

INTRODUCTION

Drug combinations can have synergistic, additive or antagonistic activity against tumor cells in vitro depending on the molar ratio of the individual agents. We used delivery technology to overcome the inherently dissimilar PK of individual drugs, thus enabling us to maintain predetermined synergistic ratios after iv administration and deliver them to tumors (Combiplex™ Technology).

The development of CPX-1 (Irinotecan HCl:Floxuridine) Liposome Injection was based on 1) defining an anti-tumor synergistic ratio of the two active moieties, Irinotecan HCl and Floxuridine, using cell-based screening assays and 2) designing a liposomal drug carrier to maintain this ratio after intravenous administration. A 1:1 molar ratio of the two drugs was determined to be synergistic based on in vitro and in vivo tumor models. CPX-1 has displayed markedly superior efficacy over conventional irinotecan:floxuridine cocktails in preclinical tumor models and has shown promising early signs of anti-tumor activity in heavily pre-treated cancer patients (Proc ASCO 2006, Abstract 2014). The pharmacokinetics of total irinotecan and floxuridine in plasma after IV administration of CPX-1 in mice, rats, dogs and humans (Phase I study CLTR0104-101) were assessed.

METHODS

On each dosing day (once per week for preclinical studies and once every two weeks in humans) escalating doses of CPX-1 were administered IV as a bolus injection (mice) or a 1 hour (rats, dogs) or 1.5 hr (humans) infusion. Plasma samples were collected at intervals after the first and second doses and analyzed for irinotecan, SN-38, floxuridine and 5-FU by HPLC (mice) or LC/MS-MS methods. For the LC/MS-MS methods, the linear ranges of the analytes were as follows:

irinotecan	0.240 – 120 ug/ml
SN-38	1.00 – 1,000 ng/ml
floxuridine	50 – 30,000 ng/ml
5-fluorouracil	10 – 2,000 ng/ml

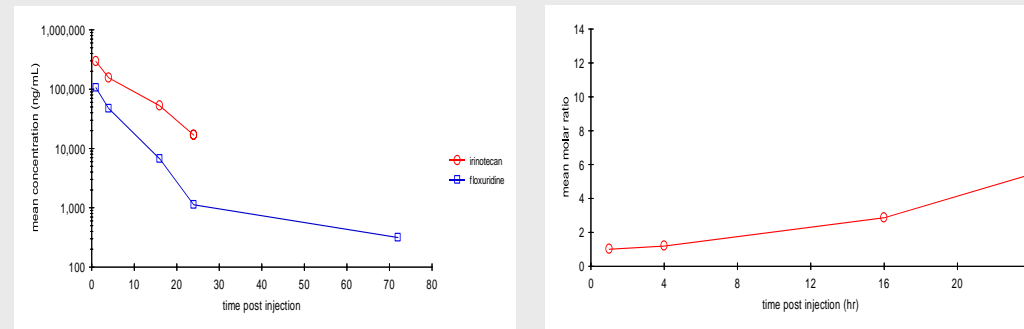
Non-compartmental PK analysis was done using WinNonLin v.4.

