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MAJOR ARTICLE

Mucormycosis in Hematopoietic Cell Transplant Recipients and in Patients With Hematological Malignancies in the Era of New Antifungal Agents

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Background. The survival benefit of combination antifungal therapy for invasive mucormycosis (IM) in patients with hematologic malignancy (HM) and hematopoietic cell transplant (HCT) is not well defined.

Methods. This multicenter, retrospective study included HM and HCT recipients with proven or probable IM between January 1, 2007 and December 31, 2017 from 10 transplant centers across North America.

Results. Sixty-four patients with proven (n = 47) or probable (n = 17) IM defined by 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) consensus definitions were included. Thirty-nine (61%) were HCT recipients (95% allogeneic). Sites of infection included rhino-orbital-cerebral (33), pulmonary (30%), disseminated (19%), gastrointestinal (3%), and cutaneous (3%). Surgical debridement was performed in 66%. Initial antifungal treatment consisted of the following: lipid formulation of amphotericin B (AmB) alone (44%), AmB + posaconazole (25%), AmB + echinocandin (13%), AmB + isavuconazole (8%), posaconazole alone (5%), and isavuconazole alone (3%). All-cause mortality at 30 days and 1 year were 38% and 66%, respectively. Initial treatment with AmB plus posaconazole or isavuconazole (n = 28) was associated with a trend toward lower treatment failure compared with AmB (n = 21) (42% vs 64%, $P = .136$).

Conclusions. Long-term survival with IM among HM and HCT populations remains poor. However, initial use of AmB + azole in conjunction with surgery may result in less treatment failure. More evidence from prospective controlled studies is needed to confirm this observation.

Keywords. Mucormycosis; Hematopoeitic cell Transplant; Isavuconazole.

Invasive mucormycosis (IM) is a rapidly progressive angioinvasive fungal infection that is associated with 40%–80% mortality [1]. Patients with hematologic malignancies (HM) and hematopoietic cell transplant (HCT) recipients are at particularly high risk due to frequent prolonged and profound neutropenia. The expanding use of HCT for HM has accordingly been associated with an increasing incidence of IM, whereas mortality from IM has remained relatively unchanged [2]. Therefore, the ability to identify treatment approaches that improve infection-related outcomes is critically important in these populations.

The generally accepted treatment approach to IM consists of early, complete surgical debridement when possible, correction of underlying predisposing conditions (eg, attenuation of immunosuppression or rapid restoration of euglycemia), and antifungal drug therapy [3]. The historical mainstay of antifungal therapy, amphotericin B deoxycholate, has largely been superseded by lipid formulations of amphotericin B (AmB), which are significantly less nephrotoxic. In the the past decade, we have seen important advances in the identification and management of IM. The sensitivity and speed of IM diagnosis have been enhanced with the introduction of molecular-based diagnostic techniques, such as quantitative polymerase chain reaction. Furthermore, the availability of posaconazole (POS) formulations with improved pharmacokinetic profiles,

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and the approval of isavuconazole (ISA), have provided treatment options with relatively safer adverse event profiles than AmB [1]. Whether these shifts in diagnostics and therapeutics translate into clinical benefit has not been characterized.

There is a paucity of data on IM outcomes in HCT and HM populations despite changes in the understanding of the treatment approach to IM over the past decade. In particular, no studies have yet evaluated the impact of combining AmB with POS or ISA on clinical outcomes in patients with IM [1]. To address these knowledge gaps, we conducted a retrospective, multicenter study to describe patient characteristics and survival outcomes in this era of newer antifungals.

METHODS

Data Source and Patient Population

Adult patients with HM with or without HCT diagnosed with IM from January 2007 through December 2017 were identified through search of microbiology and pathology databases from 10 transplant centers in North America. The 2008 European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) consensus group definitions of invasive fungal disease (IFD) were used to classify IM [4]. Cases of IM classified as "proven" and "probable" IFD were included.

