News Release

Title

A novel irreversible FLT3 inhibitor, FF-10101, shows an excellent efficacy against FLT3-ITD-driven acute myeloid leukemia cells

-Improvement of the therapeutic outcome of acute myeloid leukemia patients with FLT3 mutation is expected. -

Key Points

- **FF-10101 is a novel agent which has a high selectivity and invulnerability to mutant FLT3**
- **FF-10101 is a promising agent for the treatment of the patients with known resistant FLT3 mutations**
- **Improvement of the therapeutic outcomes of acute myeloid leukemia patients with FLT3 mutation is expected**

Summary

Hitoshi Kiyoi, Fumihiko Hayakawa and Yuichi Ishikawa at Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu) in the collaboration with FUJIFILM Corporation and Dr. Tomoki Naoe at National Hospital Organization Nagoya Medical Center demonstrated that a novel irreversible FLT3 inhibitor, FF-10101, shows a high selectivity and potent efficacy against mutant FLT3.

In about 30% of acute myeloid leukemia (AML) patients, FLT3 gene mutations consisting of internal tandem duplication in juxtamembrane domain (FLT3-ITD) and point mutations in tyrosine kinase domain (FLT3-TKD) are occurred. Mutated FLT3 drives an autonomous proliferation of leukemia cells. FLT3 mutations are known to be associated with poor prognosis of AML patients, and conventional chemotherapies could not provide patients with sufficient therapeutic effects. Therefore, development of FLT3 inhibitors effective for AML cells is highly expected. To date, several FLT3 inhibitors have been clinically developed; however, there are several problems regarding low selectivity against FLT3 and resistant mutations that FLT3 acquires.

To overcome these problems, a novel FLT3 inhibitor, FF-10101, was designed and synthesized by FUJIFILM Corporation to possess selective and irreversible FLT3 inhibition. It showed an excellent growth inhibitory effect on human AML cells with FLT3 mutations in the AML patient-derived xenotransplant mouse model. Furthermore, FF-10101 showed a high inhibitory activity against known resistant FLT3 mutations. These results suggest that FF-10101 would improve the prognosis of AML patients with FLT3 mutations. Phase 1 study is conducted by FUJIFILM Corporation in United States under the support from the Newly Extended Technology Transfer Program (NexTEP) of the Japan Science and Technology

Agency.

The research achievements were published online in the journal of Blood on 29-Nov-2017.

Research Background

Activating mutations of receptor tyrosine kinase FLT3 are identified in about 30% of acute myeloid leukemia (AML) patients, and are poor prognostic factor for AML. FLT3 mutations consist of internal tandem duplication in juxtamembrane domain (FLT3-ITD) and point mutation, insertion and deletion surrounding the D835 residue in tyrosine kinase domain (FLT3-TKD). Both mutations induce constitutive activation of FLT3 kinase resulting in the autonomous proliferation of AML cells. Based on these clinical and biological significances, FLT3 is served as an attractive therapeutic target. Previously developed FLT3 inhibitors are classified into Type 1 and Type 2 inhibitors based on the binding manner to FLT3; Type 1 inhibitor uses only an ATP-binding pocket, but Type 2 uses back-pocket in addition to an ATP-binding pocket. Since Type 2 inhibitors use both pockets for binding to FLT3, they have a higher selectivity against FLT3 compared to many Type 1 inhibitors. However, it has been indicated that the use of both pockets results in the decrease of affinity to the FLT3-TKD which are known as drug resistant mutations. Therefore, development of novel FLT3 inhibitors with high selectivity and potency against drug resistant mutations is highly expected.

