

FLT3 Inhibitors as Maintenance Therapy after Allogeneic Stem-Cell Transplantation

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Abstract: Mutations in the *FLT3* gene are associated with poor prognosis in patients with AML, even after consolidation with allogeneic hematopoietic cell transplantation (alloHCT) in first remission. Treatment failure in *FLT3*-mutated AML is largely driven by excessive risk of relapse compared to other genetic subtypes, including in patients post-alloHCT. As a result, there is substantial interest in studying posttransplant maintenance therapy in *FLT3*-mutated AML as an approach to optimize disease control and improve long-term outcomes. Clinical trials utilizing posttransplant FLT3 inhibitors, such as sorafenib and midostaurin, have shown feasibility, safety, and encouraging posttransplant outcomes, and there are ongoing studies using newer-generation tyrosine-kinase inhibitors as posttransplant maintenance therapy. Here, we review the toxicities and efficacy of FLT3 inhibitors as posttransplant maintenance, recommendations on the use of FLT3 inhibitors by international consensus guidelines, and highlight key remaining questions.

Keywords: FLT3 inhibitor, posttransplantation, maintenance, stem-cell transplantation, midostaurin, sorafenib

Introduction

Acute myeloid leukemia is a biologically complex disease, often harboring a spectrum of diverse cytogenetic and mutational abnormalities, including the finding of different subclones in a single patient at diagnosis that could evolve during the disease course.^{1,2} This renders AML a challenging disease to target and eradicate, and a sole therapeutic targeted modality frequently lacks success in preventing relapse. At the time of diagnosis, patients with AML are stratified into favorable, intermediate, and adverse risk subgroups based on cytogenetic and mutational findings, which is employed to dictate initial therapy, identify eligibility for clinical studies, and guide postremission consolidation therapy.³

Mutations in the *FLT3* gene are among the most common genetic aberrations, occurring in approximately 30% of patients with newly diagnosed AML.^{4,5} Activating mutations of the *FLT3* gene occur most commonly as in-frame internal tandem duplications (ITDs) of between 3 and more than 100 amino acids located in the juxtamembrane region or as missense point mutations in the tyrosine-kinase domain (TKD), typically involving aspartic acid 835 residue. Of the two classes of mutations, *FLT3*-ITD abnormalities are more concerning, being associated with an increased risk of relapse and leading to the routine consideration of allogeneic transplantation in these patients.^{4,6} *FLT3* encodes a membrane-bound receptor tyrosine kinase (RTK), which is expressed on normal hematopoietic progenitor cells involved in cell differentiation and proliferation.^{7,8} Upon binding of the *FLT3* ligand, the receptor dimerizes and undergoes autophosphorylation, leading to activation of downstream pathways and promoting proliferation and preventing apoptosis.

FLT3-ITD mutations interfere with the regulatory function of the juxtamembrane region, and TKD mutations affect the activation loop and loss of autoinhibition, leading to constitutive activation of *FLT3* (bypassing ligand activation), with downstream activation of pathways, including PI3K/Akt, MAPK, Ras, Mek, ERK, and STAT5 (Figure 1).^{9–15} The dependence of *FLT3*-mutated AML on *FLT3* signaling provides a biological rationale for the development of *FLT3*-targeted therapies. Considerable effort has been dedicated to the development of potent and selective *FLT3* TKIs,

