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BRIEF REPORT

Combination Antifungal Therapy for Invasive Mucormycosis in Immunocompromised Hosts: A Single-Center Experience

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Combination antifungal therapy for invasive mucormycosis remains controversial and is inconsistently defined in prior studies. In a cohort of patients with immunocompromised status and invasive mucormycosis, we found no difference in 6-week mortality with up-front or salvage combination therapy as compared with monotherapy.

Mucormycosis is an aggressive fungal infection that disproportionately affects patients who are immunocompromised. Despite diagnostic and therapeutic advancements, mortality remains high (up to 83%) [1]. The cornerstone of managing invasive mucormycosis (IM) lies with medical therapy, often with surgical debridement. However, the presence of comorbidities may hinder timely diagnostic and therapeutic intervention.

Due to poor prognosis, clinicians often prescribe combination antifungal therapy for IM. Data are mixed on the benefit of this approach. Treatment guidelines only weakly recommend combination therapy, primarily due to the absence of evidence suggesting harm, as opposed to evidence for improved efficacy [2]. Murine models [3, 4] suggest that combination therapy may decrease tissue fungal burden, and a recent retrospective observational study [5] of hematopoietic stem cell transplant recipients demonstrated a trend, though nonsignificant, toward lower mortality with up-front combination therapy. Unfortunately, the timing of combination therapy initiation, a factor that may affect outcomes, is not defined in existing literature. Additionally, most studies on combination therapy include cohorts that precede the widespread availability of molecular-based diagnostics enabling earlier diagnosis of mucormycosis, which limits their applicability in the current era.

We sought to describe diagnostic and antifungal utilization in a contemporary cohort of patients with IM who were immunocompromised. We also aimed to compare outcomes in those receiving monotherapy vs combination therapy, with detailed analysis of up-front and salvage combination regimens.

METHODS

Study Design

We included adults who were immunocompromised (hematologic malignancy, hematopoietic stem cell transplant, or solid organ transplant) and hospitalized between January 2009 and December 2022 for proven or probable IM based on the EORTC/MSG 2020 criteria (European Organization for Research and Treatment of Cancer and the Mycoses Study Group) [6]. We excluded patients who died within 72 hours of IM diagnosis and/or those coinfected with *Scedosporium* or *Lomentospora* spp.

Definitions

Primary infection sites were categorized as rhino-orbital cerebral (ROCM), pulmonary, cutaneous/wound, gastrointestinal, or disseminated. Disseminated disease was defined as ≥2 noncontiguous sites of mucormycosis involvement. Neutropenia was defined as an absolute neutrophil count <500 cells/μL. Patients were grouped into cohorts based on receipt of the following: (1) up-front combination therapy, defined as receiving at least 2 active antifungals within the first 7 days of IM diagnosis for at least 3 days; (2) salvage combination therapy, defined as initiating at least 2 active antifungals after the first 7 days of IM diagnosis and for at least 3 days; or (3) monotherapy, defined as receiving a single active antifungal. The day of IM diagnosis was the first day that EORTC/MSG criteria were met. Molecular-based techniques included polymerase chain reaction and genome sequencing.

Statistical Analysis

Demographic data were compared by analysis of variance test for continuous data and chi-square test for categorical data. Bivariate analysis was conducted to relate covariates to mortality via simple logistic regression. Covariates were based on previously identified factors affecting clinical outcomes for IM, including neutropenia, receipt of surgery, and disseminated disease. Afterward, multiple logistic regression was performed

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to evaluate the impact of combination antifungal therapy on 6-week mortality. Statistical analyses were conducted with SAS version 9.4 (SAS Institute Inc). Hypothesis testing was performed at the 0.05 alpha level of significance (2-sided).

RESULTS

Demographics

A total of 82 patients met study inclusion criteria and most (61%) had proven mucormycosis (Table 1). Most patients had a hematologic malignancy (78%), pulmonary disease (62%), and infection with *Rhizopus* spp (50%). In addition, 24 (29%) patients received monotherapy, 44 (54%) up-front combination therapy, and 14 (17%) salvage combination antifungal therapy. Baseline demographics were similar between groups, except for the causative organism of IM (Table 1). The most common antifungal regimens were liposomal amphotericin B (LAmB) monotherapy (30%), followed by LAmB plus posaconazole or isavuconazole (27%). LAmB dose was 5 mg/kg daily for most patients (96%). More patients with ROCM underwent surgery (94%) as compared with pulmonary (31%) and disseminated (13%) disease. The number of diagnoses increased each year, along with the proportion of diagnoses involving molecular-based techniques (Supplementary Figure 1). Up-front combination therapy was more common in patients with disseminated infection (88%) vs pulmonary (50%) and ROCM (63%).

