Breakthrough Invasive Fungal Disease (B-IFD) in Patients with Acute Myeloid Leukemia (AML)

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INTRODUCTION

Despite the use of antifungal prophylaxis, invasive fungal disease (IFD) remains a serious complication of AML, causing extensive morbidity and mortality. This study seeks to clarify our experience with IFD, with a focus on breakthrough IFD (B-IFD) in patients receiving chemotherapy for newly diagnosed AML.

METHODS

- Single-center retrospective cohort analysis of all patients undergoing induction chemotherapy for a new diagnosis of AML from June 2014 through January 2019
- Chart review was conducted to collect data on comorbidities, chemotherapy regimens, hematopoietic cell transplant (HCT) cumulative duration of neutropenia, antifungal exposure, development of IFD and B-IFD, and mortality
- Patients were followed for 1 year from date of first induction chemotherapy

Definitions

- Proven, Probable, and Possible IFD defined by EORTC-MSGERC 2019 revised criteria
- B-IFD: infection occurring ≥7 days after initiation of antifungal prophylaxis or <1 day after discontinuing antifungal prophylaxis

Outcomes

- Cumulative incidence of proven/probable IFD and B-IFD
- IFD mortality at 12 weeks
- 1-year survival (IFD vs no IFD)

Statistical Analysis

- Comparisons between those with B-IFD and those with non-B-IFD performed using Fisher's exact test and Wilcoxon rank sum test
- Univariable analysis accounting for competing risks (deaths) was conducted using cause-specific proportional hazard ratio (HR) to evaluate the impact of cumulative days of neutropenia (per 100 days), and other patient characteristics on time to IFD
- Kaplan-Meier survival analysis for impact of IFD on time to death.
- SAS version 9.4 statistical software used for all analyses

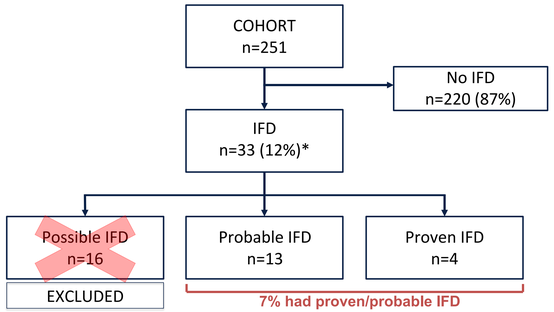
RESULTS

Patient Characteristics

Variable	n (%)
Total	251
Gender	
Male	138 (55)
Female	113 (45)
Age, yr (mean±std.dev.)	61.8±14
Selected comorbidity	
Prior myelodysplastic syndrome	76 (30)
Rounds of induction chemotherapy for AML	
1	157 (63)
2	78 (31)
3	15 (6)
4	1 (0.4)
Allo-HCT for treatment of AML	75 (30)
Matched related donor	*27 (36)*
Matched unrelated donor	*43 (57)*
Haploidentical HCT	*4 (5)*
Unmatched HCT	*1 (1)*
GVHD	*52 (69)*

RESULTS

Patient Selection



*Two patients each had 2 episodes

Risk Factors for Proven/Probable IFD

Risk factor/Demographics	No IFD (220)	IFD (17)	p value
Age, yr (mean±std.dev.)	**61±14.5**	**66±11.8**	**0.04**
Gender			
Male	119	11	0.3
Female	101	6	
Prior MDS	62	5	0.2
Rounds of induction			
1	143	10	0.8
≥2	77	7	
HCT for treatment of AML	68	4	0.09
GVHD	47	3	0.3
Cumulative neutropenic days (mean±std.dev.)	**28.1±24.9**	**33.8±20.1**	**0.0001**

Risk Factors for Non-B-IFD and B-IFD

Risk factor/Demographics	Non-B-IFD (n=9)	B-IFD (n=8)	p value
Age, years (mean±std.dev.)	70±9.7	61±12.5	0.2
Gender			
Male	7	4	0.3
Female	2	4	
Prior myelodysplastic syndrome	2	3	0.6
Rounds of induction			
1	5	5	1
≥2	4	3	
HCT for treatment of AML	1	3	0.3
GVHD	1	2	0.6
Cumulative neutropenic days (mean±std.dev.)	30.1±20.6	37.5±19.6	0.5

Proven/Probable IFD by Pathogen and Breakthrough Status

Pathogen	Non-B-IFD	B-IFD	Total IFD
Candida sp	2	0	2
Aspergillus sp	4	2	6
Fusarium sp	0	3	3
Mucorales	1	2	3
Pneumocystis jirovecii	2	1	3
Total	9	8	17

Antifungal Prophylaxis at Time of B-IFD Occurrence

Pathogen	B-IFD	Site of infection	Antifungal prophylaxis
Aspergillus sp	2	Empyema	Fluconazole 200 mg daily
		Pneumonia	Isavuconazole 372 mg daily
Fusarium sp	3	Pneumonia	Fluconazole 200 mg daily
		Pneumonia	Posaconazole 300 mg daily
		Fungemia	Fluconazole 200 mg daily
Mucorales	2	Pneumonia	Voriconazole 200 mg twice daily
		Disseminated	Voriconazole 200 mg twice daily
Pneumocystis jirovecii	1	Pneumonia	Inhaled pentamidine 300 mg monthly

Outcomes

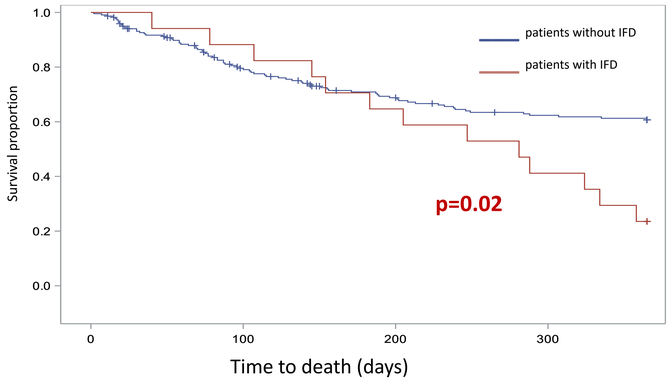
- Cumulative days of neutropenia was a predictor of IFD
  - HR = 1.038 (95% CI: 1.018-1.059)
  - Risk of IFD increases 3.8% per day of neutropenia (per 100 days)

- 1-year mortality: 92/237 (38.8%)
  - 79/220 (35.9%) with non-IFD; 13/17 (76.5%) with IFD
- 12-week mortality: 13/17 (76%) patients with IFD died
  - 7/9 with non-B-IFD; 6/8 with B-IFD

Outcomes at Week 12 for Non-B-IFD and B-IFD

Type of infection	12-week outcome	
	Alive	Dead
Non-B-IFD	**2**	**7**
Candida sp	0	2
Aspergillus sp	2	2
Mucorales	0	1
Pneumocystis jirovecii	0	2
B-IFD	**2**	**6**
Aspergillus sp	0	2
Mucorales	0	2
Fusarium sp	1	2
Pneumocystis jirovecii	1	0

Survival at 1 Year Among All Patients



CONCLUSIONS

- Despite use of antifungal prophylaxis, IFD continues to occur in patients with AML; 47% of patients with IFD had B-IFD
- Prolonged neutropenia and older age significantly increased the risk of IFD
- Patients with IFD had a significantly increased mortality rate within one year after induction therapy