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Invasive fusariosis in the era of mold active azoles and molecular targeted chemotherapy: Increasing incidence and lack of improved outcomes

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Introduction

- Invasive fusariosis (IF) is an uncommon opportunistic mold infection that primarily affects patients with leukemia and allogeneic hematopoietic cell transplant recipients.[1]
- Historically, patients with IF experienced poor outcomes when there was a lack of recovery from immunosuppression.[2]
- However, IF incidence density and outcomes are unknown in the era of new mold-active triazoles and leukemia regimens that incorporate molecularly targeted drugs.

Objectives

- To determine the incidence, risk factors for 42-day mortality, clinical features, and outcomes of microbiologically documented IF in patients with leukemia.

Materials and Methods

1

Retrospective cohort study

Jun 2009–Oct 2021 (12 years)

MD Anderson Cancer Center, TX, USA (743-beds, cancer hospital)

140 leukemia patients with IF*

*Probable/proven by revised EORTC/MSG criteria

Risk factors, clinical features, and outcome

Independent risk factors for 42-day mortality

Binary logistic regression analysis

2

The annual incidence density of IF

Nov 1998**–Oct 2021 (23 years)

**Combined with previous data 1998-2008 [3]

Poisson regression analysis

Results

1. Patients' characteristics

Characteristic	Total (N = 140)	Died* (N = 66)	P-value
Male sex, N (%)	100 (71)	48 (65)	0.852
Age (yrs), med [IQR]	59 [41-67]	59 [38-67]	0.830
Type of leukemia			0.769
AML	101 (72)	46 (70)	
ALL	19 (14)	9 (14)	
Others	20 (14)	11 (16)	
Leukemia, active	125 (89)	62 (94)	0.108
R/R leukemia**	118 (84)	60 (91)	0.061
Chemotherapy†	127 (91)	60 (91)	0.857
High-intensity	74 (53)	34 (52)	
Low-intensity	53 (38)	26 (39)	
Prior HSCT‡	41 (29)	21 (32)	0.855
Matched-related	12 (28)	4 (19)	
Matched-unrelated	19 (44)	10 (48)	
Haploidentical	7 (16)	5 (24)	
Cord blood	2 (5)	1 (5)	
Mismatched	1 (2)	1 (5)	
GVHD grade	19/43 (44)	11/21 (52)	1.000
1 and 2	13 (30)	7 (33)	
3 and 4	6 (14)	4 (19)	
Cumulative steroids within 4 weeks			0.094
None	36 (26)	14 (21)	
< 600 mg	92 (66)	43 (65)	
> 600 mg	12 (9)	9 (14)	
Liver impairment	15 (11)	10 (15)	0.170
Acute kidney injury	20 (14)	14 (21)	0.031
Chronic kidney disease	11 (8)	4 (6)	0.540
Diabetes mellitus	13 (9)	7 (11)	0.772

2: Clinical manifestations and diagnosis of IF

Characteristic	Total (N = 140)	Died (N = 66)	P-value
Neutropenia, N (%)	124 (89)	63 (96)	0.017
Lymphopenia	127 (91)	62 (94)	0.254
SOFA score* [IQR]	5 [4-7]	7 [5-9]	< 0.001
Site of infection			
Sinusitis	32 (23)	15 (23)	1.000
Pulmonary	100 (71)	52 (79)	0.091
Skin	71 (51)	32 (49)	0.735
Fungemia	48 (34)	28 (42)	0.074
Disseminated	88 (63)	47 (71)	0.057
CT findings			
Consolidation	23 (23)	12 (18)	0.345
Nodules	69 (69)	34 (52)	0.62
Masses	9 (9)	5 (8)	0.339
Ground-glass opacities	59 (59)	32 (49)	0.15
Halo sign	17 (17)	9 (14)	0.344
Reversed halo sign	2 (2)	2 (3)	0.158
Co-infections	77 (55)	44 (67)	0.011
Breakthrough infections	89 (64)	44 (67)	0.488
Voriconazole	32 (36)	14 (32)	
Posaconazole	45 (51)	23 (52)	
Isavuconazole	10 (11)	5 (11)	
Lipid AMB	2 (2)	2 (5)	0.473
(1-3)-β-D-glucan (N=65)	18/65 (28)	10/32 (31)	0.736
Aspergillus GM (N=97)	18/97 (19)	8/43 (19)	0.606

