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Pre-existing invasive fungal infection is not a contraindication for allogeneic HSCT for patients with hematologic malignancies: a CIBMTR® study

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Abstract

Background—Patients with prior invasive fungal infection (IFI) increasingly proceed to allogeneic hematopoietic cell transplantation (HSCT), however, little is known about the impact of prior IFI on survival.

Methods—Patients with pre-transplant IFI (cases; n=825) were compared to controls (n=10,247). A subset analysis assessed outcomes in leukemia patients pre- and post-2001.

Results—Cases were older with lower performance status (KPS), more advanced disease, higher likelihood of acute myeloid leukemia (AML), and having received cord blood, reduced intensity conditioning (RIC), mold-active fungal prophylaxis and more recently transplanted. *Aspergillus* spp. and *Candida* spp. were the most commonly identified pathogens. 68% of patients had primarily pulmonary involvement. Univariate and multivariable analysis demonstrated inferior progression-free (PFS) and overall (OS) survival for cases. At 2 years, cases had higher mortality and shorter PFS with significant increases in non-relapse mortality (NRM) but no difference in relapse. One year probability of post-HSCT IFI was 24% (cases) and 17% (control, p <0.001). The predominant cause of death was underlying malignancy; infectious death was higher in cases (13 vs 9%). In the subset analysis, patients transplanted before 2001 had increased NRM with inferior OS and PFS compared to later cases.

Conclusions—Pre-transplant IFI is associated with lower PFS and OS after allogeneic HSCT but significant survivorship was observed. Consequently, pre-transplant IFI should not be a contraindication to allogeneic HSCT in otherwise suitable candidates.

Introduction

Invasive fungal infections (IFI) historically portend a poor prognosis in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). An observational study of the Transplant Associated Infection Surveillance Network (TRANSNET) suggests that post-HSCT IFI remains problematic, with cumulative incidence rates varying between 5.8–7.7% in the allogeneic transplant setting[1]. Historically, prior mold infection was considered a relative contraindication to transplantation. Although the risk of reactivation of fungal infection in the setting of HSCT is high, HSCT may be the only remaining treatment option in the face of an otherwise fatal hematologic malignancy. With the advent of novel broader spectrum antifungal agents, prophylaxis and treatment of fungal infections have significantly improved. Likewise, use of granulocyte colony-stimulating growth factors has decreased the

length of neutropenia, a major risk factor for IFI[2–7]. Additionally, reduced intensity conditioning (RIC) transplantation may help to minimize opportunistic infections and to maximize graft-versus-tumor effects[8, 9]. These advances in HSCT and its associated supportive care have enabled patients to successfully receive a HSCT despite having previously documented fungal infection[8, 10–12]

To date, there are limited data from large multicenter cohorts comparing outcomes in patients who have undergone allogeneic HSCT with known prior yeast or mold infection to a matched cohort without previous IFI. Fukuda et al. reported the outcomes of 45 patients with pre-transplant invasive aspergillosis (IA) treated in the pre-mold active azole era and demonstrated that post-transplant recurrent IA was seen in 29% and that the cases had lower overall survival than controls. Notably, those patients with >1 month of antifungal therapy, received RIC or those that had resolution of radiographic disease findings had better outcomes[11]. Martino et al. reported a retrospective survey of 129 patients with a history of proven or probable IA of whom 44% had undergone RIC[12]. They observed a 22% post-transplant progression rate for IA at 2 years, which occurred more frequently in those patients undergoing conventional myeloablative HSCT, for patients with grade II–IV acute graft versus host disease (GVHD), for patients receiving bone marrow or cord blood allografts, and for patients with CMV disease. Most recently, a report from the EBMT analyzed the long term outcomes of pre-existing IA on transplant outcomes of patients with acute leukemia only[13]. Data were available from 1152 pts with a median follow-up of 52 months. There was no significant impact of the pre-existing IA on overall survival, relapse free survival, non-relapse mortality, acute or chronic GVHD, although there was a trend toward lower overall survival and higher non-relapse mortality[13]. Herein, we explore the CIBMTR data base on the influence of participating center documented preexisting IFI on clinical outcomes after HSCT and the risk factors associated with fungal disease progression post-transplant. We also examine the impact of changes in supportive care over the past decade versus earlier time periods to determine if the evolution of conditioning regimen and advances in supportive care translate into improved clinical outcomes in patients with pre-existing IFI undergoing HSCT.

Materials and Methods

Data Source and Patients

Data were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR is a research affiliate of the International Bone Marrow Transplant Registry, Autologous Blood and Marrow Transplant Registry, and the National Marrow Donor Program (NMDP) established in 2004. It comprises a voluntary working group of more than 500 transplantation centers worldwide that contribute data on consecutive allogeneic and autologous HCT procedures to a statistical center at the Medical College of Wisconsin in Milwaukee and the NMDP Coordinating Center in Minneapolis, Minnesota. Participating centers report longitudinal data on all transplants and compliance is monitored by on-site audits. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research

is collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act Privacy Rule. Studies conducted by the CIBMTR are performed under guidance and review of the Institutional Review Board of the National Marrow Donor Program. Transplant essential data, collected for consented patients participating in CIBMTR data collection, include demographic, disease type and stage, survival, relapse, graft type, the presence of GVHD, and cause of death data. A subset of CIBMTR participants are selected for comprehensive research level data collection by weighted randomization.

Subject Eligibility

The primary analysis includes all adult and pediatric patients receiving a first allogeneic HSCT for acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), chronic myeloid leukemia (CML), or myelodysplasia (MDS) between 2001 and 2009. Patients with severe aplastic anemia or lymphoma were excluded, recognizing the difference in natural history. The secondary analysis includes only patients with AML or ALL receiving a first allogeneic transplant following myeloablative conditioning between 1995 and 2009, comparing outcomes pre- and post-2001 due to improvements in supportive care and as a surrogate for emergence of novel antifungal agents with recognition that FDA approval for caspofungin and voriconazole was 2001 & 2002, respectively.

