It takes two to tango: allogeneic stem cell transplantation and *FLT3* tyrosine kinase inhibitor therapy

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The current issue of *Haematologica* publishes an important study by Schlenk *et al*.,[1] which follows an earlier report of the prospective randomized trial by the same collaborative study group evaluating quizartinib in patients with newly diagnosed acute myeloid leukemia (AML) with fms-like tyrosine kinase 3-internal tandem duplication (*FLT3*-ITD).[2] That study, the QuANTUM-First trial,[2] provided the data that led to the approval of quizartinib by several Health Agencies, including the American Food and Drug Administration and the European Medicines Agency. The drug's label implies the approval of quizartinib in combination with chemotherapy across intensive induction, consolidation, and maintenance in adult patients with *FLT3*-ITD-positive AML. In their *post-hoc* analysis in this issue of *Haematologica*, Schlenk *et al*.[1] address the impact of allogeneic hematopoietic stem cell transplantation (alloHSCT) and its interplay with quizartinib. The study convincingly shows that both alloHSCT and quizartinib are independently associated with longer overall survival, indicating that both allogeneic immunotherapy and a tyrosine kinase inhibitor (TKI) are indicated for adult patients with *FLT3*-ITD-positive AML.

It takes two to tango, but who are the partners that should take the dancing floor? In other words: which TKI is currently to be preferred and how should alloHSCT be performed in the context of *FLT3*-ITD? Currently, widespread market access has been obtained for midostaurin[3] and quizartinib for newly diagnosed adult AML patients with *FLT3*-ITD-positive AML. Midostaurin and quizartinib have not been compared head-to-head, leaving the medical community with a difficult choice. While quizartinib is a more potent inhibitor *in vitro*, it does not affect *FLT3*-tyrosine kinase domain mutations, indicating that midostaurin is still the drug of choice for patients with these mutations. However, since quizartinib is the more potent inhibitor, which was also reflected by a strong, approximately 45% reduction of death,[1,2] quizartinib may be preferred upfront for *FLT3*-ITD patients. These benefits should be weighed against the risks, which have become apparent by monitoring the short-term and long-term toxicities. In brief, no excess or unmanageable toxicities have been reported so far for either drug, although prolonged cytopenias and prevention of cardiac arrhythmia should be included in the management of patients treated with these TKI. Other TKI, still under investigation, include gilteritinib, which is currently being studied in comparison with midostaurin in the HOVON 156/AMLSG 28-18 trial (*hovon.nl/en/trials/ho156*), and crenolanib which is being compared with midostaurin (ClinicalTrials.gov identifier: NCT03258931).

These considerations, focusing on TKI use *before* alloHSCT, still leave us with the question of which TKI is to be preferred for maintenance *after* alloHSCT. In the Ratify trial, midostaurin was not continued after alloHSCT, but a small randomized phase II trial has suggested feasibility and a trend towards benefit for patients receiving midostaurin maintenance after alloHSCT.[4] The QuANTUM-First study was not powered to detect a statistically significant benefit of quizartinib *versus* placebo in the selected group of alloHSCT recipients. Therefore, undisputed evidence for both drugs in the post-transplant setting is lacking. However, two randomized trials[5,6] have been performed with sorafenib after alloHSCT and both showed a significant benefit of sorafenib on relapse-free survival and overall survival. Furthermore, translational studies by Zeiser *et al*. have shown that sorafenib may potentiate the allogeneic graft-*versus*-leukemia (GvL) effect.[7] Apart from sorafenib, gilteritinib has also been evaluated in the post-transplant setting.[8] Neither overall survival nor relapse-free survival appeared significantly improved, but a benefit was suggested in residual disease-positive patients.[8] Collectively, based on these randomized studies in different treatment phases, we would suggest that *prior* to alloHSCT quizartinib may be preferred, while sorafenib may be the drug of choice for maintenance *after* alloHSCT (Figure 1).

