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

Timothy S. Pardee MD, PhD, Kristin Stadelman MS, Scott Isom MS, Leslie R. Ellis MD, Dmitriy Berenzon MD, David D. Hurd MD, Dianna S. Howard MD, Robin Harrelson BSN, Megan Manuel MSN, Sarah Dralle MSN, Susan Lyerly PA-C and Bayard L. Powell MD

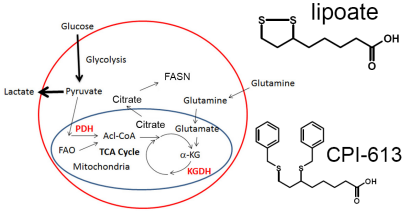
Department of Internal Medicine, Section on Hematology and Oncology, Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC

Wake Forest School of Medicine

Introduction

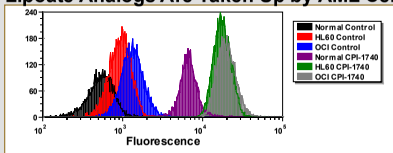
Acute myeloid leukemia (AML) is an aggressive malignancy. Outcomes in relapsed disease are dismal especially in older patients and those with poor risk cytogenetics. New therapies are desperately needed. Glycolytic and mitochondrial metabolism are aberrant in AML. Altered mitochondrial function is associated with resistance. Pyruvate dehydrogenase complex (PDH) and α-Ketoglutarate dehydrogenase complex (KGDH) 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 these enzymes.

CPI-613 is a Novel Lipoate Derivative



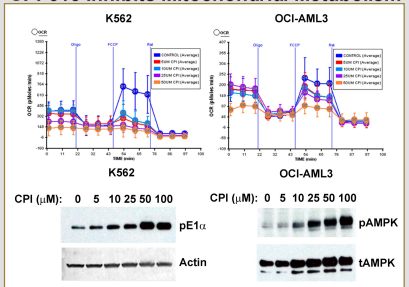
CPI-613 is a novel lipoate derivative that inhibits mitochondrial metabolism. The structure of lipoate and CPI-613 are shown on the right. Shown on the left is a simplified schematic of carbon metabolism with the CPI-613 targets PDH and KGDH shown in red.

Lipoate Analogs Are Taken Up by AML Cells



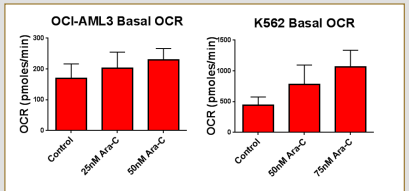
The fluorescently labeled CPI-1740 is preferentially taken up by leukemia cells. Normal murine, lineage depleted, marrow cells or AML cell lines HL60 or OCI-AML3 were incubated with 10μM CPI-1740 for 1 hour.

CPI-613 Inhibits Mitochondrial Metabolism



CPI-613 inhibits mitochondrial respiration. Top: Oxygen consumption rates (OCR) are shown for K562 and OCI-AML3 cells treated with CPI-613. Oligo=oligomycin, FCCP=Electron transport chain accelerator, RAT=Rotenone and Antimycin A. Bottom Left: PDH phosphorylation is increased by CPI-613. K562 cells were incubated with the indicated amount of CPI-613 as above and harvested for lysates. Bottom Right: AMPK phosphorylation is increased by CPI-613. OCI-AML3 cells were incubated with CPI-613 as above and harvested for lysates. Actin or total AMPK (tAMPK) was used as a loading control.

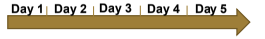
Chemotherapy Induces Mitochondrial Metabolism in AML Cells



Ara-C induces mitochondrial metabolism in AML cells. OCI-AML3 and K562 cells were treated with the concentration of Ara-C for 16 hours. Following treatment oxygen consumption was assessed using a Seahorse SFX24 Flux Analyzer. Shown are the average basal oxygen consumption rates from three independent experiments each done in triplicate. P value for OCI-AML3 is 0.0387 and for K562 is <0.0001.

Phase I Clinical Trial Schema

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

Expanded 1500, 2000 and 2500 dosing cohorts

Patient Characteristics

Patient Characteristics	HM (94)	CHM (n=67)
Poor Risk Karyotype	17%	40%
Refractory Disease	27%	31%
Pts. ≥60 y.o.	70%	54%
Pts. who went on to HSCT	24%	30%
30 Day Mortality	13%	12%

HM refers to a historical cohort of relapsed AML patients treated with HDAC, Mitoxantrone and Asaparaginase (see PMID: 26154683). HSCT=hematopoetic stem cell transplant.