Cases—Patients reported to the CIBMTR as having a documented or suspected IFI in the 12 months prior to allogeneic transplantation were considered as cases[14–16]. This information is reported as an event but diagnostic criteria used to determine IFI are not captured. Data on the organism, if available, and the site of infection are reported by the transplant center. Patients for whom CIBMTR forms indicated the site of infection was oral cavity or genitalia only were excluded from analysis, recognizing that these situations likely represented mucosal disease or colonization rather than true infection. Patients with an IFI reported more than 12 months prior to transplant were excluded.

Controls—All patients reported as "No" IFI in the 12 months prior to transplant and who were transplanted at the same centers were considered as contemporary controls. Any patients without any response (missing data) to the question of pre-transplant IFI were excluded. This approach was instituted to provide balance regarding selection criteria for HSCT as well as minimize ascertainment bias of documented/suspected IFI rather than draw controls from centers that may have different selection criteria and thus present an unintended bias toward better risk patients.

Endpoints

Non-relapse mortality (NRM) was the primary outcome. Secondary outcomes included relapse, progression-free survival (PFS), overall survival (OS), acute GVHD, and chronic GVHD. Each outcome was analyzed in both the primary and secondary analysis. NRM was defined as death within the first 28 days of transplant for any cause or death without relapse or progression of the primary malignancy. NRM was assessed at Day 100, 1 year and 2 years after HSCT. Relapse was defined as the recurrence of malignancy from a remission state. OS was determined from the date of HSCT to the time of death or last follow-up. Death was

considered a competing risk for assessment of cumulative incidence of relapse, acute and chronic GVHD. For PFS, patients were considered treatment failures at the time of relapse of underlying malignancy or death from any cause.

Statistical Analysis

Patient-, disease- and transplant-related factors were compared between groups using the Chi-square test for categorical variables and the Wilcoxon test for continuous variables. The probabilities of PFS and OS were calculated using the Kaplan-Meier estimator. Probability estimates for other endpoints were generated using cumulative incidence functions to account for competing risks.

Multivariable analyses for outcomes at 2 years were performed using pseudo-value approach to adjust for other potentially significant covariates and determine if there is an interaction with the main effect variable of the presence or absence of a pre-transplant IFI [17, 18]. Other risk factors include age, CMV serostatus, disease, disease stage, conditioning intensity, graft type, degree of HLA match, GVHD prophylaxis, peri-transplant T cell depletion and post-transplant use of growth factor. Interaction between the main effect and significant covariates were tested and reported to assess for differences between cases and controls. Multivariable models were built using a backward variable selection method. All P-values are 2-sided, the level of significance (alpha) of 0.05 was used throughout. All analyses were carried out using SAS Version 9.3 statistical software (SAS Institute, Cary, NC).

Results

Patient Characteristics

Patient, disease and transplant characteristics are presented in Table 1 for the primary analysis of the 825 patients with reported prior IFI transplanted between 2001 and 2009 and the 10,247 controls transplanted at the same center without reported prior IFI. The fungal pathogens that were identified as IFI included 199 *Candida* spp. infections, 281 *Aspergillus* spp. infections, and 50 "other" fungal infections, including *Mucormycosis*, *Fusarium* and *Cryptococcus*. Infections reported as "suspected" were identified in 295 patients and are included. Five hundred fifty-seven (68%) patients had pulmonary infections while 261 (32%) had only extra-pulmonary involvement. The median time from infection to transplant was approximately 3.5 months (range <1–12 months); thus, more than 50% of the patients experienced their IFI more than 100 days prior to HSCT. For both cases and controls, the time from diagnosis of hematologic malignancy to transplant were 7 (<1 – 310) and 8 (<1 – 607) months (p=0.277), respectively. Details of the status of the IFI at time of transplant were not available in the CIBMTR database. As expected, significant differences between the cases and the controls existed. Cases were older, more likely to have compromised performance status and more advanced acute leukemia, and to have received mold active secondary fungal prophylaxis. Cases were more likely to receive cord blood as a stem cell source, to receive reduced intensity/non-myeloablative conditioning regimens and transplants in more recent years, and to receive non-methotrexate-containing GVHD prophylaxis regimens[19]. No significant differences were found in donor/recipient CMV

status, gender, use of growth factor support, and use of steroid-containing GVHD prophylaxis between the case and control cohorts.

Survival, Non-relapse Mortality and Relapse Outcomes

Univariate probabilities of outcomes of interest after HSCT between subjects with pre-existing IFI and those without IFI are summarized in Table 2. In nearly all outcomes measured, statistical differences between the cases and the controls at 1, 3, and 5 years after HSCT were noted. There were no differences in univariate transplant outcomes for OS, TRM, DFS, RR, aGVHD or cGVHD (data not shown) when comparing *Aspergillus* spp. cases, *Candida* spp. cases, Other fungal cases, and Suspected IFI so all pre-transplant IFIs were combined for the univariate analysis. OS was 30% (95% Confidence interval (CI): 26 – 34%) at 5 years in patients with pre-transplant IFI versus 45% (95% CI: 44 – 46%) in the control population (p < 0.0001) (Figure 1). The lower OS was a composite reflection of higher relapse rates and higher NRM in the cases. Interestingly, acute GVHD by 100 days and chronic GVHD at 1, 3, and 5 years were statistically less frequent in the patients with reported pre-existing IFI (aGVHD: cases 34%, controls 39%, p=0.0022; cGVHD at 5 years: cases 36%, controls 45%, p <0.0001) (Table 2). Additionally, reported post-transplant IFI occurred more commonly in the cases versus controls at 3 months, 6 months, and 1 year after HSCT. Only 144 (17%) patients with pre-HSCT IFI were subsequently reported as developing a post-transplant IFI; of these, 46 (32%) experienced relapse with the previously identified fungal pathogen, while 97 (67%) patients had fungal pathogens different from the original pathogen reported. One patient had an unidentified fungus reported.

