Clinical Pediatric Hematology-Oncology Volume 30 · Number 1 · April 2023 ORIGINAL ARTICLE

Acute Complications of Pediatric Allogeneic Hematopoietic Stem Cell Transplantation and Their Effects on Survival: A Single-Center Experience in Korea

Kyoung Min Lee[1,2], Won Ki Ahn[1,2], Jung Woo Han[1,2], Chuhl Joo Lyu[1,2] and Seung Min Hahn[1,2]

[1]*Division of Pediatric Hematology and Oncology, Department of Pediatrics, Yonsei University College of Medicine,*
[2]*Department of Pediatric Hemato-Oncology, Yonsei Cancer Center, Yonsei University Health System, Seoul, Korea*

Background: Acute complications within 100 days after allogeneic hematopoietic stem cell transplantation (HSCT) can increase immediate mortality as well as the risk of chronic complications and morbidity. A comprehensive review collecting systemic complications following transplantation would be important in pediatric patients.

Methods: We report a retrospective study of pediatric patients who underwent allogeneic HSCT during the 11 years (2009-2020), and their acute complications after transplantation within 100 days. A total 227 pediatric patients' (90 females, 137 males) data were collected.

Results: Among the patients, 62.6% (N=142) suffered from acute graft-versus-host disease, and 118 (52.0%) patients had an acute infection. Pulmonary complications occurred in 52 (22.9%) patients followed by hepatic sinusoidal obstruction syndrome in 30 (18.1%) patients. In the study, 19 died within the first 100 days after HSCT (8.4%), and the 5-year overall survival rate of the patients was 65.4%.

Conclusion: This study widens the understanding of acute toxicities of pediatric HSCT. A significant number of children still have experienced a variety of acute infectious or non-infectious complications after allogeneic HSCT that contribute to morbidity and mortality. Therefore, continuous efforts are needed to reduce them.

Key Words: Hematopoietic stem cell transplantation, Pediatric, Graft versus host disease, Infection

pISSN 2233-5250 / eISSN 2233-4580
https://doi.org/10.15264/cpho.2023.30.1.11
Clin Pediatr Hematol Oncol 2023;30:11~20

Received on October 19, 2022
Revised on January 5, 2023
Accepted on April 19, 2023

Corresponding Author:
Seung Min Hahn
Division of Pediatric Hematology and Oncology, Department of Pediatrics, Yonsei University College of Medicine, Yonsei University Health System,
50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-2050
Fax: +82-2-393-9118
E-mail: bluenile88@yuhs.ac
ORCID ID: orcid.org/0000-0001-9832-6380

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for many pediatric diseases, from several life-threatening malignancies to non-malignant disorders such as autoimmune diseases, primary immune deficiencies, and innate metabolism errors [1].

HSCT is an effective treatment for many diseases, and sometimes it is the only curative treatment. At the same time, HSCT can cause various complications that contribute to its relatively high morbidity and mortality rates [2,3].

Graft-versus-host disease (GVHD) is one of the most important complications and a leading cause of morbidity and non-relapse mortality after allogeneic HSCT. Among all allogeneic HSCT patients, 30-50% develop

acute GVHD (grade I-IV), and 14% experience severe acute GVHD (grade III-IV) [4]. The risk of infectious complications during the course of HSCT is high and also associated with morbidity and mortality [5]. According to previous studies, viral infections were the most common (67-70%), followed by bacterial sepsis (25%), and fungal infections (8%) [3,6]. Allogeneic HSCT can also provoke systemic complications such as idiopathic pulmonary syndrome, hepatic sinusoidal obstruction syndrome (SOS), cardiac failure, and kidney injury. For pediatric patients, transplant-related complications are important issues because of their huge potential for late sequelae and their effects on patients' life-long quality of life [7].

Transplantation is a complex process for patients with various underlying diseases and requires consideration of different donor and recipient factors, multiple conditioning regimens, and immunosuppressant methods. Thus, it is important to expect and monitor complications. Acute complications after HSCT are usually defined as those that occur within 100 days after the transplant [8,9]. In addition to the immediate threat of mortality, acute complications can increase the risk of chronic complications and morbidity.

Many reviews have considered various complications separately. Here, we review the incidence of acute complications in the first 100 days after pediatric allogeneic HSCT and their outcomes.

Subjects and Methods

1) Study subjects

This is a retrospective study of pediatric patients who underwent allogeneic HSCT in the department of pediatric hematology oncology, Severance Hospital, Yonsei University of Medicine, Seoul, Korea. From 2009 to 2020, we reviewed subjects who underwent their first transplantation; for patients who underwent second and third transplantations, we consider the first 100 days after only their first transplant.

