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Sequential systematic anti-mold prophylaxis with micafungin and voriconazole results in very low incidence of invasive mold infections in patients undergoing allogeneic hematopoietic stem cell transplantation

Claudia Rosillo[1,2], **Ana Maria Avila**[1,3], **Yao-Ting Huang, PhD, MPH**[4], **Sean Devlin, PhD**[5,6], **Christina Cho, MD**[1,6], **Juan Montoro, MD**[1,7], **Molly A. Maloy**[1], **Genovefa A. Papanicolaou, MD**[4,6], **Pere Barba, MD**[1,8,*], **Miguel-Angel Perales, MD**[1,6,*]

[1]Department of Medicine, Adult Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, NY.

[2]Hospital Clinic. Universitat de Barcelona.

[3]La Sabana School of Medicine, Bogota, Colombia.

[4]Department of Medicine, Infectious Disease Service, Memorial Sloan Kettering Cancer Center, New York, NY

[5]Department of Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

[6]Weill Cornell Medical College; New York, NY

[7]Hospital Universitario La Fe, Valencia, Spain

[8]Hospital Universitario Vall d'Hebron- Universitat Autonoma de Barcelona, SPAIN.

Abstract

Background and objectives: Recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT) are at high risk for invasive mold infections (IMI). The goal of the study is to describe the incidence and outcome of IMI in patients after allo-HSCT in a large cohort of patients receiving anti-mold prophylaxis.

Methods: We conducted a retrospective review of 988 consecutive adults who underwent allo-HSCT in our center from 2008 through 2014. Standard prophylaxis consisted of micafungin 150mg IV daily from admission to day +7 +/− 3 followed by voriconazole until day +75 to +100.

CORRESPONDING AUTHOR: Miguel-Angel Perales, M.D., Adult Bone Marrow Transplantation Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Box 298, New York, NY 10065 USA, peralesm@mskcc.org, Fax: 212-717-3500, Phone: 212-639-8682 or Pere Barba, M.D., Servicio de Hematologia, Hospital Universitari Vall d'Hebrón. Universitat Autònoma de Barcelona, Pg. Vall Hebron 119, 08035., Barcelona, SPAIN, pebarba@vhebron.net, Phone: +34.93.274.64.14 .

*These authors contributed equally to this work

AUTHOR CONTRIBUTIONS

Conception and Design: Pere Barba, Miguel-Angel Perales.

Collection of data: Claudia Rossillo, Ana María Avila, Juan Montoro, Yao-Ting Huang, Molly Maloy Christina Cho.

Data analysis and interpretation: Sean Devlin, Genovefa A. Papanicolaou, Pere Barba, Miguel-Angel Perales

Manuscript writing: All authors

Final approval of manuscript: All authors

Cases meeting criteria for proven or probable IMI according to EORTC-MSG criteria were included.

Results: Median age at HSCT was 54 years. The most common diagnoses were acute myeloid leukemia (n = 351, 36%) and lymphoid malignancies (n = 248, 25%). Matched related or unrelated donors (URD) were used in 686 (69%) patients, mismatched URD in 142 (14%) and cord blood units in 154 (16%). Twenty-one patients were diagnosed with IMI after allo-HSCT, 19 probable and 2 proven, and one additional patient was diagnosed post-mortem. Microbiological diagnosis was established in 9 cases, 5 of them being *Aspergillus*. One-year cumulative incidence (CI) of IMI was 1.6% (95%CI 0.9–2.5) while 12-week overall survival after IMI was 39% (95%CI 24–65) Analyzed by disease, there was a trend for a higher 1-year CI of IMI in patients with ALL (5% [95%CI 1.6–11.4]) when compared with AML (1.4%), MDS (1.5%) and lymphoma (1.2%), p=0.06.

Conclusion: The 1-year CI of IMI after transplantation is low in patients receiving anti-mold prophylaxis with micafungin bridged to voriconazole, although these infections are associated with a higher risk of mortality.

Keywords

Invasive fungal infection; allogeneic hematopoietic stem cell transplantation; molds; antifungal

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative treatment option for many malignant and non-malignant hematological diseases. While treatment-related mortality (TRM) remains a major concern of this procedure, mostly driven by infections and graft-versus-host disease (GVHD), several studies have shown a decrease of TRM in recent years due to a variety of factors[1,2]. One such factor is the improved management of invasive mold infections (IMI), including new diagnostic tools and active drugs both in the prophylactic and treatment settings. These improvements have led to an apparent decrease in the mortality of these infections[3].