As shown in Table 3, on multivariable analysis, cases with pre-transplant IFI had higher overall mortality [Relative Risk {RR} 1.33, 95%CI (1.19 – 1.48), p <0.0001] and shorter PFS at 2 years [RR of relapse or death 1.24, 95%CI (1.11 – 1.38), p <0.0001] with significant increases in NRM [RR 1.27 (1.09 – 1.49), p = 0.002] compared to the control cohort (Figure 2). Relapse rates were not significantly increased [RR=1.04, 95%CI (0.91 – 1.18), p = 0.58]. The risk of being diagnosed with aGVHD by day 100 was similar between the cases and controls [RR 0.9, 95%CI (0.80 – 1.02), p = 0.09] with lower risk of cGVHD [RR 0.81, 95%CI (0.71 – 0.93), p = 0.002] identified in the cases. Additionally, when comparing cases with the control patients at one year, there was a greater likelihood of experiencing a post-transplant IFI [RR 1.36, 95%CI (1.16 – 1.58), p = 0.001].

Other factors negatively impacting OS and PFS include older age by decade, receipt of ATG or alemtuzumab, recipient CMV serostatus positive regardless of donor CMV serostatus, AML or ALL, more advanced disease, receiving cord blood or other related donor, and performance status <90%. OS, but not PFS, was decreased in patients receiving less than a well matched unrelated donor. PFS but not OS was improved if the patient received myeloablative conditioning. Non-relapse mortality was increased in older patients, ALL, CML, intermediate but not advanced disease status, use of either alternative related, mismatched unrelated, or cord blood as the stem cells source, and lower performance status. At 2 years, the NRM was significantly better for patients receiving RIC/NMA conditioning. Finally, the use of ATG or alemtuzumab, advanced disease stage, and RIC/NMA conditioning increased the relative risk of relapse.

The relative risk for a fungal infection of any kind at 1 year post transplant was enhanced by the presence of pre-transplant IFI compared with controls [RR 1.35, 95%CI (1.16 – 1.58)]. Other risk factors associated with increased risk of fungal infection at 1 year post-transplant include older age, receipt of alemtuzumab [RR 1.51, 95%CI (1.24 – 1.85)] or ATG exposure [RR 1.16, 95%CI (1.04 – 1.29], advanced malignancy [RR 1.45, 95%CI (1.29–1.63)] and cord blood [RR 1.48, 95%CI (1.24 – 1.75)] or mismatched related donor [RR 1.43, 95%CI (1.13 – 1.79)). For the cases, there was no impact on OS, PFS, NRM, and GVHD based on the type of pre-transplant IFI, whether yeast or mold (data not shown).

Cause of Death

There were no differences between cause of death between patients with pre-transplant IFI's and controls (see Table 4). Recurrent disease was the most likely cause of death in both cohorts. Organ failure, GVHD, and infections comprised the majority of other etiologies, with rare events including graft failure, secondary malignancy, bleeding, and idiopathic pneumonitis syndrome.

Secondary analysis

A secondary analysis was performed to determine the influence of era of diagnosis of IFI, acknowledging the impact of advances in antifungal therapy and supportive care in more recent years. This analysis was restricted to patients receiving myeloablative allogeneic transplantation for acute myeloid or lymphoid leukemia, and reflected the interval between 1995 and 2009 (suppl Table 1).

For subjects with pre-transplant IFI, the median age was lower in the earlier compared to the later time period, but again patients were more likely to have advanced disease and myeloid leukemia. Amphotericin products were most commonly used as the antifungal prophylaxis agent of choice, either solely or in conjunction with other agents, in the earlier years. No differences were seen in GVHD prophylaxis regimens containing steroids, ATG or alemtuzumab.

Similar to observations made from the primary analysis, within the secondary analysis, univariate and adjusted probabilities for overall mortality, NRM, and IFI developing within one year post-transplant were higher for patients with pre-transplant IFI versus the control cohort. PFS was also worse among patients with diagnosed pre-HSCT IFI. Interestingly, when outcomes of study subjects with pre-transplant IFI within the time frame 1995–2000 were compared to a more recent patient population who underwent myeloablative conditioning for AML and ALL performed between 2001 and 2009, improved OS (Figure 3) was noted in the modern era, which appear attributable to decreases in NRM (Figure 4).

Discussion

This retrospective CIBMTR analysis is performed on a large cohort of transplant patients reported to have documented or suspected pre-transplant IFI. The vast majority of these IFI were a consequence of infections with *Candida* spp. and *Aspergillus* spp., although other fungal infections were represented, including *Fusarium* and *Mucormycosis*. A similar analysis has recently been reported by the EBMT of a cohort of HSCT patients with acute

leukemia, transplanted between 2005 and 2010, specifically with preexisting invasive *Aspergillus* spp. (IA) infections. Their analysis identified that excellent outcomes can be achieved despite the preexisting IA. Our data substantiate these observations[13]. Historically, before the emergence of mold-active echinocandins and azoles, many centers would not consider HSCT in patients with pre-existing IFI, particularly for those patients with antecedent mold infections. This current study demonstrates that positive outcomes can be obtained in these patients and that suspected or documented pre-transplant IFI by themselves, whether they are IA, candida or other identified mycoses, should not preclude patients from pursuing potentially curative transplant procedures for underlying malignant disease. Lower PFS and OS are seen in these patients; however, this augmented mortality was not due to the identified higher rates of recurrent fungal infection, but rather, influenced by disease status. This finding is not unexpected, as patients with fungal infections would be predicted to be more likely be transplanted later, to assure ample time for antifungal therapy to achieve response to treatment prior to transplantation (often defined by radiographic remissions[11]), to receive reduced intensity conditioning or to be electively transplanted only if disease is recurrent. The data reported within this analysis would suggest that delaying HSCT for patients with effectively treated pre-HSCT IFI may not be necessary and could actually contribute to worse outcomes due to disease recurrence.

