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Allogenic Hematopoietic Stem Cell Transplantation Is Feasible in Pediatric Patients with an Active or Recently Diagnosed Invasive Fungal Infection

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A B S T R A C T

Data on the outcome of allogenic hematopoietic stem cell transplantation (HSCT) in pediatric patients with a history of invasive fungal infection (IFI) are limited. The aim of this study was to report on the feasibility and outcome of allogenic HSCT in pediatric patients with an active or recently diagnosed IFI. In this retrospective, single-center study, 317 children underwent an allogenic HSCT (January 2012 to June 2020), of whom 23 had an active or recent (<6 months before transplantation) diagnosis of a probable or proven IFI before HSCT. Medical records were reviewed for data collection. Descriptive statistics were performed. One-year survival was described with Kaplan–Meier analysis. Four proven and 19 probable IFIs were diagnosed. The lungs were the main site of infection (22 out of 23 patients); brain involvement was diagnosed in six patients (26.1%). *Aspergillus* spp. were the most frequently identified organisms. Of the four patients diagnosed with mucormycosis, three had mixed infections with *Aspergillus* spp. One patient was diagnosed with *Alternaria* sinusitis and one patient with an infection with *Curvularia* spp. with both pulmonary and cutaneous involvement. One year after HSCT, 18 of the 23 patients (78.3%) were alive. Four of the five patients who did not survive died of non–IFI-related causes. One patient died due to a newly developed IFI post-transplant. Three patients showed non-fatal progression of their original IFIs that required prolonged antifungal treatment. Survival of this cohort of high-risk pediatric patients who underwent allogenic HSCT with an active or recently diagnosed IFI was favorable. An active IFI or recent history of IFI should not be a contraindication for proceeding to allogenic HSCT.

INTRODUCTION

Allogenic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for a variety of hematologic malignancies, as well as a range of nonmalignant disorders. The evolution of transplant management and progress made in supportive care, including the initiation of antimicrobial prophylaxis, have improved survival after allogenic HSCT over the last decades.

Despite these advances, infections still contribute significantly to the morbidity and mortality from this procedure. Among such infections, invasive fungal infections (IFIs) play an important role. Based on available literature, the incidence of IFIs post-transplant varies between 5% and 17%, with a mortality rate of 35% to 50% [1-6].

Among IFIs, recently diagnosed mold infections are considered to be a contraindication for transplantation, as these infections often relapse in the setting of immunosuppression. Data on the feasibility and outcome of allogenic HSCT in patients with a history of a mold infection are therefore limited. Zhang et al. [7] reported on 49 patients with a history of IFI who underwent autologous (n = 20) or allogenic (n = 29) HSCT. Twenty-five patients achieved complete response before HSCT; most of these patients received broad-spectrum antifungal agents as secondary prophylaxis and 24 patients still had residual disease before transplantation. After a median follow-up of 1 year, eight of the 24 patients with residual disease (33.3%) experienced progression or relapse of residual infection, as opposed to one of 24 patients with complete response before transplantation (4%). Fukuda et al. [8] reviewed the

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outcomes of 45 patients who had a known history of invasive aspergillosis (IA) before HSCT. Post-transplantation IA occurred in 13 of the 45 patients (29%). Compared with other patients who received allogenic HSCT during the same period, patients with a history of IA had significantly lower overall survival (56% vs. 77%) and higher transplant-related mortality (38% vs. 21%) 100 days after HSCT. Among patients with prior IA, post-transplantation IA occurred more frequently in patients who received less than 1 month of antifungal therapy before HSCT. Notably, the probability of post-transplantation IA and overall survival among patients who received more than 1 month of antifungal therapy and whose radiographic abnormalities were resolved were not different from those of patients without prior IA. Data from the Center for International Blood and Marrow Transplant Research showed that, among patients with a history of IFI (*Aspergillus* spp. and *Candida* spp. were the most commonly identified pathogens), the 1-year probability of post-HSCT IFI was significantly higher (24%) than for controls (17%). The median time from infection to transplant was approximately 3.5 months (range, <1-12) [9]. The only study that has reported on children exclusively showed no difference in the rate of IFI (7.7% vs. 7.1%) and mortality (34.6% vs. 27.8%) after HSCT among patients with (n = 26) or without (n = 126) prior IFI [10]. Not all children had complete resolution of their fungal disease, but all had evidence of improvement before transplant.

