

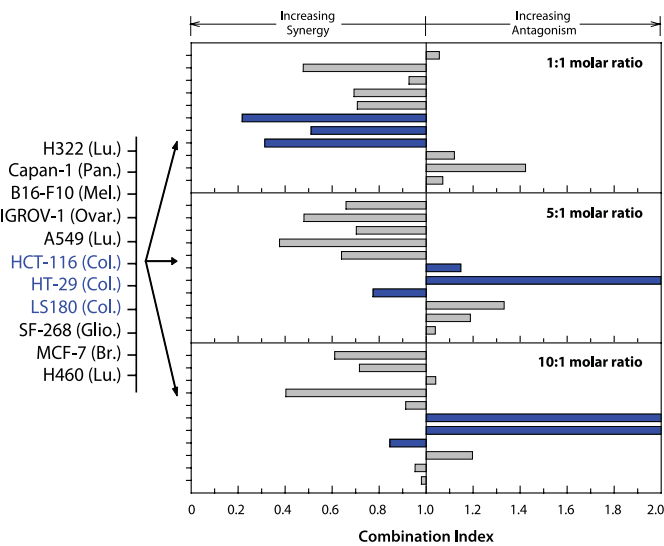
Phase 1 Study of CPX-1, a Fixed-Ratio Formulation of Irinotecan (IRI) and Floxuridine (FLOX), in Patients with Advanced Solid Tumors

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Introduction

Anticancer drug combinations can act synergistically, additively or antagonistically against tumor cells in vitro depending on the ratios of the individual agents comprising the combination. The clinical relevance of drug ratios, however, has not previously been investigated. Combination chemotherapy treatment regimens continue to be developed based on the maximum tolerated doses of the individual agents.

In Vitro Activity of Irinotecan:Floxuridine Depends on Molar Ratios



We studied the ratio dependence of Irinotecan (IRI) and Floxuridine (FLOX) in 11 cell lines by applying the Chou and Talalay algorithm. This algorithm critically defines a quantity termed the Combination Index and assigns it a value of 1 if the ratio is additive, a value of less than one if the ratio is synergistic and a value of greater than 1 if the ratio is antagonistic. For Irinotecan:Floxuridine, the 1:1 molar ratio was generally synergistic and the 10:1 molar ratio was generally antagonistic, particularly in colorectal cell lines. Due to the disparate pharmacokinetics of these two drugs, administration of the combination as an “unbridled cocktail” would result in a range of ratios including antagonistic ratios with a resultant loss of activity.

CPX-1 is a liposomal formulation of IRI and FLOX in a fixed 1:1 molar ratio (selected as optimal in vitro and confirmed to be synergistic in vivo in preclinical tumor models). CPX-1 overcomes the dissimilar pharmacokinetics (PK) of the individual drugs, enables sustained maintenance of this ratio after IV administration, and was evaluated in a Phase 1 open-label, dose escalation study.

Objectives

Primary:

- To determine the recommended Phase II dose of CPX-1 (defined as maximum tolerated dose [MTD] in this protocol) as a bi-weekly infusion for patients with advanced solid tumors.

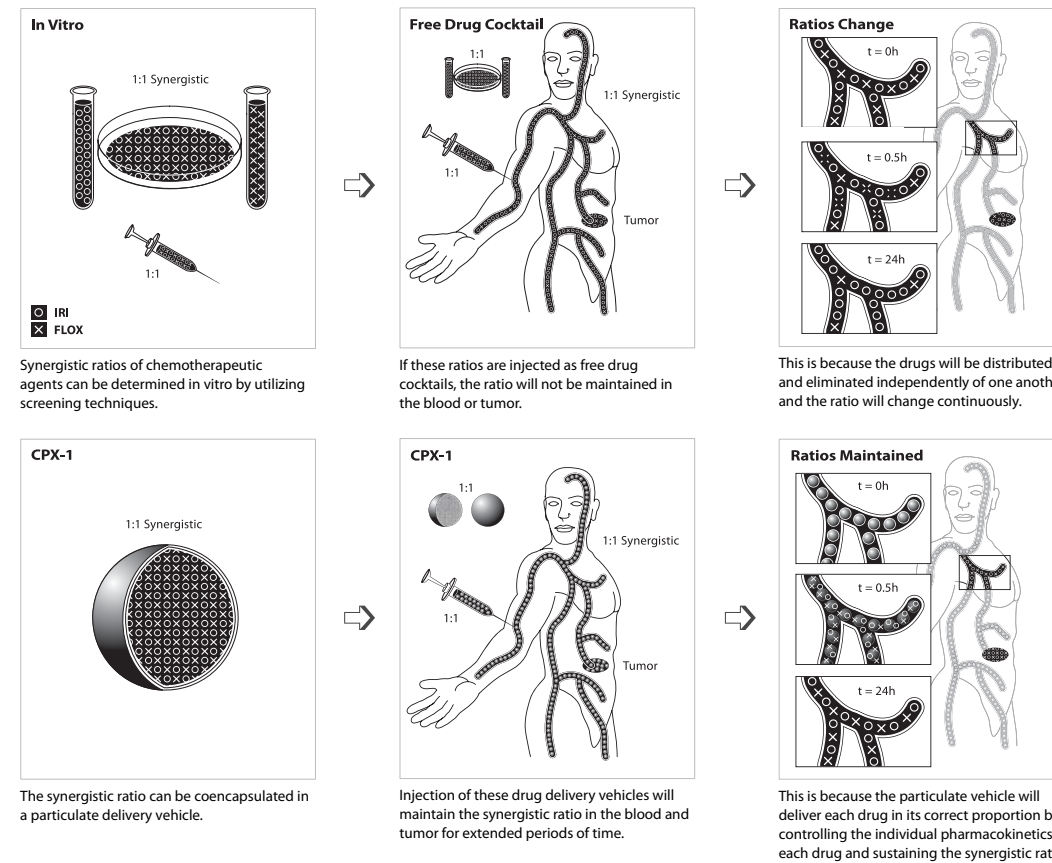
Secondary:

