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Hematopoietic Stem Cell Transplantation in Patients With Active Fungal Infection: Not a Contraindication for Transplantation

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ABSTRACT

Increasing use of more aggressive treatment approaches in patients with hematologic malignancies leads to an increased frequency of invasive fungal infections, which is a major cause of transplant-related mortality in hematopoietic stem cell recipients. In this respect, the presence of an active fungal infection prior to transplantation may hinder subsequent hematopoietic stem cell transplantation (HSCT); which sometimes is the only curative treatment. We report here the results of 13 consecutive patients transplanted with active fungal infection. Thirteen patients (7 males and 6 females) with a median age of 34 years (range, 16–53 years) underwent 15 HSCT between September 2003 and April 2007. In this group of 15 patients, consisting of hematologic malignancies with high risk of relapse or severe aplastic anemia, 11 (73%) transplants performed in subjects with active invasive fungal infection (IFI) patients survived 30 days after transplantation. Three patients (1 patient with primary disease relapse, 1 patient with graft versus host disease [GVHD] complicated with fungal pneumonia, and 1 patient with severe sinusoidal obstruction syndrome and GVHD complicated with aspiration pneumonia) died on days +66, +74, and +62 posttransplantation, respectively, within the first 100 days of HSCT. After a median follow-up time of 306 days (range, 145–680 days), four of 13 (31%) patients with active IFI were alive and disease free. Among a population of HSCT recipients with a dismal prognosis without transplantation, performing the procedure despite active IFI saved a considerable proportion of the patients. The presence of active IFI did not seem to be an absolute contraindication for HSCT, particularly among high-risk patients in whom a treatment delay could be fatal.

INVASIVE FUNGAL INFECTIONS (IFI) remain the leading cause of infectious mortality among patients with hematologic malignancies. Despite major advances in antifungal therapy, a previous IFI in a stem cell transplant candidate might lead to exclusion of the patient from the transplant program due to high risk of reactivation and transplant-related mortality.[1] In a previous analysis of 75 centers registered in the EORTC Fungal Group and EBMT, 85%, 24%, and 39% of the centers reported rejecting cases with prior cerebral, sinus, and pulmonary fungal infections, respectively.[2] Excluding these patients from hematopoietic stem cell transplant (HSCT) programs might preclude the only curative treatment modality. In fact, in some recent reports allogeneic stem cell transplantation has been suggested to be a feasible task in patients with prior invasive fungal infections.[3–7] Identifying the risk factors that increase transplant related mortality and fungal reactivation or progression might facilitate a transplant decision in a patient with IFI.

Age over 40 years, advanced hematologic malignancies, allogeneic HSCT, T-cell depletion, umblical cord as the stem cell source, HLA-mismatched transplants, corticosteroid treatment, fludarabine-based conditioning regimens, prolonged neutropenia, graft versus host disease (GVHD), cytomegalovirus infection (CMV), and respiratory viral infections have been previously defined as risk factors for

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reactivation of previous IFI in hematopoietic stem cell transplant recipients.[8,9] HSCT with an active IFI places the patient at a higher risk for transplant-related mortality. However, HSCT without delay is the only curative treatment approach in some patients. This report described is the retrospective analysis of 13 consecutive patients undergoing transplantation with active IFI. Thirteen patients underwent 15 HSCT with active IFI using therapeutic doses of various antifungal agents.

PATIENTS AND METHODS

One hundred twenty patients and 133 transplants (72 allogeneic, 51 autologous, and 5 tandem autologous/allogeneic) performed between September 2003 and April 2007 were analyzed retrospectively. Among these 133 transplants, 13 patients with active IFI underwent 15 HSCT with therapeutic doses of antifungal agents. All patients were hospitalized in single-bed rooms with high efficiency particulate air filters during transplantation. Patients with aplastic anemia were placed in single rooms with laminar air flow. All patients had Hickman catheters. All patients except two were CMV seropositive. Surveillance bacterial cultures and standard chest radiographs were obtained during admission to the transplantation unit and chest X-rays were obtained once weekly thereafter. Baseline high-resolution computerized tomography (HRCT) examinations were performed for patients with persistent IFI before HSCT and during neutropenic fever episodes whenever necessary. Galactomannan enzyme immune assay (EIA) and aspergillus PCR analysis were obtained in the presence of neutropenia and twice weekly with episodes of neutropenic fever. Patients received prophylactic trimethoprim 160 mg/ sulphomethoxazole 800 mg until day −2 of transplantation and three times a week after neutrophil engraftment. Prophylaxis for herpes simplex virus consisted of acyclovir (800 mg BID) Graft versus host disease prophylaxis consisted of cyclosporine (5 mg/kg per day in two divided doses) from day −1 and methotrexate on day +1, +3, +6, and +11. Neutropenic fever episodes were treated with broad - spectrum antibiotics according to published guidelines.[10] Additional blood, urine and sputum cultures, cultures from infected sites, bronchoscopic examinations, HRCT and paranasal CT scans were also performed as clinically indicated. IFI was defined (proven, probable, and possible) according to international consensus reported by Ascioglu et al.[11]

