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REVIEW

Midostaurin In Acute Myeloid Leukemia: An Evidence-Based Review And Patient Selection

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Abstract: *Fms-related-tyrosine kinase 3* (*FLT3*) mutations occur in approximately a third of acute myeloid leukemia (AML) patients and confer an adverse prognosis. Numerous studies have evaluated *FLT3* targeting as single agent and in combination approaches in frontline and relapsed AML. At this time, midostaurin, a multikinase inhibitor, is the only FLT3-inhibitor that is US FDA approved to be used in combination with induction therapy in the frontline *FLT3*-mutated AML setting based on improved overall survival noted in the RATIFY Phase III trial. The utility of midostaurin in maintenance post stem cell transplantation has shown promising results and further studies are still ongoing. In this review, we discuss the studies that led to the inception of midostaurin as a targeted kinase inhibitor, its evaluation in AML, the early clinical trials and the large Phase III clinical trial that led to its eventual US FDA-approval in *FLT3*-mutated AML. Our review also discusses data on midostaurin adverse effects, mechanisms of resistance and limitations of its utility. We further discuss emerging second-generation FLT3 inhibitors, with a focus on quizartinib and gilteritinib and future directions to enhance FLT3-inhibitor efficacy and overcome mechanisms of resistance.

Keywords: acute myeloid leukemia, FLT3, midostaurin

Introduction

Acute myeloid leukemia (AML) represents a malignant clonal disorder of myeloid cells that impairs normal hematopoiesis. Age, history of pre-leukemic hematologic disorders, karyotype and mutation profile provide significant prognostic information that dictate therapeutic decisions in AML.[1,2] Treatment of AML traditionally encompasses induction with high-dose anthracyclines, such as idarubicin (or daunorubicin), and cytarabine arabinoside-based regimens. Consolidation therapy traditionally includes high-dose chemotherapy (cytarabine) alone (HiDAC) or in combination with anthracycline (also referred to as "2+5") depending on regional and institutional preferences in low-risk patients, or allogeneic transplantation in the majority of intermediate and in high-risk patients, respectively.[3]

Traditionally, normal karyotype in AML conferred intermediate-risk disease. However, with the advent of mutational analysis, it became evident that there were certain clonal mutations that could significantly alter the AML pathogenesis and prognosis. Some mutations such as *nucleophosmin 1 (NPM1)* and *CCAAT/enhancer-binding protein-α* (*CEBPA*) confer favorable risk. On the other hand, mutations in genes such as *Fms-related-tyrosine kinase 3* (*FLT3), runt-related transcription factor 1* (*RUNX1), DNA methyl transferase 3 alpha* (*DNMT3A), tumor protein p53* (*TP53*)

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and others confer unfavorable risk.[2] An internal tandem duplication (ITD) mutation in *FLT3* gene on chromosome *13q12* is one of the most common mutations noted in AML, occurring in approximately a third of newly diagnosed adults with AML.[4–6] *FLT3* encodes a class III receptor tyrosine kinase (RTK), which is normally expressed in CD34+ hematopoietic stem cells and promotes diverse downstream pathways depending on the impact of co-occurring signals.[7] For instance, binding of the FLT3-ligand (FL) to FLT3 receptor in the absence of other growth factors induces monocytic differentiation of hematopoietic progenitors.[8] However, FLT3 activation induces proliferation and maintenance of progenitors when interleukin-3, stem cell factor and FL are engaged.[8–10]

Mutations in *FLT3* commonly occur in patients with AML who have diploid cytogenetics indicating that the mutated FLT3 is the driver for leukemogenesis.[11] There are two major classes of activating *FLT3* mutations reported in AML patients. The first class of mutations is 3–400 base pair in-frame duplications detected in 20% to 25% of patients with AML and referred to as internal-tandem duplications (*FLT3-ITD*).[12] *FLT3-ITD* mutations lead to constitutive activation of the FLT3-signaling cascade with subsequent stimulation of downstream signaling pathways including signal transducer and activator of transcription 5 (STAT5), phosphatidyl-inositol 3-kinase (PI3K) and protein kinase B (AKT) pathways.[13,14] The second class of *FLT3* mutations occurs as point mutations, most commonly a substitution of tyrosine for aspartic acid at codon 835 (D835Y), in the tyrosine kinase domain (*FLT3-TKD*).[15] These occur in 5% to 10% of patients with AML. Similar to *FLT3-ITD*, these point mutations lead to downstream activation of proliferative pathways.[11] Patients with *FLT3-ITD* mutations have similar complete remission (CR) rates compared with non-*FLT3* mutated patients, but inferior outcomes due to shorter CR duration, high relapse rates, and inferior overall survival when treated with induction therapy alone, without the addition of a TKI.[4,11] *FLT3-TKD* mutations on the other hand have been generally noted to have a neutral impact on overall survival (OS).[16] The significance of these mutations in clinical practice has been further fortified by the emergence of effective targeted therapies to these mutations and their implications on survival.