The study also demonstrated that progress has been made in treating IFI with improved outcomes in the more modern era[20]. Our secondary analysis could not demonstrate any major change in any outcome in the amphotericin era between patients with pre-transplant IFI's and those without when compared to the more recent expanded-spectrum azole/echinocandin era. This secondary analysis was performed as a surrogate for changes in antifungal prophylaxis since the data reported to the CIBMTR for antifungal prophylaxis collects antifungal drug received but not dose, sequence of agents or length of schedule. Notwithstanding these limitations, as a whole, patients transplanted in more recent years were more likely to survive the HSCT experience [21,22]. A higher risk of death for patients with pre-transplant IFI was noted in all years, but this has recently diminished due to a more global reduction in NRM. Interestingly, in the primary analysis we found that 83% (n = 681) of the subjects with documented or suspected pre-transplant IFI were not reported to develop post-transplant IFI's. One hundred forty-three (17%) patients were diagnosed with post-transplant IFI, similar to other reported fungal infection incidence for patients without prior history[1]. Interestingly, only one third of those patients who developed a post-transplant IFI actually reactivated their prior IFI, a lower incidence than reported previously [11] and actually could suggest that these individuals are possibly predisposed to developing IFI [23].

We do not have information about how many and which patients with pre-transplant IFI from the selected centers did not proceed to transplant. When one reviews the patient, disease and transplant variables, there are clues that indicate that these patients were indeed a selected population. They were more likely to have been treated with more aggressive antifungal prophylaxis and more likely to have been treated with reduced intensity/non-myeloablative transplant procedures. Interestingly, in the more recent patient population, there were less extra pulmonary fungal infections reported prior to transplant, possibly suggesting that new diagnostic approaches and improvements of radiologic detection may have contributed to better pre-transplant fungal detection followed by early therapy [24].

Unfortunately, we do not have documentation of the extent of the pre-transplant infection or the degree of infection control of the reported pre-transplant IFI. The patients who proceeded to transplant were more likely to have more advanced disease and lower performance status, but these observations might suggest that they were more deeply treated with chemotherapy before taking them to transplant. Additionally, it is curious to see that after transplant, there were lower rates of GVHD reported in the cases. There was a higher likelihood of utilizing RIT in the cases. One could also hypothesize that awareness of the pre-existing IFI influenced the treatment team to less aggressively taper calcineurin inhibitor immune suppression to avoid GVHD and subsequent use of high dose corticosteroid exposure, an approach that may not have been taken otherwise in patients with advanced disease. Alternatively, more frequent use of voriconazole in the cases may have led to higher levels of calcineurin inhibitors owing to drug-drug interactions, which may explain the lower rates of GVHD. Another possibility relates to recent observations that treatment of resistant candida has been augmented by adjunct therapy with calcineurin inhibitors [25,26]. These hypotheses cannot be tested, as information regarding the decision-making of the transplant teams on management in these cases is not available, as is often the case in retrospective registry studies.

There are limitations to this study. Collected CIBMTR data do not provide pre-or post-HSCT detailed antifungal prophylaxis schedules. We are limited by the data included within the CIBMTR forms; we do not have information regarding dose, duration, possible sequence of treatment nor do we have availability of drug levels. There are ongoing updates of the data collection forms, but the forms' evolution will not impact the data previously collected. Additionally, there is a dearth of immune reconstitution data that accompanies these analyses. Also, there are variations in how centers may report "suspected" IFI. We would anticipate that many of the academic centers contributing data to the CIBMTR would report "suspected" IFI for patients with "probable" IFI as defined according to established EORTC or other similar guidelines[27]. Reporting for this study is entered within the category defined as "suspected" IFI within the CIBMTR data collection fields but the congruence between the two definitions is not confirmed. Reporting is up to the transplant leaders at the transplant centers. Hopefully, as more detailed tools evolve to dissect mild, moderate and severe infections with their impact on the host, such as defined within the Manual of Procedures of the Blood & Marrow Transplant Clinical Trials Network, a greater understanding will emerge which should positively impact the transplant recipient[28, 29]. Ultimately, definitive conclusions of the impact on pre-existing IFI can only be drawn from prospective studies, but with the emergence of better antifungal prophylaxis agents, the patient numbers to perform such studies may not be present.

Overall, 30% long-term overall survival was achieved in patients with perceived life-threatening pre-transplant IFI and most commonly with advanced disease at time of transplant. Additionally, the risk of post-transplant fungal disease re-emergence was low, only recorded at 6% in this retrospective study. Forewarned is forearmed, and with more active primary or secondary fungal prophylaxis for mold and resistant *Candida* species, transplantation should remain a high priority consideration, rather than a contraindication, for patients with hematologic malignancies and prior IFI. However, these data still demonstrate that lower outcomes are seen in these patients with pre-transplant IFIs and

further analysis is required to determine if we can identify those factors that impact survival such as the presence of yeast versus mold infections, the impact of complete or partial radiographic resolution at the time of transplantation, and whether or not, longer-term utilization of post-transplant antifungal therapies could improve survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Key points

