EDITORIAL

FLT3 inhibition after transplantation: real-world evidence confirms common practice

Martin Bornhäuser[1,2]

[1]Department of Medicine I, University Hospital TU Dresden, and [2]National Center for Tumor Diseases Dresden (NCT/UCC), Dresden, Germany

Correspondence: M. Bornhäuser
Martin.Bornhaeuser@ukdd.de

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For patients with FMS-like tyrosine kinase 3 (*FLT3*)-mutated acute myeloid leukemia (AML), relapse after allogeneic hematopoietic cell transplantation (allo-HCT) remains the central obstacle to cure. Despite advances in induction therapy and improved transplant strategies, post-transplant relapse continues to cause the majority of treatment failures. The introduction of FLT3 inhibitors (FLT3i) has fundamentally reshaped the treatment algorithms of *FLT3*-mutated AML, but has raised an increasingly relevant clinical question: can sustained FLT3 inhibition after transplantation prevent relapse - if so, for how long should therapy be continued?

In this issue of *Haematologica*, Massoud and colleagues provide important real-world evidence addressing the first part of this question.[1] Using data from the German Registry for Hematopoietic Stem Cell Transplantation and Cell Therapy, the authors analyzed outcomes in 523 patients with *FLT3*-internal tandem duplication (ITD) AML who underwent allo-HCT in first complete remission. In this large multicenter cohort, FLT3i maintenance therapy was associated with significantly improved overall survival and relapse-free survival compared with no maintenance therapy.[1] Notably, sorafenib - the most frequently used inhibitor in the study - was associated with particularly favorable long-term outcomes, with exploratory analyses suggesting 5-year survival approaching 85%.[1]

These findings extend prior prospective trial results into routine clinical practice and reinforce the growing role of FLT3i maintenance as a strategy for relapse prevention after transplantation. At the same time, they highlight several key questions that remain unresolved in this rapidly evolving field: which patients benefit most from maintenance therapy, which FLT3i should be preferred, and perhaps most importantly, how long should treatment be continued?

From proof of concept to real-world validation

The rationale for FLT3i maintenance after transplantation is biologically compelling. Even in patients who achieve complete remission and undergo allo-HCT, small populations of residual leukemic cells frequently persist and may eventually lead to relapse. Targeted inhibition of FLT3 signaling offers a mechanism to suppress these clones and potentially prolong remission. Prospective clinical trials have provided proof of concept. The randomized SORMAIN trial demonstrated significantly improved relapse-free survival with sorafenib maintenance compared with placebo in patients with *FLT3*-ITD AML undergoing allo-HCT.[2] Similarly, a randomized multicenter study from China confirmed that sorafenib maintenance significantly reduced relapse incidence and improved survival following transplantation.[3] Together, these studies established sorafenib as a prototype for post-transplant FLT3i maintenance.

However, prospective trials typically enroll highly selected patient populations under tightly controlled conditions. Real-world analyses therefore play an important role in determining whether these benefits translate into routine clinical practice (Figure 1). The registry study reported by Massoud and colleagues provides such validation. Across 13 transplant centers, FLT3i maintenance was associated with superior survival outcomes compared with no maintenance therapy.[1] While the retrospective nature of the analysis introduces potential sources of bias, the consistency between these findings and prior randomized trials strengthens the overall evidence supporting FLT3i maintenance as an effective post-transplant strategy.

Measurable residual disease and relapse risk

A critical element in post-transplant relapse prevention is the assessment of measurable residual disease (MRD). Besides fluorescence-activated cell sorting-based MRD monitoring, increasingly sensitive molecular monitoring techniques now allow detection of minimal leukemic

