Risk factors for invasive fungal infection in 5-azacitidine treated patients with acute myeloid leukemia and myelodysplastic syndrome

Amanda Tey[1], Briony Shaw[2], Luke Cardamone[3], Sam Shepherd[1], Eldho Paul[4]
Ben Rogers[3,5], Jake Shortt[2,5]

[1]Pharmacy Department, Monash Health, Victoria
[2]Monash Haematology, Monash Health, Victoria
[3]Monash Infectious Diseases, Monash Health, Victoria
[4]Monash Centre for Health Research and Implementation, Monash University, Victoria
[5]School of Clinical Sciences, Monash University, Victoria

The invasive fungal infection (IFI) rate in our study was 10.9% in patients who did not receive prophylaxis. This is sufficient to warrant mould-active antifungal prophylaxis in neutropenic patients receiving 5-azacitidine (AZA) for myelodysplasia (MDS) and acute myeloid leukaemia (AML)

Introduction

The rate of IFI in patients with MDS and AML receiving AZA is incompletely defined and published recommendations for mould-active fungal prophylaxis in such patients vary according to source. Australasian guidelines[1] recommend prophylaxis when the risk of IFI is over 10% and the European Conference on Infections in Leukaemia (ECIL) [2] recommend a threshold of 8%.

Aim

This study aimed to identify contemporary 'real-world' IFI and mortality rates, in relation to known risk factors and the use of antifungal prophylaxis.

Methods

This was a single center, retrospective cohort study across a tertiary-level hospital network.

Pharmacy dispensing records were filtered to identify all adult patients who had received over 7 doses of AZA since 2011. Electronic medical and pathology records were reviewed to define patient demographics, infection risk factors, treatment data and infection and mortality outcomes.

The pre-specified primary outcome was the rate of IFI. The secondary outcome was all-cause mortality.

The European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium definitions[3] were used to classify IFI as possible, probable or proven..

Results

One-hundred and forty-two patients were treated with AZA between May 2011 and July 2019, of which 117 with MDS or AML with low bone marrow blasts met inclusion criteria. A total of 1388 cycles of AZA were delivered with a median of 8 cycles (range 1-48) per patient. Seventy-one patients (61%) received mould-active antifungal prophylaxis for a median duration of 135 days (interquartile range 51-291 days). Seventy patients received posaconazole and one patient received voriconazole.

There was a male predominance (71%) in an elderly population (median age 74 years, Interquartile Range 69-80 years).

The majority were treated for MDS (57%) while the remainder were treated for AML (25%) or chronic myelomonocytic leukemia and MDS /myeloproliferative neoplasm overlap (18%).

The study population had a high rate of baseline neutropenia (19%), which increased to 31% at 3 months of treatment. Throughout treatment, 40% of patients experienced Grade 4 neutropenia for more than 5 weeks, and 15% had profound neutropenia (Absolute Neutrophil Count < 0.1 x 10^9/L) for more than 3 weeks. Additional clinical risks factors for IFI were present in the majority of patients with iron overload (46%) and thrombocytopenia at diagnosis (29%) being the most frequent.

The IFI rate was 7.7% (9 patients) across the entire cohort: 5.6% (4 patients) in those receiving prophylaxis *vs.* 10.9% (5 patients) in the subgroup who did not (p=0.30) (Table 1.). While IFI occurred in 4 of the 71 patients in the PX group, only one of these patients had demonstrated therapeutic posaconazole levels prior to the IFI diagnosis.

Outcomes (n, %)	All (n=117)	IFI (n=9)	No IFI (n=108)	p-value	PX (n= 71)	No-PX (n= 46)	p-value
IFI	9 (7.7)	-	-	-	4 (5.6)	5 (10.9)	0.3
Death	57 (48.7)	8 (88.9)	49 (45.4)	0.012	33 (46.5)	24 (52.1)	0.55
IRM*	23 (19.7)	5 (55.6)	18 (16.7)	0.014	12 (16.9)	11 (23.9)	0.35

*Table 1. Outcomes for IFI and mortality in relation to antifungal prophylaxis (PX) use. *Infection related mortality*

The median time from start of AZA treatment to IFI was 74 days (range 1-226 days). Cases of IFI tended to occur early in the AZA treatment course in the context of ongoing neutropenia, or later in association with disease progression or relapse. Of all IFI cases, six were defined as possible, two as probable and one was proven. A mould was suspected (n=6) or confirmed (n=2) as the causative organism in eight cases, and yeast in three cases.

