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# Invasive Aspergillosis before Allogeneic Hematopoietic Stem Cell Transplantation: 10-Year Experience at a Single Transplant Center

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## ABSTRACT

**Hematopoietic stem cell transplantation (HCT) in patients with prior or active invasive aspergillosis (IA) is a frequent consideration. We reviewed outcomes of 2319 patients who underwent transplantation between 1992 and 2001 in our institution, among whom 45 patients (1.9%) had a known history of IA before HCT. Posttransplantation IA occurred in 13 of these 45 patients with a pretransplantation history (29%). Nine infections were considered recurrent by anatomic site and timing. Compared with all other patients who received allogeneic HCT during the same period, patients with histories of IA had lower overall survival (56% versus 77%; $P = .0001$) and higher transplant-related mortality (TRM; 38% versus 21%; $P = .0001$) 100 days after HCT, associated mainly with IA and other pulmonary complications. Among patients with prior IA, posttransplantation IA occurred more frequently in patients who received <1 month of antifungal therapy before HCT (4/6 versus 6/39; $P = .001$). The probability of posttransplantation IA and overall survival among patients who received >1 month of antifungal therapy and had resolution of radiographic abnormalities were not different from those of patients without prior IA. Patients with prior IA who received conditioning with total body irradiation (TBI) had higher TRM compared with those who received nonmyeloablative and non–total body irradiation–based regimens (16/31 versus 2/14; $P = .024$). Thus, the duration of antifungal therapy before transplantation, the resolution of radiographic abnormalities, and conditioning regimens are important variables to consider for minimizing the risk for IA recurrence and TRM after allogeneic HCT.**


## KEY WORDS

Invasive aspergillosis • History • Allogeneic • Hematopoietic cell transplantation

## INTRODUCTION

With the use of increasingly intensive chemotherapy regimens for the induction and consolidation of hematologic malignancies, more patients referred for hematopoietic stem cell transplantation (HCT) have a history of infections, including invasive aspergillosis (IA) [1]. Because of the perceived high risk of recurrent IA and transplant-related mortality (TRM), conventional allogeneic HCT can be considered contraindicated in such patients [2]. Factors predicting outcomes in patients with prior infection have not been fully elucidated, but more knowledge may allow for development of better transplantation and supportive care strategies. The only study published for this purpose to date is a retrospective survey of 48 patients with histories of IA before allogeneic (n = 36) or autologous (n = 11) HCT [3]. In this study, investigators reported an IA recurrence rate of 33%, with outcomes dependent on conditioning regimens; specifically, conditioning with busulfan and cyclophosphamide was associated with beneficial outcomes [3]. We and others have previously reported successful

transplantation in patients with prior pulmonary IA by using nonmyeloablative or reduced-intensity conditioning regimens [4-6]. Supportive care practices may also alter risks for recurrent infection; review of reported cases suggests that risks of recurrent IA might be reduced by the use of prophylactic granulocyte transfusions, surgical resection of lung lesions, and aggressive antifungal prophylaxis after transplantation [5,7-16].

In this retrospective study, we sought to determine the outcomes of first allogeneic HCT among a large cohort of patients (n = 2319) in our institution with and without a known history of IA before transplantation. With the goal of ultimately developing better therapeutic strategies, we evaluated pretransplantation and posttransplantation therapeutic variables that might be associated with posttransplantation outcomes in patients with pretransplantation IA.

## PATIENTS AND METHODS

### Study Patients

To identify patients with histories of IA before HCT, we reviewed the infectious diseases consultation records and computerized databases of all patients who received first allogeneic HCT between December 1, 1992, and May 15, 2001, at the Fred Hutchinson Cancer Research Center. During this time, consultation with Infectious Diseases was usually performed to evaluate all patients with severe opportunistic infections before HCT. Patients who received syngeneic or autologous grafts were not included. The study was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Transplantation was performed according to active institutional protocols. Patients were conditioned either with high-dose total body irradiation (TBI)–based (n = 1474) or non–TBI-based (n = 745) conventional regimens or with nonmyeloablative regimens (n = 100) consisting of 2 Gy of TBI with or without fludarabine [17,18]. Most conventional transplant recipients received methotrexate and cyclosporine (CSP) for graft-versus-host disease (GVHD) prophylaxis [19], and all nonmyeloablative transplant recipients received mycophenolate mofetil and CSP for that purpose [17,18]. Granulocyte colony-stimulating factor (G-CSF) was not given routinely after transplantation. Diagnosis and clinical grading of acute and chronic GVHD were performed according to established criteria [20,21]. GVHD was treated with 1 to 2 mg/kg/d of prednisolone equivalents, resumption of full-dose CSP administration (if applicable), or both. Initial doses of corticosteroids and tapering schedules of immunosuppressive medications were modified at the discretion of the attending physicians according to the presence or absence of malignant cells and the severity of GVHD.

