All patients with AML and *FLT3*-ITD should be transplanted in first remission. Also in the era of tyrosine kinase inhibitors? – the PRO

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Should all patients with newly diagnosed acute myeloid leukemia (AML) and FMS-like tyrosine kinase 3-internal tandem duplication (*FLT3*-ITD) in first complete remission (CR1) with an available HLA-matched donor be advised to proceed to allogeneic hematopoietic cell transplantation (alloHCT) in first remission? This important clinical question was answered before the advent of FLT3 inhibitors with a clear "depends on" summarized in the European LeukemiaNet (ELN) recommendations in 2010[1] and 2017.[2] In particular, the ratio of mutant to wild-type *FLT3*-ITD seemed to impact the benefit-risk ratio of alloHCT performed in CR1, in that patients with an AML exhibiting a high *FLT3*-ITD ratio gained significant benefits with regard to relapse-free survival and overall survival.[3-5] In the meanwhile, FLT3 inhibitors have been and are being evaluated in large randomized clinical trials[6-9] with authority approval intentions. However, beyond the efficacy of the respective FLT3 inhibitors, alloHCT performed during CR1 was evaluated in addition as an important confounding factor.[6,7,10] So far, the RATIFY[6] and the QuANTUM-First[7] studies have been published and include dedicated analyses evaluating the respective FLT3 inhibitors and the interaction with alloHCT, while results from the HOVON 156/AMLSG 28-18 trial[8] and a randomized trial evaluating crenolanib *versus* midostaurin (ClinicalTrials.gov identifier: NCT03258931) are expected for 2026. Furthermore, non-randomized studies add important insights into the interaction between FLT3-inhibitor treatment and alloHCT.[11-13]

However, before diving deeper into the exciting analyses of the aforementioned randomized clinical studies, we first have to discuss biometric issues with regard to the impact of alloHCT on clinical survival endpoints. Whether patients proceed or not to an alloHCT after achieving CR1 upon induction therapy depends on several factors including patient-related ones (such as age, presence of comorbidities, willingness of patients to undergo the procedure, etc.), administrative factors (such as cost coverage of the procedure by insurance companies, access to stem cell donor programs, etc.), and disease-related factors (such as *FLT3*-ITD allelic ratio, presence or absence of concurrent genetic markers including *NPM1* mutations, complex karyotype, type of AML [*de novo*, therapy-related], etc.). Thus, alloHCT as a treatment procedure is not equally available for all patients. In addition, performance of the procedure is dependent on a number of covariables (known and unknown), which may introduce bias to the performance of the procedure and its impact on survival endpoints. Additionally, the timepoint when the procedure is performed varies quite widely, ranging from right after first induction therapy to after one, two or even three cycles of standard consolidation chemotherapy. This has to be addressed by the statistical methodology used, by analyzing alloHCT as a time-dependent covariable. In univariable analysis the Mantel-Byar test[14] and for graphical illustration Simon-Makuch plots[15] may be used instead of a log-rank test and Kaplan-Meier plots, whereas in multivariable models the time dependency of alloHCT is addressed by extended Cox regression models[16] such as the Andersen-Gill model.[17]

The first evaluation within a randomized setting of the interaction between FLT3 inhibitors and alloHCT was available in the RATIFY study.[6] In this trial AML patients, 18-59 years of age with newly diagnosed *FLT3*-ITD or *FLT3*-tyrosine kinase domain (TKD) mutation, were randomized between standard 7+3 induction therapy with midostaurin or placebo starting at day 8 of induction therapy. Midostaurin or placebo was also given after each consolidation chemotherapy and in patients not proceeding to alloHCT as a single-agent maintenance therapy up to 12 months.[6] The results of the RATIFY study led to the approval of midostaurin in the USA and Europe in 2017. AlloHCT was performed during CR1 in 28.1% of the patients in the midostaurin group and in 22.7% in the placebo group. In *post-hoc* analyses of the RATIFY

trial, overall survival was improved particularly in patients receiving an alloHCT in CR1 in the midostaurin arm[6,18] with an estimated overall survival of roughly 70% after 5 years as compared to far below 60% in patients after alloHCT in CR1 in the placebo arm (Figure 1 and Figure S3A in Stone RM *et al.*[6]). Unfortunately, uni- and multivariable analyses including alloHCT as a time-dependent covariable were not performed. Furthermore, the proportion of patients exhibiting a *FLT3*-TKD in the alloHCT group was not stated. Although this proportion was probably very small because at that time alloHCT was not recommended for such patients, we do not know this for sure.