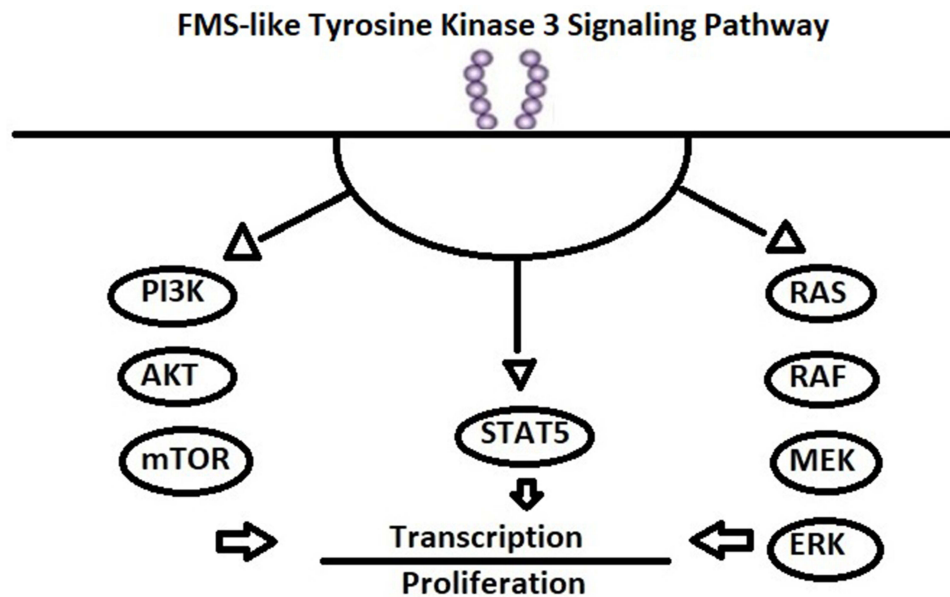


Figure 1 FLT3 signaling pathway.

culminating in the approval of midostaurin in combination with upfront chemotherapy for newly diagnosed and gilteritinib for R/R *FLT3*-mutated AML.^{16,17} However, there remains an unacceptably high risk of relapse among those with AML harboring *FLT3*-ITD mutations, who undergo allogeneic stem-cell transplantation. The application of FLT3 inhibitors as maintenance therapy after allogeneic stem-cell transplantation may have the greatest potential for improving long-term survival for patients with *FLT3* ITD-mutated AML. Here, we discuss the evidence, current recommendations, and remaining questions of FLT3-inhibitor maintenance after allogeneic hematopoietic cell transplantation (alloHCT).

Prognostic Impact of *FLT3*-ITD AML

Although patients with newly diagnosed *FLT3*-mutated AML have comparable rates of complete remission at 65%, they are associated with a higher propensity for relapse, leading to shorter remission duration and survival, than their *FLT3* wild-type (WT) counterparts.^{4,18,19} AlloHCT for patients in first complete remission has demonstrated an improvement in relapse-free survival (RFS) when compared to those receiving chemotherapy or autologous stem-cell transplant as consolidation.^{20,21} However, *FLT3*-ITD mutation remains a significant risk factor of relapse and death after alloHCT.^{22,23} A large international registry study conducted by the European Group for Blood and Marrow Transplantation (EBMT) of patients with de novo AML with normal cytogenetics who underwent myeloablative alloHCT from a matched unrelated donor demonstrated an increased incidence of relapse at 2 years (30% vs 16%, $P=0.006$) and decreased leukemia-free survival at 2 years (58% vs 71%, $P=0.04$) among those with *FLT3*-ITD mutations.²² The mutational burden or allelic ratio of *FLT3*-ITD mutations has important prognostic implications: those with high allelic ratio (>0.5 , *FLT3*-ITD^{high}), have worse outcomes with long-term disease-free survival of 20%–30% without allogeneic transplantation.^{22,24} While the data are less convincing for alloHCT in those with low allelic ratio (<0.5 , *FLT3*-ITD^{low}), it is still common practice to perform allogeneic transplants following first remission in eligible patients, regardless of cytogenetic risk group, concurrent mutations, or negative minimal residual disease (MRD).²⁵ Other factors impacting relapse risk and survival in patients with *FLT3*-ITD AML include the presence of increased ITD fragment length or measurable residual disease by FLT3 sequencing prior to alloHCT.^{26–29} *FLT3*-TKD mutations may have less influence on overall survival (OS) and disease-free survival; however, there is a suggestion this may differ among ethnicities, with more favorable outcomes in Asian patients compared to Caucasians.^{30,31}

