BLOOD RESEARCH
VOLUME 57 · NUMBER S1
April 2022
REVIEW ARTICLE

FLT3 mutations in acute myeloid leukemia: a review focusing on clinically applicable drugs

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p-ISSN 2287-979X / e-ISSN 2288-0011
https://doi.org/10.5045/br.2022.2022017
Blood Res 2022;57:S32-S36.

Received on January 19, 2022
Revised on February 28, 2022
Accepted on February 28, 2022

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Abstract

FMS-like tyrosine kinase 3 (*FLT3*) mutations, the most frequently detected genetic aberrations in patients with acute myeloid leukemia (AML), are identified in approximately 30% of patients with newly diagnosed AML and are more common in patients with normal karyotypes. Since the discovery of *FLT3* mutations in AML, clinical trials have been actively conducted in patients with *FLT3* mutated AML, and *FLT3* inhibitors have been introduced into clinical practice. The current standard treatment for patients with newly diagnosed *FLT3*-mutated AML is 7+3 induction chemotherapy combined with midostaurin. Additionally, gilteritinib is more effective than salvage chemotherapy for relapsed or refractory *FLT3*-mutated AML. Ongoing trials are expected to provide additional treatment options depending on the disease state and patient vulnerability. This review summarizes information on clinically available *FLT3* inhibitors for the management of AML with *FLT3* mutations.

Key Words Acute myeloid leukemia, *FLT3*-ITD, *FLT3*-TKD, Tyrosine kinase inhibitor, Gilteritinib, Midostaurin

INTRODUCTION

Acute myeloid leukemia (AML), the most common type of acute leukemia in adults, is characterized by poor prognosis, with a 5-year overall survival (OS) of 35% and less than 10% in patients over 65 years of age [1]. Approximately 1,300 patients are diagnosed with AML annually in South Korea [1]. In recent decades, clonal chromosomal aberrations and molecular mutations have been recognized as the most important prognostic markers in AML [2-4]. FMS-like tyrosine kinase 3 (*FLT3*) mutations, the most commonly observed genetic aberrations in patients with AML, are identified in approximately 30% of patients with newly diagnosed AML and are more frequently observed in patients with normal karyotypes. Since 1996, when the *FLT3* internal tandem duplication (ITD) mutation was first identified in AML, numerous studies have been conducted regarding its relevance in prognosis [4-6]. Moreover, several advances have been made in targeting *FLT3* mutations, and currently, *FLT3* inhibitors are actively used in clinical practice [7-12]. In this review, we summarize information on clinically available *FLT3* inhibitors for the management of AML with *FLT3* mutations.

FLT3 MUTATIONS

FLT3 transcribes FLT3 transmembrane receptor tyrosine kinase. It is usually expressed in marrow stromal cells and hematopoietic cells and is activated by the FLT3 ligand. *FLT3* plays a key role in hematopoietic cell maturation and proliferation [13, 14]. *FLT3* mutations lead to the activation of tyrosine kinase by initiating FLT3 ligand-independent dimerization activation, which results in aberrant proliferation of leukemic cells.

FLT3 mutations are heterogeneous in terms of their load, size, and location [15], and are divided into two classes: ITD involving the juxtamembrane domain and that involving the tyrosine kinase domain (TKD). *FLT3*-ITD leads to a gain-of-function by inhibiting the negative regulatory function of the juxtamembrane domain [16, 17]. *FLT3*-TKD mutations are point mutations in the activation loop of *FLT3*, mainly represented by codon D835 or deletion of codon I836, which leads to a loss of auto-inhibition [18]. Both mutations lead to the activation of downstream proliferation

cascades [19, 20].

