PHENOTYPE-SPECIFIC SAFETY DIFFERENCES BETWEEN GILTERITINIB AND MIDOSTAURIN IN AML: A FAERS ANALYSIS HIGHLIGHTING DIFFERENTIATION SYNDROME SIGNAL

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INTRODUCTION

FLT3 inhibitors are integral to the management of FLT3-mutated acute myeloid leukemia (AML), yet AML-restricted comparative real-world safety data remain limited. While cardiotoxicity is a recognized concern, broader phenotype-specific toxicity patterns across agents are not well characterized.

AIM

To compare phenotype-specific adverse-event reporting between gilteritinib and midostaurin in AML, with prespecified evaluation of cardiotoxicity

METHOD

FDA Adverse Event Reporting System (FAERS) reports from 2018–2025 were analyzed. AML cases were identified using indication-level filtering, and primary suspect reports involving gilteritinib or midostaurin were included following case-level deduplication. Adverse events were grouped into predefined clinically relevant phenotypes, including cardiac toxicity (arrhythmia, heart failure, QT prolongation), differentiation syndrome, infection, cytopenia, hepatotoxicity, gastrointestinal, and neurologic toxicity. Hospitalization and death were assessed using outcome codes. Disproportionality was evaluated using reporting odds ratios (ROR) with 95% confidence intervals (CI). Sensitivity analyses were performed restricting to primary suspect reports and alternative phenotype definitions.

RESULTS

KEY SAFETY FINDINGS

DIFFERENTIATION SYNDROME SIGNAL

ROR 16.42

95% CI 2.22–121.79

GILTERITINIB vs MIDOSTAURIN

PRIMARY SAFETY SIGNAL

Overall cardiac toxicity was comparable between agents:
ROR 1.27
95% CI 0.69–2.36 | $p = 0.441$

QT prolongation showed a non-significant trend with gilteritinib:
ROR 2.04
95% CI 0.74–5.63 | $p = 0.159$

GI toxicity was lower with gilteritinib (statistically significant):
ROR 0.46
95% CI 0.27–0.80 | $p = 0.005$

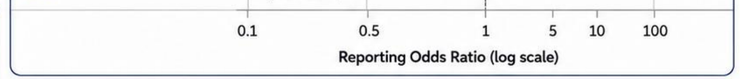
Hospitalization and death were similar between agents:

Hospitalization	Death
ROR 0.93	**ROR 1.07**
95% CI 0.70–1.22	95% CI 0.78–1.48
$p = 0.579$	$p = 0.665$

FAERS data are reporting signals, not incidence or causality. Findings are hypothesis-generating and require confirmation.

PHENOTYPE-BASED TOXICITY AND OUTCOME COMPARISON
Gilteritinib vs Midostaurin (FAERS, 2018–2025)

Phenotype	ROR (95% CI)	p-value
Differentiation syndrome	16.42 (2.22–121.79)	<0.001
QT prolongation	2.04 (0.74–5.63)	0.159
Heart failure / Cardiomyopathy	1.26 (0.38–4.22)	0.706
Overall cardiac toxicity	1.27 (0.69–2.36)	0.441
Infection	0.75 (0.55–1.03)	0.070
Cytopenia	1.17 (0.83–1.65)	0.359
Hepatotoxicity	1.22 (0.63–2.37)	0.549
GI toxicity	0.46 (0.27–0.80)	0.005
Neurologic toxicity	0.97 (0.45–2.10)	0.939
Hospitalization	0.93 (0.70–1.22)	0.579
Death	1.07 (0.78–1.48)	0.665



COHORT SUMMARY

Total reports N = 881 | Midostaurin n = 340 (38.6%) | Gilteritinib n = 541 (61.4%) | Primary suspect reports analyzed

Abbreviations: ROR, reporting odds ratio; CI, confidence interval; FAERS, FDA Adverse Event Reporting System.

CONCLUSIONS

Gilteritinib and midostaurin demonstrated broadly comparable cardiac reporting signals, while gilteritinib showed a marked differentiation-syndrome signal. These FAERS findings support phenotype-directed monitoring but should be interpreted as hypothesis-generating

ACKNOWLEDGEMENTS

Nahid Suleman, MD- University of Missouri, USA and University of Kansas–Wichita, School of Medicine

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