Patients With Active IFI

Thirteen patients (7 males and 6 females) with a median age of 34 years (range, 16–53 years) underwent 15 HSCT (13 allogeneic and 2 autologous transplants) with active IFI. Characteristics of the patients with active IFI are summarized in Table 1. Underlying hematologic diseases included acute myeloid leukemia (AML) in five patients, acute lymphoblastic leukemia in three, NK/T cell lymphoma in one, Hodgkin's disease in one, AML transformed from myelodysplastic syndrome in one, and severe aplastic anemia in two patients. Hematologic disease status prior to transplantation showed complete remission in six transplants, refractory or relapsed in six transplants, and severe aplastic anemia in three transplants. In 9 of 15 transplants the underlying hematologic disease was in an advanced states. Patient 3, with fungal pneumonia complicating severe aplastic anemia, (Fig 1) was transplanted twice; the second time for engraftment failure that was reported as patient 4. Patient 12 with Hodgkin's disease underwent tandem autologous/allogeneic SCT, and the allogeneic part of her transplantation is noted as patient 13. Patient 11 with AML, who remained in remission after his first transplant and had acquired IFI (fungal sinusitis) (Fig 2) during engraftment failure while neutropenic at 8 months after his first HSCT, received his second allogeneic HSCT with active IFI. Myeloablative conditioning regimens were administered to 9 of 15 transplants (Table 1) Twelve of 15 transplant recipients received granulocyte-macrophage colony stimulating factor (G-CSF) mobilized (10 μg/kg per day) unmanipulated peripheral blood stem cells from HLA-matched sibling donors with a median of 4.1×10^6/kg CD34$^+$ cells infused (range, $1.03–8.2 \times 10^6$/kg). Patient 8 received G-CSF mobilized (10 μg/kg per day) unmanipulated peripheral blood stem cells from a matched unrelated donor, and 5.16×10^6/kg CD34$^+$ cells were infused. Patient 7, with heavily pretreated refractory relapsed NK/T cell nasal type lymphoma, underwent autologous SCT with stem cells harvested from bone marrow.

In 10 of 15 transplant courses, therapeutic doses of liposomal amphotericin B (AmB) were used for treatment. In the remaining four transplant courses, the patients were receiving a combination of liposomal AmB with caspofungin or voriconazole. In one of the transplants, antifungal treatment was a voriconazole and caspofungin combination. Invasive fungal infection prior to SCT was demonstrated in 10 transplants, probable in one, and possible in four transplants. Clinical presentation was pneumonia in four patients, pneumonia plus sinusitis in six patients, pneumonia plus cerebral abscess in one patient (Fig 3), and disseminated candidiasis in two patients (Fig 4). Microbiologic isolates were *Aspergillus* spp. in seven patients (from sinus biopsy and bronchoscopic biopsy), *Candida albicans* in three patients two from blood culture and the other from nasopharyngeal soft tissue), and *Candida sake* in one patient from or sinus biopsy. In eight patients G-CSF (5 mcg/kg per day) was used after transplantation until neutrophil engraftment. In five patients, granulocyte transfusions were also given until neutrophil engraftment. Antifungal therapy was continued for up to 3 months posttransplantation according to the follow up HRCT or paranasal CT findings.

Granulocyte Transfusions

Granulocytes were collected from ABO-compatible volunteer donors after stimulation with G-CSF 5 μg/kg and 8 mg of dexamethasone. Granulocytes were irradiated prior to and infused within 2 to 4 hours. Written informed consent were obtained from all the donors. In five patients granulocyte transfusions were given every other day with a median granulocyte dose of 2.72×10^{11}/kg (range, $0.9–8.62 \times 10^{11}$/kg) for a median of 6.5 days (range, 3–10 days).