With the availability of more effective antifungal treatment, an increasing number of patients with previous IFIs are undergoing allogenic HSCT. The objective of this retrospective study was to report on the feasibility and outcome of allogenic HSCT in pediatric patients with an active or recently diagnosed mold infection. As most yeast infections are not considered to be chronic or persistent after treatment, recent invasive yeast infections were not included in our study.

METHODS

Patients and HSCT Treatment: General Characteristics

From January 2012 to June 2020, 317 allogenic HSCTs were performed in our unit; of these, 23 patients had an active IFI at the time of transplant or a recent (<6 months before transplantation) diagnosis of IFI. The diagnosis was documented according to European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) 2008 criteria [11]. The study was executed at the Wilhelmina Children's Hospital (January 2012 to May 2018) and at the Princess Máxima Center for Pediatric Oncology (May 2018 to June 2020) in Utrecht, The Netherlands. When the Princess Máxima Center for Pediatric Oncology opened in May 2018, the HSCT unit moved from the Wilhelmina Children's Hospital to this center.

Data collection was performed by using an electronic database (TRIASUS). Additional data on IFIs were obtained from the medical records of each patient individually. Data collection and processing were in accordance with Dutch law for patient confidentiality and the tenets of the Declaration of Helsinki. Patients received conditioning regimens according to standard protocols. For malignant indications, conditioning of fludarabine, clofarabine, and exposure-targeted busulfan (90 mg•h/L) was used. For patients with bone marrow failure, the treatment regimen was based on international European Working Group on Myelodysplastic Syndromes in Childhood protocols. For primary immunodeficiency and inborn errors of metabolism disorders, the conditioning was fludarabine and exposure-targeted busulfan (90 mg·h/L). For cases transplanted with an unrelated donor, serotherapy with antithymocyte globulin was added.

Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporin A and prednisolone after cord blood transplantation (CBT). Cyclosporin A was combined with methotrexate in patients receiving a bone marrow graft.

All CBT patients received 10 μg/kg granulocyte colony-stimulating factor (G-CSF; filgrastim) from day +7 after HSCT until neutrophils were >2000/μL.

For supportive care, patients received valaciclovir until engraftment for herpes simplex virus seropositive recipients and for 6 months for varicella zoster seropositive recipients. Neutrophil engraftment patients received *Pneumocystis jiroveci* pneumonia prophylaxis with cotrimoxazol thrice weekly until 1 month after cessation of ciclosporin, in general. Antibacterial prophylaxis was ensured by administration of ciprofloxacin from the start of the conditioning and continued until the time of neutrophil engraftment. Cefazolin was given as prophylaxis during mucositis.

Granulocyte transfusions (GTXs) are considered in our center when patients are neutropenic at the time of infection (bridge to transplant), if treatment of fungal infection is still incomplete (<6 weeks) at the time of HSCT, or to bridge a secondary post-HSCT period of neutropenia after graft failure in a patient at significant risk. The GTXs are preferentially given after day 0 to prevent the risk of HLA antibody development in the recipient to GTX donors prior to HSCT. Using a pool of at least three donors, acquaintances of the recipient, and preferably cytomegalovirus-negative recipients without major mismatches in blood group, GTX can be provided three times a week (each donor once a week). We proceed until there are significant signs of donor engraftment, usually 3 to 4 weeks after HSCT (a total of 9-12 GTXs).

Antifungal Prophylaxis and Diagnostic Strategies for Fungal Infections

Anti-yeast prophylaxis with fluconazole was given to low-risk HSCT patients and was upgraded to antifungal prophylaxis with liposomal amphotericin B (L-AmB) twice weekly or voriconazole for HSCT patients with a higher risk for IFIs. High-risk patients were defined as having prolonged aplasia due to chemotherapy, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and severe aplastic anemia. Predisposing factors such as severe GVHD, exposure to high-dose corticosteroids, and immunosuppressive agents contribute to an increased risk for IFI and therefore served as an indication for antifungal prophylaxis with L-AmB or voriconazole, as well.