Inpatients were housed in rooms equipped with high-efficiency particulate air filtration, but laminar airflow was used only in the early years of the study (before 1995). Fluconazole (400 mg/d) was given to most patients without histories of IA from the start of conditioning to day 75 after transplantation [22,23] or longer for some patients who received corticosteroids for treatment of GVHD. As part of a randomized protocol, a subset of patients without prior IA received itraconazole (200 mg/d intravenously or 2.5 mg/kg 3 times daily by mouth) for antifungal prophylaxis [24]. Pretransplantation and posttransplantation antifungal therapies of patients with histories of IA were administered at the discretion of the attending transplantation and Infectious Diseases physicians. In general, antifungal therapy was administered with the goal of stabilizing radiographic abnormalities so that transplantation could proceed. Amphotericin-based (n = 40) or azole-based (n = 5) regimens were administered after transplantation to prevent recurrent infection. Seven patients also received prophylactic granulocyte transfusions before engraftment. All other anti-infective prophylactic and therapeutic drugs were provided according to standard protocols [25]. Pulmonary toxicities, defined as signs and symptoms of pulmonary disease with no infectious etiology identified, were identified by chart review.

### Definition of Invasive Fungal Infections

Invasive fungal infections were defined as proven, probable, or possible, according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group guidelines [26]. Briefly, proven disease required histopathologic or microbiologic documentation of a fungus from biopsied tissues, and infection was considered probable if the fungus was identified from culture of bronchoalveolar lavage or sputum when consistent signs and symptoms were present. The day of diagnosis of the fungal infection was the day on which the first positive diagnostic test was performed. For patients whose diagnosis was established after death, the date of death was considered to be the day of diagnosis. Lesions that recurred in the original anatomic location within the first 100 days after HCT were considered to be recurrent; all others were considered to be newly acquired cases of IA.

### Statistical Analyses

The probabilities of posttransplantation IA and TRM were estimated by cumulative incidences, where death and relapse of underlying malignancies were regarded as competing risks. Overall survival after transplantation was estimated by using Kaplan-Meier curves. Characteristics of groups categorized by a history of IA were compared with *t* tests or Wilcoxon rank sum tests for continuous variables and $\chi^2$ tests for

categorical factors. Log-rank tests were used to compare the hazards of IA and TRM after transplantation over time across patient subgroups. The Fisher exact test was used to compare the incidence of pulmonary toxicities by receipt of TBI-containing conditioning.

For analysis of IA and TRM in patients with prior IA, host factors of interest included patient age, underlying disease risk, and pretransplantation cytomegalovirus (CMV) serostatus. Transplantation characteristics included conditioning regimen (TBI-based conventional versus non–TBI-based conventional or nonmyeloablative), hematopoietic stem cell source (bone marrow versus peripheral blood versus cord blood), donor type (related versus unrelated), HLA mismatch between donor and recipient, and donor CMV serostatus. Factors related to prior IA and its therapy included the certainty of the prior IA diagnosis (proven or probable versus possible), anatomic site of infection, pretransplantation chest x-ray (abnormal versus normal), lung surgery, extent of prior lung IA (focal versus multifocal or bilateral infiltrates), type of prior lung IA (nodular and/or cavity versus infiltrative), and duration of pretransplantation antifungal therapy ($\leq$30 versus $>$30 days; $\leq$60 versus $>$60 days). Acute GVHD and engraftment (absolute neutrophil count $>500/mm^3$) were treated as time-dependent covariates in Cox regression models for recurrent IA. Given the low numbers of patients and events, only 2 covariates were assessed at a time in multiple Cox regression models. Factors with univariate $P$ values of $\leq$.2 were considered for inclusion in the multiple regression models.

Two-sided $P$ values from fitted regression models were derived from the Wald test. No adjustments were made for multiple comparisons; $P$ values $<$.05 were considered to be statistically significant.

## RESULTS

### IA before Allogeneic HCT

Forty-five patients with histories of IA were identified among 2319 patients before first allogeneic HCT; this represented 1.9% of the total allogeneic HCT recipients. Thirty-two cases were classified as proven IA, 5 as probable IA, and 8 as possible IA. Anatomic sites of infection included lungs (n = 34), sinus (n = 12), spleen (n = 1), and external ear canal and mastoid bone (n = 1). Three patients had both proven sinus IA and probable lung IA. Among the 34 patients with pulmonary IA, 13 showed focal lung lesions and 21 showed nonfocal lesions; 22 had nodular lesions with or without a cavity, and 12 had more diffuse infiltrative lung lesions.

The median duration of antifungal treatment before HCT was 100 days (range, 7-2422 days). All 45 patients received amphotericin-based regimens for treatment of pretransplantation IA; 5 also received voriconazole, and 2 received caspofungin in combination with amphotericin-based regimens. Thirteen patients underwent surgery, which included lobectomy or wedge resection of the lung. Among the 34 patients with prior lung IA, pretransplantation chest x-rays at the time of HCT were abnormal in 19 and were either normal or showed scars after antifungal therapy and/or lung surgery in 15.

