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ARTICLE

A phase I evaluation of the effect of curcumin on dose-limiting toxicity and pharmacokinetics of irinotecan in participants with solid tumors

Olumide B. Gbolahan[1] | **Bert H. O'Neil**[2] | **Autumn J. McRee**[3] | **Hanna K. Sanoff**[3] | **John K. Fallon**[4] | **Philip C. Smith**[4] | **Anastasia Ivanova**[5] | **Dominic T. Moore**[5] | **Julie Dumond**[6] | **Gary N. Asher**[7]

[1]Division of Hematology and Oncology, University of Alabama School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

[2]Community North Cancer Center, Indianapolis, Indiana, USA

[3]Division of Hematology and Oncology, UNC School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[4]Division of Pharmacoengineering and Molecular Pharmaceutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[5]Department of Biostatistics, UNC Gillings School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[6]Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[7]Department of Family Medicine, UNC School of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA

Correspondence
Gary N. Asher, Department of Family Medicine, UNC School of Medicine, University of North Carolina, 590 Manning Drive, CB #7595, Chapel Hill, NC 27599-7595, USA.
Email: gasher@med.unc.edu

Abstract

Curcumin inhibits UDP-glucuronyltransferases, a primary metabolic pathway for cancer chemotherapeutic agents like irinotecan. Concurrent administration of both agents may exacerbate irinotecan toxicity. We conducted this phase I study to determine the safety of concurrent curcumin and irinotecan administration. Ten participants with advanced solid tumors received one of four doses (1, 2, 3, and 4 g) of a curcumin phosphatidylcholine complex (PC) orally daily, and 200 mg/m^2 of i.v. infusion irinotecan on days 1 and 15 of a 28-day cycle, to determine the maximum tolerated dose (MTD) of PC. Thirteen participants received 4 g of PC (MTD) to assess the effect on the pharmacokinetic (PK) properties of irinotecan and its metabolites, SN-38 and SN-38G. Irinotecan, SN-38, and SN-38G exposure equivalence with and without curcumin was assessed using area under the plasma concentration-time curves from 0 to 6 h ($AUC_{0\text{-}6h}$). Safety assessments and disease responses were also evaluated. The combination of irinotecan and PC was well-tolerated. Because there was no dose limiting toxicity, the maximum dose administered (4 g) was defined as the recommended phase II dose of PC. PC did not significantly alter the plasma exposure and other PK properties of irinotecan and its metabolites. There was no apparent increase in the incidence of irinotecan-associated toxicities. The objective response rate was 3/19 (22%, 95% confidence interval [CI]: 5–39%), median progression free survival and overall survival ($n = 23$) were 4 months (95% CI: 2.9–8.9 months) and 8.4 months (95% CI: 3.7 – not evaluable [NE]), respectively. Future studies are required to evaluate the efficacy of this combination.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Curcumin can be safely administered with some standard chemotherapy agents like gemcitabine, taxanes, and 5-fluorouracil.

Funding information
This study was funded by the University Cancer Research Fund (UCRF) UNC Lineberger Cancer Center

WHAT QUESTION DID THIS STUDY ADDRESS?
Both curcumin and irinotecan are metabolized by UGT enzymes and concurrent administration may affect the pharmacokinetics (PKs) and clinical effect of irinotecan. This study sought to assess the effect of curcumin on the PK properties and adverse effect profile of irinotecan.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
Up to 4 g of a phosphatidylcholine curcumin (PC) formulation can be safely administered with irinotecan without an impact on the PK and adverse event profile of irinotecan.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
Curcumin's anticancer properties have been documented. Higher doses of PC can be investigated to determine a dose that acts synergistically with irinotecan to improve clinical outcomes.

INTRODUCTION

Curcumin (diferuloylmethane), a polyphenolic compound derived from the roots of turmeric (Curcuma longa), is a commonly used dietary supplement. Most curcumin supplements contain varying proportions of the three primary curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Preclinical data provide evidence of curcumin's antineoplastic properties.[1–5] For example, in colorectal cancer cell lines, curcumin, via caspase 3 activation leads to the disruption of APC/B-Catenin complex and down regulation of *c-myc* expression.[6] In vivo data also support a tumor suppressive effect in rodent models of cancer.[7] Based on these findings, multiple oncology clinical studies have explored the safety and tolerability of curcumin preparations alone and in combination with standard cancer chemotherapy agents.[8–12]

Orally administered curcumin is principally metabolized by UDP-glucuronosyltransferases (UGT) in intestinal epithelial cells. However, curcuminoids also inhibit UGT activity.[13–16] It is therefore feasible that curcumin may affect the pharmacokinetics (PKs) of chemotherapy agents metabolized by UGT, potentially worsening the toxicity of such agents. So far, studies investigating the safety of the combination of curcumin with chemotherapy have not involved agents metabolized by UGT enzymes.

