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615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Concurrent Versus Sequential or No Triazole Anti-Fungal Therapy in Patients Undergoing 7+3 Plus Midostaurin Induction for FLT-3 Acute Myelogenous Leukemia

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Background
Midostaurin is a multikinase inhibitor approved for the treatment of adult patients with newly diagnosed FMS-like tyrosine kinase 3 (FLT3) mutated acute myeloid leukemia (AML) (Stone RM et al. NEJM 2017). Azole antifungal medications are commonly used in AML and are known to interact with anti-cancer drugs such as Midostaurin through the CYP3A pathway. This could result in an increase in midostaurin concentrations and toxicities, and lead to potential dose interruptions or modifications. However, the literature is scarce on outcomes in patients who are receiving an azole antifungal with intensive induction chemotherapy in combination with midostaurin (Sechaud R et al. Cancer Chemother Pharmacol 2022). In addition to the scarcity of literature, there are no midostaurin related dose modifications that are recommended with strong CYP3A inhibitors. The primary objective of this retrospective study was to compare induction efficacy and safety outcomes in patients receiving concurrent azole antifungal to patients receiving sequential or no azole antifungal therapy.
Methods:
From January 1, 2017, to January 30, 2023, we retrospectively reviewed all adult patients (18 or older) with newly diagnosed AML who received midostaurin in combination with cytarabine and an anthracycline (7+3). Concurrent azole therapy was defined as patients receiving an azole antifungal therapy with midostaurin for more than 70% of the midostaurin doses. Sequential azole therapy was defined as patients receiving azole antifungal therapy with midostaurin for less than 70% of the doses or no azole antifungal therapy with midostaurin therapy. Response outcome CR and CR without hematological recovery (CRi) were defined per standard International Working Group (IWG) AML response criteria. Minimal residual disease (MRD) assessment was done on post-induction bone marrow aspirate using multiparametric flow cytometric assessment. Adverse events were graded using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. We compared efficacy and safety outcomes in patients who received azole antifungals concurrently to those who did not receive an azole or received it sequentially to midostaurin for treatment of FLT3 AML. Mann-Whitney U test method was used to compare continuous variables between these two groups. Pearson Chi-square test or Fisher Exact test was used to compare categorical variables (count, rate or proportion) between these two groups. The choice of concurrent azole or sequential azole antifungal was determined by physician choice.
Results:
There were 40 patients treated with 7+3+midostaurin, 18 of whom received concurrent azole therapy, while 22 received sequential or no azole therapy. There were no significant differences in baseline characteristics (Table 1) except for more patients receiving isavuconazole (moderate CYP 3A4 inhibitor) in the concurrent group (50% vs 0%; p<0.01) and more micafungin in the sequential or no azole group (0% vs 72%; p<0.01). Overall CR/CRi rate with concurrent versus sequential or no azole was 72% (13/18) vs 77% (17/22), with no significant difference in median days to ANC recovery (27 vs 29; p=0.98), platelet recovery (28 vs 32 days; p=0.67), and non-hematologic grade 3 toxicities (22% and 45%; p=0.13), respectively. There were higher, but not significant, rates of midostaurin dose reductions (6% vs 0%; p=0.26) and holds (17% vs 14%; p=0.79) in the concurrent azole group.
Conclusion:

In conclusion, the addition of azole antifungal was found to be equally safe and effective in the treatment of newly diagnosed FTL3 AML. Dose modifications in midostaurin appeared not to be necessary with concurrent azole antifungal therapy. Further analysis based on a larger cohort is needed to confirm the outcomes and safety endpoints reported in the current study. Given the importance of azole anti-fungal therapy in the treatment of AML and specifically in induction therapy for AML (Cornely et al, NEJM 2007), dose modifications for this drug interaction should be studied in the future to help guide clinicians on how to appropriately dose these drugs.

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Table 1. Baseline characteristics

	Concurrent Azole (n=18)	Sequential or No Azole (n=22)	p-value
Gender, n (%)			
• Male	9 (50)	11 (50)	1
Median age, yrs (range)	54.5 (26-75)	55.5 (28-71)	0.71
AML Type, n (%)			
• De-Novo	17 (94)	20 (91)	0.67
• s-AML or t-AML	1 (6)	2 (9)	0.67
FLT3 Mutation, n (%)			
• ITD	13 (72)	16 (73)	0.97
• TKD	5 (28)	6 (27)	0.97
NPM1 Mutation, n (%)			
• YES	6 (33)	11 (50)	0.29
• NO	10 (56)	0 (0)	0.11
• NA	2 (11)	11 (50)	0.73
Median blasts on BM biopsy, % (range)	65% (40-95)	70% (0-95)	0.21
Median WBC on presentation, n (range)	22.2 (0.7–177)	38 (0.6–303)	0.31
Median peripheral blasts, % (range)	37 % (2-95)	47% (2-90)	0.88
Antifungal used during treatment, n (%)			
• Posaconazole	6 (33)	5 (23)	0.45
• Isavuconazole	9 (50)	0 (0)	<0.01
• Fluconazole	3 (17)	0 (0)	0.046
• Voriconazole	0 (0)	1 (5)	0.36
• Micafungin	0 (0)	16 (72)	<0.01

Table 2. Outcomes of 7+3 with midostaurin for newly diagnosed FLT3 AML with concurrent or sequential azole.

	Concurrent Azole (n=18)	Sequential or No Azole (n=22)	p-value
Response to treatment, n (%)			
• ORR	13 (72)	17 (77)	
o CR/CRi/MLFS with MRD negative	7 (39)	13 (59)	0.2
o CR/CRi/MLFS with MRD positive	6 (33)	4 (18)	0.27
o Partial response or Persistent Disease	5 (28)	4 (18)	0.47
o Not evaluable	0 (0)	1 (5)	0.36
Hematologic count recovery			
• Median days to ANC recovery (Range)	27 (26-84)	29 (26-63)	0.98
• Median days to platelet recovery (Range)	28 (23-84)	32 (23-63)	0.67
Consolidate with HCT, n (%)	13 (72)	15 (68)	0.78
6-month survival rate, rate (95% C.I.)	0.85 (0.72-1.00)	0.87(0.71-1.00)	0.95
Median follow-up, days (range)	244 (21–1637)	577 (42–1839)	0.24
Incidence of non-hematologic Grade 3 or 4 adverse event, n (%)	4 (22)	9 (40)	0.21
• Cardiac Disorders	2 (11)	4 (18)	
• Transaminitis	1 (5.5)	1 (4.5)	
• Rash	1 (5.5)	0 (0)	
• Hyperbilirubinemia	0 (0)	3 (14)	
• AKI	0 (0)	1 (4.5)	
Midostaurin dose reduced, n (%)	1 (6)	0 (0)	0.26
Midostaurin dose held, n(%)	3 (17)	3 (14)	0.79
All Grade Hepatotoxicity, n (%)			
• Transaminitis	4 (22)	4 (18)	0.75
• Hyperbilirubinemia	2 (11)	5 (23)	0.34
All Grade Cardiac Disorders, n(%)	3 (17)	5 (23)	0.63
All Grade Pulmonary Toxicities	0 (0)	0 (0)	NA
Incidence of new invasive fungal infection during induction, n (%)	5 (28)	4 (18)	0.47
30-day mortality, n (%)	1 (6)	0 (0)	0.26
90-day mortality, n (%)	1 (6)	2 (9)	0.67

Figure 1

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