RESULTS

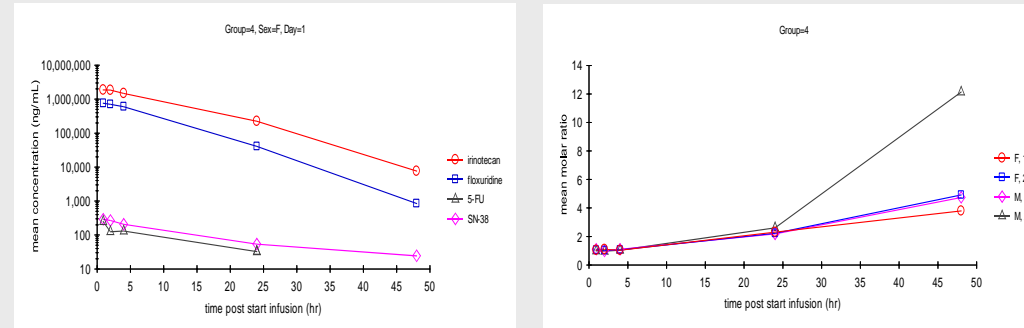
The maximum tolerated dose of CPX-1 in mice was ~150 units/m² (where 1 unit=1 mg irinotecan HCl trihydrate + 0.36 mg floxuridine); >600 units/m² in rats, 200 units/m² in dogs and 210 units/m² in humans. The targeted 1:1 molar ratio of irinotecan and floxuridine was maintained for 8-24 hours in the plasma after IV administration to mice, rats, dogs and humans. The metabolites SN-38 and 5-FU were present in all subjects examined indicating that both drugs in CPX-1 are bioavailable. In all cases, the AUC 0-inf of total irinotecan in the plasma after CPX-1 greatly exceeded the AUC 0-inf of conventional irinotecan (based on historical data). Both peak concentration and total systemic exposure tended to increase proportionately with dose. The dog provides a reasonable model for the human safety of CPX-1 based on maximum tolerated dose (in units/m²) and overall exposure (plasma AUC 0-last) to total irinotecan, total floxuridine, SN-38 and 5-FU.

RESULTS

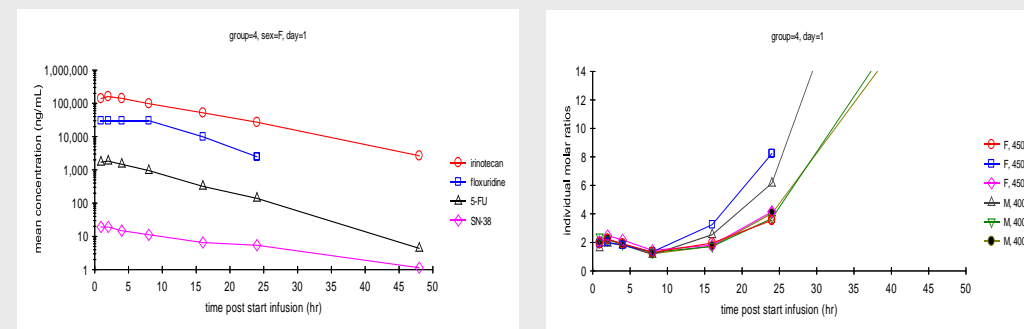
Mean plasma concentrations and molar ratio vs time in mice after a single iv bolus injection of 50 units/m² CPX-1 (50 mg/m² irinotecan + 20 mg/m² floxuridine)



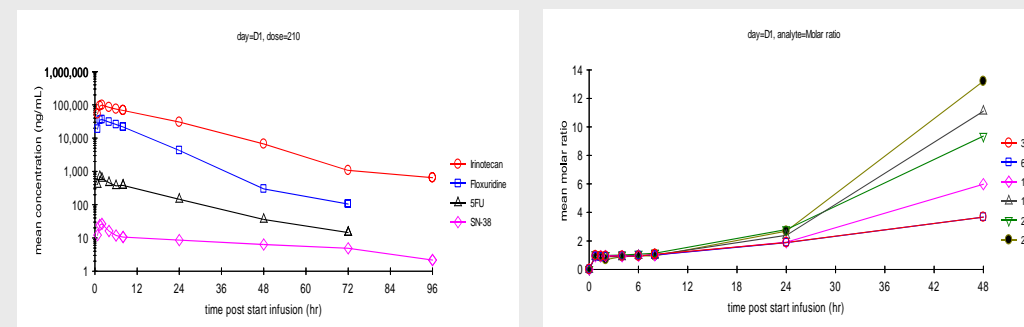
Mean plasma concentrations and molar ratio vs time in rats after a single infusion of 600 units/m² CPX-1 (600 mg/m² irinotecan + 216 mg/m² floxuridine)



Mean plasma concentrations and molar ratio vs time in dogs after a single iv bolus injection of 200 units/m² CPX-1 (200 mg/m² irinotecan + 72 mg/m² floxuridine)