RESULTS

Thirteen patients with active fungal infection underwent 15 HSCT courses with full therapeutic doses of antifungal treatment. In 11 of 15 transplants, patients were also receiving broad-spectrum antibiotics in addition to antifungal treatment during conditioning. In five transplants, surgical resection was performed for invasive fungal sinusitis in addition to antifungal therapy. Seven patients received G-CSF posttransplantation and five of these patients also received additional granulocyte transfusion with a median dose of 2.72×10^{11}/kg (range, $0.9–8.62 \times 10^{11}$/kg) for a median of 6.5 days (range, 3–10 days). Neutrophil engraftment occurred at a median of 21 days (range, 13–28 days) in 12 of 15 transplants. In a high-risk patient population with

Table 1. Patients With Active Fungal Infection at the Time of Transplantation

No.	Age/Sex	Diagnosis	Disease Status	Type of TX	Conditioning Regimen	Pre-tx IFT Status	Clinical Presentation	Pre-tx IFI Etiology	GM/Asp Ag	Duration of Neutropenia (days)	OS/Cause of Death	Granulocyte Transfusion	Post-tx G-CSF
1	39/F	AML-M4	Relapse	Allo	Bu/Cy	Possible	Pneumonia	—	−/−	45	66/relapse	No	No
2	37/M	ALL	Relapse	Allo	Bu/Cy	Proven	Sinusitis/Pneumonia	*Aspergillus* spp	−/−	27	7/infection	No	No
3	26/M	SAA	—	Allo	Cy	Proven	Pneumonia	*Aspergillus* spp	−/−	31	680/alive	Yes	No
4	26/M	SAA	—	Allo	Bu/Flu/ATG	Proven	Pneumonia	*Aspergillus* spp	+/−	92	527/alive	Yes	Yes/17 days
5	16/F	SAA	—	Allo	Cy/ATG	Probable	Pneumonia/NF soft issue/cerebral	*C. albicans*	−/−	21	11/infection	Yes	Yes/2 days
6	39/M	AML-M1	CR1	Allo	Bu/Cy	Proven/ sinusitis	Sinusitis/Pneumonia	*Candida* sake	−/−	25	306/alive	No	Yes/21 days
7	27/M	T-ALL	CR2	Allo	Bu/Cy/ Thiotepa	Possible	Pneumonia/sinusitis	—	+/+	29	170/infection	Yes	Yes/16 days
8	34/M	NK/T cell lymphoma	Refractory relapse	Auto	BEAM	Proven/ sinusitis	Sinusitis/Pneumonia	*Aspergillus* spp	−/−	25	25/infection	No	Yes/22 days
9	30/M	T-ALL	Refractory relapse	MUD	Busulfex/ Cy	Proven/ sinusitis	Sinusitis/Pneumonia	*Aspergillus* spp	−/+	10	13/infection	Yes	No
10*	38/F	AML-M1	Remission with salvage	Allo	Flu/TBI	Proven/ sinusitis	Larynx/Pneumonia	*Aspergillus* spp	−/−	10	74/gvhd + infection	No	No
11†	53/M	AML-M6	CR1	Allo	Flu/TBI	Proven/ sinusitis	Sinusitis + pneumonia	*Aspergillus* spp	−/−	26	283/alive	Yes	Yes/13 days
12	28/F	HD	Primary refractory	Auto	BEAM	Proven	Hepatosplenic candidiasis	*C. albicans*	−/−	12	162/relapse	No	No
13	28/F	HD	Primary refractory	Allo	Bu/Cy/Flu	Proven	Hepatosplenic candidiasis + Pneumonia	*C. albicans*	+/−	18	162/relapse	No	No
14‡	52/F	AML-M0	Remission with salvage	Allo	Busulfex/ Cy	Possible	Pneumonia	—	+/+	27	62/gvhd + asp. pneumonia	No	Yes/17 days
15	25/F	MDS/AML	CR1	Allo	Bu/Cy	Possible	Disseminated candidiasis	—	−/−	30	145/alive	No	No

Abbreviations: Bu, busulphan; Cy, cyclophosphamide; Flu, fludarabine; TBI, total body irradiation; ATG, antithymocyte globuline; BEAM regimen, BCNU 300 mg/m^2, etoposide; 200 mg/m^2, cytarabine 100 mg/m^2, melphalan 140 mg/m^2; MUD, matched unrelated donor; GM, galactomannan; Asp, aspergillus antigen; NF, nazopharynx.

