MAJOR ARTICLE

Fusarium Infection in Hematopoietic Stem Cell Transplant Recipients

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To characterize the epidemiology and prognostic factors of invasive fusariosis in hematopoietic stem cell transplant (HSCT) recipients, the records of HSCT recipients from 9 hospitals (7 in Brazil and 2 in the United States) were retrospectively reviewed. Sixty-one cases were identified: 54 in allogeneic HSCT recipients and 7 in autologous HSCT recipients. The incidence of fusariosis among allogeneic HSCT recipients varied between a range of 4.21–5.0 cases per 1000 in human leukocyte antigen (HLA)—matched related transplant recipients to 20.19 cases per 1000 in HLA-mismatched transplant recipients. The median time period between transplantation and diagnosis of fusariosis was 48 days. Among allogeneic HSCT recipients, a trimodal distribution was observed: a first peak before engraftment, a second peak at a median of 62 days after transplantation, and a third peak >1 year after transplantation. The actuarial survival was 13% (median, 13 days). Persistent neutropenia was the single prognostic factor for death identified by multivariate analysis.

The epidemiology of fungal infections in hematopoietic stem cell transplant (HSCT) recipients has changed in the past decade, with a decrease in infections caused by *Candida* species after the introduction of triazole prophylaxis and an increase in invasive aspergillosis [1] and other mold infections [2]. Among the latter, *Fusarium* infections have been reported with increasing frequency. In patients with hematological malignancies, fusariosis is associated with a very poor prognosis [3]. However, the clinicopathologic features and outcome of HSCT recipients with invasive fusariosis have not been previously described. In this study, we describe the clinical features and prognostic outcome factors of 61 patients with fusariosis after HSCT.

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PATIENTS AND METHODS

All patients with invasive fusariosis after HSCT who were cared for at 2 US centers and 7 Brazilian centers from 1985 through 2001 were identified by a review of the clinical records of patients with invasive fungal infections. A standardized case report form containing the pertinent clinical information was completed by all investigators and sent to one of us (M.N.) for analysis. The study was approved by the ethical review committees of the participating institutions.

The diagnosis of fusariosis was classified as proven, probable, or possible, according to previously established criteria [4]. Briefly, proven fusariosis was defined as the growth of *Fusarium* species in cultures of blood or cultures of samples obtained from other sterile sites in patients with clinical signs of infection or the demonstration of hyphae in tissue together with recovery of *Fusarium* species from the same tissue. Probable fu-

sariosis was defined as the growth of *Fusarium* species from respiratory tract secretions obtained from patients with clinical signs of infection compatible with fusariosis in the absence of other pathogens. Patients with positive cultures of skin lesions (e.g., cellulitis, nodules) without histopathologic demonstration of hyphae were also included in this category. Cases of possible infection were excluded.

The incidence of fusariosis was calculated by using the number of HSCTs performed during the same period as a denominator. Survival was defined as the time between the date of diagnosis of fusariosis and death or last follow-up. The date of diagnosis was defined as the day of the first culture positive for *Fusarium*. If the diagnosis of fusariosis was made postmortem, the date of death was considered the date of diagnosis. Persistent neutropenia was defined as an absolute neutrophil count of <500 neutrophils/mm^3 for >7 days. Acute graft-versus-host disease (aGVHD) was classified in grades 1 to 4, and chronic graft-versus-host disease (cGVHD) was classified as localized or extensive, as defined previously [5, 6]. Disseminated infection was defined as involvement of $\geqslant$2 noncontiguous organs. Data were censored after 90 days.

Prognostic factors for fusariosis were assessed by univariate and multivariate Cox proportional-hazard regression analyses, with survival as the end point variable. Variables with $P < .10$ in the univariate analysis were included in the multivariate analysis model. $P \leqslant .05$ was considered statistically significant. The following variables were analyzed: age, sex, type and status of underlying disease, type of HSCT, presence of neutropenia (<500 neutrophils/mm^3), presence and grade of aGVHD and cGVHD, use of corticosteroids, concomitant infections, extent of fusarial infection (localized or disseminated), antifungal therapy, use of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor, and WBC transfusions.

