

A multi-center, phase 2 study of CPX-1 liposome injection in patients with advanced colorectal cancer

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INTRODUCTION

CPX-1 is a liposomal formulation of a fixed combination of the antineoplastic drugs irinotecan HCl and floxuridine. The two drugs are present in a fixed 1:1 molar ratio within a liposomal carrier. This ratio was found *in vitro* to have synergy against cancer cell models, while other molar ratios produced only additive or antagonistic effects. Ratio-dependent synergistic activity of drug combinations was examined in cell lines *in vitro* utilizing MTT cytotoxicity assays and median-effect mathematical analysis derived by Chou & Talalay, which defines a quantity termed the Combination Index (CI). A CI value of 0.9-1.1 is additive, a value <0.9 indicates a ratio is synergistic and a CI value > 1.1 indicates a ratio is antagonistic.

Drug Combination	Cell Line	Tumor type	CI @ ED75				
			10:1	5:1	1:1	1:5	1:10
Irinotecan + Floxuridine	Capan-1	pancreatic	0.7	0.5	0.5	0.5	1.3
	HT-29	colorectal	10.0	3.4	0.5	0.3	0.8
	SF-268	CNS/glioma	1.2	1.3	1.1	1.1	0.8
	HCT-116	colorectal	4.4	1.0	0.2	0.2	0.2
	LS180	colorectal	0.5	1.1	0.3	0.8	0.9
	A549	lung	0.9	1.0	0.7	0.6	0.9
	L1210	leukemia	0.6	0.8	0.8	0.9	1.0
	A375	melanoma	1.2	0.8	0.6	0.6	0.9

The liposomal carrier enables maintenance of synergistic ratios following systemic administration and resulted in enhanced efficacy within *in vivo* preclinical models and produced promising antitumor activity in a Phase I study (Proc ASCO 2006, Abstract 1014). The phase II study evaluated CPX-1 treatment for irinotecan-naïve and irinotecan-refractory subjects with metastatic colorectal cancer.

METHODS

This study was a multicenter, open-label, trial. Patients received CPX-1 210 u/m² (210 mg/m² irinotecan + 75.6 mg/m² floxuridine) over 90 minutes every two weeks. One cycle was defined as 2 treatments over 4 weeks. Patients were restaged every two cycles and all patients restaged at least once are included for efficacy analysis. All patients who received at least part of a dose are included for safety analysis.

Adults with histologically confirmed advanced metastatic colorectal cancer, measurable disease as defined by RECIST, and ECOG performance status of 0 or 1 were eligible. Minimum organ function included: ANC > 1.5x 10⁹/L, Platelet count > 100 x 10⁹/L, serum creatinine < 1.5x ULN, serum AST and ALT <3x ULN (5x if caused by liver metastases), and serum bilirubin < 1.25x ULN (< 2x if caused by liver metastases). Irinotecan-naïve subjects had prior treatment with ≤ two regimens overall; one adjuvant/neoadjuvant regimen and no more than one regimen for advanced/metastatic disease. Irinotecan-refractory subjects had disease progression within 6 months of prior irinotecan-containing treatment and started CPX-1 treatment within 12 months of disease progression following irinotecan.

DEMOGRAPHICS

Patient characteristics of the irinotecan-naïve and irinotecan-refractory groups were very similar for sex, age, race, ethnicity, weight, height and BSA. The irinotecan-naïve group had a higher proportion of patients with an ECOG Performance Status 1 (61.5%) whereas the irinotecan-refractory group had a slight majority of patients with an ECOG Performance Status 0 (51.5%).

