Addition of Crenolanib to Induction Chemotherapy Overcomes the Poor Prognostic Impact of Co-Occurring Driver Mutations in Patients with Newly Diagnosed FLT3-Mutated AML


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Background: Patients with AML harboring FLT3 mutations have poor clinical outcomes. Furthermore, FLT3 mutations frequently co-occur with other driver mutations, such as NPM1 with DNMT3A, WT1, and RUNX1, that are associated with poor prognosis. Crenolanib is a highly potent and specific type-III FLT3 inhibitor, which has shown promising safety and efficacy in combination with chemotherapy. Here we report the outcomes of newly diagnosed FLT3-mutated AML patients treated with crenolanib and induction chemotherapy (IC) for up to 7+3 cycles.

Methods: Patients were treated on clinical trial with 7+3 induction chemotherapy combined with crenolanib, consolidation with high-dose cytarabine (HDAC) combined with crenolanib, and/or allo-HCT followed by crenolanib consolidation. Altogether 54 pts were enrolled and treated. 26 pts had sequencing performed at baseline. The median survival follow-up for these patients was 20.7 months with data cut-off July 25, 2019. A post hoc analysis was performed to assess the impact of genomic profile on patient outcomes using published data from the German-Australian AML Study Group.

Results: Concurrent FLT3-ITD, NPM1, and DNMT3A mutations (‘triple mutants’) were present in 9 pts. Three patients demonstrated improved OS with crenolanib treatment compared with historical controls. Similarly, patients with FLT3-ITD and WT1 mutations (n = 8) showed dramatically improved OS compared with historical controls with no deaths occurring within 18 months. Patients with FLT3-ITD (n=10) had a median survival of 23.1 months and FLT3-RUNX1 (n=10) had a median survival of 25.4 months. Among the patients studied by Tyner et al., crenolanib can kill patient samples that have been relapsed of standard chemotherapy combined with either crenolanib or midostaurin in newly diagnosed patients with FLT3-mutated AML, (NCT0250931).

Conclusion: This analysis demonstrates that patients with FLT3-ITD and/or WT1 mutations can overcome the poor prognostic implication of adverse mutations co-occurring with mutated FLT3. These data support the combination of crenolanib with chemotherapy to improve the overall outcome of FLT3mutated AML with diverse mutational profiles. Furthermore, a randomized trial has been initiated of standard chemotherapy combined with either crenolanib or midostaurin in newly diagnosed patients with FLT3-mutated AML. (NCT0250931).

Abstract

Crenolanib Has Excellent in vitro Cytotoxic Activity Against Primary AML Blasts

Study Design

Mutations Occurring in the Background ofFLT3 Mutations Can Lead to Resistance to FLT3 TKIs

Crenolanib in AML Patients Can Overcome Poor Prognostic Mutations

Favorable Results With Chemo Plus Crenolanib in AML Patients With DNMT3A, FLT3, and NPM1 Mutations

Favorable Results With Chemo Plus Crenolanib in AML Patients With FLT3 and WT1 Mutations

References