Documented pre-transplant IFI is associated with lower PFS and OS after allogeneic HSCT. However, mortality post-transplant is more influenced by advanced disease status than previous IFI. Pre-transplant IFI does not appear to be a contraindication to allogeneic HSCT
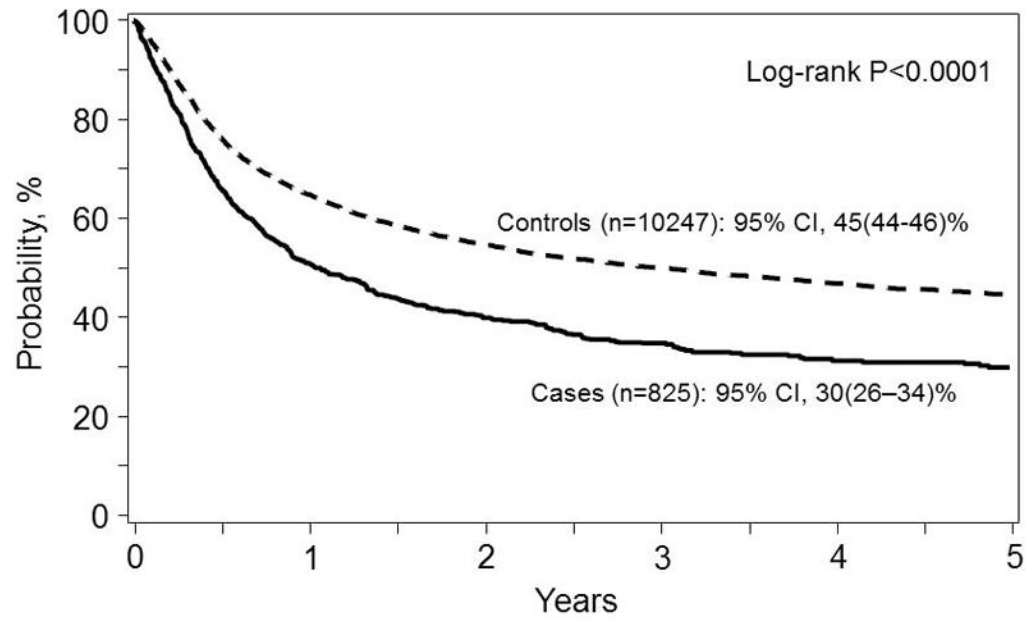
Figure 1.
Overall survival from the time of transplant for patients with (Cases, solid line) and without (Controls, dashed line) an invasive fungal infection in the 12 months prior to allogeneic transplantation. The point-wise comparison at 5 years is shown.
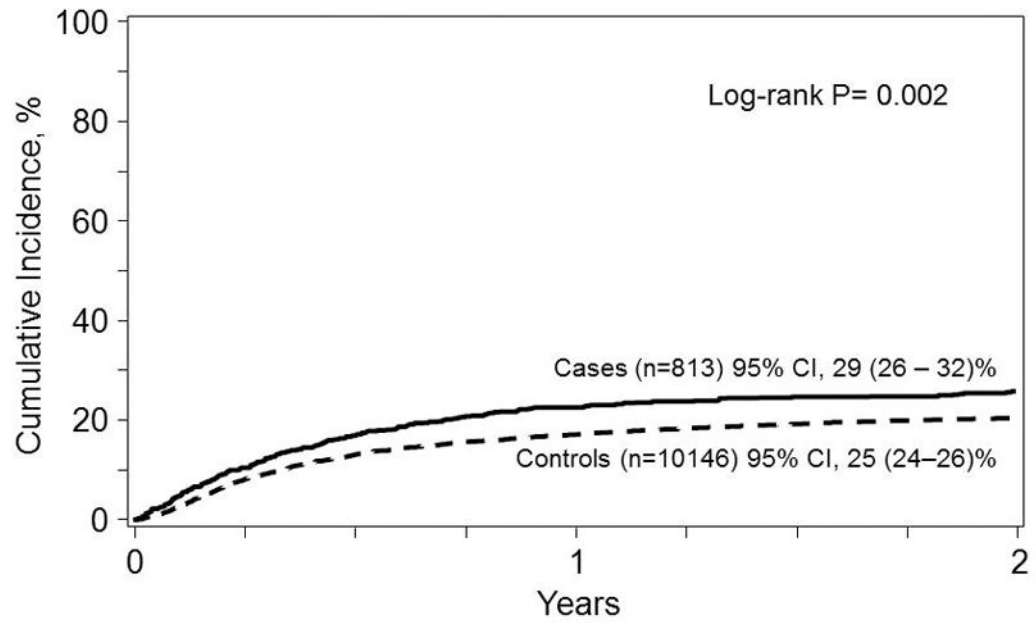
Figure 2.
Non-relapse mortality from the time of transplant for patients with (Cases, solid line) and without (Controls, dashed line) an invasive fungal infection in the 12 months prior to allogeneic transplantation. The point-wise comparison at 5 years is shown.

