A University of Colorado Phase I Trial of Irinotecan (CPT-11) and Carboplatin in Advanced Lung Cancer

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ABSTRACT

Irinotecan (CPT-11) plus cisplatin has shown promising efficacy in the treatment of extensive-stage small-cell lung cancer (SCLC). In the United States, carboplatin is frequently substituted for cisplatin in the treatment of these patients (pts). Thus, this phase I trial was undertaken to determine the maximum tolerated dose (MTD) of CPT-11 with carboplatin. Secondary objectives were to describe the toxicity and pharmacokinetic (PK) profiles of this combination. CPT-11 was given on days 1 and 8, and the carboplatin was given on day 1, every 3 weeks in pts with advanced solid tumors. MTD was defined as the dose level below that which resulted in dose-limiting toxicity (DLT) in $\geq$ 2 of 6 new patients. From October 2000 to September 2002, 14 pts were evaluable. Of these, 10 pts had non–small cell lung cancer (NSCLC), 2 pts had SCLC, 1 pt had gastric cancer, and 1 pt had esophageal cancer. The male: female ratio was 1:1 and the mean age was 61 years (range 48–77). Most patients had a performance status of 0-1 (N = 11) and had received at least 1 prior chemotherapy regimen (71%). After both pts with GI tumors developed DLTs at the starting dose level, the regimen was modified. Neutropenia and thrombocytopenia were the primary DLTs. Grade 3-4 diarrhea occurred in 3 patients. One pt with untreated NSCLC and 1 pt with treated SCLC achieved a partial response. Overall this combination was well tolerated and CPT-11 50 mg/m^2 on days 1, 8 with carboplatin AUC 5 on day 1 were recommended for further study. A phase II trial in untreated extensive-stage SCLC is underway. Detailed analyses of safety, efficacy, and PK profiles will be presented.

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INTRODUCTION

- CPT-11 plus cisplatin has shown promising efficacy in the treatment of extensive-stage small-cell lung cancer (ES-SCLC)
- Carboplatin is frequently substituted for cisplatin in ES-SCLC with comparable therapeutic benefit
- Optimal doses and schedules of CPT-11 with carboplatin in ES-SCLC need to be established

OBJECTIVES

- Determine the maximum tolerated doses (MTDs) of CPT-11 with carboplatin in patients with advanced solid tumors
- Describe the toxicity and pharmacokinetic (PK) profile of this combination

MATERIALS AND METHODS

Eligibility Criteria

- Untreated or treated, pathologically confirmed solid tumors
- SWOG Performance Status (PS) 0-2
- Evaluable or measurable disease
- Adequate vital organ functions

Treatment Plan

- CPT-11 as a 60-min infusion on days 1, 8
- Carboplatin as a 30-min infusion on day 1 after CPT-11
- Repeated every 21 days

Dose Escalation

Dose Level	n	CPT-11 (mg/m^2)	Carboplatin (AUC)
1	3–6	60	6
-1	3–6	60	5
-2	3–6	50	5

Endpoint Definitions

- MTD: The dose level below that which results in dose-limiting toxicity (DLT) in ≥ 2 of 6 patients
- DLT: Grade 4 neutropenia lasting > 5 days; febrile neutropenia; Grade 4 thrombocytopenia; Grade ≥ 3 nonhematologic toxicity excluding alopecia, diarrhea, nausea and vomiting; treatment delay due to toxicity > 2 wk

Blood Sampling Schedule for PK: First Treatment Course

- Day 1: **CPT-11** (total, SN-38): baseline (BL), end-of-infusion (EOI), 5, 10, 15, 30 min, and 1, 2, 4, 6, 24, and 48 h post-EOI; **Carboplatin** (total, free platinum): BL, EOI, 5, 10, 30, 45 min, and 1, 2, 4, 6, and 24 h post-EOI
- Day 8: **CPT-11** (total, SN-38): BL, EOI, 5, 10, 15, 30 min, and 1, 2, 4, 6, 24, and 48 h post-EOI

PK Study

- Plasma concentrations of CPT-11, SN-38, carboplatin, and free platinum were tabulated
- The variables analyzed: C_{max}, AUC, $t_{1/2}$, CL

RESULTS

Patient Demographics (N = 14)

Sex	n
Male	7
Female	7
Age	
< 60	5
≥ 60	9
PS	
0	2
1	9
2	3
Prior chemotherapy	
0	4
1	4
2	3
3	2
4	1

