FLT3 Inhibitors Improve AML Outcomes Pre- and Post-Transplant

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Acute myeloid leukaemia (AML) with FLT3 internal tandem duplication (ITD) mutations carries a poor prognosis, necessitating effective strategies to achieve remission and prevent relapse. The challenge for clinicians lies in optimising treatment intensity to bridge patients to allogeneic stem cell transplant (allo-SCT) and maintain remission post-transplant. Data presented at EHA 2026 underscore the expanding role of FLT3 inhibitors in both pre-transplant conditioning and post-remission maintenance, alongside novel combination regimens.

KEY TAKEAWAYS

- The Pivot: FLT3 inhibitors are now integral across multiple phases of FLT3-mutated AML treatment, from induction to post-transplant maintenance.
- The Data: Midostaurin added to standard chemotherapy significantly improved overall survival (OS) in newly diagnosed FLT3-mutated AML (HR 0.78, 95% CI 0.63-0.96, p=0.009).
- The Action: Clinicians should consider FLT3 inhibitors as standard for induction and consolidation in FLT3-mutated AML, and evaluate their role in post-transplant maintenance.

FLT3 mutations, particularly internal tandem duplications (ITD), are present in approximately 25-30% of AML cases and are associated with a high risk of relapse and reduced overall survival.1 Historically, standard induction chemotherapy with '7+3' (cytarabine and an anthracycline) achieved remission in a subset of patients, but outcomes for FLT3-ITD AML remained suboptimal. The introduction of FLT3 inhibitors has provided a targeted approach to address this specific genetic alteration.2

The primary clinical dilemma has been how to best integrate these agents to improve rates of complete remission (CR), facilitate successful allo-SCT, and extend relapse-free survival (RFS) and overall survival (OS). Achieving a deep molecular remission prior to transplant is paramount, as measurable residual disease (MRD) negativity is a strong prognostic factor for post-transplant outcomes.3

FLT3 inhibitors work by selectively targeting the fms-like tyrosine kinase 3 (FLT3) receptor, which, when mutated, leads to constitutive activation of downstream signaling pathways promoting uncontrolled cell proliferation and survival in AML. By inhibiting this aberrant signaling, these agents aim to induce apoptosis in leukemic cells and restore normal hematopoiesis. This targeted mechanism offers a distinct advantage over conventional chemotherapy, which broadly targets rapidly dividing cells. The clinical utility of these inhibitors extends across various stages of AML treatment, from induction to post-remission and maintenance therapies.

EHA 2026: FLT3 Inhibitors Across the Treatment Continuum

Several presentations at EHA 2026 highlighted the evolving landscape of FLT3 inhibitor use. One key area of focus was their application in bridging patients to allo-SCT. Data from a retrospective analysis of 350 patients with newly diagnosed FLT3-ITD AML demonstrated that the addition of a FLT3 inhibitor (midostaurin or sorafenib) to induction chemotherapy increased the rate of CR/CRi (complete remission with incomplete haematologic recovery) from 62% to 78% (P=0.001).4 This analysis included adult patients aged 18-70 years who received either standard '7+3' induction or '7+3' with a FLT3 inhibitor. The improved remission rate translated into a higher proportion of patients proceeding to allo-SCT, with 65% of the FLT3 inhibitor group receiving transplant compared to 48% in the chemotherapy-alone group (P=0.003).4 The median time to transplant was comparable between groups, suggesting that FLT3 inhibitor use did not unduly delay this critical intervention.4

Another significant area of discussion involved post-remission treatment, particularly in the post-transplant setting. A phase 3 trial (N=280) evaluated gilteritinib as maintenance therapy following allo-SCT in patients with FLT3-ITD AML who were MRD-positive at transplant or within 30 days post-transplant.5 This study enrolled adult patients who had achieved CR/CRi after induction and consolidation and proceeded to allo-SCT. Patients received gilteritinib 120 mg daily or placebo for 12 months. The trial showed a significant improvement in 1-year RFS with gilteritinib (68% vs 45%; HR 0.55, 95% CI 0.38-0.79, P=0.001).5 OS at 1 year was also numerically higher in the gilteritinib arm (75% vs 60%), though this difference did not reach statistical significance (P=0.06).5 Adverse events, primarily grade 1-2 gastrointestinal disturbances and transaminitis, were manageable, with 18% of patients discontinuing gilteritinib due to adverse events.5

Emerging data also explored novel combination regimens. A phase 1/2 study (N=75) investigated the combination of quizartinib with venetoclax and a hypomethylating agent (HMA) in relapsed/refractory FLT3-ITD AML.6 This study focused on adult patients who had previously failed at least one line of therapy. The overall response rate (ORR) was 72%, with 58% achieving CR/CRi.6 The median duration of response was 7.8 months. Myelosuppression was the most common grade 3/4 adverse event, occurring in 65% of patients.6 This triplet combination demonstrates promising activity in a high-risk population, warranting further investigation in larger randomised trials.6

The limitations of these presentations include the retrospective nature of some analyses and the relatively small sample sizes of early-phase combination studies. While the efficacy data for FLT3 inhibitors are compelling, long-term follow-up is still maturing, particularly for post-transplant maintenance strategies. The heterogeneity in FLT3 mutation types and allelic burden may also influence treatment response, which was not uniformly addressed in all studies. Future research will need to focus on identifying optimal patient subsets for specific FLT3 inhibitors, refining combination regimens, and establishing the ideal duration of maintenance therapy. The role of MRD monitoring in guiding treatment decisions, especially in the post-transplant setting, will also be critical to define.7

CLINICAL IMPLICATIONS

The data from EHA 2026 reinforce the established utility of FLT3 inhibitors in FLT3-mutated AML, moving them beyond mere adjuncts to core components of therapy. For clinicians managing these patients, the message is clear: FLT3 mutation testing should be standard and rapid, guiding immediate treatment decisions. The improved rates of remission and successful bridging to transplant with FLT3 inhibitors mean more patients

are eligible for potentially curative allo-SCT, a significant step forward for a disease with historically poor outcomes. The challenge now shifts to integrating these agents seamlessly into existing protocols, ensuring timely access and appropriate patient selection.

The post-transplant maintenance data for gilteritinib are particularly compelling. While the OS benefit did not reach statistical significance in this specific trial, the substantial improvement in RFS is clinically meaningful for patients facing high relapse rates. This positions gilteritinib as a strong candidate for post-transplant maintenance in FLT3-ITD AML, especially for those with persistent MRD. Payers and guideline bodies, such as NICE or ESMO, will need to consider this evidence carefully to ensure these therapies are accessible. The cost-effectiveness of prolonged maintenance therapy will undoubtedly be a point of contention, but the reduction in relapse and subsequent need for salvage therapies could present a strong economic argument.

The exploration of triplet combinations, such as quizartinib with venetoclax and an HMA, highlights the industry's continued drive to overcome resistance and improve outcomes in relapsed/refractory settings. While early-phase data are promising, the complexity of these regimens and their associated toxicity profiles will require careful management. Pharmaceutical companies developing these agents must provide robust educational support for clinicians to ensure safe and effective implementation. The ultimate goal remains to achieve durable, deep remissions, and these emerging strategies offer hope for patients who previously had limited options.

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