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Invasive fungal infections in allogeneic and autologous stem cell transplant recipients: a single-center study of 166 transplanted patients

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Abstract: *Objectives.* Invasive fungal infections (IFIs) remain a major cause of infection-related morbidity and mortality following hematopoietic stem cell transplantation (HSCT).
Patients and methods. We retrospectively analyzed the incidence of IFIs in 166 patients undergoing either allogeneic or autologous HSCT at our institution between January 2000 and December 2003.
Results. Incidence of invasive aspergillosis (IA) and invasive candidiasis among allogeneic HSCT recipients was 23% (16–32%, 95% confidence interval [CI]) and 3% (1–9%, 95% CI), respectively. Duration of neutropenia and reduced-intensity conditioning were the only risk factors for IA in the multivariate model. Patients with IA had significantly reduced overall survival (8% versus 56%, $P = 0.01$) due to higher transplant-related mortality (63% versus 31%, $P = 0.03$). Following autologous HSCT, incidence of IA and invasive candidiasis was 8% (4–19%, 95% CI) and 2% (0.2–11%, 95% CI), respectively. Duration of neutropenia was the only risk factor for the development of IA following autologous HSCT. Overall survival of autologous HSCT recipients with IA was similar to that of patients without IA. Seventeen percent of autologous HSCT recipients were colonized with *Candida* species. Compared with non-colonized patients these patients had significantly reduced overall survival (72% versus 23%, $P = 0.004$), due to increased treatment-related mortality (23% versus 9%, $P = 0.02$).
Conclusion. Diagnosis of IA following allogeneic HSCT and *Candida* colonization in the setting of autologous HSCT defines patient populations with poor outcome but primarily not as a result of the fungal pathogen. Regarding the incidence of IA, duration of neutropenia is the main risk factor, and dose-reduced conditioning is an additional risk factor for the development of IA following allogeneic HSCT, probably owing to increased recipient age in this patient cohort, requiring further studies in this transplantation setting.

M.J. Post[1], C. Lass-Floerl[2], G. Gastl[1], D. Nachbaur[1]

[1]Clinical Division of Hematology and Oncology, [2]Department of Microbiology, Innsbruck Medical University, Innsbruck, Austria

Key words: stem cell transplantation; invasive fungal infection; invasive aspergillosis; invasive candidiasis

Correspondence to:
David Nachbaur, MD, Division of Hematology and Oncology, Innsbruck Medical University, Anichstrasse 35, A-6020 Innsbruck, Austria
Tel: + 0043 512 504 23255
Fax: + 0043 512 504 23338
E-mail: david.nachbaur@i-med.ac.at

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Invasive fungal infections (IFI) are increasingly recognized as one of the leading infection causes of mortality and morbidity following hematopoietic stem cell transplantation (HSCT) with a case-fatality rate of up to 87% (1–8). Despite defining some risk factors for the development of IFI including certain conditioning, prolonged neutropenia, genetic disparities between donor and recipient, presence and treatment of graft-versus-host disease (GVHD), use of steroids, lack of laminar air-flow, patient age, and certain viral infections such as cytomegalovirus (CMV), there is strong interest in better defining high-risk patient populations in need of an intensified antifungal approach (9). Moreover, the increasing and extensive use of fluconazole and newer azoles with broader (anti-mold) activity prompts the emergence not only of resistant *Candida* species (i.e., *C. albicans*, *C. tropicalis*, *C. parapsilosis*) but also

of serious invasive infections caused by less commonly encountered fungi that frequently exhibit intrinsic resistance to many antifungal agents (10–13).

We therefore retrospectively analyzed the incidence of and risk factors for the development of IFI in patients undergoing allogeneic or autologous HSCT at our institution between the years 2000 and 2003.

Patients and methods

Enrolled in this study were 166 patients undergoing either autologous or allogeneic HSCT between January 2000 and December 2003. Detailed patient characteristics are listed in Tables 1 and 2.