The use of anti-mold prophylaxis in contemporary patients undergoing allo-HSCT has been evaluated in some clinical trials with strict inclusion criteria[4–7]. However, there is a paucity of studies addressing this issue in large cohorts of “real-life” allo-HSCT patients[8–10].

The goal of this study was to describe the incidence and outcome of IMI in a large contemporary cohort of allo-HSCT from a single center receiving anti-mold prophylaxis.

Methods

Patients and transplant procedure

All consecutive patients 18 years old or older who received their first allo-HSCT for hematological malignancies from January 2008 to December 2014 at Memorial Sloan Kettering Cancer Center (MSKCC) were included. Patients with hematological non-malignant diseases and solid tumors were excluded.

All stem cell sources, conditioning regimens and GVHD prophylactic strategies were included and have been previously described[11–13]. In brief, pre-transplant conditioning intensity varied according to patient age, comorbidities and previous therapy received, and could be either chemotherapy-based or in combination with total body irradiation. GVHD prophylaxis was calcineurin inhibitor-based in the majority of patients, except for patients receiving CD34+ selected grafts who did not receive any prophylactic immunosuppressive agents post-transplant[11].

Diagnosis of IMI and prophylaxis strategy

IMI cases were identified through a systematic review of histopathology reports consistent with invasive mold infection in microbiology records, fungal stains and cultures, fungal markers (including β-D-glucan [Fungitell, Associates of Cape Cod, Inc.], Galactomannan [Platellia, Bio-Rad, Hercules, CA, USA]) and clinical reports. In our center, patients with persistent fever underwent thoracic CT-scan routinely. β-D-Glucan and Galactomannan were ordered at the discretion of the treating clinician and positive tests were followed. The tests were routinely performed in allo-HSCT patients with neutropenic fever on broad-spectrum antibiotics, corticosteroid therapy and/or active GVHD, as well as patients with pulmonary symptoms or findings or abnormal chest imaging. This approach remained unchanged during all study period. Only proven and probable IMI according to the European Organization for Research and Treatment of Cancer/ Mycoses Study Group (EORTC/MSG) criteria[14] were included. Cut off points used for determination of a positive result for β-D-Glucan and Galactomannan were 80pg/mL and index > 0.5, respectively.

During the study period the standard of care for antifungal prophylaxis was micafungin 150mg IV daily given from the start of conditioning to day +7 +/− 3 days after HSCT and changed to voriconazole until day +75 to +100 after transplantation, initially IV and switched to PO when oral intake by the patient could be assured. Patients at higher risk for IMI including recipients of cord blood or T-cell depleted allografts, CMV infection, neutropenia requiring growth factor support or receiving >1mg/kg prednisone or equivalent for GVHD or other conditions remained on prophylaxis at least till day +100 or longer as clinically indicated. Patients with grade ≥ 2 liver toxicity on day +7 were maintained under micafungin and switched to voriconazole when toxicity resolved or to posaconazole in those with incomplete resolution of the hepatic toxicity. Calcineurin inhibitors and sirolimus doses were adjusted in patients switched to an azole as previously reported[13].

β-D-Glucan and Galactomannan were ordered at the discretion of the clinician as adjunctive diagnostic tools in patients with clinical or radiological suspicion of aspergillosis. Diagnostic and treatment of IMI followed institutional and national guidelines[15,16].

Endpoints, definitions and statistical analysis

The primary endpoint of the study was the cumulative incidence of IMI. Secondary endpoints included overall survival after IMI and description of IMI characteristics. Causes of death were established according to the Copelan algorithm[17]. Mold related mortality was attributed to patients who died within 12 weeks from the time of IMI diagnosis in the absence of relapse of the hematological malignancy.

The cumulative incidence of IMI was estimated treating relapse and death in the absence of diagnosed IMI as competitive events. Gray's test was used to compare IMI incidence by disease and treatment characteristics. Kaplan-Meier methods were used to estimate overall survival following IMI. All analyses were done by using R v3.1.2.

Results

A total of 988 patients undergoing allo-HSCT during the study period were included. Patients' characteristics are summarized in table 1. In brief, median age at HSCT was 54 (range 18–75). Most common transplantable malignant hematological diseases were present in the cohort. The most frequent diagnoses were acute myeloid leukemia and lymphoid malignancies. Stem cells from matched-related and unrelated donors were used in most patients, mainly obtained from mobilized peripheral blood. The treatment conditioning was mostly myeloablative with ex vivo T cell depletion through CD34+ selection being used in almost half of the patients. Median follow-up for survivors was 2.55 years (range 0.22 – 7.37).