Development of FLT3 Inhibitors

Despite a strong biological rationale for inhibiting the FLT3 pathway in *FLT3* ITD–mutated AML, translating these findings into the successful development of FLT3 inhibitors in the clinic has been challenging. First-generation FLT3 TKIs (sorafenib, sunitinib, lestaurtinib, and midostaurin) have lower specificity for FLT3 with more off-target activity. These agents inhibit various kinases, including Kit, VEGFR, PDGFR, and Ras/RAF, among others.³² The relatively broad inhibition can lead to toxicity, including fatigue, GI toxicity, HTN, and bleeding. In many cases, these inhibitors were initially developed for indications other than FLT3 inhibition. Sorafenib was originally developed as a B-Raf and multikinase inhibitor in renal and hepatocellular carcinoma before demonstrating potent inhibitory activity in *FLT3*-ITD AML.³³ Midostaurin was initially developed as a protein kinase C inhibitor and was subsequently found to have inhibitory activity against multiple tyrosine kinases, including FLT3.³⁴ These agents have demonstrated modest activity as single agents in the R/R AML setting. In phase I studies of sorafenib in R/R AML, there were transient reductions in blast counts; however, most patients had stable disease, and increase in dose was limited by toxicity.^{35,36} Lestaurtinib phase I/II data showed activity in 14 heavily pretreated patients with AML, with five having blast reduction and improvement in normal hematopoiesis; however, no patients had a CR.³⁷ Similarly, midostaurin demonstrated blast reduction in phase I/II studies in R/R AML; however, no patients attained a CR, suggesting that midostaurin may not be sufficient as monotherapy.^{38,39}

The first-generation FLT3 inhibitors have had more success when used in combination with induction and consolidation chemotherapy. The German SORAML trial was a phase II study evaluating sorafenib or placebo in combination with induction chemotherapy (7+3).⁴⁰ The sorafenib arm had improved EFS (21 vs 9 months); however, there were significantly more grade 3 AEs, particularly fever, diarrhea, bleeding, cardiac events, and skin rash. The approval of midostaurin followed the multicenter phase III RATIFY trials, which showed a survival benefit when adding midostaurin to induction chemotherapy. In this study, younger patients with newly diagnosed *FLT3*-TKD or *FLT3* ITD–mutated AML randomized to midostaurin in combination with induction and consolidation chemotherapy had significantly longer median OS (74.7 vs 25.6 months, $P=0.009$) when compared to placebo.¹⁷

Second-generation TKIs have higher potency and less off-target activity, with a lower half-maximal inhibitory concentration (IC_{50}). These include gilteritinib, quizartinib, and crenolanib.³² Second-generation inhibitors have demonstrated greater single-agent activity in the R/R setting than salvage chemotherapy.^{16,41,42} Quizartinib demonstrated significantly longer survival (median OS 6.2 months vs 4.7 months, $P=0.02$) in a phase III study of patients with R/R AML with *FLT3*-ITD mutations when compared to patients receiving salvage chemotherapy.⁴³ However, treatment with quizartinib was limited by the frequent emergence of resistance-conferring *FLT3*-TKD mutations at the time of relapse.⁴⁴ Gilteritinib is an oral highly potent pan-FLT3 inhibitor and the only FLT3 inhibitor currently approved for patients with R/R AML harboring *FLT3* mutations. Approval was based on the seminal phase III ADMIRAL trial, which demonstrated higher complete remission rates with full or partial hematologic recovery (34% vs 15%), prolonged survival (median OS 9.3 months vs 5.6 months, $P<0.001$), and a higher rate of alloHCT (26% vs 15%) among patients with *FLT3*-mutated R/R AML randomized to gilteritinib when compared to salvage chemotherapy.¹⁶ Crenolanib is a promising pan-FLT3 (ITD and TKD) inhibitor currently in phase III studies.

FLT3 inhibitors are further classified as type I or type II depending on their mechanism of action. Type I inhibitors (midostaurin, lestaurtinib, crenolanib, and gilteritinib) work by competitive inhibition of the ATP-binding site of the intracellular TKD. Type II inhibitors (sorafenib, quizartinib, and ponatinib) interact with the inactive receptor at a hydrophobic region adjacent to the ATP-binding site, preventing activation.³² Type I inhibitors have activity against ITD and TKD mutations, while type II inhibitors have less activity in TKD mutations, as these mutations often lead to the active conformation of the receptor. Furthermore, the acquisition of TKD mutations is a major mechanism of secondary resistance for patients with ITD mutations receiving type II inhibitors.^{45–47} We discuss sorafenib and midostaurin more in depth as they have been evaluated in the posttransplantation setting.