Outcomes

The overall 6-week mortality rate was 31%. No covariate was associated with 6-week mortality on univariate analysis (Table 2). With multiple logistic regression, we detected no difference in odds of mortality for combination antifungal therapy —up-front (odds ratio [OR], 1.44; 95% CI, .29–7.23; $P = .66$) and salvage (OR, 2.15; 95% CI, .61–7.66; $P = .24$)—as compared with monotherapy (Table 2). Similarly, we detected no significant difference in odds of mortality with receipt of surgical intervention (OR, 0.44; 95% CI, .14–1.36; $P = .15$) and neutropenia (OR, 2.26; 95% CI, .80–6.35; $P = .12$).

DISCUSSION

In a contemporary cohort of patients with immunocompromised status and IM spanning a 14-year period, neither up-front nor salvage combination therapy was associated with a difference in 6-week mortality when compared with monotherapy. These findings mirror the results of most clinical studies published to date [7, 8].

Combination therapy for mucormycosis remains controversial. Murine models evaluating amphotericin B with echinocandins or azoles have produced mixed results [3, 4, 9], and most retrospective studies follow similar patterns. Reed et al found that combination polyene-caspofungin was associated with improved survival in ROCM [10]. However, few patients were included who were immunocompromised, and all patients underwent surgical intervention. In contrast, in a study of patients who were immunocompromised, Abidi et al reported no difference in 90-day survival between amphotericin B alone and amphotericin B with an echinocandin and/or posaconazole [11]. In a similar study of primarily sinopulmonary mucormycosis, Kyvernitakis et al showed no benefit of up-front combination therapy vs monotherapy [8]. Unfortunately, these studies included periods that preceded the approval of isavuconazole and pharmacokinetically favorable formulations of posaconazole. Additionally, both studies predated the widespread availability of molecular-based tests. In a more recent publication, Miiler et al [5] observed a nonsignificant trend toward improved outcomes with initial combination therapy, although differences in time to surgery between groups may have influenced this finding.

Prior studies provide no clear definition of combination therapy, despite the emphasis placed on it as a potentially beneficial approach [5, 7, 8, 10, 11]. Since studies of mucormycosis are often retrospective and limited by sample size, accounting for real-world practice variation through rigorous definitions may help delineate strategies associated with benefit. We defined combination antifungal therapy using a minimum duration of 3 days of combination antifungal use, characterized as either up-front or salvage therapy, which are temporal components in our analysis that were not defined consistently in prior studies of IM [5, 7, 8, 10, 11]. In a study of patients with invasive aspergillosis, benefit was seen with salvage combination therapy defined as >7 days after diagnosis; thus, we adapted this salvage definition for our study [12].

Six-week mortality in this study was 31%, which is consistent with prior studies of IM [5, 8]. To our knowledge, this is the first study to include surgical intervention as a covariate when analyzing clinical outcomes with combination therapy for IM. The inability to perform surgical debridement is a known risk factor for poor outcomes with mucormycosis [7, 13]. After adjusting for surgical intervention, we found nonsignificant but numerically higher odds of mortality for combination therapy as compared with monotherapy. This difference may reflect confounding by indication, where patients with severe disease may be more likely to receive combination therapy. This association was also observed in a study by Singh et al in solid organ transplant recipients with IM [7]. An alternative explanation for this mortality difference may be the enhanced toxicity of multiple antifungals. While the impact of toxicity from combination therapy has not been assessed in mucormycosis, data in patients with aspergillosis suggest a potential negative effect [14].

Modalities for diagnosis of IM have evolved over the last decade, as evidenced by the inclusion of molecular-based techniques in the recent EORTC/MSG invasive fungal infection criteria [6]. Although increased molecular-based diagnostic utilization could