FLT3 Inhibitors In AML

AML patients with *FLT3-ITD* mutations have shorter CR durations, higher rates of recurrence, and inferior OS compared to patients without *FLT3* mutations.[11,17,18] Of significance, the *FLT3* allelic burden is also important and has a prognostic impact.[19] Polymerase chain reaction (PCR) technique is the most commonly used tool to assay for FLT3 allelic burden. However, because of the competition from wildtype allele, the sensitivity of the PCR assay is low which may be overcome by using patient-specific primers.[20] A more recent assay detects FLT3-positive minimal residual disease AML with higher sensitivity and specificity. The proposed approach starts with a PCR amplification step, followed by next-generation sequencing, and uses a unique software program to quantify the findings.[21] Further, developing assays to measure the inhibitory effects of an oral drug is also important. Plasma inhibitory activity is the first assay to measure the efficacy of target inhibition of FLT3.[22]

Given the significance of *FLT3* mutations in AML, there has been significant interest in developing and applying targeted therapies for *FLT3*-mutated AML patients in the induction, consolidation, and/or maintenance phases, to decrease the risk of relapse and improve OS, as well as in relapsed *FLT3*-mutated AML.[23] Thomas and Campbell (2019) recently reviewed four agents that showed promising results in AML FLT3 inhibition.[24] Briefly, ponatinib, sunitinib, and sorafenib are non-specific tyrosine kinase inhibitors approved in multiple solid tumor malignancies with known FLT3-inhibitory activity.[25] Ponatinib showed modest activity in a small cohort of AML patients with overall response rate of 25% but had significant adverse events.[26] Sunitinib showed activity in inhibiting FLT3 in AML patients but the duration of response was short lived.[25,27] Both ponatinib and sunitinib have not been widely incorporated in AML therapy. Sorafenib, while not approved in AML, has been used effectively for many years as a maintenance post stem cell transplantation in FLT3-mutated AML patients,[28] as well as in combination with induction chemotherapy in newly diagnosed *FLT3-ITD* mutated AML and in combination with azacitidine in frontline and relapsed older *FLT3*-mutated AML.[29,30] Interestingly, sorafenib improved event-free survival (EFS), but not OS when added to 3+7 induction regimen even among *FLT3*-wildtype patients, likely more through its multi-kinase inhibitory activity rather than its direct FLT3-inhibitory activity,[31] and this study is ongoing with follow-up data eagerly awaited. Of note, gilteritinib a potent second-generation FLT3-inhibitor was also recently approved as single-agent therapy for patients with relapsed/refractory *FLT3* mutated (both ITD and TKD) AML based on improved OS and response rates compared

to conventional cytotoxic or low-intensity therapies in a randomized Phase III setting.[32] The only agent that is currently FDA approved in combination with induction and consolidation therapy for newly diagnosed *FLT3*-mutated AML patients is midostaurin, and will be the focus of this review article.

Midostaurin Development

Midostaurin, formerly known as PKC412, is an orally administered multi-targeted tyrosine kinase inhibitor that inhibits multiple kinases including proto-oncogene c-Kit (KIT), platelet-derived growth factor (PDGFR)-α/-β, protein kinase C (PKC), spleen associated tyrosine kinase (SYK), cellular Src kinase (SRC), and vascular endothelial growth factor receptor (VEGFR)-1/-2.[23] Midostaurin was developed as a therapeutic alternative to the naturally available staurosporine in order to inhibit PKC activity.[33,34] Several in vitro and animal studies demonstrated the efficacy of midostaurin in halting cellular proliferation.[35–38] These findings led to a Phase I study in 32 patients with advanced solid tumors whereby midostaurin demonstrated a relatively safe profile with low-grade gastrointestinal and hematological toxicities.[39] A treatment dose of 150 mg/day was considered adequate for further investigation although subsequent studies used different regimens. Subsequent clinical trials investigated the utility of midostaurin in solid cancers and lymphomas but failed to replicate the preclinical findings. Specifically, midostaurin was tested in lymphoproliferative disorders as a single agent,[40] different solid tumors in combination with 5-fluorouracil,[41] non-small cell lung cancer in combination with gemcitabine and cisplatin,[42] and metastatic melanoma as a single agent,[43] without demonstrating significant activity but notably with a maintained low toxicity profile. Further, the anti-angiogenic activity of midostaurin via inhibition of vascular endothelial growth factor (VEGF) in animal models led to clinical studies that examined its role in diabetic retinopathy and macular edema.[44,45] Midostaurin at a lower dose of 100 mg/day demonstrated activity in reducing diabetic retinopathy and macular edema but the gastrointestinal toxicity profile noted in these patients with chronic use of midostaurin limited its further clinical development in diabetic patients.[46]

