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ORIGINAL ARTICLE

Incidence and risk factors of probable and proven invasive fungal infection in adult patients receiving allogeneic hematopoietic stem cell transplantation

Yao-Chung Liu [a,b,c], Sheng-Hsuan Chien [b,c], Nai-Wen Fan [c,d], Ming-Hung Hu [b,e], Jyh-Pyng Gau [b,c,*], Chia-Jen Liu [b,c], Yuan-Bin Yu [b,c], Chun-Yu Liu [b,c], Liang-Tsai Hsiao [b,c], Jin-Hwang Liu [b,c], Tzeon-Jye Chiou [b,c], Po-Min Chen [b,c], Cheng-Hwai Tzeng [b,c]

[a] *Department of Medicine of Yang-Ming Branch, Taipei City Hospital, Taiwan*
[b] *Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*
[c] *Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan*
[d] *Department of Ophthalmology, Taipei Veterans General Hospital, Taipei, Taiwan*
[e] *Department of Medicine, Cardinal Tien Hospital, Taipei, Taiwan*

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KEYWORDS
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Background: To investigate the incidence and risk factors for the occurrence of proven or probable invasive fungal infection (IFI) in adult patients receiving allogeneic hematopoietic stem cell transplantation (HSCT).
Methods: We retrospectively analyzed 421 patients undergoing HSCT between 2002 and 2013 in our hospital. The risk factors for the occurrence of IFI were analyzed using Cox regression models.
Results: Thirty-one patients with the median age of 42 years (range, 19–60 years) developed IFI after HSCT. The post-HSCT IFI incidence was 7.4% and median time from HSCT to the diagnosis of IFI was 139 days (range, 2–1809 days). Of the pretransplant factors, European Group for Blood and Marrow Transplantation (EBMT) risk score > 2 ($p = 0.001$) and prior history of IFI ($p = 0.006$) or type 2 diabetes mellitus (DM; $p = 0.042$) were the significant predictors for

* Corresponding author. Division of Hematology and Oncology, Department of Medicine, Taipei Veterans General Hospital, Number 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan.
E-mail address: jpgau@vghtpe.gov.tw (J.-P. Gau).

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post-HSCT IFI in univariate analyses. In multivariate analysis, EBMT risk score > 2 ($p = 0.015$) and prior history of IFI ($p = 0.006$) retained significance. Of the post-transplant factors, acute graft-versus-disease (GVHD) overall Grade III–IV ($p < 0.001$), extensive chronic GVHD ($p = 0.002$), development of post-transplant lymphoproliferative disorders ($p = 0.005$), and the use of high-dose steroids ($p < 0.001$) were statistically significant in univariate analyses. After multivariate analysis, high-dose steroids ($p < 0.001$) and acute GVHD overall Grade III–IV ($p = 0.045$) retained significance.

Conclusion: These results suggest that risk group stratification prior to HSCT and monitoring of IFI in patients with severe GVHD receiving high-dose steroids is mandatory to reduce the mortality and morbidity of post-HSCT IFI, especially in those with prior history of IFI.

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Introduction

Invasive fungal infection (IFI), especially aspergillosis, is a serious complication following hematopoietic stem cell transplant (HSCT) and can cause significant morbidity and mortality in recipients of the procedure.[1,2] Recent studies have demonstrated that routine prophylactic use of fluconazole during HSCT decreased the risk of invasive candidiasis to a low incidence of 1.1–5%.[2–6] On the contrary, increasing incidence of invasive mold infection has been reported in recent series.[7,8] Analyses of The Transplant-Associated Infection Surveillance Network (TRANSNET) database showed that the cumulative annual incidence of IFIs were 7.7, 8.1, 5.8, and 1.7 in every 100 transplants for matched-unrelated allogeneic, mismatch-related allogeneic, matched-related allogeneic, and autologous HSCT, respectively.[2] In the TRANSNET database, the estimated post-HSCT 1-year survivals of invasive candidiasis and invasive aspergillosis are only 33% and 25%, respectively.[2] In the other prospective study, high post-HSCT mortality in invasive candidiasis, about 49% at 12 weeks, was also noted.[9]