FLT3-ITD has a poor prognostic impact in patients with AML at diagnosis. However, *FLT3*-TKD mutations have not been associated with AML prognosis [4]. Owing to its prognostic significance and the choice of tyrosine kinase inhibitors, the European LeukemiaNet (ELN) recommends including molecular genetic testing for mutations of *FLT3*, both for ITD with allelic ratio and TKD, at diagnostic workup [4]. Testing for *FLT3* mutations at relapse is also necessary because acquisition or loss of *FLT3* mutations occurs due to clonal evolution in 20% of patients with relapsed AML [21, 22]. Rapid assays to identify *FLT3* mutations are essential for the use of *FLT3*-targeting agents [4, 7, 23]. Clinically available assays include *FLT3* polymerase chain reaction (PCR) and targeted DNA next-generation sequencing (NGS) [24]; however, their sensitivities and accuracies are different. Furthermore, turn-around time, an obstacle in deciding the treatment, varies according to the test. As NGS usually takes 2–4 weeks to generate mutation data, it is critical to obtain rapid results using *FLT3* PCR tests when treatment decisions need to be made quickly. In addition, to determine prognosis at diagnosis, it is necessary to conduct a quantitative analysis of *FLT3*-ITD [4]. In the 2017 ELN risk stratification model, the presence of *FLT3*-ITD mutations is classified according to allelic ratio [4]. The allelic ratio is calculated as the ratio of the area under the curve of the mutant allele to the wild-type allele. However, NGS can quantify *FLT3*-ITD results in variant allele frequency (VAF). VAF is calculated as the fraction of mutant alleles as a percentage of all *FLT3* alleles (wild-type+mutant). Therefore, there is a need for caution in the interpretation of the *FLT3*-ITD mutant burden based on the VAF and allelic ratio.

PROGNOSTIC SIGNIFICANCE OF *FLT3*-ITD IN AML

The prognostic impact of *FLT3*-ITD in AML is affected by the mutant allelic ratio and co-mutation status of nucleophosmin 1 (*NPM1*) [4]. The 2017 ELN guidelines stratify *FLT3*-ITD AML into three risk groups: 1) AML with an *FLT3*-ITD high allelic ratio (>0.5) in the absence of *NPM1* mutations is stratified as an adverse risk category; 2) *FLT3*-ITD low allelic ratio (≤0.5) is associated with favorable risk in patients with *NPM1* co-mutation; and 3) intermediate risk is observed in patients with *NPM1* wild-type and *FLT3*-ITD low allelic ratio or *NPM1* mutated and *FLT3*-ITD high allelic ratio [4, 25]. However, a study on patients with intermediate cytogenetic risk showed a high relapse rate (68–79%) regardless of the allelic burden of *FLT3*-ITD in patients with *NPM1* and *FLT3*-ITD mutated AML [26]. Oran *et al.* [27] also reported that allogeneic hematopoietic cell transplantation (HCT) improves relapse-free survival (RFS) and OS compared with those with consolidation chemotherapy, regardless of the allelic ratio in *FLT3*-ITD mutated AML. An *FLT3*-ITD low allelic ratio is not as favorable as the *FLT3*-ITD wild-type in patients with AML and *NPM1* mutations, as seen previously. Allogeneic HCT for post-remission therapy may be considered to reduce the relapse risk even in patients with *FLT3*-ITD low allelic ratio, regardless of *NPM1* mutation status [12, 26-28].

The prognostic relevance of *FLT3*-TKD mutations is conflicting [29]. However, the importance of *FLT3*-TKD mutations is emerging as targetable *FLT3* inhibitors have been introduced [7, 23, 30].

CLINICALLY APPLICABLE *FLT3* INHIBITORS

FLT3 tyrosine kinase inhibitors differ in potency, selectivity, mode of binding, and protein binding [31]. Type I *FLT3* inhibitors bind in the kinase-active conformation, whereas type II inhibitors bind in the inactive conformation [24]. Representative type I inhibitors include midostaurin, gilteritinib, and crenolanib, whereas type II inhibitors include quizartinib and sorafenib. In general, type II *FLT3* inhibitors have increased selectivity compared with that for type I *FLT3* inhibitors (Table 1) [32].

MIDOSTAURIN

Midostaurin was one of the first *FLT3* inhibitors to be studied in patients with AML. In the phase 3 RATIFY trial, midostaurin was evaluated in combination with standard induction and consolidation therapy and maintenance in young adults (<60 yr) with newly diagnosed *FLT3*-mutated AML [7]. This regimen was used for *FLT3*-ITD- and TKD-mutated AML. The combination of midostaurin with standard 7+3 induction chemotherapy has been shown to improve OS significantly, with a median OS of 74.7 months in patients receiving midostaurin plus chemotherapy vs. 25.6 months in patients receiving 7+3 chemotherapy alone (hazard ratio=0.78, P=0.009). Based on the results of this study, midostaurin was approved for clinical use by the U.S. Food and Drug Administration (FDA) in April 2017. The RATIFY trial was designed for maintenance with midostaurin for 12 months in young patients (18–60 yr). Older patients (≥60 yr) were not enrolled in the RATIFY trial; however, no age restrictions were imposed for midostaurin combination therapy in the FDA approval. A phase 2 trial was extended to patients up to 70 years of age for midostaurin plus intensive chemotherapy [33]. Compared with that for historical controls, midostaurin significantly improved event-free survival in overall age (hazard ratio=0.58, 95% CI, 0.48–0.70) and in older patients (hazard ratio=0.42, 95% CI, 0.29–0.61). However, the FDA has not approved midostaurin for maintenance therapy after consolidation or allogeneic transplantation. The European Medicines Agency (EMA) granted marketing authorization for midostaurin in 2017. The EMA included an indication for midostaurin maintenance therapy until relapse for up to 12 months in adult patients in complete remission following induction and consolidation.

