Combination Antifungal Therapy for Invasive Aspergillosis Among Patients With Hematopoietic Cell Transplantation and Positive Galactomannan

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Background

Recently published post hoc analysis of mortality in invasive aspergillosis (IA), among patients with hematopoietic cell transplantation (HCT) and galactomannan (GM) antigen positivity in serum or bronchoalveolar lavage (BAL) fluid suggested an increase in all-cause mortality with monotherapy compared to combination therapy.

Objectives

To compare treatment with combination therapy to monotherapy among patients with HCT and GM antigen-based diagnosis of IA.

Methods

- Retrospective cohort study
- Inclusion criteria:
  - All adult HCT patients >18 years with positive GM
  - Diagnosed with a first episode of proven or probable IA 2008–2015
- Exclusion criteria:
  - Possible IA
  - Prior episode of IA with in one year
- Study period: 2008–2015
- Study setting: single center study at the Cleveland Clinic, Ohio
- Primary end point : all-cause mortality at 6 weeks

Definitions

- **Proven IA:** histologic evidence of Aspergillus on biopsy with tissue destruction/ invasion
- **Probable IA:** recovery of Aspergillus by culture or by 2 serum samples or a single bronchoalveolar lavage (BAL) sample GM
- **Complete response:** resolution of all signs and symptoms, and more than 90% radiographic improvement compared with baseline

Results

- We identified 8 patients with HCT and GM antigen-based diagnosis of IA
- Total number of HCT: 1368
- Overall incidence of GM antigen-based diagnosis of IA among HCT: 0.6%
- Median time to diagnosis of IA from HCT: 144 days (IQR 46–396)
- All patients received allogeneic BMT
- 7 (88%) received myeloablative conditioning
- 5 (63%) were receiving mold-active antifungal prophylaxis at the time of diagnosis
- 2 (25%) had pre-existing lung disease
- 4 (50%) were active smokers
- 4 (50%) reported voriconazole-induced altered mental status

Clinical Features

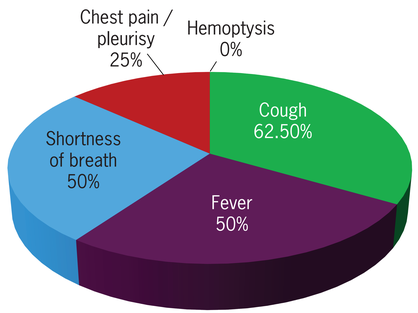

Table 1: Baseline Characteristics

No.	Age (yrs)	Gender	Indication for HCT	Time from BMT to IA (days)	Neutropenia (in days)
1	49	Female	AML	307	0
2	42	Female	T- cell ALL	84	3
3	48	Male	MDS	23	570
4	52	Male	AML	664	0
5	61	Male	AML	797	18
6	33	Female	AML	53	0
7	21	Male	APML	26	0
8	58	Male	Undiff. leukemia	204	0

NOTE. AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; MDS, myelodysplastic syndrome; APML, acute pro-myelocytic leukemia

Table 2: Laboratory Diagnosis and Outcome

No.	Type of IA	Serum GM	BAL GM	Serum β-D-glucan	Combination therapy	42-day all cause mortality
1	Proven	1.75	—	112	No	Died
2	Probable	0.69	—	—	No	CR (8 weeks)
3	Probable	0.51	—	—	V+M	CR (4 weeks)
4	Proven	—	3.038	—	No	CR (72 weeks)
5	Probable	6.46	—	—	V / P + M	Died
6	Probable	<0.5	1.478	—	V / AM-B + M	Died
7	Proven	0.13	0.56	—	No	CR (6 weeks)
8	Proven	>3.75	<0.05	9441	No	CR (25 weeks)

NOTE. V, voriconazole; M, micafungin; P, posaconazole; AM-B, amphotericin B; CR, complete response.

Table 3: Comparison between monotherapy and combination therapy

	Monotherapy (n=5)	Combination Therapy (n=3)	p value
Median age, years	49	48	
Sex, n (%)			
Men	3 (60)	2 (67)	
Women	2 (40)	1 (33)	
Median BMI (kg/m^2), (IQR)	23.7 (17.6-26.1)	21.6 (16.8-27.1)	
Smoking, n (%)	2 (40)	2 (67)	
Pre-existing lung disease, n (%)	1 (20)	1 (20)	
Underlying conditions, n (%)			
AML	3 (60)	2 (67)	
ALL	1 (20)	0	
MDS	0	1 (33)	
Undifferentiated leukemia	1 (20)	0	
Pre-HCT conditioning, n (%)			
Myeloablative	5 (100)	2 (67)	
Reduced intensity	0	1 (33)	
CMV viremia in the past one month, n (%)	3 (60)	0	
Associated GVHD, n (%)	2 (40)	0	
Diagnosis of IA, n (%)			
Proven	4 (80)	0	
Probable	1 (20)	3 (100)	
Median GM	1.75	3.485	
All-cause mortality	20%	67%	0.46

Conclusions

- In patients with HCT, GM antigen-based diagnosis of IA in the current era appears to be uncommon at our institution.
- Among these patients, 6-week mortality was not significantly different in those who received combination therapy compared to monotherapy.