Data were cut off on December 31, 2021, and all analyses were conducted using only archived data. This retrospective study was approved by the Institutional Review Board of Yonsei Health System, Severance Hospital (IRB-4-2022-1001).

Baseline patient-related variables (sex, age, primary disease), transplantation-related variables (donor, stem cell source, conditioning regimen), and complications in the first 100 days after HSCT (systemic complications, infections, GVHD) are summarized.

2) Variable definitions

Our definition and grading of acute GVHD follows the modified Glucksberg criteria [10-12]. Most grades of GVHD were based on retrospectively reviewed clinical data; few cases were histologically confirmed.

Viral reactivation/infection was defined as a positive antigenemia test or increased viral load. At our institution, blood and urine polymerase chain reaction (PCR) examinations for cytomegalovirus (CMV), Epstein-Barr virus (EBV), and BK virus (BKV) are part of routine patient surveillance. Titer elevation was considered to indicate reactivation. CMV reactivation after HSCT was defined as a detectable plasma virus load (ex. CMV DNA loads $>$500 IU/mL). Viral disease was diagnosed among patients with an increased viral load and evidence of end organ involvement [13]. Respiratory or diarrheal virus panels were done when a patient had related symptoms, and they were considered positive according to the results.

Bacterial sepsis was defined as the isolation of a bacterial agent in blood culture tests. The tests were done when a patient had fever or other signs of infection. Fungal infections were classified as proven, probable, and possible infections [14]. *Proven* indicates an invasive fungal disease proved by demonstration of fungal elements in diseased tissue for most conditions. *Probable* indicates the presence of host factor, clinical features, and mycological evidence, and *possible* indicates the presence of host factor and clinical features without mycological evidence.

The pulmonary complications were pneumonia, pleural effusion, bronchiolitis obliterans syndrome (BOS) or cryptogenic organizing pneumonia (COP), and acute respiratory failure [15]. Pneumonia was defined using respi-

ratory symptoms with meaningful radiologic findings. Pleural effusion was defined as an accumulation of extravascular fluid in the lung confirmed by radiologic findings with no evidence of definite pulmonary infection. BOS or COP was diagnosed by chest computed tomography, pulmonary function tests, and the exclusion of other pulmonary diseases. Respiratory failure was diagnosed when a patient needed mechanical ventilator support.

Among the cardiac complications, pericardial effusion and heart failure were defined through an echocardiographic evaluation. Hypertension and arrhythmia were defined by medical intervention after HSCT, with or without a cardiologist's consultation.

Hepatic SOS was diagnosed according to the pediatric European bone marrow transplantation model (more than 2 of the following: unexplained transfusion refractory or consumptive thrombocytopenia, weight gain >5 percent above baseline value, hepatomegaly, ascites, and rising bilirubin >2 mg/dL within 72 hr) [16].

Acute kidney injury (AKI) was defined according to the Kidney Disease: Improving Global Outcomes definition: increase in serum creatinine of >0.3 mg/dL from baseline within 48 hours, increase in serum creatinine to >1.5 times baseline from the prior seven days, or urine volume <0.5 mL/kg/hr for 6 hours [17].

3) Statistics

Continuous patient characteristic variables are reported as medians with interquartile ranges; categorical variables are reported as counts and percentages. The baseline characteristics of subjects with and without acute complications were compared using the chi square test or Fisher's exact test for categorical variables and independent t-testing for parametric variables. Univariate and multivariate binary logistic regression analyses were used to test the association between acute complications and clinical factors of transplantation such as sex, age, donor, stem cell source, and conditioning method.

The overall survival rates from the time of HSCT were estimated using the Kaplan-Meier method. All statistical analyses were performed using SPSS software version 26.0 (SPSS Inc., Chicago, IL, USA). In the analysis, a value of $P<0.05$ was considered statistically significant.

Results

1) Patient and stem cell characteristics

During the 11-year study period, 227 pediatric patients (90 females, 137 males) underwent allogeneic HSCT, as shown in Table 1. The underlying disease in 137 (60.4%) patients was leukemia, and 25 (11.0%) patients had solid tumors. Patients with non-malignant diseases (N=64, 28.2%) also received transplantation, mostly to treat severe aplastic anemia (N=27, 11.9%) and various other bone marrow failure syndromes, primary immune deficiency disorders, and rare neurometabolic disorders such as adrenoleukodystrophy. Most patients (72.7%, N=165) used peripheral blood as a stem cell source, and the others (27.3%, N=62) used bone marrow stem cells. None used cord blood stem cells. Unrelated donor transplantation (N=156, 68.7%) was performed more often than family donor transplantation (N=71, 31.3%). Full human leukocyte antigen (HLA)-matched transplantation was done in 67.4% of patients, and HLA mismatch HSCT was done in 69 patients (30.4%), with a few cases of haploidentical transplantation (N=5, 2.2%).