Table 1. Summary of clinically applicable *FLT3* inhibitors for *FLT3*-mutated AML.

Patient eligibility	Disease status	Drug	Target mutated lesion	Representative trial	Usage	Benefit	Approval	In Korea
Intensive induction eligible	Newly diagnosed	Midostaurin	*FLT3*-ITD/TKD	RATIFY (Phase3) [7]	Combination with 7+3 induction and consolidation chemotherapy	Median OS (74.7 vs. 25.6 mo), P=0.009	FDA, EMA	Available
	Maintenance	Midostaurin	*FLT3*-ITD/TKD	RATIFY (Phase3) [7]	Maintain until relapse for up to 12 monthsas the extension of RATIFY trial		EMA	Not available
	Post-HCT maintenance	Sorafenib	*FLT3*-ITD	SORMAIN (Phase 2) [9]	Maintain until relapse for up to 24 months	2-year RFS (85 vs. 53%), P=0.002	Off-label	Not available
	Relapsed or refractory	Gilteritinib	*FLT3*-ITD/TKD	ADMIRAL (Phase 3)	Monotherapy	Median OS (9.3 vs. 5.6 mo), P<0.001	FDA, EMA	Available
Intensive induction ineligible	Newly diagnosed	Sorafenib	*FLT3*-ITD	NCT02196857 (Phase 2) and NCT01254890 Phase 1/2) [35]	Combination with azacitidine	Median OS (8.3 mo)	Off-label	Not available
	Relapsed or refractory	Sorafenib	*FLT3*-ITD	NCT01254890 [36]	Combination with azacitidine	Response rate: 46%	Off-label	Not available

Abbreviations: AML, acute myeloid leukemia; EMA, European Medicines Agency; FDA, Food and Drug Administration; FLT3, FMS-like tyrosine kinase 3; HCT, hematopoietic cell transplantation; ITD, internal tandem duplication; mo, months; OS, overall survival; RFS, relapse-free survival; TKD, tyrosine kinase domain.

GILTERITINIB

Gilteritinib is a potent type I *FLT3* inhibitor that targets *FLT3*-ITD and *FLT3*-TKD mutations. The FDA and EMA approved gilteritinib monotherapy for relapsed or refractory (R/R) *FLT3*-mutated AML based on the interim data of the Phase 3 ADMIRAL trial [23]. The ADMIRAL trial evaluated gilteritinib monotherapy vs. investigator-choice salvage chemotherapy in patients with R/R *FLT3*-mutated AML. Compared with that for salvage chemotherapy, gilteritinib showed significantly superior complete remission (CR) and CR with hematologic improvement (CRh) rate (34% vs. 15%, P=0.0001) and decreased the death rate by 36%, with a median OS of 9.3 months vs. 5.6 months (P<0.001).

A phase 3 trial is ongoing to determine whether gilteritinib has therapeutic benefits similar to those of midostaurin in newly diagnosed AML with *FLT3* mutations (NCT04027309, HOVON 156 AML trial). The HOVON 156 AML trial compared gilteritinib with midostaurin combined with intensive chemotherapy, followed by maintenance therapy. Additionally, an ongoing phase 3 trial is being conducted to elucidate the role of gilteritinib in post-transplant maintenance (NCT 02997202, MORPHO trial) and following induction/consolidation therapy (NCT02927262) in patients with *FLT3*-ITD-mutated AML.

