

Context

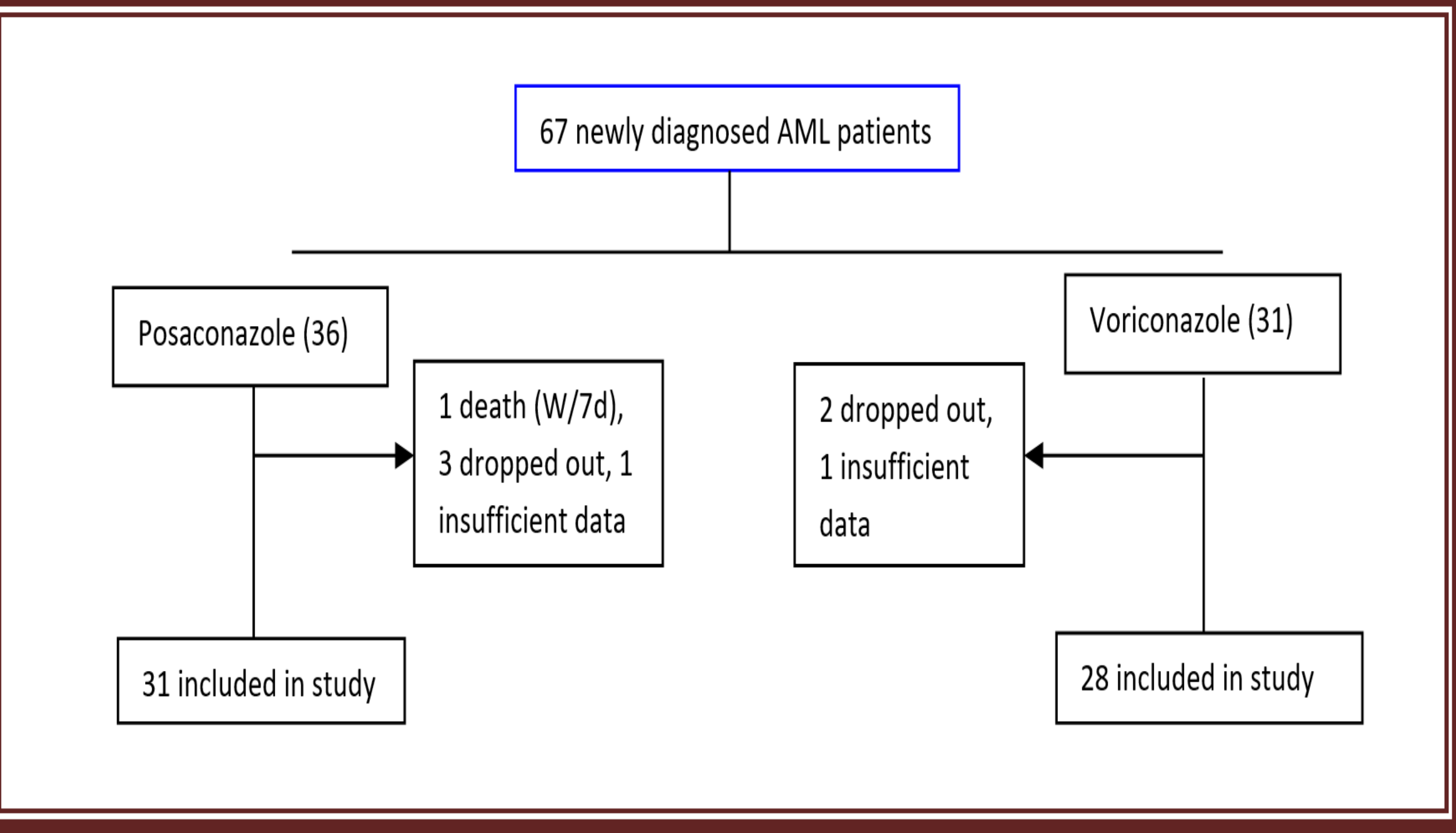
Invasive fungal infections are the main cause of morbidity and mortality in patients of Acute Myeloid Leukemia undergoing induction chemotherapy. Prophylaxis is a commonly used treatment strategy, because delay in diagnosis and antifungal treatment increases mortality. Posaconazole is currently the preferred drug for fungal prophylaxis, but it is costly and inappropriate in certain resource-limiting Indian setting. Being a cheaper option, which is of important relevance in resource poor setting like ours, and the fact that breakthrough infections were primarily by filamentous fungi, we changed our prophylactic antifungal to Voriconazole. Both posaconazole and voriconazole have been used as antifungal prophylaxis but there are very few studies comparing the efficacy of these two drugs.

Design and Methods

Institute of Hematology and Transfusion Medicine, Kolkata is a 42-bed tertiary care centre for the care of patients with hematologic cancers. Patients with AML who underwent remission induction chemotherapy in three years, 2014 to 2016, and received 7days or more of either posaconazole or voriconazole prophylaxis, defining a course, were included for the current study. Prophylaxis consists of Susp Posaconazole 200mg tds administered with fatty food, or Tab Voriconazole 400mg od administered on the day or one day prior to starting induction chemotherapy. Prophylaxis was continued till neutrophil recovery to more than 500 cells/ μ l and increasing, drug related toxicity/intolerance and occurrence of a suspected IFI.