Dose Level and Toxicity—DLT

Dose Level	No. Cycles	No. Pts	No. Pts With DLT/ Cycle With DLT	DLT	Grade 3	Grade 4
1*	2	2	1 treated GI/Cycle 1	Neutropenia	0	2
			1 untreated GI/Cycle 1	Thrombocytopenia	0	1
				Diarrhea	1	0
				Renal impairment	1	0
				Hyponatremia	1	0
-1†	18	5	1 treated SCLC/Cycle 1	Neutropenia	0	2
			1 untreated NSCLC/Cycle 2	Thrombocytopenia	0	1
				Diarrhea	1	0
				Fatigue	1	0
-2‡	22	7	2 treated NSCLC/Cycle 1	Neutropenia	0	1
				Prolonged thrombocytopenia	1	0
				Diarrhea	0	1
				Cardiovascular	1	0
				Dehydration	0	1
				Abdominal pain	1	0

*Both patients in dose level 1 developed DLT, resulting in a dose reduction to the -1 dose level for subsequent new patients

†Two of 5 patients in the -1 dose level developed DLT; a dose reduction to the -2 level was mandated for subsequent new patients

‡In dose level - 2, 2 of 7 patients developed DLT, making this dose level the MTD

All Toxicities (N = 14)

Toxicity	Grades	No. Pts 1	2	3	4
Hematologic					
Thrombocytopenia		4	1	3	2
Leukopenia		0	2	1	1
Neutropenia		0	2	1	5
Febrile neutropenia		0	0	2	0
Anemia		5	4	0	1
Nonhematologic					
Diarrhea		5	1	2	1
Dehydration		0	0	0	1
Constipation		1	1	0	0
Increased creatinine		0	0	1	0
Pain		1	2	1	0
Fatigue		3	5	1	0
Neuropathy-sensory		0	1	0	0
Nausea		5	3	0	0
Vomiting		5	3	0	0
Hypersensitivity		0	0	1	0
Weight loss		2	0	0	0
Anorexia		2	0	0	0
Hyperkalemia		2	0	0	0
Hyponatremia		0	0	1	0
ALP		1	0	0	0
LFTs		0	1	0	0
Hypoalbuminemia		0	1	0	0
Skin (red palms, soles)		1	0	0	0
Alopecia		1	1	0	0

Best Evaluable Responses

	No. Pts N = 14	Primary Tumors
PR	2	1 NSCLC, 1 SCLC
MR	4	3 NSCLC, 1 SCLC
SD	2	2 NSCLC
PD	4	1 GI, 3 NSCLC
Not assessable	2	1 GI, 1 NSCLC

Noncompartmental PK Parameters for Free Platinum

Dose Level	No. of Pts	Mean Values ± SD CL, mL/min	$t_{1/2}$, min	$AUC_{0\text{-}inf}$, µg/mL x min
-1	2	244.5 ± 17.7	273.5 ± 79.9	1912.0 ± 807.5
-2	4	335.3 ± 183.0	176.3 ± 65.2	1753.8 ± 891.0

Compartmental PK Parameters for Free Platinum

Dose Level	No. of Pts	Mean Values ± SD C_{max}, g/mL	CL, mL/min	AUC, µg/mL x min
-1	2	10.1 ± 2.3	209.0 ± 52.3	2173.5 ± 238.3
-2	4	16.1 ± 5.7	267.5 ± 157.5	2272.0 ± 1224.1

PK Parameters for CPT-11 (Cycle 1 Day 1)

Dose Level	No. of Pts	Mean Values ± SD C_{max}, ng/mL	$t_{1/2}$, hr	AUC, ng/mL/h
-1	2	913.2 ± 659.6	8.9 ± 2.2	4347.2 ± 3366.2
-2	4	747.5 ± 225.2	8.0 ± 2.2	3036.2 ± 833.2

PK Parameters for SN-38 (Cycle 1 Day 1)

Dose Level	No. of Pts	Mean Values ± SD C_{max}, ng/mL	AUC, ng/mL/h
-1	2	10.1 ± 2.6	32.9 ± 14.5
-2	4	16.4 ± 7.5	56.5 ± 23.3

FUTURE DIRECTION

Untreated ES-SCLC → CPT-11 50 mg/m², D1 and 8 + Carboplatin AUC = 5, D1 every 21 days

Statistical Plan

- The smallest success rate justifiable for further study is 60%
- A 2-stage modified Fleming design will be applied
  - Stage 1: Enter 14 pts; if no success observed, the accrual will be terminated and the regimen declared ineffective; otherwise, proceed to stage 2
  - Stage 2: Enter additional 13 patients to further assess the activity of this combination

CONCLUSIONS

- Overall, CPT-11 and carboplatin was well tolerated
- Major grade 3/4 toxicities were neutropenia and thrombocytopenia
- Our PK data were comparable to the previously published data
- CPT-11 50 mg/m² on days 1, 8 with carboplatin AUC 5 on day 1 was recommended for further study