Irinotecan (CPT-11), a semi-synthetic camptothecin derivative and an inhibitor of topoisomerase II, is one such agent. It is converted by carboxylesterases to its active metabolite SN-38, which is 100–1000 times more cytotoxic. SN-38 is then inactivated by cytochrome P450 family enzymes (CYP 3A4 and CYP 3A5) and by glucuronidation to its inactive conjugate SN-38G via UGT1A1 enzymes.[17,18] UGT1A1 polymorphisms are associated with defective UGT1A1 enzymes, impaired inactivation of SN-38, and increased toxicity of irinotecan.[19–21] Concomitant use of irinotecan with agents like curcumin, which may competitively inhibit UGT1A1 activity, may affect irinotecan metabolism and thus influence either systemic exposure or intestinal toxicity.

The aim of this study (NCT01859858) was to determine the safety profile and maximum tolerated dose (MTD) of Meriva, a curcumin phosphatidylcholine complex (PC) administered concurrently with a fixed dose of irinotecan. Among four dose levels administered, we established a recommended phase II dose (RP2D) for PC based on the maximum dose tested and evaluated the effect of PC on the PK profile of irinotecan and its metabolites, SN-38, and SN-38G. Finally, we sought to determine potential clinical benefits with the combination.

PARTICIPANTS AND METHODS

Participants

Participants were eligible for enrollment if their treating oncologist determined that single agent irinotecan was appropriate, after failure (response or tolerability) of accepted standard of care options. In addition, participants were required to be adults (21 years or older), with good functional status (Eastern Cooperative Oncology Group performance status 0 or 1) adequate organ function: renal (serum creatinine $<1.5 \times$ upper limit of normal), hepatic (aspartate aminotransferase and alanine aminotransferase <2.5 times the upper limit of normal, and serum bilirubin $<1.5 \times$ upper limit of normal), bone marrow (absolute neutrophil count $\geq 1500/mm^3$, platelets $\geq 100{,}000/mm^3$, hemoglobin ≥ 9 g/dl), and a life expectancy of at least 3 months. Treating oncologists had to agree that a 4-day

run-in period with curcumin alone was safe and acceptable, prior to initiation of irinotecan. Participants who had previously received irinotecan (in combination with other agents) were allowed on study.

The exclusion criteria included allergies to turmeric, curcumin, or curcumin products; previous intolerance of irinotecan requiring a dose reduction greater than 20%; history of Gilberts' Syndrome; or participants known to be homozygous for UGT1A1*28 allele, and those of Asian descent homozygous or heterozygous for UGT1A1*6 allele. Additional exclusion criteria included pregnancy, breastfeeding, active cardiac disease, ongoing infection, ongoing diarrhea (Common Terminology Criteria for Adverse Events [CTCAE] version 4 ≥ grade 2 or higher), symptomatic central nervous system disease, HIV, inability to swallow, a documented history of malabsorption, or participant unwillingness to refrain from moderate/strong CYP3A inhibitors/inducers. Participants with unresolved symptoms greater than grade 1 from prior therapy were also excluded.

The trial was approved by the institutional review boards of the University of North Carolina at Chapel Hill and the Indiana University Simon Cancer Center. The study was conducted according to the Declaration of Helsinki. Written informed consent was obtained from each participant prior to enrollment.

Study drugs

Numerous approaches, including nanoparticle and phospholipid formulation, have been investigated to improve the bioavailability of curcumin, because this is a major impediment to effectively evaluating therapeutic utility.[22–25] We utilized a PC formulation because this is associated with improved absorption compared to standard curcumin powder.[26–28] After adjusting for doses, PC is associated with up to an eight-fold increase in plasma curcumin compared to curcumin powder.[28]

PC standardized extract capsules (Meriva) were obtained from Indena Corporation in 500 mg capsules. Extracts were formulated to contain ~ 81% curcumin, 17% demethoxycurcumin, and 2% bisdemethoxycurcumin. Each capsule contained ~ 200 mg curcuminoids. Capsule contents were independently tested and verified (ChromaDex, Irvine, CA, USA).