Figure 3.
Overall survival from the time of transplant for AML and ALL patients receiving myeloablative conditioning with IFI transplanted between 1995 – 2000 (solid line) and between 2001 – 2009 (dashed line). The point-wise comparison at 5 years is shown.
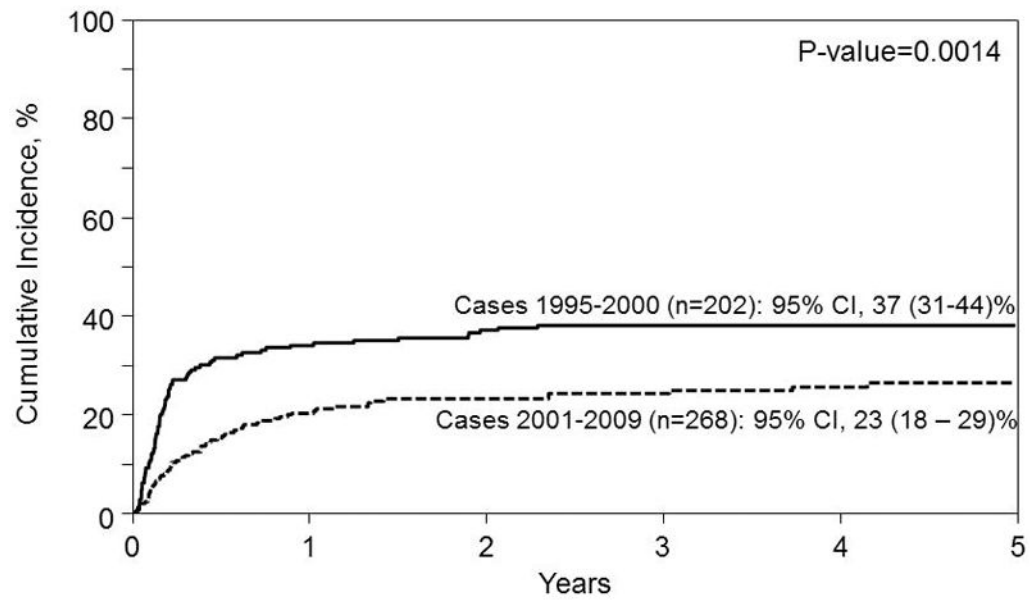
Figure 4.
Non-relapse mortality from the time of transplant for AML and ALL patients receiving myeloablative conditioning with IFI transplanted between 1995 – 2000 (solid line) and between 2001 – 2009 (dashed line). The point-wise comparison at 5 years is shown.

Table 1

Characteristics of patients who underwent allogeneic transplants for AML, ALL, CML, MDS and had Invasive fungal infection within 12 months prior to transplant vs. those who had no documented invasive fungal infection within 12 months prior to transplant, reported to the CIBMTR, from 2001 to 2009

Variable	Pre-tx invasive fungal infection N (%)	All others N (%)	p_value
Patient related			
Number of patients	825	10247	
Number of centers	158	158	
Age, median(range), years (age)	44 (1 – 74)	39 (<1 – 79)	<0.001
Age at transplant, years			<0.001
<=10	81 (10)	1039 (10)	
11–20	96 (12)	1313 (13)	
21–30	97 (12)	1417 (14)	
31–40	89 (11)	1495 (15)	
41–50	150 (18)	1848 (18)	
>50	312 (38)	3135 (31)	
Gender			0.937
Male	465 (56)	5761 (56)	
Female	360 (44)	4486 (44)	
Lansky/Karnofsky score at transplant			<0.001
<90	282 (34)	2507 (24)	
>=90	504 (61)	7294 (71)	
Missing	39 (5)	446 (4)	
Disease-related			
Disease			<0.001
AML	609 (74)	5310 (52)	
ALL	171 (21)	2548 (25)	
CML	22 (3)	1578 (15)	
MDS	23 (3)	811 (8)	
Disease stage at transplant			<0.001
AML/ALL/CML/MDS Early	378 (46)	5335 (52)	
AML/ALL/CML Intermediate	218 (26)	2701 (26)	
AML/ALL/CML/MDS Advanced	229 (28)	2211 (22)	
Time from Infection to transplant (months)			
0–2	211 (26)		
2–6	479 (58)		
6–12	135 (16)		
Time from Infection to transplant, median(range), days	105 (7 – 362)		
Time from Infection to transplant			
0–29 days	49 (6)		
30–59 days	154 (19)		
60–99 days	186 (23)		

Variable	Pre-tx invasive fungal infection N (%)	All others N (%)	p_value
100–179 days	291 (35)		
180–365 days	145 (18)		
Type of fungal infection			
Aspergillus	281 (34)		
Mucormycosis	9 (1)		
Other Mold infection	19 (2)		
Candida albicans	56 (7)		
Other Candida	143 (17)		
Suspected fungal infection	295 (36)		
Other	22 (3)		
Infection Location			
Localized extrapulmonary	261 (32)		
Pulmonary	557 (68)		
Combine Pulmonary and extrapulmonary	7 (<1)		
Received antifungal prophylaxis			<0.001
None	108 (13)	1555 (15)	
Amphotericin +/− others	136 (16)	885 (9)	
Fluconazole +/− others	279 (34)	5764 (56)	
Itraconazole +/− others	54 (7)	674 (7)	
Voriconazole +/− others	175 (21)	994 (10)	
Posiconazole +/− others	23 (3)	163 (2)	
Echinocandin +/− others	50 (6)	212 (2)	
Transplant-related			
Donor/Recipient CMV status			0.268
+/+	303 (37)	3652 (36)	
+/−	81 (10)	1041 (10)	
−/+	215 (26)	2631 (26)	
−/−	187 (23)	2563 (25)	
Missing	39 (5)	360 (4)	
Donor/recipient gender match			0.002
Male-Male	289 (35)	3541 (35)	
Male-Female	195 (24)	2456 (24)	
Female-Male	150 (18)	2024 (20)	
Female-Female	133 (16)	1802 (18)	
Donor gender missing	58 (7)	424 (4)	
Donor/recipient HLA match			0.003
Cord blood	124 (15)	1196 (12)	
HLA-identical siblings	356 (43)	4340 (42)	
Other related	34 (4)	345 (3)	
Well matched unrelated	180 (22)	2722 (27)	
Partially matched unrelated	87 (11)	1149 (11)	
Mismatched unrelated	19 (2)	290 (3)	