- To evaluate the safety and dose-limiting toxicities (DLT) of CPX-1.
- To determine the pharmacokinetic parameters of CPX-1 administered in this schedule.
- To assess preliminary efficacy information of CPX-1 administered in this schedule.

Materials and Methods

Starting dose was 30 U/m² (1 Unit of CPX-1 contains 1 mg IRI + 0.36 mg FLOX) given on day 1 and 15 of each 28-day cycle. Dose escalation was by modified Fibonacci with 4 subjects/cohort. Eligibility included: adults (≥18 yo) with advanced solid tumor; ECOG PS ≤ 2; adequate bone marrow/liver/renal function. PK analysis was done on day 1 and 15 of the first cycle.

Synergistic Molar Ratios Enhance Anti-Tumor Activity



CPX-1 Maintains Synergistic Molar Ratios in Patients

Pharmacokinetic Methods

Analytical Assay

Validated LC-MS/MS methods were used to measure the following analytes:

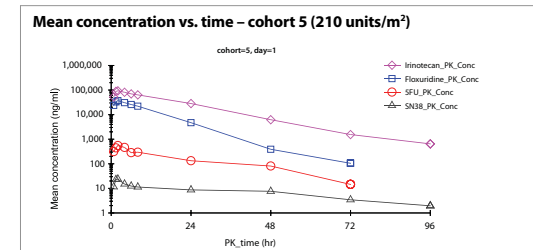
Irinotecan	linear range = 0.240 – 120 ug/ml
SN-38	linear range = 1.00 – 1,000 ng/ml
Floxuridine	linear range = 50 – 30,000 ng/ml
5-fluorouracil	linear range = 10 – 2,000 ng/ml

Sampling

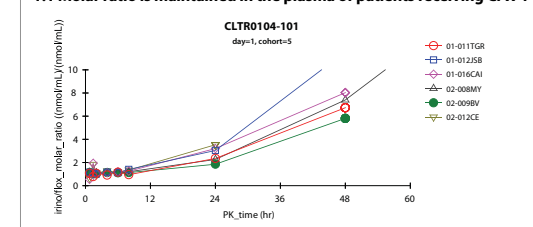
Day 1: 0, 0.75, 1.42, 2, 4, 6, 8, 24, 48, 72, 96, 168 hrs post start infusion
Day 15: 0, 0.75, 1.42, 2, 4, 6, 8 hrs post start infusion

PK Data Analysis

Non-compartmental analysis with WinNonLin v. 4.1



1:1 Molar ratio is maintained in the plasma of patients receiving CPX-1



Comparison of PK of Irinotecan when given as conventional drug or CPX-1

Rx	dose ^a mg/m ²	N	IRINOTECAN		SN38	
			C _{max} ng/ml	AUC ng-h/ml	C _{max} ng/ml	AUC ng-h/ml
Irinotecan ^b	240	3	2,810	18,091	41	638
	340	6	3,392	22,998	56	714
CPX-1	30	4	13,782	285,601	5	226
	60	4	25,179	536,680	6	192
	100	4	52,773	1,011,357	14	500
	150	4	78,706	1,688,366	16	533
	210	6	93,552	1,831,229	24	730
	270	4	147,849	3,567,793	31	1,161

^a Dose of Irinotecan HCl trihydrate

^b Irinotecan data from Pitot, HC et. al. (2000) Clin. Cancer Res. 6:2236-44

Preliminary Pharmacokinetic Conclusions

- Both parent drugs and their major circulating metabolites were detected in the plasma of all patients. All analytes disappeared from the plasma in a monophasic manner.
- The 1:1 molar ratio of Irinotecan to Floxuridine was maintained in the plasma for 8-24 hours on days 1 and 15 in all patients.
- Both peak systemic concentration and total systemic exposure tended to increase proportionately with dose on days 1 and 15.
- For all doses, the accumulation ratios of systemic exposure (AUC₀₋₂₄ on day 15 divided by AUC₀₋₂₄ on day 1) and peak concentration (C_{max} on day 15 divided by C_{max} on day 1) showed values very close to 1, suggesting no plasma accumulation for both drugs after multiple doses.