Conditioning and GVHD prophylaxis

Conditioning regimen for allogeneic HSCT consisted of myeloablative high-dose chemotherapy ± total body irradiation (TBI) or reduced-intensity busulfan/fludarabine-based chemotherapy (RIC) in patients ineligible for conventional myeloablative allografting. For autologous HSCT, patients were conditioned with high-dose chemotherapy alone depending on the underlying disease.

GVHD prophylaxis consisted of cyclosporine A (CsA) plus either methotrexate or mycophenolate mofetil according to the Seattle protocols (14, 15). Acute and chronic GVHD were diagnosed from clinical symptoms and/or biopsies from skin, oral mucosa, liver, and gut and classified according to the published standard Seattle criteria (16, 17).

Supportive care

During neutropenia following allogeneic HSCT no systemic antibiotic prophylaxis was administered. *Pneumocystis jiroveci* pneumonia prophylaxis consisted of trimethoprim–sulfamethoxazole 160/800 mg 3 times weekly for at least 180 days after HSCT or until CD4 counts rose to $>200/\mu L$. As prophylaxis against Herpes simplex and Varicella zoster virus infection, patients received valacyclovir 500 mg by mouth (p.o.) b.i.d. or acyclovir 250 mg/m^2 intravenously (i.v.) q 8 h from the beginning of conditioning until the end of the first year. In allogeneic HSCT recipients, antifungal prophylaxis consisted of fluconazole 400 mg p.o. or i.v. from the beginning of conditioning until day +73 (10).

Patients with a history of IA prophylactically received combinations of amphotericin B ± voriconazole ± caspofungin during neutropenia followed by voriconazole maintenance in order to prevent reactivation ($n = 7$).

Autologous HSCT recipients underwent selective bowel decontamination with ciprofloxacin (500 mg p.o. b.i.d.) plus oral nystatin (2.4×10^6 IU/day).

Irradiated (25 Gy) leukocyte-depleted red cells and platelet transfusions from single donors were administered to

Patient characteristics of allogeneic HSCT recipients ($n = 104$)

	n (%)
Median patient age (years)	45 (6–76)
Median donor age (years)	39 (5–79)
Diagnosis	
Acute leukemia	67 (63%)
Myelodysplastic syndrome	9 (9%)
Chronic myeloid leukemia	11 (11%)
Lymphoma	7 (7%)
Multiple myeloma	5 (5%))
Other	5 (5%)
Risk	
Standard risk	42 (40%)
High risk	62 (60%)
Donor type	
HLA-identical sibling	49 (47%)
Unrelated donor	55 (53%)
Stem cell source	
Peripheral blood stem cells (PBSC)	86 (83%)
Bone marrow stem cells (BMSC)	18 (17%)
Conditioning	
Total body irradiation	34 (33%)
Chemotherapy alone	23 (22%)
Reduced-intensity conditioning	47 (45%)
GVHD prophylaxis	
Cyclosporine A + methotrexate	49 (47%)
Cyclosporine A + mycophenolate mofetil	47 (45%)
Others	8 (8%)
Sex match (recipient/donor)	
Male/female	23 (22%)
Cytomegalovirus serostatus (recipient/donor)	
−/−	23 (22%)
−/+	10 (10%)
+/−	33 (31%)
+/+	41 (37%)

HSCT, hematopoietic stem cell transplant; GVHD, graft-versus-host disease.

Table 1

Patient characteristics of autologous HSCT recipients ($n = 62$)

	n (%)
Median patient age (years)	56 (20–64)
Diagnosis	
Acute leukemia	7 (11%)
Lymphoma	20 (32%)
Multiple myeloma	33 (54%)
Solid tumor	2 (3%)
Stem cell source	
Peripheral blood stem cells (PBSC)	62 (100%)

HSCT, hematopoietic stem cell transplant.

Table 2

maintain hemoglobin levels >8.0 g/dL and platelet counts >20.0 G/L.