Data were abstracted from the electronic medical record or patient chart at each institution. Data collected included patient demographics, underlying comorbidities, histopathological findings, prior antifungal use, coinfecting organisms, clinical manifestations, graft-versus-host disease (GvHD), antifungal therapy, surgical intervention, and 30-day and 1-year mortality. Associated conditions collected included neutropenia (absolute neutrophil count [ANC] <1000 cells/μL), severe neutropenia (ANC <500 cells/μL), and GvHD.

Patient Consent Statement

All patients consented to use of their medical records for research purposes. This study protocol was approved by the Colorado Multiple Institutional Review Board (IRB) and local participating site IRBs.

Definitions

At-risk populations for IM were classified into 2 groups: (1) HMs and (2) autologous and allogeneic HCT. The date of first documented clinical suspicion for IM was designated as the date of diagnosis. Clinical manifestations of IM were categorized as rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous, surgical wound, or disseminated. Disseminated IM was defined as 2 or more noncontinuous sites of involvement. Based on individual clinician's assessment, treatment failure was defined as death related to IM or change in initial antifungal therapy for IM due to clinical and/or radiographic progression.

Statistical Analysis

The primary objective of this study was to describe patient characteristics, management, and prognosis associated with IM diagnosis. Secondary outcomes were treatment failure, mortality, and adverse events associated with initial AmB monotherapy compared with AmB + POS or ISA. Primary and secondary outcomes between AmB and AmB + POS/ISA were compared using univariate analysis. Survival was assessed using Cox proportional hazards model, with surgical intervention included as a time-dependent covariate. The net benefit-risk profile of using combination antifungal therapy was analyzed using desirability of outcome ranking (DOOR), whereby an overall ordinal outcome was assigned based on occurrence of mortality, treatment failure, and adverse events. The ordinal outcomes levels were as follows: (1) death; (2) survival with treatment failure and adverse event; (3) survival with treatment failure and no adverse event; (4) survival with treatment success and adverse event; (5) survival with treatment success and no adverse event. Analyses were performed using SPSS statistics version 23.0 (IBM Corp., Armonk, NY).

RESULTS

In total, 53 patients with Mucorales-positive cultures and 13 patients identified from histopathology records during the study period were screened. After application of the EORTC/MSG criteria, 64 patients with IM were included in this study. Patient baseline demographics and clinical characteristics are displayed in Table 1. Overall, the median age at IM diagnosis was 57 (interquartile range [IQR], 45–64) years, 57% (n = 36 of 64) were male, and the majority (75%, n = 48 of 64) were white. More patients had undergone HCT (61%, n = 39 of 64) than had HM without HCT (39%, n = 25 of 64). Acute and chronic leukemias accounted for most HMs (75%, n = 48 of 64), followed by myelodysplastic syndrome (6%, n = 4 of 64). Neutropenia at time of IM diagnosis was common (56% n = 36 of 64), with the vast majority (92%, n = 33 of 36) characterized as severe (ANC <500 cells/μL). Almost all HCT recipients were allogeneic (95%, n = 37 of 39). Among allogeneic HCT recipients, human leucocyte antigen (HLA)-matched unrelated donors (MURD) (47%, n = 17 of 37) were more common than other donor types (Table 1). Other key transplant characteristics included a predominance of myeloablative conditioning (46%), receipt of lymphocyte-depleting agents (26%), and presence of acute or chronic GvHD (59%). The majority of HCT recipients (59%, n = 22 of 39) had an IM diagnosis within 12 months posttransplant, with median time from transplant to IM diagnosis of 263 (IQR, 108–659) days. Few patients (8%, n = 3 of 39) were diagnosed before neutrophil engraftment.