Antifungal treatment was adapted to the suspected or isolated pathogen for patients with IFIs in the last 6 months preceding transplant as ongoing treatment or secondary prophylaxis. Secondary antifungal prophylaxis continued during HSCT until adequate immune recovery was observed (CD4 counts > 200/μL).

All patients were monitored for IFIs with a galactomannan test twice a week during neutropenia and weekly until CD3 recovery to >300 cells/μL. For cases of suspected IFI (ie, positive galactomannan, defined as >0.5 ng/mL in two consecutive blood samples, and/or clinical suspicion), high-resolution computed tomography (HRCT) scans of the thorax were made. HRCT sinus and brain scans were indicated in cases of suspected fungal lesions on imaging, as well as bronchoalveolar lavage. The bronchoalveolar lavage provided material for microbiological and molecular diagnostics and phenotypic and genotypic resistance determination profiles for azole agents.

Definitions and Data Analysis

Patients diagnosed with IFIs in the last 6 months prior to HSCT were included in this study. We considered patients as having active disease if they had begun antifungal therapy less than 6 weeks previously or if they had received prolonged antifungal treatment because of inadequate resolution of their fungal lesions on imaging. Secondary prophylaxis during ongoing immunosuppressive treatment was defined as prolonged antifungal treatment after at least 6 weeks of therapy and adequate improvement or complete resolution of lesions on imaging. IFI was defined using the revised definitions of the EORTC/MSG Consensus Group. Only patients with probable and proven IFIs were included in the study [11]. Invasive yeast infections were excluded. The date of the IFI was defined as the date on which the IFI diagnosis was made and antifungal treatment was started. Outcome was assessed as being alive, relapse, or death 1 year after allogenic HSCT. IFI-related mortality was determined based on the cause of death as stated in the patient's medical records.

For statistical analysis, SPSS Statistics 25 (IBM, Armonk, NY) was used. Descriptive statistics are reported as absolute frequencies and percentages, and quantitative data are reported as medians and ranges. One-year survival was described with the Kaplan–Meier method.

RESULTS

From January 2012 to June 2020, 317 children received allogenic HSCTs at our center; of these, 23 patients had an active IFI or a recent history of IFI. The included 23 patients had a median age of 12.7 years (range, 1.6-17.6). Most of them were treated with HSCT for de novo or relapsed ALL (n = 9) or AML (n = 7), and a small number of patients were transplanted for a variety of non-malignant indications (n = 7) (Table 1). The cohort consisted of 14 first transplants and seven second or third transplants (Table 2). All 23 children received an allogeneic stem cell transplantation with myeloablative conditioning. More than half received a CBT; the others, matched bone marrow.

Four proven and 19 probable IFIs were diagnosed in 14 boys and nine girls. The lungs were the main site of infection; brain involvement was diagnosed in six of the patients (26.1%). *Aspergillus* spp. were the most frequently identified organisms. Four patients were diagnosed with mucormycosis;