On univariate analysis (Table 2.), the presence of neutropenia at three months of treatment was associated with increased IFI risk.

	Univariate analysis	
Variable	**HR (95% CI)**	**p-value**
No. of prior therapies	1.05 (0.18-6.18)	0.95
Use of prophylaxis	0.49 (0.13-1.86)	0.28
Total number of risk factors	0.92 (0.15-1.62)	0.76
Neutropenia at baseline	2.19 (0.53-8.99)	0.27
Neutropenia for > 5 weeks	2.91 (0.71-11.96)	0.13
Neutropenia at 3 months	8.29 (1.61-42.64)	0.01
Neutropenia at 6 months	1.39 (0.14-13.99)	0.78
AML	1.58 (0.38-6.51)	0.52
MDS/CMML	0.63 (0.15-2.6)	0.52
CR/CRi/CRu	0.82 (0.17-4.09)	0.81
PD	1.27 (0.31-5.26)	0.74

Table 2. Univariate Cox regression analysis of risk factors for IFI

On both multivariate (Table 3.) and Kaplan Meier (Figure 1.) analyses, IFI was independently associated with increased all-cause mortality risk.

	Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
IFI	3.12 (1.44-6.75)	0.003	8.37 (3.67-19.11)	<0.0001
Use of PX	0.77 (0.45-1.32)	0.335		
CR/CRi/CRu	0.31 (0.14-0.67)	0.002	0.36 (0.15-0.86)	0.021
PD	5.39 (3.03-9.59)	<0.0001	4.57 (2.51-8.33)	<0.0001

Table 3. Cox regression analysis of risk factors for Overall Survival

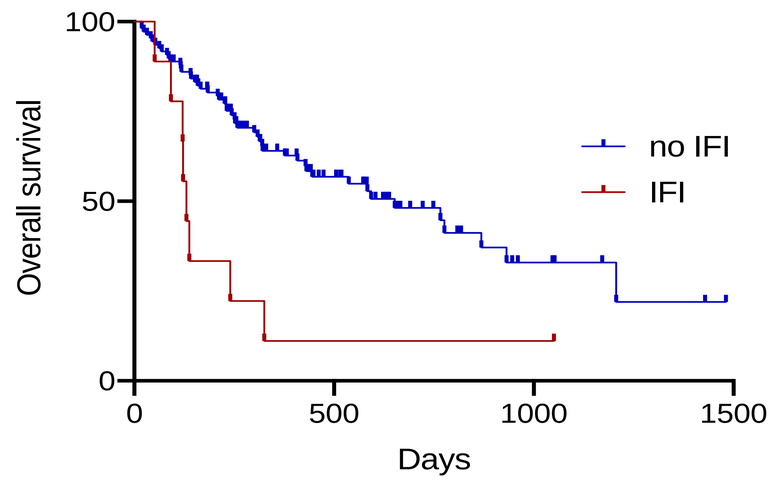

Figure 1. Overall survival for subjects with or without IFI complicating AZA treatment. Median OS no-IFI 652d vs IFI 130d; p = 0.0019.

Conclusions

Our study demonstrated an IFI rate of 10.9% in patients who did not receive fungal prophylaxis. This is greater than the 8% threshold for which fungal prophylaxis is recommended by ECIL and the 10% threshold in Australasian guidelines. This IFI risk is sufficient to warrant mould-active antifungal prophylaxis in neutropenic patients receiving AZA for MDS and AML with low bone marrow blasts. A heightened sense of clinical risk should be appreciated in early treatment cycles, prior to neutrophil recovery in AZA-responsive patients.

References

1. Fleming S, Yannakou CK, Haeusler GM, et al. Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2014. Internal medicine journal. 2014 Dec;44(12b):1283-97.

2. Maertens JA, Girmenia C, Bruggemann RJ, et al. European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. The Journal of antimicrobial chemotherapy. 2018 Dec 1;73(12):3221-3230.

3. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clinical Infectious Diseases. 2019.

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