In the total cohort, 73% (n = 47 of 64) were classified as proven IFD and 27% (n = 17 of 64) as probable IFD by EORTC/MSG definitions (Table 2). Among patients with available

Table 1. Demographics, Comorbidities, and Transplant-Related Characteristics

Characteristic, Median (IQR) or %(n)	Total (N = 64)	AmB (n = 28)	AmB + POS/ ISA (n = 21)
Age, years	57 (45–65)	58 (42–66)	58 (44–64)
Male	57 (36)	61 (17)	52 (11)
Race			
White	75 (48)	68 (19)	71 (15)
Asian	6 (4)	11 (3)	5 (1)
Other/not reported	19 (12)	21 (6)	24 (5)
Hematological Malignancy[a]			
Acute myeloid leukemia	47 (30)	50 (14)	48 (10)
Acute lymphoblastic leukemia	14 (9)	11 (3)	14 (3)
Chronic lymphocytic leukemia	11 (7)	7 (2)	14 (3)
Myelodysplastic syndrome	6 (4)	4 (1)	10 (2)
Diffuse large B-cell lymphoma	5 (3)	0	5 (1)
Multiple myeloma	3 (2)	7 (2)	0
Chronic myelogenous leukemia	3 (2)	4 (1)	(5) 1
Other[b]	16 (10)	18 (4)	10 (2)
HCT	61 (39)	61 (17)	67 (14)
HCT Donor Type			
Allogeneic	95 (37)	88 (15)	100 (14)
Matched, unrelated	44 (17)	46 (7)	50 (7)
Matched, related sibling	23 (9)	20 (3)	14 (2)
Umbilical cord blood	14 (5)	20 (3)	14 (2)
Matched, related other	8 (3)	6 (1)	7 (1)
Haploidentical	3 (1)	6 (1)	7 (1)
Mismatched	3 (1)	6 (1)	0
Unknown	3 (1)	0	0
Autologous	5 (2)	12 (2)	0
HCT Source			
Peripheral blood stem cell	70 (27)	53 (9)	78 (11)
Bone marrow	15 (6)	24 (4)	14 (1)
Umbilical cord blood	13 (5)	20 (3)	14 (2)
Unknown	3 (1)	0	0
Conditioning Regimen			
Intensity			
Myeloablative	46 (18)	53 (9)	43 (6)
Reduced intensity	43 (17)	29 (5)	50 (7)
Non-myeloablative	8 (3)	12 (2)	7 (1)
Lymphocyte depletion	28 (11)	18 (3)	29 (4)
Risk Factors			
Diabetes	23 (15)	21 (6)	33 (7)
Neutropenia	56 (36)	50 (14)	52 (11)
ANC <500 cells/μL	92 (33)	100 (14)	48 (10)
Transplant-Related			
Pre-engraftment at diagnosis	8 (3)	12 (2)	0
Within 1st year posttransplant	56 (22)	71 (12)	50 (7)
Acute or chronic GVHD	56 (11)	47 (8)	64 (9)

Abbreviations: AmB, lipid formulation of amphotericin B; ANC, absolute neutrophil count; DLBCL, diffuse large B-cell lymphoma; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; IQR, interquartile range; ISA, isavuconazole; MDS, myeloproliferative syndrome; MPS, myelodysplastic syndrome; POS, posaconazole.

[a]Five patients had more than 1 hematologic malignancy: AML + other (2), AML + MPS (1), AML + MDS (1), AML + DLBCL (1).

[b]Other hematologic malignancies: myelofibrosis (2), red cell aplasia (1) acute promyelocytic leukemia (2), plasma cell leukemia (1), Hodgkin's lymphoma (1), myeloproliferative syndrome (2), T-cell lymphoblastic lymphoma (1), undefined (4).

Mucorales genus-level identification, the predominant genera were *Rhizopus* (65%, n = 33 of 51) and *Mucor* (29%, n = 15 of 51), with considerably fewer other genera; *Lictheimia* (formerly *Absidia)* (n = 2) and *Cunninghamella* (n = 1). Coinfection with bacteria, fungi, and/or viruses was noted in 48% (n = 31 of 64). Of these, bacterial coinfections were the most common (34%, n = 22 of 64), followed by fungal (19%, n = 12 of 64) and viral (9%, n = 6 of 64). Fungal coinfecting organisms were as follows: *Fusarium* (n = 5), *Aspergillus* (n = 2), *Geotrichum* (n = 1), *Penicillium* (n = 1), *Alternaria* (n = 1), and an unidentified hyaline mold (n = 1). Among viral coinfections, 67% (n = 4 of 6) had cytomegalovirus detected, all of which were viremia without tissue invasive disease.

