The Mitochondrial Metabolism Inhibitor CPI-613 in Combination with High Dose Ara-C (HDAC) and Mitoxantrone is Highly Active in High Risk Relapsed or Refractory AML

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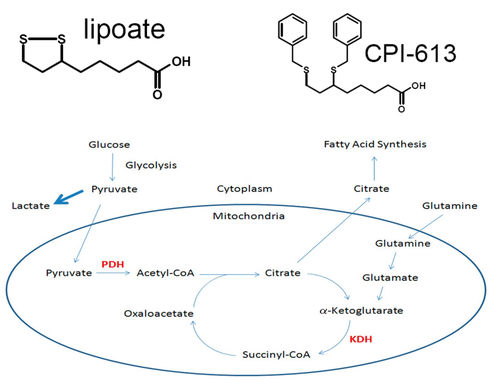
Introduction

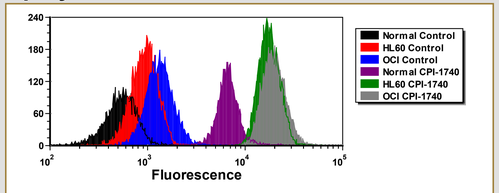
Acute myeloid leukemia (AML) is an aggressive malignancy of the bone marrow. Outcomes in relapsed disease are dismal especially in older patients and those with poor risk cytogenetics. New therapies are desperately needed. Glycolytic and mitochondrial metabolism are aberrant in cancers including AML. Altered mitochondrial function is associated with therapy-resistant leukemia cells. Pyruvate dehydrogenase complex (PDH) and α-Ketoglutarate dehydrogenase complex (KDH) are 2 key mitochondrial enzymes that require lipoate for their function. CPI-613 is a non-redox active lipoate derivative developed by Cornerstone Pharmaceuticals that inhibits lipoate dependent enzymes.

CPI-613 is a Novel Lipoate Derivative



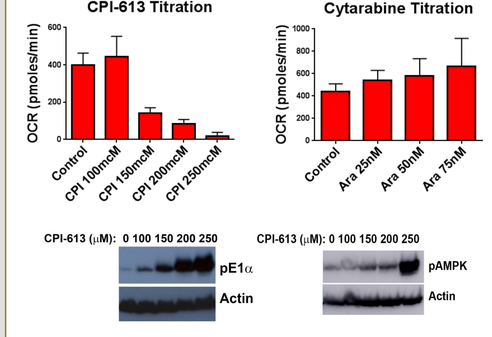
CPI-613 is a novel lipoate derivative that inhibits mitochondrial metabolism. The structure of lipoate and CPI-613 are shown above. Shown below is a simplified schematic of carbon metabolism with the CPI-613 targets PDH and KDH shown in red.

Lipoate Analogs are Preferentially Taken Up by AML Cells



The fluorescently labeled lipoate analog CPI-1740 is preferentially taken up by leukemia cells. Normal murine, lineage depleted, bone marrow cells and the human leukemia cell lines HL60 and OCI-AML3 were incubated with vehicle control or 10μM CPI-1740 for 1 hour. Cells were then analyzed for uptake by flow cytometry.

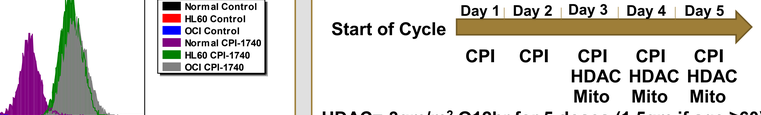
CPI-613 Inhibits and Cytarabine Stimulates Mitochondrial Metabolism



CPI-613 inhibits mitochondrial respiration. Top Left: Oxygen consumption rates (OCR) are shown for MFL2 cells treated with CPI-613 for 2 hours. Cytarabine stimulates mitochondrial respiration. Top Right: Oxygen consumption rates (OCR) are shown for MFL2 cells treated with cytarabine for 8 hours. PDH phosphorylation is increased by CPI-613. Bottom Left: MFL2 cells were incubated with CPI-613 as above and harvested for lysates. PDH E1a phosphorylation shown. Actin was used as a loading control. AMPK phosphorylation is increased by CPI-613. Bottom Right: MFL2 cells were incubated with CPI-613 as above and harvested for lysates. Actin was used as a loading control.

Phase I Clinical Trial for Patients with Relapsed or Refractory AML

Schema:



HDAC= 3gm/m² Q12hr for 5 doses (1.5gm if age ≥60)
Mito = 6mg/m² QD for 3 doses

Nadir marrow done on day 14 and if residual leukemia present a second cycle was allowed

Starting dose =500 mg/m², 1-3-6 Escalation Scheme

CPI-613 Clinical Activity Summary

Patient Characteristics	HM (94)	CHM (n=48)
Poor Risk Karyotype	17%	48%
Refractory Disease	27%	27%
Pts. with CR1 <1yr	63%	72%
Pts. ≥60 y.o.	70%	54%
Pts. who went on to HSCT	24%	27%
30 Day Mortality	13%	13%