Twenty-one patients (2.1%) developed an IMI at a median of 234 days (range 7–1327) after allo-HSCT: 2 of them were proven (10%) and 19 were probable (90%). Nine of the 21 diagnoses (43%) were in the first 180 days with a median onset of 103 days (range: 7–164). Six (29%) were diagnosed between 180 days and 1 year following HSCT, with a median of 292 days (range: 200–355). The remaining 6 patients were diagnosed at a median of 525 days (range: 384–1327). There was one additional patient (proven mucormycosis) who was diagnosed post-mortem. Overall, the 1-year cumulative incidence of proven or probable IMI was 1.6% (95%CI 0.9–2.5). Among patients with IMI, microbiological diagnosis was established in 9 cases (41%): 4 patients with Aspergillus spp., 2 with Mucor spp., 1 with Absidia spp., 1 with Rhizomucor spp. and 1 patient with concomitant Aspergillus spp. and Rhizopus spp. In the other thirteen cases (59%) diagnosis was driven by a positive β-D-Glucan assay and identification of genus and species was not possible. Pneumonia was the most common clinical presentation (n = 19, 86%), followed by nasal sinusitis (n= 2) and tracheo-bronchitis (n= 1).

Thirteen (59%) patients with IMI had received systemic corticosteroids within the 30 days prior to diagnosis, eleven for GVHD. Ten patients (45%) were not receiving the planned anti-mold prophylaxis at the time of IMI, due to azole-related hepatotoxicity (n = 7), drug allergy (n = 1), patient preference (n = 1) and unknown reason (n = 1). Three patients were off prophylaxis as they were beyond day +100 and had no additional risk factors. The remaining 9 patients were receiving the planned anti-mold prophylaxis at the time of IMI diagnosis. Detailed clinical characteristics of patients with IMI are shown in supplementary table 1.

No risk factors for the development of IMI were identified, which may be due to the low IMI event rate. When analyzed by disease, there was a trend for a higher cumulative incidence of IMI at 1 year in patients with ALL (5% [95%CI 1.6–11.4]) when compared with AML (1.4% [95%CI 0.5–3.1]), MDS (1.5% [95%CI 0.3–4.8]), lymphoma (1.2% [95%CI 0.3–3.3]), and all other malignancies (0.7% [95%CI 0.1–3.5%]) p=0.06 (Figure 1). By transplant

procedure, there were no differences in the cumulative incidence of IMI at 1 year between patients receiving unmodified grafts from related or unrelated donors (0.6% [95%CI 0.2–2.2]), CD34+ selected grafts (1.9% [95%CI 0.9–3.4]) or cord blood units (2.6% [95%CI 0.9–6.1]), p=0.583 (Figure 1).

The 12-week and 1-year overall survival after IMI was 39% (95%CI 24–65) and 25% (95%CI 13–52), respectively (Figure 2). All 5 patients with Mucorales died at a median of 23 days (range 1–616) of diagnosis (4/5 related to IMI). Causes of death in patients with IMI included GVHD (n = 8), disease relapse (n = 6), infection (n = 2), toxicity from treatment (n = 2) and unknown cause (n = 2).

Discussion

This study of a large contemporary cohort of HCT recipients at a major cancer center with a standardized anti-mold prophylactic strategy reports a low overall incidence of IMI and identifies some populations with a very low risk of developing these infections.

The cumulative incidence of IMI at 1 year reported in our single center study is somewhat lower than the reported in contemporary studies. In clinical trials of mold active prophylactic agents conducted in HSCT the incidence of IMI ranges from 1.3–5%[5–7]. In the neutropenic phase of allo-HSCT, micafungin prophylaxis was effective in preventing invasive fungal infections[5]. In randomized studies of voriconazole vs. itraconazole,[6] and voriconazole vs. fluconazole (BMT CTN 0101)[7], only 1 of 224 and 9 of 305 patients in the voriconazole arms developed aspergillosis, respectively. In the only randomized trial conducted exclusively in patients with GVHD, only 7 patients (2.3%) receiving posaconazole developed aspergillosis. IMI infections by mucor or other zygomyctes were rare in all these studies. However, the selected time points for analysis of the incidence of IMI were shorter than in our study, suggesting that with longer follow-up the reported incidences in these trials would have been higher. Noteworthy, our population seemed at a higher risk for developing IMI than the patients included in the aforementioned studies, not only by the well described bias in enrolling patients into clinical trials[18], but also because our patients were older and had received more immunosuppressive transplant strategies (e.g. CD34+ selection and cord blood transplantation) than those included in the clinical trials.