Sorafenib

Sorafenib was one of the earliest agents discovered to have activity in *FLT3*-mutated AML. It is an oral multikinase inhibitor approved for the treatment of advanced thyroid, hepatocellular, and renal cell carcinoma with potent inhibitory

activity against RAF kinase, VEGF receptors, PDGF receptors, c-Kit, Ret kinase, and wild-type and ITD-mutated *FLT3*.⁴⁸ In addition to targeting *FLT3*, sorafenib may enhance alloimmunity following transplantation. Treatment with sorafenib monotherapy leads to more durable responses among relapsed or refractory *FLT3* ITD-mutated AML patients with a prior allogeneic stem-cell transplantation compared to conventional therapy.^{43,44,49} In a murine allogeneic stem-cell transplant model, maintenance sorafenib led to an increase in donor T cells and an increase in clinical graft-versus-host disease (GVHD) in T cell-replete donors.⁵⁰ Sorafenib enhances the graft-versus-leukemia effect by inducing IL15 production in *FLT3* ITD-mutated AML cells, which promotes the cytotoxicity and longevity of donor CD8⁺ T cells.⁵¹ Several retrospective studies have shown that compassionate use of sorafenib after alloHCT may reduce relapse and improve survival.^{52–56} In a phase I study of 22 patients, sorafenib given for 12 28-day cycles posttransplant was safe, and the maximum tolerated dose was found to be 400 mg twice daily. In this study, there were no episodes of significant acute GVHD after starting sorafenib and a comparable incidence of chronic GVHD to historical outcomes. Among the 19 patients in a conventional complete remission (CR1/CR2) before alloHCT, progression-free survival was 86% and OS at 2 years was 78%.⁵⁷ A German randomized phase II study (SORMAIN trial) was conducted to evaluate sorafenib maintenance vs placebo in TKI-naïve patients with *FLT3* ITD-mutated AML in CR after dose-reduced or myeloablative alloHCT from a 9/10 or 10/10 HLA-matched unrelated or sibling donor.⁵⁸ Sorafenib was started at day +60 to day +100 at 400 mg daily, with the dose escalated every 2 weeks to a maximum of 800 mg daily and to be given continuously for 24 months until occurrence of relapse or intolerable toxicity. The trial was discontinued early due to slow accrual, but still met the primary end point by demonstrating longer RFS among patients receiving sorafenib vs placebo (median RFS: 30.9 months vs not reached, HR 0.39, 95% CI 0.18–0.85). The sorafenib arm also had superior 24-month RFS (85% vs 53%, HR 0.256, 95% CI 0.1–0.65) and OS (91% vs 66%, HR 0.241, 95% CI 0.08–0.74) compared to the placebo arm. Sorafenib was generally well tolerated, with dose reductions occurring in 49% and treatment discontinuation due to an adverse event occurring in 22% of patients in the sorafenib arm. The most common grade ≥ 3 adverse event was acute and/or chronic GVHD, which occurred in 32 of 42 patients (77%) in the sorafenib arm and 23 of 39 patients (60%) in the placebo arm. Other grade ≥ 3 adverse events that occurring at a higher frequency in the sorafenib than placebo arm included infections, GI toxicity, cardiotoxicity, renal insufficiency, skin toxicity, and electrolyte alterations.

A randomized phase III study compared maintenance therapy with sorafenib or placebo in patients aged 18–60 years with *FLT3* ITD-mutated AML in composite CR after alloHCT.⁵⁹ Patients enrolled received either a matched sibling donor, matched unrelated donor, or a haploidentical transplant with modified busulfan and cyclophosphamide myeloablative conditioning. Sorafenib was dosed at 400 mg twice daily from day 31–60 until day 180, but 60% of patients required dose reduction and the median dose was 200 mg twice daily. The study met the primary end point by demonstrating a reduced risk of relapse at 1 year compared to placebo (1-year cumulative incidence of relapse [CIR] 7% vs 24.5%, HR 0.25, 95% CI 0.11–0.57; $P=0.001$). Treatment with sorafenib also led to superior 2-year CIR and OS without adversely impacting 2-year NRM or rates of acute and chronic GVHD compared to placebo. Notably, there was no difference in rates of acute and chronic GVHD between treatment arms. Grade 3/4 adverse events occurring more commonly in the sorafenib arm than control included hematologic, skin-related, and gastrointestinal. Sorafenib required a dose modification due to adverse events in 60% of patients, and the median duration of treatment was 134 days. Treatment with sorafenib did not seem to increase the risk of acquiring *FLT3*-TKD mutations, which occurred in only one of eleven relapsing patients.