As the conditioning regimen, myeloablative conditioning was used in 168 (74.0%), and the others (N=59, 26.0%) received reduced intensity conditioning. Irradiation-containing conditioning regimens were used in 93 (41%) patients.

For the long-term outcomes, we evaluated chronic GVHD, disease relapse, and deaths during the follow-up period. During a median follow-up duration of 2.95 years (IQR, 1.01, 5.43), 59.9% patients had any form of chronic GVHD, 51 patients (22.5%) had disease relapse, and 74 (32.6%) patients died.

2) Acute complications in the first 100 days

Among the patients, 62.6% (N=142) suffered from acute GVHD (Table 2). Acute skin GVHD was observed in 53.3% (N=121), liver GVHD in 20.7% (N=47), and gastrointestinal GVHD in 15.4% (N=35) of cases. Stage I skin

Table 1. Demographic characteristics of all subjects

		All (N=227)	Acute complications (N=186)	No acute complications (N=41)	*P*-value
Sex	Male	137 (60.4)	113 (60.8)	24 (58.5)	0.793
Age at HSCT		9.71 (4.90, 14.53)	9.71 (4.94, 14.25)	8.16 (4.41, 15.26)	0.663
Diagnosis	ALL	79 (34.8)	66 (35.5)	13 (31.7)	0.060
	AML	49 (21.6)	38 (20.4)	11 (26.8)	
	Other leukemia	9 (4.0)	8 (4.3)	1 (2.4)	
	Lymphoma	16 (7.0)	16 (8.6)	0	
	Neuroblastoma, other solid tumor	10 (4.4)	10 (5.4)	0	
	Bone marrow failure syndrome, other bone marrow diseases**	35 (15.4)	29 (15.6)	6 (14.6)	
	Other***	29 (12.8)	19 (10.2)	10 (24.4)	
	Malignancy	163 (71.8)	138 (74.2)	25 (61.0)	0.089
	Non-malignancy	64 (28.2)	48 (25.8)	16 (39.0)	
Stem cell	Peripheral blood	165 (72.7)	139 (75.1)	26 (61.9)	0.082
	Bone marrow	62 (27.3)	46 (24.9)	16 (38.1)	
Donor	Family	71 (31.3)	49 (26.5)	22 (52.4)	0.001
	Unrelated	156 (68.7)	136 (73.5)	20 (47.6)	
HLA-match	Full match	153 (67.4)	121 (65.1)	32 (78.0)	0.246
	Mismatch	69 (30.4)	61 (33.0)	8 (19.0)	
	Haplo-match	5 (2.2)	4 (2.2)	1 (2.4)	
Conditioning	Myeloablative	168 (74.0)	137 (73.9)	31 (75.6)	0.796
	Reduced intensity	59 (26.0)	49 (26.3)	10 (24.4)	
	Irradiation	93 (41.0)	85 (45.9)	8 (19.0)	0.002
Follow-up (yr)		2.95 (1.01, 5.43)	2.74 (0.85, 5.47)	3.14 (2.04, 4.83)	0.223

**Severe aplastic anemia (N=27), Fanconi anemia (N=3), MDS (N=3), pure red cell aplasia (N=1), diamond-Blackfan anemia (N=1).
***Other: β thalassemia (N=5), hemophagocytic lymphohistiocytosis (N=5), adrenoleukodystrophy (N=4), severe combined immunodeficiency (N=2), chronic granulomatous disease (N=2), hyper IgM syndrome (N=2), pyruvate kinase deficiency (N=2), Krabbe disease (N=2), IL-10 receptor deficiency (N=1), GATA2 deficiency (N=1), Wiskott Aldrich syndrome (N=1), chronic active Epstein-Barr virus infection (N=1), mucopolysaccharidosis type 4 (N=1).
HSCT, hematopoietic stem cell transplantation; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HLA, human leukocyte antigen; GVHD, graft versus host disease.

Table 2. Acute graft-versus-host disease (GVHD) among subjects

Type	Stage	N (%)
Skin (N=121, 53.3)	1	66 (29.1)
	2	39 (17.2)
	3	13 (5.7)
	4	3 (1.3)
Gastrointestinal (N=35, 15.4)	1	17 (7.5)
	2	11 (4.9)
	3	6 (2.6)
	4	1 (0.4)
Liver (N=47, 20.7)	1	27 (11.9)
	2	8 (3.5)
	3	7 (3.1)
	4	5 (2.2)
Overall grade of acute GVHD (N=142, 62.6)	1	74 (32.6)
	2	32 (14.1)
	3	28 (12.3)
	4	8 (3.5)

GVHD was the most frequent GVHD symptom, affecting 66 (29.1%) patients. The next most common was stage II skin GVHD (N=39, 17.2%), followed by stage I hepatic GVHD (N=27, 11.9%). Stage IV skin, liver, and gastrointestinal GVHD occurred in 1.3%, 0.4%, and 2.2% of patients, respectively. Overall grade II-IV GVHD occurred in 68 patients (30.0%).