*Failed remission induction therapy and achieved hematologic remission after salvage therapy with FLAG-Ida regimen.

†Retransplanted due to engraftman failure during cyclosporine A taper on day + 245.

‡Failed remission induction therapy and achieved hematologic remission after salvage therapy with FLAG-Ida regimen combined with anti-CD33 monoclonal antibody treatment.

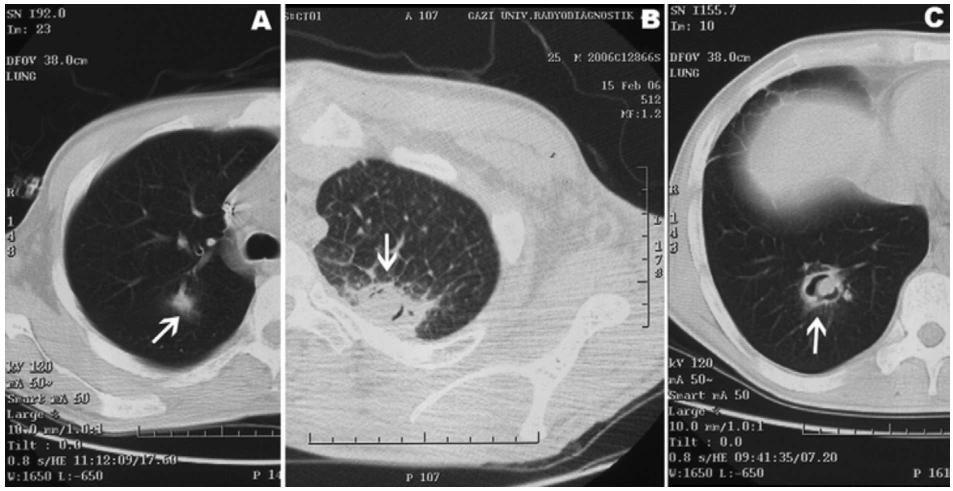

Fig 1. **A** Nodule with halo sign in posterior segment of right upper lobe. **B** Nodule with irregular margins, halo sign and, minimal central necrosis in left upper lobe. **C** Nodule with air crescent sign.

respect to both primary hematologic disease and persistent IFI, we were able to discharge 11 of 15 transplants (73%) from the BMT Unit without clinical signs of IFI or other infections. Four of 15 transplants (26.6%) (patients 2, 5, 8, and 9) died early after transplantation on days +7, +11, +25, and +13, respectively. The cause of death in these four patients was progressive fungal infection. Two of these four patients underwent mechanical ventilation due to respiratory failure secondary to bacterial infection. However, it was not possible to exclude the role of progression of the underlying fungal infection. Contributing causes of death were multi-organ failure in patient 8 and sinusoidal obstruction syndrome in patient 9. Three more patients died between days + 30 and 100 after discharge from the BMT unit. While patient 1 died of a relapse of leukemia on day +66, patients 10 and 14 developed gastrointestinal system GVHD complicated by the reactivation of fungal pneumonia and died on days +74 and +62, respectively. On day +100 posttransplantation 6 of 13 patients (40%) were alive. In the analysis of the data with regard to disease status prior to transplantation, 4 of 6 transplants (66.6%) who were in complete remission prior to transplantation were alive on day +100. However 3 of 9 HSCT (33.3%) with advanced hematologic disease (3 transplants for severe aplastic anemia and 6 for advanced hematological malignancies) survived the first 100 days. Currently, with a median follow-up of 306 days (range, 145–680 days), 4 of 15 HSCT (3 of 6 patients who were in complete remission and 1 of 9 HSCTs with advanced hematologic disease) remain alive and free of disease. Nine patients died after transplantation. Two of these nine deaths were relapse related. Nonrelapse mortality was 59% (7 of 13 patients). All of these transplant-related deaths were infection related. It should be mentioned that late infectious mortality was associated with GVHD. The first-100-day mortality was 40% (6 of 15 transplants; 6 of 13 patients) During the same period, 118 transplants were performed among a cohort of 107 patients without any previous history of IFI. IFI-related death occurred in 3 of those 118 (2.54%) transplants (Table 2). Day +100 fungal infection-related mortality rate was 40% in HSCT with active IFI and 2.54% for HSCT without a history of fungal infection prior to transplantation.

