplant characteristics are summarized in Table 1.

### Transplant procedure

Donor-recipient pairs were matched on human leukocyte antigen (HLA)-A, B, C, and DRB1 alleles. Patients treated for malignant disease received either a total body irradiation (TBI) or a busulfan-based myeloablative conditioning regimen, while patients treated for bone marrow failure received a cyclophosphamide-fludarabine-based regimen. Pre-HSCT conditioning regimens for this study population included antithymocyte globulin (ATG) (n=126, 80.3%), fludarabine phosphate (n=107, 68.2%), cyclophosphamide (n=92, 58.6%), busulfan (n=74, 47.1%), cytarabine (n=33, 21.0%), and etoposide (n=4, 2.5%). TBI before HSCT was done for 39 (24.8%) patients. Stem cell sources included bone marrow (n=27), peripheral blood stem cells (n=129), and cord blood (n=1).

The regimen for GVHD prophylaxis included cyclosporine (3 mg/kg/day, intravenous continuous infusion, initially) starting from one day before transplant and 4 doses of mini-dose methotrexate (5 mg/m<sup>2</sup>) administered on days 1, 3, 6, and 11 after HSCT. For patients who received a transplant from an unrelated donor, ATG was given at a total dosage of 7.5 mg/kg during a period of three days as part

of the conditioning procedure. All patients received inpatient care for at least 3-4 weeks until trilineage hematopoietic engraftment was confirmed by follow-up bone marrow aspiration and biopsy. During this period of admitted care, all patients had their vital signs, including blood pressure, checked at least thrice daily.

### Study parameters

Data were retrieved through a retrospective review of medical records. Blood pressure data were collected at five time points: day 0 (day of transplant), 7, 14, 21, and 28. Blood pressure was measured by attending nurses on the basis of a routine clinical practice at least 3 separate times a day, with manual sphygmomanometers and appropriate cuffs for the patient's body size. Average blood pressures were derived from at least three blood pressure measurements checked per day at each time point in 6-hour intervals, at least.

The definition of hypertension determined by the National Heart, Lung, and Blood Institute's Working Group on High Blood Pressure in Children and Adolescents was used in this study. Each diagnosis was based on the patient's blood pressure percentile; hypertension was defined as having an average systolic and/or diastolic blood pressure ≥95th percentile for sex, age, and height on at least three separate occasions.<sup>13)</sup> The outcome variable of interest for this study was the diagnosis of post-transplant "early-onset hypertension". Any patient who met the criteria for hypertension on at least one time point during the post-transplant engraftment period was diagnosed with early onset hypertension, and was subsequently classified into the hypertensive group.

The following factors were analyzed as possible risk factors for post-transplant hypertension: patient age at HSCT, gender, underlying disease, HLA compatibility, cell source, conditioning regimen, antecedent acute GVHD, antecedent SOS, serum cyclosporine level, and serum creatinine (Cr) level during admission. Serum Cr level data were collected on the day of transplant (baseline Cr), and on days 7, 14, 21, and 28 after transplant.

### Statistical methods

Data were analyzed using commercially available software, PASW Statistics (version 18 for windows; IBM, Armonk, NY, USA). Data were expressed as the mean±standard deviation. Demographic and transplant characteristics, and laboratory data were compared between the "normotensive" and "hypertensive" groups using a 2-tailed, unpaired Student's t-test for normally distributed data and a 2-tailed Mann-Whitney U test for data that were not normally distributed, or Fisher's exact test was used where appropriate.

