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Research Article

Real-World Outcomes of FLT3 Inhibitors in Acute Myeloid Leukemia, a Multicenter Study

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Abstract

Background: *Acute myeloid leukemia (AML) with FLT3 mutations carries a poor prognosis. FLT3 inhibitors, such as midostaurin, combined with standard chemotherapy, have shown improved outcomes for FLT3-mutated AML patients. However, real-world data on their efficacy and safety are limited. This study assesses midostaurin's real-world efficacy, the timing of molecular diagnosis, and the impact of antifungal prophylaxis management.*

Methods: *This retrospective multicenter study was conducted across four Spanish hospitals, including 15 patients with FLT3-mutated AML treated between 2019 and 2024. Data on demographics, clinical characteristics, diagnostic timelines, and treatments were collected and analyzed.*

Results: *The average time to obtain FLT3 mutation results was 13.3 days, exceeding the recommended 8-day window per PETHEMA, NCCN, and ELN guidelines, and delaying midostaurin initiation to a mean of 24.5 days post-diagnosis. Despite these delays, 80% of patients achieved complete remission (CR), with 62.5% attaining negative minimal residual disease (MRD) status post-induction. Antifungal prophylaxis was administered to 60% of patients, primarily with posaconazole (62.5%), without midostaurin dose adjustments. Alternative antifungals (micafungin or fluconazole) were used to avoid CYP3A interactions per PETHEMA recommendations. No significant differences in adverse event rates were observed between antifungal regimens.*

Conclusion: *The real-world use of midostaurin demonstrates efficacy comparable to clinical trials. However, delays in FLT3 mutation testing hinder adherence to treatment initiation guidelines, potentially impacting outcomes. Additionally, the lack of robust evidence regarding interactions between midostaurin and antifungal agents highlights the need for standardized antifungal prophylaxis strategies in FLT3-mutated AML. Addressing these challenges is essential to optimize outcomes in real-world settings.*

Key words: *Acute myeloid leukemia; FLT3 mutation; Midostaurin; Real-world evidence; Antifungal prophylaxis; Minimal residual disease.*

Background

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy characterized by the uncontrolled clonal proliferation of immature myeloid cells in the bone marrow, leading to suppressed normal hematopoiesis and peripheral tissue infiltration. AML is molecularly heterogeneous, exhibiting diverse clinical, morphological, and immunophenotypic features. It has a rapid onset, progressive course, and frequent resistance to chemotherapy [1,2]. With a median diagnosis age of 68, AML is the most common acute leukemia in adults, with a 5-year survival rate of approximately 30%, varying significantly by age group [2,3]. FLT3 gene mutations are common in AML and hold significant prognostic and therapeutic implications. FLT3 (FMS-like tyrosine kinase 3) encodes a receptor tyrosine kinase crucial for hematopoiesis. Activating mutations, such as internal tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations, are among the most frequent molecular abnormalities in AML [4,5]. FLT3 mutations occur in ~30% of AML cases at diagnosis, notably in 70% of patients with a normal karyotype and 35% of those with t(15;17), with a higher frequency in de novo AML (26%) than secondary AML (9%). These mutations correlate with hypercellularity, higher relapse rates, and are more common in women [6].

FLT3-ITD mutations are linked to poor AML prognosis, leading to leukocytosis, high blast cell percentages, greater treatment resistance, increased relapse risk, and reduced overall survival (OS) and progression-free survival (PFS) [6]. While FLT3-ITD AML patients can achieve complete remission with intensive chemotherapy, they have higher relapse rates and worse OS, particularly those with normal karyotype and intermediate cytogenetic risk [7,8]. In contrast, FLT3-TKD mutations have not demonstrated significant prognostic relevance despite multiple large-cohort studies [9–11].

Advances in genetic profiling have reshaped AML diagnostics, prognosis, and treatment strategies [2]. In 2022, an updated AML classification [12] and a new system [13] incorporated molecular findings into routine clinical practice, expanding recognized genetic abnormalities. Though FLT3 mutations are not considered AML-defining, they hold critical prognostic and therapeutic value.

FLT3 inhibitors targeting the ATP-binding site of the tyrosine kinase domain have improved survival in FLT3+ AML [14,15]. The FDA has approved two FLT3 inhibitors: midostaurin and gilteritinib. Since 2019, the Spanish Hematology Treatment Program (PETHEMA) has recommended midostaurin with daunorubicin and cytarabine as first-line therapy for FLT3+ AML, to be administered from days +8 to +21 (or up to day 24 if induction extends to day 11). Midostaurin should not be initiated beyond this window. During consolidation with high-dose cytarabine, midostaurin is continued uninterrupted. It is also recommended during maintenance for patients post-consolidation (high-dose Ara-C or autologous transplant) for 12 cycles of 28 days but not after allogeneic transplantation. There is no survival benefit in adding midostaurin in consolidation if omitted during induction [16]. Gilteritinib is indicated as monotherapy for relapsed/refractory FLT3+ AML [16].