### Patient and Transplantation Characteristics

Patient and transplantation characteristics of the 2319 first allogeneic HCT recipients stratified by history of IA are summarized in Table 1. The median follow-up time was 507 days (range, 1-3573 days) after HCT; more than 75% of patients were followed up for at least 100 days after transplantation. Median ages were 34 years (range, 2-70 years) and 39 years (range, 1-73 years) for patients with or without histories of IA, respectively ($P$ = .020). Aspergillosis before HCT occurred more frequently among patients with acute leukemia (73% versus 36%). The distributions of donor type, cell source, and conditioning regimen also differed significantly between groups: more patients with prior IA received grafts from unrelated donors (60% versus 43%), received G-CSF–mobilized peripheral blood stem cells (PBSC) rather than bone marrow (33% versus 20%), and received nonmyeloablative conditioning (17% versus 4%). All of these therapeutic factors were associated with transplantation during more recent years.

### Incidence of Posttransplantation IA and Survival Outcomes

The incidence of proven or probable IA diagnosed after transplantation was significantly higher among patients with histories of IA compared with those without prior IA (22% versus 7% at day 100; 29% versus 10% at 1 year; $P$ = .001; Figure 1A). Thirteen patients with histories of IA developed posttransplantation IA between day 1 and day 242 after HCT. Posttransplantation IA was found in the original anatomic location in all but 2 cases. Ten patients developed IA within the first 100 days, and 3 developed IA at days 122, 190, and 242 after HCT. The median times to posttransplantation IA within 100 days after HCT were 26 and 54 days among patients with or without prior IA, respectively ($P$ = .030). Seven of the patients with prior IA developed posttransplantation IA before neutrophil engraftment, 6 of whom died before engraftment.

All 13 patients with IA before HCT who subsequently developed posttransplantation IA died despite antifungal therapy. The overall survival of patients with histories of IA was significantly worse compared

**Table 1.** *Patient and Transplantation Characteristics of Allogeneic HCT Recipients with or without Histories of Invasive Aspergillosis (IA)*

| Factor | History of IA | | *P* Value |
|---|---|---|---|
| | Yes (n = 45) | No (n = 2274) | |
| **Patient age, y, median (range)** | **34 (2-70)** | **39 (1-73)** | **.020** |
| **Conditioning, No. patients (% total)** | | | |
| **TBI-based conventional** | **31 (69%)** | **1443 (63%)** | |
| **Non–TBI-based conventional** | **6 (13%)** | **739 (32%)** | |
| **Nonmyeloablative** | **8 (18%)** | **92 (4%)** | **.001** |
| **Donor, No. patients (% total)** | | | |
| **Related** | **18 (40%)** | **1285 (57%)** | |
| **Unrelated** | **27 (60%)** | **989 (43%)** | **.027** |
| **Stem cell source, No. patients (% total)*** | | | |
| **PBSC** | **15 (33%)** | **451 (20%)** | |
| **Bone marrow** | **28 (62%)** | **1800 (79%)** | |
| **Cord blood** | **2 (4%)** | **23 (1%)** | **.005** |
| **Underlying diagnosis, No. patients (% total)†** | | | |
| **Acute leukemia** | **33 (73%)** | **822 (36%)** | |
| **Other malignancy** | **6 (13%)** | **1345 (59%)** | |
| **Nonmalignant disease** | **6 (13%)** | **107 (5%)** | **.001** |
| **Disease risk, No. patients (% total)‡** | | | |
| **Low** | **21 (47%)** | **1345 (59%)** | |
| **High** | **24 (53%)** | **929 (41%)** | **.092** |

*Peripheral blood stem cell (PBSC) group included 15 patients who received both PBSC and bone marrow.

†Acute leukemia indicates acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL); other malignancy indicates myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), lymphoma, multiple myeloma (MM), and other tumors; nonmalignant disease indicates aplastic anemia, immunodeficiencies, and other diseases such as paroxysmal nocturnal hemoglobinuria.

‡Patients were stratified on the basis of underlying disease, as described previously [32]: high risk was defined as active, de novo, or relapsed AML, MDS (refractory anemia with excess of blasts or excess blasts in transformation), myeloproliferative disorder, ALL, CLL, lymphoma, MM regardless of status, accelerated phase or blastic crisis of CML, or other tumors such as renal cell carcinoma. Low risk was defined as nonmalignant diseases, any of the above diseases with unknown disease status or in remission except for MM, CML chronic phase, and MDS (refractory anemia with or without ringed sideroblasts).

with those without prior IA (56% versus 77% at day 100; 37% versus 58% at 1 year; $P \leq .001$; Figure 1B). The probability of TRM among patients with histories of IA was significantly higher than in those without prior IA (38% versus 21% at day 100; 54% versus 32% at 1 year; $P = .001$; Figure 1C). Although most of the difference in TRM was associated with recurrent IA, there was a trend toward an increased risk for TRM that was independent of recurrent infection (18% versus 16% at day 100; 27% versus 24% at 1 year; $P = .055$).