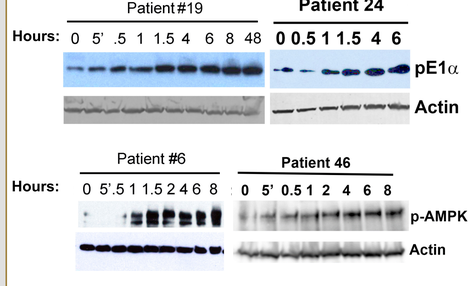
Response	HM (94)		CHM (n=48)	
	CR	CR + CRi	CR	CR + CRi
Overall	34%	41%	40%	48%
≥60 y.o.	27%	33%	38%	46%
CR1 <1yr	22%	36%	30%	38%
Poor Risk Karyotype	6%	19%	35%	48%

HM refers to a historical cohort of relapsed AML patients treated with HDAC, Mitoxantrone and Asaparaginase. HSCT=hematopoetic stem cell transplant, CR1= 1st complete remission.

Toxicities

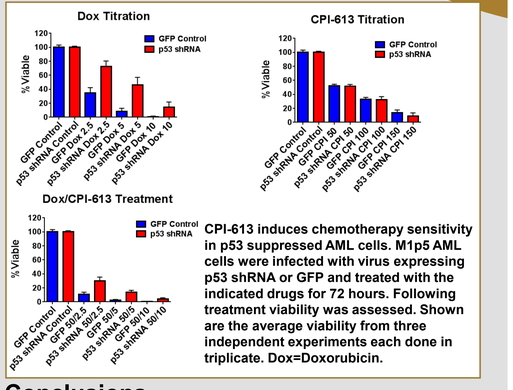
32 Most Common Toxicities	Grade 1	Grade 2	Grade 3	Grade 4	Total
Glucose, serum-high (hyperglycemia)	21	14	13	0	48
Hemoglobin (gender based)	0	5	39	4	48
Neutrophils/granulocytes (ANC)	0	0	1	47	48
Low Platelets	0	0	1	47	48
Albumin, serum-low	11	33	3	0	47
Leukocytes (total WBC)	0	0	0	47	47
Lymphopenia	0	0	0	47	47
Magnesium, serum-low	46	1	0	0	47
Potassium, serum-low	27	0	15	0	42
Calcium, serum-low	13	21	5	1	40
DIC	0	28	11	1	40
Diarrhea	5	27	7	0	39
Sodium, serum-low	28	0	5	0	33
Phosphate, serum-low	0	14	17	0	31
AST, SGOT	21	3	6	0	30
ALT, SGPT	19	5	3	0	27
Proteinuria	14	12	0	0	26
Bilirubin	14	7	4	0	25
Fatigue (asthenia, lethargy, malaise)	5	19	1	0	25
PTT (Partial Thromboplastin Time)	21	0	4	0	25
Nausea	16	8	0	0	24
Cardiac troponin T (cTnT)	5	6	7	5	23
Alkaline phosphatase	19	3	0	0	22
Febrile neutropenia	0	0	21	1	22
Left ventricular systolic dysfunction	14	5	3	0	22
Prolonged QTc interval	9	4	9	0	22
Pain: Head/headache	13	8	0	0	21
Bicarbonate, serum-low	16	4	0	0	20
Cough	18	1	0	0	19
Dyspnea (shortness of breath)	3	4	10	2	19
Pleural effusion (non-malignant)	5	8	3	2	18
Glomerular filtration rate	7	5	5	0	17

CPI-613 Induces PDH and AMPK Phosphorylation in Patients



CPI-613 induces PDH and AMPK phosphorylation. Blood samples were taken on day one of treatment at the indicated time points following infusion of CPI-613. Red blood cells were lysed, and mononuclear cells were isolated. Extracts were prepared and blotted for phosphorylated PDH and AMPK. All patients had circulating blasts at the time of sampling. Actin was used as a loading control.

CPI-613 Induces Chemotherapy Sensitivity In p53 Suppressed AML Cells



CPI-613 induces chemotherapy sensitivity in p53 suppressed AML cells. M1p5 AML cells were infected with virus expressing p53 shRNA or GFP and treated with the indicated drugs for 72 hours. Following treatment viability was assessed. Shown are the average viability from three independent experiments each done in triplicate. Dox=Doxorubicin.

Conclusions

CPI-613 is a first in class non-redox active lipoate derivative being tested in phase I clinical trial in combination with HDAC and Mitoxantrone for relapse or refractory AML.

- In the intent to treat population the response rate was 48% (19CR+4CRi out of 48 patients).
- In patients ≥60 years old the CR/CRi rate was 46% (10CR+2CRi out of 26 patients).
- In patients with poor risk cytogenetics the CR/CRi rate was 48% (8CR+3CRi out of 23 patients).
- In a historical cohort of patients treated with HDAC, mitoxantrone and asparaginase, only 19% of patients with poor risk cytogenetics achieved a CR/CRi (1CR+2CRi out of 16 patients).
- Six patients (13%) died on or before day 30 compared to 13% in the historical cohort.
- CPI-613 in combination with HDAC and mitoxantrone is a promising salvage regimen, especially in older patients and those with high risk disease.

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