CPI-613 Clinical Activity Summary

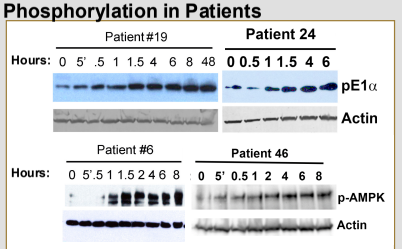
Cohort	HM (94)		CHM (n=63)	
Response	CR	CR + CRi	CR	CR + CRi
Overall	34%	41%	41%	49%
≥60 y.o.	27%	33%	36%	45%
Poor Karyotype	6%	19%	36%	44%
FLT3 Mutated	NA	NA	54%	69%

CR= complete remission, CRi= complete remission with incomplete count recovery. Four patients were not evaluable for a response.

Toxicities

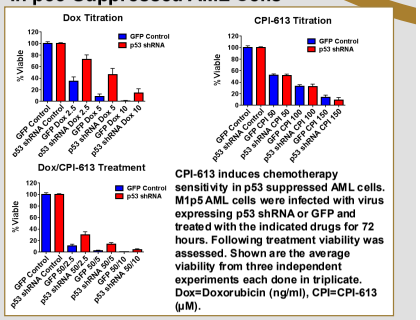
Experienced By ≥30%	Grade 1	Grade 2	Grade 3	Grade 4	Total
Hyperglycemia	29	19	18	1	67
Hemoglobin	0	5	53	9	67
Neutrophils/granulocytes	0	0	1	66	67
Platelets	0	0	1	66	67
Leukocytes	0	0	0	66	66
Lymphopenia	0	0	0	66	66
Hypomagnesemia	61	4	1	0	66
Hypoalbuminemia	17	44	4	0	65
Hypokalemia	37	0	23	0	60
Hypocalcemia	18	29	9	1	57
Diarrhea (DLT)	10	32	13	0	55
Hyponatremia	38	0	8	1	47
DIC	0	32	13	1	46
Hypophosphatemia	0	23	23	0	46
AST	28	6	7	0	41
Nausea (DLT)	21	16	1	0	38
Hyperbilirubinemia	21	10	5	1	37
ALT	23	9	4	0	36
Fatigue	10	20	3	0	33
Proteinuria	18	14	0	0	32
Partial Thromboplastin Time	25	1	5	0	31
Alkaline phosphatase	24	6	0	0	30
Febrile neutropenia	0	0	27	1	28
Cardiac troponin T	6	7	8	6	27
LV systolic dysfunction	16	6	4	0	26
Headache	16	9	1	0	26
Cough	22	3	0	0	25
Prolonged QTc interval	9	6	9	1	25
Bicarbonate, serum-low	19	5	0	0	24
Dyspnea	4	5	13	2	24
Edema: limb	17	7	0	0	24
Anorexia	9	10	4	0	23

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 (ng/ml), CPI=CPI-613 (μM).

Conclusions

- The MTD of CPI-613 when given in combination with HDAC and mitoxantrone was 2500mg/m², the DLTs were nausea and diarrhea.
- Median overall survival for the entire cohort and responders was 6.4 and 12.3 months respectively, with a median follow up of 5.2 months.
- In the intent to treat population the response rate was 46% (26CR+5CRi out of 67 patients), it was 49% in the evaluable population (63 patients).
- In patients ≥60 years old the CR/CRi rate was 45% (12CR+3CRi out of 33 evaluable patients).
- In patients with poor risk cytogenetics the CR/CRi rate was 44% (9CR+2CRi out of 25 evaluable patients) with a median survival of 4.9 months.
- In a cohort of patients treated with HDAC, mitoxantrone and asparaginase, only 19% with poor risk cytogenetics achieved a CR/CRi (1CR+2CRi out of 16) with a median survival of 2.8 months.
- In patients with mutated FLT3 the CR/CRi rate was 67% (7CR+2CRi out of 13 evaluable patients (9 ITD, 3 TKD, 1 dual)).
- Early mortality (30 day) occurred in 12% (8 patients) compared to 14% in the historical cohort.
- CPI-613 in combination with HDAC and mitoxantrone is a promising salvage regimen, especially in older patients and those with either high risk cytogenetics or FLT3 mutations. These data support a randomized trial of the CPI-613 in this patient population.

We gratefully acknowledge support from: Cornerstone Pharmaceuticals, The Doug Coley Foundation for Leukemia Research, The MacKay Foundation for Cancer Research, and the Frances P Tutwiler Fund. TSP is supported by NCI 1K08CA169809-04.