Within the first 100 days, 118 (52.0%) patients had an acute infection (Table 3). Viral reactivation or disease was the most common infectious complication (N=97, 42.7%), followed by bacterial sepsis (N=34, 15.0%), and fungal infections (N=13, 5.7%). Quantitative PCR confirmed CMV reactivation in 63 patients (27.8%), and CMV infection was treated in 44 patients (19.4%). CMV disease was in 10 patients (4.4%). BKV was detected in 44 (19.4%)

Table 3. Complications other than GVHD

Complication type	Details of the complications	N (%)
Infection		118 (52.0)
Viral		97 (42.7)
	CMV reactivation	63 (27.8)
	CMV disease	10 (4.4)
	EBV reactivation	2 (0.9)
	BKV reactivation	44 (19.4)
	BKV disease	27 (11.9)
	Other (rhinovirus, boca virus, influenza)	5 (2.2)
Bacterial sepsis		34 (15.0)
Fungal		13 (5.7)
	Possible	4 (1.85)
	Probable	7 (3.1)
	Proven	2 (0.9)
Pulmonary		52 (22.9)
	Pneumonia	21 (9.7)
	Pleural effusion	8 (3.5)
	Bronchiolitis obliterans or cryptogenic organic pneumonia	6 (2.2)
	Acute respiratory failure	20 (7.2)
Hepatic sinusoidal obstructive syndrome		30 (18.1)
	Mild	6 (2.6)
	Moderate	17 (10.6)
	Severe	3 (1.4)
	Very severe	4 (1.8)
Cardiologic		16 (5.8)
	Pericardial effusion	7 (2.5)
	Hypertension	4 (1.8)
	Heart failure	3 (1.3)
	Arrhythmia	2 (0.9)
Renal		27 (11.9)
	Acute kidney injury	25 (11.0)
	Thrombotic microangiopathy	1 (0.44)
	Renal tubular acidosis	1 (0.44)
Neurologic		9 (4.0)
Other (hyperglycemia, pancreatitis)		4 (1.76)
Engraftment failure		3 (1.1)

GVHD, graft versus host disease; CMV, cytomegalovirus; EBV, Epstein-Barr virus; BKV, BK virus.

subjects during the first 100 days after HSCT, and 27 (11.9%) of those patients required treatment. Most frequent pathogen was S. Epidermidis (N=11, 31.4%). E.faecium (N=6, 17.1%), K.pneumonia (N=6, 17.1%), E.coli (N=5, 14.3%), A. Baumani (N=5, 14.3%) were also detected. S. Mitis, S. Oralis, P. Aeruginosa, Sphingomonas paucimonilis were also detected. Some patients showed multiple pathogens. Two cases of proven fungal infections occurred, both bloodstream candidemia (*Candida parapsilosis*, *Candida krusei*). Seven cases (3.1%) were probable fungal infections, and four (1.85%) cases were possible fungal infections.

Pulmonary complications occurred in 52 (22.9%) patients, most of whom developed pneumonia (N=22, 9.7%), and 9 of which required oxygen support. Respiratory failure requiring ventilator support occurred in 20 patients (7.2%). Among them, 16 patients died, and 4 recovered. Hepatic SOS were found in 30 (18.1%), and 7 patients were included in the severe to very severe group. Cardiac complications were found in 16 (5.8%) patients, with pericardial effusion being the most common cardiac complication (7 patients). Renal complications were ob-

Table 4. Multivariable analysis of factors related to acute complications within 100 days after HSCT

	OR (95% CI)	*P*-value
Age	0.99 (0.994-1.00)	0.723
male (vs. female)	1.09 (0.50-2.35)	0.828
Underlying disease of malignancy (vs. non-malignant disease)	3.45 (1.31-9.11)	0.012
Bone marrow stem cell (vs. peripheral stem cell)	0.69 (0.28-1.67)	0.413
Unrelated donor (vs. family donor)	3.36 (1.40-8.03)	0.006
Irradiation (vs. no irradiation)	3.77 (1.51-9.38)	0.004
Reduced intensity conditioning (vs. MAC)	0.35 (0.12-1.02)	0.055

HSCT, hematopoietic stem cell transplantation; OR, odds ratio; CI, confidence interval; MAC, myeloablative conditioning.

served in 39 (14.1%) patients, mostly (N=27, 9.7%) AKI. Nine of 25 AKI patients (36.0%) needed dialysis. Nine (4.0%) patients had neurologic complications such as seizures (N=4), intracerebral hemorrhage (N=3), and encephalopathy or polyneuropathy.