Research Results

In collaboration with FUJIFILM Corporation, we demonstrated that the novel FLT3 inhibitor, FF-10101, designed to specifically form a covalent bond to the FLT3 C695 residue, exhibits selective and potent FLT3 inhibition. The unique binding brought high selectivity and inhibitory activity against FLT3 kinase without using back pocket of FLT3. In addition, FF-10101 retained its inhibitory activity against FLT3 with drug resistant mutations which induce large conformational changes of back pocket. Of note, in the cells expressing drug-resistant FLT3 mutations, FF-10101 successfully demonstrated excellent growth inhibitory effect. Furthermore, we demonstrated that effective blood concentration of FF-10101 was maintained over a long time after the oral administration.

FF-10101 showed potent growth-inhibitory effects on primary AML cells and all tested types of mutant FLT3-expressing cells including known resistant mutations. Importantly, oral administration of FF-10101 showed excellent therapeutic effects on AML cells harboring FLT3 mutations in patient-derived xenotransplant mouse models.

These results indicated that FF-10101 has overcome the weak points of previously developed FLT3 inhibitors, and is highly expected as a therapeutic agent against AML with FLT3 mutations.

Research Summary and Future Perspective

Since the FLT3 mutation is a poor prognostic factor of AML, development of FLT3 inhibitors are highly expected in the clinical field. The present study highly indicates the clinical

usefulness of FF-10101. Now, FUJIFILM Corporation is conducting a phase 1 clinical study for evaluating safety and optimal dose of FF-10101 under the support from the Newly Extended Technology Transfer Program (NexTEP) of the Japan Science and Technology Agency. In Nagoya University, we continue to further address the pharmacological characterization of FF-10101 leading to optimization of the treatment modality for AML patients using FF-10101.

Publication

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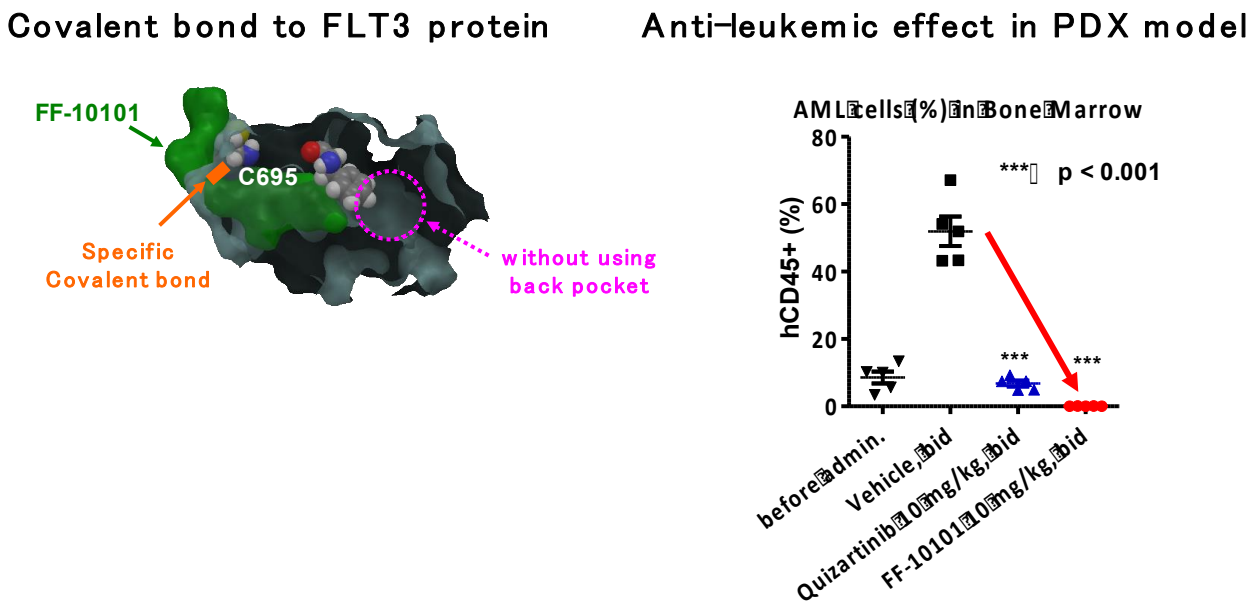

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