A phase I Study of the Mitochondrial Metabolism Inhibitor CPI-613 in Combination with High Dose Ara-C and Mitoxantrone for Relapsed or Refractory Acute Myeloid Leukemia

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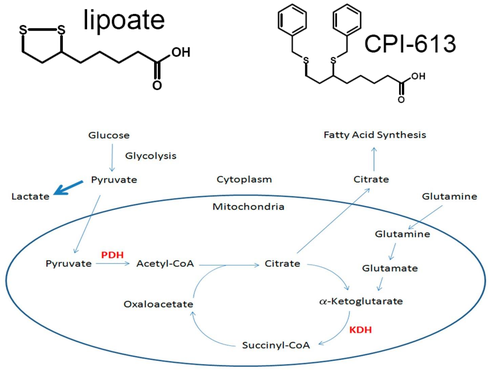
Introduction

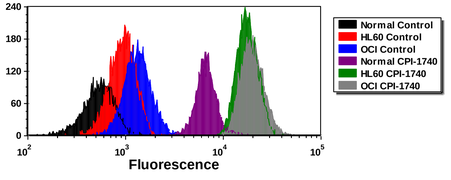
Acute myeloid leukemia (AML) is an aggressive malignancy of the bone marrow. Outcomes in relapsed disease are dismal especially in older patients and those with poor risk cytogenetics. New therapies are desperately needed. Glycolytic and mitochondrial metabolism are aberrant in cancers including AML. 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



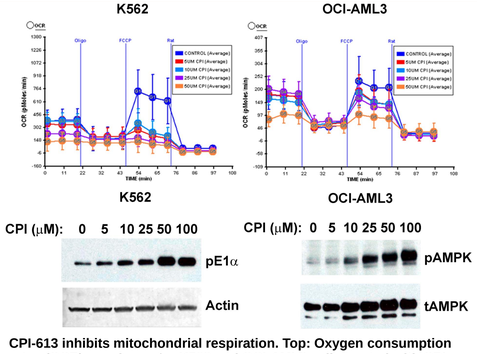
CPI-613 is a novel lipoate derivative that inhibits mitochondrial metabolism. The structure of lipoate and CPI-613 are shown above. Shown below is a simplified schematic of carbon metabolism with the CPI-613 targets PDH and KDH shown in red.

Lipoate Analogs are Preferentially Taken Up by Leukemia 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 or 10μM CPI-1740 for 1 hour. Cells were then analyzed for uptake by flow cytometry.

CPI-613 Inhibits Mitochondrial Metabolism In AML cells



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.

Phase I Clinical Trial for Patients with Relapsed or Refractory AML

Schema:

Start of Cycle — Day 1 | Day 2 | Day 3 | Day 4 | Day 5

CPI | CPI | CPI HDAC Mito | CPI HDAC Mito | CPI HDAC Mito

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.

Responders could be treated with additional cycles.

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

CPI-613 Clinical Activity Summary

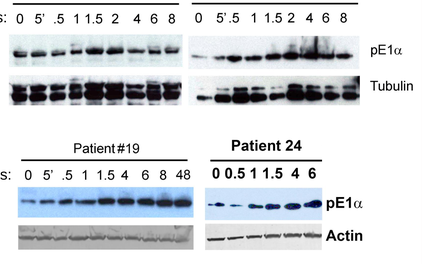
Patient	Relapsed or Refractory	Dose mg/m²	Age	Best response	Cytogenetic risk
1	Relapsed	500	56	CR	Poor
2	Relapsed	1000	73	NA	Intermediate
3	Relapsed	1000	28	MLFS	Poor
4	Relapsed	1000	55	CR	Intermediate
5	Relapsed	1000	54	CR	Poor
6	Relapsed	1000	27	MLFS	Poor
7	Relapsed	1000	58	CRi	Poor
8	Relapsed	1250	73	NA	Intermediate
9	Relapsed	1250	46	CR	Good
10	Refractory	1250	52	TF	Intermediate
11	Relapsed	1250	66	CRi	Poor
12	Relapsed	1500	67	CR	Poor
13	Refractory	1500	28	CR	Poor
14	Relapsed	1500	72	CR	Intermediate
15	Relapsed	1750	48	CR	Good
16	Relapsed	1750	58	TF	Intermediate
17	Relapsed	1750	64	CR	Intermediate
18	Refractory	2000	60	CR	Poor
19	Relapsed	2000	48	NA	Poor
20	Relapsed	2000	76	CR	Good
21	Relapsed	2000	21	TF	Poor
22	Relapsed	2250	60	TF	Poor
23	Relapsed	2250	62	TF	Intermediate
24	Refractory	2250	70	TF	Poor

NA=not assessable, CR=Complete Remission, CRi=Complete Remission with incomplete count recovery, MLFS= Morphologically Leukemia Free State, TF=Treatment Failure

Toxicities

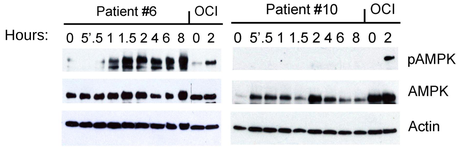
Attribution = Definite + Probable				
Toxicity	Grade 2	Grade 3	Grade 4	Grade 5
Leukocytes (total WBC) (4.8-10.8)	0	0	9	0
Platelets (160-360)	0	0	11	0
Hemoglobin (gender based)	1	7	0	0
Neutrophils (ANC) 1.6-7.3	0	0	11	0
Lymphopenia (1-5.1)	0	0	6	0
Nausea	1	0	0	0
Diarrhea	0	2	0	0
Creatinine (0.5-1.5)	0	1	0	0
Febrile neutropenia	0	1	0	0
Glomerular filtration rate	0	1	0	0
Infection with Grade 3/4 ANC: Lung	0	2	0	0
Infection with Grade 3/4 ANC: Mucosa	1	0	0	0
Infection with Grade 3/4 ANC: Blood	0	1	0	0

CPI-613 Induces PDH Phosphorylation



CPI-613 induces PDH 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. All patients had circulating blasts at the time of sampling. Actin was used as a loading control.

CPI-613 Induces AMPK Phosphorylation



CPI-613 induces 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 blotted for phos-phorylated AMPK. Both patients had circulating blasts at the time of sampling with patient 10 having a higher absolute blast count. Patient 6 was treated with 1000 mg/m² while patient 10 received 1250mg/m² Actin was used as a loading control. Patient #6 cleared her bone marrow of leukemia while patient #10 had refractory disease.

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.

- ❑ In the intention to treat population the response rate was 54% (11CR+2CRi out of 24 patients).
- ❑In patients ≥60 years old the CR/CRi rate was 55% (6/11).
- ❑In patients with poor risk cytogenetics the CR/CRi rate was 53% (7/13).
- ❑In a historical cohort of patients treated with HDAC, mitoxantrone and asparaginase, only 25% (4/16) of patients with poor risk cytogenetics achieved a CR/CRi.
- ❑Five patients (21%) died on or before day 30 compared to 22% 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. Induction of AMPK phosphorylation may serve as a predictor of response.

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