Correlations between the acute complications were found in aGVHD with VOD, infectious complications with pulmonary complications, VOD with pulmonary, renal complications, and cardiac with renal complications.

Patients who had aGVHD were affected by the occurrence of VOD (OR 29.33, 3.47-242.62, *P*=0.002) or aGVHD contributed to the occurrence of VOD (OR 33.04, 3.5-309.85, *P*=0.002). Pulmonary complications contributed to infectious complications (OR 3.73, 1.71-8.15, *P*=0.001), while VOD contributed to the occurrence of pulmonary complications (OR 3.62, 1.33-9.83, *P*=0.009), and infectious complications also contributed to pulmonary complications (OR 3.98, 1.80-8.83, *P*=0.001). Renal complications were related with age (OR 1.17, 1.06-1.29, *P*=0.002), VOD (OR 6.44, 1.67-24.85, *P*=0.007), cardiac complications (OR 11.47, 2.76-47.69, *P*=0.001) in multivariate analysis.

3) Comparison of variables between patients with and without acute complications

Among all the patients, 186 patients (81.9%) suffered from early complications, and 41 (18.1%) were free of complications (Table 1). Among the variables, donor type (family or unrelated), and irradiation were statistically relevant to acute complications. In the multivariable analysis (Table 4), malignancy as the underlying disease, unrelated donor transplantation, and irradiation were

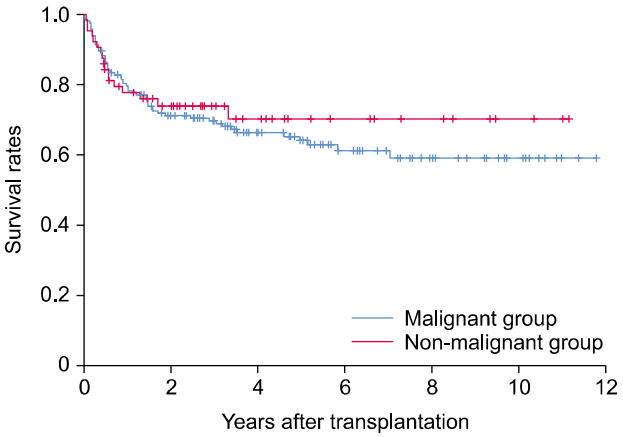

Fig. 1. Overall survival rate.

factors that contributed to acute complications after transplantation, with odds ratios of 3.45 (1.31-9.11), 3.36 (1.40-8.03), and 3.77 (1.51-9.38), respectively.

4) Deaths and the long-term survival rate

5-year survival of the malignant group was 64.1% ±4.0, and non-malignant group was 73.9%±5.7%. (Fig. 1). Among our patients, 19 died within the first 100 days after HSCT (8.4%) (Table 5, Fig. 2). The expired patients' median age at HSCT was 11.5 (IQR 5.7-16.1) years. Median number of days from HSCT to expiry was 59 (IQR 26.5-70.0). The most frequent cause of death was infection (N=9, 47%), followed by disease progression and GVHD, which each killed 4 (21.1%) patients. Two patients died of unknown causes after a sudden collapse within 48 hours after HSCT.

Table 5. Characteristics of patients who died within 100 days

Patient number	Age at HSCT	Sex	Underlying disease	Days after transplant	Cause of death
7	19.3	F	Aplastic anemia	66	CMV pneumonitis
8	2.3	F	Hemophagocytic syndrome	71	CMV colitis
16	10.5	F	Ewing's sarcoma	95	Pneumonia, pneumothorax, ARDS
19	10.3	F	AML	69	CMV pneumonitis
23	5.8	F	Malignant melanoma	44	Disease progression
26	4.9	M	Neuroblastoma	1	Shock, multiorgan failure (cause unknown)
39	16.2	M	Aplastic anemia	25	Fungal sepsis
52	13.9	M	ALL	51	Acute GVHD (skin)
59	11.5	M	Non-Hodgkin's lymphoma	59	Hemorrhagic cystitis, acute kidney injury, bacterial sepsis
60	16.1	M	ALL	11	Pneumonia, ARDS
79	0.82	F	ALL	95	Acute GVHD (hepatic, GI)
134	16.7	M	AML	54	Disease progression, liver failure
155	20.2	M	ALL	67	GVHD (liver, GI), hepatic SOS, bacterial sepsis
159	5.4	F	Burkitt leukemia	28	Disease progression
169	16.7	M	Burkitt lymphoma	91	Disease progression, CMV colitis
206	2.2	M	Neuroblastoma	69	Fungal sepsis
210	7.7	F	Aplastic anemia	15	Bacterial sepsis
213	16.0	M	ALL	2	Unknown origin of shock (r/o cardiogenic shock)
225	13.4	F	AML	99	Hepatic SOS