Preclinical Studies Of Midostaurin In AML

The first evidence of the activity of midostaurin in AML was in 2002. In a drug screening assay, Weisberg et al demonstrated the efficacy of midostaurin in inducing G1 arrest and apoptosis in *FLT3*-mutated Ba/F3 leukemia cell lines and mouse models.[47] In a subsequent study, Grundler et al demonstrated that midostaurin can inhibit *FLT3-ITD* encoded protein, which by then was known to be one of the most common and aggressive mutations in AML.[48] Combining midostaurin with the histone deacetylase inhibitor LAQ824, now known as dacinostat, demonstrated synergistic activity in inhibiting *FLT3*-mutated AML cell lines, which was one of the first preclinical experiments suggesting a role for combining midostaurin with other established leukemia drugs.[49] Also, midostaurin demonstrated more potent synergism when combined with conventional anti-leukemic agents such as cytarabine, doxorubicin and idarubicin in inhibiting *FLT3* mutated, compared with *FLT3* wildtype leukemia cell lines in vitro.[50,51] Interestingly, midostaurin elicited apoptotic cell death in *FLT3*-mutated AML cell lines, while it induced cell cycle arrest in *FLT3*-wildtype cell lines.[52] Hence, the context in which midostaurin was used likely mattered in dictating its response. These preclinical studies in AML and the relatively safe profile of midostaurin in solid tumor clinical trials supported the development of clinical trials to evaluate midostaurin in the treatment of patients with AML.

Early Phase Clinical Trials Of Midostaurin In AML

The relatively safe profile of midostaurin in prior clinical trials in non-leukemia patients paved the way for the initiation of a Phase II clinical trial in AML. To that end, a total of 20 patients with relapsed/refractory AML with an *FLT3-ITD* or *FLT3-D835Y* mutation received midostaurin at a dose of 75 mg orally for 3 times daily (TID).[53] The drug was relatively well tolerated. The most common toxicities were gastrointestinal side effects including nausea, vomiting and diarrhea. Grade 1/2 gastrointestinal toxicities occurred in 65% of the patients on trial. Of note, 3 patients developed fatal pulmonary events in the context of progressive leukocytosis, pulmonary infiltrates of unclear etiology and pneumonia, respectively. Midostaurin demonstrated measurable responses. Specifically, 14/20 (70%) and 6/20 (30%) of treated patients had 50% reduction in peripheral blood and bone marrow blasts, respectively. However, none of the patient attained CR, despite the significant blast reductions, although 1 patient had <5% blasts in a hypocellular bone marrow and was documented as a partial remission. A subsequent Phase

IIB trial treated 95 patients with relapsed/refractory AML and myelodysplastic syndrome (MDS) with mutant or wild-type *FLT3* with midostaurin as a single agent.[54] Similar to the prior study, there was a reduction in blasts on treatment in 71% of *FLT3*-mutant and 42% of *FLT3* wildtype-treated patients.[54] Blast reduction of 50% of more was observed in 42% of treated patients. However, only one patient experienced a partial remission and no patients experienced a CR or CR with incomplete hematologic recovery (CRi) suggesting that midostaurin would likely not be sufficient as a monotherapy agent. Subsequent studies explored combining midostaurin with other agents. In a Phase I/II trial, the combination of midostaurin with the hypomethylating agent 5-azacitidine in 54 untreated and relapsed/refractory AML and high-risk MDS patients showed a modest overall response rate of 26% (1/54 CR, 6/54 CRi), 6/54 morphologic leukemia-free state (MLFS) and 1/54 partial remission).[55] The median response duration was 20 weeks and median overall survival was 22 weeks at a median follow-up of 15 weeks (range, 1–85 weeks). The longest response duration was noted in patients without prior exposure to FLT3 inhibitors and patients who did not have a previous bone marrow transplantation.[55]

With the emergence of greater understanding of potential efficacy requisites with FLT3 inhibition in AML, Levis et al demonstrated that the lack of response to midostaurin may be due to the lack of a sufficient inhibitory effect on FLT3 as demonstrated by plasma inhibitory levels.[22] This led to considerations that utilizing midostaurin in an *FLT3*-inhibitor naïve population, ensuring adequate inhibition of FLT3 by monitoring plasma inhibitory levels, and combining midostaurin with other agents in frontline setting may be a better approach to use this agent in patients with AML. In a Phase Ib study, midostaurin at different dosing schedules in combination with chemotherapy in 79 younger adults (<60 years of age) newly diagnosed AML patients with mutant or wild-type *FLT3* demonstrated CR rates of 80% in the 50 mg twice a day dosing schedule cohort (40 patients).[56] The OS probabilities at 1 and 2 years were 85% and 62% in patients with *FLT3*-mutated AML, and 78% and 52% in patients with *FLT3*-wildtype AML, respectively. Interestingly, the median OS of *FLT3*-mutated patients was similar to that of the *FLT3* wildtype patients, leading to the hypothesis that the addition of TKI midostaurin could potentially neutralize the adverse impact of the FLT3 mutation and improve the outcomes of these patients. Midostaurin was not well tolerated when administered at a dose of 50 mg twice a day or 100mg twice a day starting from Day 1 of induction due to significant gastrointestinal side effects during days 1–7 when patients received midostaurin concomitantly with the cytotoxic therapy (3+7). The tolerance improved significantly when patient received 3+7 alone on Days 1 to 7 and the midostaurin was introduced from Day 8 onwards, especially with the 50 mg twice a day dose. Collectively, these data supported the potential benefit of midostaurin in combination with induction therapy in younger patients with *FLT3*-mutated AML, and was the basis for the Phase III RATIFY trial.