CMV screening and definition and treatment of CMV infection

CMV screening (CMV pp65 antigenemia) was performed on a weekly basis using peripheral blood samples at least until day +100. CMV infection and disease were diagnosed according to the established standard criteria (18). Preemptive ganciclovir (5–10 mg/kg/day) or valgancyclovir (900 mg p.o. b.i.d.) was administered at first detection of CMV in peripheral blood for 2–3 weeks followed by maintenance therapy 3 times weekly for at least 2 more weeks.

Definition of IFI and *Candida* colonization

IFI was classified as proven, probable, or possible according to the consensus criteria of the European Organization for Research and Treatment of Cancer (EORTC) and the National Institute of Allergy and Infectious Diseases (NIAID) Mycosis Study Group (19).

Candida colonization was defined as 1 *Candida* spp.-positive surveillance culture performed weekly upon admission until death or discharge.

Statistical analysis

Overall survival was calculated from the date of stem cell transplantation to the date of death from any cause or date of last follow-up. Probability of overall survival was estimated using the method of Kaplan and Meier and compared using the log-rank test (20). Cumulative incidence estimate was calculated for IA and candidiasis, transplant-related mortality (TRM), and relapse using the NCSS statistical software package (Kaysville, Utah, USA) with death without previous diagnosis of IFI as competing risk (21). TRM was defined as the probability of dying without previous occurrence of a relapse, which is a competing event. Relapse incidence was calculated from the date of HSCT to the date of documented disease relapse/progression with death without relapse/progression as competing risk (22). Differences between patient cohorts were calculated using the Mann–Whitney *U*-test for quantitative variables or the χ^2 test for dichotomous variables.

Risk factors for IFI were assessed using the log-rank test in the univariate analysis and the Cox regression in the multivariate model for allogeneic transplants including the following variables: patient age, donor age, prior IA, risk category according to the underlying disease, donor type, human leukocyte antigen (HLA) match, sex match, myeloablative conditioning versus RIC, TBI versus chemotherapy conditioning, recipient CMV serostatus, donor CMV serostatus, duration of neutropenia (continuous), stem cell source, $CD34^+$ cell counts (continuous), $CD3^+$ cell counts (continuous), $CD56^+CD3^-$ cell counts (continuous), and mononuclear cell counts (continuous) in the graft.

Median day numbers of neutropenia were used as cut-off points for the definition of 'prolonged neutropenia' in the univariate analysis (i.e., 12 days following allogeneic and 9 days following autologous HSCT) for the univariate analysis.

Allogeneic HSCT recipients were categorized as standard risk if they had chronic myeloid leukemia in first chronic phase or acute myelogeneous leukemia in first remission and acute lymphoblastic leukemia in first or second complete remission. All other indications for allogeneic HSCT were classified as high-risk disease (23).

Results

IFIs following allogeneic HSCT

Invasive aspergillosis (IA)

IA was diagnosed in 23/104 allogeneic HSCT recipients (cumulative incidence 23%; 16–23%, 95% confidence interval [CI]). According to the international consensus criteria on definition of IFI, 3/23 (13%) IA infections were classified as proven, 3/23 (13%) as probable, and 17/23 (74%) as possible IFI. The median time to onset of IA was 28 (range, 2–714) days after transplantation. According to the time interval between HSCT and IFI diagnosis 15/23 (65%) IA were classified as early (<day +41) and 8/23 (35%) as late (>day +41) IFIs. Three of the late infections were diagnosed more

than 6 months after allogeneic HSCT and only 1 of these patients was diagnosed with chronic GVHD (24).

None of the 7 patients with documented IA (1 proven and 6 possible) before allogeneic HSCT showed signs of breakthrough infection during intensified double or triple prophylaxis with amphotericin B ± voriconazole ± caspofungin during neutropenia followed by voriconazole maintenance.