CMV, cytomegalovirus; ARDS, acute respiratory distress syndrome; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; GVHD, graft versus host disease; SOS, sinusoidal obstructive syndrome.

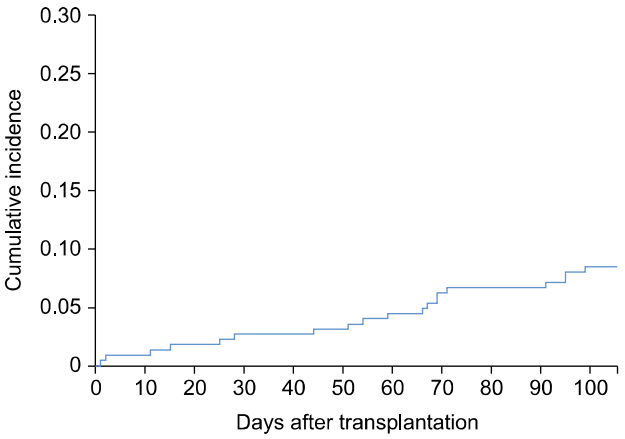

Fig. 2. Cumulative incidence of death within 100 days after transplantation.

Discussion

In this study, we have presented the incidence and profiles of acute complications (within 100 days) after pediatric HSCT. Although complications after HSCT are a well-known subject, this study has several novel findings.

Comparison with other studies is difficult due to the heterogeneity of patients and transplantation settings; however, we found trends similar to those previously reported in that acute GVHD and infectious complications were the most common problems during the acute phase after transplantation.

Acute GVHD is a common, well-known, and life-threatening complication, but data focusing on pediatrics are rarely reported. Compared with the report of MacMillan et al., which was a single-center experience of pediatric patients with GVHD, the overall incidence of grade 2-4 GVHD was not different in our population [18]. Among the 19 patients who died within 100 days of HSCT, only 3 patients were directly influenced by GVHD.

Infectious complications within 100 days can be divided into the pre-engraftment phase (first 2-4 wk after HSCT) and the early-post-engraftment phase (until 100 days after HSCT). CMV is the most frequent viral infection, with a CMV reactivation rate of 30-70% after allogeneic HSCT [19]. In Studer's study, the CMV reactivation rate was 30.7%, and CMV disease occurred in 8.5% of patients. In our study, the CMV reactivation rate

was 27.8%, similar to the previous study; however, CMV disease occurred in 4.4% of patients, small numbers compared to the previous report. It is suspected that the reason for the low incidence of CMV disease is due to the active preemptive treatment of CMV when re-activation occurs. 19.4% of patients used ganciclovir for treatment or preemptive purpose. However, there is also a possibility that fewer cases of CMV disease were counted in reality due to the limitations of retrospective studies.

In an Italian study, fungal infections (proven/probable) were reported in 6.7% of patients within 100 days after allo-HSCT [20]. In our study, only 5.7% of patients developed fungal infections (possible/probable/proven), and proven/probable infections occurred in only 4.0%, which is lower than in the previous study. That difference could have originated in the time difference or the difference between adults and children. The median age in the Italian study was 43 years. In a prospective study, *Candida* species were the leading pathogen causing fungal infections in the early pre-engraftment phase. In the whole period, *Aspergillus* species were more frequent than other fungal infections, including candidiasis [21]. In our study, only 2 proven fungal infections occurred, and both of them were candidiasis. The patients were diagnosed 7 and 59 days after HSCT, and they both died of their infections. Including the probable and possible fungal infections, 5 cases of aspergillosis, 5 of candidiasis, and 3 of unknown pathogens occurred.

Pneumonia or pneumonitis is the main pulmonary complication after HSCT, with several studies reporting acute infectious or noninfectious pulmonary infiltrates in up to 50% of patients [22] and acute pneumonitis in 5% within 100 days after HSCT [23]. In our study, the total pulmonary complication rate was 22.9% (N=52), which is similar to the rate in a previous study. Pneumonia (N=22) and acute respiratory failure (N=20) were the most common conditions. Most patients recovered, though severe pulmonary complications did cause the deaths of a few patients.