Independent risk factors for hypertension after HSCT were determined using a binary logistic regression model. We included as covariates in the multivariate analysis any risk factors that were sig-

nificantly associated with hypertension in our univariate analyses: age, antecedent acute GVHD, treatment with amphotericin B, diagnosis of SOS, and changes in serum Cr from baseline to day 14, and

from baseline to day 21 after transplant. Changes in serum Cr level after HSCT were compared using the paired Student's t-test or a general linear model (GLM) repeated-measure analysis of variance

**Table 1.** Characteristics of transplant patients and comparison between normotensive and hypertensive transplant patients

	Total	Normotensive group	Hypertensive group	p
Number of patients	157	98	59	
Sex, n (%)				
Female	68 (43.3)	46 (46.9)	22 (37.3)	ns
Male	89 (56.7)	52 (53.1)	37 (62.7)	ns
Diagnosis at transplant, n (%)				
Malignancy	105 (66.9)	69 (70.4)	36 (61.0)	ns
Non-malignancy	52 (33.1)	29 (29.6)	23 (39.0)	ns
Age at transplant, years	9.1±5.1	9.9±5.0	7.6±5.1	<0.01
BMI (kg/m <sup>2</sup> )	19.1±4.7	19.3±4.8	19.3±4.5	ns
HLA compatibility, n (%)				
Mismatch	61 (38.9)	35 (35.7)	26 (44.1)	ns
Match*	96 (61.1)	63 (64.3)	33 (55.9)	ns
Cell source, n (%)				
Bone marrow	27 (17.2)	18 (18.4)	9 (15.2)	ns
Peripheral blood stem cell	129 (82.2)	80 (81.6)	49 (83.1)	ns
Cord blood	1 (0.6)	0 (0)	1 (1.7)	ns
Transplant preparative regimen, n (%)				
TBI based	39 (24.8)	22 (22.4)	17 (28.8)	ns
Non-TBI based	118 (75.2)	76 (77.6)	42 (71.2)	ns
Mean serum cyclosporine level (ng/mL)	266±61	271±62	258±60	ns
Acute GVHD, n (%)	59 (37.6)	29 (29.6)	30 (50.8)	<0.01
CMV infection, n (%)	41 (26.1)	22 (22.4)	19 (32.2)	ns
Amphotericin B treatment, n (%)	14 (8.9)	5 (5.1)	9 (15.3)	<0.05
SOS, n (%)	5 (3.2)	1 (1.0)	4 (6.8)	0.01
Hematuria <sup>†</sup> , n (%)	11 (7.0)	5 (5.1)	6 (10.2)	ns
Antihypertensive medication, n (%)	12 (7.6)	0 (0.0)	12 (20.3)	0.00
Hospital stay, day	35±22	31±19	40±25	<0.05
Death <sup>‡</sup> , n (%)	3 (1.9)	3 (3.1)	0 (0.0)	ns
Serum Cr level				
Day 0	0.30±0.14	0.32±0.13	0.26±0.13	<0.01
Day 7	0.31±0.15	0.33±0.14	0.27±0.15	<0.05
Day 14	0.36±0.18	0.36±0.15	0.35±0.22	ns
Day 21	0.39±0.17	0.39±0.16	0.39±0.19	ns
Day 28	0.40±0.17	0.41±0.17	0.38±0.17	ns
Change in serum Cr level				
Baseline to day 7	0.01±0.07	0.007±0.062	0.018±0.087	ns
Baseline to day 14	0.06±0.13	0.041±0.100	0.089±0.167	<0.05
Baseline to day 21	0.08±0.13	0.053±0.122	0.131±0.129	<0.01
Baseline to day 28	0.10±0.14	0.078±0.153	0.128±0.110	0.08

\*Indicates when HLA-A, B, C, and DRB1 alleles are entirely matched, <sup>†</sup>Is a clinical symptom caused by hemorrhagic cystitis after transplantation, <sup>‡</sup>Defines incidence of in-hospital mortality after transplantation. BMI: body mass index, HLA: human leukocyte antigen, TBI: total body irradiation, GVHD: graft-versus-host disease, CMV: cytomegalovirus, SOS: sinusoidal obstruction syndrome, Cr: creatinine

(ANOVA). A  $p < 0.05$  was considered statistically significant.