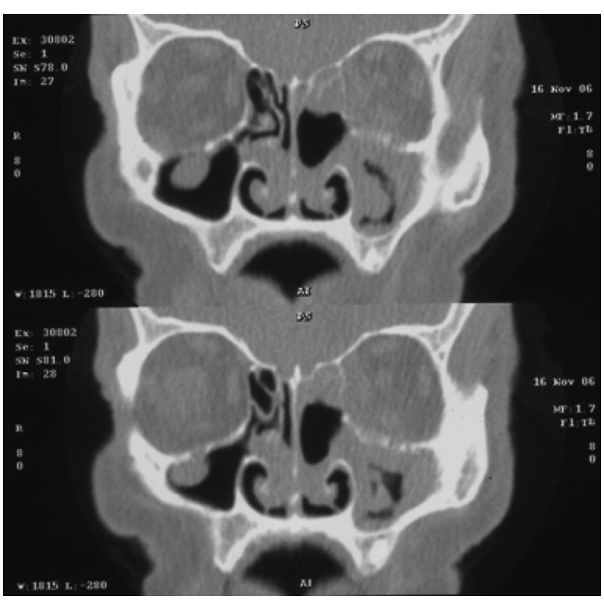

Fig 2. Paranasal sinus CT in coronal plain; diffuse soft tissue obliterating left maxillar sinus aeration and bone erosion at inferior orbital wall.

DISCUSSION

Invasive fungal infections are the leading cause of infectious mortality among patients with hematologic malignancies receiving chemotherapy and undergoing HSCT. Since IFI has the potential for reactivation during successive chemotherapy courses, patients with IFI have previously been excluded from transplant programs due to a high risk of transplant-related mortality.[12] However, in recent years the feasibility of HSCT among patients with prior fungal infec-

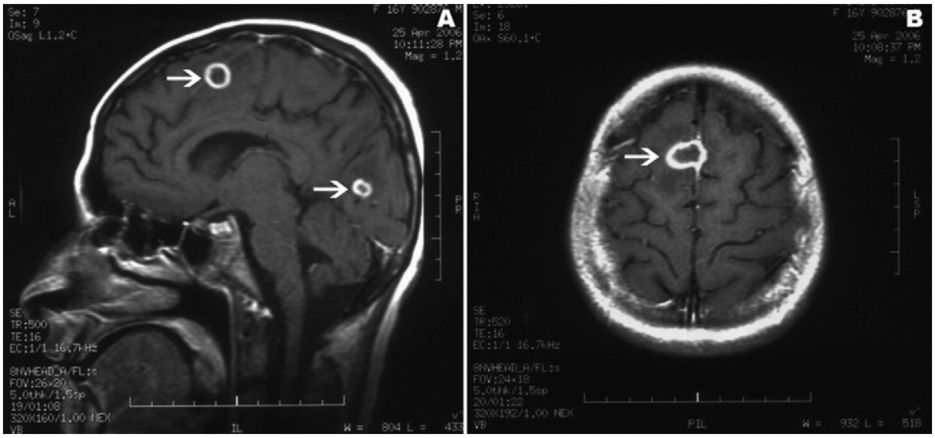

Fig 3. **A** T1 weighted contrast enhanced sagittal MRI. Right frontal lobe and occipital lobe lesions showed ring enhancement and accompanying edema halo. **B** T1 weighted contrast enhanced axial MRI of right frontal lobe.

tion has been reported using amphotericin B treatment.[3–7] These reports assessed a small cohort of patients with active fungal infection showing higher mortality rates early after transplantation.[6,13] The presence of proven fungal infection prior to transplantation has been reported to be associated with higher mortality rates when compared to probable or possible fungal infection.[5] Similarly, in our cohort, the mortality rate was higher in patients with proven IFI compared to possible or probable IFI namely, 40% vs 25%, respectively.