Commercially available formulations of irinotecan were used. Irinotecan is available in single-dose amber glass vials containing 40 mg/2 ml or 100 mg/5 ml. Irinotecan was diluted prior to intravenous infusion.

Study design and treatment schedule

This was a two-center, two-part, open-label, dose escalation study to define the MTD of curcumin when given with irinotecan, and the effects of PC on the PK properties of intravenously (i.v.) administered irinotecan. Irinotecan was administered by intravenous infusion over 90 min. The dose escalation part of the trial (DE trial) tested four orally administered dose levels of PC (1, 2, 3, and 4 g once per day) in combination with a fixed dose of irinotecan 200 mg/m^2 i.v. every 2 weeks (day 1 and day 15). We previously showed detectable levels of curcuminoids (and metabolites) in the tissue and plasma of healthy volunteers after a once daily dosing regimen.[28] Each cycle was a 28-day period (Figure 1). Using a cumulative cohort design, eligible participants were enrolled

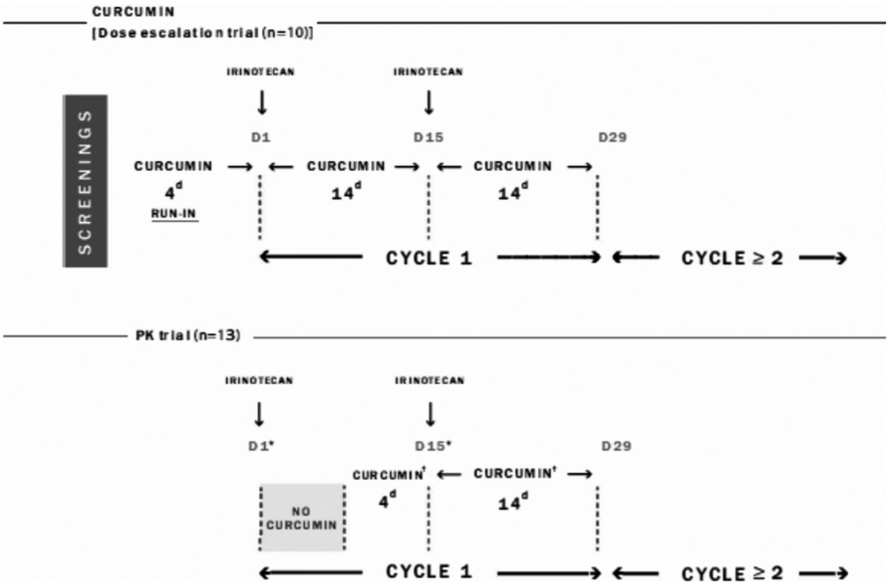

FIGURE 1 Study schema. *PK sampling: pre-irinotecan, 0 h post irinotecan, 0.5, 1, 1.5, 2, 4, 6, and 24 h post irinotecan. PK, pharmacokinetic

in two-participant cohorts at each curcumin dose level.[29] MTD was defined as the dose with probability of a DLT of 0.33. Curcumin dose level was assigned initially at 1 g daily until 2 patients fully completed 1 cycle. If no DLT occurred, the next patient was assigned at the next higher dose level. Assignment proceeded through the four dose levels (1, 2, 3, 4 g) until either a dose-limiting toxicity (DLT) occurred, or two patients completed each dose level without any DLT. If DLT was observed, DLT rates at each dose were to be estimated using isotonic regression. For that, proportions of DLTs were to be computed at each dose first, then, if there was a violation of monotonicity, data at the violating dose levels were to be pooled and new proportions computed. The estimated DLT rate at the current dose would be used to determine whether the dose will be increased, decreased, or remained unchanged. The dose was to remain unchanged if the estimated DLT rate at the current dose is between 0.17 and 0.33; the dose was to be decreased if the estimated DLT was higher than 0.33; and the dose increased if the estimated DLT was lower than 0.17. If no DLT occurred at the maximum dose tested (4 g), this dose would be the RP2D.

Participants in the DE trial received a 4-day run in with PC only (dosed at the assigned PC dose level) and then continued cycle 1 day 1 (C1D1) of treatment with irinotecan if curcumin run-in dosing was tolerated. The run-in period was used to identify participants who may experience side effects due to curcumin alone.