## Results

Table 1 shows the main pre-transplant and transplant characteristics of the study participants as well as comparisons between the normotensive group ( $n=98$ ) and the hypertensive group ( $n=59$ ). Of the 157 patients in the study group, 59 (38%) were diagnosed with early-onset hypertension. Thirty-two patients (54%) had systolic and diastolic, 8 (14%) had only systolic, and 19 (32%) had only diastolic hypertension. The incidences of hypertension at each time point were 11.2% on the day of transplant (day 0), 12.1% on day 7, 10.2% on day 14, 16.8% on day 21, and 25.9% on day 28. Thirty-five patients (22.3%) were hypertensive at more than two time points.

Management of hypertension was done with intermittent antihypertensive medications, such as hydralazine, nifedipine, nicardipine, or diuretics, according to the attending physicians' clinical decision making. Twelve patients (7.6%) required long-term antihypertensive medications, including captopril, enalapril, or atenolol as first-line therapy, after discharge. The hypertensive group had longer hospital stays compared with the normotensive group. There were 3 cases (1.9%) of in-hospital mortality after HSCT.

The hypertensive group had a significantly lower age at transplant compared to the normotensive group ( $7.6 \pm 5.1$  years vs.  $9.9 \pm 5.0$  years,  $p=0.006$ ). The hypertensive group also had significantly lower serum Cr levels on day 0 and day 7 than the normotensive group, but both groups had similar serum Cr levels on days 14, 21, and 28; in other words, the hypertensive group experienced a significantly greater increase in serum Cr levels by days 14, 21, and 28 from their baseline (day 0), than the normotensive group (Table 1). In all patients, serum Cr levels tended to increase after HSCT from baseline to the later time points ( $p=0.001$ ), and the increase in serum Cr level was significantly greater in the hypertensive group ( $p=0.012$ ), according to GLM ANOVA results.

After HSCT, acute GVHD developed in 59 patients (37.6%), cytomegalovirus infection requiring antiviral agents in 41 (26.1%), fungal infections requiring amphotericin B treatment in 14 (8.9%), and SOS in 5 (3.2%).

In univariate analysis, younger age at transplant, antecedent acute GVHD, treatment with amphotericin B, diagnosis of SOS, and a greater increase in serum Cr from baseline to 14 or 21 days after transplant were significantly associated with the development of early-onset hypertension (Table 1). In multivariate binary logistic regression analysis, only age at transplant and change in serum Cr level from baseline to 21 days after transplant were independent risk factors for the development of hypertension (Table 2). Despite the significant increases in Cr levels among some study participants,

**Table 2.** Results from multivariable logistic regression of risk factors for hypertension after hematopoietic stem cell transplantation

	<b>p</b>	<b>Odd ratio</b>	<b>95% CI</b>
Age at transplant	0.002	0.88	0.81–0.96
Acute GVHD	0.174	1.77	0.78–4.02
Amphotericin B treatment	0.102	3.56	0.78–16.35
SOS	0.304	3.51	0.32–38.61
Cr change (baseline–day 14)	0.584	2.81	0.07–113.70
Cr change (baseline–day 21)	0.002	919.07	12.39–68181.60

GVHD: graft-versus-host disease, SOS: sinusoidal obstruction syndrome, Cr: creatinine, CI: confidence interval

there were no patients in our study who developed clinical manifestation of acute renal injury that required special therapy.

Sex, underlying diagnosis, body mass index (BMI), HLA compatibility, cell source, conditioning regimen, mean serum cyclosporine level, cytomegalovirus infection, and hematuria associated with hemorrhagic cystitis were not significantly associated with the development of hypertension.

Acute GVHD occurred in 59 patients (38%). Patients with acute GVHD had significantly lower serum cyclosporine levels compared to patients who did not develop GVHD ( $250 \pm 67$  ng/mL vs.  $275 \pm 56$  ng/mL,  $p < 0.05$ ).

## Discussion

This is the first study to evaluate the incidence and risk factors for hypertension in HSCT recipients during the initial phase of transplant, from the time of transplant until engraftment.