Among 45 patients with histories of IA, 18 patients died of transplant-related causes within the first 100 days, and an additional 7 patients within 1 year after transplantation. A large number of deaths were due to pulmonary complications among patients with prior IA. These included posttransplantation IA (n = 13), idiopathic pneumonia syndrome/diffuse alveolar hemorrhage (n = 5), and non-IA infectious pneumonias (n = 5; *Klebsiella* species, CMV, respiratory syncytial virus, Zygomycetes, and *Acremonium* species).

### Risk Factors for Posttransplantation IA and TRM among Patients with Prior IA

Six patients received antifungal therapy for ≤30 days before proceeding to HCT because of severe aplastic anemia (n = 3) or refractory leukemia (n = 3). Of these 6 patients, 4 developed IA within 100 days after HCT. In univariate analysis (Table 2), a shorter duration of pretransplantation antifungal therapy (≤30 versus >30 days) was associated with increased risks for posttransplantation IA (4/6 versus 6/39; $P = .001$; Figure 2A) and TRM (4/6 versus 14/39; $P = .033$, Figure 3A). Patients who received antifungal therapy for >60 days had a trend toward a decreased risk of posttransplantation IA compared with those who received antifungal therapy for ≤60 days (16% versus 36%; $P = .14$).

Additional risk factors for posttransplantation IA within the first 100 days after HCT included hematopoietic stem cell source (cord blood versus bone marrow versus PBSC; 2/2 versus 6/28 versus 2/15; $P = .001$) and proven or probable diagnosis of prior IA (versus possible IA; 10/37 versus 0/8; $P = .086$). Failure to engraft after HCT was also associated with an increased risk of posttransplantation IA in a Cox regression model. Probabilities of posttransplantation IA at day 100 were not significantly different by conditioning regimens (TBI-based conventional, 26%; non–TBI-based conventional or nonmyeloablative, 14%; $P = .30$). Among patients with a history of IA, receipt of TBI-based conventional conditioning was

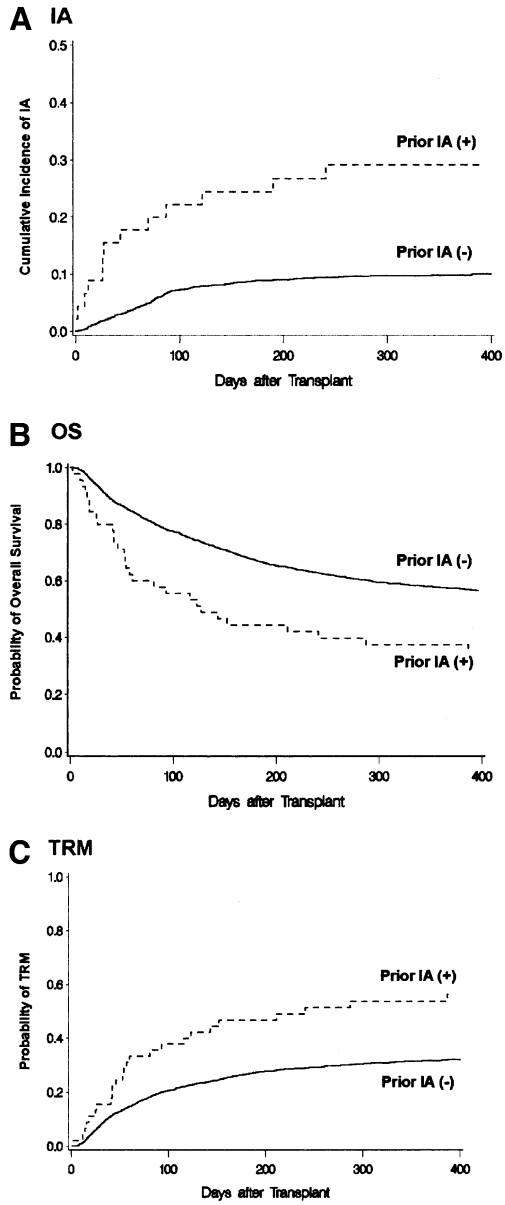


**Figure 1.** Cumulative incidence of invasive aspergillosis (IA), overall survival (OS), and transplant-related mortality (TRM) among allogeneic HCT recipients with or without histories of IA. A, The cumulative incidence of proven or probable IA was significantly higher among patients with histories of IA (broken line; n = 45) as compared with those without prior IA (solid line; n = 2274; 22% versus 7% at day 100; 29% versus 10% at 1 year; $P = .001$). B, The OS of patients with histories of IA (broken line; n = 45) was significantly worse as compared with those without prior IA (solid line; n = 2274; 56% versus 77% at day 100; 37% versus 58% at 1 year; $P = .001$). C, The probability of TRM among patients with histories of IA (broken line; n = 45) was significantly higher as compared with those without prior IA (solid line; n = 2274; 38% versus 21% at day 100; 54% versus 32% at 1 year; $P = .001$).

associated with an increased risk of day 100 TRM compared with nonmyeloablative or non–TBI-based conventional conditioning (TBI-based conventional, 52%; non–TBI-based conventional or nonmyeloablative, 14%; $P = .024$; Figure 3B). Patients who received TBI-based conditioning regimens showed a trend to more pulmonary toxicities after HCT compared with those who received other conditioning regimens (15/31 versus 3/14; $P = .11$).

