VARIANT FLT3 MUTATIONS CAN BE ERADICATED BY CYTARABINE/ANTHRACYCLINE/CRENOLANIB 

IN ADULT PATIENTS WITH NEWLY DIAGNOSED FLT3 (ITD/TKD) MUTANT AML

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Abstract

Crenolanib is a Type I, Pan-FLT3 TKI.

Crenolanib has activity against activation loop mutations: D835V/Y/H/R, Y842H/C.

Background: Patients (pts) with FLT3-ITD, kinase domain (TKD) and juxtamembrane (JM) mutations have a high relapse rate. These releases are typically due to outgrowth of mutant FLT3 clones. Previously available PCR-based tests only checked for presence of FLT3-ITD and FLT3-D835V/R mutations. Whole genome sequencing of 799 pediatric AML samples from COG trials have shown novel FLT3 variants in not only the tyrosine kinase domain but also the juxtamembrane (JM) and transmembrane domains in 7.6% of these samples (Tarlock et al. ASCO 2015). Some of these mutations result in autophosphorylation of FLT3 and therefore may be oncogenic.

Aims: Identify novel FLT3 mutations in pts with FLT3 mutant AML and further investigate whether these novel clones are sensitive to induction chemotherapy plus a potent pan-FLT3 inhibitor, crenolanib.

Methods: Pts with FLT3-ITD, JM, and/or TKD mutations were treated with standard induction chemotherapy and the FLT3 inhibitor, crenolanib in combination with standard induction chemotherapy and FLT3 sequencing results available on juxtamembrane domain (JM, exons 14 and 15), kinase domain 1 (exon 16), and kinase domain 2 (activation loop, exon 20). FLT3 sequencing was performed at baseline and at the time of clinical relapse assessment. Sequencing of the entire FLT3 gene was performed through FoundationOne Heme panel (n=18) and MSDKC mutigene panel (n=5). Sequencing of exons 14, 15, 16, and 20 was performed through the Rapid Heme Panel at Dana-Farber Cancer Institute in additional 6 pts.

Results: Out of 20 newly diagnosed FLT3 mutant AML patients with full/partial FLT3 gene sequencing performed, 4 pts were found to have novel variant FLT3 mutations consisting of V491L, W288fs, D593H, and I836del (Table 1). The majority of these novel mutations were located at the JM, kinase domain 1 and the activation loop (kinase domain 2). The allele fractions of these new variants ranged as high as 29% (higher than that of FLT3-ITD in pts), suggesting that some of these clones may have been potentially driving clinical leukemia progression in some pts. All 4 pts had NPM1 mutations, and two also had DNMT3A mutations. All 4 pts achieved CR with full count recovery (3/4 pts achieved CR after just one cycle of cytarabine/anthracycline/crenalanib induction). The pt with FLT3-DESYD/ND1417 achieved a CR after cytarabine/anthracycline/crenalanib induction and one cycle of HDAC consolidation. All pts became FLT3-ITD and had remained FLT3-ve. 3 out of 4 pts received 4-1 cycles of HDAC consolidation followed by crenalanib maintenance. Only one pt underwent allo SCT. With a median follow up of 13 months, one pt relapsed (at 8.4-month following treatment). This 61F pt was found to have FLT3-ITD, D593H and I836del FLT3 abnormalities at the time of diagnosis. A full FoundationOne gene panel done at the time of relapse, showed no residual FLT3 mutant clones.

FLT3 Variants detected in pediatric AML

- FLT3-ITD
- JM and TKD
- activation loop

Methods

Previously available PCR-based tests only checked for presence of FLT3-ITD and FLT3-D835V/R mutations. Herein, we reported a subset of patients treated with 7-3 and crenolanib with FLT3 sequencing results available on juxtamembrane domain (JM, exons 14 and 15), kinase domain 1 (exon 16), and kinase domain 2 (activation loop, exon 20). FLT3 sequencing was performed at baseline and at the time of clinical relapse assessment. Sequencing coverage may vary among laboratories, as summarized below.

Conclusions

- Novel FLT3 variant mutations can be found in adult AML patients.
- The allelic burden of these FLT3 variant mutations can sometimes be higher than that of FLT3-ITD.
- Crenolanib in combination with standard induction chemotherapy has the ability to eradicate variant FLT3 clones.
- All 4 pts treated with chemotherapy followed by crenalanib showed clearance of FLT3-ITD, TKD, as well as other novel variant.
- To achieve maximal clinical benefit, a potent pan-FLT3 inhibitor with the ability to inhibit ITD, D835, as well as other activating mutations maybe beneficial.

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