(PB2778) DOES MODERATE CYP3A4 INHIBITION REQUIRE VENETOCLAX DOSE REDUCTION IN ACUTE MYELOID LEUKEMIA? REAL-WORLD EVIDENCE WITH ISAVUCONAZOLE.

Topic: 04. Acute myeloid leukemia - Clinical

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Background

Isavuconazole, a moderate CYP3A4 inhibitor, is used for antifungal prophylaxis in patients receiving venetoclax-based therapy for AML. Venetoclax dose reduction is frequently performed to prevent toxicity, although its impact on treatment efficacy remains uncertain.

Aims

To compare toxicity and clinical outcomes of venetoclax 200 mg vs. 400 mg in AML patients receiving concomitant isavuconazole.

Methods

Retrospective single-center cohort study including adults with AML/myeloid sarcoma treated with venetoclax and isavuconazole (2015–2026). Baseline characteristics, early toxicities, response (CR/MLFS), OS, and PFS were analyzed using Fisher's exact test, Mann–Whitney U test, and Kaplan–Meier estimates.

Results

Thirty-nine patients were included (median age 74 years, IQR 64–81); 22 received venetoclax 200 mg and 17 received 400 mg. Baseline characteristics are shown in Table 1. The 200 mg group was older (77 vs 64 years, p=0.006) with worse ECOG (p=0.003). Genetic risk and comorbidity index were comparable. Early toxicities are summarized in Table 2. TLS parameters were similar. Renal TLS occurred in 5/22 patients receiving 200 mg vs 0/17 with 400 mg (p=0.056), with no cardiac or neurologic events. The 200 mg group had longer severe anemia duration (Hb <8 g/dL; p=0.004), while neutropenia and thrombocytopenia duration did not differ. Infections were more frequent with 200 mg (17/22 vs 3/17, p<0.001). Given baseline imbalances, these differences likely reflect patient frailty rather than a dose effect. No invasive fungal infections were observed, and hepatotoxicity was similar. Responses were numerically higher with 400 mg (10/15 vs 7/21; p=0.090), with no significant differences in OS (1.12 vs 1.41 years; p=0.424) or PFS (p=0.336).

Table 1. **Baseline characteristics**

		Venetoclax dose				
		200 mg (n= 22)		400 mg (n=17)		p
		n	%	n	%	
Age (median, [IQR])		77 [74-83]		64 [54-78]		0.006
Women		9	40.9	4	23.5	0.318
Diagnosis	AML	6	27.3	14	82.4	0.001
	AML-MDr	16	72.2	2	11.8	
	Myeloid sarcoma	0	0	1	5.9	
Genetic risk (ELN_2022)	High	18	81.8	11	64.7	0.455
	Intermediate	3	13.6	5	29.4	
	Low	1	4.5	1	5.9	
ECOG	0	5	22.7	13	76.5	0.003
	1	16	72.7	3	17.6	
	2	0	0%	1	5.9	
	3	1	4.5%	0	0	
Charlson index (median [IQR])		6 [5-7]		5 [4-9]		0.585
Line of treatment	1	15	68.2%	8	47.1	0.095
	2	5	22.7%	9	52.9	
	3	2	9.1%	0	0	
Previous allo-SCT		1	4,5%	6	35.3	0.030
Bridge to allo-SCT (transplant delay)		0	0%	4	23.5	0.029