DEMOGRAPHICS AND DISPOSITION

		Irinotecan-Naïve n=26	Irinotecan-Refractory n=33	Total N=59
Gender	Male	13 (50%)	18 (54.5%)	31 (52.5%)
	Female	13 (50%)	15 (45.5%)	28 (47.5%)
Age (yr)	Mean	60	60.2	60.1
	Median	59	59	59
	Min-Max	46-77	36-81	36-81
Race	Caucasian	20 (76.9%)	26 (78.8%)	46 (78.0%)
	Black	4 (15.4%)	2 (6.1%)	6 (10.2%)
	Asian	1 (3.8%)	2 (6.1%)	3 (5.1%)
	Other	1 (3.8%)	2 (6.1%)	3 (5.1%)
	Unknown	0	1 (3.0%)	1 (1.7%)
Ethnic Group	Hispanic	1 (3.8%)	2 (6.1%)	3 (5.1%)
	Non-Hispanic	25 (96.2%)	31 (93.9%)	56 (94.9%)
Weight (kg)	Median	73.4	73.6	73.6
	Min-Max	51.6 - 114.5	48.2 - 137.7	48.2 - 137.7
Height	Median	165.1	162.6	163.7
	Min-Max	154.9 - 193.0	152.4 - 182.9	152.4 - 193.0
BSA	Median	1.84	1.83	1.83
	Min-Max	1.5 - 2.4	1.5 - 2.5	1.5 - 2.5
ECOG	0	10 (38.5%)	17 (51.5%)	27 (45.8%)
	1	16 (61.5%)	16 (48.5%)	32 (54.2%)
Patients (%) Ongoing Treatment		1 (3.8%)	3 (9.1%)	4 (6.8%)
		25 (96.2%)	30 (90.9%)	55 (93.2%)
Patients (%) Terminating Study	Consent withdrawn	1 (3.8%)	3 (9.1%)	4 (6.8%)
	Death	2 (7.7%)	0	2 (3.4%)
	Disease progression	16 (61.5%)	19 (57.6%)	35 (59.3%)
	Adverse Event			
	Study Drug Related	6 (23.1%)	6 (18.2%)	12 (20.3%)
	Not Study Drug Related	0	2 (6.1%)	2 (3.4%)

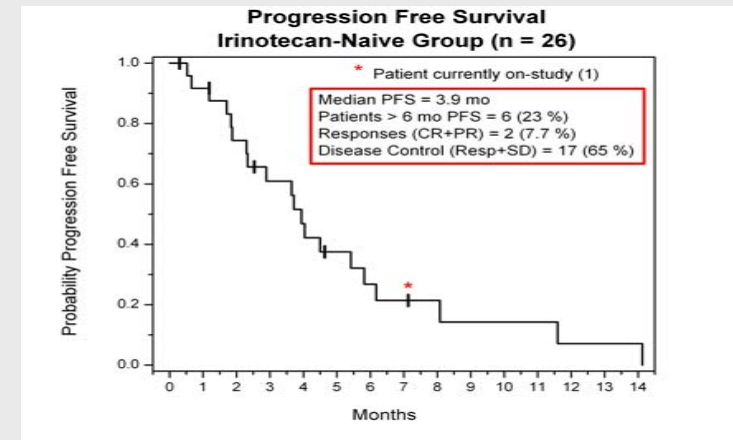
DOSE INTENSITY

	Irinotecan-Naïve n=26	Irinotecan-Refractory n=33	Total n=59
Single Dose Received	5	3	8 (13.6%)
Multiple Doses Received			
All doses on time (delay < 7 days) and at 210 u/m ²	8	10	18 (30.5%)
All doses on time and with dose reduction to 150 u/m ²	1	0	1 (1.7%)
One or more doses delayed but all doses at 210 u/m ²	1	5	6 (10.2%)
One or more doses delayed and dose reduction to 150 u/m ²	7	12	19 (32.2%)
One or more doses delayed and dose reduction to 100 u/m ²	4	3	7 (11.9%)
Total	26	33	59 (100.0%)
Dose Intensity for patients with 2 or more doses			
100- 90%	8	10	18 (30.5%)
89- 80%	2	4	6 (10.2%)
79- 70%	3	2	5 (8.5%)
69- 60%	4	4	8 (13.6%)
59- 50%	0	5	6 (10.2%)
40- 49%	4	4	8 (13.6%)
Total	21	30	51 (86.4%)

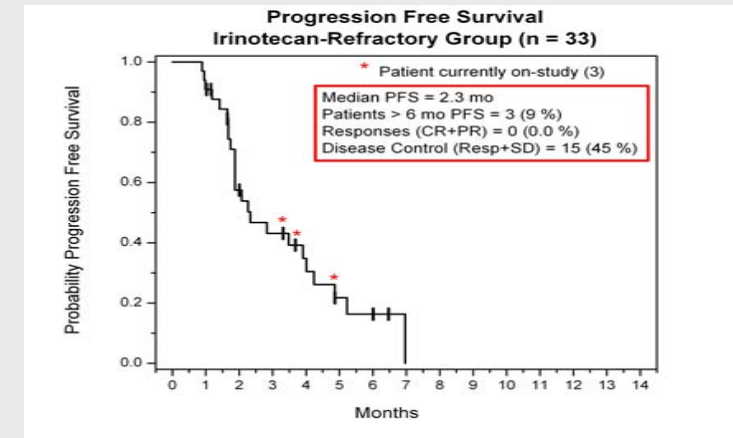
Treatment intensity of ≥ 80% was achieved in 24 of 59 patients (40%). The remainder received less intensive treatment including 8 of 59 patients (13.6%) who had only a single dose. Patients in the irinotecan-refractory group had dosing intensity similar to those in the irinotecan-naïve group.