The next evaluation within a randomized setting of the interaction between FLT3 inhibitors and alloHCT was available in the QuANTUM-First study.[7] In this trial, patients 18-75 years of age with newly diagnosed *FLT3*-ITD AML were randomized between standard 7+3 induction therapy with quizartinib or placebo starting at day 8 of induction therapy. Quizartinib or placebo was also given after each consolidation chemotherapy and in patients proceeding or not to an alloHCT as single-agent maintenance therapy for up to 36 months. The results of the QuANTUM-First study led to the approval of quizartinib in the USA and Europe in 2023. AlloHCT was performed during CR1 in 41% of the patients in the quizartinib arm and in 32% in the placebo arm. In *post-hoc* analyses of the QuANTUM-First trial using appropriate biometric methods, overall survival was improved particularly in patients receiving an alloHCT in CR1 in the quizartinib arm of the study.[10] In both arms patients who achieved complete remission (CR) by the end of induction had a statistically significant overall survival benefit with alloHCT in CR1. Furthermore, an extended Cox regression analysis in patients who achieved CR by the end of induction revealed quizartinib treatment (hazard ratio [HR]=0.553, 95% confidence interval [95% CI]: 0.383-0.798; *P*=0.0015) and alloHCT in CR1 (HR=0.527, 95% CI: 0.349-0.796, *P*=0.0023) as key factors predicting better overall survival. Although these biometric methods cannot completely exclude bias towards alloHCT, they very convincingly show that quizartinib both added to standard chemotherapy and as single-agent maintenance therapy as well as alloHCT performed in CR1 improve outcomes in AML patients exhibiting *FLT3*-ITD, paraphrased by Jan J Cornelissen and Jurjen Versluis as “It takes two to tango”.[19] Based on the QuANTUM-First analysis, quizartinib-treated patients who achieved a CR by the end of induction and