BOS is considered to be a pulmonary manifestation of chronic GVHD that usually develops more than 100 days after HSCT. However pulmonary function might start to decrease within 100 days, 5 (2.2%) patients in this study showed evidence of BOS within 100 days. We routinely do pulmonary function tests around 3 months after HSCT, which might explain our early detection of BOS.

In a review article, including adults, showed that the rate of total cardiac complications after HSCT is less than 10% [24]. In a previous study, arrhythmia (4-9%) was the most frequent acute cardiac complication within 100 days. Arrhythmia is usually detected within 10 days in about 5% of patients following HSCT [25]. In our study, only 2 cases of arrhythmia developed, and they happened at 29 and 19 days after HSCT. Pericardial effusion occurred in 2.5% (N=7) of our patients, similar to the 3% reported in a study of 391 adults, whose median time of onset was 270 days [26]. Life-threatening pleural effusion developed in only 1 patient. Hypertension was rare (1.8%) compared with a previous study that reported that 7.6% of patients required hypertension medication after transplantation [27].

The incidence of hepatic SOS in other studies is highly variable, ranging from 5% to 60%, depending on the setting of HSCT [28]. In our study, hepatic SOS was diagnosed in 13.2% (N=30) of patients, with 7 patients (3.2%) having severe to very severe cases. That was because we applied the drug defibrotide to some patients earlier than they fulfilled the diagnostic criteria. The incidence of SOS has become lower since 2013, when defibrotide was introduced.

AKI is a well-known complication after allo-HSCT, affecting 42-84% of pediatric transplant recipients within the first 100 days [29]. We detected lower rates of kidney complications than in previous reports. This inconsistency may be due to the racial differences. Kizilbash et al. reported that the incidence of AKI in Asian patients was lower than other races [30]. And serum creatinine level can fluctuate, so KDIGO grade 1 could detected lower. According to KDIGO AKI definition, grade 1 include 0.3 mg/dL elevation within 48 hours, or increase in serum creatinine by 1.5 fold above baseline which is known or presumed to have occured within 7 days. But, some patients don't have 48 hours results, and baseline

serum creatinine level can fluctuate, so some of KDIGO grade 1 cases could be excluded. Considering these reasons, we need further evaluation to find out the lower incidence of AKI.

Complications could be related to other complications. As mentioned in the results, in multivariate analysis, aGVHD and VOD occurrence is contributed to each other. Other complications had similar relationships. But we think that cardiac complications and infectious complications are not closely related. Further research is needed to figure out the mechanism, and prevention of provocation of one complication to others.

This study has outlined the various complications that occurred within 100 days after allogeneic HSCT. Many studies have focused on individual complications in detail, but few studies have collected systemic complications together following pediatric transplantation. By describing the total landscape of acute complications after HSCT, we were able to look into the factors that affect patients' final outcomes. Underlying malignancy, unrelated donor transplantation, and irradiation as conditioning increased toxicity in the patients.

This study has some limitations. First, this is a retrospective study, so subjective factors might have affected the results, especially when patients' signs and symptoms recorded in the archive were important. Second, most patients received full matched family donor or unrelated donor transplantation, with only a few cases of haploidentical transplantation. Because the number of haploidentical transplants being performed is increasing, the acute complications reported in this study might not reflect recent trends in HSCT complications. Moreover, this study considered only acute events. The long-term outcomes of the patients would be affected by other factors after our study period.

Despite those limitations, we were able to describe the incidence and types of acute toxicity and complications after pediatric allogeneic HSCT. This study widens the understanding of HSCT and could be used to make decisions about using HSCT as a treatment for pediatric patients. More well-designed retrospective and prospective studies investigating pediatric HSCT are needed to balance the complications and effectiveness of transplantation.

A significant number of children still have experienced a variety of acute infectious or non-infectious complications after allogeneic HSCT that contribute to morbidity and mortality. Therefore, continuous efforts are needed to reduce them.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