Although the reported values differ according to ethnicity, the average prevalence of hypertension in children is 2–5%.<sup>14</sup> A recent study indicates that 5.4% of children have a blood pressure in the hypertensive range ( $\geq 95$ th percentile), while only 3.8% of children are eventually diagnosed with hypertension after repetitive testing.<sup>15</sup> Blood pressure tends to increase with age, thus, prevalence of hypertension is much greater in the adult population. Past studies on hypertension cases that were diagnosed after organ transplant have focused mostly on patients who received kidney, lung, or heart transplants because the function of these organs can directly affect blood pressure. Although reports vary, up to 47% of heart transplant recipients may have hypertension one year after transplant, and the incidence increases with longer follow-up.<sup>16</sup> With regard to kidney transplant, the incidence of hypertension usually plateaus at one year post-transplant at a prevalence of 27.6%.<sup>17</sup> For adult recipients of HSCT, the prevalence of hypertension at two years post-transplant is as high as 70%, with 61% of patients newly found to have hypertension within the first month after transplant.<sup>2</sup>

In our study, the prevalence of early onset hypertension after

HSCT was higher than expected. Nearly one third of patients (36%) fit the criteria for high blood pressure during the engraftment period and required various antihypertensive medications for blood-pressure control. For 12 of the patients (7.6%), hypertension could not be controlled with short-term antihypertensive measures; thus, they were administered oral antihypertensive agents for a lengthy period, beyond discharge from admitted care. Although stressful environmental conditions, such as being admitted to a hospital and anxiety about personal health problems, may influence the high prevalence of hypertension, the results of this study is note worthy to focus attention on the cardiovascular problems in patients after HSCT.

Factors such as patient gender, underlying diagnosis, BMI, HLA compatibility, cell source, conditioning regimen, and mean serum cyclosporine level were not associated with the increased risk of hypertension. Younger patient age at transplant, acute GVHD, amphotericin B treatment for fungal infection, SOS, and greater increase in serum Cr level during admission were associated with the early-onset hypertension in univariate analyses. Multivariate analysis showed that younger patient age at transplant and greater increase in serum Cr level from baseline to day 21 were independent risk factors.

Acute GVHD tends to occur within 100 days after HSCT, and is known to involve the skin, liver and GI tract, resulting in rash, hyperbilirubinemia, and diarrhea. Donor-derived T-cells are activated by recipient tissue minor histocompatibility antigens, resulting in cytokine dysregulation, and subsequent cell apoptosis and tissue injury. In a previous study, patients with acute GVHD were found to have a higher risk for hypertension, with the risk proportionate to the severity of acute GVHD.<sup>18)</sup> Patients with grades 0-I acute GVHD had 2-5 times higher risk for hypertension than recipients of an autologous transplant; for patients with grades II-IV acute GVHD, the risk increased to nine-fold.<sup>6)</sup> Medications used to control GVHD may cause hypertension.<sup>19)</sup> Steroids that are used as first-line treatment for GVHD are known to cause hypertension, which is often characterized by nighttime elevation of blood pressure.<sup>20,21)</sup> In our study, the incidence of hypertension was significantly higher in patients diagnosed with acute GVHD ( $p=0.002$ ).

Patients with hypertension experienced greater increases in serum Cr level, compared with normotensive patients, especially at 2-3 weeks post-transplantation from baseline. Although there were no patients showing clinical manifestation of acute renal injury, hypertension in these cases seems to be a result of acute subclinical renal injury. Possible causes of acute renal injury in these patients are multifactorial, including having SOS or having received previous administration of chemotherapy agents, TBI, antifungal or antiviral agents, aminoglycoside antibiotics, or immunosuppressants.<sup>22)</sup>

It is worth noting that the incidence of acute renal injury was simi-

lar among patients who received either conventional amphotericin B or the liposomal formulation. SOS stems from endothelial cell injury in the hepatic sinusoids, resulting in venous outflow obstruction, hepatic dysfunction, and portal hypertension. Renal insufficiency in this context is due to decreased renal perfusion. Fluid overload and subsequent weight gain also contribute to the development of hypertension. This study showed that antifungal treatment and SOS are associated with hypertension.