Table 1
Characteristics of 23 Patients with IFI Undergoing Allogenic HSCT

Characteristic			
Gender, *n* (%)			
	Male		14 (60.9)
	Female		9 (39.1)
Age at HSCT (yr), median (range)			12.7 (1.6-17.6)
Diagnosis, *n* (%)			
	Malignant		
		ALL	9 (39.1)
		AML	7 (30.4)
		Myelodysplastic syndrome	1 (4.4)
	Non-malignant		
		SAA	2 (8.7)
		Chronic granulomatous disease	1 (4.4)
		Combined immunodeficiency	1 (4.4)
		Common variable immune deficiency	1 (4.4)
		Hemophagocytic lymphohistiocytosis	1 (4.4)
Clinical condition, median (range)			
	Lansky/Karnofsky score		80 (40-100)
	HCT-CI		4 (1-7)
Invasive fungal infection, *n* (%)			
	Probable		19 (82.6)
	Proven		4 (17.4)
Fungal species, *n* (%)			
	Aspergillus spp.		17 (73.9)
	Alternaria spp.		1 (4.4)
	Mucor spp.		1 (4.4)
	Curvularia spp.		1 (4.4)
	Combination of *Aspergillus* and mucormycosis		3 (13)
Site of fungal infection, *n* (%)			
	Pulmonary		13 (56.5)
	Sinus		1 (4.4)
	Pulmonary/brain*		6 (26.1)
	Pulmonary/sinus*		1 (4.4)
	Pulmonary/skin		2 (8.7)
Evaluation treatment at start of conditioning, *n* (%)			
	Active antifungal treatment		9 (39.1)
	Secondary prophylaxis		14 (60.9)

SAA indicates severe aplastic anemia; HCT-CI, hematopoietic cell transplantation-specific comorbidity index.
* Imaging based.

three of these patients had mixed infections with *Aspergillus* spp. One patient was diagnosed with *Alternaria* sinusitis and one patient with an infection with *Curvularia* spp., with both pulmonary and cutaneous involvement.

Fourteen patients had a recent diagnosis of IFI and were still on secondary prophylaxis when they proceeded to allogenic HSCT. Most patients received secondary prophylaxis with L-AmB twice a week (2.5 mg/kg i.v.) or an azole agent (trough-concentration–controlled voriconazole being the most common). Nine other patients had active disease and still received treatment for their IFIs at the start of conditioning. For most of these patients, antifungal therapy consisted of combination treatment with L-AmB and voriconazole. Four of these nine patients also received donor GTXs to successfully prevent neutropenia post-transplant. The purpose of the GTXs was primarily to bridge the gap between marrow suppression and engraftment. One patient needed a surgical resection of the lung lesion approximately 2 months before transplantation, combined with antifungal therapy and GTXs. She was also treated with GTXs after the HSCT.

Table 2
Transplantation Characteristics of the Evaluable 23 Patients

Characteristic			
Number of HSCT procedures, *n* (%)*			
	1		17 (70.8)
	2		6 (25)
	3		1 (4.1)
Source of stem cells, *n* (%)†			
	Cord blood		13 (54.2)
	Bone marrow		
		Sibling	7 (30.4)
		Matched unrelated donor	4 (16.7)
Neutrophilic engraftment (d), median (range)			
	Cord blood		18 (7-29)
	Bone marrow		
		Sibling	18 (14-23)
		Matched unrelated donor	21 (19-21)
Weeks to CD3 recovery (>300 cells), median (range)			
	Cord blood		8 (4.7-61.6)
	Bone marrow		
		Sibling	7.2 (4.7-23.6)
		Matched unrelated donor	5 (5-5.43)
Grade of acute GVHD, *n* (%)			
	None		14 (60.9)
	1		2 (8.3)
	2		3 (13.0)
	3		4 (17.4)
	4		0 (0)

* Twenty-three patients underwent 24 HSCT procedures.
† In one HSCT procedure, there was a combination of a cord blood and haplo donor due to pulmonary aspergillosis.

Overall health status was suboptimal, as described in Table 1, with a median performance score of 80 (range, 40-100); seven patients had a score of <80. The median hematopoietic cell transplantation-specific comorbidity index (HCT-CI) was 4 (range, 1-7), clearly reflecting a group with significant comorbidities [12]. The engraftment cumulative incidence at day 60 after HSCT was 86%, with a median of 19 days (range, 7-29). Among the 23 transplants described as going in with prior IFIs, three went on to experience graft failure. Two of these three underwent re-transplantation, and one of them died of GVHD. The third was in too poor condition for re-transplantation and also died. Graft rejection was never preceded by a progression of IFI post- transplant.