Risk factors for IA

Uni- and multivariate analyses were performed to determine risk factors for the development of IA following allogeneic HSCT. There was a trend toward a higher incidence of IA in patients receiving lower $CD34^+$ and NK cell numbers (25% versus 14% and 29% versus 15%, respectively) and in patients with prolonged neutropenia (>12 days, 32% versus 18%), although differences did not reach statistical significance. All other clinical parameters tested had no significant impact on the incidence of IA in the univariate analysis.

Multivariate analysis including recipient age, $CD3^+$ counts, $CD34^+$ counts, duration of neutropenia as continuous variables and recipient age, donor type, conditioning (RIC versus myeloablative), risk category (standard versus high-risk), sex match, recipient and donor CMV serostatus as categorical variables showed only RIC and prolonged neutropenia to be associated with a significantly higher risk for IA ($P = 0.01$ and 0.03, respectively; Table 3).

Acute GVHD grades II–IV was diagnosed in 54/104 (52%) HSCT recipients at a median of 48 (5–150) days following transplantation. No differences were seen according to the incidence of IA between patients with or without acute GVHD grades II–IV (12/54 versus 11/50 patients). Acute GVHD preceded IA diagnosis in 10/12 (83%) patients.

No correlation was found between chronic GVHD and IA in 7 patients developing fungal infection after day +100 (data not shown).

Overall survival and TRM

For the entire cohort, the 5-year overall survival following allogeneic HSCT was 46% (36–55%, 95% CI). Among patients with documented IA, overall survival was significantly reduced as compared with patients without IA (8% versus 56%, $P = 0.01$; Fig. 1), although both cohorts were balanced regarding patient and donor age, risk category by underlying disease, donor type, HLA match, sex match, conditioning regimen, stem cell source, time interval between diagnosis and HSCT, duration of neutropenia, and $CD3^+$, $CD34^+$, and NK cell counts in the graft (data not shown).

This survival disadvantage was mainly a result of significantly increased TRM in patients with documented IA (64% versus 31%, $P = 0.03$). However, only 3/18 (17%) patients with documented IA died from IFI.

Risk factors for invasive aspergillosis following allogeneic HSCT

Risk factor	Relative risk	95% CI	*P* value
Unrelated donor	2.31	0.35–15.1	NS
Reduced-intensity conditioning	23.6	6.0–277.8	0.01
Age of recipient	0.95	0.91–1.01	NS
$CD3^+$ T lymphocytes	0.68	0.34–1.37	NS
$CD34^+$ stem cells	0.89	0.71–1.09	NS
Duration of neutropenia	1.33	1.03–1.72	0.03
High risk	1.22	0.24–6.05	NS
Male recipient/female donor	0.63	0.13–2.99	NS
CMV-positive recipient	0.55	0.12–2.40	NS
CMV-positive donor	2.61	0.68–1.01	NS

HSCT, hematopoietic stem cell transplant; NS, not significant; CI, confidence interval; CMV, cytomegalovirus.

Table 3

Documented IA diagnosis before allogeneic HSCT (1 proven and 6 possible cases) did not impact overall survival following allogeneic HSCT (overall survival 57% versus 45%, P = NS).

Invasive *Candida* infection

Invasive candidiasis was diagnosed in 3/104 recipients of allogeneic HSCT (cumulative incidence 3%; 1–9%, 95% CI). Median time to diagnosis was 116 (range, 54–147) days after allogeneic HSCT. Fluconazole-resistant *Candida* species (*C. glabrata* and *C. krusei*) were shown to be causative in

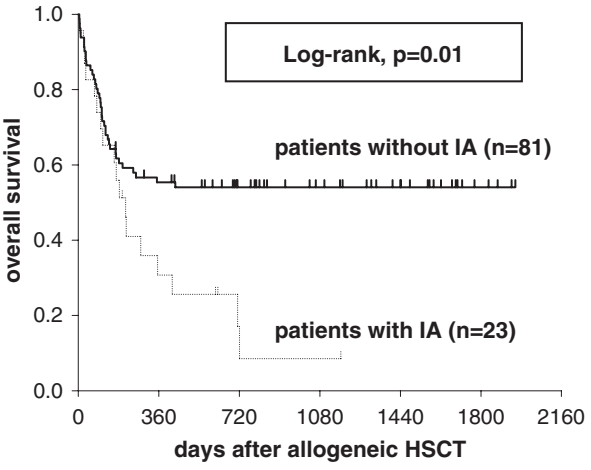

Fig. 1. Invasive aspergillosis (IA) and overall survival following allogeneic hematopoietic stem cell transplantation (HSCT).