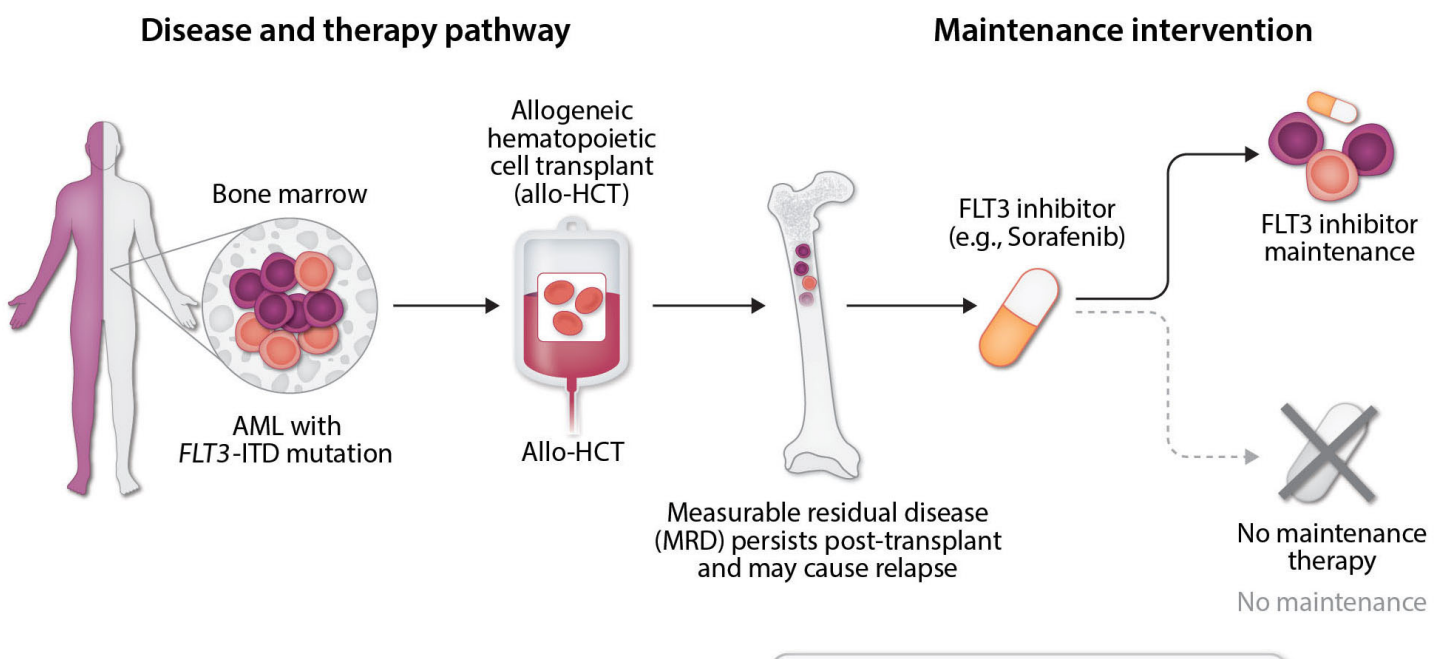


Figure 1. Real-world evidence supports FLT3 inhibitor maintenance after allogeneic hematopoietic cell transplant in *FLT3*-internal tandem duplication acute myeloid leukemia. allo-HCT: allogeneic hematopoietic cell transplant; AML: acute myeloid leukemia; ITD: internal tandem duplication; FLT3: FMS-like tyrosine kinase 3.

burden and provide valuable prognostic information regarding relapse risk.[4] In the analysis by Massoud *et al.*, FLT3i maintenance improved survival outcomes in both MRD-positive and MRD-negative patients at the time of transplantation.[1] While MRD-positive patients are generally considered particularly high risk for relapse, these findings suggest that maintenance therapy may also provide benefit even in patients who appear to be in deep remission.

This observation highlights an important limitation of current MRD assays. Even highly sensitive molecular techniques may fail to detect rare leukemic stem cells that persist below the threshold of detection. Consequently, MRD negativity does not necessarily equate with complete eradication of the disease. Maintenance therapy may therefore function not only as treatment for MRD but also as prophylaxis against the expansion of occult leukemic clones.

Synergy with graft-*versus*-leukemia effects

Beyond direct kinase inhibition, FLT3i may also interact with immune-mediated graft-*versus*-leukemia (GVL) effects after transplantation. Experimental studies have demonstrated that sorafenib can enhance antileukemic immune responses by promoting interleukin-15 production and stimulating donor-derived T-cell and natural killer cell activity.[4]

These findings suggest that the clinical benefit of FLT3i maintenance may not solely reflect suppression of leukemic proliferation but also amplification of immune-mediated antileukemic surveillance. In the post-transplant environment, where donor-derived immune responses are central to long-term disease control, such immunologic interactions may contribute significantly to sustained remission. Importantly, these effects should be considered when evaluating newer FLT3i in the maintenance setting.

Agents with similar kinase inhibition profiles may differ in their capacity to enhance - or potentially interfere with - immune-mediated antileukemic responses.

The unanswered question: duration of therapy?

While the evidence supporting FLT3i maintenance continues to grow, the optimal duration of therapy remains uncertain. Most clinical trials have employed fixed treatment periods of approximately 2 years, and many clinicians currently recommend maintenance therapy for 2 to 3 years following transplantation. However, clinical observations increasingly suggest that this duration may not be adequate for all patients. Relapse after discontinuation of prolonged FLT3i therapy has been described even after sustained molecular remission, raising the possibility that continued suppression of residual leukemic clones may be required in selected cases.[6] The optimal duration of therapy is likely influenced by several factors, including MRD status, the clonal architecture of the leukemia, prior FLT3i exposure, and the strength of the GVL effect. Future studies incorporating dynamic MRD monitoring may help define individualized strategies for both the initiation and duration of maintenance therapy.

An evolving therapeutic landscape

The treatment landscape of *FLT3*-mutated AML continues to evolve rapidly. In addition to sorafenib and midostaurin, newer inhibitors such as gilteritinib and quizartinib are increasingly incorporated into treatment algorithms. As these agents move earlier in the disease course, the post-transplant setting will increasingly involve patients previously exposed to targeted therapy. This shift raises important questions regarding resistance mechanisms, optimal sequencing of FLT3i, and the most effective maintenance strategies after transplantation.

Looking ahead

The registry analysis by Massoud and colleagues provides compelling real-world evidence supporting the use of FLT3i maintenance after allo-HCT in patients with *FLT3*-ITD AML.[1] Taken together with existing randomized trials, these findings bring clinical practice closer to recognizing post-transplant FLT3 inhibition as an important component of relapse prevention in this high-risk disease. Nevertheless, key questions remain regarding the optimal inhibitor, patient selection, and duration of therapy (Figure 1). Addressing these issues will require prospective studies integrating molecular monitoring, targeted therapy, and immune-based approaches. The next challenge for the field is not whether to maintain FLT3 inhibition after transplantation, but to decide when it is safe to stop.

Disclosures

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