QUIZARTINIB

Quizartinib is a second-generation potent type II *FLT3* inhibitor. A phase 3 randomized controlled trial (QuANTUM-R) evaluated quizartinib monotherapy vs. investigator choice salvage chemotherapy in patients with R/R *FLT3*-ITD-mutated AML [8]. OS was longer in the quizartinib group than that in the chemotherapy group [hazard ratio 0.76 (95% CI, 0.58–0.98; P=0.02)]. The median OS was 6.2 months (5.3–7.2) in the quizartinib group and 4.7 months (4.0–5.5) in the chemotherapy group, and 32% of the patients in the quizartinib group underwent allogeneic transplantation compared with 11% of the patients in the salvage chemotherapy group. Despite these positive results, both the FDA and EMA have rejected the marketing authorization for quizartinib because of various reasons, such as dropouts (23% of the control group did not receive chemotherapy) and concerns about cardiac and infection adverse events. However, Japan has approved quizartinib as a monotherapy for R/R *FLT3*-ITD-mutated AML. In patients with newly diagnosed AML, quizartinib is currently being evaluated in the Phase 3 QuANTUM-First trial, which compares quizartinib vs. placebo with 7+3 induction, consolidation, and maintenance (NCT02668653). Owing to improved efficacy and selectivity, the second-generation type II *FLT3* inhibitor quizartinib achieved much higher single-agent clinical response rates than those with the first-generation type I *FLT3* inhibitor midostaurin. Despite the high response rates achieved

with quizartinib in patients with R/R *FLT3*-ITD-mutated AML, the responses were not strong. Most patients relapsed because of secondary *FLT3*-TKD mutations, impairing quizartinib binding [34].

SORAFENIB

Sorafenib is a first-generation, type II *FLT3* inhibitor. It remains unapproved for use in patients with AML; however, several studies have shown its potential in *FLT3*-ITD-mutated AML. A phase 2, randomized, placebo-controlled trial (SORAML) evaluated 7+3 induction and consolidation with or without sorafenib in young individuals (<60 yr) with newly diagnosed AML, regardless of *FLT3*-ITD mutation status. Sorafenib improved event-free survival (21 mo vs. 9 mo, *P*=0.013) but not OS. Sorafenib with azacitidine, as a front-line strategy in older patients (≥60 yr) with *FLT3*-ITD-mutated AML who could not tolerate intensive induction, reported an overall response rate of 78% [CR: 26%, CR with incomplete count recovery (CRi)/CR with incomplete platelet recovery (CRp): 44%, and partial response (PR): 7%] [35]. Sorafenib combined with azacitidine demonstrated an overall response rate of 46% (CR: 16%, CRi: 27%, PR: 3%) for *FLT3*-ITD-mutated R/R AML [36].

The SORMAIN trial (a placebo-controlled, randomized, phase 2 trial) evaluated sorafenib maintenance therapy in patients with *FLT3*-ITD-mutated AML undergoing allogeneic HCT. The hazard ratio (HR) for relapse or death for sorafenib vs. placebo was 0.39 (95% CI, 0.18–0.85; log-rank *P*=0.013). The probability of 24-month RFS was 85.0% (95% CI, 0.70–0.93) with sorafenib (HR, 0.256; 95% CI, 0.10–0.65) and 53.3% (95% CI, 0.36–0.68) with placebo (log-rank *P*=0.002) [9]. In another phase 3 trial, sorafenib also demonstrated a decreased 1-year cumulative incidence of relapse (7.0% vs. 24.5%, *P*=0.001) and improved OS (82.1% vs. 68%, *P*=0.012) without treatment-related deaths [11]. The post-transplant maintenance results for sorafenib suggest potential synergy with post-transplant alloimmune effects [12, 37].

CONCLUSION

Rapid determination of *FLT3* mutations during diagnosis or relapse is essential for making treatment decisions to manage AML and for the early selection of *FLT3*-targeting agents. The current standard treatment for a patient with a newly diagnosed *FLT3*-mutated AML is 7+3 induction chemotherapy combined with midostaurin [10]. In *FLT3*-mutated AML, allogeneic HCT as a post-remission therapy is considered to lower the risk of relapse. Although the role of post-transplant maintenance with *FLT3* inhibitors has not been established, experts recommend maintenance therapy to reduce relapse risk [10, 12]. Gilteritinib is more effective than salvage chemotherapy for R/R *FLT3*-mutated AML. Ongoing trials are expected to provide additional treatment options depending on the disease state and patient vulnerability to *FLT3*-mutated AML.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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