- Patients receiving all doses on time and at the full dose (210u/m²) were identical in the 2 groups (30.7% versus 30.3%)
- Patients that received a single dose only and patients that received dose reductions to 100u/m² were more common in the irinotecan-naïve group than the irinotecan-refractory group.
- The irinotecan-refractory group had slightly more patients with dose delays and dose reductions to 150u/m² (36.4% irinotecan-refractory versus 26.9% irinotecan-naïve)

EFFICACY



Results for progression-free-survival (3.9 mo), response rate (7.7%) and disease control (65%) appeared better than results reported by Tournigand, *et al.* for second-line FOLFIRI (4% RR and median PFS of 2.5 mo) and by Sobrero, *et al.* for second-line irinotecan alone (4.2% RR and median PFS of 2.6 mo), in spite of early discontinuation of treatment, dose reductions, and treatment delays. There were 6 patients (23%) with PFS greater than 6 months.



The irinotecan-refractory group was similarly affected by dose reductions, treatment delays, and early discontinuations and still achieved a median PFS of 2.3 months, disease control rate of 45%, and had 3 patients (9%) with PFS exceeding 6 months. No objective responses were seen in this group. In spite of the small sample size (n=33) the PFS results appear to be similar to results reported by Van Cutsem *et al.* for panitumumab in the third line treatment setting (PFS=1.8 months) and cetuximab monotherapy by Cunningham *et al.*

ADVERSE EVENTS

Safety and dosing data from all 59 subjects indicate that only 18 (30%) subjects remained at full dose with minimal delays in treatment and only 24 (40%) subjects received > 80% of the planned dose intensity. All of the remaining subjects had dose reductions or delays and 8 subjects (13.6%) discontinued treatment after a single dose. Safety data confirm that CPX-1 adverse events were qualitatively similar to that of irinotecan and 5-FU with neutropenia, diarrhea, nausea, vomiting, and fluid loss events (dehydration and hypokalemia) dominating the list of severe AEs and causing discontinuation of treatment more frequently than other adverse events.

Grade 3 and 4 Adverse Events that occurred in ≥ 2 patients

	Irinotecan-Naïve n= 26		Irinotecan-Refractory n= 33		Total n= 59
	Grade 3	Grade 4	Grade 3	Grade 4	
Diarrhea	10	0	8	0	18 (30.5%)
Neutropenia	3	2	5	7	17 (28.9%)
Fatigue	2	0	7	0	9 (15.3%)
Dehydration	5	0	3	0	8 (13.6%)
Nausea	4	0	3	0	7 (11.9%)
Abdominal Pain	2	0	2	0	4 (6.8%)
Hypokalemia	2	0	2	0	4 (6.8%)
Anemia	1	0	2	0	3 (5.1%)
Anorexia	2	0	1	0	3 (5.1%)
Vomiting	3	0	0	0	3 (5.1%)
Catheter Related Complications	1	0	1	0	2 (3.4%)
Febrile Neutropenia	0	0	2	0	2 (3.4%)
Pain	0	1	0	1	2 (3.4%)
Total number of patients	16 (61.5%)	3 (11.5%)	20 (60.6%)	8 (24.2%)	47 (79.7%)

Grade 3 and 4 adverse events were qualitatively similar to what is expected following irinotecan and fluoropyrimidine treatment. As expected, neutropenia, GI toxicities (diarrhea, nausea, vomiting, abdominal pain) and events related to the consequences of fluid loss (dehydration, hypokalemia) were observed.

14 patients experienced 30 adverse events that were associated with discontinuation. 12 of 14 had a drug-related adverse event that was associated with discontinuation. In some cases, multiple, simultaneous adverse events contributed to discontinuation of study drug.

CONCLUSIONS

- The 210 u/m² starting dose produced grade 3 and 4 toxicities in patients higher than expected based on the phase I study. Future studies should start treatment at 150 u/m² with dose adjustments following the first dose.
- Adverse events observed were qualitatively similar to that of irinotecan
- Efficacy was promising with the irinotecan-naïve group appearing better than literature reports for second-line FOLFIRI and second-line irinotecan and the irinotecan-refractory group appearing to be as effective, if not slightly better than panitumumab or cetuximab monotherapy