Table 1. Demographics

			Combination Therapy		
	All Patients (n = 82)	Monotherapy (n = 24)	Up-front (n = 44)[a]	Salvage (n = 14)[b]	*P* Value
Male	50 (61)	14 (58)	28 (64)	8 (57)	.87
Age, y	58 (23–86)	62 (23–81)	56 (24–86)	55 (34–69)	.35
Immunocompromising condition					.99
Hematologic malignancy	64 (78)	19 (79)	35 (80)	10 (71)	
Acute myeloid leukemia	30 (37)	11 (46)	15 (34)	4 (29)	
Acute lymphoblastic leukemia	10 (12)	2 (8)	7 (16)	1 (7)	
Chronic lymphocytic leukemia	3 (4)	1 (4)	1 (2)	1 (7)	
Myelodysplastic syndrome	7 (9)	1 (4)	5 (11)	1 (7)	
DLBCL	4 (5)	1 (4)	2 (5)	1 (7)	
Multiple myeloma	1 (1)	0 (0)	1 (2)	0 (0)	
Chronic myelogenous leukemia	2 (2)	1 (4)	1 (2)	0 (0)	
Other	7 (9)	2 (8)	3 (7)	2 (14)	
Transplant					
Solid organ	18 (22)	5 (21)	9 (20)	4 (29)	
Lung	10 (12)	3 (13)	5 (11)	2 (14)	
Heart	3 (4)	1 (4)	2 (5)	0 (0)	
Kidney	4 (5)	1 (4)	1 (2)	2 (14)	
Liver	1 (1)	0 (0)	1 (2)	0 (0)	
HSCT					.24
Allogeneic	28 (34)	5 (21)	18 (41)	5 (36)	
Autologous	0 (0)	0 (0)	0 (0)	0 (0)	
None	54 (66)	19 (79)	26 (59)	9 (64)	
HSCT source					.62
Bone marrow	5 (6)	1 (4)	2 (5)	2 (14)	
Peripheral blood	22 (27)	3 (13)	18 (36)	3 (21)	
Cord blood	1 (1)	1 (4)	0 (0)	0 (0)	
ICU at diagnosis	16 (20)	5 (21)	10 (23)	1 (7)	.43
Diabetes	27 (33)	6 (25)	16 (36)	5 (36)	.62
Neutropenia[c]	25 (30)	7 (29)	12 (27)	6 (43)	.54
Neutrophil recovery[d]	17 (68)	5 (71)	8 (67)	4 (67)	.97
GVHD	11 (13)	3 (13)	7 (16)	1 (7)	.91
Organism					**.005**
Rhizopus spp	41 (50)	7 (29)	27 (61)	7 (50)	
Rhizomucor spp	5 (6)	0 (0)	5 (11)	0 (0)	
Cunninghamella spp	2 (2)	1 (4)	1 (2)	0 (0)	
Mucorales agent	24 (29)	14 (58)	5 (11)	5 (36)	
Syncephalastrum spp	1 (1)	0 (0)	1 (2)	0 (0)	
Unknown	9 (11)	2 (8)	5 (11)	2 (14)	
Fungal coinfection					.99
Candida spp	4 (5)	1 (4)	2 (5)	1 (7)	
Aspergillus spp	11 (13)	5 (21)	4 (9)	2 (14)	
Proven mucormycosis[e]	50 (61)	16 (67)	26 (59)	8 (57)	.79
Primary infection site					.1
ROCM	16 (20)	2 (8)	10 (23)	4 (29)	
Pulmonary	51 (62)	18 (75)	25 (57)	8 (57)	
Cutaneous/wound	5 (6)	3 (13)	1 (2)	1 (7)	
Gastrointestinal	1 (1)	0 (0)	1 (2)	0 (0)	
Disseminated	8 (10)	0 (0)	7 (16)	1 (7)	
Other	1 (1)	1 (4)	0 (0)	0 (0)	
Prophylactic antifungal at time of diagnosis					.59
None	23 (28)	7 (29)	11 (25)	5 (36)	
Fluconazole	6 (7)	1 (4)	3 (7)	2 (14)	
Itraconazole	5 (6)	1 (4)	4 (9)	0 (0)	
Voriconazole	22 (27)	7 (29)	14 (32)	1 (7)	
Posaconazole	20 (24)	7 (29)	8 (18)	5 (36)	