IFI may occur during the pre-engraftment neutropenic period, the early postengraftment period or in the late postengraftment period after Day +100.[10,11] The reported risk factors for IFI after HSCT include transplant type, use of antifungal prophylaxis, conditioning regimen, compatibility of human leukocyte antigen between donor and recipient, cytotoxic conditioning therapy-related intestinal mucosal damage, stem cell source, and disease status.[7,11–13] In addition, other important recipient-related factors were age at HSCT, duration of pre-engraftment neutropenia, graft failure or rejection, the severity of acute and chronic graft-versus-host disease (GVHD), use of steroids, the presence of cytomegalovirus (CMV) infection, and geoclimatic factor.[5,7,11–14] Taiwan is located in Southeastern Asia with generally hot and wet climatic condition. It is presumed that patients receiving HSCT here may have an increased incidence of IFI. Our study attempts to look at the incidence of IFI after HSCT in a single medical center of Taiwan and to explore the associated risk factors and the final outcome after the infection.

Materials and methods

Study patient population

We retrospectively reviewed the medical records of 421 adult patients (age ≥ 18 years) who received allogeneic HSCT between January 1, 2002 and December 31, 2013 in the Blood and Marrow Transplant Center of Taipei Veterans General Hospital in Taipei, Taiwan. Transplant-related clinical data including age, gender, disease diagnosis, type of transplant, human leukocyte antigen (HLA) matching, conditioning regimen, GVHD, and other clinical complications were all retrospectively collected. For those undergoing multiple transplants, only the data pertinent to the last procedure were included. The retrospective review of medical records was approved by the Institutional Ethical Committee in agreement with the Helsinki Declaration of 1975, revised in 2008.

Transplant details and conditioning regimens

HLA-typing tests of low to intermediate resolution for six or eight alleles (HLA-A, -B, -DR, or -C) were performed to select donors for allogeneic HSCT. Donor's types included sibling donor, matched unrelated marrow, haploidentical donor (father or mother) or umbilical cord blood. Accordingly, patients were categorized into the fully matched group or mismatched group. Myeloablative conditioning regimens including busulfan combined with cyclophosphamide, or total body irradiation of 1200 cGy combined with cyclophosphamide. Fludarabine-based nonmyeloablative conditioning regimens were administered to elderly patients or those with comorbidities.

Antifungal prophylaxis, monitoring, and treatment

Standard antifungal prophylaxis with fluconazole was started on initiation of conditioning till the end of neutropenia. From 2010 onwards, echinocandin, such as micafungin or caspofungin, was given to patients with history of pre-transplant fungal infection, intolerance to fluconazole toxicity, high EBMT risk score, or as the clinical physician's option.

From October 2009 onwards, galactomannan (GM) antigen assay was performed for clinical suspicion of IFI at our hospital. For those pre- or post-transplant patients with positive GM test and clinically suspicious fungal infection based on symptoms and imaging studies, medications against *Aspergillus* infection were given for prophylaxis or treatment.

Empirical antifungal therapy with voriconazole or liposomal amphotericin-B were used in post-transplant patients with diagnosis of aspergillosis, or invasive yeast infection. Voriconazole, posaconazole, or liposomal amphotericin-B were not used as routine antifungal prophylaxis.

GVHD prophylaxis and treatment

Standard protocol including cyclosporine and short-term low dose methotrexate were adopted for GVHD prophylaxis. In addition, recipients of unrelated donor transplants also received rabbit antithymocyte globulin. Severity of acute GVHD (aGVHD) was graded according to the system developed by Glucksberg and Thomas and the severity of the chronic GVHD (cGVHD) in each organ was determined according to NIH scoring system.[15,16] Patients that developed aGVHD $>$ functional overall Grade II, extensive cGVHD, or alloimmune lung disease would usually receive high-dose methylprednisolone 1–2 mg/kg/d.

Transplantation risk evaluation

According to the age at HSCT, disease stage prior transplantation, time interval from diagnosis to transplant, donor type, and donor recipient sex combination, we retrospectively calculated transplantation risk for all study patients based on EBMT risk scoring system.[17] The EBMT risk score was also used as a variable factor in our analysis.

