Survival among Patients with Hematologic Malignancies and Recipients of Hematopoietic Cell Transplant with Invasive Mucormycosis

Matthew A. Miller,[1] Kyle C. Molina,[1] Sias Scherger,[2] Jessica M. Lum,[3] Sherif B. Mossad,[3] Mary Burgess,[4] Matthew Cheng, [5] Sally Chuang, [6] Samantha Jacobs,[7] D. Paolo Melendez, [8] Dimpy Shah, [9] M. Rizwan Sohail, [10] Sadia Syed,[10] Randall C. Walker,[10] Andrea Zimmer, [11] Johnathan A. Gutman, [12] Maheen Z. Abidi[2]

[1]Department of Pharmacy, University of Colorado Hospital; [2]Division of Infectious Diseases, University of Colorado Denver; [3]Department of Infectious Diseases, Cleveland Clinic Foundation; [4]Division of Infectious Diseases, University of Arkansas; [5]Division of Infectious Diseases, McGill University; [6]Division of Infectious Diseases, University of Rochester; [7]Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai; [8]Division of Infectious Diseases, University of Oklahoma; [9]Division of Infectious Diseases, University of Texas San Antonio; [10]Division of Infectious Diseases, Mayo Clinic College of Medicine; [11]Division of Infectious Diseases, University of Nebraska; [12]Division of Hematology & Oncology, University of Colorado Denver

Background

- Invasive mucormycosis (IM) is a rare, rapidly progressive infection associated with significant morbidity and mortality, with all-cause mortality ranging from 40-80%.
- Those with underlying hematologic malignancies (HM) and/or following hematopoietic-cell transplantation (HCT) are at elevated risk for this infection as well as poor prognosis.
- Recent publication of global guidelines for diagnosis and management of mucormycosis from the European Confederation on Medical Mycology suggest the following management strategies:
  - Early surgical debridement
  - First-line monotherapy with lipid formulations of amphotericin-b (LFAB)
    - Initial combination therapies are not strongly recommended due to limited data and potential for enhanced toxicity
- Improved treatment strategies are desperately needed to improve survival among HM and HCT populations

Primary Objective

- Primary outcome was treatment failure, defined as IM-related death or change in initial antifungals for clinical progression between those treated with LFAB alone and LFAB plus POS/ISA.

Methods

- **Study Design:** Multi-center, retrospective cohort study
  - Adults diagnosed with proven or probable mucormycosis between 2007-2017 and presence of HM and/or HCT receipt were included.
  - Transplant and infection related characteristics were collected from electronic medical records following local IRB approval.
  - Secondary outcomes included comparison of 30-day and 1-year all-cause mortality
- **Statistical Analysis:**
  - Primary and secondary outcomes between LFAB and LFAB plus POS/ISA were compared using Fisher's Exact
  - Survival analysis was performed using Kaplan Meier, with comparisons made using log-rank test
  - Desirability of outcome ranking (DOOR) analysis was performed to compare Risk:Benefit of initial treatment strategies