FLT3+ AML and antifungal prophylaxis pose challenges due to a high risk of invasive fungal infections (IFI). During AML induction, posaconazole prophylaxis is standard due to severe prolonged neutropenia from intensive chemotherapy [16]. IFI incidence in FLT3-mutated AML patients is 10.5% (probable/proven) and 9.7% (possible) during induction, decreasing to 2.4% and 1.8% in consolidation [17]. Both midostaurin and gilteritinib are metabolized via CYP3A, which is inhibited by azoles like voriconazole, itraconazole, and posaconazole, increasing FLT3 inhibitor plasma levels [18]. PETHEMA advises avoiding CYP3A inducers and allows midostaurin dose adjustment to 50% (25 mg every 12 hours) if posaconazole or voriconazole prophylaxis is initiated during induction or consolidation [16].

This study evaluates real-world outcomes of FLT3 inhibitor therapy in FLT3+ AML, focusing on efficacy, safety, and the impact of antifungal prophylaxis.

Materials and Methods

Study Design

This retrospective multicenter study was conducted across four Spanish hospitals: University Hospital of Guadalajara, University Hospital of Getafe, University Hospital Príncipe de Asturias, and University Hospital Infanta Leonor. Ethical approval was obtained from the respective Ethics Committees. Patients aged ≥18 years diagnosed with FLT3+ AML between January 2019 and March 2024 were included.

Study Population

Fifteen patients were enrolled, with their demographic and clinical characteristics summarized in Table 1.

Table 1. Baseline Characteristics of the Study Population

Variable	N (%)
Age	53 años (rango 31 – 76).
Women	6 (40)
Type of AML	
De novo	13 (87)
Secondary	2 (13)
FLT3 mutation	
ITD	11 (73)
TKD	4 (27)

NPM1 mutated	
No	4 (33)
Yes	11 (60)
Karyotype	
Normal	12 (80)
Altered	1 (7)
Not performed	2 (13)
ELN 2022 Risk Classification	
Low	1 (7)
Intermediate	11 (73)
High	3 (20)

In the patient with an altered karyotype, t(8;21) and del(9)(q21q32) were identified, with t(8;21) classified as favorable risk despite coexisting with an FLT3 mutation. Among patients with high-risk AML, the key determinants were:

- RUNX1 and ASXL1 mutations in one patient.
- RUNX1 mutation in the second patient.
- RUNX1 and TP53 mutations in the third patient.

Data Collection

Data were extracted from electronic medical records, including demographic variables, disease characteristics, and treatment outcomes.

Statistical Analysis

Descriptive statistics were applied. Qualitative variables are presented as frequencies and percentages, while quantitative variables are summarized by mean, median, and range.

Results

Descriptive Analysis of FLT3 Inhibitor Treatment

All patients received midostaurin (50 mg every 12 hours) during induction, in combination with intensive 3+7 chemotherapy (Idarubicin 12 mg/m²/day IV on days 1–3 and Cytarabine 200 mg/m²/day IV as a continuous infusion on days 1–7). However, the two patients diagnosed with secondary AML received midostaurin in combination with VYXEOS.

The time from diagnosis to FLT3 mutation result and subsequent initiation of FLT3 inhibitor therapy is

summarized in Table 2.

Table 2. Timing of FLT3 Mutation Diagnosis and Targeted Treatment Initiation

Patient	Time to FLT3 Mutation Result from Date of Request (days)	Time to start of FLT3 Inhibitor treatment from FLT3 Mutation Result (days)	Time to start of FLT3 Inhibitor from Date of Diagnosis (days).
1	4	5	9
2	9	1	10
3	7	1	8
4	5	1	6
5	8	7	15
6	21	20	41
7	9	0	9
8	41	0	41
9	14	24	38
10	13	44	58
11	3	4	7
12	32	20	52
13	8	1	9
14	17	38	55
15	9	1	10

FLT3 mutation analysis was requested for all patients at the time of bone marrow biopsy upon diagnosis. The mean turnaround time for FLT3 mutation results was 13.3 days. Treatment initiation occurred a mean of 11.3 days after receiving FLT3 results, with FLT3 inhibitor therapy commencing a mean of 24.5 days post-diagnosis.

