A Phase II Trial of Sirolimus with Standard Induction Chemotherapy in Patients with De Novo Acute Myeloid Leukemia

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Background:

The initial treatment of FLT3 wild type acute myeloid leukemia (AML) has not significantly changed since induction therapy with Ara-C and anthracyclines was first developed. Preclinical data suggests constitutive activation of the AKT3/mammalian target of rapamycin (mTOR) pathway may play a role in pathogenesis of this disease in a subset of AML patients. Previous data from our group has shown that the presence of phosphorylated ribosomal S6 (pS6) in AML blasts as detected by flow cytometry may predict response to the combination of sirolimus and chemotherapy. Here we report the clinical and pharmacodynamics results of a phase II study of the combination of these drugs.

Methods:

Subjects had newly diagnosed AML based on WHO criteria. Subjects received oral sirolimus starting on day 1 (12 mg loading dose) then 4 mg daily on days 2–10 with idarubicin 12mg/m² days 4-7 and cytarabine 100mg/m² days 4-10. Clinical response was assessed at hematologic recovery or by day 42 using IWG for response. Samples for pharmacodynamic studies of blasts were drawn prior to treatment with sirolimus on day 1, and then again prior to dosing of idarubicin and cytarabine on day 4. Assessment of pS6 on gated blasts, a biomarker of mTORC1 activation, was assessed by flow cytometry using previously described methods.

Results:

Patient Characteristics	
AML	= 55
Age - Median	62(21-75)
Risk Classification	
High Risk	29 (53%)
Inter Risk	15 (27%)
Low	11 (20%)

Response by Risk				
	High Risk (n=29)	Intermediate Risk (n=15)	Low Risk (n=11)	Total (n=55)
CR/CRp	13	11	11	35 (64%)
PR	0	2	0	1 (2%)
Non-Response	14	2	0	17 (30%)
Death in Aplasia	2	0	0	2 (4%)

Pharmacodynamic Data:

Phospho-Flow Data by Risk Category						
	High Risk		Intermediate Risk		Low Risk	
n total	29		15		11	55
n evaluable	25	86%	7	47%	9	82%
n active	25	100%	7	100%	9	100%
n inhibited	17	68%	2	29%	8	89%
CR[p], n	13	45%	11	73%	11	100%
CR, evaluable	10	77%	5	45%	9	82%
CR, inhibited	5	50%	2	40%	8	89%
PR, n	1	3%	1	7%	0	2
PR, evaluable	1	100%	0	0%		1
PR, inhibited	0	0%				0
NR, n	13	45%	3	20%	0	16
NR, evaluable	12	92%	2	67%		14
NR, inhibited	11	92%	0	0%		11
died in aplasia	2	7%	0		0	2

PhosphoFlow Example:

Phosphoflow Data and Clinical Response in AML patients stratified by risk

Discussion:

Sirolimus and 7+3 is a well-tolerated regimen. mTORC1 appears to be activated in almost all patients at the time of diagnosis of AML as assessed by flow cytometric assessment of ribosomal S6. Inhibition of mTORC1 did not correlate with response, suggesting that AML cells may have redundant signaling pathways that regulate chemosensitivity when mTORC1 is inhibited. This data suggests further investigation of the mTORC1/2 pathway is warranted.