2 cases (67%). All patients with invasive candidiasis received steroids ($\geqslant$1.0 mg/kg q.d.) because of either acute or chronic GVHD. All 3 patients with candidiasis died of septic multiorgan failure, which was at least partly related to the IFI.

Of 104 (63%) allogeneic stem cell transplant recipients, 65 were identified as being colonized with *Candida* species. Two of 3 patients with candidemia were colonized before infection. However, *Candida* colonization was not a risk factor for the development of IA or associated with a poorer survival (data not shown).

IFIs following autologous HSCT

IA

IA was diagnosed in 6/62 patients following autologous HSCT (cumulative incidence 8%; 4–19%, 95% CI). Median time to diagnosis was 23 (range, 12–46) days after HSCT. Using uni- and multivariate analysis prolonged neutropenia was shown to be the only significant risk factor (duration of neutropenia >9 days, 17% versus 0%, $P = 0.021$ in the univariate analysis; Cox regression: relative risk 1.22, 1.04–1.44, 95% CI, $P = 0.02$).

Overall survival and TRM

Five-year overall survival for recipients of autologous HSCT was 60% (38–83%, 95% CI). Patients with and without IA had similar overall survival following autologous HSCT (80% versus 58%, $P = 0.98$). Only the IA group showed a trend to higher TRM (20% versus 0%, $P =$ NS).

Candida species colonization

Candida colonization was documented in 17/62 autologous HSCT recipients. Overall survival was significantly reduced in patients with *Candida* colonization (23% versus 72%, $P = 0.004$) (Fig. 2), mainly due to a significantly higher incidence of treatment-related mortality (50% versus 9%, $P = 0.02$). Causes of death following autologous HSCT in patients with *Candida* colonization ($n = 17$) were infection due to candidiasis in 1, bleeding in 1, toxicity in 2, and relapse in 3 patients.

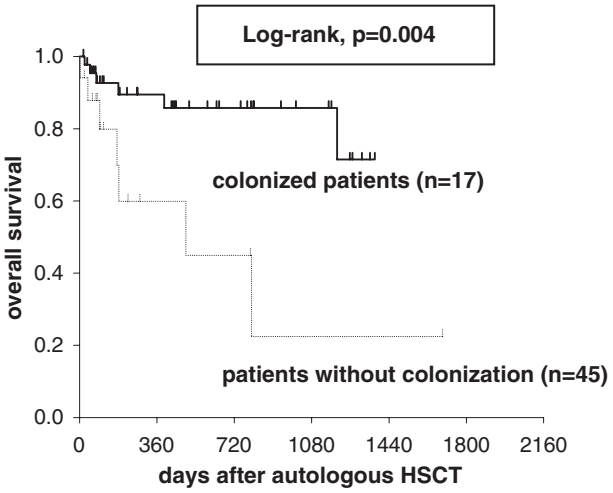

Fig. 2. Candida colonization and overall survival following autologous hematopoietic stem cell transplantation (HSCT).

Discussion

The present retrospective single-center study reports a 23% and 3% cumulative incidence of IA and invasive candidiasis following allogeneic HSCT and an 8% and 2% incidence of these complications following autologous HSCT. These data are in line with the incidence of infection with *Aspergillus* and *Candida* spp. reported by other centers and several retrospective analyses, although practices and demographics at individual centers will influence the rate and type of IFI. (1–6, 24–26).

