Clinical use of FLT3 inhibitors in acute myeloid leukemia

Grerk Sutamtewagul
Carlos E Vigil

Division of Hematology, Oncology and
Blood and Marrow Transplantation,
University of Iowa Hospitals and
Clinics, Iowa City, IA, USA

Abstract: Acute myeloid leukemia (AML) is a highly heterogeneous disease. Mutation with internal tandem duplication of fms-like tyrosine kinase-3 (*FLT3*-ITD) is one of the two most common driver mutations and the presence of *FLT3*-ITD delivers poor prognosis. A number of ongoing clinical efforts are focused on FLT3 inhibitor use to improve the outcomes of this otherwise difficult leukemia. Midostaurin has been shown to improve outcomes in *FLT3*-mutated AML in the frontline setting. Several FLT3 inhibitors, especially second-generation agents, have shown clinically meaningful activity in relapsed or refractory AML and in patients not amenable to intensive therapy. In this article, we briefly review the biology of FLT3 in the physiological state and its role in leukemogenesis. We present a detailed review of current clinical evidence of FLT3 inhibitors and their use in the induction, treatment of relapsed or refractory disease, and maintenance setting.

Keywords: fms-like tyrosine kinase 3, FLT3 inhibitor, FLT3-ITD mutation, leukemia, myeloid, acute, protein kinase inhibitors

Introduction

Acute myeloid leukemia (AML) is a highly heterogeneous disease defined mainly by cytogenetic or mutational characteristics.¹ Mutation with internal tandem duplication of fms-like tyrosine kinase-3 (*FLT3*-ITD) is one of the two most common driver mutations, along with NPM mutation, identified in 22% of a large study cohort of AML.² *FLT3*-ITD is one of the earliest molecular markers described in AML, first reported in 1996³ and later associated with marked leukocytosis, higher blast percentage, increased risk of relapse, and poor overall survival (OS).⁴

A high total mutant level adversely impacts the rate of relapse and OS, especially when the allelic ratio is >50%.^{5–7} The 2017 European Leukemia Net risk stratification classified *FLT3*-ITD into low (<50%) and high (≥50%) allelic burden by DNA fragment analysis; therefore, AML with mutated *NPM1* and *FLT3*-ITD^{low} was reclassified into a favorable risk category.⁸ Hematopoietic stem cell transplant (HSCT) is not recommended in first remission in these favorable risk patients since no OS benefit is found.⁹ However, this allelic burden cut-point is being challenged as there are some data indicating that even low allelic burden by this definition is not necessarily associated with better prognosis.¹⁰

Patients with wild-type *NPM1* and *FLT3*-ITD^{high} have a poor prognosis, with 5-year relapse rate as high as 79% and 5-year OS rate of only 15%.⁵ With allogeneic HSCT, relapse is still high, with a 2-year cumulative incidence of relapse of 44%–46%.⁹ These data indicate the unmet clinical need and warrant experimental therapeutic approaches.

Correspondence: Carlos E Vigil
Division of Hematology, Oncology and
Bone Marrow Transplantation, University
of Iowa Hospitals and Clinics,
200 Hawkins Dr, C32 GH, Iowa City,
IA 52242, USA
Tel +1 319 356 1206
Email carlos-vigil@uiowa.edu

FLT3 is a targetable tyrosine kinase. Several clinical trials have focused on various FLT3 inhibitors for each setting of AML treatment – frontline therapy, treatment of relapsed refractory disease, and as maintenance therapy after allogeneic HSCT. Moreover, many second-generation FLT3 inhibitor trials are ongoing, as reviewed later in the text.

Function of FLT3 in normal hematopoiesis

FLT3 belongs to the class III receptor tyrosine kinase (RTK) family that also includes c-KIT, colony-stimulating factor one receptor (formerly FMS), and platelet-derived growth factor receptors α and β (PDGFRA and PDGFRB). Class III RTKs have five immunoglobulin G-like motifs within their extracellular domain. The outer three act as a ligand-binding domain and the remaining two tyrosine kinase domains (TKDs) are located in the C-terminal, intracytoplasmic side, and are usually in an auto-inhibited state when they are not bound to their ligands. Upon ligand binding, class III RTKs oligomerize (homodimerize in the case of FLT3), causing transphosphorylation of tyrosine residues within the TKDs, leading to their activation and signal transduction through PI3K and MAPK pathways.¹¹ FLT3 function is involved in normal hematopoiesis and is normally expressed in early hematopoietic progenitor cells including uncommitted precursors, early progenitors with lymphoid and myeloid potential, common myeloid progenitors, granulocyte-macrophage progenitors (GMPs), and common lymphoid progenitors. FLT3 is not expressed in the megakaryocyte-erythrocyte progenitor. However, knockout mice with *Flt3*^{-/-} have shown no significant abnormality in hematopoiesis aside from a reduction in B-cell progenitors, indicating that presence of FLT3 signaling is not essential for hematopoiesis or granulopoiesis.¹² FLT3 signaling is important in the growth of pre-GMPs but with significant heterogeneity among stem cells.¹³ FLT3 signaling also plays a crucial role in B-lymphopoiesis.¹⁴

FLT3 mutation in myeloid neoplasms

FLT3 has been found to be overexpressed in many AMLs, myelodysplastic syndrome, B-lineage acute lymphoblastic leukemias, and, in a smaller proportion, other leukemias.¹⁵ Aberrancy in the *FLT3* gene is one of the most common abnormalities and is among the first genetic abnormalities identified in AML. There are two major types of *FLT3* mutations: internal tandem duplication (ITD) and point mutations in the TKD.