Clinical evaluation and definitions

This retrospective review was to determine the incidence of probable or proven IFI, according to the revised definitions of European Organization for Research and Treatment of Cancer (EORTC)/the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) Consensus Group.[18] In addition to host factor, the probable IFI requires the presence of both a clinical criterion and a mycological criterion. In our study, patients with clinical criteria of IFI, including typical signs on lung computed tomography, images showing sinonasal, or CNS infection, required supplementary evidence from mycological criteria including positive results from cytology, direct microscopic examinations, or fungal culture or indirect test of the GM antigen in plasma, serum, bronchoalveolar lavage fluid, or cerebrospinal fluid. The proven IFI required proof of IFI by demonstration of fungal elements by microscopic examination or positive results of fungal culture in diseased tissue or blood.

Statistical analysis

Possible predictors for IFI were retrospectively analyzed using Cox proportional hazard models. Factors with statistical significance ($p < 0.05$) upon univariate analysis were included in multivariate analysis. Results are expressed as hazard ratios and their corresponding 95% confidence intervals (CIs). Age of 40 years was adopted as the cutoff value based on median age at HSCT and the results of receiver operating characteristic curve. For statistical analysis, SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) was used.

Results

Clinical characteristics of study patients

In total, 421 patients who received HSCT between January 2002 and December 2013 were analyzed. The median age at HSCT was 40 years (range, 18-67 years). Hematological malignancies comprised 88.4% ($n = 372$) of indications for HSCT and the other nonmalignant disease 11.6% ($n = 49$). Donor type included 208 matched sibling donors (49.4%), 203 unrelated donors (48.2%), eight haploidentical donors (1.9%), and two umbilical cord blood donors (0.5%). Median time of follow-up after HSCT was 445 days (range, 10–4434 days). The clinical characteristics of patients are summarized in Table 1.

Incidence of IFI

The annual incidence of post-HSCT IFI between 2002 and 2013 presented with a bimodal pattern in our study (Fig. 1). The overall cumulative IFI incidence was 7.4% (31/421), including 23 (5.5%) proven and eight (1.9%) probable cases. Median time from HSCT to the diagnosis of IFI was 139 days (range, 2–1809 days). Sixteen of 31 patients were diagnosed with IFI prior to post-HSCT Day +139 and the other 15 patients after Day +139. In our study, 15 of 421 patients (3.6%) had a history of IFI prior to HSCT. Among the 15 patients, four (26.6%) were diagnosed with recurrent IFI. Among the 31 patients with IFI, nine were confirmed as infection with *Aspergillus* spp. (29%), 17 with *Candida* spp. (54.8%), and one patient (3.24%) each with *Acremonium* spp, mucormycosis, *Trichosporon asahii*, unidentified yeast, and *Cryptococcus neoformans*. We also adopted the median time for all IFI as cutoff time point to define early- and late-onset infection (occurring prior to or after Day +139). Invasive mold infection tended to occur late after transplant with eight of 11 (73%) mold IFIs presenting as late infection in contrast to seven of 20 (35%) in yeast IFI. Regarding the pretransplant diagnosis of the 31 patients with IFI, 16 (51.6%) were myeloid malignancies, 12 (38.7%) had lymphoid malignancies and three had the diagnosis of severe aplastic anemia.

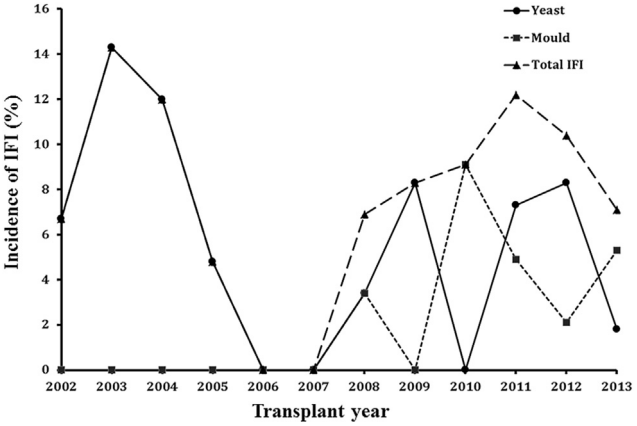
Pretransplant predictors for the occurrence of IFI