Evidence of acute GVHD was observed in nine patients (39.1%) after allogeneic HSCT. Severe GVHD (grades 3 and 4) was observed in four patients (17.4%). Chronic GVHD (cGVHD) was diagnosed in three patients; one patient developed extensive cGVHD/severe cGVHD according to National Institutes of Health criteria [13].Only one of the 14 patients (7.1%) with a recent history of an IFI prior to transplantation but adequate improvement or complete resolution of fungal lesions developed an IFI post-transplant.

Four of the nine patients with active IFIs (44.4%) developed a new IFI post-transplant (n = 2) or experienced progression of their original IFIs (n = 2) (Table 3). All of these patients had a probable pulmonary aspergillosis. Severe GVHD was present in one patient with a newly diagnosed IFI post-transplant. Although the patient was, after discontinuation of treatment, on secondary prophylaxis with L-AmB throughout, it is likely that the ongoing necessity for immune suppression with steroids contributed to the breakthrough IFI. This patient

Table 3
Patients with Prior Recent IFIs Who Were Diagnosed with Post-Transplant IFIs

Primary Disease	Conditioning	Donor	Post-Transplant IFI	GTX	GVHD	Outcome
ALL	Bu/Flu + ATG	CBU	New IFI	–	–	Engrafted, died
PID	Treo/Flu + ATG	First CBU	–	–	–	Graft failure
		Second CBU	New IFI	+	Grade III	Engrafted, died
ALL	Bu/Flu/Clo + ATG	MUD	New IFI	–	Grade III	Alive
PID	Bu/Flu + ATG	CBU	Progression	–	Grade III	Alive
BMF	First Flu/Cy + ATG	First CBU	–	+	–	Graft failure
	Second Bu/Flu + alemtuzumab	Second CBU	–, after second SCT	+	–	Alive

Bu indicates busulfan; Flu, fludarabine; ATG, antithymocyte globulin; CBU, cord blood unit; PID, primary immunodeficiency; Treo, treosulfan; Clo, clofarabine; MUD, matched unrelated donor; BMF, bone marrow failure; Cy, cyclophosphamide.

ultimately died of the IFI. Of the 23 patients, six had been admitted to the pediatric intensive care during some point of their transplant admission (four ventilated). Three of the patients who required admission to the intensive care unit survived.

One year after HSCT, 18 of the 23 patients (78.3%) were alive. Five children had died. One patient died because of uncontrolled pulmonary aspergillosis in the context of GVHD post-transplant, as mentioned above. A second patient died due to his underlying malignant disease without evidence of an IFI. A third patient died because of graft failure 2 months after transplantation and was still using secondary prophylaxis for a probable pulmonary aspergillosis prior to transplantation. There were no signs of active IFI. A fourth patient died 4 months after transplantation because of severe GVHD without signs of active IFI. At the time of death he still used secondary prophylaxis because of probable pulmonary and cerebral aspergillosis prior to transplantation. A fifth patient died 2.5 months after transplantation due to septic shock with multiple organ failure in the context of end-stage renal disease, GVHD, and ongoing therapy for unresolved probable pulmonary aspergillosis (Table 4, Figure 1). One year after HSCT, six of the 18 survivors still received antifungal therapy, two as ongoing treatment for IFIs and four as antifungal prophylaxis as they still had inadequate immune recovery (CD4 counts $< 200/\mu$L).

DISCUSSION

With this study we aimed to assess outcomes of allogeneic HSCT in pediatric patients with an active or recent diagnosis of a probable or proven invasive fungal disease, as data on this subject are limited. In our study, all 23 included patients received secondary antifungal prophylaxis or were still on active antifungal treatment during transplant. Five patients showed progression of their IFI or developed a new IFI post-transplant. In agreement with Zhang et al. [7], children with active disease at the time of transplantation (4/9, 44.4%) were more at risk than children with adequate improvement or complete resolution of lesions before transplantation (1/14, 7.1%). Eighteen of 23 patients (78%) were alive 1 year after transplant. Five patients died, but only one patient died because of IFI.

These results demonstrate the relatively safety and favorable outcomes of allogenic HSCT in pediatric patients with a recent history of fungal infection and impaired health status (median HCT-CI, 4) using the strategies described. Although the cohort was too small to evaluate the significance of HCT-CI for survival, it should be noted that all five patients who died (one relapse, four transplant-related mortality) were in the HCT-CI ≥ 3 group.