FLT3-ITD is more common than the TKD mutation. It can involve highly variable numbers of in-frame base

pair duplications, from three to more than 400 in the juxta-membrane domain. Elongation of this juxta-membrane domain allows homodimerization of RTKs without ligand binding, which results in constitutive activation. In addition to the PI3K and MAPK pathways, suppression of antiapoptotic FOXO31 can confer survival advantage, and activation of STAT5 may lead to genomic instability through generation of reactive oxygen species and subsequent double-strand DNA breakage, both of which may be associated with poor outcomes.^{4,14} STAT5 activation is an example of a different qualitative action of the mutated FLT3 that would not usually occur with binding of ligand to wild-type FLT3.¹⁶ The role of *FLT3*-ITD in leukemogenesis has been clarified in several cell lines and in vivo studies. A knock-in approach in which human *FLT3*-ITD was inserted into the normal *Flt3* locus in mice showed that mice with *Flt3*^{wt/ITD} developed splenomegaly, leukocytosis, and expansion of myeloid cells, all of which are characteristics of myeloproliferative disease, indicating that *FLT3*-ITD can enhance myeloid expansion but not at a level adequate to cause AML.¹⁷

FLT3-TKD mutation is less common, found in approximately 5%–10% of all AML cases. Several *FLT3*-TKD point mutations can cause ligand-independent RTK activation. The most common mutation occurs in the TKD2 at the D835 gatekeeper position.¹⁸ These point mutations in the intracellular TKD may signal through different transduction pathways from *FLT3*-ITD that could explain its smaller effect on prognosis. *FLT3*-TKD mutation seems to have prognostic significance only through interaction with other genes. For example, presence of both *KMT2A* (formerly *MLL*) partial tandem duplication and *FLT3*-TKD is associated with poorer prognosis, while co-occurrence of *NPM1* and *FLT3*-TKD is associated with improved OS.²

Wild-type *FLT3* overexpression is also found in up to 70%–100% of cases of AML. Clinical data on prognosis of FLT3 overexpression are scarce, though association with poor prognosis has been reported.¹⁹ Overexpression of *FLT3* may partly explain the beneficial effect of FLT3 inhibition in wild-type FLT3 AML.

While *FLT3* mutations, especially *FLT3*-ITD, are common in acute promyelocytic leukemia, adverse effects on clinical outcomes are not consistent among published studies.²⁰

Therapeutic agents targeting FLT3: pharmacology and development

Due to the high frequency and adverse significance of FLT3, several FLT3 tyrosine kinase inhibitors (FLT3 inhibitors) have been developed. These agents act via competitive inhibition

with adenosine triphosphate on the TKD, resulting in decreased autophosphorylation and its successive activation.

First-generation FLT3 inhibitors are relatively nonspecific for FLT3 and usually inhibit other class III RTKs such as KIT and PDGFR.²¹ Off-target inhibition may be associated with increased toxicity and modest clinical benefit. First-generation FLT3 inhibitors include tandutinib (MLN518, CT53518), sunitinib, sorafenib, midostaurin (PKC412), and lestaurtinib (CEP701).

Second-generation FLT3 inhibitors, including quizartinib (AC220), crenolanib (CP-868–596), ponatinib, pacritinib (SB1518), and gilteritinib (ASP2215), are more potent and selective. These drugs are currently undergoing testing in various clinical settings (Table 1).

There are several FLT3 inhibitors for AML in current Phase I or Phase I/II development including E6201 (dual MEK/FLT3 inhibitor, NCT05418000), TAK-659 (dual SYK/FLT3 inhibitor, NCT02323113), SKLB1028 (multikinase inhibitor, NCT02859948), and CT053PTSA (multikinase inhibitor, NCT03125876). Most other non-TKI agents targeting FLT3 are in preclinical development, including FLYSYN (chimeric and Fc-optimized IgG1 antibody to FLT3, NCT02789254), miR-150 nanoparticles,¹⁹ FLT3-redIRECTED chimeric antigen receptor T-cell immunotherapy,²² and arsenic trioxide.²³

FLT3 inhibitor in combination with intensive induction chemotherapy in newly diagnosed AML