RATIFY Trial

The RATIFY trial enrolled *FLT3*-ITD or *FLT3*-TKD patients with newly diagnosed AML 18–60 years of age from 13 AML cooperative groups (225 sites). A total of 3277 patients were screened and 717 were randomized patients to receive either midostaurin or placebo with 3+7 (daunorubicin with cytarabine) induction and high-dose cytarabine consolidation therapy (up to 4 consolidations), followed by 12 months of maintenance with either midostaurin or placebo.[57] Midostaurin was administered at a dose of 50 mg twice a day on Days 8–21 in induction and each consolidation cycle. During maintenance midostaurin 50 mg twice a day was administered continuously from Cycle 1 Day 1 onwards, without interruption. In order to ensure rapid *FLT3* mutational testing and support enrollment to the trial across multiple sites in different countries, a large-scale cooperative effort established an efficient polymerase chain reaction-based *FLT3* mutation assay with turnaround time of less than 48 hrs.[58] This milestone allowed rapid accrual of patients into the trial, frequently within 4 to 5 days of AML presentation.

Patients were stratified based on the type and frequency of *FLT3* mutation into 3 groups: *FLT3*-TKD, high allelic ratio FLT3-ITD (>0.70) and low allelic ratio *FLT3-ITD* (</=0.70). The primary end point of the trial was overall survival uncensored for transplant. The RATIFY trial demonstrated a significant improvement in the 4-year overall survival in patients who received midostaurin compared to placebo with induction therapy (51.4% versus 44.3%, hazard ratio (HR), 0.78, p=0.009). On per protocol response assessment (up to 60 days from start of induction) the rates of complete remission were not significantly different between the two groups (58.9% versus 53.5%, p=0.15). However, there were an additional 14% of all patients who had achieved CR after the protocol-specified 60 days timepoint of assessment: 32 additional patients on midostaurin arm and 25 additional patients on control arm, leading to intent-to-

treat complete remission rates of 68% with midostaurin compared with 61% on the control arm (p=0.04). Of note, the median duration of midostaurin exposure for all patients on study was 3 months, because a number of patients who achieved remission went to allogeneic stem cell transplant (ASCT) and received only 2 to 3 cycles of therapy. Post-ASCT maintenance with midostaurin was not a part of the RATIFY trial. The cut-off for entry into the RATIFY study was an FLT3 allelic ratio of >/=0.05. On a post-hoc analysis using an arbitrarily selected FLT3 allelic ratio cut-off of 0.7 (to separate what the RATIFY authors called high >/=0.7 versus low allelic ratio <0.7) it was noted that statistically, a similar degree of benefit appeared to be noted in both "high" and "low" allelic ratio. At this time what we can conclude from the RATIFY data is that there is no data regarding the use of midostaurin in patients with an FLT3 allelic ratio <0.05 at diagnosis, and that addition of midostaurin to induction therapy is recommended in all patients with an FLT3 allelic ration >0.05, irrespective of the allelic ratio.

RATIFY represented a landmark study as this was the first-ever study to demonstrate the effectiveness of targeted biomarker-driven therapy in patients with AML, a critical proof of concept success that has galvanized the further development and approval of numerous additional-targeted therapies in AML. The RATIFY findings led to US Food and Drug Administration (FDA) approval of midostaurin in combination with cytarabine and daunorubicin induction and cytarabine consolidation in newly diagnosed adult AML patients of all ages with *FLT3*-ITD or *FLT3*-TKD mutations in April 2017. Of significance, midostaurin was the first drug to be approved for AML in 15 years. A companion *FLT3* diagnostic testing was developed and also US FDA approved through a partnership between Invivoscribe and Novartis.[58] Accordingly, *FLT3* mutational analysis and incorporation of midostaurin into frontline therapy have been integrated into the standard of care work up and treatment for patients with AML in US and Europe. The recommended dosage of midostaurin is 50 mg twice a day with food on Days 8 to 21 of each induction therapy cycle with cytarabine and daunorubicin, and on Days 8 to 21 of each consolidation cycle with high-dose cytarabine.