In the PK part of the trial (PK trial), participants were enrolled at the maximum dose tested in the DE trial. Participants received fixed-dose irinotecan 200 mg/m^2 i.v. on days 1 and 15. PC was administered once daily starting on day 11, to allow a potential to reach steady-state before day 15 of irinotecan, and continued until the end of the cycle (day 28). We assumed curcumin steady-state would be reached after five doses based on a previous trial using once daily dosing of the same curcumin formulation.[28] All enrolled participants who remained clinically stable on the combination continued therapy for additional cycles at the PC maximum dose administered daily, with irinotecan administered on days 1 and 15. Participants were instructed to take PC orally daily in the morning with ~ 8 ounces of water (250 ml).

Safety assessments

During both the DE and PK trials, safety assessments were performed on C1D1, C1D15, and C2D1. Participants received focused history, physical examination, and review of medication list before treatment. Venous blood was collected for complete blood count with differential, electrolytes, urea, creatinine, and liver function. Toxicity was assessed by the National Cancer Institute Common Terminology Criteria version 4.0.

DLT was assessed during cycle 1 of the DE trial; defined as any grade 3 to grade 5 toxicity, with certain exceptions. Grade 3 diarrhea was only considered a DLT if despite appropriate supportive therapy, the subsequent dose of irinotecan (C1D15 or C2D1) was delayed by more than 1 week. Similar determination was made for nausea or vomiting and hematologic toxicity. Asymptomatic laboratory abnormalities were only to be considered as DLT if the abnormalities were felt to be conclusively related to the combination therapy.

Pharmacokinetic assessments

Samples of blood were collected into K3-EDTA tubes on irinotecan infusion days during the first cycle of the PK trial (C1D1 and C1D15). Samples were collected prior to irinotecan treatment (baseline), 30 and 60-min during infusion, immediately following infusion (i.e., 90 min), then at 0.5, 1, 1.5, 2, 4, and 6 h (±5 min) and 24 h (±4 h). The plasma was separated and immediately frozen at −70° Celsius until analyzed. The SN-38G was assumed to be stable because it is an ether glucuronide. Following thawing, the protein was precipitated with acetonitrile and the supernatant evaporated before reconstitution at acidic pH (~2–3). Thus, the irinotecan was present in the lactone form. Analysis was by nano-liquid chromatography-tandem mass spectrometry[30] with the mass spectrometer operated in the positive multiple reaction monitoring (MRM) mode and peak areas determined. Camptothecin was the internal standard for each analyte and the MRM transitions used for quantification were 587.3/195.2, 568.9/392.8, 393.1/349.2, and 348.8/305.0 for irinotecan, SN-38G, SN-38, and camptothecin, respectively. The three analytes were quantified together in a single assay with the analysis being completed in seven batches. Six calibrants, each containing the three analytes, were analyzed with each batch. The calibration ranges were 94 to 3766, 50 to 2000, and 5 to 200 ng/ml for irinotecan, SN-38G, and SN-38, respectively. Irinotecan hydrochloride, camptothecin, and SN-38 were purchased from Cayman Chemical Company (Ann Arbor, MI; products #14180, #11,694, and #15,632, respectively). SN-38G was purchased from Toronto Research Chemicals Inc, North York, ON, Canada (product S589980). Two quality controls (QCs) prepared from pooled blank plasma were analyzed in triplicate with each batch. The higher concentration control contained the three analytes within the calibration range and the lower concentration contained irinotecan and SN-38

within the range. Between assay precision (coefficient of variation) for the higher QC for the seven batches, where triplicate results were averaged for each batch, was 12%, 11%, and 6% for irinotecan (1923 ng/ml), SN-38G (215 ng/ml), and SN-38 (93 ng/ml), respectively. The corresponding results for the lower QC were 42% and 14% for the irinotecan and SN-38, respectively (121 and 9 ng/ml, respectively). Lower limit of quantification (LLOQ) for irinotecan, SN-38, and SN38G were 100, 50, and 5 ng/ml, respectively.

