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Abstract

Background: Crenolanib besylate is a selective and potent type I tyrosine kinase inhibitor (TKI) of wildtype 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 FLT3+ AML have been treated with crenolanib. 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 (9 females and 7 males) had undergone HSCT prior to initiation of crenolanib. The median age was 51 years (range: 24-72). 15 patients had received salvage chemotherapies (median of 3 systemic therapies; range: 1-5) following their recurrence post-transplant and prior to initiation of crenolanib. 11/16 patients also had prior exposure to FLT3 TKIs, including sorafenib (9 patients), ASP2215 (2 patients) and quizartinib (3 patients). The median time between allogeneic stem cell transplantation and initiation of crenolanib was 9 months (range; 1 to 69 months). One patient began maintenance crenolanib one month following transplant. Crenolanib was initially given at a dose of 100 mg TID (7 patients) and subsequently escalated to a higher dose of 200 mg/m² (9 patients). The highest total dose of crenolanib was 400 mg daily (2 patients). Patients were monitored for serious adverse events while on crenolanib, specifically for elevated liver transaminases and GI toxicities. Regular assessments of chemistry and hematologic 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 7 patients treated at 300 mg daily dose of crenolanib required dose reduction. Of the 9 patients treated at the higher dose of 200 mg/m², 4 patients (total daily doses of 400, 360, 340 and 320 mg) did require 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 all patients treated with crenolanib. For those patients who received crenolanib at 100 mg TID, the median C_{max} was 149 nM (range: 105-624 nM). Those patients who received crenolanib at 200 mg/m² had a median C_{max} of 391 nM (range: 328-1497 nM). Grade 1 and 2 nausea and vomiting were seen but were well controlled with standard anti-emetics, requiring no dose reductions or discontinuation. Two patients experienced grade 1 ALT and AST elevation, and one patient experienced grade 1 ALT, AST and bilirubin elevation; no patient required dose interruption or reduction. The only grade 3 elevation of AST was attributed to graft versus host disease (GVHD), improved with treatment of GVHD and did not require crenolanib discontinuation. One patient developed grade 3 hyperbilirubinemia on day 53 of crenolanib. This patient had achieved a CRi on crenolanib, and liver biopsy showed development of acute graft versus host disease. Following treatment of GVHD, the patient was able to restart crenolanib at 280 mg daily. One patient received crenolanib maintenance in the immediate post-transplant setting. This patient was able to stay on crenolanib at a dose of 280 mg a day for 5 months with full recovery of neutrophils and platelet counts, and became transfusion independent.

Conclusions: Post-transplant maintenance with a FLT3 inhibitor can potentially be beneficial in reducing posttransplant recurrence and improving overall outcomes. This retrospective study shows that crenolanib was welltolerated in patients with leukemia who have undergone a prior allogeneic transplant at the full therapeutic dose of 100 mg TID (300 mg daily). A formal study of crenolanib maintenance post-allogeneic stem cell transplantation has been initiated (ARO-009; NCT 02400255).

Retrospective Analysis

Post-transplant maintenance therapy with a FLT3 inhibitor has the potential to reduce a disease recurrance and improve clinical outcomes

This is a retrospective subset analysis of patients who underwent hematopoietic stem cell transplant across two Phase II trials, ARO-004 (NCT01522469) and ARO-005 (NCT01657682), conducted with crenolanib monotherapy in relapsed/refractory FLT3+ AML.

Key eligibility criteria:

- Relapsed/refractory FLT3+ AML (ITD, D835, or ITD+D835)
- Any number of prior transplants
- Any number of prior salvage chemotherapy regimens
- Prior treatment with FLT3 tyrosine kinase inhibitors (TKIs) allowed

Crenolanib treatment regimen:

- Crenolanib was administered every day until progression of disease or unacceptable toxicity
- 7 patients were given a flat dose 100 mg TID
- 9 patients were given body surface area (BSA)-adjusted dosing of 200 mg/m²

Pharmacokinetics:

- On the first day of treatment, a single dose of crenolanib was given to each patient, and the concentration of crenolanib in blood was monitored over 24 hours
- Trough levels were measured at day 15 to investigate whether drug accumulation occurred

Disease assessments:

Bone marrow aspirates were performed every 4 weeks of crenolanib treatment

Safety assessments:

• Non-hematological and hematological toxicities were assessed by regular clinic visits and laboratory assessments

Crenolanib Monotherapy Post Transplant in Relapsed / Refractory FLT3+ AML



Objectives:

- To assess the safety and tolerability of crenolanib in the post transplant setting
- To assess the pharmacokinetics of crenolanib in the post transplant setting
- To assess the clinical benefit of crenolanib in relapsed/refractory FLT3+ AML post transplant

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



• Patients were heavily pretreated, with a median of 3 prior systemic therapies. All patients had failed prior HSCT. One patient had failed 2 prior transplants, and another patient had failed 3 prior transplants before starting crenolanib.

