COMMENTARY

Quizartinib is a good option for AML patients with FLT3-ITD mutations

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FMS-like tyrosine kinase-3 internal tandem duplication (*FLT3*-ITD) is one of the most frequent mutations in acute myeloid leukemia (AML). This mutation is present in up to 30% of de novo AML cases and is often associated with a high leukemic burden. Unfortunately, *FLT3*-ITD mutations are linked to poor prognosis, with patients with *FLT3*-ITD having an increased risk of relapse and shorter overall survival (OS) than individuals with wild-type *FLT3*.

Given the negative impact of *FLT3*-ITD on disease recurrence and survival, several *FLT3* inhibitors, such as sorafenib and midostaurin, have emerged in recent years and were initially used as salvage treatment for relapsed or refractory *FLT3*-ITD AML.[1,2] Subsequently, some studies attempted to add *FLT3* inhibitors to standard first-line chemotherapy for AML, but the results were controversial. In the UK AML15 and AML17 trials, no overall clinical benefit was observed after the addition of lestaurtinib to standard chemotherapy for newly diagnosed *FLT3*-mutated AML. However, in the randomized RATIFY trial,[2] which aimed to determine whether the addition of midostaurin to standard chemotherapy could further improve the survival of patients with *FLT3*-mutated AML, the OS and event-free survival (EFS) were both significantly longer in the midostaurin group than in the placebo group. However, the OS did not differ significantly according to trial regimen within each subgroup, particularly in those with *FLT3*-ITD mutations. In addition, 22.6% of the patients enrolled in this trial had *FLT3*-TKD mutations, and the effect of these mutations on prognosis is uncertain. Therefore, although midostaurin has gained approval from the US Food and Drug Administration (FDA) and European Medicines Agency for the treatment of newly diagnosed AML with either ITD or TKD mutations, it still does not meet the clinical requirement for the treatment of AML patients with *FLT3*-ITD mutations. The ongoing HOVON 156 AML trial aims to assess the clinical outcomes of gilteritinib versus midostaurin in combination with standard chemotherapy for *FLT3*-mutated AML.

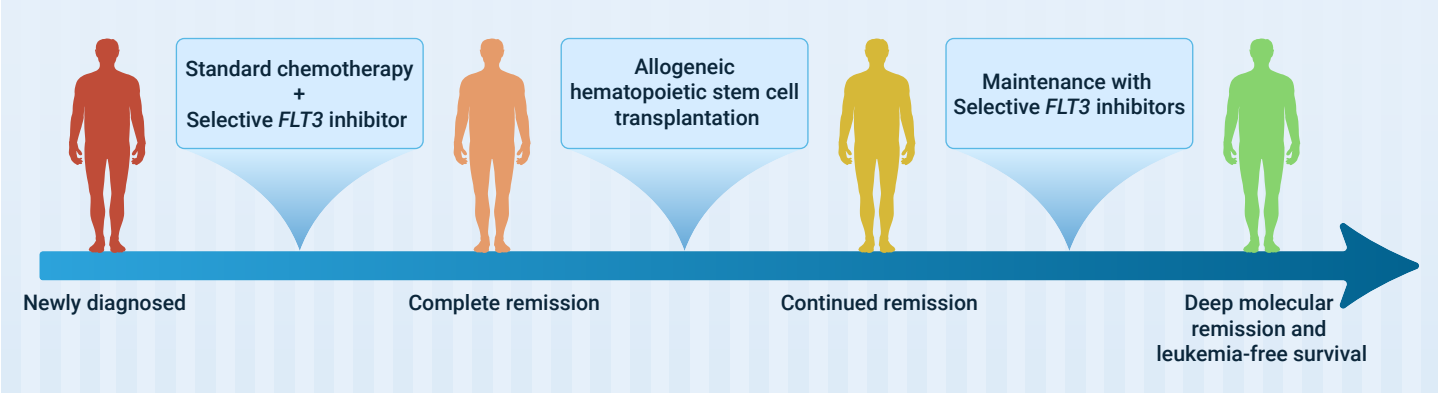

Figure 1. The proposed treatment paradigm for *FLT3*-ITD AML.