A total of 256 patients were defined as high risk of transplantation based on EBMT risk score $>$ 2 at starting HSCT. Among these patients, 26 (10.3%) developed IFI. Comparing patients of early IFI with those of late onset, early IFI had a higher proportion of patients with EBMT risk score $>$ 2 [14/16 (87.5%) versus 12/15 (80%)]. The median EBMT risk score was 4 for the early IFI and was 3 for the late infection

Table 1 Clinical characteristics of study patients ($n = 421$)

Patient characteristics	*n*	%
Gender		
Female	179	42.5
Male	242	57.5
Age at HSCT (y), median		
≤ 40	203	48.2
> 40	218	51.8
EBMT risk		
≤ 2	169	38.5
> 2	252	61.5
Indication for HSCT		
AML/MDS	173	41.1
MPD	31	7.4
ALL	77	18.3
Lymphoma	64	15.2
MM	21	5.0
SAA	49	11.6
Other	6	1.4
Transplant number		
1	379	90.0
Multiple	42	10.0
Prior history of IFI		
Yeast	9	2.1
Mold	6	1.4
Donor type		
MSD	208	49.4
Unrelated marrow	203	48.2
Haploidentical	8	1.9
Umbilical cord blood	2	0.5
Donor relation		
Related	208	49.4
Unrelated	213	50.6
Conditioning regimen		
TBI based	182	43.2
Chemobased	239	56.8
Myeloablative	276	65.6
Nonmyeloablative	145	34.4
Antifungal prophylaxis		
Fluconazole	368	87.4
Echinocandin	53	12.6
Mycological detection of IFI		
No detection	390	92.6
Yeast	20	4.8
Blood culture	17	4.0
Biopsy	2	0.5
BAL	1	0.3
Mold	11	2.6
GM in serum, BAL or CSF	9	2.1
Biopsy	2	0.5

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; BAL = bronchoalveolar lavage; CSF = cerebrospinal fluid; EBMT = European Group for Blood and Marrow Transplantation; GM = galactomannan antigen assay; HSCT = hematopoietic stem cell transplantation; IFI = invasive fungal infection; MDS = myelodysplastic syndromes; MM = multiple myeloma; MPD = myeloproliferative disorders; MSD = matched sibling donor; MUD = matched unrelated donor; SAA = severe aplastic anemia; TBI = total body irradiation.



Transplant year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Total IFI (%)	6.7	14.3	12	4.8	0	0	6.9	8.3	9.1	12.2	10.4	7.1
Yeast (%)	6.7	14.3	12	4.8	0	0	3.4	8.3	0	7.3	8.3	1.8
Mould (%)	0	0	0	0	0	0	3.4	0	9.1	4.9	2.1	5.3

Figure 1. The annual cumulative incidence of probable and proven IFI. IFI = invasive fungal infection.

subgroup. In addition, of all the patients in the study, only 19 (4.5%) patients had a prior history of type 2 DM before transplantation. However, three of the 19 DM patients (15.7%) developed IFI. In univariate analyses for age at HSCT, EBMT risk score, gender, disease type, antifungal prophylaxis, prior history of IFI or DM, conditioning regimen, donor type, and numbers of transplantation, we found that EBMT risk score > 2 ($p = 0.001$) and prior history of IFI ($p = 0.006$) or DM ($p = 0.042$) were the significant predictors for IFI. After multivariate analysis, only EBMT risk score > 2 ($p = 0.015$) and a prior history of IFI ($p = 0.006$) retained significance. The analyses are detailed in Table 2.

Post-transplant risk factors for the occurrence of IFI

Acute GVHD was documented in 138 (32.9%) patients including 22.8% with overall Grade I–II ($n = 96$) and 9.98% with overall Grade III–IV ($n = 42$). The incidence of IFI was 3.2% ($n = 12$) in patients with overall Grade I–II or absence of aGVHD and 35.1% ($n = 19$) in those with overall Grade III–IV. In our study, 86.5% of patients ($n = 364$) developed no or only limited cGVHD and the other 13.5% of patients ($n = 57$) suffered from extensive cGVHD. In those with extensive cGVHD, 21% of patients ($n = 12$) developed IFI. In addition, PTLD developed in 16 of the 421 patients (3.8%), proven by pathological biopsy. Among the 16 patients with PTLD, four (25%) developed IFI. High-dose methylprednisolone was used in GVHD, PTLD, or alloimmune lung disease. Among the 54 patients (12.8%) receiving high-dose steroids, subsequent IFI developed in 12 cases (35.1%). In univariate analysis, aGVHD overall Grade III–IV ($p < 0.001$), extensive cGVHD ($p = 0.002$), PTLD ($p = 0.005$), and the use of post-transplant high-dose steroids ($p < 0.001$) were significantly associated with post-HSCT IFI. After multivariate analysis, only high-dose steroids ($p < 0.001$) and aGVHD overall Grade III–IV ($p = 0.045$) retained significance. The