After adjusting for duration of pretransplantation antifungal therapy (≤30 versus >30 days), no other factor was significantly associated with day 100 IA. Conditioning regimen (TBI-based conventional versus non–TBI-based conventional or nonmyeloablative) and duration of pretransplantation antifungal therapy (≤30 versus >30 days) seemed to confound one another in the model for TRM; ie, neither factor was significantly associated with the outcome in a multiple regression model. Cell source and certainty of prior IA diagnosis were not included in multiple regression models because of small numbers.

We also analyzed the risks for posttransplantation IA only among a subset of patients who had a prior diagnosis of IA that involved the lungs (n = 34). In these patients, as in the larger group of patients with prior IA, a shorter duration of pretransplantation antifungal therapy (≤30 versus >30 days; 2/4 versus 5/30; $P = .048$) and hematopoietic stem cell source (cord blood versus bone marrow versus PBSC; 2/2 versus 4/20 versus 1/12; $P = .002$) were associated with increased risks of posttransplantation IA. There was a trend toward an increased risk of posttransplantation IA in patients with abnormal pretransplantation chest x-ray as compared with patients with normal pretransplantation chest x-ray (6/19 versus 1/15; $P = .064$; Figure 2B). Pretransplantation lung surgery and the extent and type of lung lesions did not significantly influence the probability of developing posttransplantation IA.

To elucidate the combined importance of the 2 identified risk factors before transplantation, we determined the probabilities of IA and overall survival within patient subsets according to pretransplantation antifungal therapy and chest x-ray (Figure 4). For this analysis, high-risk patients were considered to be those who received ≤30 days of pretransplantation antifungal therapy or had pretransplantation abnormalities on chest x-ray, and low-risk patients were considered to be those who received more than 30 days of pretransplantation antifungal therapy and had normal chest x-rays before transplantation. High-risk patients with prior IA (n = 22) had a significantly higher incidence of posttransplantation IA and lower survival at 1 year after HCT as compared with those without prior IA (45% versus 10%, $P = .001$; and 23% versus 58%, $P = .001$, respectively). However, the cumulative incidence of posttransplantation IA and overall survival among low-risk patients with prior IA (n = 23) were not statistically different from those

**Table 2.** *Risk Factor Analysis for Posttransplantation Invasive Aspergillosis (IA) and Transplant-Related Mortality (TRM) within 100 Days after Allogeneic HCT among 45 Patients with Histories of IA*

| Factor | Total No. | Day 100 IA, No. Patients (% Total) | *P* Value | Day 100 TRM, No. Patients (% Total) | *P* Value |
|---|---|---|---|---|---|
| **Duration of pretransplantation antifungal Rx (d)** | | | | | |
| ≤30 | 6 | 4 (67%) | | 4 (67%) | |
| >30 | 39 | 6 (15%) | .001 | 14 (36%) | .033 |
| ≤60 | 14 | 5 (36%) | | 7 (50%) | |
| >60 | 31 | 5 (16%) | .14 | 11 (35%) | .350 |
| **Donor** | | | | | |
| Related | 18 | 2 (11%) | | 5 (28%) | |
| Unrelated | 27 | 8 (30%) | .21 | 13 (48%) | .300 |
| **Conditioning regimen** | | | | | |
| TBI-based conventional | 31 | 8 (26%) | | 16 (52%) | |
| Non–TBI or nonmyeloablative | 14 | 2 (14%) | .30 | 2 (14%) | .024 |
| **CMV serostatus** | | | | | |
| D−/R− | 11 | 1 (9%) | | 3 (27%) | |
| D+/R− | 6 | 3 (50%) | | 3 (50%) | |
| Any D/R+ | 28 | 6 (21%) | .24 | 12 (43%) | .640 |
| **Patient age at transplantation (y)** | | | | | |
| <19 | 16 | 4 (25%) | | 6 (38%) | |
| 19-40 | 13 | 4 (31%) | | 4 (31%) | |
| >40 | 16 | 2 (13%) | .70 | 8 (50%) | .530 |
| **Disease risk*** | | | | | |
| Low | 21 | 3 (14%) | | 6 (29%) | |
| High | 24 | 7 (29%) | .21 | 12 (50%) | .130 |
| **HLA mismatch** | | | | | |
| No | 26 | 7 (27%) | | 11 (42%) | |
| Yes | 19 | 3 (16%) | .47 | 7 (37%) | .840 |
| **Stem cell source†** | | | | | |
| PBSC | 15 | 2 (13%) | | 4 (27%) | |
| Bone marrow | 28 | 6 (21%) | | 12 (43%) | |
| Cord blood | 2 | 2 (100%) | .001 | 2 (100%) | .008 |
| **Prior IA diagnosis** | | | | | |
| Proven/probable | 37 | 10 (27%) | | 18 (49%) | |
| Possible | 8 | 0 (0%) | .086 | 0 (0%) | .020 |
| **Prior IA lung involvement** | | | | | |
| No | 11 | 3 (27%) | | 4 (36%) | |
| Yes | 34 | 7 (21%) | .75 | 14 (41%) | .710 |
| **Acute GVHD grade‡** | | | | | |
| 0 or I | 13 | 5 (38%) | | | |
| II–IV | 32 | 5 (16%) | .87 | | |
| **Engraftment‡** | | | | | |
| No | 12 | 7 (58%) | | | |
| Yes | 33 | 3 (9%) | .029 | | |