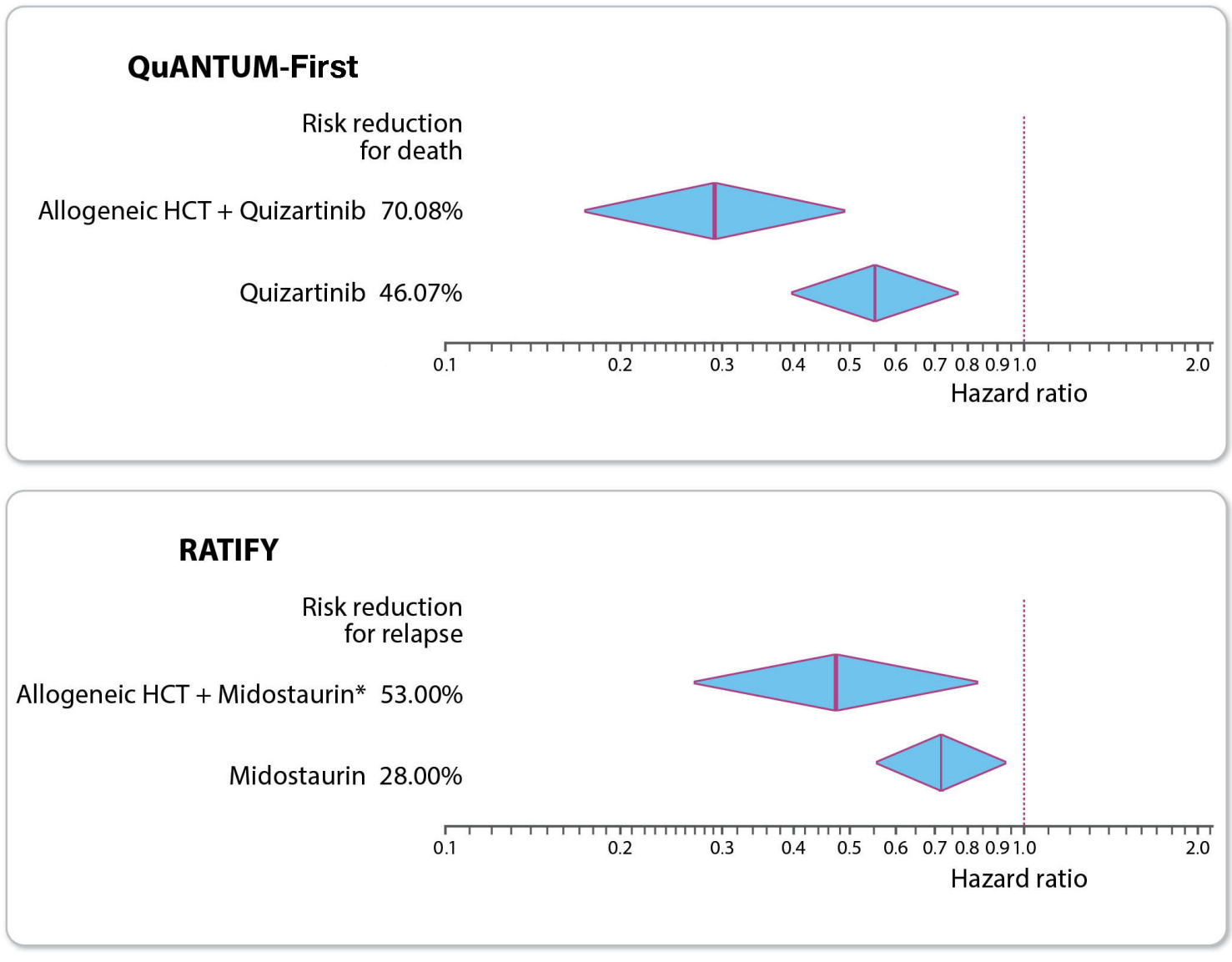

Figure 1. Hazard ratios and corresponding 95% confidence intervals for outcomes of patients with acute myeloid leukemia in the QuANTUM-First and RATIFY trials. Top. Hazard ratio for overall survival of patients in the QuANTUM-First trial achieving complete remission after induction therapy. Bottom. Hazard ratio for cumulative incidence of relapse in the RATIFY trial of patients achieving complete remission after induction therapy. *Only patients receiving allogeneic hematopoietic cell transplantation (HCT).

proceeded to alloHCT in CR1 had an overall survival advantage with a hazard ratio of 0.292 (95% CI: 0.168-0.505) translating into a risk reduction with respect to death of 70.08% (Figure 1).[10] However, patients proceeding to alloHCT were on average 10 years younger (Table 2 in Schlenk *et al.*[10]) pointing to at least some bias. With regards to age and alloHCT, the AMLSG 16-10 trial evaluated midostaurin in combination with intensive chemotherapy according to the 7+3 scheme followed by an early alloHCT and 12 months of midostaurin maintenance therapy in adult patients (18-70 years) with newly diagnosed AML and *FLT3*-ITD mutations.[11,12] Primary and key secondary endpoints were event-free survival and overall survival. Results were compared with those of a historical cohort of 415 patients treated on five prior AMLSG trials as well as with patients (18-59 years) treated on the placebo arm of the Cancer and Leukemia Group B 10603/RATIFY trial. Overall, the trial accrued 440 patients (18-60 years, N=312; 61-70 years, N=128). An alloHCT from a matched-related or unrelated donor was intended for all patients achieving CR or CR with incomplete hematologic recovery (CRi) after induction therapy. Overall, 199 (45%) patients received alloHCT in first CR/CRi, 150 (48%) and 49 (38%) patients in the younger and older cohorts, respectively. The median time to alloHCT was 98 days (range, 49-202 days). Within this trial, the addition of midostaurin to intensive induction chemotherapy and alloHCT led to a significant improvement in outcome in younger and an even more pronounced improvement in older patients with *FLT3*-ITD-mutated AML as compared to historical controls.[11,12] The reduction of cumulative incidence of relapse was substantial, in particular in patients 60-70 years of age proceeding to an alloHCT in CR1 compared to standard chemo-consolidation (Supplementary Figure 1 in Schlenk *et al.*[11]). Overall, multivariate analyses revealed that midostaurin treatment had a significant beneficial effect on event-free survival (HR=0.55; *P*<0.001) and overall survival (HR=0.56; *P*<0.001) in patients with *FLT3*-ITD AML. Of note, the improvements in event-free and overall survival were more pronounced in older (61-70 years) than younger (18-60 years) patients. In sensitivity analysis, adjusting for alloHCT in first CR/CRi as a time-dependent covariate, the treatment effect of midostaurin remained significant.

In conclusion, FLT3-inhibitor treatment before and after alloHCT currently offers the highest chance of cure in AML with *FLT3*-ITD in CR1.

Disclosures

RFS reports consulting fees from Daiichi Sankyo for participation on a steering committee and from AbbVie, Jazz Pharmaceuticals, and Pfizer for participation on advisory boards; reports payment for lectures from Daiichi Sankyo, Novartis, and Pfizer; is a member of a data safety monitoring board or advisory board for BerGenBio and Novartis; and has been provided with research funding from AbbVie, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, PharmaMar, Pfizer, Roche and Recordati. SK has no conflicts of interest to disclose.

Contributions

SK and RFS wrote and approved the manuscript.

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