In this report, we have presented 15 HSCT courses in 13 patients with active IFI under full antifungal treatment. Seven of 15 HSCTs (46.6%) with active IFI survived +100 days posttransplantation. Transplant-related mortality on day +100 was 40% among patients with active IFI. One patient (patient 12) survived the first 100 days of the autologous part of the autologous/allogeneic tandem HSCT but died in the first 100 days after the allogeneic stem cell transplantation. Posttransplant fungal infection was the cause of death on day +100 in 6 of 15 HSCTs (40%), though there were other contributing factors. Patient 1, with active IFI, died of progressive hematologic disease.

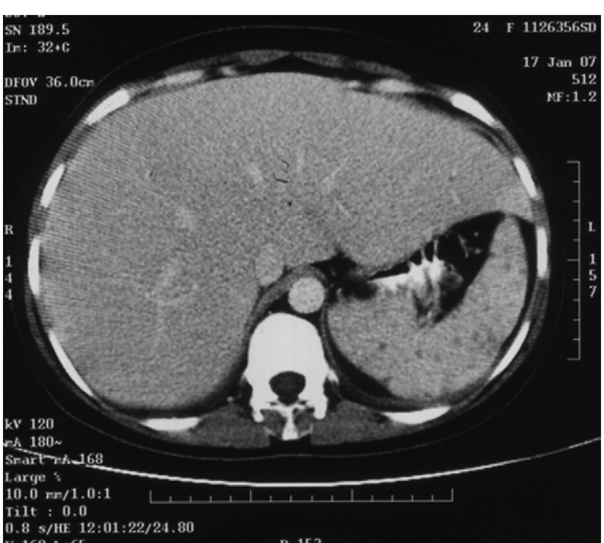

Fig 4. Multiple millimetric hypodens lesions in spleen.

Nine of 15 HSCT (60%) had been heavily pretreated for their primary hematologic disorder with a small chance of cure from any treatment modality. Among patients with active IFI and a median follow-up time of 306 days (range, 145–680 days), 4 of 13 patients (31%) remain alive and in complete remission. When we analyzed the role of primary disease status prior to transplantation on day +100 mortality rate among patients with active IFI, 6 of 9 HSCTs with advanced hematologic disease died (66.6%): two transplants with relapse of primary hematological disease, four transplants with transplant related causes. However, in patients with complete remission prior to transplantation, 2 of 6 patients (33.3%) died, and the cause of death was GVHD and reactivation of fungal infection after initiation of corticosteroid treatment for GVHD. Patient 3, with severe aplastic anemia, (retransplantation of this patient was reported as 4) was transplanted twice 5 months apart survived both transplants. This patient had a persistent fever ≥40°C due to progressive IFI, receiving his first conditioning regimen while febrile. He defervesced after neutrophil engraftment. He lost his graft 3 months after the first transplant and received the second allograft from an alternative sibling donor. He is disease free and off immunosuppressive treatment at 18 months post-second HSCT. Three more patients (patients 6, 11, and 15) are also alive and free of both leukemia and fungal infection. Patients with progressive hematologic disease prior to transplantation showed a tendency toward a higher transplant-related mortality, either from relapse or progressive fungal infection. Avivi et al reported 18 consecutive patients with a history of invasive fungal infection.[13] Similarly, their patients with advanced hematologic disease had higher transplant-related mortality. Only one of their 6 patients with active leukemia survived the transplant compared with 10 of 12 of patients who are in complete remission. Five of their patients with active fungal infection were treated with amphotericin B and granulocyte transfusion; which actually

Table 2. Characteristics of Patients and Disease Status on Day +100 After HSCT

Characteristics	Active IFI (*n* = 13)	Other (*n* = 107)
Sex (M/F)	7/6	64/43
Age (median; range years)	34; 16–53	39; 16–71
Underlying disease		
Acute leukemia	8	34
Lymphoma	2	19
Severe aplastic anemia	2	9
MDS transformed AML	1	—
Chronic myeloid leukemia	—	6
Multiple myeloma	—	36
Other	—	3
Hematologic status at HSCT		
First remission	3	28
Remission with salvage	2	2
≥second remission	1	15
Refractory and/or relapse	7	18
Other	—	45
Transplant type¶		
Allogeneic matched related	11	56
Allogeneic MUD*	1	1
Haploidentical	—	3
Autologous	1	50
Tandem auto/allo	1/1	4/4
Conditioning regimen		
Myeloablative	9	96
Reduced intensity	2	6
Nonmyeloablative	4	16
GVHD type		
Acute	5	15
Chronic	1	13
Status on day +100		
Alive	6	76
IFI-related death	5	3
Death related to other causes	2	28