Adverse Effects

During midostaurin treatment, 9 of 15 patients (60%) experienced adverse effects (Table 3), with QT interval prolongation and diarrhea being the most frequent (33% each). Treatment was suspended in 4 patients (44%): two due to QT interval prolongation, one for liver function abnormalities, and one for enteritis. Among them, two (67%) resumed treatment at a reduced dose (25 mg every 12 hours). Patient 5 succumbed to intestinal obstruction. Additionally, Patient 1, who developed QT interval prolongation, required a dose reduction to 25 mg every 12 hours but did not necessitate treatment suspension.

Table 3. Adverse effects and treatment evolution with midostaurin

Patient	Adverse Effect	Required Treatment Suspension	Treatment Resumed (Dose)
1	QT interval prolongation	No	
2	Diarrhea	No	
3	Liver profile alteration and abdominal pain	Yes	No
4	Diarrhea and moderate thrombocytopenia	No	
5	Enteritis	Yes	Deceased
7	Diarrhea	No	
8	Severe thrombocytopenia	No	
13	QT interval prolongation	Yes	Yes (25 mg/12h)
14	QT interval prolongation	Yes	Yes (25 mg/12h)

Antifungal prophylaxis prescription

Among the 15 patients, 9 (60%) received antifungal prophylaxis during chemotherapy induction, while 6 (40%) did not. All 9 patients who received midostaurin during induction also received antifungal prophylaxis: 5 with posaconazole (62.5%), 3 with micafungin (37.5%), and 1 with fluconazole (12.5%). No significant differences were observed in adverse effects or treatment suspension rates between patients receiving posaconazole and those on antifungals with lower CYP3A4 inhibition.

Response to induction and consolidation

Following induction, 12 patients (80%) achieved complete remission (CR), including 7 of 9 (78%) treated with midostaurin. Of these 12, 10 (83%) attained minimal residual disease (MRD) negativity. Seven patients (58%) proceeded to allogeneic stem cell transplantation (allo-SCT), while 5 (42%) underwent consolidation with high-dose Ara-C and midostaurin. One patient (Patient 5) died before reevaluation, one (Patient 8) was refractory, and another (Patient 15) achieved partial response (PR) but progressed before allo-SCT.

Among the 8 patients who received midostaurin and were reevaluated, 5 (62.5%) achieved CR with MRD negativity, 2 (25%) achieved CR with MRD positivity, and 1 (12.5%) remained refractory. Detailed reevaluation and consolidation outcomes are summarized in Table 4.

Table 4. Reevaluation and Consolidation Therapy

Patient	Response after Induction	MRD after Induction	Consolidation Therapy
1	CR	Negative	Allo-SCT
2	CR	Negative	Ara-C + midostaurin
3	CR	Positive	Allo-SCT
4	CR	Negative	Ara-C + midostaurin
5	Death	Death	Death
6	CR	Negative	Allo-SCT
7	CR	Negative	Allo-SCT
8	Refractory	Positive	Second-line treatment
9	CR	Negative	Ara-C + midostaurin
10	CR	Negative	Ara-C + midostaurin
11	CR	Negative	Allo-SCT
12	CR	Negative	Allo-SCT
13	CR	Positive	Ara-C + midostaurin
14	CR	Negative	Allo-SCT
15	PR	Positive	Progression, Second-line treatment

EMR: Minimal Residual Disease; CR: Complete Remission; PR: Partial Remission; Allo-SCT: Allogeneic Stem Cell Transplantation.

Follow-up

The median follow-up duration for patients in this study was 6 months (range: 1–48 months). Among the 12 patients who responded to induction therapy and completed consolidation, 7 remain in complete remission, while 4 died during follow-up. One patient is currently undergoing allogeneic stem cell transplantation (allo-SCT). Detailed follow-up data for each patient are presented in Table 5.

Table 5. Post-Consolidation Therapy Follow-up

Patient	Consolidation Therapy	Current Status	Follow-up Time (months)
1	Allo-SCT	CR	11
2	Ara-C + midostaurin	CR	3
3	Allo-SCT	Death	6
4	Ara-C + midostaurin	Death	2
5	Death	Death	1
6	Allo-SCT	CR	37
7	Allo-SCT	CR	14
8	NA	Death	7
9	Ara-C + midostaurin	CR	49
10	Ara-C + midostaurin	CR	37
11	Allo-SCT	Allo-SCT	5
12	Allo-SCT	CR	6
13	Ara-C + midostaurin	Death	9
14	Allo-SCT	Death	11
15	NA	Death	5

Allo-SCT: Allogeneic hematopoietic stem cell transplantation, CR: Complete Remision,

Discussion

This study confirms that midostaurin's clinical benefits and tolerability, as observed in clinical trials, are reproducible in real-world settings, even in small patient cohorts. Notably, antifungal prophylaxis choice did not significantly affect tolerability or necessitate treatment discontinuation.