Multivariate analysis showed the duration of neutropenia to be the only risk factor for IA following both allogeneic and autologous HSCT. Additionally, allogeneic HSCT following RIC was a significant risk factor for the development of IA in our study group. By contrast, the Seattle group and others reported similar rates of invasive mold infection following non-myeloablative transplants and conventional conditioning (2, 27–30). This discrepancy, however, might be due to the more myeloablative conditioning (busulfan/fludarabine) used at our center as compared with the true non-ablative Seattle regimen (31). Additionally, differences in patient demographics (i.e., age of recipient and/or donor and co-morbidities), underlying disease and disease stage, as well as inter-center differences in indication for dose-reduced conditioning, could have contributed to this phenomenon. Another risk factor, especially for late IFI, might be the need for prolonged immunosuppressive medication in order to treat delayed GVHD following non-myeloablative or reduced-intensity transplantation (32, 33). The outcome of patients with IA following allogeneic HSCT was significantly inferior to that of patients without IA. Despite published case-fatality rates of up to 80% in patients with IA following allogeneic HSCT, only 17% of our IA patients died from IFI. Nonetheless, TRM in this patient cohort was significantly higher than in patients without IA, suggesting that this group of patients represents a high-risk population as yet not defined in detail. In this context it is of note that the 2 groups, namely those patients with and those without IA, were comparable regarding patient characteristics such as age, risk category by under-

lying disease, donor type, conditioning, CMV serostatus of recipient/donor, etc. Further studies in larger cohorts will help clarify the reasons for this increased TRM following allogeneic HSCT not due to IFI found in patients with IA.

Besides other risk factors, several studies have demonstrated a significant association between IA and acute and/or chronic GVHD (3, 24, 34). Moreover, our analysis showed more than 80% of allogeneic HSCT recipients with documented IA to have acute GVHD $\geq$ grade II, which required treatment with steroids and was diagnosed before IFI.

In contrast to the time to onset of IA, which occurred at a median of 23 days following allogeneic HSCT in our study and was in a similar range in several other studies, median time to onset of invasive *Candida* infection following allogeneic HSCT was $>$100 days in our study (1, 3, 6). These late-occurring invasive *Candida* infections were probably a result of either the prolonged use of fluconazole prophylaxis and or the low frequency of Hickman catheter use at our institution for the transplant procedures (35). Moreover, prolonged fluconazole prophylaxis may result in the emergence of resistant *Candida* strains or an increase in the incidence of infection with species intrinsically resistant to fluconazole (6, 7). In our cohort 2/3 cases of invasive *Candida* infection were caused by fluconazole-resistant *Candida* species.

In contrast to allogeneic HSCT, recipients of autologous HSCT had a relatively low incidence of IFI. Just as following allogeneic HSCT, duration of neutropenia was also the only significant risk factor for IA following autologous HSCT as shown by uni- and multivariate analysis (1). In contrast to the allogeneic setting, survival of patients with IA following autologous HSCT was similar to that of patients without IA, findings that are in accordance with the report by Jantunen et al. (1).

Finally, although more allogeneic than autologous HSCT recipients were colonized with *Candida* species (63% versus 27%), only after autologous HSCT was *Candida* species colonization associated with significantly increased TRM and poorer outcome. These findings confirm the results of an earlier study and suggest that in the autologous HSCT setting patients with *Candida* colonization define a high-risk population irrespective of the risk for IFI (36).

In conclusion, our retrospective single-center analysis shows that in the setting of allogeneic HSCT IA and in the setting of autologous HSCT *Candida* colonization are independent risk factors for high TRM resulting in significantly reduced overall survival. Although the fungal infection itself seems not to be the primary cause of treatment failure, probably thanks to improved diagnostic approaches and a growing armamentarium of better tolerated and more broadly active antifungal agents, both situations involve patients at high risk because of poor immune reactivity and/or extensive pre-treatment toxicity resulting in significant transplant-related morbidity and mortality.

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