Table 2 Possible factors for invasive fungal infection (IFI) after adult allogeneic hematopoietic stem cell transplantation (HSCT)

Factors	No. of patients	IFI		Univariate analysis			Multivariate analysis		
		n	%	HR	95%CI	*p*	HR	95%CI	*p*
Age at HSCT (y)									
≤ 40	203	10	4.9						
> 40	218	21	9.6	1.548	0.757–3.164	0.231			
EBMT risk scores									
≤ 2	169	5	2.9						
> 2	252	26	10.3	5.038	1.930–13.151	**0.001**	3.390	1.273–9.029	**0.015**
Gender									
Female	179	11	6.1						
Male	242	20	8.2	1.412	0.676–2.947	0.359			
Disease type									
Myeloid	205	16	7.8						
Nonmyeloid	216	15	6.9	0.859	0.424–1.739	0.672			
Prophylaxis									
Fluconazole	368	25	6.7						
Echinocandin	53	6	11.3	2.326	0.938–5.769	0.069			
Prior history IFI									
No	406	27	6.6						
Yes	15	4	26.6	4.457	1.551–12.806	**0.006**	5.807	1.675–20.129	**0.006**
Prior history DM									
No	402	28	6.9						
Yes	19	3	15.7	3.490	1.045–11.653	**0.042**			
Conditioning									
Nonmyeloablative	145	8	5.5						
Myeloablative	276	2	8.3	1.592	0.712–3.561	0.258			
Conditioning									
Chemobased	239	19	7.9						
TBI-based	182	12	6.5	0.799	0.388–1.646	0.543			
Donor relation									
Related	208	13	6.2						
Unrelated	213	18	8.4	1.695	0.828–3.472	0.149			
Transplant no.									
One	379	27	7.1						
Multiple	42	4	9.5	2.012	0.699–5.788	0.195			
Donor type									
MSD	208	13	6.2	1	x	x			
Unrelated donor	203	16	7.8	1.544	0.740–3.221	0.247			
Haploidentical	8	1	12.5	4.713	0.612–36.294	0.137			
UCB	2	1	50	x	x	x			
aGVHD									
No or Overall Gr. I-II	379	23	6.0						
Gr. III-IV	42	8	19.0	6.936	3.046–15.796	**<0.001**	2.627	1.023–6.748	**0.045**
High steroids post SCT									
No	367	12	3.2						
Yes	54	19	35.1	11.148	5.401–23.008	**<0.001**	11.185	3.875–32.289	**<0.001**
cGVHD									
No or limited	364	19	5.2						
Extensive	57	12	21.0	3.131	1.518–6.459	**0.002**			
CMV-reactivation									
No	214	17	7.9						
Yes	207	14	6.7	1.043	0.511–2.131	0.907			
PTLD									
No	405	27	6.6						
Yes	16	4	25	4.627	1.607–13.320	**0.005**			

Significant values ($P < 0.05$) are given in bold.
aGVHD = acute GVHD; cGVHD = chronic GVHD; CI = confidence interval; CMV = cytomegalovirus; DM = Diabetes mellitus; EBMT = European Group for Blood and Marrow Transplantation; Gr. = grade; GVHD = graft-versus-host disease; HR = hazard ratio; MSD = matched sibling donor; MUD = matched unrelated donor; PTLD = Post-transplant lymphoproliferative disorders. TBI = total body irradiation; UCB = umbilical cord blood.

descriptions of HSCT complications and their relationships to IFI are given in Table 2.