Table 1. Continued

	All Patients (n = 82)	Monotherapy (n = 24)	Combination Therapy		*P* Value
			Up-front (n = 44)[a]	Salvage (n = 14)[b]	
Isavuconazole	4 (5)	1 (4)	3 (7)	0 (0)	
Caspofungin	2 (2)	0 (0)	1 (2)	1 (7)	
All cause mortality at 6 wk	25 (31)	6 (25)	15 (34)	4 (29)	.73
Time to initial therapeutic antifungal, d[f]	0 (0–2)	0 (0–1)	0 (0–1)	0 (0–2)	.78
Duration of combination antifungal therapy, d	13 (3–21)	—	15 (3–25)	8 (3–11)	.18
Combination with ≥3 antifungals at any time	23 (28)	0 (0)	21 (48)	2 (14)	**<.0001**
Surgical intervention	36 (44)	5 (21)	23 (52)	8 (57)	.24
Time to first surgery, d[f]	2 (0–145)	1 (0–4)	2 (0–145)	4 (0–17)	.42
No. of surgical interventions					.11
0	46 (56)	19 (79)	21 (48)	6 (43)	
1	20 (24)	4 (17)	11 (25)	5 (36)	
2	6 (7)	1 (4)	5 (11)	0 (0)	
3	8 (10)	0 (0)	6 (14)	2 (14)	
4	2 (2)	0 (0)	1 (2)	1 (7)	

Data are presented as No. (%) or median (range). Bold indicates $P < .05$.

Abbreviations: DLBCL, diffuse large B-cell lymphoma; GVHD, graft-vs-host disease; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; ROCM, rhino-orbital cerebral mucormycosis.

[a]Receipt of at least 2 *Mucor*-active antifungal agents for at least 3 days within the first 7 days of mucormycosis diagnosis.

[b]Receipt of at least 2 *Mucor*-active antifungal agents starting after 7 days after diagnosis of mucormycosis.

[c]Absolute neutrophil count <500 cells/μL at time of diagnosis.

[d]Recovery of absolute neutrophil count to >500 cells/μL within 6 weeks after diagnosis, if initially neutropenic.

[e]Based on 2020 criteria from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group.

[f]Defined by time from diagnosis.

Table 2. Multivariate Logistic Regression for 6-Week Mortality

	Univariate			Multivariate		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Combination therapy						
Upfront[a] vs none	1.20	.27–5.29	.81	1.44	.29–7.23	.66
Salvage[b] vs none	1.55	.51–4.73	.44	2.15	.61–7.66	.24
Upfront vs salvage	1.29	.35–4.76	.70	1.49	.37–6.25	.57
Surgery	0.49	.18–1.31	.15	0.44	.14–1.36	.15
Disseminated	1.46	.31–6.46	.65	0.89	.27–4.82	.90
Neutropenia[c]	2.41	.89–6.52	.08	2.26	.80–6.35	.12

Abbreviation: OR, odds ratio.

[a]Receipt of at least 2 *Mucor*-active antifungal agents for at least 3 days within the first 7 days of mucormycosis diagnosis.

[b]Receipt of at least 2 *Mucor*-active antifungal agents starting after the first 7 days of mucormycosis diagnosis.

[c]Absolute neutrophil count <500 cells/μL.

have led to the observed increase in IM diagnoses over time, other factors, such as transplant program expansion, may have contributed. In our cohort, 58% of patients receiving monotherapy were diagnosed by molecular-based diagnostics and lacked culture growth. This contrasts with patients receiving combination therapy, where only 17% involved molecular-based diagnostics without an associated organism. It is possible that a lack of culture growth may lead clinicians to select antifungal monotherapy based on a presumed lower burden of disease, given the high sensitivity of these tests [15, 16].

There are several limitations to note. First, this was a retrospective study with possible treatment selection bias. Additionally, the small sample size may have limited our ability to detect meaningful differences between patients receiving monotherapy and combination therapy. Second, the long study period includes years where certain antifungals, such as isavuconazole, were not available. Third, molecular-based diagnostics are a more recent development that could facilitate more rapid IM diagnoses, which may limit comparisons of this study with historical cohorts. Last, we did not evaluate the impact of coinfection on mortality.

CONCLUSION

Patients with IM who are immunocompromised are at high risk of poor outcomes. Combination antifungal therapy is often utilized, despite lacking data supporting a clear, clinical benefit. We did not observe a significant difference in 6-week mortality between up-front or salvage combination antifungal therapy and monotherapy. The optimal chemotherapy of patients with mucormycosis should be determined with large collaborative prospective studies.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. B. L. contributed to data collection, designed the study, analyzed data, and wrote the article. D. H. and W. A. designed the study, analyzed data, and wrote the article. J. F. T., E. M., S. D., and M. H. designed the study and wrote the article. S. S. performed statistical analysis and wrote the article. A. K. and S. K. contributed to data collection.

Patient consent statement. This study does not include factors necessitating patient consent.

Potential conflicts of interest. All authors: No reported conflicts.

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