

Emergence of PTPN11 mutations is associated with Clinical Resistance to the Combination of Azacitidine and Rigosertib in patients with Higher-Risk Myelodysplastic Syndrome

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BACKGROUND

The treatment of patients with MDS with Azacitidine (AZA) is associated with hematologic responses, and a significant increase in overall survival. AZA has become the standard of care for patients with higher-risk disease. However, all pts ultimately fail treatment due to either primary or secondary resistance. MDS, a hematopoietic stem cell disorder, is characterized by intricate complexities at the molecular, genetic and epigenetic levels contributing to the therapeutic challenge. Rigosertib (RIG) is a small molecule Ras mimetic that interferes with cellular signaling. This is believed to be mediated by the binding of RIG to the Ras-binding domain (RBD) and may inhibit multiple Ras-driven signaling pathways including RAS-RAF-MEK and the PI3K. In vitro, we demonstrated that the combination of RIG with AZA synergistically inhibits growth and induces apoptosis of leukemic cells in a sequence-dependent manner (Skidan et al, AACR 2006). RIG combined with AZA in a phase I/II study in MDS pts demonstrated an overall response rate of 76%; 84% in pts that were HMA naive and 64% in pts following HMA failure (Navada EHA 2017). Reversal of the clinical resistance phenotype represents a novel observation. Recently, we observed that RIG appears to act as a chromatin modifying agent and is associated with histone post-translational modifications (Silverman EHA 2017). Mutations that activate Ras signaling such as mutations in Ras genes or Ras regulators (NF1, PTPN11, or CBL) have been found in 30% of AML patients (Papaemmanuil, 2016). Exploring the Ras pathway in patients treated with these agents can inform on potential mechanisms associated with clinical resistance.

PTPN11 Mutations in Patients Treated with RIG/AZA compared to a control population

	Comparator Group		RIG/AZA		
	No of Patients	%	No of Patients	%	
Total No of Patients	333				
Total No with PTPN11 mutation	9	3%			
No of Patients	300		33		
PTPN11 Mutations	4	1%	5	15%	P=0.0002
PTPN11 at Study Entry	3		2		
PTPN11 Emergent all treated	1		3		
RIG/AZA Responders Prior	149		23		
< 6 mo Treatment	0		0		
> 6 mo Treatment	1	3%	3	10%	P=0.0036

Comparison of changes in mutational analysis of pts treated with RIG/AZA revealed an emergence of PTPN11 mutations in a higher percentage of patients compared to the larger MDS population not treated with the combination.

PTPN11 mutations were present at baseline in a total of 9 (2.7%) of 333 MDS patients studied; 4/300 (1.3%) comparator group (CG) vs 5/33 (15%) RIG/AZA group (P=0.0002). Of note the mutation emerged in 3 of the responding patients to RIG/AZA who had received treatment for > 6 months, and the appearance of the mutation correlated with the onset of clinical resistance to the combination. The emergence of the mutation in 3 (10%) patients compares to 1 (0.03%) in the CG, P=0.0036.

The appearance of the mutation was associated with progressive marrow failure and transformation to AML.

METHODS

Patients participating in a clinical trial of the combination of RIG in combination with AZA had gene mutation analyses conducted serially at one of the participating institutions (Mount Sinai) while on the study.

RIG was administered on day 1 - 21 orally and AZA was administered parenterally on day 8 - 15. The cycle was repeated every 28 days. Serial samples were obtained from bone marrow and/or peripheral blood for NGS mutation analysis in conjunction with scheduled bone marrow samples.

Data from the patients on this study were compared to a broad data set of patients in the MDS program at Mount Sinai.

Efficacy Results in MDS

Number of MDS patients treated	40
Evaluable for response (8 Ph1, 25 Ph2)	33
Overall response	25 (76%)
Complete remission (CR)	8 (24%)
Partial remission	0
Marrow CR + Hematologic Improvement	10 (30%)
Marrow CR alone	6 (18%)
Hematologic Improvement alone	1 (3%)
Stable disease	8 (24%)
Progression	0
Not evaluable for response (per protocol)	7 (18%)
Median duration of treatment (months)	6 (1-37+)
Median time to initial/best response (cycles)	2/3

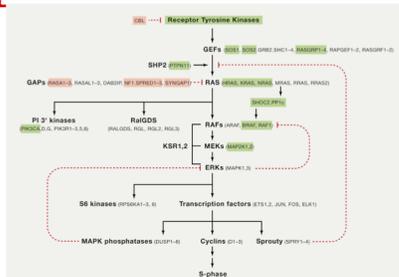
* Per IWG 2006

CONCLUSIONS

PTPN11 mutations occur much less frequently than other mutations.

The appearance of these mutations in patients treated with the RIG/AZA combination in a disproportionately higher rate than the CG suggests that the dysregulation of the Ras pathway may lead to a clinical resistance phenotype to this combination and provide insight into mechanisms of resistance.

Further correlative studies of the Ras pathway are underway.



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