RESULTS

Sixty-one HSCT recipients (54 allogeneic, 7 autologous) with fusariosis were identified. The donor source for the 54 allogeneic HSCT patients was an HLA-compatible related donor (MRD) for 29 (48%) of the patients, an HLA-compatible unrelated donor (MUD) for 19 (31%) of the patients, and an HLA-mismatched related donor (MMRD) for 6 (10%) of the patients. The stem cell source for the 54 allogeneic HSCT recipients was bone marrow in 51 patients and peripheral blood in 3, whereas 6 of the 7 autologous stem cell transplant (AuSCT) recipients received a bone marrow stem cell product.

The diagnosis of fusariosis was established on the basis of specimens obtained from various organs: blood (in 28% of cases), skin (in 20%), blood and skin (in 16%), lungs and sinuses (in 11% each), and others (in 14%). Fifty-six patients (92%) had proven and 5 (8%) had probable fusariosis. Disseminated infection with metastatic skin lesions was the most frequent clinical presentation, occurring in 46 (75%) of patients, followed by fungemia alone (11%) and sinusitis and pneumonia (4 patients each).

The overall incidence of fusariosis was 5.97 cases per 1000 transplants and varied among the different institutions (range, 5.00–11.33 cases per 1000 transplants), but not between the 2 countries (6.18 cases per 1000 transplants in Brazil vs. 5.89 cases per 1000 transplants in the United States). The incidence differed according to the type of allogeneic HSCT: 4.21–5.0 cases per 1000 MRDs, 2.28 per 1000 HLA-compatible MUDs, and 20.19 per 1000 MMRDs. An incidence of 1.4 –2.0 per 1000 AuSCTs was observed.

The majority of allogeneic HSCT recipients had leukemia and were not in complete remission at the time of transplantation. At diagnosis of fusariosis, 46% of patients were neutropenic and most had aGVHD or cGVHD (table 1). Patients from Brazil differed from American patients. They were younger (median age, 22 years vs. 41 years), more likely to have chronic myeloid leukemia or aplastic anemia, more likely to have received an MRD transplant, and more likely to be neutropenic at the time of diagnosis of fusariosis. On the other hand, patients from the United States were more likely to have received a diagnosis of acute myeloid leukemia and more likely to have received a non-MRD transplant (i.e, an AuSCT or a transplant from an MUD or MMRD).

Disseminated infection was most commonly observed during the first 100 days after transplantation (table 2) and was associated with neutropenia (OR, 10.11; 95% CI, 1.03–50.14; $P = .005$). The median time period between stem cell transplantation and diagnosis of fusariosis was 64 days (range, 1–1017 days) with a trimodal distribution: a first peak (early fusariosis) before engraftment (median, 16 days), a second peak (late fusariosis) between day 61 and day 80 (median, 64 days), and a third peak (very late fusariosis) after day 360 (figure 1). All 8 allogeneic HSCT recipients in the latter group had adequate neutrophil counts at diagnosis of fusariosis. Five had received an MUD (4 patients) or MMRD (1 patient) transplant. Among the 4 MUD transplant recipients, 3 received a second allogeneic HSCT provided for treatment of their relapsing acute leukemia and developed fusariosis after engraftment, whereas the remaining patient was receiving therapy for extensive cGVHD. One MMRD transplant recipient and 3 MRD transplant recipients were also receiving treatment for extensive cGVHD. As shown in figure 2, a greater number of cases was observed during the late 1990s, especially cases occurring >30 days after transplantation.

Among the 8 AuSCT recipients, the median time between

Table 1. Demographic and clinical characteristics of 61 hematopoietic stem cell transplant (HSCT) recipients with fusariosis, by country of origin.