*SOFA: Sequential Organ Failure Assessment

3: Interventions and outcomes

Treatment and outcomes	Total (N = 140)
Antifungal therapy, N (%)	
Combination therapy	117 (84)
Monotherapy	21 (15)
No active treatment	2 (1)
Other treatment	
WBC transfusions	33 (24)
GM-CSF	7 (5)
G-CSF	51 (36)
Gamma interferon	4 (3)
Hyperbaric oxygen	6 (4)
Surgery	21 (15)
ID consult	136 (97)
ICU after diagnosis	39 (28)
Leukemia, active at day 42	122 (87)
Neutrophil recovery at day 42	53 (38)
Death at day 42	66 (47)
Death at day 84	86 (61)

4: Multivariable analysis of 42-day mortality

Predictors	aOR	95% CI	P-value
Pneumonia	3.28	1.11 to 9.70	0.032
Neutrophil recovery	0.04	0.01 to 0.14	< 0.001
SOFA	1.91	1.47 to 2.50	< 0.001

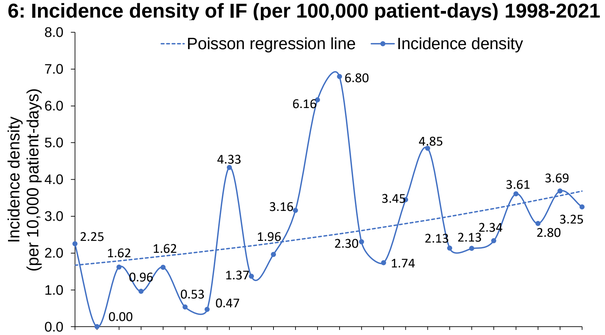
*Died at day 42 from IF diagnosis, **R/R: refractory/relapsed, †High-intensity chemotherapies: high-dose cytarabine-containing regimens and hyper-CVAD. Low-intensity: all others, ‡hematopoietic stem cell transplant

5: Trend analysis from 1998-2021

	1998-2003 (N = 13)	2004-2009 (N = 34)	2010-2015 (N = 64)	2016-2021 (N = 66)	P-value
R/R leukemia*	9 (69)	22 (65)	53 (83)	57 (86)	0.006
Breakthrough infections	2 (15)	15 (44)	29 (45)	55 (83)	0.056
Low intensity chemo	2 (15)	8 (24)	24 (38)	27 (41)	0.07

*R/R: refractory/relapsed

6: Incidence density of IF (per 100,000 patient-days) 1998-2021



Discussion

- To our knowledge, this is the largest study of IF to identify prognostic factors of mortality focusing on leukemia patients with IF
- Consistent with previous studies [2-4], we found that lack of neutrophil recovery, high SOFA, and pneumonia were independent risk factors of 42-day mortality
- Interventions had no impact on 42-day mortality including
  - Frequent use (85%) of combination antifungals
  - Adjunct WBC transfusions/surgery
  - Low intensity chemotherapy
- Only 19% of culture proven IF were GM positive
  - Much lower than in previous studies (GM 73%) [5]
- Co-infections were common (55%)
- An increasing incidence of IF in leukemia patients over the 23-year period, corelating with
  - Refractory/relapsed acute leukemia
  - Breakthrough infection to mold-active agents (44% in 2004-2009, vs 83% in 2016-2021)
- Our study, by its nature, could not investigate whether there were other exogenous factors (e.g. geoclimatic changes or increased community exposures to *Fusarium*) to account for this increase in IF incidence

Conclusion

- Over the past 23 years, IF incidence has been increasing.
- IF is predominantly seen in patients with R/R acute leukemia and typically seen as a breakthrough infection to mold-active triazoles.
- Even in contemporary patient cohorts, IF has high mortality in the setting of persistent myelosuppression despite aggressive therapy.

References

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