Midostaurin

Midostaurin is a potent oral multikinase inhibitor of *FLT3* TKD and ITD, as well as Kit, VEGF, Ret, Syk, and PDGFR.⁶⁰ In the RATIFY trial, patients did not continue midostaurin maintenance therapy after alloHCT. However, among those undergoing alloHCT, midostaurin in combination with chemotherapy led to a significant decrease in CIR (HR 0.47, $P=0.02$). MRD testing was not performed in this study; however, the improved posttransplant outcomes in the midostaurin arm suggest that the *FLT3* inhibitor with chemotherapy led to deeper remission prior to alloHCT.⁶¹

In contrast to the RATIFY trial, the phase II AMLSG 16–10 trial included maintenance midostaurin after alloHCT following induction and consolidation chemotherapy with midostaurin for younger patients with *FLT3* ITD-mutated AML.⁶² Posttransplant midostaurin was administered at 50 mg twice daily between 30 and 100 days after transplantation

for 1 year. The trial demonstrated improved 1-year EFS compared to that of historical controls with *FLT3* ITD–mutated AML (HR 0.58, 95% CI 0.48–0.7; $P < 0.001$). Additionally, a landmark analysis in patients proceeding to alloHCT in CR1 who were event-free at day 100 after transplant demonstrated significantly longer EFS and OS among patients receiving midostaurin maintenance than the historical control patients who did not. The median time on maintenance therapy was 9 months after alloHCT, and early discontinuation from nonrelapse causes occurred in 86% of patients, most commonly due to nausea/vomiting, infection, cytopenia (mostly thrombocytopenia), elevated liver enzymes, pain, allergy, and dermatologic adverse events.

The RADIUS trial was a randomized phase II study comparing maintenance therapy with or without midostaurin 50 mg twice daily for 1 year after alloHCT for patients with *FLT3* ITD–mutated AML in CR1.⁶³ The trial showed no significant difference between treatment arms in RFS or OS. However, the trial was unable to detect differences between treatment arms due to being inadequately powered. (Table 1). The median midostaurin exposure was 10.5 months, and a majority of these patients had not had previous midostaurin with induction. Treatment discontinuation due to adverse events was less likely than AMLSG 16–10, at 27%, which may have been due to more stringent selection criteria. Notably, the addition of midostaurin did not increase rates of acute or chronic GVHD compared to standard of care (Table 1).

Next-Generation *FLT3*-Inhibitor Posttransplant Maintenance

Based on promising results of early-phase trials, current phase III trials are evaluating next-generation *FLT3* inhibitors vs placebo (quizartinib, QUANTUM-First trial) or midostaurin (gilteritinib, HOVON/AML-SG; crenolanib) in combination with induction and consolidation chemotherapy. Additionally, in several clinical trials evaluating *FLT3* inhibitors in R/R AML, *FLT3*-inhibitor treatment was continued after alloHCT. In the ADMIRAL trial comparing gilteritinib to salvage chemotherapy in R/R *FLT3*-mutated AML, ~20% (49 of 247) of patients on the gilteritinib arm and ~10% (14 of 124) of patients on salvage chemotherapy arm were alive for ≥ 2 years.⁶⁴ Of the patients who survived, 18 of 49 underwent alloHCT and 16 continued gilteritinib posttransplant.⁶⁴ Gilteritinib was well tolerated, with the most common adverse event being elevated transaminases. Similarly, in the QUANTUM-R trial comparing quizartinib to salvage chemotherapy in R/R AML, more patients were able to undergo alloHCT on the quizartinib arm (32% [n=78] vs 11% [n=14]), and 62% of these patients continued quizartinib posttransplantation.⁶⁵ There were no new safety signals in those continuing quizartinib posttransplant compared to the entire quizartinib arm.

BMT CTN 1506 is a randomized, double-blinded phase III trial evaluating posttransplant maintenance with gilteritinib vs placebo in patients with *FLT3* ITD–mutated AML in CR1 that is currently enrolling patients (NCT02997202). Gilteritinib will be administered between days 30 to 90 after alloHCT at 120 mg daily for 2 years.⁶⁶ The study includes a deep-sequencing assay that is highly sensitive and specific for *FLT3*-ITD mutations for MRD testing that will determine patients most likely to benefit from maintenance therapy.^{66,67} A key objective of BMT CTN 1506 is defining the impact of MRD on outcomes with post-HCT maintenance.