Characteristic	United States (n = 42)	Brazil (n = 19)	Total (n = 61)
No. of male subjects/no. of female subjects	20/22	14/5	34/27
Age at diagnosis of fusariosis, median years (range)[a]	41 (2–67)	22 (7–48)	34 (2–67)
Underlying condition			
Acute myeloid leukemia[a]	17 (40)	2 (11)	19 (31)
Chronic myeloid leukemia[a]	6 (14)	8 (42)	14 (23)
Acute lymphoid leukemia	6 (14)	3 (16)	9 (15)
Aplastic anemia[a]	1 (2.4)	4 (21)	5 (8)
Myelodysplastic syndrome	1 (2.4)	2 (10.5)	3 (5)
Non-Hodgkin lymphoma	3 (7)	0	3 (5)
Multiple myeloma	2 (5)	0	2 (3)
Chronic lymphocytic leukemia	2 (5)	0	2 (3)
Solid tumor	2 (5)	0	2 (3)
Hodgkin disease	1 (2.4)	0	1 (2)
Genetic disorder	1 (2.4)	0	1 (2)
Underlying condition not in complete remission[b]	34/39 (87)	10/15 (67)	44/54 (81)
Type of stem cell transplant			
Allogeneic, HLA-compatible, related donor[a]	15 (36)	14 (74)	29 (48)
Allogeneic, mismatched, related donor	5 (12)	1 (5)	6 (10)
Allogeneic, HLA-compatible, unrelated donor	15 (36)	4 (21)	19 (31)
Autologous	7 (17)	0	7 (11)
Characteristics at diagnosis of fusariosis in 54 allogeneic HSCT recipients			
Neutropenia[a]	11/35 (31)	14/19 (74)	25 (41)
Acute GVHD	16/35 (46)	6/19 (32)	31/54 (57)
Grade 1	0	1	1
Grade 2	4	2	11
Grade 3	8	0	12
Grade 4	4	3	7
Chronic GVHD	10/35 (29)	2 (11)	11/54 (20)
Localized	1	1	2
Extensive	9	1	9
Use of corticosteroids	21 (50)	11 (58)	32 (52)

NOTE. Data are expressed as n (%) unless otherwise indicated. GVHD, graft-versus-host disease.

[a] $P < .05$.

[b] For patients with chronic myeloid leukemia, accelerated phase, or blast crisis.

transplantation and diagnosis of fusariosis was 14 days (range, 7–564 days), and 7 of these patients were neutropenic at the time of diagnosis. One patient with an adequate neutrophil count had fusarial endocarditis.

The diagnosis of fusariosis was made at postmortem examination in 16 (26%) of the patients, and 45 patients received therapy, including deoxycholate amphotericin B (30 patients), lipid-based amphotericin B (14 patients), and caspofungin (1 patient). G-CSF and granulocyte-macrophage colony-stimulating factor were provided to 26 patients and 4 patients, respectively. Granulocyte transfusions were used in 13 patients (including 4 transfusions from donors stimulated with G-CSF).

The median duration of survival after diagnosis was 13 days, with only 13% of patients remaining alive at 90 days after diagnosis. The death rates of patients with early, late, and very late fusariosis were 92%, 72%, and 74%, respectively ($P = .12$). There was no difference in the death rate according to the type of transplantation (100% for AuSCTs, 83% for MRD transplants, 89% for MUD transplants, and 83% for MMRD transplants; $P = .64$). Univariate predictors of death among

Table 2. Clinical variables of 54 allogeneic hematopoietic stem cell transplant (HSCT) recipients, by time after receipt of transplant.

Variable	Patients receiving diagnosis of fusariosis, by no. of days after receipt of HSCT				
	0–30 (n = 20)	31–100 (n = 16)	100–365 (n = 10)	>365 (n = 8)	P
Neutropenia	17 (85)	5 (31)	3 (30)	0	<.0001
Corticosteroid use	12 (60)	12 (75)	5 (50)	3 (38)	.31
Acute GVHD	4 (20)	13 (81)	NA	2[a] (25)	.004
Chronic GVHD	NA	1 (6)	5 (50)	6 (75)	<.0001
Disseminated infection	18 (90)	12 (75)	4 (40)	6 (75)	.03

NOTE. Data are expressed as no. (%) unless otherwise indicated. GVHD, graft-versus-host disease; NA, not applicable.

