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A never-ending FLT3 story

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Kiyoi H. FLT3 inhibitors: recent advances and problems for clinical application. ***Nagoya J Med Sci*****. 2015; 77(1–2): 7–17.**

FLT3, a type III receptor tyrosine kinase, expresses on most acute leukemia cells as well as normal hematopoietic stem/progenitor cells. Mutation in the *FLT3* gene is the most frequent genetic alteration in acute myeloid leukemia (AML) and is well known as an important driver mutation for the development of myeloid malignancies. *FLT3* mutation is a strong poor prognostic factor for the long-term survival in AML patients, while neither high-dose chemotherapy nor allogeneic hematopoietic stem cell transplantation can overcome a poor prognosis. Development of an FLT3 inhibitor is, therefore, much awaited. To date, several potent FLT3 inhibitors have been developed and some of them were evaluated for efficacy in clinical trials, although no FLT3 inhibitor has been yet approved. Moreover, several problems for clinical use, such as adverse effects, blood concentration and resistance have been apparent. Recently developed AC220 is a highly selective and sensitive FLT3 inhibitor. In Phase I and II trials, AC220 so far showed the best efficacy of AML cells harboring *FLT3* mutation among clinically evaluated FLT3 inhibitors, while severe bone marrow suppression and QTc prolongation should be resolved for the clinical use. In this review, I summarize the characteristics of FLT3 inhibitors in clinical development and discuss important issues to be resolved for clinical use.

Keywords: FLT3, inhibitors, leukemia, molecular target, resistance

I would like to congratulate the "Nagoya Journal of Medical Science" on its 100th anniversary. My review article entitled "FLT3 inhibitors: Recent advances and problems for clinical application" was published in the Nagoya J Med Sci in 2015,[1] and I sincerely appreciate the opportunity to present subsequent progress in this field in this 100th anniversary issue.

There has been a remarkable progress in the development of FLT3 inhibitors since the publication of my article. A randomized phase 3 study for newly diagnosed FLT3-mutated acute myeloid leukemia (AML) patients (RATIFY study) demonstrated the superiority of midostaurin

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Table 1 FLT3 inhibitors approved in Japan

	Gilteritinib	Quizartinib
FLT3 kinase inhibition IC_{50} (nM)	0.29	1.6
Inhibitory target	FLT3-ITD, FLT3-TKD	FLT3-ITD
Other targets	AXL, LTK, ALK	KIT
Approved usage and indications in Japan	Single agent for relapsed or refractory AML with *FLT3* mutation	Single agent for relapsed or refractory AML with *FLT3*-ITD mutation

in addition to the conventional induction and consolidation chemotherapies for overall survival (OS).[2] Based on the results of this study, midostaurin was approved as a combination agent with standard chemotherapy by the US Food and Drug Administration in 2017. Although midostaurin has not yet been approved in Japan, two FLT3 inhibitors, gliteritinib and quizartinib, have been approved (Table 1). Gilteritinib is a selective FLT3 inhibitor that inhibits internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations. A randomized phase 3 study for relapsed or refractory (R/R) AML patients with *FLT3* mutations (ADMIRAL study) showed that the median OS of gilteritinib-treated patients significantly longer than that of conventional chemotherapy-treated patients.[3] Gilteritinib was approved for R/R AML patients with *FLT3* mutations as the first single-agent FLT3 inhibitor in Japan in 2018. Quizartinib has strong inhibitory activity against FLT3-ITD but not against FLT3-TKD. Quizartinib also demonstrated a significantly longer OS than conventional chemotherapy in a randomized phase 3 study for R/R AML patients with *FLT3*-ITD mutation (QuANTUM-R study),[4] and was approved only in Japan in 2019. Furthermore, at the European Hematology Association 2022 Congress, quizartinib combined with conventional induction and consolidation chemotherapies was shown to exhibit superior OS in a randomized phase 3 study for newly diagnosed AML patients with *FLT3*-ITD mutation (QuANTUM-FIRST study).

Twenty years after the discovery of the *FLT3* mutation, FLT3 inhibitors have become clinically available for AML patients with *FLT3* mutations. However, several issues regarding the clinical use of FLT3 inhibitors have been raised.[5] For example, several mechanisms of resistance to FLT3 inhibitors have been identified in clinical studies and daily clinical practice. In particular, the gatekeeper *FLT3*-F691L mutation and RAS/MAPK pathway mutations are serious issues that must be resolved. To overcome the resistance of the *FLT3*-F691L mutation, we developed a novel FLT3 inhibitor, FF-10101, in collaboration with FUJIFILM Corporation (Kanagawa, Japan), which was designed to form a covalent binding between the C695 residue of FLT3.[6] The formation of covalent binding induces irreversible inhibition of FLT3, maintaining the inhibitory activity against FLT3 kinase harboring the gatekeeper mutation. Additionally, the most suitable therapeutic strategy for each inhibitor remains unclear. Our study along with other studies demonstrated that an allogeneic hematopoietic stem cell transplantation at the first complete remission improved the relapse-free survival of AML patients with *FLT3*-ITD.[7] Currently, synergizing chemotherapy with an FLT3 inhibitor to reduce AML cell volume as much as possible before transplantation, followed by maintenance therapy with an FLT3 inhibitor, is highly desirable. AML is a genetically heterogeneous disease and *FLT3* mutation is a late event during leukemogenesis; hence, further studies are required to establish biomarkers for selecting the best therapeutic strategy and predicting the clinical response. We have established many patient-derived xenotransplant models to resolve this critical issue[8] and are still in the middle of the never-ending FLT3 story.

CONFLICT OF INTEREST

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