Key Remaining Questions

Is *FLT3*-Inhibitor Maintenance Necessary for All *FLT3* ITD–Mutated AML Patients Undergoing AlloHCT?

The detection of MRD at the time of allogeneic stem-cell transplantation is well established as one of the most significant factors in determining relapse risk.^{68,69} However, patients with MRD-negative disease prior to transplantation have a lower risk of relapse, and thus the risks of treatment toxicity need to be considered in addition to potential benefit from *FLT3*-inhibitor treatment. Additionally, mutations in *FLT3* alone do not result in leukemogenesis, and preclinical studies have identified leukemic stem cells that do not harbor *FLT3* mutations, suggesting this may not always be enough for higher-risk patients.⁷⁰ In the SORMAIN trial, patients with MRD negativity prior to transplantation benefited from posttransplant maintenance with sorafenib; however, MRD-positive patients derived the greatest benefit.⁵⁸ In the phase III trial of Xuan et al, both MRD-positive and -negative patients after alloHCT randomized to sorafenib had a reduced risk when compared to placebo on subgroup analysis.⁵⁹ These results suggest that all patients, regardless of MRD status, should receive *FLT3* inhibitors for posttransplant maintenance. However,

Table I Clinical trials evaluating FLT3 inhibitor maintenance after allogeneic hematopoietic cell transplantation

FLT3 inhibitor	Phase	Transplant type	Dosing	GVHD	Grade ¼ toxicities	Outcomes	Reference
Sorafenib (2014)	I (n=22)	MA (13) MSD (4) MUD (8) DUCB (1) NMA (9) MSD (4) MUD (3) MMUD (1) Haplo (1) *3/22 received sorafenib pretransplant	<u>Start:</u> Between 45 and 120 days post-HSCT <u>End:</u> After completion of 12 months, physician discretion to continue DL1: 200 mg PO BID DL2: 400 mg PO QAM/200 mg PO QPM DL3: 400 mg PO BID	4/22 patients had aGVHD prior to starting sorafenib — no flare after starting treatment 1/22 with new aGVHD grade 2 skin 38% with any cGVHD	Rash 4/22 Anemia 5/22 HTN 3/22 Abdominal pain 3/22	1-year PFS 85% 1-year OS 95%	Chen et al ⁵⁷
Sorafenib (2020)	I (n=44)	MA (16) MSD (9) MUD (3) Haplo (4) NMA (28) MSD (6) MUD (4) Haplo (15) DUCB (3) *21/44 received sorafenib maintenance pretransplant	<u>Start:</u> 30 days postinduction and/or 30–120 days post-HSCT <u>End:</u> Until 24 months Individualized dosing based on tolerability, starting at 200 mg BID	aGVHD (grade 3/4) 25% at 360 days	Hepatic (23%) Hematologic (16%) HTN (7%) Skin (5%)	OS 24 months 76% 36 months 76% 48 months 57% EFS 24 months 74% 36 months 64% 48 months 64%	Pratz et al ⁷¹
Sorafenib (2020)	II (n=83)	MA (37) RIC (46) MUD (63) MSD (20) *Patients were excluded if sorafenib used prior to transplant *Other FLT3-targeting TKIs were allowed pretransplant: 9 patients received upfront midostaurin	<u>Start:</u> Between d+60 and d+100 post-HSCT in CHR <u>End:</u> Until 24 months 400 mg daily for 2 weeks, 600 mg daily for 2 weeks, then 800 mg daily ongoing 48.8% of patients required dose reduction	aGVHD (grade ≥2) 24% vs 18% in placebo cGVHD (mild/moderate) 42.9% vs 35.9% in placebo cGVHD (severe) 19.2% vs 10.4% in placebo	Skin 11.9% vs 2.6% in placebo Cardiotoxicity and renal insufficiency 9.5% vs 2.6% in placebo Electrolyte alterations 14.3% vs 2.6% in placebo Hepatic and GI toxicity, infection (similar between groups)	Estimated 24-month OS 90% for sorafenib and 66% for placebo Estimated 24-month RFS 85% in sorafenib and 53% in placebo With median follow-up 41.8 months, RFS not reached in sorafenib and 30.9 months in placebo	Burchert et al ⁵⁸

