

Phase I Study of a Liposomal Carrier (CPX-351) Containing a Synergistic, Fixed Molar Ratio of Cytarabine (Ara-C) and Daunorubicin (DNR) in Advanced Leukemias

E. Feldman, J. Lancet, J.E. Koltitz, E. Asatiani, L. Mayer, A. Louie

Weill Medical College of Cornell University and New York Presbyterian Hospital, New York, NY; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; North Shore University Hospital, Manhasset, NY; Lombardi Cancer Center, Georgetown University Medical Center, Washington DC; Celator Pharmaceuticals, Inc., Princeton, NJ

Introduction

In vitro efficacy of some chemotherapy doublets has been shown to be sensitive to the molar ratio of the combination. In vivo maintenance of a particular molar ratio that maximizes synergy and avoids antagonism is not possible with current formulations due to differences of drug distribution and elimination for each agent. This obstacle to enhancing antitumor efficacy has been overcome by encapsulating chemotherapies within drug carriers (liposomes or nanoparticles) which control drug elimination, enabling delivery of synergistic drug ratios to tumor cells (CombiPlex® technology). Applying this "ratiometric" approach has enabled translation of observed in vitro synergy to the in vivo setting resulting in fixed molar ratio formulations with potent therapeutic activity. CPX-351 is a liposomal formulation of Cytarabine and Daunorubicin encapsulated at the 5:1 molar ratio, a ratio that is synergistic and avoids antagonism across multiple leukemic and solid tumor cell lines. A phase I dose escalating study was conducted with CPX-351 in patients with relapsed or refractory acute leukemia.

Methods

Patients with advanced AML, ALL and high risk MDS were eligible. CPX-351 was given by 90 minute infusion on Days 1, 3 and 5 of each induction course. Second inductions were permitted with evidence of antileukemic effect and persistence of leukemia in a Day 14 bone marrow. The starting dose was 3 u/m² (1 u = 1 mg cytarabine and 0.44 mg daunorubicin) and doses were doubled with each single patient cohort until evidence of drug effect was observed. Thereafter, 3-patient cohorts and 33% dose increments were continued until limiting toxicities signaled the end of dose escalation. Pharmacokinetic samples were collected on Days 1, 3 and 5 of the first induction course and analyzed for cytarabine, daunorubicin, Ara-U and daunorubicin by LC-MS/MS. The cut-off date for data collection was September 30, 2008.

Demographics and Disposition

Thirty-seven patients were recruited in 10 cohorts during the study's dose escalation phase. Maximum Tolerated Dose (MTD) was declared at the cohort 9 dose level (101u/m²). To confirm tolerability and collect preliminary information on efficacy, the protocol was amended to include an additional 10 patients at the MTD bringing the total number of patients to 47.

Treatment outcome: 55% had persistent leukemia, 23% achieved CR, 17% were discontinued following adverse events, 4.3% received stem cell transplant (one after CR and one after PR) and 2% were lost to follow up.

Patient Demographics and Disposition:	Cohort 1-3										Cohort 4-9										TOTAL
	CPX-351 dose(u/m ²)		3:0.2	24	32	43	57	76	101(MTD)	134	n/N		n/N		n/N		n/N		n/N		
Gender	Male	3	3	4	0	2	3	12	4	3	67	66	66	66	66	66	66	66	66	66	66
Age (yr)	Median	44.3	0.5	64.5	74	61	60	57	64.5	52	64.5	52	64.5	52	64.5	52	64.5	52	64.5	52	64.5
Race	Black/African American	1	0	1	1	1	1	11	2	21	45	45	45	45	45	45	45	45	45	45	45
ECOG	1	1	4	3	0	2	2	8	2	22	47	47	47	47	47	47	47	47	47	47	47
Diagnosis	AML	1	0	0	2	3	0	15	0	11	67	67	67	67	67	67	67	67	67	67	67
Response to Last Line of Therapy	None	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Reason Off Study	CR	0	2	3	2	3	2	7	4	27	57	57	57	57	57	57	57	57	57	57	57
(SAEs) Adverse Event		0	1	1	1	0	0	4	1	8	17	17	17	17	17	17	17	17	17	17	17
Persistent Leukemia		4	3	2	1	3	3	7	3	28	59	59	59	59	59	59	59	59	59	59	59
Second Marrow Transplant		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Discontinuation of Sponsor		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lost to Follow-up		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Complete Remission		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CR		0	2	3	2	3	2	7	4	27	57	57	57	57	57	57	57	57	57	57	57
CR		0	2	1	2	0	1	12	2	20	43	43	43	43	43	43	43	43	43	43	43

* One of the 33 patients achieved a CR
* One of the 10 patients transferred to CR2 in another trial.

Conflict of Interest Disclosure

L. Mayer and A. Louie are employees of Celator Pharmaceuticals and own stock or stock options in the company. There are no other relevant conflicts of interest to disclose.