[a] Indicates receipt of a second HSCT.

allogeneic HSCT recipients were aGVHD (HR, 2.05; 95% CI, 1.04–4.05; $P = .04$) and persistent neutropenia (HR, 3.64; 95% CI, 1.29–10.36; $P = .01$), with persistent neutropenia remaining the only significant prognostic factor by multivariate analysis (HR, 3.65; 95% CI, 1.29–20.36; $P = .01$).

DISCUSSION

Our study is the first to report the clinical characteristics, outcome, and prognostic factors of fusariosis in HSCT recipients. Our results indicate that the cumulative incidence of fusariosis among HSCT recipients varies according to the type of transplantation: lowest among autologous recipients and highest among the allogeneic MMRD transplant recipients (a 4- and 10-fold higher incidence compared with allogeneic MRD transplant and AuSCT recipients, respectively). This trend is comparable to that seen with invasive aspergillosis [7]. We were surprised to observe a lower incidence of fusariosis among the MUD HSCT recipients, which may be because of the fact that patients who received MUD transplants in our series were cared for at only 1 of the 9 participating centers. A study from this center had previously reported that fusariosis was more likely to occur among mismatched or unrelated transplant recipients than among recipients of a matched related donor product [8]. Of interest, the incidence of fusariosis among HSCT recipients at this center was lower (5.01 cases per 1000 HSCTs) than that observed at the other centers (9.11–11.33 per 1000 HSCTs). It is possible that geographic or other nosocomial factors may influence the incidence of fusariosis. We also observed that patients from Brazil and the United States differed in some aspects. These differences may simply reflect different HSCT practices among these countries, rather than differences in the characteristics of fusariosis. In Brazil most centers do not perform MUD or MMRD transplantations, and the majority of transplantations are performed in patients with chronic myeloid leukemia.

Aspergillosis after receipt of an allogeneic HSCT has been reported as having a bimodal distribution (early during neutropenia and a second peak at around day 100 after receipt of transplant) [9–11], although very late cases of aspergillosis (>1 year after receipt of HSCT) do occur [12]. Our results suggest that, like aspergillosis, fusarial infections have a trimodal distribution (early, late, and >1 year after receipt of HSCT). Of note, the second peak of fusariosis occurred 1 month earlier than that of aspergillosis (median, day 64 vs. day 100, respectively). Our data also suggest that very late (>1 year) fusariosis occurred among patients with adequate neutrophil counts and who had received MUD or MMRD HSCT and/or were receiving

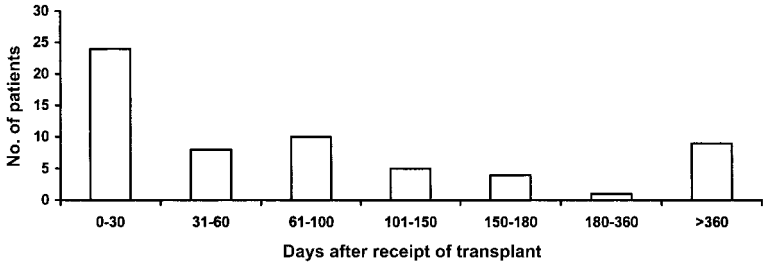

Figure 1. Trimodal distribution of cases of fusariosis diagnosed after allogeneic hematopoietic stem cell transplant: early (median, 16 days after receipt of transplant), late (median, 64 days after receipt of transplant), and very late (median, 508 days after receipt of transplant).