Results

Table 1: Baseline Characteristics

	Total, n=64	LFAB alone, n= 28	LFAB + POS/ISA, n= 23
Median age, years (IQR)	57 (45-64)	55 (42-66)	58 (47-63)
Sex, % male (n)	55 (35)	61 (17)	48 (11)
Race, % (n)			
White	77 (49)	68 (19)	78 (18)
Asian	6 (4)	11 (3)	4 (1)
Other/Not Reported	17 (11)	21 (6)	17 (4)
Underlying hematological malignancy, % (n)			
Acute myeloid leukemia	47 (30)	50 (14)	48 (11)
Acute lymphoblastic leukemia	16 (10)	11 (3)	17 (4)
Chronic lymphocytic leukemia	11 (7)	7 (2)	17 (4)
Myelodysplastic syndrome	6 (4)	4 (1)	9 (2)
Diffuse large B-cell lymphoma	5 (3)	0	4 (1)
Multiple myeloma	3 (2)	7 (2)	0
Chronic myelogenous leukemia	2 (1)	4 (1)	0
Other	14 (9)	18 (5)	9 (2)
HSCT, % (n)	61 (39)	61 (17)	70 (16)
Autologous	5 (2)	12 (2)	0
Allogeneic	95 (37)	88 (15)	100 (16)
Matched, unrelated	46 (17)	46 (7)	44 (7)
Matched, related sibling	24 (9)	20 (3)	25 (4)
Umbilical cord	14 (5)	20 (3)	13 (2)
Matched, related other	8 (3)	7 (1)	6 (1)
Haploidentical	3 (1)	0	6 (1)
Mismatch	3 (1)	7 (1)	0
Unknown	3 (1)	0	6 (1)
Graft source from bone marrow, % (n)	15 (6)	24 (4)	6 (1)
Conditioning regimen, % (n)			
Myeloablative	46 (18)	53 (9)	38 (6)
Reduced intensity	44 (17)	29 (5)	56 (9)
Non-myeloablative	8 (3)	12 (2)	6 (1)
Lymphocyte depletion, % (n)	26 (10)	18 (3)	25 (4)
Risk factors at baseline, % (n)			
Diabetes	23 (15)	21 (6)	35 (8)
Neutropenia at diagnosis	56 (36)	50 (14)	52 (12)
ANC < 500	92 (33)	100 (14)	92 (11)
Transplant-related (n=39)			
Pre-engraftment at diagnosis	10 (4)	12 (2)	0
Diagnosis within 1st year post-transplant	59 (23)	76 (13)	44 (7)
GVHD (acute or chronic)	59 (23)	47 (8)	69 (11)

Table 2:Treatment Related Characteristics

	Total, n=64	LFAB alone, n= 28	LFAB + POS/ISA, n= 23
Diagnostic certainty			
Proven	73 (47)	64 (18)	83 (19)
Probable	27 (17)	36 (10)	17 (4)
Baseline pathogen genus, % (n)			
Rhizopus spp.	52 (33)	39 (11)	65 (15)
Mucor spp.	23 (15)	29 (8)	17 (4)
Lichteimia spp.	3 (2)	0	4 (1)
Cunninghamella spp.	2 (1)	0	4 (1)
Unknown	20 (13)	32 (9)	9 (2)
Primary site(s) of infection, % (n)			
Rhino-orbital-cerebral	33 (21)	29 (8)	39 (9)
Pulmonary	31 (20)	32 (9)	26 (6)
Disseminated	13 (8)	11 (3)	9 (2)
Cutaneous/wound	5 (3)	7 (2)	4 (1)
Gastrointestinal	5 (3)	3 (1)	9 (2)
Other	14 (9)	18 (5)	13 (3)
Fungal infection in 2 weeks before transplant, % (n)	3 (2)	6 (1)	0

Table 2:Treatment Related Characteristics, Continued

	Total, n=64	LFAB alone, n= 28	LFAB + POS/ISA, n= 23
Co-infections, % (n)	48 (31)	43 (12)	61 (14)
Bacterial	34 (22)	25 (7)	48 (11)
Fusarium spp.	8 (5)	14 (4)	4 (1)
Aspergillus spp.	3 (2)	4 (1)	4 (1)
Alternaria spp.	2 (1)	0	0
Other fungi	6 (4)	7 (2)	4 (1)
CMV[a]	6 (4)	7 (2)	4 (1)
Other virus	3 (2)	4 (1)	4 (1)
Antifungal prophylaxis at diagnosis, % (n)	91 (58)	93 (26)	83 (19)
Voriconazole	47 (27)	38 (10)	58 (11)
Fluconazole	19 (11)	19 (5)	21 (4)
Echinocandin	16 (9)	12 (3)	16 (3)
Posaconazole	16 (9)	23 (6)	5 (1)
Liposomal amphotericin-b	3 (2)	8 (2)	0
Surgical debridement performed, % (n)	66 (42)	57 (16)	78 (18)
Median time to surgery, days (IQR)	0.5 (0-3)	2 (0-3)	0 (0-2)
Initial antifungal treatment, % (n)			
Liposomal amphotericin-b (LAmB)[b]	44 (28)	100 (28)	0
Posaconazole	5 (3)	0	0
Isavuconazole	3 (2)	0	0
Combination of antifungals	48 (31)	0	100 (23)
LAmB + posaconazole	52 (16)	0	70 (16)
LAmB + echinocandin	26 (8)	0	0
LAmB + Isavuconazole	16 (5)	0	21 (5)
LAmB + posaconazole + echinocandin	6 (2)	0	9 (2)