Efficacy assessments

Baseline scans were obtained at screening. Tumor response was evaluated every 8 weeks after C1D1 of irinotecan using computed tomography scans or magnetic resonance imaging of the chest, abdomen, and pelvis, as appropriate. Tumor response was defined per Response Evaluation Criteria in Solid Tumors 1.1.[31] The analysis set for disease control assessment included participants who received at least one dose of irinotecan in both DE and PK trials. Objective response rate (ORR) was a composite of complete and partial responses, and disease control rate (DCR; and without a time component) included stable disease (SD) and objective responses. The Agresti-Coull method was used for calculating 95% confidence intervals (CIs) for each proportion of interest (reported as percentages).[32]

Pharmacokinetic and statistical methods

PK data were generated for irinotecan, SN-38, and SN-38G using noncompartmental analyses with WinNonLin Pro version 8.1.0 (Certara, Princeton, NJ). Area under the plasma concentration-time curves (AUC) were computed using the linear up/log down trapezoidal rule. To construct 24-h concentration-time curves, plasma analyte values that were below the LLOQ (BLOQ) at the 24-h timepoint were set to the LLOQ for each analyte. At the 24-h timepoint, all irinotecan plasma values, 65% of SN-38, and 8% of SN-38G were BLOQ. No plasma analyte levels were BLOQ for other timepoints. AUC_{last} is equivalent to AUC_{0-24}. Concentration-time curves are reported as medians (interquartile range). Geometric mean (95% CI), maximum concentration (C_{max}), and time to C_{max} (T_{max}) values were obtained for irinotecan/SN-38/SN-38G with and without curcumin. C_{max} and T_{max} were compared using the Wilcoxon signed-rank test.

To assess whether exposure to irinotecan or its metabolites was affected by curcumin exposure, a test of bioequivalence was calculated using the geometric mean of the ratio of AUC_{0-6h} for irinotecan/SN-38/SN-38G given with curcumin (collected C1D15) divided by AUC_{0-6h} for irinotecan/SN-38/SN-38G alone (collected C1D1). The 90% CI was set at 0.8–1.25. A geometric mean ratio outside of 0.8–1.25 was set to indicate nonequivalence. Because the majority of plasma values at the 24-h time were BLOQ, we used AUC_{0-6h} to avoid using falsely elevated AUC curves for statistical comparisons.

Patients' baseline characteristics were summarized using descriptive statistics and toxicities were reported using frequency tables. The counts represent the maximum grade per patient, per toxicity group, with no duplicates and have been determined to have "definite," "probable," or "possible" attribution to treatment.

The Kaplan-Meier method was used to estimate the time-to-event functions of overall survival (OS) and progression free survival (PFS). OS was calculated from the start of treatment date to the date of death from any cause, or date of last contact (censored). PFS was calculated from start of treatment date to either the date of progression, the date of death from any cause, or date of last contact (censored). The "loglog" method (based on the log of the hazard) was used for calculating 95% CI for median OS and PFS. All reported *p* values are two-sided with *p* values less than 0.05 considered significant.

Based on the specified assumptions for the test of bioequivalence, it was estimated that with 10 participants, a paired *t*-test (2-tailed) at the 0.05 significance level will have 71% power to detect a difference of 0.174 in the log of the AUC values of irinotecan, SN-38 and SN-38G between the irinotecan cycles with and without curcumin, assuming a standard deviation of differences of 0.195.

Statistical analyses were performed using both SAS (version 9.4; Cary, NC) and R (2019): A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/.

RESULTS

Participants

Between August 2013 and June 2016, there were 28 participants with chemotherapy refractory, histologically proven solid tumors were screened for the study. Twenty-three participants were enrolled and received study treatments; 10 in the DE trial and 13 in the PK trial. Most participants were men (70%), with a median age of 65 years (range 36–72 years). Most participants had cancers involving the digestive system (83%) and had received a median of three (range 1–5) lines of systemic therapy prior to enrollment (Table 1).

DLT and tolerability of curcumin administered with irinotecan

In the DE trial, two participants received 1 g of curcumin, three each received 2 g, and 3 g dose, respectively, and two were treated at the 4 g dose level. Altogether, there was no DLT attributable to the addition of PC to irinotecan at doses tested. We did not administer doses higher than 4 g due to concerns about large pill burden (>8 pills) and potential impact on compliance. An MTD was therefore not established but we proceeded with the maximum dose administered as the RP2D.

The combination was well-tolerated. Among the 10 participants enrolled in the DE trial, five (50%) discontinued therapy due to disease progression, one chose to pursue other treatment options, another was withdrawn after cardiac arrest, and a third participant was withdrawn due to worsening liver enzymes on C1D4. This participant's total bilirubin was at 1.5 times the upper limit of normal on C1D1. Leukopenia was the most described adverse event (AE; 40%), reported as grades 1 and 2 in two participants each. Grade 1 nausea and diarrhea were reported in 30% and 10% of participants, respectively (Table S1). There were no grade 4 or 5 toxicities thought to be related to the combination. Grade 3 toxicities possibly or probably related to the combination were reported in three different participants (30%) with dysarthria (10%), with neutropenia (10%), and with vomiting (10%). None of these grade 3 events were thought to be definitely related to curcumin only (Table 2).