AML with *FLT3* mutation, especially *FLT3*-ITD, has a relatively high relapse rate. Although one could hypothesize that targeting FLT3 in the upfront treatment of *FLT3*-mutated AML may result in better outcome, there are still several problems. First, certain first-generation FLT3 inhibitors may have inadequate inhibitory properties that may halt the clinical efficacy shown in lestaurtinib. Second, there are multiple subclones present even at the time of diagnosis of AML,²⁴ and *FLT3* mutation is known to be a later event and present in only some subclones. In vitro data have shown that in newly diagnosed *FLT3*-mutated AML, the AML cells did not seem to be highly “addicted” to FLT3 signaling as in the relapsed setting.²⁵ Monotherapy with selective FLT3 inhibitor in this setting is very unlikely to yield a complete remission; thus, combination with standard induction chemotherapy along with the use of multi-targeted TKIs is likely needed. However, complete in vivo inhibition of FLT3 by the first-generation TKI is difficult due to excess toxicity from this off-target inhibition. It has been proposed that the use of first-generation TKI during induction followed by

more specific second-generation maintenance could be the optimal approach.²⁶

First-generation FLT3 inhibitors

Sorafenib is a multikinase inhibitor against intracellular Raf kinases and cell surface kinase receptors (VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- β , cKIT, FLT3, and RET). These cell surface kinase receptors are present in AML and bone marrow stromal cells, supporting AML cell proliferation and survival. Serve et al reported a Phase III study of sorafenib sequentially administered after intensive chemotherapy in elderly patients.²⁷ Twenty-eight of 211 patients had *FLT3*-ITD-positive AML. There was no difference in response rate, event-free survival (EFS) or OS in either the overall or the *FLT3*-mutated populations. A similar treatment schedule was also tested in a younger population in a randomized Phase II study.²⁸ This showed statistically significant improvement in 3-year EFS in the sorafenib group vs placebo (40% and 22%, respectively; $P=0.013$). However, the sorafenib treatment also demonstrated an increase in toxicity, especially diarrhea and skin rash. There was no difference in OS. In a small subgroup with *FLT3*-ITD ($n=43$), sorafenib seemed to result in better, though not statistically significant, relapse-free survival (RFS) and OS.

Midostaurin is also a multikinase inhibitor, originally developed to target protein kinase C. It was also found to inhibit wild-type and mutant (both ITD and TKD) FLT3, PDGFR- α and β , VEGFR-2, and KIT (wild-type and D816V mutant). The RATIFY study (CALGB 10603), a Phase III, randomized, controlled trial, has shown that midostaurin, added to intensive induction and consolidation therapy followed by 1-year maintenance, leads to a significant improvement of OS (median OS 74.7 vs 25.6 months, $P=0.009$) and EFS, even though complete response (CR) rates were not different between midostaurin and placebo arms.²⁹ The OS benefit does not seem to vary by the type of *FLT3* mutation (ITD-high, ITD-low, or TKD) and is maintained in both censored and uncensored analyses at the time of transplant. Midostaurin was also well tolerated, with the most common adverse events being nausea and skin rash. Anemia was also found to be more common in the midostaurin group. In clinical practice, most patients also complain of its distinctive unpleasant odor. The results of the RATIFY study led to the approval of midostaurin by the US FDA in April 2017 for use in newly diagnosed *FLT3* mutation-positive AML. Currently, this is the only approved FLT3 inhibitor.

Lestaurtinib is another first-generation FLT3 inhibitor with broad-spectrum activity, including tropomyosin receptor kinase A, JAK2, and other kinases similar to midostaurin.

Table 1 Selected clinical trials of agents targeting FLT3 or for FLT3 mutation-positive AML or MDS in adults

Drug	Phase/year published, presented	Study population	N (FTL3)	Treatment regimen(s)	Response	Survival	Adverse reactions
Frontline treatment for newly diagnosed AML							
First-generation FLT3 inhibitors							
Lestaurtinib ³⁰ (CEP701)	Phase III, 2017	<ul style="list-style-type: none"> Newly diagnosed AML, high-risk MDS, suitable for intensive therapy Presence of FLT3 mutation to be randomized to lestaurtinib Median age 49 	500	<ul style="list-style-type: none"> Intensive chemotherapy (varied) Lestaurtinib 80 mg bid starting 2 days after each chemo up to 28 days, increased to 100 mg bid if tolerated 	ORR (CR+CRi) 91%–93% vs 92%–96% (NS)	<ul style="list-style-type: none"> 5-y OS 43%–50% vs 41%–45% (NS) 5-y RFS 39%–40% vs 34%–36% (NS) 	Nausea, diarrhea, increased bilirubin
Midostaurin ⁵² (PKC412)	Phase IB, 2012	<ul style="list-style-type: none"> AML age 18–60, KPS ≥ 70 Mutation in FLT3 not required Median age 39 	69 (13)	<ul style="list-style-type: none"> Cytarabine 200 mg/m²/d day 1–7 Daurorubicin 60 mg/m²/d day 1–3 Midostaurin 50 or 100 mg bid day 1–7 and 15–21 or day 8–21 	<ul style="list-style-type: none"> All pts: CR 80% FLT3 mutant: CR 12/13 (92%) 	FLT3 mutant 1-y DFS 50% 1-y OS 85% 2-y OS 62%	Nausea, diarrhea, vomiting
Midostaurin ²⁹	Phase III, 2017	<ul style="list-style-type: none"> AML age 18–59 Presence of FLT3 mutation required (TKD or ITD) Median age 47.9 	717	<ul style="list-style-type: none"> Cytarabine 200 mg/m²/d day 1–7 Daurorubicin 60 mg/m²/d day 1–3 Midostaurin 50 mg bid or placebo days 8–21 Midostaurin 50 mg bid day 8–21 with high-dose cytarabine consolidation Midostaurin 50 mg bid maintenance for 12 of 28-day cycles 	CR 58.9% vs 53.5% (P=0.15)	<ul style="list-style-type: none"> mOS 74.7 vs 25.6 mo (P=0.009) 4-y OS 51.4% vs 44.3% mEFS 8.2 vs 3.0 mo 4-y EFS 28.2% vs 20.6% 	Anemia, rash, nausea
Sorafenib ^{53,54}	Phase I/II, 2010, 2014	<ul style="list-style-type: none"> Newly diagnosed AML for Phase II (R/R for Phase I) Mutation in FLT3 not required Median age 53 	62 (23)	<ul style="list-style-type: none"> Cytarabine 1.5 g/m²/d day 1–4 Idarubicin 12 mg/m²/d day 1–3 Sorafenib (MTD) 400 mg bid 	<ul style="list-style-type: none"> All pts: CR 79%; CRi 8% 3 pts to allogeneic HSCT FLT3-ITD (n=19): mDFS 9.9 mo; mOS 15.5 mo 17/19; CRi 1/19 	All pts: mDFS 13.8 mo; mOS 29 mo FLT3-ITD (n=19): mDFS 9.9 mo; mOS 15.5 mo	Nausea, vomiting, diarrhea
Sorafenib ²⁷	Phase III, 2013	<ul style="list-style-type: none"> Newly diagnosed AML, age > 60 Mutation in FLT3 not required Median age 68 	211 (28)	<ul style="list-style-type: none"> Cytarabine 100 mg/m²/d day 1–7 Daurorubicin 60 mg/m²/d day 3–5 Sorafenib 400 mg bid start day 3 or placebo 	<ul style="list-style-type: none"> All pts: CR 48 vs 60% (NS); CRi 9 vs 4%; ORR 57 vs 64% (NS) FLT3-ITD (n=28): CR 40 vs 77% (NS) 	All pts: mEFS 5 vs 7 mo (NS); mOS 13 vs 15 mo (NS)	Not reported