The large number of patients included in this study allowed subgroup analyses in patients with various diseases and receiving different transplant approaches. We observed a trend towards a relatively higher incidence of IMI in patients with ALL when compared with other diseases. This non-statistical significant trend could be explained by the prolonged corticosteroid exposure during ALL therapy and by a less well established anti-mold prophylactic strategy in patients with this disease in the induction/consolidation phase as opposed to AML and MDS. However, other transplant related factors as the incidence of GVHD (not addressed in this study) could also play a role in the incidence of IMI in this population. Contrary to other studies, we did not observe a higher incidence of IMI in patients receiving more immunosuppressive transplant modalities such as CD34+ selection or cord blood[19]. While it is possible that the more aggressive prophylactic approach used at our center may overcome a higher risk for mold infections in patients receiving highly

immunosuppressive transplant modalities, this would need to be confirmed in comparative studies.

Forty-five percent of the patients who developed an IMI in our study were not receiving the planned anti-mold prophylaxis, mostly because of drug-related toxicity. Although identification of risk factors for the development of IMI was not possible in our cohort due to the low number of events, it appears that patients who are not able to comply with the planned prophylaxis could benefit from individually targeted strategies such as sparing of corticosteroids and use of pre-emptive use of G-CSF for neutropenia, since they have a higher risk of developing IMI. With the approval of isavuconazonium sulfate, this may represent an alternative option for patients intolerant to voriconazole.

Our prophylactic anti-mold strategy with micafungin 150 mg daily and voriconazole deserves further discussion. The use of micafungin from admission to day +7 avoids the potential interaction of azoles with the drugs used in the conditioning regimen and ensures a more rapid achievement of steady-state levels of immunosuppressant drugs. The dose of micafungin was chosen based on initial studies suggesting the need for higher doses of anti-mold prophylaxis compared to the dose needed for Candida[20,21]. It is possible that a lower dose of micafungin could be equally effective based on recent data showing effective anti-mold prophylaxis with a daily dose of 50–100mg[22,23].

Mortality after IMI was high in our patients, consistent with prior reports[8,24], especially for those with Mucorales, reflecting the aggressiveness of these infections even in the prophylactic era and indicating the need for continuing improvement in this field despite the low prevalence of IMI.

Our study has several limitations. The goal of the study was to evaluate the effectiveness of a standardized approach. Since the actual prophylaxis of individual patients was not examined we do not report rates of compliance, toxicity or use of alternative approaches for individual patients. Work up for IMI was done by institutional standards and at the discretion of the clinician, thus there could be greater variability than in controlled clinical trials. Acknowledging these limitations, our study nevertheless provides real world experience on the efficacy of mold active prophylaxis of large heterogeneous, high risk cohort with contemporary transplant practices and supportive care.

In conclusion, our anti-mold prophylactic strategy consisting of micafungin bridged to voriconazole resulted in a very low incidence of IMI in recipients of allo-HSCT, although mortality in patients developing IMI remains high.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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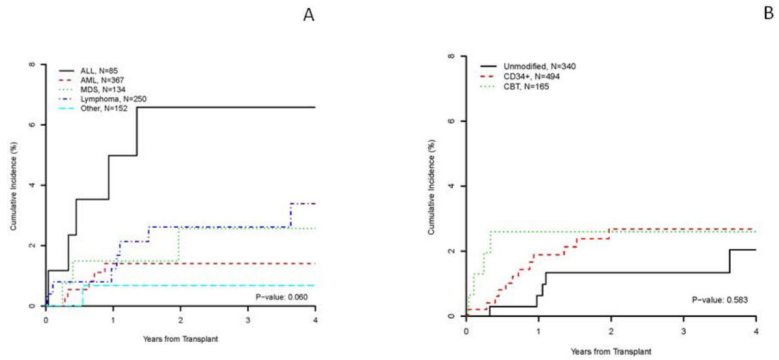

Figure 1. Cumulative incidence of invasive mold infections by disease (A) and transplant modality (B).

Footnote Figure 1. A: Cumulative incidences of IMI in patients with acute myeloid leukemia, acute lymphoblastic leukemia, lymphoproliferative disorders and other diseases. B: Cumulative incidences of IMI in patients receiving CD34+ selected grafts, vs. Unmodified grafts vs. Cord bloods.