Overall, 20 of the 23 participants evaluable for toxicity had at least one AE. There were no treatment-related grade 4 or 5 AEs. Nausea was the most reported AE with 13 participants (56%) followed by fatigue (8 participants, 35%) and diarrhea (7 participants, 31%). Six participants (27%) had reductions in white cell counts, two (9%) reported grade 3 leukopenia and two (9%) reported grade 3 neutropenia (Table 3).

TABLE 1 Baseline participant characteristics

	All *n* (%)	DE study *n* (%)	PK study *n* (%)
Number of participants[a]	23	10	13
Age, median (range)	65 (36–72)	68 (38–72)	63 (36–72)
Sex			
Male	7 (30%)	4 (40%)	3 (23%)
Female	16 (70%)	6 (60%)	10 (77%)
Race			
African American	3 (14%)	2 (20%)	1 (8%)
White	19 (86%)	8 (80%)	11 (92%)
ECOG performance status			
0	8 (35%)	3 (30%)	5 (38%)
1	15 (65%)	7 (70%)	8 (62%)
Tumor type			
Breast	1 (5%)	0	1 (9%)
Colorectal	5 (26%)	3 (39%)	2 (18%)
Gastric-esophageal	5 (26%)	2 (25%)	3 (27%)
Liver	1 (5%)	1 (12%)	0
Lung	2 (12%)	1 (12%)	1 (9%)
Pancreatic	5 (26%)	1 (12%)	4 (37%)
Number of prior treatments, median (range)	3 (1–5)	3.5 (1–4)	3 (1–5)

Abbreviations:: DE, dose escalation; ECOG, Eastern Cooperative Oncology Group; PK, pharmacokinetic.

[a]With the exception of age and prior treatments, values represent number of participants and percent within each category.

Effect of PC on the pharmacokinetics of irinotecan and metabolites

The 4 g dose of PC was administered in the PK trial and 13 participants received this dose daily in combination with

TABLE 2 Summary of grade 3 or higher toxicities at each curcumin dose level in the dose-escalation trial ($n = 13$)

Curcumin dose level	Description of adverse event	Toxicity grade[a]	Treatment cycle	DLT (yes/no)	Attribution[b]
1000 mg	Dysarthria	3	1	No	Possible
	Cardiac arrest	4	1	No	Unrelated
2000 mg	Vomiting	3	4	No	Possible
	T7 vertebra fracture	3	3	No	Unrelated
3000 mg	Neutropenia	3	1	No	Probable
	Hyponatremia	3	2	No	Unrelated
4000 mg	None	–	–	–	–

Abbreviation: DLT, dose limiting toxicity.

[a]Toxicity grade assessed using the National Cancer Institute Common Terminology Criteria, version 4.0.

[b]Options for attribution included unrelated, possible, probable, and related.

TABLE 3 Summary of adverse events reported in all study participants ($N = 23$)

Adverse event[a]	Grade 1		Grade 2		Grade 3	
	(*n*)	%[b]	(*n*)	%	(*n*)	%
*Abdominal pain	2	9%	1	4%		
Alanine aminotransferase increased	1	4%	1	4%		
Alkaline phosphatase increased			2	9%		
Alopecia	1	4%	3	13%		
Anemia	3	13%	2	9%		
Anorexia	1	4%	1	4%	2	9%
Aspartate aminotransferase increased	2	9%	1	4%		
Back pain			1	4%		
Constipation	1	4%				
Creatinine increased	1	4%				
Dehydration			1	4%		
Diarrhea	5	22%	2	9%		
Dysarthria					1	4%
Epistaxis	1	4%				
Fatigue	3	13%	5	22%		
Fever	1	4%				
Hematuria	1	4%				
Hoarseness	1	4%				
Hot flashes	1	4%				
Hypertension			1	4%		
Hyponatremia	1	4%				
Lymphocyte count decreased	4	17%	3	13%		
Movements involuntary			1	4%		
*Nausea	6	26%	7	30%		
Neutrophil count decreased	1	4%	1	4%	2	9%
Platelet count decreased	2	9%				
Rash maculo-papular	1	4%				
*Vomiting	2	9%	4	17%	1	4%
White blood cell decreased	2	9%	2	9%	2	9%

Note: *Adverse events with definite, probable, or possible attribution to phosphatidyl curcumin.