Sorafenib ²⁸	Phase II, 2015	<ul style="list-style-type: none"> Newly diagnosed AML, age ≤ 60 Mutation in <i>FLT3</i> not required Median age 50 	276 (46)	<p>Induction:</p> <ul style="list-style-type: none"> Cytarabine 100 mg/m²/d day 1–7 Daurorubicin 60 mg/m²/d day 3–5 Sorafenib 400 mg bid day 10–19 or placebo <p>Consolidation:</p> <ul style="list-style-type: none"> HiDAC $\pm$ sorafenib 400 mg bid day 8 to 3 days before next cycle or Allogeneic HSCT <p>Maintenance:</p> <ul style="list-style-type: none"> Sorafenib 400 mg bid or placebo 	Not reported	<ul style="list-style-type: none"> All pts: mOS HR 0.86, NS; mEFS 21 vs 9 mo; 3-y EFS 40% vs 22% <i>FLT3</i>-ITD (n=46): mEFS 5 vs 6 mo; mRFS 18 vs 6 mo; mOS NR vs 19 mo 	Fever, diarrhea, rash, bleeding, hand-foot skin reaction, hypertension
Sunitinib ⁵⁵	Phase I/II, 2015	<ul style="list-style-type: none"> Newly diagnosed AML, age ≥ 60 Presence of <i>FLT3</i>-ITD or TKD Median age 70.2 	22	<ul style="list-style-type: none"> Cytarabine 100 mg/m²/d day 1–7 Daurorubicin 60 mg/m²/d day 1–3 Sunitinib MTD 25 mg/d day 1–7 	<ul style="list-style-type: none"> CR 45.5%; CRi 13.6%; PR 9.1% 3 pts to allogeneic HSCT 	All pts: mOS 1.6 y; mRFS 1.0 y; mEFS 0.4 y	Myelosuppression
Second-generation FLT3 inhibitors							
Crenolanib ⁵⁶ (AC220)	Phase II, 2016	<ul style="list-style-type: none"> Newly diagnosed AML, age ≥ 18 Presence of <i>FLT3</i>-ITD or TKD Median age 55 	26	<p>Induction:</p> <ul style="list-style-type: none"> Cytarabine 100 mg/m²/d day 1–7 Daurorubicin 90 mg/m²/d or Idarubicin 12 mg/m²/d day 1–3 (Daurorubicin 60 mg/m² for age ≥ 60) Crenolanib 100 mg TID start day 9 until 72 hrs prior to next chemo <p>Consolidation:</p> <ul style="list-style-type: none"> Cytarabine 3 g/m² (or 1 g/m² for age ≥ 60) day 1–6 Crenolanib 100 mg TID start day 7 Eligible pts proceed to allogeneic HSCT 	ORR 96%; CR 88%	Median follow-up 6.2 mo, OS rate 23/26 (88%)	Periorbital edema, delayed count recovery, LFT elevation, nausea, rash
Relapsed and refractory disease or patients not amenable to conventional therapy							
First-generation FLT3 inhibitors							
Lestaurtinib ³⁷ (CEP701)	Phase II, 2006	<ul style="list-style-type: none"> Newly diagnosed AML, unfit for intensive chemo (age > 70 or age 60–70 with ECOG PS 2 or cardiac disease) 	29	Monotherapy (60 mg bid with escalation to 80 mg bid from day 29)	<ul style="list-style-type: none"> All pts: CR 0%; PR 0% 5 pts with <i>FLT3</i> mutation: CR 0%; PR 0% 	Not reported	Nausea, vomiting, diarrhea, increased ALP