Outcome of the patients with post-HSCT IFI

The median age of the 31 patients with IFI was 42 years (range: 19—60 years). Seventeen (54.8%) patients experienced intensive care unit (ICU) care with a median of 8 days staying at ICU (range, 2—96 days). In comparison to late-diagnosed IFI, higher proportion of patients with early IFI needed ICU care [10/16 (62.5%) vs. 7/15 (46.7%)] and patients with early mold infection had higher mortality rate compared to late infection [3/3 (100%) vs. 4/8 (50%)]. The death rate was all high in yeast infection whether the IFI was diagnosed early [11/13 (85%)] or late [7/7 (100%)]. Only 19.4% (6/31) of patients with IFI survived while 56.4% ($n = 220$) of patients without IFI achieved long-term survival. The overall survival after HSCT was significantly worse in IFI group as compared with the other patients (log-rank $p < 0.001$; Fig. 2). The probability of OS was 82.1% at Day +100, 75.1% at Day +180, and 64.9% at 1 year post-transplantation for patients without IFI, compared with 74.2%, 54.8%, and 45.2%, respectively, in those with IFI. Of the patients dying of IFI ($n = 25$), death occurred in 17 (68%) patients prior to Day +30 and in 22 (88%) patients prior to Day +90. The causes of death were a direct result of IFI in 18 (58.1%) patients, complications associated with IFI in three (9.7%) patients, and other unrelated causes such as disease relapse, progressive GVHD, or other causes in four (12.9%) patients.

Discussion

Our study demonstrated a 7.4% cumulative incidence of probable and proven IFI within a period of 12 years in a single Asian institute. The annual incidence curve presented with a bimodal pattern with two peaks of high IFI incidence rate in 2003 (14.3%) and 2011 (12.2%). The characteristic variation cannot be well explained. However, gradually increased patient age in recent years, accumulation of experience in HSCT, adoption of policy with routine antifungal prophylaxis and advance in diagnostic technology could lead to the unusual presentation. The median age at HSCT was 39 years prior to 2005, which was younger when compared to the median age of 43 years after 2008. Routine use of antifungal prophylaxis could be the cause of decreasing IFI incidence after 2003. Increasing patient age, enhanced awareness of IFI, introduction of GM test for diagnosis, and increased incidence of mold IFI could contribute to the second peak since 2008, which sloped down thereafter with increased use of echinocandin for prophylaxis. Our observations are actually similar to a recent report of IFI in a pediatric cohort.[19] However, as compared with the study prior to 2000, IFI rate has already improved significantly (7.4% vs 15%).[20] Consistent with previous reports, our study also found that the median time of developing IFI after transplant is around Day +100.[5,11,21,22]

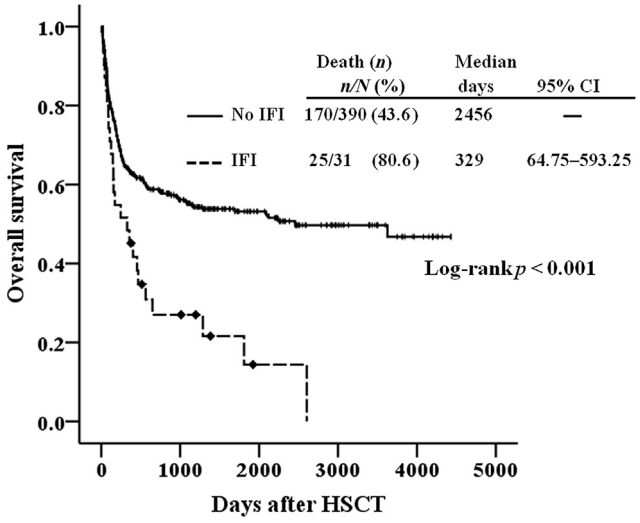


Figure 2. Overall survival after HSCT. HSCT = hematopoietic stem cell transplantation.