The Role Of Midostaurin In Maintenance

We discuss maintenance in this section using currently available (and unfortunately insufficient) data. We agree that the efficacy of midostaurin in maintenance therapy based on currently evaluable data is unclear and unfortunately no matter how we dissect and analyze the RATIFY data this is a topic on which we (or others) will not be able to make any definitive conclusions or recommendations,[59] until post-consolidation randomized trials of maintenance that include pre-maintenance and sequential MRD assessment (ideally both flow and NGS based) both prior to and post stem cell transplant are conducted and analyzed. Such trials should ideally help establish not only whether maintenance is beneficial or not in a general fashion, but more importantly help identify patients who benefits most from maintenance versus those who do not benefit or benefit marginally: is it MRD-negative patients who benefit from maintenance by further suppressing emergence of a resistance clone or is it in fact MRD+ patients who can be converted to MRD-negative status by maintenance improving their survival with or without a subsequent SCT. Similarly, could maintenance obviate the need for SCT in a subset of patients versus conversely would maintenance not obviate SCT but actually serve as a bridge to make SCT better by reducing preSCT disease burden? These are questions being studied in Ph+ ALL, a disease with similar development history to FLT3, but with a longer history and more advanced longitudinal datasets. An example of such an ongoing well-designed trial with rich correlative analysis including sequential MRD assessment is the MORPHO-trial of gilteritinib versus observation in the post-SCT setting in FLT3 (ITD or D835) mutated patients who under allogeneic SCT. At this time with the currently available-limited randomized data in FLT3 AML maintenance and based on our experience with TKIs in other disease such as CML, Ph+ ALL, sorafenib in AML our groups recommendation has been to continue maintenance and furthermore to consider prolonged maintenance rather than 1 year maintenance given that late relapses have been seen at 2 and 3 years post-induction and consolidation and these may be prevented by prolonged maintenance. At this time this is a recommendation without available randomized clinical trial data.

Recently, the German-Austrian AML Study Group investigated the efficacy of midostaurin plus intensive chemotherapy, followed by allogeneic hematopoietic stem cell transplantation and single-agent midostaurin maintenance therapy in *FLT3-ITD*-mutated AML patients.[60] In this Phase II study, 284 AML patients received induction therapy and 76.4% (217/284) attained CR/CRi at first or second induction, of which 134/217 (61.7%) underwent allogeneic hematopoietic stem cell

transplantation as consolidation. Seventy-five of 134 patients (56%) eventually received maintenance midostaurin. The median overall survival was 26 months (95% CI, 18.8–36 months). In univariable analysis, patients who started maintenance therapy with midostaurin within 100 days of consolidation had better OS compared to those who did not. While older patients (61–70 years) also benefited from this regimen, there were more frequent cardiac toxicities (22%) and induction death rate (10.5%) in this population. This Phase II study demonstrated an efficacious use of midostaurin in maintenance therapy which also extended to older patients, albeit in a non-randomized fashion. However, a randomized controlled study is needed to further validate these findings.

Adverse Events And Pharmacokinetic Considerations

The most common adverse effects of midostaurin were nausea, vomiting, diarrhea, fatigue and headaches. Given the gastrointestinal side effect profile of midostaurin, prophylactic anti-emetics, such as ondansetron, olanzapine or lorazepam, are recommended prior to its administration. While midostaurin was not associated with QTc prolongation in healthy individuals, 10.1% of AML patients on midostaurin had QTc prolongation, compared to 5.7% on placebo.[61] No clinical events related to QTc prolongation were noted. It is recommended to assess QTc intervals in AML patients receiving midostaurin, especially concomitantly with other QTc-prolonging medications such as some of the anti-emetics, quinolones, and azoles and if possible to avoid concomitant QTc prolonging medications or replace them with suitable alternatives, when feasible.

Midostaurin is metabolized to its active metabolites GGP6221 and CGP52421 via CYP3A4 in the liver, and then excreted through feces.[24] Midostaurin levels significantly increased when concomitantly administered with ketoconazole, posaconazole or voriconazole, and levels decreased when rifampicin was co-administered.[24,62] Since most AML patients are usually on second-generation anti-fungals as a prophylaxis or as treatment, dose adjustments and monitoring for toxicities are warranted. In patients taking a concomitant strong CYP3A4 inhibitor (such as posaconazole or voriconazole), it is recommended that the midostaurin dose be reduced to 25 mg twice a day. Some experts may recommend using isavuconazole as the preferred azole in this scenario as it is considered a moderate inhibitor of CYP3A4 and is still quite an effective anti-fungal.[63] While this may be a reasonable option there are no clear consensus guidelines on this topic.