(Continued)

Table 1 (Continued)

Drug	Phase/year published, presented	Study population	N (FTL3)	Treatment regimen(s)	Response	Survival	Adverse reactions
		<ul style="list-style-type: none"> • Mutation in <i>FLT3</i> not required • Median age 73 					
Lestaurtinib ⁴⁰ (CEP701)	Phase III, 2011	<ul style="list-style-type: none"> • <i>FLT3</i> mutant AML in first relapse (ITD or TKD) • Median age 54 (chemo), 59 (chemo + lestaurtinib) 	224	Relapse in 1–6 mo: MEC <ul style="list-style-type: none"> • Mitoxantrone 8 mg/m²/d day 1–5 • Etoposide 100 mg/m²/d day 1–5 • Cytarabine 1,000 mg/m²/d day 1–5 Relapse in 6–24 mo: HiDAC <ul style="list-style-type: none"> • Cytarabine 1,500 mg/m²/d day 1–5 • Randomized to lestaurtinib 80 mg q12 h day 7 up to day 112 based on clinical benefit 	CR 17% vs 12% (P=0.25)	mOS no difference (approx 140 days)	24% (21% vs 7%) discontinuation rate due to toxicity, mostly due to infection
Midostaurin ³⁹ (PKC412)	Phase I/II, 2010	<ul style="list-style-type: none"> • AML, MDS (RAEB), CMML • Mutation in <i>FLT3</i> not required • 64% were age ≥65 	95 (35)	Monotherapy (50 or 100 mg bid)	<i>FLT3</i> mutant CR 0%, PR 1/35 Blast response 49%	<ul style="list-style-type: none"> • All pts: mOS 130 days • <i>FLT3</i> mutant: mOS 100 days 	Nausea, vomiting
Midostaurin ⁵⁷	Phase I, 2006	<ul style="list-style-type: none"> • AML newly diagnosed or R/R • Age ≥70 or not suitable for standard therapy • Median age 73 	17 (0)	<ul style="list-style-type: none"> • Azacitidine 75 mg/m² IV day 1–7 • Escalating dose of midostaurin day 8–21 (MTD 75 mg bid) 	CR 3/17	mOS 6 mo	Neutropenic fever, neutropenia
Midostaurin ⁴²	Phase I/II, 2015	<ul style="list-style-type: none"> • AML, MDS • Mutation in <i>FLT3</i> not required • Median age 65 	54 (40)	<ul style="list-style-type: none"> • Azacitidine day 1–7 • Midostaurin (MTD 50 mg bid) 	<ul style="list-style-type: none"> • All pts: ORR 26%; CR 2%, CRi 11%; DoR 20 wks • <i>FLT3</i>-ITD unexposed to FLT3i (n=27): ORR 33%; DoR 30 wks 	mOS 22 wks	Neutropenia, thrombocytopenia, anemia, decreased LVEF, diarrhea, nausea, vomiting
Sorafenib ⁴¹	Phase I/II, 2013	<ul style="list-style-type: none"> • AML • Mutation in <i>FLT3</i> not required (FLT3-ITD detected in 40 pts (93%)) • Median age 64 	43 (40)	<ul style="list-style-type: none"> • Azacitidine 75 mg/m²/d day 1–7 • Sorafenib 400 mg bid • 4–8-week cycle 	<ul style="list-style-type: none"> • CR 16%; CRi 27%; DoR 2.3 mo • Six pts to allogeneic HSCT 	mOS 6.2 mo	Thrombocytopenia, neutropenia, anemia, fatigue