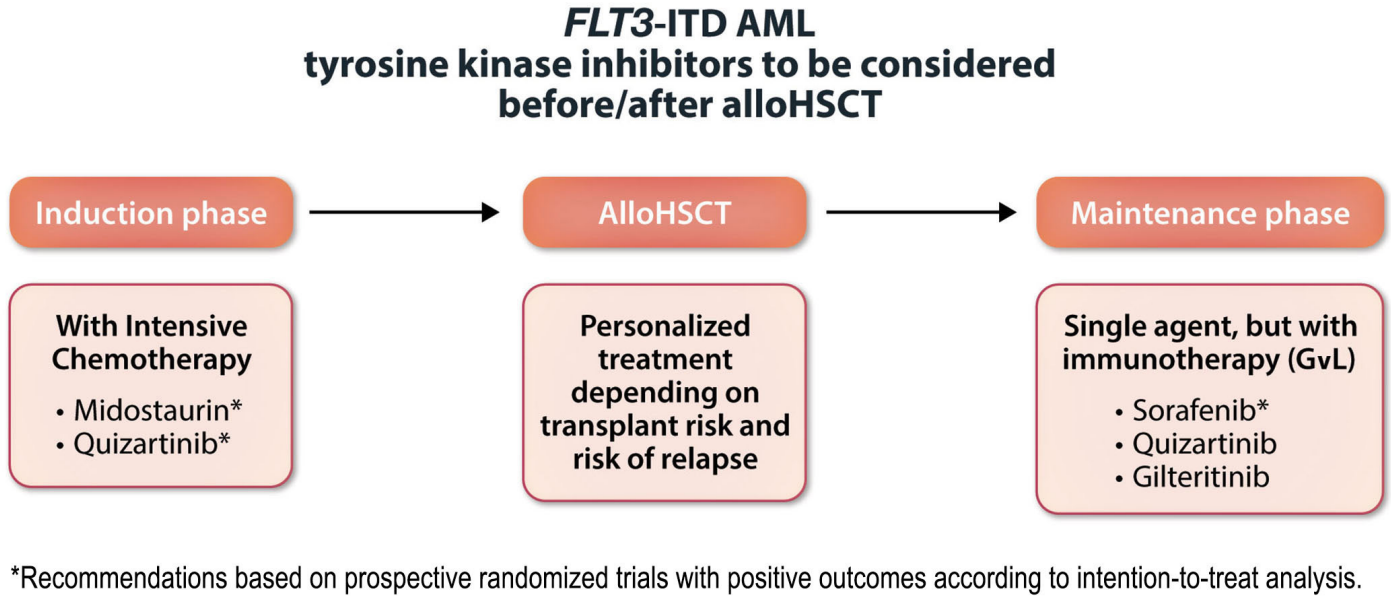

Figure 1. Tyrosine kinase inhibitors to be considered in the context of allogeneic hematopoietic stem cell transplantation in patients with *FLT3*-mutated acute myeloid leukemia in first remission. ITD: internal tandem duplication; AML: acute myeloid leukemia; alloHSCT: allogeneic stem cell transplantation; GvL: graft-*versus*-leukemia.

The preferred TKI then dances and circles around her immunotherapeutic dancing partner. The latter is, however, a strange guy, changing looks from one transplant center to another. In other words: how should the transplant be performed? Eligibility criteria, conditioning regimen, type of donor, prevention of graft-*versus*-host disease, and maintenance after alloHSCT are among the parameters that each deserve as much attention as type of TKI and its scheme of administration, especially because alloHSCT is still associated with considerable morbidity and mortality. Obviously, it goes beyond the scope of this editorial to touch upon each of these parameters in detail, but some general remarks can be made. First, as we previously outlined,[9] it is imperative to carefully weigh the risk of treatment-related mortality *versus* the risk of relapse before transplantation in order to project the putative gain in relapse-free survival after the transplant. Such considerations are underpinned by our observation that the relative reduction of relapse (the GvL-effect) by alloHSCT is fairly similar in each cytogenetic subcategory of patients and also occurs irrespective of the presence of minimal residual disease.[10] A similar observation was made in *FLT3*-ITD-positive AML patients, who had similar relative reductions of relapse, but with absolute rates of relapse depending on *NPM1* co-occurrence (Table 1).[11] This illustrates the strong GvL effect of alloHSCT, but also highlights the high risk of relapse after such transplants, urging the need for continued therapy after alloHSCT. Apart from sorafenib maintenance as outlined above, continued immunotherapy by either donor lymphocyte infusions or early tapering of immunosuppressive therapy for prevention of graft-*versus*-host disease may also be part of such an approach. Recently Grob *et al*. showed that monitoring for *FLT3*-ITD residual disease by next-generation sequencing enabled the identification of alloHSCT recipients with a high risk of relapse.[12] Given the imminent and rapid hematologic relapse in residual disease-positive patients shortly after alloHSCT, immunotherapy and TKI should again be the two dancing partners in this challenging and ongoing tango.

Table 1. Relapse risk by post-remission treatment in patients with acute myeloid leukemia in first complete remission.

ELN risk group	Relapse risk Non-alloHSCT %	Relapse risk AlloHSCT %	Absolute relapse risk reduction by allo-HSCT, %
Favorable	35-40	15-20	~20
FLT3-ITD *NPM1*^{mut}	50-55	25-30	~25
Intermediate	50-55	20-25	~30
FLT3-ITD *NPM1*^{mut}	60-70	25-30	~35
Adverse	70-80	30-40	~40

Unpublished HOVON data, presented according to a concept reported earlier.[9] ELN: European LeukemiaNet; alloHSCT: allogeneic hematopoietic stem cell transplantation; *FLT3*: fms-like tyrosine kinase 3; ITD: internal tandem duplication; *NPM1*: nucleophosmin 1.

Disclosures

JV has received speaker's fees from Novartis, AbbVie and Daiichi Sankyo and has participated in advisory boards for Cordex and Rigel. JJC has no conflicts of interest to disclose.

Contributions

JJC and JV wrote the manuscript. JV analyzed the data.

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