References

1. Kanate AS, Majhail NS, Savani BN, et al. Indications for hematopoietic cell transplantation and immune effector cell therapy: guidelines from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant 2020;26:1247-56.
2. Jardim TAP, Jardim BA, Breda GL, Bonfim C, Raboni SM. Mortality among pediatric hematopoietic stem cell transplantation patients: report from a single center in southern Brazil. Pediatr Transplant 2021;25:e13944.
3. Yamada M, Sakamoto K, Tomizawa D, et al. A prospective viral monitoring study after pediatric allogeneic hematopoietic stem cell transplantation for malignant and non-malignant diseases. Transplant Cell Ther 2021;27:872, e1-8.
4. Zeiser R, Blazar BR. Acute graft-versus-host disease - biologic process, prevention, and therapy. N Engl J Med 2017;377:2167-79.
5. Ardura MI. Overview of infections complicating pediatric hematopoietic cell transplantation. Infect Dis Clin North Am 2018;32:237-52.
6. Pinto TA, Jardim BA, Breda GL, Morales HMP, Bonfim C, Raboni SM. Infectious complications in pediatric allogeneic hematopoietic stem cell transplantation recipients-a retrospective clinical and epidemiological cohort study. Transpl Infect Dis 2020;22:e13369.
7. Diesch-Furlanetto T, Gabriel M, Zajac-Spychala O, Cattoni A, Hoeben BAW, Balduzzi A. Late effects after haematopoietic stem cell transplantation in ALL, long-term follow-up and transition: a step into adult life. Front Pediatr 2021;9:773895.
8. Carreras E, Dufour C, Mohty M, Kröger N. The EBMT handbook: hematopoietic stem cell transplantation and cellular therapies. 7th ed. Cham: Springer Open, 2019.
9. Wallhult E, Quinn B. Early and acute complications and the principles of HSCT nursing care. In: Kenyon M, Babic A, editors. The European blood and marrow transplantation textbook for nurses: under the auspices of EBMT. Cham: Springer Open, 2018;163-95.
10. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations

of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation 1974;18: 295-304.
11. Thomas ED, Storb R, Clift RA, et al. Bone-marrow transplantation (second of two parts). N Engl J Med 1975;292: 895-902.
12. Harris AC, Young R, Devine S, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant 2016;22:4-10.
13. Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. Clin Infect Dis 2017;64:87-91.
14. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis 2020;71:1367-76.
15. Haider S, Durairajan N, Soubani AO. Noninfectious pulmonary complications of haematopoietic stem cell transplantation. Eur Respir Rev 2020;29:190119.
16. Corbacioglu S, Carreras E, Ansari M, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in pediatric patients: a new classification from the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant 2018;53:138-45.
17. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120:c179-84.
18. MacMillan ML, Holtan SG, Rashidi A, DeFor TE, Blazar BR, Weisdorf DJ. Pediatric acute GVHD: clinical phenotype and response to upfront steroids. Bone Marrow Transplant 2020; 55:165-71.
19. Studer U, Khanna N, Leuzinger K, et al. Incidence of CMV replication and the role of letermovir primary/secondary prophylaxis in the early phase after allogeneic hematopoietic stem cell transplantation - a single centre study. Anticancer Res 2020;40:5909-17.
20. Girmenia C, Raiola AM, Piciocchi A, et al. Incidence and outcome of invasive fungal diseases after allogeneic stem cell transplantation: a prospective study of the Gruppo Italiano Trapianto Midollo Osseo (GITMO). Biol Blood Marrow Transplant 2014;20:872-80.
21. Sahin U, Toprak SK, Atilla PA, Atilla E, Demirer T. An overview of infectious complications after allogeneic hematopoietic stem cell transplantation. J Infect Chemother 2016; 22:505-14.
22. Gea-Banacloche J. Pulmonary infectious complications after hematopoietic stem cell transplantation: a practical guide to clinicians. Curr Opin Organ Transplant 2018;23:375-80.
23. Broglie L, Fretham C, Al-Seraihy A, et al. Pulmonary complications in pediatric and adolescent patients following allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2019;25:2024-30.
24. Ohmoto A, Fuji S. Cardiac complications associated with hematopoietic stem-cell transplantation. Bone Marrow Transplant 2021;56:2637-43.
25. Tonorezos ES, Stillwell EE, Calloway JJ, et al. Arrhythmias in the setting of hematopoietic cell transplants. Bone Marrow Transplant 2015;50:1212-6.
26. Liu YC, Chien SH, Fan NW, et al. Risk factors for pericardial effusion in adult patients receiving allogeneic haematopoietic stem cell transplantation. Br J Haematol 2015;169:737-45.
27. Kwon DH, Jung S, Lee EJ, et al. Incidence and risk factors for early-onset hypertension after allogeneic hematopoietic stem cell transplantation in children. Korean Circ J 2013;43: 804-10.
28. Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives-a position statement from the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 2015;50:781-9.
29. Matsuoka D, Hirabayashi K, Murase T, Saito S, Nakazawa Y. Impact of acute kidney injury on overall survival in children and young adults undergoing allogeneic hematopoietic stem cell transplantation. Pediatr Blood Cancer 2021;68:e29167.
30. Broglie L, Fretham C, Al-Seraihy A, et al. Pulmonary complications in pediatric and adolescent patients following allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2019;25:2024-30.