Sunitinib ⁵⁸	Phase I, 2005	<ul style="list-style-type: none"> • AML • Mutation in <i>FLT3</i> not required • Median age 72 	16	Monotherapy (MTD 50 mg daily)	<ul style="list-style-type: none"> • <i>FLT3</i>-ITD: PR: 2/2 • <i>FLT3</i>-TKD: CRi 1/2; PR 1/2 • Non-<i>FLT3</i>: PR: 2/7 	Not reported	Nausea, vomiting, edema, hypertension, bleeding
Tandutinib ³⁸ (MLN518, CT53518)	Phase I, 2006	<ul style="list-style-type: none"> • AML, MDS-EB, CMML • Mutation in <i>FLT3</i> not required • Median age 70.5 	40	Monotherapy (MTD 525 mg bid)	<ul style="list-style-type: none"> • CR 0%; PR 0% • <i>FLT3</i>-ITD (n=2): >99% decrease in blast count 	Not reported	Myelosuppression, increased AST, ALT, muscle weakness
Second-generation FLT3 inhibitors							
Crenolanib ³⁹	Phase II, 2014	<ul style="list-style-type: none"> • R/R <i>FLT3</i>-mutated AML • Median age 61 	38	Crenolanib 200 mg/d in 3 divided dose monotherapy	ORR 47%; CRi 12%; hematological improvement 32%	mEFS 8 wk mOS 19 wk	Abdominal pain, nausea
Crenolanib ⁴⁴	Phase II, 2016	<ul style="list-style-type: none"> • R/R <i>FLT3</i>-mutated AML • Median age 60 	69	<ul style="list-style-type: none"> • Crenolanib 100 mg TID (43 pts) • Crenolanib 66 mg/m² TID (26 pts) 	<ul style="list-style-type: none"> • TKI-naïve: ORR 47%; CRi 37% • Prior TKI: mOS 94 days • ORR 28%; CRi 15% • 6 pts able to go HSCT 	TKI-naïve mOS 238 days Prior TKI mOS 94 days	Nausea, vomiting, AST or ALT elevation
Crenolanib ⁴⁶	Phase II, 2016	<ul style="list-style-type: none"> • First relapsed or primary refractory AML • <i>FLT3</i> mutation not required • Median age 64 	8 (3)	<ul style="list-style-type: none"> • Cytarabine 1 g/m²/d day 1–6 • Mitoxantrone 10 mg/m² day 1–3 • Crenolanib 100 mg TID start day 8 to max of 49 days/cycle 	CR 2/6, CRi 2/6	Not reported	AST, ALT elevation
Crenolanib ³³	Phase I, 2016	<ul style="list-style-type: none"> • R/R <i>FLT3</i>-mutated AML • Median age 51 	13	<ul style="list-style-type: none"> • Idarubicin 12 mg/m²/d day 1–3 • Cytarabine 1.5 g/m²/d day 1–4 (or 1–3 if age >60) • Crenolanib 60–100 mg TID start day 5 continued until 72 hr prior to next cycle (no dose-limiting toxicity observed) 	ORR 36% (1 CR, 3 CRi)	mOS 259 d	Nausea, vomiting, diarrhea, abdominal pain
Gilteritinib ⁴³ (ASP2215)	Phase I/II, 2017	<ul style="list-style-type: none"> • R/R AML • <i>FLT3</i> mutation not required • Median age 64 (expansion cohort) 	265 (191)	Monotherapy (MTD 300 mg/d)	ORR 40%; CR 8%; CRi 22%; DoR 17 wk	mOS 25 wk – <i>FLT3</i> mut 30 wk – <i>FLT3</i> wt 17 wk	Diarrhea, fatigue, elevated AST, ALT

(Continued)

Table 1 (Continued)

Drug	Phase/year published, presented	Study population	N (FTL3)	Treatment regimen(s)	Response	Survival	Adverse reactions
Quizartinib ⁶⁰ (AC220, ASP2689)	Phase I, 2013	<ul style="list-style-type: none"> AML R/R or not amenable to standard chemotherapy FLT3 mutation is not required for enrollment Median age 59.5 	76 (17)	Monotherapy (or with hydroxyurea up to 5 days) MTD 200 mg/day	CR 13%; PR 17%; mDoR 13 weeks	mOS 14 wk (18 wk for FLT3-ITD+; 35 wk for pt achieving CR)	QT prolongation, nausea, dysgeusia, vomiting
Quizartinib ⁶¹	Phase II, 2014	R/R FLT3-ITD+ AML after second-line therapy or HSCT	76	Quizartinib 30 mg/d (A) or 60 mg/d (B) monotherapy	CRc 47%; ORR 61% (A), 71% (B); DoR 22–26 weeks	mOS 20.7 wk (A) mOS 25.4 wk (B)	QTc prolongation, diarrhea
Quizartinib ⁶²	Phase I/II, 2016	<ul style="list-style-type: none"> Phase II: AML, high-risk MDS, CMML previously untreated age >60 or any age for first salvage treatment FLT3-ITD required for phase II enrollment Median age 67 	52 (48)	<ul style="list-style-type: none"> Azacitidine 75 mg/m²/d day 1–7 (or cytarabine 20 mg sc bid day 1–10) every 28 days Quizartinib 60 or 90 mg daily 	<ul style="list-style-type: none"> ORR 67%; CR 8, CRp 7, CRI 18, PR 2 FLT3-ITD: ORR 73% 	mOS 14.8 mo (7.5 mo for LDAC and not reached for AZA) mEFS not reached	Hypokalemia, hypotension, hypophosphatemia, hyponatremia, hypocalcemia
Maintenance therapy							
Sorafenib ⁴⁸	Phase I, 2014	<ul style="list-style-type: none"> AML with FLT3-ITD mutation who underwent first allogeneic HSCT, ECOG PS 0–2 Median age 54 	16	Sorafenib started between day +45 to +120, continuous dosing (MTD 400 mg bid)		2-y PFS 72%; 2-y OS 78%	Rash, diarrhea, nausea, anemia, thrombocytopenia

Abbreviations: AML, acute myeloid leukemia; CR, complete response; CRI, incomplete hematologic recovery; DFS, disease-free survival; DoR, duration of response; EFS, event-free survival; FLT3, fms-like tyrosine kinase-3; HSCT, hematopoietic stem cell transplant; ITD, internal tandem duplication; MDS, myelodysplastic syndromes; OS, overall survival; PR, partial response; RFS, relapse-free survival; TKD, tyrosine kinase domain; d, days; wk, weeks; mo, months; pts, patients.