Mortality

All-cause mortality after IM diagnosis was 36% at 30 days and 63% at 1 year within the total cohort. Among HM patients without HCT, 30-day and 1-year all-cause mortality were 36% (n = 9 of 25) and 56% (n = 11 of 25), respectively. In comparison, HCT recipients 30-day and 1-year all-cause mortalities were 33% (n = 13 of 39) and 62% (n = 24 of 39). There were no differences in all-cause mortality at 30 days (P = .827) or 1 year (P = .660) between HCT recipients and nonrecipients. Invasive mucormycosis-related death occurred in 45% (29 of 64) of all patients and did not differ between HCT recipients and nonrecipients (49% vs 40% [P = .494], respectively).

Antifungal Prophylaxis and Treatment

Fifty-eight patients (91%, n = 58 of 64) received antifungal prophylaxis before the diagnosis of IM. Voriconazole was the most common prophylactic agent (47%; n = 27 of 58), followed by fluconazole (19%, n = 11 of 58), echinocandin (EC) or POS (16%, n = 9 of 58 each), and AmB in 3% (n = 2 of 58).

Initial antifungal therapy for IM consisted of AmB monotherapy in 44% (n = 28) and combination therapy in 48% (n = 31). Of combinations that included AmB with a mold-active triazole, POS was most common in 58% (n = 18 of 31), followed by ISA in 16% (n = 5 of 31). Other AmB combinations prescribed included an EC in 26% (n = 8 of 31) and EC plus POS in 6% (n = 2 of 31). Combination therapy with AmB + POS or ISA was not more common from 2007 to 2011 than from 2012 to 2017 (38% [n = 6 of 16] vs 45% [n = 15 of 33], P = .6, respectively). No significant differences in baseline characteristics were detected between those who received AMB and AMB + POS or ISA (Table 1). Furthermore, combination AmB + POS or ISA was not more common than AmB alone at any site of infection (Table 2).

The incidence of treatment failure was 64% (n = 18 of 28) for AmB-treated patients compared with 43% (n = 9 of 21) for those treated with AmB + POS or ISA (P = .136). Of patients initially treated with AmB, 10% (n = 3 of 28) were escalated to AmB + ISA after treatment failure. Thirty-day and one-year