Sorafenib (2020)	III (n=202)	All received MAC with modified Bu/Cy regimen MSD (83) MUD (14) Haplo (105) *116/202 patients received sorafenib pretransplant	<u>Start:</u> Between d+30 and d+60 with hematopoietic recovery <u>End:</u> D+180 Initial dose 400 mg BID, dose reductions allowed for grade ≥ 3 AE	aGVHD (grade 3/4) 23% sorafenib and 21% placebo cGVHD (gr3/4 AE), 18% sorafenib, and 17% placebo	Hematologic 15% sorafenib vs 7% placebo Skin 7% sorafenib vs 1% placebo GI 11% sorafenib vs 8% placebo	2-year CIR 11.9% with sorafenib and 31.6% in placebo 2-year OS 82.1% with sorafenib and 68% in placebo Median OS not reached in either group with median follow-up 21.3 months	Xuan et al ⁵⁹
Midostaurin (2021)	II (n=60)	Bu/Cy (21) Bu/Flu (31) Cy/TBI (3) FluMel (4) MUD (35) MSD (24) Syngeneic (1) *No pretransplant TKI exposure	<u>Start:</u> Between d+28 and d+60 after engraftment post-HSCT <u>End:</u> Up to 12 4-week cycles 50 mg BID	aGVHD (grade ≥ 2) 27% vs 37% in SOC cGVHD 30% vs 33% in SOC (most mild to moderate; severe in 1 patient SOC and 2 in midostaurin)	Nausea 10% vs 3% in SOC Elevated AST/ALT 13% vs 10% in SOC HTN 13% vs 0% in SOC Serious AE: Diarrhea 13% vs 7% in SOC	Estimated 24-month OS 85% midostaurin and 76% with SOC Estimated 24-month RFS 85% midostaurin and 76% SOC (no SS difference in OS or RFS) Median RFS and OS were not reached in either arm (at 24 months post-HSCT)	Maziarz et al ⁶³
Midostaurin (2019/ updated 2022)	II (n=440)	199 patients transplanted in CRI: MUD (148) MSD (51) *Patients received midostaurin pretransplant	Induction and consolidation given with midostaurin in standard fashion <u>Start:</u> At least d+30 post-HSCT <u>End:</u> 1 year of therapy 50 mg BID	Not discussed	Blood and lymphatic disorder 95% Infection 66% GI 39% (single arm)	EFS HR 0.55 ($P < 0.001$) for patients treated on AMLSG 16–10 trial compared to the AMLSG control	Schlenk et al ^{62,74}

Note: *Information regarding prior FLT3-inhibitor use.

Abbreviations: MA, myeloablative; NMA, non-MA; RIC, reduced-intensity conditioning; MSD, matched sibling donor; MUD, matched unrelated donor; Haplo, haploidentical donor; DUCB, double umbilical cord blood; CHR, complete hematologic remission; BID, twice daily; AE, adverse event; HSCT, hematopoietic stem-cell transplantation; aGVHD, acute graft-versus-host disease; cGVHD, chronic GVHD; OS, overall survival; RFS, relapse-free survival; EFS, event-free survival; CIR, cumulative incidence of relapse.

midostaurin was only recently approved as frontline therapy, and most patients enrolled in the SORMAIN, RADIUS, or the phase III trial of Xuan et al did not receive prior FLT3-inhibitor treatment with chemotherapy.⁶⁶ This is notable, since patients randomized to midostaurin with induction and consolidation that proceeded to alloHCT in the RATIFY trial also had a reduction in relapse risk, likely as a result of MRD eradication.¹⁷ The phase III BMT-CTN 1506 study with gilteritinib vs placebo as posttransplant maintenance will be essential in determining the role of FLT3-inhibitor maintenance posttransplant for patients who have previously received FLT3 inhibitors in combination with chemotherapy. Additionally, the BMT-CTN study includes a novel highly sensitive and specific FLT3-ITD MRD assay to further determine patients most likely to benefit from FLT3-inhibitor maintenance therapy after alloHCT.

What is the Optimal Duration of FLT3-Inhibitor Therapy?