Variable	Pre-tx invasive fungal infection N (%)	All others N (%)	p_value
Unrelated (HLA match information missing)	25 (3)	205 (2)	
GVHD prophylaxis			<0.001
t-cell depletion	47 (6)	601 (6)	
FK506+MTX +/− other	222 (27)	2969 (29)	
FK506 +/− other	98 (12)	1289 (13)	
MTX+CsA +/− other	252 (31)	3589 (35)	
CsA +/− other	206 (25)	1799 (18)	
Conditioning regimen			<0.001
Myeloablative	506 (61)	7276 (71)	
Non-myeloablative/RIC	319 (39)	2971 (29)	
Lymphocyte depleting agents (ATG/alemtuzumab as conditioning or GVHD prophylaxis)			0.034
ATG alone	270 (33)	2920 (28)	
Alemtuzumab alone	31 (4)	437 (4)	
No ATG or Alemtuzumab	524 (64)	6890 (67)	
G-CSF, GM-CSF			0.512
No	466 (56)	5667 (55)	
Yes	359 (44)	4580 (45)	
Steroid containing GVHD prophylaxis			0.703
No	790 (96)	9840 (96)	
Yes	35 (4)	407 (4)	
Graft type			0.005
Bone Marrow	193 (23)	2752 (27)	
Peripheral blood	508 (62)	6299 (61)	
Cord blood	124 (15)	1196 (12)	
Year of transplant			<0.001
2001–2002	146 (18)	1969 (19)	
2003–2004	123 (15)	1972 (19)	
2005–2006	174 (21)	2571 (25)	
2007–2008	236 (29)	2546 (25)	
2009	146 (18)	1189 (12)	
Median follow-up of survivors, months	37 (2 – 120)	48 (1 – 128)	

Abbreviations: AML = acute myelogenous leukemia; ALL = acute lymphoblastic leukemia; CML = chronic myelogenous leukemia; GVHD = graft versus host disease; MTX = methotrexate; CsA = cyclosporine; FK506 = tacrolimus; BM = bone marrow; PB = peripheral blood; CB = cord blood; TBI = total body irradiation.

[a] Other mould infections included: Fusarium species and Cryptococcus species

[b] Other infections included: Histoplasmosis and other fungus

Table 2

Univariate outcomes of patients who underwent allogeneic transplants for AML, ALL, CML, MDS and had Invasive fungal infection within 12 months prior to transplant vs. those who had no documented invasive fungal infection within 12 months prior to transplant, reported to the CIBMTR, from 2001 to 2009

Outcomes	Pre-tx invasive fungal infection		All others		
	N Eval	Probability (95% CI)	N Eval	Probability (95% CI)	P-value
Overall survival from transplant	825		10247		
@ 1 year		54 (48–55)%		65(64–66) %	<.0001
@ 3 years		35 (31–38)%		50 (49–51)%	<.0001
@ 5 years		30 (26–34)%		45 (44–46)%	<.0001
Relapse	813		10146		
@ 1 year		33 (29–36) %		26(25–27) %	0.0002
@ 3 years		42 (39–46) %		35 (34–36)%	<.0001
@ 5 years		45 (41–49) %		39 (38–40)%	0.0018
Non-relapse mortality	813		10146		
@ 1 year		23 (20–26) %		17(17–18) %	0.0003
@ 3 years		27 (24–30) %		22 (21–23)%	0.0046
@ 5 years		29 (26–32) %		25 (24–26)%	0.0347
Disease free survival	813		10146		
@ 1 year		45 (41–48) %		57(56–58) %	<.0001
@ 3 years		31(28–34) %		44 (43–45)%	<.0001
@ 5 years		27(23–31) %		37 (36–38)%	<.0001
Acute GVHD (grade 2–4)	822		10224		
@ 100 days		34 (31–37) %		39(38–40) %	0.0022
Chronic GVHD	810		10098		
@ 1 year		31 (28–34) %		39(38–40) %	<.0001
@ 3 years		35 (32–38) %		44 (43–45)%	<.0001
@ 5 years		36 (32–39) %		45 (44–46)%	<.0001
Fungal infection within 1 year post TX	824		10168		
@ 100 days		17 (15–20) %		11(10–11) %	<.0001
@ 6 months		21 (19–24) %		14 (13–14)%	<.0001

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Outcomes	Pre-tx invasive fungal infection		All others		
	N Eval	Probability (95% CI)	N Eval	Probability (95% CI)	P-value
@ 1 years		24(21–27) %		17 (16–18)%	<.0001

Table 3

Multivariable analysis of patients who underwent allogeneic transplants for AML, ALL, CML, MDS and had Invasive fungal infection within 12 months prior to transplant vs. those who had no documented invasive fungal infection within 12 months prior to transplant, reported to the CIBMTR, from 2001 to 2009