Suspicion of invasive fungal infection lead to high resolution CT of Lung or contrast based CT of paranasal sinuses and head as indicated. Tissue sampling and serologic assays were not routinely performed. AML induction regimens were predominantly anthracycline and cytarabine based. Most of the patients received the standard 3+7 induction, 5 patients in 2014 and 2015 received BFM 2004 protocol and 3 patients in 2016 received 2+5 modification. Neutropenic fever was treated with piperacillin tazobactam with or without aminoglycoside initially and with teicoplanin later on.

Empiric antifungal therapy (EAF^T), either Liposomal AMB or Amphotericin-B deoxycholate, was typically initiated, or if not tolerated Caspofungin was used. Therapeutic drug monitoring (TDM) was not done here.



Objective

Collected information included host and treatment related characteristics, remission rate, infectious complications, use of empirical antifungals and their duration, 30-day mortality rate, and intolerance/toxicity to azoles. Breakthrough-IFD was defined as occurrence of IFD in patients during azole prophylaxis or seven days or less from drug cessation. All the CT scans were reported from a single center, by one radiologist for the presence of accepted IFD-related lesions, as distinct from non-specific pulmonary infiltrates

Primary objective: To evaluate the requirement of empirical antifungal and its duration.

Secondary outcomes: Toxicity/intolerance of prophylactic azoles and incidences of early mortality (30 days). Categorical variables were analyzed using the χ^2 test. For analyses, SPSS 20.0 software was used. For each analyses, p value of ≤ 0.05 was considered significant

Results

	Posaconazole (n=31)	Voriconazole (n=28)
Age in yrs; (median)	15-68; (40)	2-68; (36)
Sex: M/F	15/16	15/13
Significant comorbidities: n	4	4
Risk groups:	Standard: 6	Standard: 5
	Intermediate: 11	Intermediate: 13
	Poor: 9	Poor: 6
	Not Known: 5	Not Known: 4

Prophylactic Antifungal	Posaconazole	Voriconazole
Induction regimen: n	3+7: 26	3+7: 25
	BFM 2004: 5	2+5: 3
Proven or Probable IFI	3	1
EAF ^T	AmphoB deoxycholate: 2	AmphoB deoxycholate: 2
	Caspofungin: 3	Lipo. Amphotericin B: 2
	Lipo. AmphotericinB: 3	Caspo + AmB: 2
	>1 EAF: 2	
Median time of EAF ^T (day of induction)	17	20
Mean duration of EAF ^T (days)	13.1	11.2
Azole intolerance	5 (16.1%)	10 (35.7%)
Azole W/D due to intolerance	0	2
CR1 rate	21 (67%)	19 (67.8%)
Induction mortality	7 (22.5%)	5 (17.8%)

Discussion

Out of 67 AML patients (31 in voriconazole, and 36 in Posaconazole), data of 59 AML patients were analyzed. Adoption of voriconazole as antifungal prophylaxis has resulted in a trend towards decreased incidence of breakthrough IFIs (1 vs 3), and use of EAF^T (21.4% vs 32.2%; p=0.067). All proven IFIs were invasive aspergillosis. Induction mortality rate (7 vs 5; p= 0.27), and CR rate (67% in both) are not statistically different. Drug intolerance is higher with voriconazole (10/28 vs 5/31; p= 0.04), and 2 patients had premature discontinuation due to significant side effects

Summary

In our centre, evidences point towards decreased IFI and EAF^T in patients with voriconazole prophylaxis as compared to posaconazole, albeit with some increased drug related adverse effects. In a resource limiting centre, voriconazole may be a useful alternative to posaconazole as prophylactic antifungal drug in acute myeloid leukemia.

References

1. Pagano L, Caira M, Candoni A, et al. (2010) Invasive aspergillosis in patients with acute myeloid leukemia: a SEIFEM-2008 registry study. *Haematologica* **95**(4):644–50

2. Bow EJ, Loewen R, Cheang MS, Schacter B (1995) Invasive fungal disease in adults undergoing remission-induction therapy for acute myeloid leukemia: the pathogenetic role of the antileukemic regimen. *Clin Infect Dis* **21**(2):361–9.

3. Cornely OA, Maertens J, Winston DJ, et al.(2007) Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* **356**(4):348–59

4. DePauw B, Walsh TJ, Donnelly JP, et al.(2008) Revised definitions of invasive fungal disease from the EORTC/MSG Consensus Group. *Clin Infect Dis* **46**(12):1813–21

5. Vehreschild JJ, Ruping MJ, Farowski F, et al.(2010)Clinical effectiveness of posaconazole prophylaxis in patients with acute myelogenous leukaemia (AML): a 6 year experience of the Cologne AML cohort. *J Antimicrob Chemother* **65**(7):1466–77