As also mentioned in the study by Aftandilian et al. [10], the relatively favorable survival data are especially relevant for the group of patients with high-risk hematological malignancies, as these patients have a narrow window of opportunity to undergo transplant. In that study, in line with our findings, 26 patients had a history of IFIs before undergoing HSCT. Two of 26 patients with pretransplant fungal infection developed a probable post-transplant IFI and died. No patient had a proven fungal disease after transplant. However, their cohort of pretransplant fungal infections differed in that the presence of pretransplant fungal infections was mainly determined based on imaging findings without microbiological confirmation. As a consequence, it was not possible to classify pretransplant fungal infections (possible, probable, or proven) or determine whether a subsequent fungal infection was due to recurrence of the same organism or a new infection. As mentioned earlier, our cohort classified IFI before and after transplantation, and we studied only proven and probable IFI cases [11]. In the study by Aftandilian et al. [10], all pretransplant fungal infections showed evidence of improvement prior to stem cell transplantation. This was not the case in our study, as nine patients still had ongoing treatment for their IFIs.

The IFI-related mortality and development of post-transplant IFIs in our study are relatively low in comparison with other studies [7,8] analyzing the outcomes of allogenic HSCT with a history of fungal disease. However, these studies were based on adult populations and were studied in another time frame. Today, there is a broader spectrum of antifungal agents available for prophylaxis and therapy, which has subsequently improved outcomes. In addition, GTXs reduce the neutropenic period after a stem cell transplantation and may prevent further progression of existing invasive fungal infections. In our study, four out of nine patients received GTXs with their antifungal agents from the start of conditioning until suspected engraftment. It is clearly feasible in this population to prevent post-transplant neutropenia with this procedure, but, because of the small numbers, it is not possible to draw conclusions

Table 4
One-Year Outcome of the Evaluable 23 Patients

Outcome		*n* (%)
One-year follow-up		
	Alive and disease free	16 (69.6)
	Relapse underlying disease	2 (8.7)
	Death	5 (21.7)
Cause of death		
	Underlying disease	1 (20)
	Graft failure	1 (20)
	GVHD	1 (20)
	IFI	1 (20)
	Septic shock	1 (20)

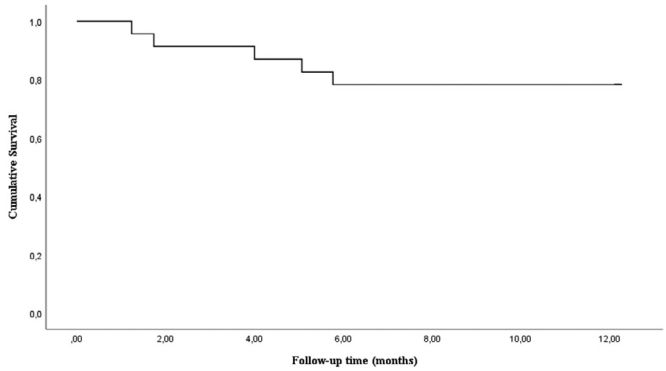

Figure 1. One-year survival curve for 23 patients with IFIs who underwent allogenic HSCT.

about the relative contribution of GTXs to survival after transplant when IFIs are involved. It may be noted that graft failure was 13% in our cohort. As our general population has graft failure rate of 5% to 7%, we cannot rule out that recent IFIs can make patients somehow more susceptible to graft failure.

With respect to diagnostics, improved early detection of IFIs and more accurate follow-up of active lesions after transplantation are needed, as radiological imaging is typically nonspecific in pediatrics. Furthermore, no recommendations are available for the diagnosis and management of invasive aspergillosis in pediatric patients in relation to molecular amplification tests such as PCR.

In conclusion, we found that most patients with active or recent invasive fungal diseases went through their stem cell transplantation without a major risk of developing IFIs after transplant or increased mortality. Therefore, a recent history of IFI should not be a contraindication for allogenic HSCT.

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