Variable	2 yr OS RR (95% CI)	p	2 yr PFS RR (95% CI)	p	2 yr NRM RR (95% CI)	p	2 yr Relapse RR (95% CI)	p
Main Effect		**<0.0001**		**<0.0001**		**0.002**		**NS**
Control	1.00		1.00		1.00		1.00	
Pre-HSCT IFI	1.33 (1.19 – 1.48)		1.24 (1.11 – 1.38)		1.27 (1.09 – 1.49)		1.04 (0.91 – 1.18)	
Age, years		**<0.0001**		**<0.0001**		**<0.0001**		**NS**
10	1.00		1.00		1.00			
11 – 20	1.21 (1.06 – 1.39)	0.0051	1.21 (1.06 – 1.37)	0.0039	1.75 (1.41 – 2.17)	<0.0001		
21 – 30	1.28 (1.12 – 1.48)	0.0004	1.33 (1.17 – 1.51)	<0.0001	1.79 (1.43 – 2.24)	<0.0001		
31 – 40	1.47 (1.28 – 1.69)	<0.0001	1.44 (1.27 – 1.65)	<0.0001	2.32 (1.86 – 2.89)	<0.0001		
41 – 50	1.58 (1.38 – 1.81)	<0.0001	1.56 (1.37 – 1.77)	<0.0001	2.48 (1.99 – 3.08)	<0.0001		
> 50	1.81 (1.59 – 2.06)	<0.0001	1.70 (1.50 – 1.93)	<0.0001	2.86 (2.30 – 3.55)	<0.0001		
Ex vivo TCD		**0.0008**		**<0.0001**		**NS**		**<0.0001**
None	1.00		1.00				1.00	
ATG	1.09 (1.02 – 1.18)	0.0128	1.13 (1.06 – 1.22)	0.0002			1.12 (1.03 – 1.22)	0.0109
Alemtuzumab	1.28 (1.11 – 1.48)	0.0006	1.58 (1.37 – 1.81)	<0.0001			1.71 (1.46 – 2.01)	<0.0001
D/R CMV status		**<0.0001**		**0.0003**		**0.0136**		**0.0295**
Neg/Neg	1.00		1.00		1.00		1.00	
Pos/Pos	1.19 (1.10 – 1.29)	<0.0001	1.16 (1.07 – 1.25)	0.0002	1.16 (1.02 – 1.31)	0.0206	1.10 (1.00 – 1.21)	0.0540
Pos/Neg	1.12 (1.00 – 1.26)	0.0459	1.07 (0.96 – 1.20)	0.1948	1.17 (0.99 – 1.38)	0.0614	1.00 (0.87 – 1.15)	0.9923
Neg/Pos	1.21 (1.10 – 1.32)	<0.0001	1.19 (1.10 – 1.29)	<0.0001	1.17 (1.03 – 1.33)	0.0127	1.14 (1.03 – 1.26)	0.0113
Missing	1.20 (1.12 – 1.41)	0.0319	1.15 (0.98 – 1.35)	0.0873	1.44 (1.15 – 1.80)	0.0015	0.93 (0.75 – 1.14)	0.4886
Disease		**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**
AML	1.00		1.00		1.00		1.00	
ALL	1.10 (1.02 – 1.19)	0.0119	1.17 (1.08 – 1.26)	<0.0001	1.36 (1.21 – 1.53)	<0.0001	0.95 (0.87 – 1.04)	0.2955
CML	0.84 (0.78 – 0.93)	0.0004	1.02 (0.93 – 1.11)	0.6934	1.32 (1.15 – 1.50)	<0.0001	0.82 (0.73 – 0.92)	0.0006

Variable	2 yr OS RR (95% CI)	p	2 yr PFS RR (95% CI)	p	2 yr NRM RR (95% CI)	p	2 yr Relapse RR (95% CI)	p
MDS	0.64 (0.56 – 0.73)	<0.0001	0.67 (0.59 – 0.75)	<0.0001	1.02 (0.85 – 1.23)	0.8239	0.60 (0.52 – 0.69)	<0.0001
Disease Stage		**<0.0001**		**<0.0001**		**0.0286**		**<0.0001**
Early	1.00		1.00		1.00		1.00	
Intermediate	1.27 (1.18 – 1.36)	<0.0001	1.24 (1.15 – 1.33)	<0.0001	1.15 (1.03 – 1.28)	0.0094	1.24 (1.14 – 1.36)	<0.0001
Advanced	2.24 (2.01 – 2.42)	<0.0001	2.13 (1.98 – 2.30)	<0.0001	1.10 (0.97 – 12.3)	0.1289	2.33 (2.13 – 2.54)	<0.0001
Donor		**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**
HLA ID-sib	1.00		1.00		1.00		1.00	
Other related	1.64 (1.38 – 1.93)	<0.0001	1.47 (1.25 – 1.72)	<0.0001	1.82 (1.47 – 2.27)	<0.0001	0.93 (0.77 – 1.13)	0.4968
Cord	1.32 (1.18 – 1.47)	<0.0001	1.21 (1.09 – 1.35)	<0.0001	2.01 (1.70 – 2.38)	<0.0001	0.77 (0.67 – 0.89)	0.0004
WM unrelated	0.88 (0.81 – 0.95)	0.0015	0.87 (0.80 – 0.93)	0.0002	1.11 (0.98 – 1.25)	0.0870	0.76 (0.69 – 0.84)	<0.0001
Other unrelated	1.14 (1.04 – 1.25)	0.0038	1.04 (0.95 – 1.13)	0.3625	1.78 (1.56 – 2.01)	<0.0001	0.66 (0.59 – 0.74)	<0.0001
Karnosky PS		**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**
90%	1.00		1.00		1.00		1.00	
< 90%	1.38 (1.29 – 1.47)	<0.0001	1.32 (1.24 – 1.41)	<0.0001	1.26 (1.14 – 1.39)	<0.0001	1.21 (1.12 – 1.31)	<0.0001
Missing	1.27 (1.04 – 1.40)	0.0114	1.14 (1.00 – 1.31)	0.0588	1.15 (0.94 – 1.42)	0.1807	1.12 (0.95 – 1.33)	0.1746
Conditioning		**NS**		**<0.0001**		**<0.0001**		**<0.0001**
Myeloablative	1.00		1.00		1.00		1.00	
RIC/NMA			1.15 (1.07 – 1.23)		0.79 (0.71 – 0.88)		1.36 (1.25 – 1.47)	

Table 4

Cause of death of patients who underwent allogeneic transplants for AML, ALL, CML, MDS and had IFI within 12 months prior to HSCT vs. those who had no documented IFI within 12 months prior to HSCT, reported to the CIBMTR, from 2001 to 2009

Variable	Pre-tx invasive fungal infection N(%)	All others N(%)
Cause of death		
Graft rejection	2 (<1)	63 (1)
Infection	107 (21)	919 (18)
IPN	7 (1)	93 (2)
Organ Failure	76 (15)	733 (14)
GVHD	46 (9)	585 (11)
Recurrent/Persistent Disease	242 (47)	2173 (42)
Secondary malignancy	6 (1)	52 (1)
Hemorrhage	13 (3)	131 (3)
other cause	15 (3)	288 (6)
Unknown	5 (<1)	77 (2)