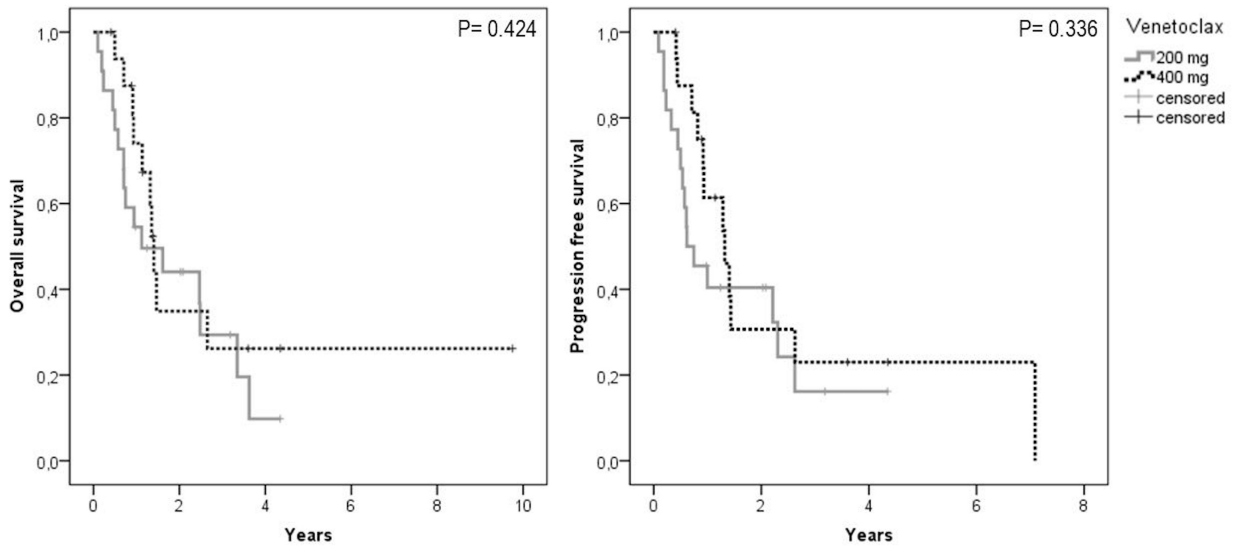
Table 2. **Toxicities**

		Venetoclax Dose				
		200 mg (n= 22)		400 mg (n=17)		p
		Median	IQR	Median	IQR	
TLS	Max uric acid	5.1	4.0 – 6.5	5.5	4.8 – 6.1	0.591
	Max potassium	4.7	4.4 – 5.1	4.5	4.3 – 4.7	0.232
	Max phosphate	4.6	3.3 – 4.9	3.8	3.5 – 4.2	0.172
	Min calcium	8.0	7.7 – 8.1	8.7	8.0 – 8.8	0.012
	Max Creatinine	1.08	0.79 – 1.86	1.01	0.82 – 1.26	0.457
Aplasia	Days Hb <8 g/dL	2	1 - 5	0	0 - 1	0.004
	Days neutrophils <500/µL	26	14 - 30	16	3 - 33	0.644
	Days platelets <20.000/µL	1	0 - 12	0	0 - 2	0.347
	RBC units transfused	3	1 - 5	1	0 - 3	0.092
	Platelet pools transfused	0.5	0 - 3	0	0 - 0	0.081
Hepatotoxicity	Max ALP level	116	80 – 153	87	70 - 131	0.311
	Max GGT level	43	29 - 163	49	35 - 199	0.798
	Max AST level	29	21 - 42	29	23 - 40	0.908
	Max ALT level	33	18.0 - 61	35	19 - 57	0.931
	Max bilirrubine level	0.80	0.61 – 0.9	0.70	0.60 – 1.10	0.581

Summary/Conclusion

In this real-world cohort, venetoclax 400 mg administered with isavuconazole did not increase early toxicity compared with 200 mg. Although infections were less frequent in the 400 mg group, baseline differences likely influenced this result. A numerical improvement in response to 400 mg suggests that routine dose reduction of venetoclax in the setting of moderate CYP3A4 inhibition may not be universally required. These findings are hypothesis-generating and warrant validation in larger prospective studies.

Figure 1. Kaplan-Meier analysis of overall survival and progression free survival.



Abbreviations: OS, overall survival; PFS, progression-free survival. Survival curves estimated by the Kaplan–Meier method and compared using the log-rank test. Tick marks represent censored patients.