D indicates donor; R, recipient.

*Patients were stratified on the basis of underlying disease, as described previously [32]: high risk was defined as active, de novo, or relapsed acute myeloid leukemia, myelodysplastic syndrome (refractory anemia with excess of blasts or excess blasts in transformation), myeloproliferative disorder, acute lymphocytic leukemia, chronic lymphocytic leukemia, lymphoma, multiple myeloma regardless of status, accelerated phase or blastic crisis of chronic myeloid leukemia, or other tumors such as renal cell carcinoma; low risk was defined as nonmalignant diseases, any of the above diseases with unknown disease status or in remission except for multiple myeloma, chronic myeloid leukemia chronic phase, and myelodysplastic syndrome (refractory anemia with or without ringed sideroblasts).

†Peripheral blood stem cell (PBSC) group included 1 patient who received both PBSC and bone marrow.

‡*P* values were determined by Cox regression models, with acute GVHD and engraftment treated as treated as time-dependent covariates.

among patients without prior IA (13% versus 10%, $P = .65$; and 52% versus 58%, $P = .47$, respectively).

### Outcomes and Risks among Patients with Proven and Probable prior IA

Outcomes were also analyzed after the 8 patients with "possible IA" diagnoses were eliminated from the cohort, leaving 37 patients with proven or probable IA before HCT. Results were similar to those in the overall analysis. Receipt of antifungal therapy for less than 30 days before HCT, receipt of cord blood as compared with bone marrow or PBSC, presence of an abnormal chest x-ray at the time of HCT, and delayed neutrophil engraftment were associated with higher risks of recurrent IA (data not shown). Probability of IA and TRM curves were not substantially different

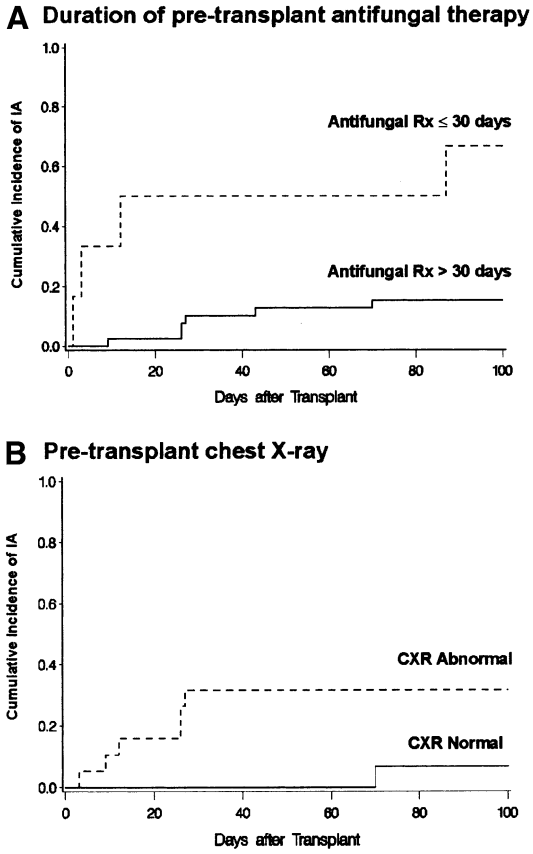


**Figure 2.** Invasive aspergillosis (IA) after allogeneic HCT among patients with histories of IA. A, The cumulative incidence of proven or probable IA was significantly higher among patients with histories of IA who received pretransplantation antifungal therapy (Rx) for ≤30 days (broken line; n = 6) as compared with >30 days (solid line; n = 39; 67% versus 15% at day 100; $P = .001$). B, Among patients with histories of IA that involved the lungs, the cumulative incidence of proven or probable IA was somewhat higher in patients whose pretransplantation chest x-ray (CXR) was abnormal (broken line; n = 19) as compared to those with normal CXR (solid line; n = 16; 32% versus 7% at day 100; $P = .064$).

after the 8 patients with possible IA were eliminated from the analyses (data not shown).