Table 2. Mucormycosis Infection-Related Characteristics

Characteristic, Median (IQR) or % (n)	Total (N = 64)	AmB (n = 28)	AmB + POS/ISA (n = 21)
Invasive Fungal Disease[a]			
Proven	73 (47)	64 (18)	81 (17)
Probable	27 (17)	36 (10)	19 (4)
Pathogen Genus			
Rhizopus spp	52 (33)	39 (11)	67 (14)
Mucor spp	23 (15)	29 (8)	14 (3)
Lictheimia spp	3 (2)	0	5 (1)
Cunninghamella spp	2 (1)	0	5 (1)
Unknown	20 (13)	32 (9)	10 (2)
Primary Infection Site			
Rhino-orbital-cerebral	33 (21)	25 (7)	39 (9)
Pulmonary	30 (19)	29 (8)	19 (4)
Disseminated	19 (12)	18 (5)	19 (4)
Cutaneous/wound	3 (2)	4 (1)	5 (1)
Gastrointestinal	3 (2)	4 (1)	5 (1)
Other	13 (8)	21 (6)	10 (2)
Coinfection(s)	48 (31)	43 (12)	61 (14)
Bacterial	34 (22)	25 (7)	48 (10)
Fusarium spp	8 (5)	14 (4)	4 (1)
Aspergillus spp	3 (2)	4 (1)	4 (1)
Alternaria spp	2 (1)	0	0
CMV[b]	6 (4)	7 (2)	4 (1)
Other fungi	6 (4)	7 (2)	4 (1)
Other virus	3 (2)	4 (1)	4 (1)
Antifungal PROPHylaxis at DIAGNOsis	91 (58)	93 (26)	81 (17)
VRC	48 (28)	38 (10)	65 (11)
FLC	17 (10)	19 (5)	12 (2)
EC	16 (9)	12 (3)	18 (3)
POS	16 (9)	23 (6)	6 (1)
AmB	3 (2)	8 (2)	0
Duration of prophylaxis, days	46 (18–177)	58 (18–299)	20 (15–177)
Surgical Debridement	64 (41)	57 (16)	81 (17)
Time from diagnosis to surgery, days	0 (0–3)	2 (0–4)	0 (0–1)
Initial Antifungal Treatment			
AmB	44 (28)	100 (28)	—
5 mg/kg per day	75 (48)	86 (24)	90 (19)[c]
7.5 mg/kg per day	14 (9)	11 (3)	10 (2)[c]
10 mg/kg per day	5 (3)	4 (1)	0
POS	5 (3)	—	—
ISA	3 (2)	—	—
AmB-containing combination	48 (31)	—	100 (21)
+POS	52 (16)	—	70 (16)
+EC	26 (8)	—	0
+ISA	16 (5)	—	21 (5)
+POS and EC	6 (2)	—	0
Mortality			
All-cause	36 (23)	43 (12)	28 (6)
30-day	63 (40)	64 (18)	42 (9)
1-year			
Mucor-Related Mortality			
30-day	33 (21)	39 (11)	24 (5)
1-year	38 (24)	43 (12)	33 (7)

Abbreviations: AmB, lipid formulation of amphotericin B; CMV, cytomegalovirus; EC, echinocandin; FLC, fluconazole; ISA, isavuconazole; IQR, interquartile range; POS, posaconazole; VRC, voriconazole.

[a]By 2008 EORTC/MSG consensus definitions for invasive fungal diseases.

[b]All cases of CMV were viremia without tissue invasive disease.

[c]Dose of AMB as part of AMB-containing combination.

all-cause mortalities were 43% and 68% for AmB versus 28% and 57% for AmB + POS or ISA, respectively ($P > .1$). In survival analysis, the hazard ratio was 0.397 (95% confidence interval [CI], 0.173–0.917; $P = .30$) for surgical control and 0.667 (95% CI, 0.667–1.557; $P = .349$) for AmB + POS or ISA. In the DOOR analysis (Figure 1), 33.3% of patients treated with combination therapy were alive without treatment failure and adverse events compared with 10.7% in the AmB monotherapy group, largely due to differences in death and switch to other agents.

DISCUSSION

Using a network of 10 transplant centers in distinct geographic locations across North America, we analyzed the characteristics and outcomes of 64 patients with IM over a 10-year period when POS and ISA were available for antifungal treatment. Our findings indicate that despite the improvements in management of IM, the overall prognosis in HCT and HM populations remains extremely poor after diagnosis, with only a 37% survival rate at 1 year.

Although IM is relatively rare, HCT recipients at particular risk. In the TRANSNET study, the 12-month cumulative incidence of IM in HCT recipients was 0.29% between 2001 and 2006 in the United States [2]. This was noted to be higher in allogeneic HCT recipients from HLA-MURD. In the present study, across the 10-year interval from 2007 to 2017, we noted similar findings. Similar to previous reports that have identified an association between voriconazole exposure and increased incidence of IM diagnosis among HM and HCT populations [5], we noted a high frequency of voriconazole prophylaxis within our cohort. Since voriconazole was introduced, newer triazoles with in vitro activity against Mucorales, POS, and ISA have been released. However, limited data have evaluated changes in IM mortality since the introduction of these agents. The VITAL study reported 42-day all-cause mortality to be 33% among those treated with open-label ISA, which is similar to our observed 30-day mortality of 36% [6].