However, one Phase III, randomized study of lestaurtinib administered sequentially to intensive induction chemotherapy demonstrated no OS or RFS benefit.³⁰ A correlative study as a part of the trial showed OS and RFS benefit in patients who achieved at least 85% FLT3 inhibition. The difference in outcomes between midostaurin and lestaurtinib indicates the importance of the level of FLT3 inhibition and possibly maintenance use after induction chemotherapy.

Second-generation FLT3 inhibitors

Crenolanib is a selective FLT3 inhibitor and is active against both ITD and TKD mutants.³¹ It also inhibits PDGFR but not c-KIT. This dual FLT3 inhibition feature is important since it has been observed that relapse after initial response to FLT3 inhibitor could emerge from the acquired TKD mutation, especially at the D835 and F691 gatekeeper positions.³² Preliminary results of an ongoing Phase II study of crenolanib sequentially added to an intensive induction regimen (NCT02283177) have shown high efficacy in newly diagnosed *FLT3*-mutated AML, demonstrating an overall response rate (ORR) of 96% (CR 88%) and an OS rate of 88%, with a median follow-up of 6.2 months.³³ Moreover, this combination has also resulted in minimal residual disease-negative status (measured by flow cytometry) in 80% of patients.³⁴ A Phase III study of crenolanib vs midostaurin in this setting has been planned (NCT03258931). One of the drawbacks of crenolanib is its short half-life (6–8 hours) without any accumulation after chronic dosing; thus, a thrice-daily dosing regimen is required.

Gilteritinib is a pan-FLT3 and AXL inhibitor. A Phase I clinical trial is ongoing to evaluate the combination of gilteritinib and cytarabine/idarubicin induction followed by consolidation and gilteritinib maintenance (NCT02236013). Preliminary results show a CR rate of 82.6% in *FLT3*-mutated patients.³⁵ It is being tested for maintenance after first CR and in combination with azacitidine for patients not amenable to intensive treatment.

Quizartinib is a selective inhibitor of FLT3-ITD but is not active against the TKD variant, as demonstrated in patients who experienced relapse after CR from quizartinib acquired the TKD mutation (either D385 or F691).³⁶ A Phase III QuANTUM-First trial is ongoing to evaluate its efficacy in newly diagnosed patients (NCT02668653).

FLT3 inhibitor in relapsed/refractory AML or patients not amenable to conventional therapy

As already noted, relapse of FLT3-mutated subclones is addicted to FLT3 signaling.²⁵ It is more reasonable to use

a potent selective FLT3 inhibitor, especially the agents that possess an activity against both *FLT3*-ITD and TKD variants, such as gilteritinib and crenolanib. Overall response rates of first-generation FLT3 inhibitors to date have ranged from only 0%–3% as monotherapy (lestaurtinib,³⁷ tandutinib,³⁸ and midostaurin³⁹) to 20%–40% when combined with azacitidine or other chemotherapy.^{40–42} Although the response rate of second-generation FLT3 inhibitor appears to be 40%–50% as monotherapy, duration of response (DoR) is relatively short (around 20 weeks); thus, benefit without allogeneic HSCT may not be clinically meaningful. Monotherapy with second-generation FLT3 inhibitors usually induces complete response with incomplete hematologic recovery (CRi) for reasons not yet elucidated.⁴³ Some monotherapy clinical trials include newly diagnosed patients who are not fit for intensive therapy.

First-generation FLT3 inhibitors

Midostaurin monotherapy has yielded a disappointing response rate in relapsed/refractory patients. A phase IIB study demonstrated a 71% “blast response” rate (defined by >50% reduction in peripheral blood or bone marrow blast count) in *FLT3*-mutated AML; however, no patient experienced CR and only a few experienced partial response (PR).³⁹ An attempt to improve response in combination with azacitidine has demonstrated an increase in response rate (33%) with DoR of 30 weeks in a Phase I/II study.⁴²

Sorafenib in combination with azacitidine was tested in a Phase I/II study, with a 16% CR rate and 27% CRi.⁴¹ In this study, six patients were able to undergo allogeneic HSCT. This combination is quite well tolerated despite several patients experiencing grade 3–4 rash. One of the benefits of sorafenib is that it is readily available for off-label use.

Second-generation FLT3 inhibitors

Crenolanib monotherapy is currently in ongoing trials in multiply relapsed or refractory AML (NCT01657682, NCT01522469).⁴⁴ To date, TKI-naïve patients have had a better response (ORR 50%; 39% CRi and 11% PR) compared to patients who previously received TKIs (ORR 31%, CRi 17%). Median OS has been highest in the TKI-naïve, *FLT3*-ITD group (238 days) and worst in dual *FLT3*-ITD and TKD patients who previously received TKI (63 days). Elevations in aspartate aminotransferase and alanine aminotransferase have been common, but of low grade, and the rate of drug discontinuation due to adverse events is low. Crenolanib in combination with idarubicin and high-dose cytarabine as induction followed by allogeneic HSCT or consolidation

and crenolanib maintenance so far has shown one CR and three CRi in eleven evaluable patients (NCT02400281).⁴⁵ Another combination Phase I/II study with high-dose cytarabine and mitoxantrone (HAM) showed two CR and two CRi from eight evaluable patients and was well tolerated (NCT02626338).⁴⁶ A randomized Phase III study with this combination is ongoing (NCT02298166).