[a]Toxicity grade assessed using the National Cancer Institute Common Terminology Criteria, version 4.0.

[b]Percentages are calculated as the number of participants experiencing the adverse event of all study participants ($N = 23$).

i.v. irinotecan. Twelve participants had sufficient data for full PK analysis.

PC administration did not alter the PKs of irinotecan and its metabolites (Figure 2). The geometric mean ratios of the $AUC_{0\text{-}6h}$ (90% CI) without and with exposure to PC were for irinotecan 0.97 (0.90–1.04), SN-38 1.01 (0.92–1.10), and SN-38G 1.06 (0.93–1.20), respectively (Table S2). The 90% CIs fell within pre-stated boundaries of 0.80–1.25 for all three analytes.

Similarly, there was no significant change in the geometric means of other key PK parameters for irinotecan and its metabolites following exposure to PC (Table 4). The time to peak irinotecan concentration (T_{max}) increased from 1.6 to 1.7 h ($p = 0.64$), whereas the T_{max} for SN-38 (2.4 vs. 1.8 h, $p = 0.05$) and SN-38G (3.2 vs. 2.5 h, $p = 0.27$) dropped following exposure to PC. The administration of PC was not accompanied by a significant difference in the C_{max} of irinotecan (1681 vs. 1797 ng/ml, $p = 0.53$), SN-38 (25.4 vs. 26.8 ng/ml, $p = 0.75$), or SN38G (620 vs. 613 ng/ml, $p = 0.88$). Other key PK parameters are summarized in Table 4.

Clinical effect of PC and irinotecan combination

All 23 participants who received at least one cycle of study treatments were assessed for the clinical activity of the