From a therapeutic viewpoint, several studies evaluating antifungal drug therapy within the last decade have impacted the current approach to IM. The AmBizygo trial, was a prospective, multicenter pilot study, that investigated high dose (10 mg/kg per day) AmB as a first-line treatment [7]. High-dose AmB plus surgery resulted in 62% survival at week 12; however, 40% of subjects had a doubling of serum creatinine with approximately one third not recovering to baseline creatinine by week 12. Presence of HM or cancer was the only factor associated with mortality, emphasizing the poor outcomes in this subgroup. High-dose AmB approaches clearly carry substantial nephrotoxic risk, particularly in those with preexisting renal disease or receiving concurrent nephrotoxic agents, such as calcineurin inhibitors. In the VITAL study, researchers investigated the efficacy of ISA in 46 patients with IM, including 21 patients in whom ISA was used as first-line therapy. In that study, 52% had underlying HM and 19%

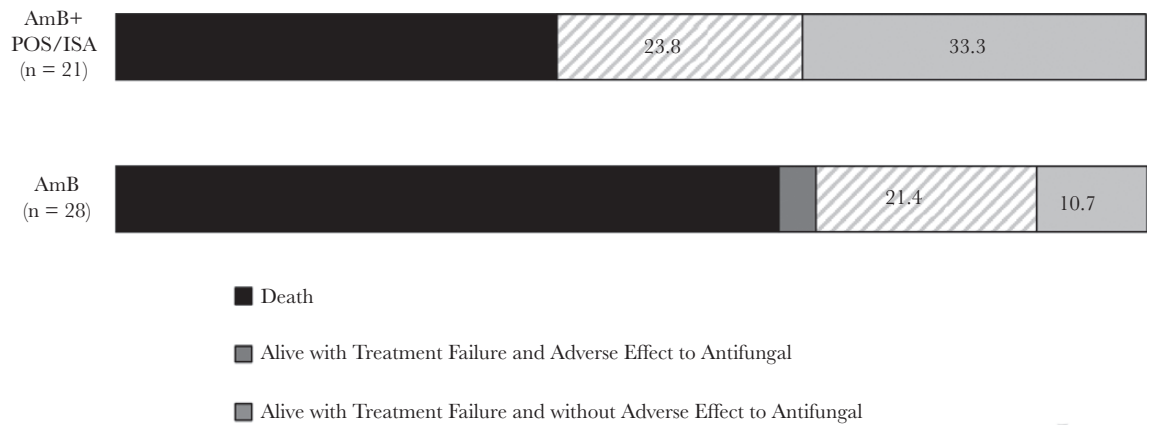

Figure 1. Desirability of outcome ranking (DOOR) analysis comparing lipid formulation of amphotericin B (AmB) monotherapy and combination therapy with AmB + posaconazole/isavuconazole (POS/ISA).

were allogeneic HCT recipients. Complete or partial response to therapy was achieved in 32% by the end of therapy, and all-cause mortality was just 43% at week 12 [6]. These data justified regulatory approval of ISA for treatment of IM in the United States and Europe. Additional data have since shown ISA has an improved safety profile compared with POS [8]. Finally, poor oral bioavailability of the POS solution led to the development of intravenous and delayed release tablet formulations, which provide more consistent drug exposure [9–11].