Although EBMT guidelines recommend 2 years of maintenance therapy, the duration of FLT3-inhibitor treatment is often limited by tolerability. In the SORMAIN trial, ~50% of patients required dose reduction, 21% of patients discontinued treatment due to toxicity, and the median duration of treatment was ~9 months.⁵⁸ In the phase III trial of Xuan et al, the intended duration of sorafenib maintenance was shorter until day 180 to reduce the risk of developing drug resistance.⁵⁹ Although the duration of treatment was half as long in the phase III study, the rates of relapse in each study seemed similar (SORMAIN — 2-year RFS, 85%; Xuan et al — 2-year CIR 12%).^{58,59} Therefore, further studies are needed to determine the optimal duration of FLT3-inhibitor maintenance. Pratz et al demonstrated that individualized dosing of sorafenib titrated to tolerability allowed for a longer duration of treatment of around ~22 months without impacting levels of FLT3 inhibition on pharmacodynamic studies.⁷¹ Next-generation FLT3 inhibitors, such as gilteritinib, crenolanib, and quizartinib, are more selective and reduce off-target toxicities. This may enhance tolerability and enable a longer duration of FLT3-inhibitor treatment after alloHCT.

What is the Optimal FLT3 Inhibitor for Post-AlloHCT Maintenance?

Currently, only sorafenib has demonstrated a decreased risk of relapse in phase II and phase III trials of maintenance therapy after transplant. The efficacy of sorafenib in the posttransplant setting may be due to FLT3-ITD targeting and other FLT3-independent immunomechanisms. It is not known if other more potent and selective FLT3 inhibitors will have similar benefit in randomized prospective trials. The RADIUS trial did not show an improvement in median RFS or OS for patients randomized to posttransplant maintenance with midostaurin, but the study was not adequately powered. Enrollment in clinical trials evaluating FLT3 inhibitors is encouraged. For patients unable to enroll in a clinical trial, sorafenib would be the treatment of choice, but may be more difficult to obtain than other current FLT3 inhibitors FDA-approved for AML, such as midostaurin and gilteritinib. Another consideration for choosing an FLT3 inhibitor would be the co-occurrence of a FLT3 ITD and FLT3KD mutation, which would be associated with resistance to sorafenib, but not other type 1 inhibitors, such as gilteritinib, crenolanib, and midostaurin. Lastly, as we have more patients who now are failing sequential FLT3 inhibitors, this will be important in choosing the best posttransplant maintenance option.

Current Recommendations

As the data on *FLT3*-mutated AML continues to expand, the guidelines are evolving. Currently, the European Society for Blood and Marrow Transplantation (EBMT) recommends transplantation in CR1 in patients with *FLT3*-ITD AML. In patients with an *NPM1*-mutated disease and low *FLT3*-ITD allelic ratio disease, several European cooperative groups do not recommend allogeneic transplant in CR1, while the National Comprehensive Cancer Network (NCCN) does recommend transplant in CR1 for this group.⁷² The acute leukemia working party (ALWP) of EBMT also recommends posttransplant maintenance therapy in those without acute GVHD with sorafenib at a dose of 400 mg daily (or 800 mg daily in those with MRD-positive disease) to begin at the time of hematologic reconstitution and to be continued for a minimum of 2 years, depending on tolerance. The NCCN also recommends the use of sorafenib post-alloHCT in patients with a history of *FLT3* ITD-mutated AML.^{58,59,73}

Conclusion

As *FLT3* ITD-mutant AML has a striking propensity for relapse after allogeneic stem-cell transplantation, *FLT3* inhibitors as posttransplant maintenance represent a very promising approach for both reducing relapse risk and increasing long-term survival. In accordance with retrospective studies, prospective randomized clinical trials of the *FLT3* inhibitor sorafenib as posttransplant maintenance have demonstrated a survival benefit. Additional randomized trials with more selective and less toxic *FLT3* inhibitors as posttransplant maintenance are ongoing. Although the practice of administering posttransplant TKI maintenance therapy has gained popularity lately and is recommended by international consensus guidelines, challenges remain regarding management related to TKI toxicities, and many unanswered questions, including which TKI to administer, for how long, and to which patient population, remain.

Disclosure

Dr Brian Ball reports an NIH K12 grant and personal fees from Oncovalent outside the submitted work. Ibrahim Aldoss serves on advisory boards for Amgen, Pfizer, Kite pharmaceuticals, Jazz, AbbVie and Agios Pharmaceuticals, and is a consultant for Autolus Therapeutics, Pfizer and Amgen, research support by MacroGenics and Abbvie. The authors report no other conflicts of interest in this work.

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