Our study showed that a prior history of fungal infection was a significant risk factor for IFI after transplantation. This is in agreement with previous reports. Cornely et al[23] described an increased risk of subsequent IFI and worse outcomes in patients with a previous history of IFI. Another preliminary analysis by Maziarz et al[24] also described an increased risk (24%) for subsequent IFI in patients with a history of IFI prior to undergoing allogeneic HSCT. All these observations suggest that constant vigilance should be given to patients with history of pretransplant fungal infection and monitoring recurrent IFI after the procedure is mandatory. In a preliminary analysis, Maziarz et al[24] described an increased risk for subsequent IFI and lower 1-, 3-, and 5-year disease-free survival and OS in patients with a prior history of IFI undergoing allogeneic HSCT for acute leukemia, myelodysplastic syndrome, and chronic myelogenous leukemia. In our study, patients with hematological malignancies ($p = 0.879$, data not shown in Table 2) or nonmyeloid malignancies ($p = 0.672$) did not have an increased risk of subsequent IFI after HSCT. Our study also confirmed that the occurrence of IFI was associated with a pretransplant EBMT risk score > 2 ($p = 0.015$). IFI contributed to the causes of mortality in patients with a high EBMT risk score. The result was also similar to pediatric data and demonstrated an increased risk of IFI with a prior determined HSCT treatment-related mortality risk > 20%.[19] Post-HSCT risk factors including the use of high-dose steroids, GVHD, and PTLD could be associated with IFI. Consistent with previous reports,[5,10,11,20,25] our study confirms that overall Grade III—IV aGVHD ($p = 0.045$) is a significant risk factor. In addition, PTLD was also an important issue for IFI. The overall frequency of PTLD in our hospital was 3.8% (16/421), which was similar to the results from a large study.[26] However, high incidence with a proportion up to 25% (4/16) of the PTLD patients developed IFI. The association was statistically significant ($p = 0.005$) in univariate analysis, but lost significance in multivariate analysis, probably confounded by high-dose steroid use and poor immunity. The small numbers of PTLD cases in our study preclude further in-depth analysis. High-dose steroids were often used for advanced aGVHD, extensive cGVHD, or alloimmune lung disease.[27,28] Our study also confirmed the strong association between the use of high-dose steroids and IFI, either in univariate ($p < 0.001$) or multivariate analysis ($p < 0.001$).

Previous studies reported that haploidentical HSCT had an increased risk for opportunistic fungal infections (range, 7.1—24%) but pertinent data in this particular patient group were limited.[11,29,30] In our study, a relatively similar risk for IFI in haploidentical HSCT (1/8; 12.5%) was noted. However, the limited patient number of haploidentical HSCT rendered statistics insignificant in terms of IFI. The increased risk of IFI may be caused by delayed engraftment and delayed immune reconstitution and GVHD in these mismatched transplantation recipients.

Patients afflicted by IFI had high mortality rate, even after correction for *a priori* determined EBMT risk. Regarding the timing for IFI, in comparison to late yeast infection (35%), invasive mold infection tended to occur late after the transplant (73%). The observation was similar to the findings in previous studies.[2,3,7,31] In our study, the median EBMT risk score in patients with IFI was high ($>$ 2 points) with median risk Scores 4 and 3 for the early and late IFI subgroups, respectively. In comparison to late-diagnosed IFI, the early IFI subgroup had higher proportion of patients with EBMT risk score $>$ 2 (87.5%), necessity of ICU care (62.5%), and higher mortality in patients with mold infection (100%). Our standard prophylaxis using fluconazole is conceivably ineffective in preventing mold infection. All three patients with mold infection occurring prior to Day +139 had received fluconazole prophylaxis. They all died of the infection. Three of eight patients with late-onset mold infection had received echinocandin prophylaxis, which probably contributed to delaying onset of the infection and improved outcome. Echinocandin agents have been used increasingly for antifungal prophylaxis in recent years; however, we did not observe any significant reduction in the incidence of IFI as compared with the standard fluconazole prophylaxis ($p = 0.069$). When confronting the challenge of invasive mold infection, in addition to the hematological recovery and prophylactic antifungal agents, delayed immune reconstitution after allogeneic HSCT also played an important role influencing the poor survival of mold infection developing prior to Day +139.

In our study, based on diagnosing proven and probable cases of IFI according to the standard definitions of EORTC/MSG Consensus Group,[18] we demonstrated the cumulative incidence of IFI and clinical characteristics of post-transplant IFI and identified advanced GVHD and use of high-dose steroid as risk factors for IFI. Development of IFI significantly jeopardizes survival after HSCT. Recognition of patients with high risk stratification for IFI would allow physicians to give effective prophylactic agents and vigilantly monitor these patients to reduce the mortality and morbidity associated with IFI.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

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