An important result of our study is that, the younger the patients were when receiving HSCT, the more likely they were to develop hypertension within one month of transplant, despite children typically having a lower incidence of both GVHD and pre-transplant hypertension than adults. Along with the finding of a greater increase in serum Cr levels after transplant in younger children with hypertension, these results underscore the possibility of greater susceptibility of younger children to kidney that, which may be related to the multiple contributing factors mentioned above. More careful surveillance for possible renal injury in younger children with HSCT should be a focus of clinicians dealing with these cases.

The association between the use of calcineurin inhibitors and hypertension is well known, including cyclosporine A-associated hypertension, which has been found to occur even in the absence of nephrotoxicity; blood pressure usually normalizes after withdrawal from these agents.<sup>23)</sup> In our study, patients with hypertension had a relatively low mean serum cyclosporine drug level during admission. A previous study showed that low serum cyclosporine A levels during the early post-transplant period were associated with increased incidence and severity of acute GVHD. In contrast, a 1 ng/mL increase in the serum drug level, five hours after administration of cyclosporine A, led to a decreased incidence of acute GVHD (hazard ratio=0.994, 95% CI: 0.989-0.999).<sup>24)</sup> Therefore, hypertension in our patients may have derived from acute GVHD, rather than the use of immunosuppressants.

The major limitation of our study was that blood pressure data were collected in each patient at intermittent time intervals, not during each day of the hospital stay, so it is possible that very short bouts of hypertension that occurred between these measurement points may not have been observed. However, this is not likely to have a major impact on our findings because the duration of significant hypertension would have most likely overlapped with any of the measurement points. Also, patients who remained in stable condition were discharged between 21 and 28 days after transplant, thereby resulting in possibly inaccurate analysis of the day 28 measurements and a weaker statistical power. Therefore the definition we used to identify the hypertensive group may be controversial, leading to another important limitation of this study. This study was done on patients during their admission to the hospital and



hypertension was defined as average systolic and/or diastolic blood pressure  $\geq$ 95th percentile for sex, age, and height, on at least three separate occasions.<sup>13)</sup>

Other factors, such as the "white coat" hypertension effect, post-transplant stress, or fever, may have influenced patients' blood pressure and lead to instances of transient hypertension, thereby increasing the prevalence of hypertension in our study population. A comparative study of hypertension with another cohort of patients admitted for different conditions and treatments may allow a gauge of these effects on hypertension. Despite these factors, which were not fully addressed in this study, the high prevalence of hypertension within our cohort remains a significant finding and, therefore, we believe that it is worthwhile to focus attention on the cardiovascular problems in patients after HSCT.

In conclusion, the prevalence of hypertension in the early post-transplant period was high, with a greater incidence found in younger children. The development of early-onset hypertension is associated with multiple factors: younger patient age at transplant, acute GVHD, amphotericin B treatment for fungal infection, SOS, and greater increase in serum Cr level during admission. In particular, the significant increase in serum Cr level, suggesting subclinical acute renal injury, was the most important independent risk factor for hypertension.

An important issue to bear in mind is that the incidence of hypertension tends to increase with longer follow-up from transplant.<sup>25)</sup> Management of chronic GVHD, an important long-term complication after HSCT, may cause GVHD-associated chronic kidney disease, while antecedent acute kidney injury and antifungal treatment may also portend chronic kidney disease.<sup>26)</sup> Hence, careful, long-term follow-up evaluations for possible chronic GVHD, renal function, blood pressure, and potential cardiovascular complications in these patients is mandatory. A long-term follow-up study is required to elucidate the effect of early onset post-transplant hypertension on chronic hypertension and long-term cardiovascular morbidities in these patients.

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The Institutional Review Board of the Seoul St. Mary's Hospital approved this study.

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