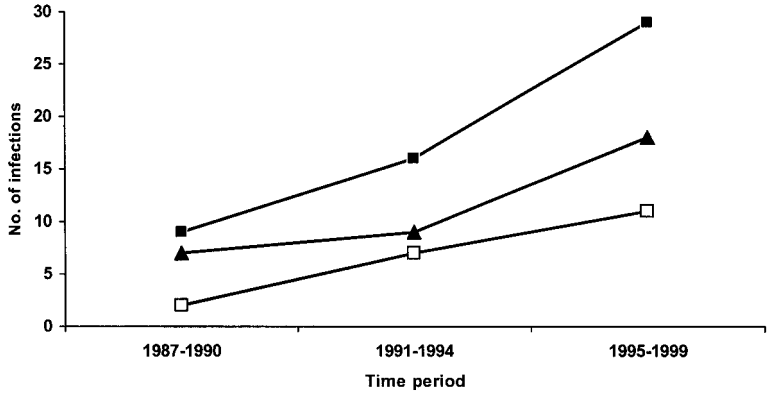

Figure 2. Number of cases of fusariosis from 1987 through 1999: all infections *(solid squares),* fusariosis occurring ⩽30 days after receipt of transplant *(open squares),* and fusariosis occurring >30 days after receipt of transplant *(solid triangles).*

therapy for extensive cGVHD. This population of patients could be at risk for fusariosis because of the severe T cell—mediated immunodeficiency, rendering these patients functionally neutropenic [13].

The prognosis of fusariosis among HSCT patients is very poor, with a median survival of only 13 days after receipt of transplant, similar to that reported among patients with hematological malignancies who did not receive HSCT [3, 14]. As expected, persistent neutropenia was an important prognostic variable [14]. The lack of significance of corticosteroid therapy as a prognostic factor may be related to the fact that almost two-thirds of our patients were receiving corticosteroids at the time of diagnosis, a factor that may have overshadowed the importance of this variable. GVHD was a significant factor by univariate analysis but failed to reach statistical significance by multivariate analysis, probably as a result of the small sample size of patients with this variable.

In our study, a greater number of cases of fusariosis were diagnosed in the late 1990s. It is likely that the incidence of early fusariosis will decline with the more frequent use of nonmyeloablative HSCTs (with shorter duration of neutropenia). However, the higher incidence and severity of GVHD associated with nonmyeloablative HSCTs may result in an increased rate of late fusariosis, as has been reported with aspergillosis [7]. On the other hand, the almost exclusive use of peripheral blood as a source of autologous stem cells has resulted in a significant shortening of the duration of neutropenia in this setting, a fact likely to translate into a marked reduction of fusariosis in this patient population. Whether the use of CD34 selected grafts, which is associated with delayed T cell immune reconstitution, will increase the risk for fusariosis among AuSCT recipients remains unknown [15].

Of interest, the rate of proven infection in our series (92%) was significantly higher than that reported with aspergillosis (~40%) [10, 16]. This is best explained by the fact that, unlike *Aspergillus* species, *Fusarium* species have a propensity for invading 2 sites (blood and skin) that can be easily sampled for diagnostic purposes.

Our study suffers from the limitations of all retrospective studies. Thus, potentially important prognostic variables could have been missed. Our findings have several clinical implications. Because patients with very late fusariosis had GVHD and adequate neutrophil counts, a high index of suspicion for this infection should be kept in this patient population, regardless of the number of circulating neutrophils. Given the poor outcome of fusariosis in HSCT recipients and the relative resistance of these fungi to antifungal agents, preventive nonchemotherapeutic measures are of paramount importance. Such measures include a thorough evaluation and treatment of skin lesions and tissue breakdown (particularly onychomycoses that serve as a portal of entry for *Fusarium* species) before and after receipt of HSCTs [17] and adequate air and water infection control practices to avoid environmental exposure to this fungus [18, 19]. Because fusarial infections may recur after immunosuppression, judicious use of immunomodulatory agents after receipt of a HSCT is critical in patients with a history of fusariosis. Future research should be focused on the evaluation of strategies derived to reduce the duration of neutropenia (e.g., nonmyeloablative regimens, colony-stimulating factors, and colony-stimulating factors and dexamethasone-elicited WBC transfusion), as well as the usefulness of new antifungal drugs, such as voriconazole and posaconazole [20, 21].

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