Given the unacceptably high mortality associated with IM, combination antifungal therapy has been evaluated within in vitro, animal, and clinical studies. Ibrahim et al [12] demonstrated effective targeting of *Rhizopus oryzae* with low-dose EC due to expression of 1,3-β-D-glucan synthase, the active target of EC. In *R oryzae* murine models, combination AmB with low-dose micafungin (1 mg/kg per day) improved survival compared with monotherapy, with diminished response at higher doses [13]. A small retrospective study (n = 41) of patients with IM treated with amphotericin B lipid complex suggested superior clinical success rates among those receiving simultaneous caspofungin compared with monotherapy [14]. Despite data indicating a potential synergistic benefit with AmB + EC, triazole-containing combinations, in contrast, have not thus far demonstrated comparable results. In a *R oryzae* murine model, use of AmB + POS combination did not reduce fungal burden or improve survival compared with POS alone [15]. Isavuconazole in combination with EC similarly showed no notable survival benefit in other murine models of IM [16]. A retrospective analysis of 32 patients who received POS + AmB, largely as second-line therapy, reported an overall response rate of 56% at 90 days, and alnmost 60% of patients died before day 90 [17]. Collectively, these data do not provide evidence for therapeutic synergy that would support combination antifungal approaches in IM. Collectively, these data do not provide evidence for therapeutic synergy that would support combination antifungal approaches in IM.

We previously described similar findings in a cohort of 101 IM cases with presence of HM, HCT, or solid organ transplantation across 2 periods, 1995–2003 and 2004–2011 [18]. Despite the availability of newer antifungals (EC and POS) and a corresponding increase in the use of combination antifungal approaches in the latter period, no significant improvements in overall 90-day survival were observed in those who received AmB with an EC and/or POS compared with AmB alone (54% vs 59%, $P = .67$). Similarly, an analysis of 106 patients with IM and underlying HM showed that initial combination antifungal treatment using 2 or 3 antifungal agents did not impact survival beyond monotherapy [19]. In our current study (2007–2017), we were able to assess antifungal treatment rates of AmB monotherapy (44% n = 28) versus combination antifungal therapy of AmB with EC, POS, or ISA (48%). Although an apparent trend toward decreased rates of treatment failure was noted for those receiving initial antifungal combination therapy, the all-cause 1-year mortality was not statistically different between AmB versus combination AmB + POS or ISA group (68% vs 57%).

Guidelines published by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM) study groups [1] and the European Conference of Infections in Leukemia (ECIL) [20] before and after the availability of ISA, respectively, continue to recommend the use of AmB as first-line therapy. In cases of central nervous system involvement, these guidelines recommend the AmB at 5 to 10 mg/kg per day in combination with radical surgery. Because definitive data on combination antifungal therapy are lacking, current guidelines do not recommend combination as a first-line strategy. Intravenous or delayed release POS and intravenous ISA are strongly recommended for salvage therapy [1, 20]. In

our study, initial combination therapy with AmB+ POS/ISA appeared on DOOR analysis to have fewer treatment failures, cumulatively due to fewer deaths, safety events and need to switch to alternative agents. Whether combination therapy should be routinely considered an initial therapy may depend on patients underlying risk for progression, ability to achieve surgical control, and likelihood of developing an adverse event based on comorbid conditions.

There are several important limitations to our study. First, the retrospective nature of the study may have introduced biases and cofounding inherent to this design. Namely, treatment selection bias may be present between those receiving monotherapy and combination therapy. However, no significant differences in baseline or clinical characteristics between treatment groups were identified. Despite this, there were potential trends observed toward a higher proportion of patients in the combination therapy group who underwent surgical debridement with a shorter median time to surgical intervention compared with monotherapy. This may have impacted the trend towards improved survival observed in the combination group and be an indicator that unmeasured confounding is present. Finally, the small sample size, particularly in the comparison between monotherapy and combination therapy, does not preclude the possibility of type II error.

CONCLUSIONS

In conclusion, despite frequent use of combination antifungal therapy in the era of new antifungals (POS, ISA), we were unable detect a significant change in short-term survival compared with AmB monotherapy. Thirty-day and 1-year mortality after IM diagnosis remains high at 43% and 68% in the AmB treatment group versus 28% and 57% for combination antifungal group AmB + POS or ISA, respectively. The results serve to improve our understanding of the mortality impact after diagnosis of IM. Larger, prospective studies are needed to better characterize the incidence and clinical outcomes of IM and whether initial combination therapy with AmB with POS/ISA improve outcomes in immunocompromised hosts.

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