## DISCUSSION

Invasive infections with *Aspergillus* species are common in patients who receive cytotoxic therapies for hematologic malignancies, both before and after HCT [1,27-29], and clinicians are often faced with the dilemma of balancing necessary cytotoxic therapies with the risk of infection-related death. With this study, we sought to determine the answer to 2 primary questions: (1) are recurrent IA and TRM rates so high in patients with histories of IA so as to make the HCT unwise? and (2) are there pretransplantation variables that may affect overall outcomes? Our review suggested that although the risk of TRM was still high in such patients, patients with IA who had resolution of radiographic abnormalities after receipt of more than 1 month of antifungal therapy had similar risks for infection and death to patients with no prior IA. The conditioning regimen and stem cell source may affect the risks for recurrent IA and TRM.

The probability of posttransplantation IA among patients with histories of infection in this study (29% at 1 year) was similar to that of the previous European Organization for Research and Treatment of Cancer study (33%; 16/48 patients) [3]. The absence of sensitive diagnostic tests and microbiology limit conclusions with regard the to timing of acquisition; however, when considering the early onset of symptoms and anatomic site of involvement, it seemed that a substantial number of patients developed recurrent rather than newly acquired infection. Analysis of pretransplantation variables revealed that a shorter duration of pretransplantation antifungal therapy and per-

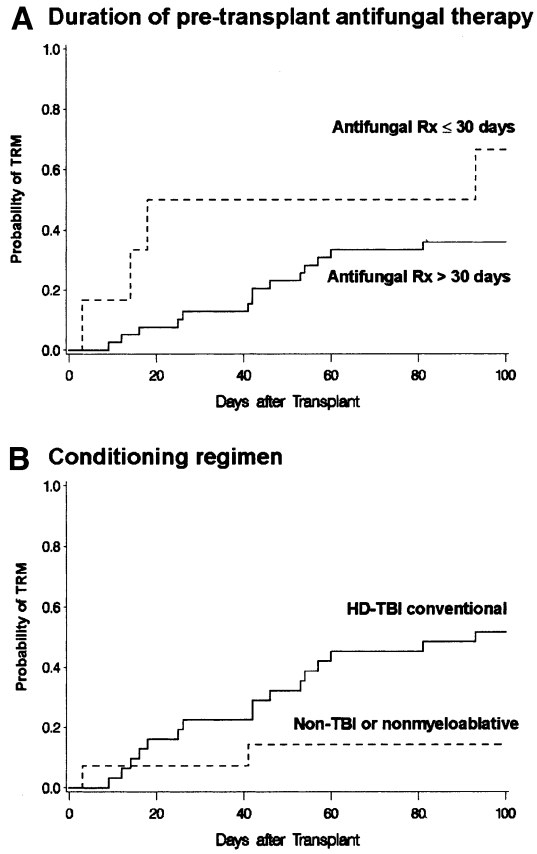


**Figure 3.** Transplant-related mortality (TRM) after allogeneic HCT among patients with histories of IA. A, The probability of TRM was significantly higher among patients with histories of IA who received pretransplantation antifungal therapy (Rx) for ≤30 days (broken line; n = 6) compared with >30 days (solid line; n = 39; 67% versus 36% at day 100; $P = .033$). B, The probability of TRM was significantly higher among patients with histories of IA who received high-dose (HD) TBI-based conventional conditioning (solid line; n = 31) as compared with those who received non–TBI-based conventional or nonmyeloablative conditioning (broken line; n = 14; 52% versus 14% at day 100; $P = .024$).