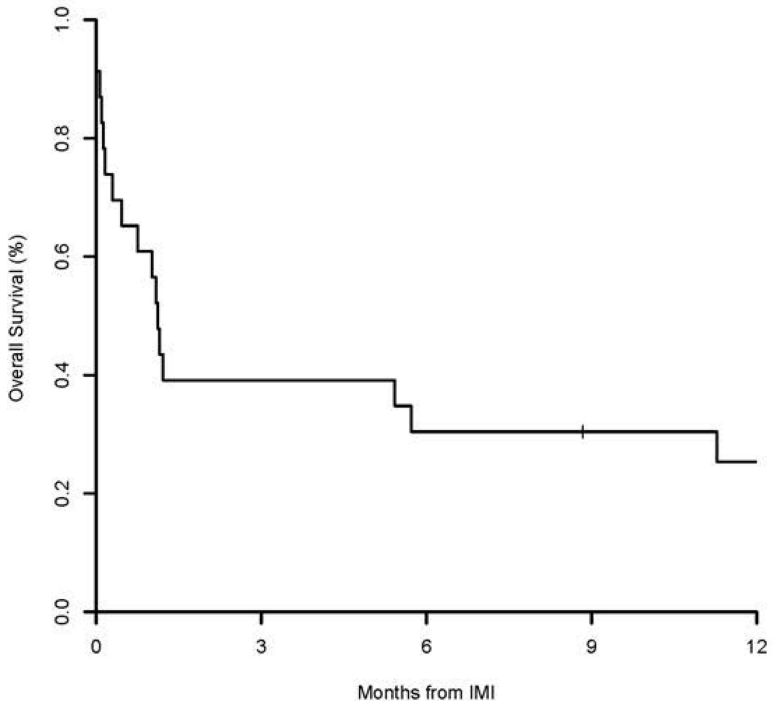

Figure 2.
Overall survival after IMI diagnosis (n=21).

Table 1.

Patient and transplant characteristics

Characteristics	**All patients n=988**	**IMI patients n=22[&]**	**Non-IMI patients n= 966**
Age, median (range**)**	54 (18–75)	53 (31–68)	54 (18–75)
Gender Male, n (%)	590 (60)	10 (45)	580 (60)
Diagnosis			
Acute myeloid leukemia	351 (36)	5 (23)	346 (36)
Acute lymphoblastic leukemia	85 (9)	5 (23)	80 (8)
Acute leukemia- other	16 (2)	0 (0)	16 (2)
Chronic myelogenous leukemia	25 (3)	0 (0)	25 (3)
Lymphoid malignancy	248 (25)	8 (36)	240 (25)
Multiple myeloma	103 (10)	1 (5)	102 (11)
Myelodisplastic syndrome	127 (13)	3 (14)	124 (13)
Myeloproliferative neoplasm	33 (3)	0 (0)	33 (3)
Previous autologous transplant, n (%)	181 (18)	3 (14)	178 (18)
Conditioning, n (%)			
Chemotherapy-based	537 (54)	8 (36)	529 (55)
TBI-based	451 (46)	14 (64)	437 (45)
Donor type, n (%)			
Matched related	319 (32)	4 (18)	315 (33)
Mismatched related	9 (1)	0 (0)	9 (<1)
Matched unrelated	364 (37)	8 (36)	356 (51)
Mismatched unrelated	142 (14)	6 (27)	136 (14)
Cord blood[a]	154 (16)	4 (18)	150 (15)
Source[b], n (%)			
- Bone marrow	34 (3)	1 (5)	33 (3)
- Peripheral blood	798 (81)	17 (77)	781 (81)
- Cord blood[a]	154 (16)	4 (18)	150 (16)
Manipulation, n (%)[c]			
- Unmodified	349 (35)	7 (32)	342 (35)
- CD34+ selection	485 (49)	11 (50)	474 (49)
- In vivo TCD (ATG or Campath)	154 (16)	4 (18)	150 (16)

Abbreviations: IMI, invasive mold infection; TCD, T-cell depletion; TBI, total body irradiation.

[a]Includes patients receiving cord blood transplantation with support of haploidentical CD34+selected grafts.

[b]Two patients received bone marrow and peripheral blood as part of a clinical trial.

[c]Cord blood not included.

[&]Includes the 21 patients diagnosed during follow-up and one additional patient diagnosed post-mortem