Gilteritinib monotherapy was studied in a Phase I/II trial for relapsed or refractory AML.⁴³ Most of the patients in this trial (191 of 256) harbored a *FLT3* mutation. ORR was 49% in patients who had *FLT3* mutation with 9% CR and 27% CRi. DoR was 20 weeks and median OS was 30 weeks. Only 19% of the patients underwent HSCT. Patients who received prior TKI had lower ORR (37%) and CR/CRi (26%). DoR was also shorter (14 weeks). Gilteritinib seems to be well tolerated. For less amenable patients, combination of gilteritinib and azacitidine is being tested in a Phase II/III study (NCT02752035).

Quizartinib monotherapy was shown to be effective in relapsed or refractory AML with *FLT3*-ITD mutation in the final results of a Phase II study, showing an ORR of 61% with a composite CR rate of 47%.⁴⁷ A Phase III QuANTUM-R study is currently evaluating the efficacy of quizartinib monotherapy in this setting compared to standard salvage chemotherapy (NCT02039726). Combination therapy trial with omacetaxine has also been planned (NCT03135054).

FLT3 inhibitor as maintenance therapy after induction/consolidation or allogeneic HSCT

Maintenance therapy is usually given to prevent relapse or prolong RFS. Ideal maintenance agent not only has to have efficacy but also has to be minimally toxic and relatively safe for long-term use. Currently, there are no Phase III data available to guide its use after allogeneic HSCT and only Phase I data were published for sorafenib. Several *FLT3* inhibitor protocols have integrated maintenance therapy after achieving first complete remission.

First-generation FLT3 inhibitors

In a Phase I study, sorafenib was used as maintenance therapy after HSCT in *FLT3*-ITD AML.⁴⁸ Maximal tolerated dose was 400 mg twice a day. One-year progression-free survival was 85%. Five out of 22 patients in this study discontinued treatment due to toxicity. A presented abstract from a similar study also showed that sorafenib was well-tolerated and seemed to be effective in the peri-transplant setting.⁴⁹

Sorafenib is also currently undergoing investigation in patients with *FLT3*-ITD mutated AML in complete or partial remission after induction therapy (NCT01578109).

Midostaurin maintenance for one year after combination therapy with induction and consolidation was included in the treatment protocol of the RATIFY trial.²⁹ This was thought to contribute to the efficacy and high transplant rate. Nevertheless, unplanned post hoc analysis of patients who received maintenance therapy within the RATIFY trial showed no difference in disease-free survival or OS in patients receiving midostaurin maintenance vs placebo.⁵⁰ Maintenance therapy seems to be well tolerated with a low rate of discontinuation due to adverse events (8% for midostaurin vs 6% for placebo). Of note, maintenance midostaurin is not included in the FDA-approved indication and usage guidelines. An extension clinical trial is planned to explore the benefit of midostaurin maintenance in elderly patients after allogeneic HSCT (NCT02723435).

Second-generation FLT3 inhibitors

At the time of this writing, there are several planned or ongoing clinical trials using second-generation *FLT3* inhibitor as maintenance therapy after first CR including gilteritinib (NCT02997202) and quizartinib (NCT02668653), or after allogeneic HSCT including crenolanib (NCT02400255) and gilteritinib (NCT02997202).

Resistance to FLT3 inhibition

Primary resistance to TKI treatment is not well elucidated. Secondary resistance is almost universally seen after prolonged use in various types of malignancies, usually due to emerging mutation in or near the kinase domain of the RTK. Some TKI-resistant mutations have a predominant pattern, eg, *ABL1* T315I in TKI-treated chronic myeloid leukemia or *EGFR* T790M in EGFR TKI-treated non-small-cell lung cancer. As previously noted, *FLT3* mutation is not the early event in the evolution of AML and thus not required for AML growth and proliferation; thus, loss of *FLT3* mutation is common and may result in loss of response to *FLT3* inhibitor (*FLT3* independence). Several secondary RTK-resistant mutations have been described after quizartinib use and could be heterogeneous even within a single patient.³⁶ Most of the mutations after quizartinib use happen at D835 residue. However, a subanalysis of the RATIFY study suggested that a *FLT3*-independent mechanism, such as loss of *FLT3*-ITD, is the main finding at relapse after midostaurin use.⁵¹

Conclusion

Several clinical efforts in FLT3 inhibition are currently underway, either as combination or monotherapy for controlling AML. The incorporation of midostaurin into the induction regimen, showing early significant improvement in EFS and OS, appears promising. Early phase studies especially on more selective FLT3 inhibitors as single agent or in combination with hypomethylating agents have shown potential benefits in patients who are not candidates for intensive therapy as well as those with relapsed disease.

The role of maintenance FLT3 inhibition is being explored in several ongoing studies. Confirmatory clinical trial results are eagerly awaited and may have the potential to change clinical practice in *FLT3*-mutated leukemia.

Disclosure

The authors report no conflicts of interest in this work.

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