*MUD, matched unrelated donor.
¶In patients with active IFI, 13 patients underwent 15 transplants. In another group, 107 patients underwent 118 transplants.

corresponded to our patient population. Only one patient with active infection of five (20%) survived the transplant procedure. In contrast, patients with a history of IFI but no clinical and radiologic sign of active infection displayed a survival rate of 83%. While all the patients in our cohort of 13 patients and 15 transplants had active IFI, 31% (4/13) of our patients survived the transplantation.[13] In our cohort, 5 of 15 transplant patients received a combination of new generation antifungal drugs: liposomal amphotericin B ± caspofungin or voriconazole (n = 4) and caspofungin + voriconazole (n = 1). Three of the five patients treated with combination of new generation antifungals survived the transplantation. Offner et al in a retrospective analysis of 48 patients with a history of invasive aspergillosis (IA), undergoing HSCT with secondary prophylaxis after a diagnosis of documented or probable IA found 33% of patients to have reactivation of fungal infection after HSCT. Reactivation occurred more frequently among patients with documented IA and had a fatal course in 88%.[12] In our cohort with active IFI with a more advanced status of fungal infection, a higher proportion of patients (31%) survived the transplantation procedure. In the report by Offner et al, patients reported to have reactivation of their fungal infection might actually have had active fungal disease prior to transplantation and may have been undertreated with prophylactic instead of therapeutic doses of the drug. Namely, undertreatment of the underlying fungal infection might be the cause of relatively higher mortality of 88% in patients with reactivation. In the report by Martino et al, 14 patients with hematologic malignancies who had previous IFI (11 patients with previous IFI and 4 patients with active IFI) received intensive chemotherapy or HSCT under amphotericin B treatment.[6] Three of the four patients with active IFI had undergone HSCT. Two of these three patients with active IFI died early after transplantation with progressive disease. Namely, 66% of their patients with active fungal infection succumbed to progressive infection early after HSCT. The remaining patient also died of progressive IFI at 6 months after the transplant resulting in an IFI-related death of 100%. Fungal infection-related death in our cohort was 53% (7/13 patients), which was slightly better. In fact, in our experience 31% of our patients remain free of infection and in remission with a median follow-up of 306 days. Relatively optimistic results seen in our patient population were probably the result of treating our patients with a new generation of antifungals including caspofungin and voriconasole or combination of various antifungal drugs, which were not available when the above-mentioned study was reported. Modifying antifungal protocols in patients with active IFI during HSCT might further improve the results of active IFI.

Martino et al claimed that the type of transplantation, a longer period from the start of antifungal therapy to allogeneic SCT, and infection response at the time of transplant were important variables predicting outcome.[6] In our cohort of 118 transplants in 107 patients without fungal infection, empiric antifungal treatment was commenced in 24 transplants (20.33%) with a mortality rate of 2.32% (3/118 transplants) due to fungal infection by day +100. Considering the group of patients with dismal prognosis without HSCT, HSCT with antifungal treatment seems to be a reasonable treatment approach.

In a more recent report by Martino et al, 129 patients with previous IA were analyzed for the impact of intensity of the pretransplantation conditioning regimen.[14] IA progressed in 21% of patients after transplantation. The incidence of progression of IA was similar in reduced intensity conditioning and myeloablative regimens. During the entire posttransplant period three variables increased the risk of progression of IA; prolonged duration of neutropenia, advanced status of the underlying disease, and a short interval between start of antifungal therapy and the allogeneic HSCT. Similarly, in our cohort patients with advanced hematologic disease had a relatively worse clinical course. It should also be mentioned that sometimes it is not possible to control the fungal infection without curing the underlying disease like the patient presented as subject 3 and 4.

In conclusion, active IFI should not be considered to be an absolute contraindication to subsequent HSCT. With concurrent use of antifungal agents, even high-risk patients with hematologic malignancies, may benefit from HSCT, which is the only curative treatment approach in certain groups of patients. The status of the underlying hematologic malignancy remains the major factor determining the outcome. The role of modifying the treatment with new-generation antifungal agents, such as caspofungin and voriconasole or a combination of the agents, on the results of patients with active IFI undergoing HSCT remains to be elucidated.

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