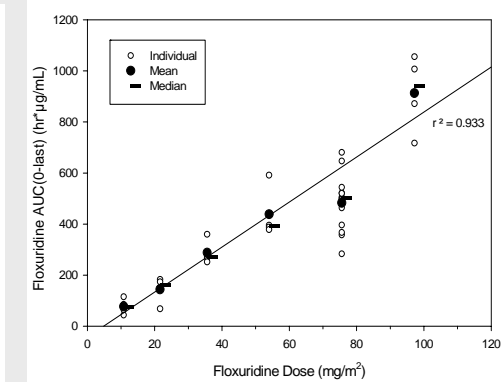
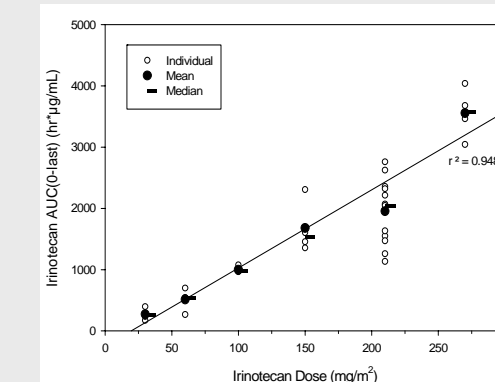
Mean plasma concentrations and molar ratio vs time in patients after a single infusion of 210 units/m² CPX-1 (210 mg/m² irinotecan + 76 mg/m² floxuridine) (n=13)



RESULTS

In the phase I trial of CPX-1 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 8-12 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 (AUC0-8 on day 15 divided by AUC0-8 on day 1) and peak concentration (Cmax on day 15 divided by Cmax on day 1) showed values very close to 1 suggesting no plasma accumulation for both drugs after multiple doses.

	Dose	units/m ²	30	60	100	150	210	270
		N	mean	mean	mean	mean	mean	mean
Irinotecan	Cmax	ng/ml	13,783	25,179	52,773	78,706	98,611	151,033
	AUCinf	hr*ng/ml	282,174	532,910	1,003,331	1,686,604	1,964,375	3,569,151
	T 1/2	hr	11.26	11.58	9.49	9.63	8.61	8.91
	Cl	ml/hr	174.19	215.56	154.68	137.88	180.66	124.13
	Vd	ml	2,756.50	3,507.57	2,111.24	1,873.48	2,198.20	1,600.96
SN-38	Cmax	ng/ml	4.50	6.29	14.08	15.77	26.58	31.07
	AUCinf	hr*ng/ml	223.83	189.20	497.83	532.71	769.06	1,158.64
	T 1/2	hr	42.81	26.30	33.57	67.71	31.51	31.32
Floxuridine	Cmax	ng/ml	5,547	10,258	20,641	33,314	36,954	61,164
	AUCinf	hr*ng/ml	79,304	147,463	290,581	440,089	486,905	914,658
	T 1/2	hr	7.47	7.29	6.85	6.47	6.02	6.16
	Cl	ml/hr	259.43	327.72	224.22	218.86	293.18	203.30
	Vd	ml	2,820.92	3,363.02	2,208.58	2,031.39	2,508.00	1,794.80
5-Fluorouracil	Cmax	ng/ml	200.47	147.55	384.34	456.57	789.36	1,480.02
	AUCinf	hr*ng/ml	3,062.18	3,876.84	9,328.97	12,444.25	10,382.63	18,912.89
	T 1/2	hr	12.87	14.14	17.45	11.89	12.96	8.45



CONCLUSIONS

CPX-1 is a novel drug that represents a new approach to developing drug combinations in which drug ratios are pre-selected in vitro based on synergistic anti-tumor activity and maintained systemically using drug delivery technology. Such pharmacokinetic control is achieved across animal species and is associated with significant therapeutic activity, both preclinically and clinically. CPX-1 is in a phase II trial in patients with metastatic colorectal cancer.