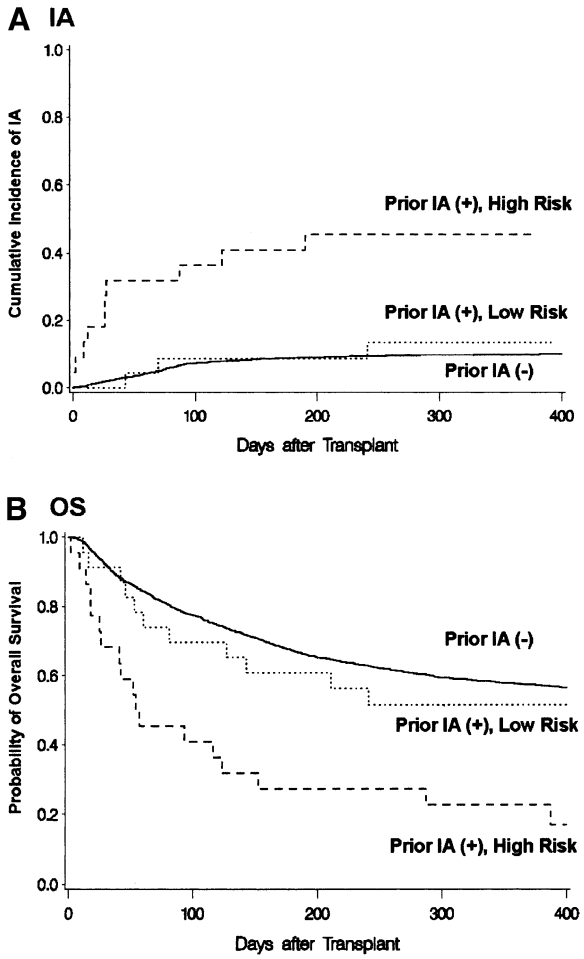


**Figure 4.** Cumulative incidence of invasive aspergillosis (IA) and overall survival (OS) after allogeneic HCT. Patients with prior IA who were at high risk (defined by pretransplantation antifungal therapy for ≤30 days or abnormal chest x-ray; broken line; n = 22) had a significantly higher incidence of posttransplantation IA (A) and lower survival (B) at 1 year after HCT as compared with those without prior IA (solid line; n = 2274; 45% versus 10%, $P = .001$; and 23% versus 58%, $P = .001$, respectively). However, the cumulative incidence of posttransplantation IA (A) and survival (B) among patients with prior IA who were at low risk (defined by pretransplantation antifungal therapy for >30 days and normal chest x-ray; dotted line; n = 23) were not statistically different from those among patients without prior IA (solid line; n = 2274; 13% versus 10%, $P = .65$; and 52% versus 58%, $P = .47$, respectively).

sistent radiographic abnormalities were associated with increased risks of posttransplantation IA. It was not possible to determine the optimal duration of antifungal therapy with these data, because the patients who underwent HCT with evidence of active pulmonary infection were more likely to have a condition warranting expedited conditioning therapy, such as relapsed malignancy. Our data also suggest that there may be a subset of patients with prior IA who essentially have "normal" risks for aspergillosis after transplantation; specifically, patients who received more than 1 month of antifungal therapy and had resolution of radiographic abnormalities before conditioning had equivalent risks for infection and death compared with patients who had no IA history.

Prior case reports suggested successful control of recurrent invasive fungal infections by prophylactic granulocyte transfusion and G-CSF administration to shorten the duration of neutropenia after HCT [5,7-9]. Our study did demonstrate that failure to engraft after HCT was associated with an increased risk of recurrent IA. However, in our study, 7 patients received prophylactic granulocyte transfusions without apparent benefit. This lack of effect is consistent with recent data on granulocyte transfusion for the treatment of infections [30,31], but the small numbers of patients evaluated and the inherent selection bias associated with elected granulocyte therapy limit our abilities to draw conclusions relating to utility. Stem cell sources may affect the risk for recurrent infection. In our study, 2 of 2 cord blood recipients with prior IA developed post-HCT infection; it may be that delayed engraftment in this setting may encourage reactivation of pulmonary IA [30]. Finally, several reports previously indicated that surgical resection of lung lesions might reduce the risk of recurrent IA after HCT [10-16]. Our data failed to confirm this suggestion; however, this could be a function of small number of cases and variability in surgical approaches.

Several prior reports have described small series of patients with histories of IA who underwent successful allogeneic HCT with nonmyeloablative (2 Gy of TBI alone) or reduced-intensity (fludarabine, busulfan, and antithymocyte globulin; melphalan) conditioning regimens [4-6]. Our data suggested that high-dose TBI-based conditioning was associated with an increased risk for TRM, primarily because of pulmonary toxicity, compared with the other regimens. Patients with histories of IA may be more vulnerable to lung damage by high-dose TBI, other organisms, or local activation of inflammatory cytokines [32]. This observation, which should be confirmed by more detailed prospective studies, might have important implications for the selection of conditioning regimens for patients with histories of IA.

This study has several strengths and weaknesses. The most important limitation is that this retrospective study compared outcomes in groups of patients who differed with regard to underlying diseases and other transplant variables. Also, we did not routinely perform sensitive screening tests to identify occult IA in asymptomatic patients before transplantation. Finally, the low number of cases of recurrent IA limited our ability to perform multiple Cox regression models to analyze the relative importance of multiple variables. However, prospective identification of patients with histories of IA, use of conservative and consensus-derived definitions for IA, and evaluation of out-

comes among a very large cohort of allogeneic HCT recipients (n = 2319) allowed us to make a number of potentially therapeutically relevant observations.

In summary, our data indicate that a history of IA is not an absolute contraindication for allogeneic HCT, especially if adequate therapy is administered before transplantation. These data suggest that pretransplantation antifungal therapy should be given for at least 30 days or longer until radiographic abnormalities become significantly reduced or normalize. Nonmyeloablative or non–TBI-based myeloablative regimens might be preferable for the conditioning of allogeneic HCT if underlying disease can be controlled and the risk of graft rejection can be overcome. Because of delayed engraftment, cord blood transplantation may be associated with increased risks for reactivated disease. Additional methods to measure disease activity and response to antifungal therapy (eg, galactomannan antigenemia or polymerase chain reaction) may be useful in future strategies to stage IA before myeloablative HCT or subsequent immunosuppressive therapies.

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