Efficacy and Safety of FLT3 Inhibitors in Combination with Intensive Chemotherapy in Newly Diagnosed FLT3-Mutated Acute Myeloid Leukemia: A Systematic Review

Gowrishankar Palaniswamy [1], Swetha Chintala [2], Snigdha Mandava [3], Tarun Kumar Suvvari [4], Meghana Chennupati [5], Aadhiti Kandula [6], Srilasya Pamidi [7], Nischitha Vallurupalli [8]

1.Medical University of South Carolina, Lancaster, South Carolina, USA
2.Davao Medical School Foundation, Davao Del Sur, Philippines
3.NRI Medical College & General Hospital, Chinakakani, Andhra Pradesh, India
4.Rangaraya Medical College,Kakinada, Andhra Pradesh, India
5.Mamata Academy of Medical Sciences, Hyderabad,Telangana, India
6.Mamata Academy of Medical Sciences, Hyderabad, Telangana, India
7.ACSR Government Medical College, Nellore, Andhra Pradesh, India
8.All India Institute of Medical Sciences Bhubaneswar, Odisha, India

MUSC Health
Medical University of South Carolina

Introduction

FLT3 mutations occur in approximately 30% of patients with newly diagnosed acute myeloid leukemia (AML) and are known to have an adverse prognosis. The combination of FLT3 inhibitors and intensive chemotherapy has shown to demonstrate survival benefits, and our systematic review evaluates the safety and effectiveness of FLT3 inhibitors in newly diagnosed FLT3 mutated AML.

Aim

To systematically evaluate the efficacy and safety of adding FLT3 inhibitors to intensive chemotherapy, compared with standard chemotherapy alone, in newly diagnosed FLT3-mutated acute myeloid leukemia.

Objectives

Primary: Compare overall survival (OS) and event-free survival (EFS) between FLT3 inhibitor–chemotherapy combinations and control arms across randomized trials (2015–2025).

Secondary:

- Compare complete remission (CR/CRi) rates and disease-/relapse-free survival (DFS/RFS).
- Characterize grade ≥3 adverse events (hematologic toxicities, infections, QTc prolongation, and other cardiac events) and treatment-related mortality.
- Explore heterogeneity of effect by specific FLT3 inhibitor (e.g., midostaurin, sorafenib, gilteritinib/quizartinib where applicable), FLT3 mutation subtype (ITD vs TKD), age, and transplant/maintenance use when reported.
- Assess risk of bias of included RCTs and, where data permit, synthesize pooled effect sizes (HRs for time-to-event outcomes; risk ratios for dichotomous outcomes) using random-effects models, otherwise provide a narrative synthesis.

Methods

A systematic search of electronic databases including PubMed, Embase and Cochrane Library was conducted from 2015 to 2025, following PRISMA guidelines.

We included 5 randomized controlled trials (RCTs) that evaluated FLT3 inhibitors combined with intensive chemotherapy in newly diagnosed FLT3-mutated acute myeloid leukemia (AML).

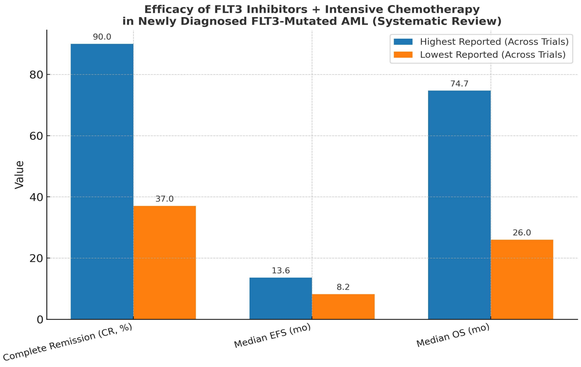
Data on complete remission (CR), event-free survival (EFS), disease free survival (DFS)/ risk free survival(RFS), overall survival (OS) and Adverse Events/ grade >3 was extracted.

Results

FLT3 inhibitors with intensive chemotherapy resulted in improved remission and survival when compared with control in newly diagnosed cases of FLT3- mutated acute myeloid leukemia (AML) across five reports of prospective studies (N=1569).

Rates of CR were between 37% and 90%, with the greatest contributions observed in gilteritinib containing regimens, followed by sorafenib (78%) and midostaurin (37% to 58.9%). Median EFS ranged from 8.2 to 13.6 months, and median OS was also favorable for midostaurin trials 26–74.7 months.

The adverse events (Grade >3) were primarily hematologic such as thrombocytopenia, febrile neutropenia along with infections and less frequently QTc prolongation and other cardiac associated adverse events.



Discussion

FLT3 inhibitors when added to intensive chemotherapy improved response and outcomes for newly diagnosis FLT3 mutated AML (in addition to some range of toxicities). This study provides a strong support for adding FLT3 inhibitors, especially midostaurin, in combination with standard chemotherapy in this subset of AML as they have shown improved therapeutic benefits over standard chemotherapy alone.

Further prospective investigations should aim to assess overall survival and optimal sequencing with other novel agents (eg, maintenance therapy or transplant).

References

1.Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377(5):454-464. doi:10.1056/NEJMoa1614359

2.Short NJ, Daver N, DiNardo CD, et al. Azacitidine, venetoclax, and gilteritinib in newly diagnosed and relapsed or refractory FLT3-mutated AML. J Clin Oncol. 2024;42(13):1499-1508. doi:10.1200/JCO.23.01911

3.Döhner H, Weber D, Krzykalla J, et al. Midostaurin plus intensive chemotherapy for younger and older patients with AML and FLT3 internal tandem duplications. Blood Adv. 2022;6(18):5345-5355. doi:10.1182/bloodadvances.2022007223

4.Schlenk RF, Weber D, Fiedler W, et al. Midostaurin added to chemotherapy and continued single-agent maintenance therapy in acute myeloid leukemia with FLT3-ITD. Blood. 2019;133(8):840-851. doi:10.1182/blood-2018-08-869453

5.Loo S, Roberts AW, Anstee NS, et al. Sorafenib plus intensive chemotherapy in newly diagnosed FLT3-ITD AML: a randomized, placebo-controlled study by the ALLG. Blood. 2023;142(23):1960-1971. doi:10.1182/blood.2023020301