Mechanisms Of Resistance

Further correlative analysis on midostaurin-treated patients and subset analysis of the RATIFY study set have attempted to elucidate the mechanisms of primary and secondary resistance to midostaurin in patients with AML. Upregulation of myeloid cell leukemia 1 protein (MCL-1) was shown to be an important mechanism of primary resistance to midostaurin in AML.[64] Similarly, upregulation of anti-apoptotic genes and down-regulation of proapoptotic genes were demonstrated to be associated with acquired resistance to midostaurin in AML.[65] A single amino acid substitution at position 676 (N676K) within the FLT3 kinase domain was identified to be the cause of resistance in 1 of 6 evaluable relapsed/refractory AML patients who relapsed while on midostaurin treatment in the Phase II trial of single-agent midostaurin.[53,66] Subsequent work demonstrated that the allelic burden of mutant FLT3 dictated responses and established the basis for assessing the allelic frequency in AML.[67] These findings were the impetus for attempting to combine midostaurin with other drugs and to generate other, potentially more potent, specific and better tolerated FLT3 inhibitors.

Limitation And Future Direction

Better understanding of the underlying AML biology, clonal evolution and selection, emergence of a number of effective-targeted therapies and combinations with FLT3 and isocitrate dehydrogenase (IDH) inhibitors have transformed the way we treat AML. Recently the US FDA approved second-generation FLT3 inhibitor gilteritinib as a single agent in patients with *FLT3*-mutated relapsed/refractory AML (ITD or D835) based on impressive CR/CRi and OS compared with conventional chemotherapy (cytotoxic combination chemotherapy or hypomethylating agent therapy) in a randomized Phase III (ADMIRAL trial).[68] Another highly potent and very selective FLT3 inhibitor quizartinib improved CR/CRi and OS in a randomized Phase III trial in relapsed/refractory *FLT3-ITD* mutated AML and is anticipated to have US FDA approval in the near future.[69,70] A third second-generation FLT3-inhibitor is crenolanib and this agent targets both FLT3-ITD and -D835 potently (Figure 1).[71,72] These FLT3 inhibitors have a high FLT3-specificity and high response rates as single agents compared with first-generation FLT3-inhibitors such as midostaurin and sorafenib with a relatively good tolerability profile, and as such, are being evaluated in frontline combinations

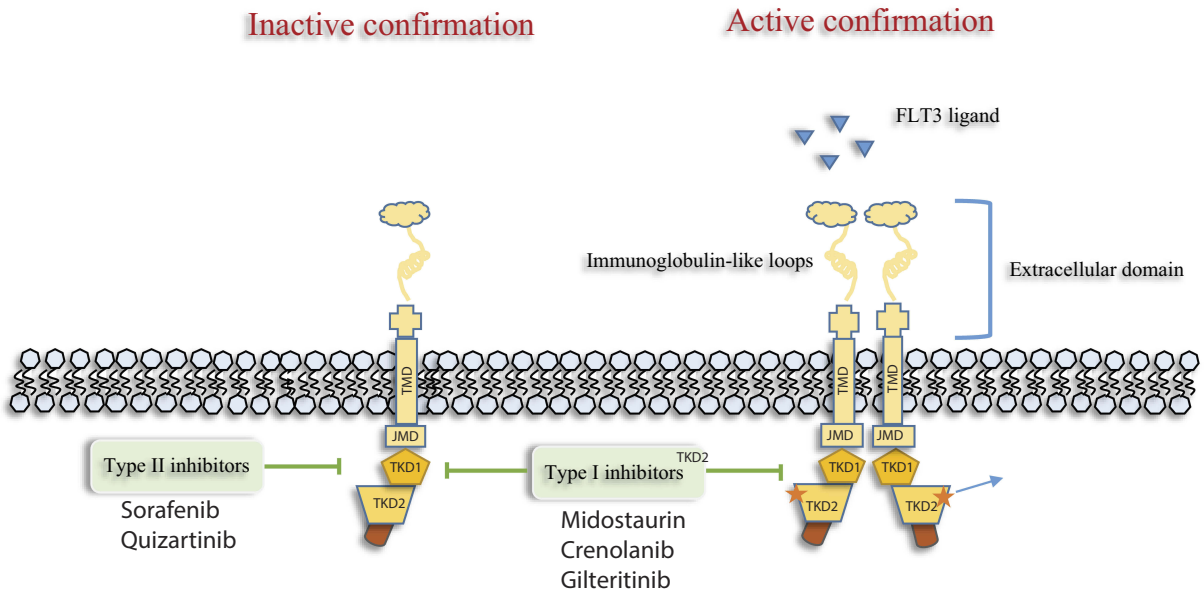

Figure 1 Type I FLT3 inhibitors (Midostaurin, Gilteritinib and crenolanib) bind the FLT3 receptor in the active as well as inactive conformation, while Type II FLT3 inhibitors (Sorafenib, Quizartinib) bind the FLT3 receptor in the inactive conformation. As a result of this affinity, type I acts on both FLT3-ITD and TKD mutations, whereas type II act only on FLT3-ITD. Abbreviations: FLT3, FMS-like tyrosine kinase; TMD, transmembrane domain; JMD, juxtamembrane domain; TKD, tyrosine kinase domain.