Quizartinib, a more specific *FLT3* inhibitor, has also been used as salvage therapy in relapsed or refractory *FLT3*-ITD AML. The QuANTUM-R trial showed that quizartinib monotherapy improved OS compared to salvage chemotherapy for patients aged ≥18 years. Therefore, quizartinib may be a new standard of care for patients with rapidly proliferating disease. Recently, Erba *et al.*[3] reported excellent results from a randomized, double-blind, placebo-controlled, phase 3 trial that aimed to compare quizartinib with placebo in combination with standard chemotherapy in newly diagnosed *FLT3*-ITD-mutated adult AML patients (i.e., the QuANTUM-First trial). Quizartinib was associated with a lower 3-year cumulative incidence of relapse (30% versus 42%) and a better median OS (31.9 months versus 15.1 months, P=0.032). Clinically meaningful improvements in relapse-free survival (RFS), increased duration of complete remission, reduced cumulative incidence of relapse, and reduction in measurable residual disease (MRD) were found in addition to the OS benefit. This study was the first to provide clinical evidence that AML patients with *FLT3*-ITD mutations can benefit from treatment with quizartinib, a potent and specific *FLT3* inhibitor, and the results may reveal a new, effective, and generally well-tolerated treatment option for these patients.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the most effective therapy for AML and can overcome the poor prognostic implications of *FLT3* mutation at diagnosis.[4] For de novo AML with *FLT3*-ITD mutations, allo-HSCT provides an additional 20%-30% survival benefit over chemotherapy with a 2-year RFS of 50-55% without any *FLT3* inhibitor maintenance.[1] In the QuANTUM-First trial, allo-HSCT was allowed as consolidation therapy in both the quizartinib and placebo groups. In the prespecified OS sensitivity analysis that censored patients who received allo-HSCT at any time, the quizartinib group only showed a trend toward better OS than the placebo group (20.8 months versus 12.9 months, HR=0.75, 95% CI 0.56–1.01, P = 0.055). Similar results were observed in the RATIFY trial. These results provide several important reminders. First, quizartinib may help AML patients with a *FLT3*-ITD mutation obtain more opportunities for allo-HSCT. Second, considering that the proportion of patients receiving allo-HSCT was comparable between the quizartinib and placebo groups, allo-HSCT may add an additional survival benefit to quizartinib treatment, with superior OS in the quizartinib group compared to the placebo group in the final OS analysis. Thus, specific *FLT3* inhibitors cannot replace the role of allo-HSCT as consolidation therapy in these patients, and allo-HSCT remains the

mainstay of total therapy for young and fit patients who are eligible for transplantation.

However, in a post hoc subgroup analysis by age, the OS was comparable between the quizartinib and placebo groups in patients older than 60 years. One of the underlying reasons is that elderly patients may not be suitable candidates for allo-HSCT, although the proportion of patients older than 60 years who received allo-HSCT was not provided in this study. In addition, intensive chemotherapy may also increase treatment-related mortality in elderly AML patients. Considering that venetoclax plus a selective *FLT3* inhibitor (e.g., gilteritinib) was associated with high modified composite complete response and *FLT3* molecular response rates in relapsed and/or refractory AML with *FLT3* mutations,[5] it is worth exploring whether quizartinib plus new drugs with lower toxicities used as first-line chemotherapy could further improve the OS of elderly AML patients with *FLT3* mutations.

As mentioned above, selected *FLT3* inhibitors and allo-HSCT are both critical treatments for AML with *FLT3*-ITD mutations, but the optimal combination scheme for these two treatments remains unknown. The efficacy of sorafenib maintenance therapy after allo-HSCT has been supported by multicenter randomized controlled trials[1]. With the addition of quizartinib, patients can achieve a higher complete remission rate after induction chemotherapy and a deeper molecular response before allo-HSCT. Furthermore, quizartinib maintenance therapy after allo-HSCT may further reduce the risk of post-transplant relapse. As the role of long-term quizartinib continuation therapy will be reported elsewhere, we anticipate results that may change the treatment paradigm for AML with *FLT3*-ITD mutations.

In summary, quizartinib is a novel, effective, and generally well-tolerated therapeutic option for adult AML patients with *FLT3*-ITD mutations. With potent *FLT3* inhibitors incorporated into induction and consolidation chemotherapy regimens, more patients are likely to achieve deep molecular remission and have the chance to bridge to allo-HSCT. Deeper molecular remission may also serve to reduce the relapse risk after allo-HSCT. Additionally, quizartinib maintenance therapy may be a reliable means of achieving durable molecular remission after allo-HSCT. Whether quizartinib can provide a superior antileukemia effect over other *FLT3* inhibitors (e.g., midostaurin) is worthy of further study (Figure 1).

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DECLARATION OF INTERESTS

The authors declare no competing interests.