Crenolanib Treatment

Patient (Age/Gender)	Starting Dose	Daily Dose of Crenolanib	Dose Reduction Required?	Dose After Dose Reduction	Dose Delays?	Reason for Discontinuation
MDA-015 (38/F)	100 mg TID	300 mg/day	Ν	-	Ν	PD
MDA-019 (66/M)	100 mg TID	300 mg/day	Y	240 mg/day	Y	PD
MDA-102 (68/M)	100 mg TID	300 mg/day	Ν	-	Ν	PD
MDA-105 (48/M)	100 mg TID	300 mg/day	Ν	-	Y	PD
MDA-110 (64/F)	100 mg TID	300 mg/day	Ν	-	Y	Inability to swallow
MDA-130 (28/F)	100 mg TID	300 mg/day	Ν	-	Ν	PD
UTSW-008 (47/F)	100 mg TID	300 mg/day	Ν	-	Ν	PD
MDA-010 (37/F)	200 mg/m² TID	340 mg/day	Y	280 mg/day	Y	PD
MDA-013 (44/F)	200 mg/m² TID	340 mg/day	Ν	-	Ν	PD
MDA-115 (72/F)	200 mg/m² TID	300 mg/day	Ν	_	Y	Patient request
MDA-118 (55/M)	200 mg/m² TID	340 mg/day	Ν	_	Y	PD
MDA-121 (31/M)	200 mg/m² TID	360 mg/day	Ν	_	Y	PD
MDA-124 (55/F)	200 mg/m² TID	320 mg/day	Y	280 mg/day	Y	PD
MDA-125 (60/F)	200 mg/m² TID	300 mg/day	Ν	_	Ν	PD
MDA-126 (24/M)	200 mg/m² TID	400 mg/day	Ν	_	Ν	PD
UTSW-010 (63/M)	200 mg/m² TID	400 mg/day	Y	360 mg/day	Υ	PD

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

	All Events	All Grade 3 Events	All Grade 4 Events
Nausea	12	3	0
Vomiting	11	3	0
Edema Limbs	6	1	0
Fatigue	6	1	0
Febrile Neutropenia	6	4	1
Epistaxis	5	3	0
Pneumonia	5	5	0
Fever	4	1	0
Headaches	4	1	0
Abdominal Pain	3	1	0
Blood Bilirubin Increased	3	1	0
Gastric Hemorrhage	3	1	1
Mucositis Oral	3	1	0
Acute Kidney Injury	2	1	0
Alanine Aminotransferase Increased	2	1	0
Back Pain	2	1	0
Aspartate Aminotransferase Increased	1	1	0
Creatinine Increase	1	0	1
GGT increased	1	1	0
Hypercalcemia	1	1	0
Hyperkalemia	1	1	0
Hyponatremia	1	1	0
Multi-organ Dysfunction	1	0	1
Neck Pain	1	1	0
Pain	1	1	0
Pancytopenia	1	1	0

Two patients experienced grade 1 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation, and one patient experienced grade 1 ALT, AST and bilirubin elevation; no patient required dose interruption or reductions. The only grade 3 elevation of AST was attributed to GVHD, improved with treatment of GVHD and did not require crenolanib discontinuation. One patient developed grade 3 hyperbilirubinemia on day 53 of crenolanib. This patient had achieved a CRi on crenolanib, and liver biopsy showed development of acute graft versus host disease.

Efficacy									
	Number of Patients	CR/CRi	PR	Blast Response	Resistant Disease				
Overall	16	4 (25%)	1 (6%)	3 (19%)	8 (50%)				
FLT3-D835 only	3	1 (33%)	0 (0%)	2 (67%)	0 (0%)				
FLT3-ITD only	7	2 (29%)	0 (0%)	1 (14%)	4 (57%)				
FLT3-ITD and FLT3-D835	6	1 (17%)	1 (17%)	0 (0%)	4 (67%)				

• Blast response was defined as a \geq 50% reduction in blast percentage in peripheral blood (if > 5%) or bone

Crenolanib Demonstrates Clinical Activity Against FLT3-ITD, FLT3-D835, and Compound FLT3-ITD+D835 Mutations Following Allogeneic Transplant

Crenolanib Demonstrates Clinical Activity in Patients Who have Received

Days on Crenolanib

transplantation has been initiated (NCT 02400255).

Conclusion

• This retrospective analysis shows that crenolanib at the full therapeutic dose of 100 mg TID (300 mg daily) was well tolerated in patients with acute myeloid leukemia who have undergone a prior hematopoietic stem cell transplant. • A prospective phase II study of crenolanib maintenance post-allogeneic stem cell

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