with induction therapy and hypomethylating agent-based therapy in newly diagnosed *FLT3*-mutated AML. Clinical trials in newly diagnosed AML with quizartinib (NCT01390337, NCT03723681, NCT02668653, NCT02834390), gilteritinib (NCT03836209, NCT02752035, NCT02236013, NCT02310321) and crenolanib (NCT03258931, NCT02283177) in combination with induction therapy (3+7 or HMA) are ongoing, and preliminary-reported data appear encouraging.[73–75] An emerging question is regarding how these more selective, potent TKIs such as quizartinib, gilteritinib and crenolanib will compare to broad, non-selective multikinase inhibitors such as midostaurin and sorafenib when combined with frontline induction therapy in FLT3-mutated AML. It has been postulated that newly diagnosed FLT3-mutated AML is less addicted to FLT3 signaling but more dependent on multiple kinase pathways for growth and proliferation suggesting that broad kinase inhibitors may be of benefit and potentially preferable over selective TKIs. This is in contrast to the time of relapse wherein FLT3 is often selected out or emerges as the resistance driver clone and more specific, potent FLT3 inhibitors may be more effective as single agents or even more so in combinations. This assumption is being explored in ongoing-randomized studies of frontline induction with second-generation FLT3 TKIs (including crenolanib and gilteritinib) versus frontline induction with midostaurin (NCT03258931, NCT03836209).

Given the nature of midostaurin as a broad, multikinase inhibitor, and the recognition that it inhibits number of kinases and pro-survival pathways that are essential to leukemic cell growth, survival, and proliferation, and taking into account the clinical activity seen with midostaurin in patients with wildtype *FLT3*,[54] it is possible that the on-leukemia, off-FLT3 effects of midostaurin afford benefit regardless of the FLT3 status. The impact of midostaurin in FLT3 wildtype AML is currently being explored in an ongoing Phase III clinical trial (NCT03512197).

Midostaurin was approved in young patients fit for high-intensity chemotherapy who received 3+7 regimen based on the RATIFY trial results. The impact of adding midostaurin to low-intensity therapies such as hypomethylating agents (azacitidine or decitabine) or to low dose cytarabine in older patients with AML who are not fit for high-intensity chemotherapy is yet to be defined. In vitro the combination of decitabine and midostaurin was synergistically active against FLT3-ITD mutation expressing AML cells, advocating for such combinations.[76] In a Phase I/II trial of midostaurin combined with azacitidine the combination appeared to be effective and safe in patients with AML and high-risk MDS.[55] A number of midostaurin containing low-intensity combinations in elderly unfit population are actively been investigated (NCT01130662, NCT01093573, NCT01093573, NCT02634827, NCT01846624).

Another potential use of midostaurin in AML is in core binding leukemia (CBF), with or without *FLT3* mutations, as KIT mutations are commonly seen and thought to impact prognosis in CBFs.[77,78] This is currently being explored in two clinical trials (NCT03686345, NCT01830361). Post-transplant maintenance with midostaurin is also of interest in FLT3-mutated AML and is being evaluated in an ongoing-randomized Phase II clinical trial (NCT01883362; RADIUS trial) with preliminary data suggesting a trend for improved EFS and OS with post-allogeneic SCT midostaurin maintenance,[79] similar to what was noted with sorafenib in the SORMAIN trial, but not yet achieving statistical significance in the RADIUS trial. It must be noted though that midostaurin and sorafenib maintenance, particularly post-