[a] All cases of CMV were viremia, no episodes of tissue invasive disease reported
[b] Dosing: 5mg/kg (n=46, 78%), 7.5mg/kg (n=9, 15%), 10mg/kg (n=3, 5%)

Table 3: Outcomes

	Total, n=64	LFAB alone, n= 28	LFAB + POS/ISA, n= 23	P-value*
30-day all-cause mortality, % (n)	38 (24)	46 (13)	22 (5)	0.08
1-year all-cause mortality, % (n)	66 (42)	71 (20)	57 (13)	0.38
Mucor-related mortality, % (n)	45 (29)	50 (14)	39 (9)	0.57
Antifungal changed for failure/progression, % (n)	5 (3)	11 (3)	0	0.24
Adverse effect to antifungals, % (n)	41 (26)	46 (13)	39 (9)	0.78

* Comparisons made between LFAB alone and LFAB + POS/ISA

Figure 1: Kaplan-Meier Curve

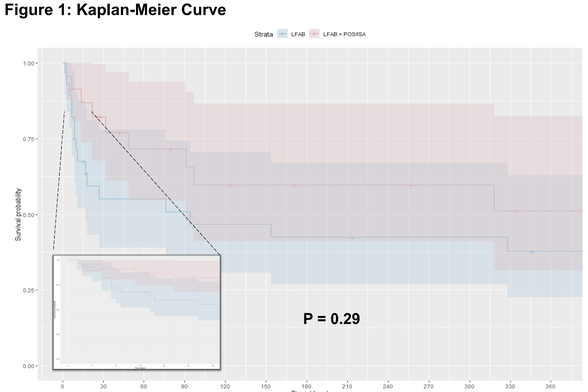
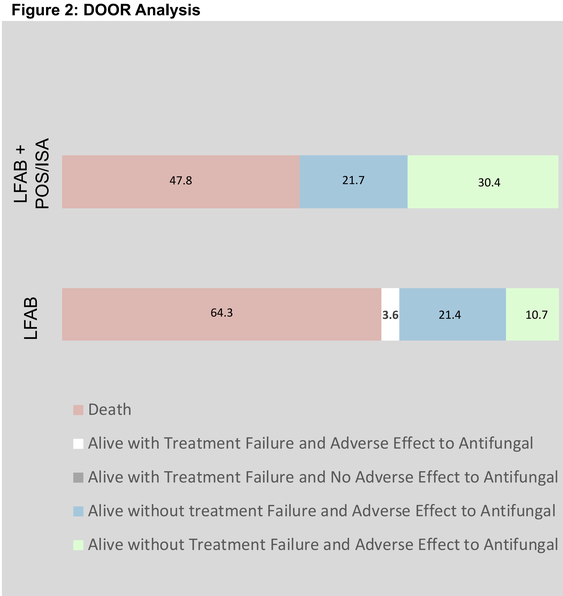


Figure 2: DOOR Analysis



Conclusions

- Mucormycosis continues to represent significant morbidity and mortality for HM and HCT populations.
- High-rates of 1-year all-cause mortality were noted, contributing from underlying malignancy and infections.
- Trend towards improved 30-day and 1-year all-cause mortality was noted for those receiving initial combination antifungal therapy with LFAB plus POS or ISA in addition to early surgical debridement.
- Continued research to address whether initial combination therapy with LFAB and POS or ISA improves outcomes for HM and/or HCT patients with mucormycosis are needed.

Disclosures

Authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation.

Poster No. LBA17; TCT 2020: February 22, 2020
Contact information: Matthew Miller, PharmD, BCIDP: matthew.miller@uchealth.org