Full Doses of Crenolanib, a Type I FLT3 Inhibitor, Can be Safely Administered in AML Patients Post Allogeneic Stem Cell Transplant

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Abstract

Crenolanib besylate is a selective and potent type I tyrosine kinase inhibitor (TKI) of wild type and mutant FMS-like tyrosine kinase 3 (FLT3). Crenolanib is being studied in patients with relapsed/refractory AML with FLT3-ITD and/or FLT3-D835 mutations. A total of 65 patients with relapsed/refractory AML have been treated across two Phase II trials, ARO-004 (NCT01522469) and ARO-005 (NCT01657682), conducted with crenolanib monotherapy in relapsed/refractory FLT3+ AML.

This is a retrospective subset analysis of patients who underwent hematopoietic stem cell transplant (HSCT) and who received crenolanib pre-transplant. This retrospective analysis was done to assess whether full doses of crenolanib can be given safely to patients who have had an allogeneic stem cell transplant (HSCT).

Methods:

- Of the 65 patients treated with crenolanib, 16 patients (8 females and 8 males) had undergone HSCT prior to crenolanib treatment. The median age was 55 years (range 24-72). 15 patients had received previous chemotherapy and 13 had received prior TKI treatment for AML.
- FLT3-ITD (21/M), FLT3-D835 (25/M) and FLT3-ITD+D835 (19/M) were observed. The majority of crenolanib was administered for 6 months (range, 1-15 months).
- One patient began maintenance crenolanib one month following transplantation. Crenolanib was well tolerated with a median total dose of 150 mg (17 patients) and subsequently to a higher dose of 200 mg (9 patients). The highest total dose of crenolanib was 400 mg (2 patients). Patients were monitored for adverse events while on crenolanib, specifically for myelosuppression and 53 toxicities. Regular assessments of chemistry and hematology laboratory values were performed to ensure safety of crenolanib in this patient population.

Results:

- Crenolanib was well tolerated in patients with prior HSCT, and none of the 16 patients treated at 300 mg daily dose of crenolanib required dose reduction. Of the 8 patients treated at the higher dose of 200 mg, 4 patients (total daily doses of 400, 360, 340 and 320 mg) required dose reductions; no patients required drug discontinuation due to toxicities attributed to crenolanib. The pharmacokinetic profile in this patient population was consistent with that seen in patients treated with crenolanib. For those patients who received crenolanib at 100 mg TD, the median Cmax was 149 nM (range 105-624 nM). Those patients who received crenolanib at 200 mg TD had a median Cmax of 301 nM (range 210-487 nM).

- Patients who received crenolanib at 100 mg TD achieved a CRi on crenolanib, and liver biopsy showed development of acute graft versus host disease.

- Pain was the only grade 3 elevation of AST was attributed to graft versus host disease.

- Acute Kidney Injury, Gastrointestinal hemorrhage, and Neutropenic fever were grade 3 adverse events; neutropenic fever was grade 4.

- Only one grade 3 elevation of ALT was observed.

- Acute Kidney Injury was the only grade 3 elevation of creatinine.

- Missed dose interruption or reduction. The only grade 3 elevation of AST was attributed to graft versus host disease.

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- No patients were discontinued from crenolanib due to side effects.

Conclusion

Crenolanib Demonstrates Clinical Activity Against FLT3-ITD, FLT3-D835, and Compound FLT3-ITD/D835 Mutations Following Post-Transplantation Treatment.

Crenolanib Demonstrates Clinical Activity in Patients Who have Received Prior TKI Treatment With Midostaurin and Gilteritinib.

The Pharmacokinetic Profile in this Patient Population was Consistent With that Seen in all Patients Treated With Crenolanib

Treatment History Prior to Starting Crenolanib

<table>
<thead>
<tr>
<th>Patient (Age/Gender) Starting Dose Daily Dose of Crenolanib</th>
<th>Days on Crenolanib</th>
<th>patients given</th>
<th>Pain</th>
<th>Gastrointestinal hemorrhage</th>
<th>Neutropenic Fever</th>
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<tbody>
<tr>
<td>UTSW_008 (63/M) 100 mg TID 300 mg/day</td>
<td>29</td>
<td>0</td>
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<td>MDA_138 (44/F) 200 mg/m2 TID 200 mg/day</td>
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</tr>
</tbody>
</table>

- Patients were heavily pretreated, with a median of 3 prior systemic therapies. All patients had failed prior TKI treatments.
- All patients received 2 prior probopans, and another patient had failed 3 prior transplant treatments before starting crenolanib.