Table 1 Ongoing Or Planned Clinical Trials Of Midostaurin In AML

#	NCT Number	Other Identifiers	Indication	Start Date	Status	Phase
1	NCT03951961	MAURITIUS	Midostaurin in MRD positive AML post-allogeneic SCT	July 1, 2019	Not yet recruiting	II
2	NCT03900949	NCI-2019-01726	Standard induction with GO and Midostaurin in newly diagnosed FLT3-mutated AML	March 21, 2019	Recruiting	I
3	NCT03836209	PrE0905	Gilteritinib vs Midostaurin in FLT3-mutated newly diagnosed AML	July 2019	Not yet recruiting	II
4	NCT03686345	REL-AML 001/2017	Midostaurin with standard chemotherapy in CBF leukemia	July 1, 2018	Recruiting	II
5	NCT03591510	CPKC412A2218	Midostaurin + chemotherapy in pediatric newly diagnosed FLT3-mutated AML (global study)	March 13, 2019	Recruiting	II
6	NCT03512197	CPKC412E2301	Midostaurin + chemotherapy in newly diagnosed FLT3 wildtype AML (global study)	January 7, 2018	Recruiting	III
7	NCT03379727	CPKC412A2408	Midostaurin + chemotherapy in induction and consolidation followed by 12 months of maintenance monotherapy in newly diagnosed FLT3-mutated AML.	February 13, 2018	Recruiting	III
8	NCT03280030	CPKC412A2220	Midostaurin + chemotherapy in induction and consolidation followed by maintenance monotherapy in newly diagnosed FLT3-mutated AML	April 6, 2018	Recruiting	II
9	NCT03258931	ARO-021	Crenolanib vs Midostaurin with induction and consolidation in newly diagnosed FLT3-mutated AML	August 15, 2018	Recruiting	III
10	NCT02634827	MC1483	Midostaurin + Decitabine in newly diagnosed elderly (>60yr) FLT3-mutated AML	December 30, 2015	Active, not recruiting	II
11	NCT01830361	TUD-MIDOKI-052	Midostaurin + chemotherapy in c-KIT or FLT3-mutated t(8;21) AML	April 2012	Active, not recruiting	II
12	NCT01477606	AMLSG 16-10	Midostaurin + chemotherapy in induction and consolidation followed by maintenance in FLT3-ITD AML	May 2012	Active, not recruiting	II
13	NCT00819546	08-269	Midostaurin + Everolimus in R/R AML or MDS	January 2009	Active, not recruiting	I
14	NCT00651261	CALGB-10,603	Midostaurin + chemotherapy in newly diagnosed AML	April 2008	Active, not recruiting	III

Abbreviations: FLT3, FMS-like tyrosine kinase; MRD, minimal residual disease; AML, acute myeloid leukemia; SCT, stem cell transplantation; GO, Gemtuzumab ozogamicin; CBF, core binding factor; R/R, relapsed/refractory.

allogeneic SCT, are associated with more toxicities and require frequent and liberal dose adjustments to allow patients to stay on therapy. As FLT3 inhibitors are more frequently being used in FLT3-mutated AML, the role of stem cell transplant needs to be better defined. In the RATIFY trial, patients who received midostaurin with induction/consolidation and then underwent subsequent SCT in first remission had the best outcomes, supporting the choice of transplant in the frontline setting once remission was achieved. Of note, midostaurin was recommended to be used as a maintenance for 1 year in this clinical trial preASCT or in patients who did not got to ASCT, but post-ASCT midostaurin maintenance was not part of the RATIFY trial. The duration of midostaurin and other TKI usage (such as BCR-ABL inhibitors in Ph+ ALL) is not yet definitely defined, both post-transplant and in patients who do not go for transplant. It is possible that longer FLT3 inhibitor maintenance beyond 1 year may change the prognostic significance of FLT3-ITD mutation and potentially even the need for SCT (especially is specific molecularly select, favorable groups) and this is being evaluated in ongoing Phase II studies.

Additional expected developments in the usage of midostaurin, particularly as we better understand the underlying mechanisms of resistance to TKIs in general and FLT3 inhibitors specifically, are rationally designed treatment combinations with agents targeting known resistance pathways. One expected combination is with Bcl-2 inhibitor venetoclax and HMA or LDAC (triple combination). As was discussed earlier, up-regulation of anti-apoptotic and down-regulation of pro-apoptotic proteins is a known major mechanism of resistance to FLT3 inhibitor therapy that may be circumvented with the addition of venetoclax. One report showed that FLT3-ITD cells have higher level of Bcl-2 compared to FLT3 wildtype cells.[80] In addition, venetoclax primary and secondary resistance appears to be driven by FLT3-ITD mutation.[81] MCL-1 has been reported to be an essential effector of FLT3-ITD-mediated drug resistance.[82] A number of FLT3 inhibitors down-regulate MCL1, and may thus reduce resistance to BCL2 inhibitors.[83] Hence, in addition to synergism with HMAs, the triple combination of midostaurin plus venetoclax with HMA (or LDAC) in FLT3-mutated AML is rational and its evaluation in clinical trial is anticipated in the near future.

In summary, a number of active trials combining midostaurin with other agents are ongoing (Table 1). We hope to identify and further refine in the coming years the patient subgroups with the greatest potential benefit from midostaurin, disease biomarkers of response and resistance, the optimal time of usage, and rationally designed treatment combinations that will result in improved efficacy and survival.

Disclosure

MA and HAA have no conflicts of interest in this work. TK has received honoraria and consulting from Novartis. FRK has received research support from Astellas, and honoraria from Novartis and Astellas. ND has received honoraria and research support from Jazz, Pfizer, Daiichi-Sankyo, BMS, Astellas, Novartis, Celgene, Abbvie, Daiichi-Sankyo and Genentech. The authors report no other conflicts of interest in this work.

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