Phase I/II Study of Crenolanib Combined with Standard Salvage Chemotherapy and Crenolanib Combined with 5-Azacitidine in Acute Myeloid Leukemia Patients with FLT3 Activating Mutations

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Abstract

Background: With a single-arm study of R/R FLT3-ITD, 37
treated patients, FLT3 inhibitors are generally well tolerated,
with single grade 3/4 (G3/4) treatment-related adverse events
(TREs) of 15% or greater, Grade 3/4 G3/4 hematologic
TREs: 14.6% or higher, and 6% or greater Grade 3/4
toxicities of 12% or higher. The FLT3-TKD selectivity
of crenolanib is 250-375 fold lower than the FLT3-ITD
selectivity. Among 12 patients who received crenolanib
in combination with chemotherapy, 50% of those
patients had a hematologic TRE Grade 3 or 4. These
findings prompted us to evaluate the combination of
standard salvage chemotherapy with crenolanib, and
standard salvage chemotherapy with 5-azacitidine
in patients with FLT3-TKD and FLT3-ITD mutations.

Methods: A phase I/II study was conducted at a single
center. In the phase I part, patients received crenolanib
3 mg/m² over 24 hours for 1 cycle (Arm 1) and then 7
mg/m² over 24 hours for 1 cycle (Arm 2). The starting dose
of crenolanib was 2.3 mg/m² for patients with any level of
prior exposure. Patients were treated on an outpatient
basis with a safety margin of ± 10% of the planned dose.
Chemotherapy in Cycle 2 was at the same dose level.

Results: All doses were considered feasible. In both
arms, 50% of patients had hematologic G3/4 events.
Median OS for Arm 1 was 8.4 months and OS for Arm 2
was 4.6 months (p = 0.0005). OS was compared with
historical controls from a phase 1 study of FLAG
therapy for AML (Arm 2: 5-azacitidine + crenolanib
Arm 1: chemotherapy + crenolanib). There was no
difference in OS at 2.7 years (Arm 1: 36% Arm 2: 33%)

Conclusions: These studies demonstrated the feasibility
and tolerability of the combination of standard salvage
chemotherapy with crenolanib or 5-azacitidine in patients
with FLT3-TKD and FLT3-ITD mutations. In both
arms, 50% of patients had hematologic G3/4 events. The
OS of patients was lower compared with historical
controls from AML.