Study Limitations

As a retrospective descriptive study with a limited sample size, the generalizability of our findings is constrained. Additionally, the study lacks the ability to perform advanced statistical analyses or fully control for confounding variables. Descriptive retrospective studies primarily identify patterns within a population at a given time and cannot establish causal relationships.

An important finding concerns PETHEMA's protocol, which does not recommend initiating FLT3 inhibitors beyond the first 11 days of induction chemotherapy. The delay in obtaining FLT3 mutation results is therefore critical [16]. In our study, the mean time to receive results was 13.3 days, exceeding PETHEMA's target of three days from sample submission, set in 2019 [16]. Only one patient (Patient 11) met this target, while six received results after the first 11 days, precluding FLT3 inhibitor initiation during induction. Despite the lack of evidence supporting midostaurin initiation during consolidation when omitted in induction, all six patients received it during consolidation.

Adverse Effects

The most common adverse events were QT interval prolongation and diarrhea, classified as "very frequent" and "frequent" in midostaurin's prescribing information [18]. Among the three patients with QT prolongation, one (QTc 470–500 ms) required dose reduction without discontinuation, while two (QTc > 500 ms) had temporary treatment suspension until ECG normalization, followed by reintroduction at 25 mg/12h as recommended [18]. None of the three patients with diarrhea required dose modification or treatment cessation. One patient discontinued therapy due to abdominal pain and persistent transaminase elevation. The only grade V adverse event (death) occurred in Patient 5 due to enteritis, gastrointestinal bleeding, and intestinal obstruction.

Antifungal Prophylaxis Prescription

PETHEMA advises against potent CYP3A inducers and permits midostaurin dose reduction (25 mg every 12 hours) when antifungal prophylaxis with posaconazole or voriconazole is required during induction or consolidation [16]. A 2023 study reported that 46% of patients were switched from posaconazole to micafungin due to pharmacokinetic concerns [20]. Similarly, in our study, 44% of patients receiving midostaurin during induction were prescribed alternative antifungals, including micafungin (n=3) and fluconazole (n=1). No significant differences in adverse events were observed between patients receiving posaconazole and those on alternative antifungals [19].

Complete Response Rates

The complete response rate following induction chemotherapy was 77.8%, higher than the 59% reported in the RATIFY trial. Additionally, minimal residual disease (MRD) negativity post-induction was 62.5%, compared to 50% in RATIFY [20]. These findings suggest midostaurin's effectiveness in FLT3+ AML extends beyond clinical trials, demonstrating promising real-world outcomes.

Conclusion

All patients received midostaurin as a first-line FLT3 inhibitor alongside standard chemotherapy, adhering to the PETHEMA protocol. However, prolonged turnaround time for FLT3 mutation results delayed treatment initiation in several cases.

Adverse effects were consistent with those reported in midostaurin's prescribing information, with QT prolongation and diarrhea being most common. A significant proportion of patients did not receive posaconazole due to interactions with midostaurin, but no differences in adverse event incidence were noted between posaconazole and alternative antifungals.

The observed complete response and MRD-negative rates exceeded those reported in the RATIFY trial, reinforcing midostaurin's potential benefit in real-world settings. These results emphasize the need for optimizing diagnostic timelines, ensuring proper adverse effect management, and addressing inconsistencies in antifungal prophylaxis guidelines to mitigate invasive fungal infection risks in AML patients.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to privacy and ethical restrictions, individual patient data are not publicly available.

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Conflicts of Interest

The authors declare that they have no conflicts of interest related to the content of this manuscript. None of the authors have any financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board/Ethics Committee of each participating center (Hospital Universitario de Guadalajara, Hospital Universitario de Getafe, Hospital Universitario Príncipe de Asturias, and Hospital Universitario Infanta Leonor). The Ethics Committees granted a waiver of informed consent due to the retrospective nature of the study.

Authors' Contributions

M.A.M. conceived and designed the study, collected and analyzed data, and drafted the manuscript. I.A.M., G.L.H.T., and M.F. contributed to data collection and critical revision of the manuscript for important intellectual content. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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