Safety Profile of CPX-351

Table 2: Non-hematological High Grade Adverse Events	CPX-351 dose (u/m ²)	Cohort 1-3		Cohort 4		Cohort 5		Cohort 6		Cohort 7		Cohort 8		Cohort 9		TOTAL
		n/N	n/N	n/N	n/N	n/N	n/N	n/N	n/N	n/N	n/N	n/N	n/N	n/N	n/N	
Infections																
Febri/Neutropenia		3	0	8	2	4	0	4	0	17	7	47				
Bacteremia		0	0	7	0	1	0	0	0	9	25					
Fungemia		0	0	7	0	0	0	0	0	9	25					
Septic/Shock		0	0	4	0	0	0	0	0	11	34					
UTI		0	0	0	0	0	0	0	0	1	3					
Candida		0	0	1	0	0	0	0	0	1	3					
Cryptococcal Infection		0	0	1	0	0	0	0	0	2	6					
Feeding Events																
GI bleeding		1	0	0	0	0	0	0	0	1	3					
Mucocystitis		1	0	0	0	0	0	0	0	1	3					
CR		0	0	2	1	0	0	0	0	4	11					
GI																
Apnea		0	0	0	0	0	0	0	0	1	3					
Constipation		0	0	0	0	0	0	0	0	1	3					
Depressed Level of Consciousness		0	0	0	0	0	0	0	0	1	3					
Metabolic																
Hypocalcemia		0	0	2	1	1	1	1	1	14	34					
Metabolic Acidosis		0	0	1	0	0	0	0	0	1	3					
Hypophosphatemia		1	0	0	0	0	0	0	0	1	3					
Skin																
Rash		1	0	1	0	0	0	0	0	3	8					
Cardiovascular																
LV Dysfunction/Edema		0	0	1	0	0	0	0	0	2	6					
Pericardial Effusion		0	0	1	0	0	0	0	0	1	3					
Arrhythmia		0	0	0	0	0	0	0	0	0	0					
Altered Perfusion		0	0	0	0	0	0	0	0	1	3					
Hypertensive Crisis/Stroke		0	0	0	0	0	0	0	0	1	3					
Respiratory																
Dyspnea		1	0	2	0	0	0	0	0	3	8					
ARDS		0	0	0	0	0	0	0	0	0	0					
Hypoxia		1	0	0	0	0	0	0	0	2	6					
Aspiration		0	0	0	0	0	0	0	0	1	3					
Cough		1	0	0	0	0	0	0	0	1	3					
Gastrointestinal																
Nausea/vomiting		0	0	0	0	0	0	0	0	1	3					
Diarrhea		0	0	0	0	0	0	0	0	0	0					
Mucositis		0	0	0	0	0	0	0	0	2	6					
Hepatic																
Hepatitis/ALT		0	0	1	0	0	0	0	0	1	3					
AST/ALT		0	0	1	0	0	0	0	0	1	3					
Renal																
Acute Renal Failure		1	0	1	0	0	0	0	0	2	6					
General																
Fatigue		0	0	1	0	0	0	0	0	1	3					
Lithium toxicity		0	0	1	0	0	0	0	0	1	3					
Pyrexia		1	0	0	0	2	0	3	8							
Asthenia/Weakness		0	0	0	0	1	0	1	3							

- 29 deaths occurred during the study with 19 (66%) due to persistent leukemia and 4 (14%) due to infections, 2 (7%) respiratory failure, 1 (3%) cerebral hemorrhage, 1 (3%) status epilepticus, 1 (3%) diarrhea, 1 (3%) uremia;
- At 101 u/m² 3 deaths (16%) occurred by day 30, one death (5%) by day 60 and 3 deaths (16%) after day 60;
- Days 31-60 mortality was 15% (7 patients), days 61-90 was 11% (5 patients) and long term mortality beyond day 90 stood at 23% (11 patients).
- 34 SAEs occurred in 30 patients with nearly half caused by potential or documented infections including febrile neutropenia (10 events), fever (5), pneumonia (5), bacteremia (2), sepsis (1), cellulitis (1) and death secondary to infection (1) or to bleeding episodes including mucosal bleeding (2), epistaxis (1), GI bleeding (1) and hemorrhagic stroke (1);
- Grade 3-4 non-hematological AEs are shown for the dose levels 5-10 in Table 2, Grade 3 and 4 AEs, especially infections, are dose dependent;
- Dose limiting toxicities occurred in cohort 10 (134 u/m²) and included single patients with hypertensive crisis (Grade 4), LV dysfunction (Grade 3) and persistent thrombocytopenia requiring platelet transfusion support beyond Day 56;
- Major GI toxicity was uncommon with 1 patient having Grade 3 N+V (134 u/m²), 1 patient with Grade 5 diarrhea (101 u/m²) and single patients having Grade 3 (134 u/m²) and Grade 4 (101 u/m²) mucositis, no other major GI toxicities were observed;
- At 134u/m² 1 patient had shortness of breath (LVEF52%—29%) in the setting of enterococcal bacteremia after 546mg/m² of lifetime cumulative DNR exposure, a second patient who received 101u/m² x 2 inductions (lifetime cumulative DNR=966mg/m²) had orthopnea, both patients recovered. Among the 17 patients documented to have received at least 400mg/m² of anthracycline only 2, described above, developed clinically apparent cardiac dysfunction.

Table 3:

Table 3: Mortality by period	Cohort 1-3		Cohort 4		Cohort 5		Cohort 6		Cohort 7		Cohort 8		Cohort 9		TOTAL
	n/N	n/N	n/N	n/N	n/N	n/N	n/N	n/N	n/N	n/N	n/N	n/N	n/N	n/N	
Deaths															
0-30 days	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31-60 days	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
61-90 days	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
>90 days	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CR															
0-30 days	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31-60 days	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
61-90 days	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
>90 days	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pharmacokinetics of CPX-351

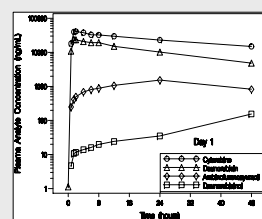


Figure 1. Day 1 Mean Plasma Cytarabine, Daunorubic