CPX-1 Demonstrates Anti-Tumor Activity

CPX-1 Phase 1 Trial Data

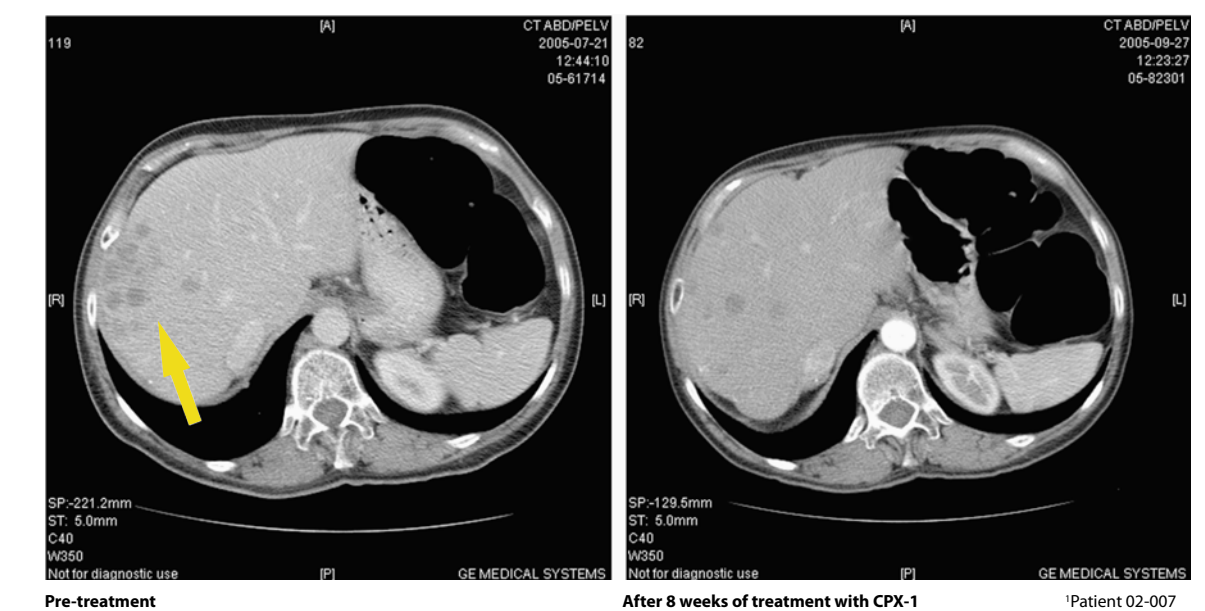
Patient #	dose mg/m ²	Primary	Best Response	Progression-free survival (mos.)	Overall survival (mos.)
02-002	30	Gastric	Prog	1.6	1.6
02-001	30	Renal	Prog	1.8	5.3
01-001	30	Breast	Stable	3.6	9.8+
01-002	30	Breast	Stable	3.6	6.9
01-004	60	Colon	Prog	0.8	3.6
01-005	60	Esophageal	Prog	1.5	1.5
01-003	60	Prostate	Stable	3.5	7.5+
02-003	60	Gastric	Stable	5.3	6.3+
02-004	100	Colon	Stable	3.5	4.2+
01-006	100	Pancreatic	Stable	3.4	3.4
01-007	100	Ovarian	Stable	8.8+	10.6+ ^a
02-005	100	Colon	Stable	10.4+	10.4+ ^a
01-010	150	Ovarian	Stable	1.9+ ^b	3.0+
02-006	150	Sarcoma	Stable	4.2+	4.2+
01-008	150	NSCLC	PR	6.3	7.3+
02-007	150	Colon	PR	5.6	5.6+
02-008	210	Pancreatic	Stable	7.2	7.2+
02-009	210	Pancreatic	Prog	1.8	4.4+
01-011	210	Colon	Stable	3.8	3.8+
01-012	210	Colon	Stable	3.5+	3.5+
02-012	210	Colon	Prog	1.9	1.9+
01-016	210	Osteosarcoma	Stable	3.2	3.7
02-010	270	Colon	N/A ^c	N/A	0.8+
02-011	270	Sphenoid Sinus	Stable	3.9+	4.7+
01-014	270	Esophageal	N/A ^c	N/A	0.4
01-015	270	Ovarian	N/A ^c	N/A	3.6+

^a The last evaluation was not verified.

^b Patient withdrew consent; stable disease censored at 1.9 months.

^c Patients withdrawn before disease evaluation.

Decrease in Liver Metastasis in a Patient¹ with Colorectal Cancer



Conclusion

CPX-1 represents a new approach to developing drug combinations in which drug ratios are pre-selected in vitro based on optimal anti-tumor activity and maintained systemically through pharmacokinetic control. Phase 2 studies are planned with a recommended dose of 210 U/m² of CPX-1.