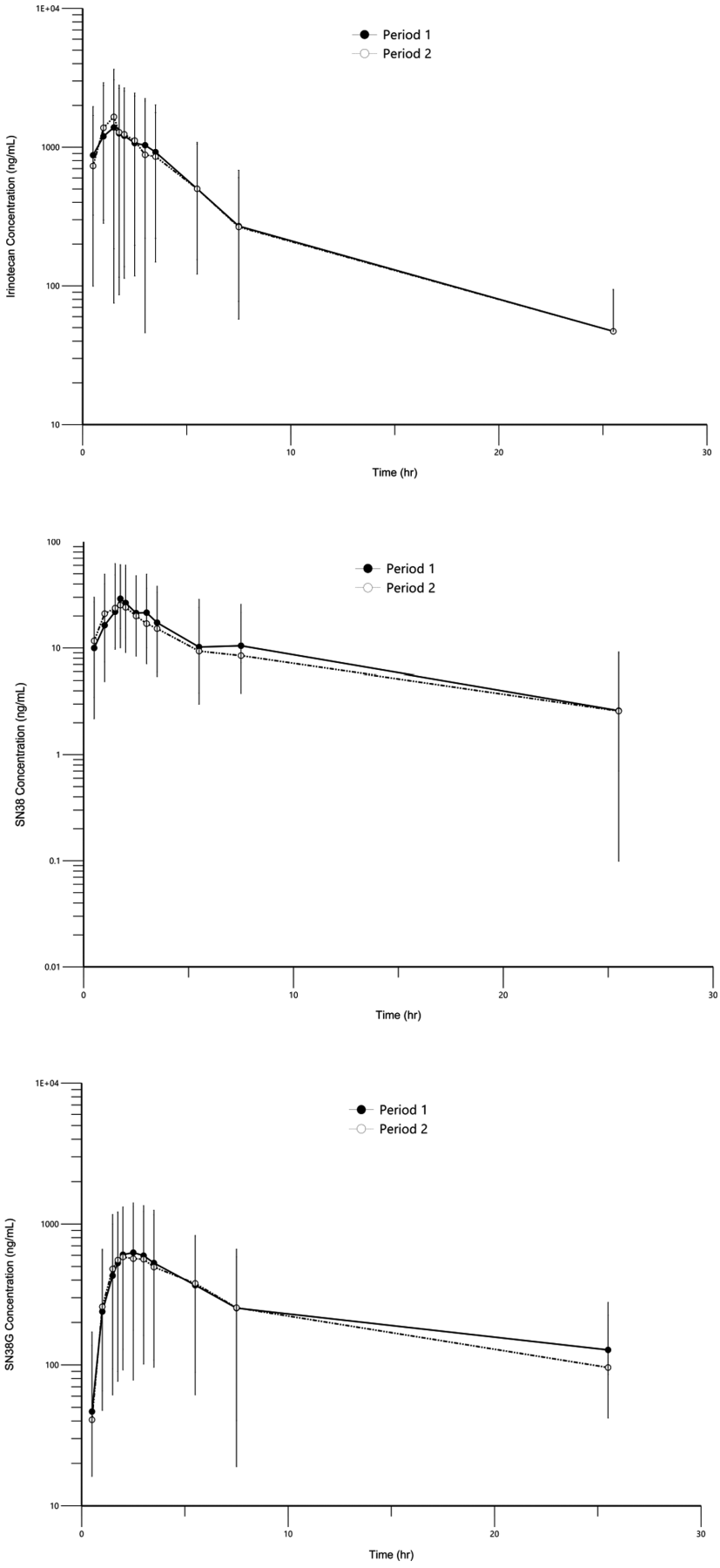

FIGURE 2 Median (interquartile range) plasma concentration versus time for irinotecan and metabolites (SN-38, SN-38G). Dark circles (period 1) without curcumin, open circles (period 2) with curcumin. Plasma concentration values at 24 h that fell below the lower limit of quantification (LLOQ) were set to the LLOQ to generate these curves. $N = 12$

combination. Fifteen participants (65%) who received PC at the maximum dose level (4 g daily, two in the DE trial and 13 in PK trial) were also separately analyzed. At the time of data analysis, all enrolled participants had discontinued study treatments. Among the 18 participants with data available to assess ORR, the best response was partial response, reported in three participants (17%; 95% CI 0.04–0.41). Seven participants (39%) had SD leading to a DCR of 56% (95% CI 0.31–0.78).

By the end of study, 13 (56%) participants had demonstrated disease progression or were deceased and 10 (43%) had neither died nor progressed. After a median follow-up of 3.7 months, median PFS was 4 months (95% CI 2.9–8.9 months) and median OS was 8.4 months (95% CI 3.7 months to not evaluable [NE]; Figure 3). For the 15 participants who received 4 g of curcumin, median PFS was 3.7 months (95% CI 1.9–8.9 months) and median OS was 8.9 months (95% CI 2.9 months to NE; Figure S1).

TABLE 4 Effect of curcumin on the pharmacokinetic profile of irinotecan ($n = 12$)

	Without curcumin	With curcumin
Irinotecan		
T_{max}, h	1.6 (0.6–4.5)	1.7 (1.3–2.3)
C_{max}, ng/ml	1681 (1002–2820)	1797 (1144–2824)
AUC_{0-6h}, ng·h/ml	5673 (3375–9537)	5496 (3482–8674)
AUC_{last}, ng·h/ml	8737 (5145–14,838)	7839 (4131–14,874)
SN−38		
T_{max}, h	2.4 (1.4–4.1)	1.8 (1.0–3.7)
C_{max}, ng/ml	25.4 (8–85)	26.8 (8–87)
AUC_{0-6h}, ng·h/ml	87 (31–248)	88 (30–262)
AUC_{last}, ng·h/ml	173 (34–871)	156 (30–829)
SN−38G		
T_{max}, h	3.2 (1.5–6.9)	2.5 (1.4–4.5)
C_{max}, ng/ml	620 (249–1546)	613 (283–1330)
AUC_{0-6h}, ng·h/ml	2233 (805–6195)	2358 (1075–5176)
AUC_{last}, ng·h/ml	5520 (1976–15,424)	4942 (1949–12,533)

Abbreviations: AUC, area under the curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration.

C_{max}, T_{max}, and AUC values expressed as geometric mean (95% confidence interval).

DISCUSSION

A few studies have shown that curcumin can be safely combined with chemotherapy.[9–11,33] However, there has been no investigation of its combination with chemotherapy agents like irinotecan, which share similar metabolic enzymes. This is important as the competitive inhibition of these enzymes by curcumin may worsen the toxicity profile of such chemotherapy agents. In this phase I study, we found that the combination of up to 4 g of PC and i.v. irinotecan (200 mg/m^2) was well-tolerated, and that PC does not appear to affect the PKs of irinotecan or its metabolites.

Our findings are consistent with several studies that curcumin, even when administered in high doses, is tolerable when combined with chemotherapy.[10,12] Epelbaum and colleagues reduced the dose of curcumin (combined with gemcitabine) from 8000 to 4000 mg daily because of abdominal complaints in 40% ($N = 17$) of participants.[9] However, other investigators reported 100% treatment

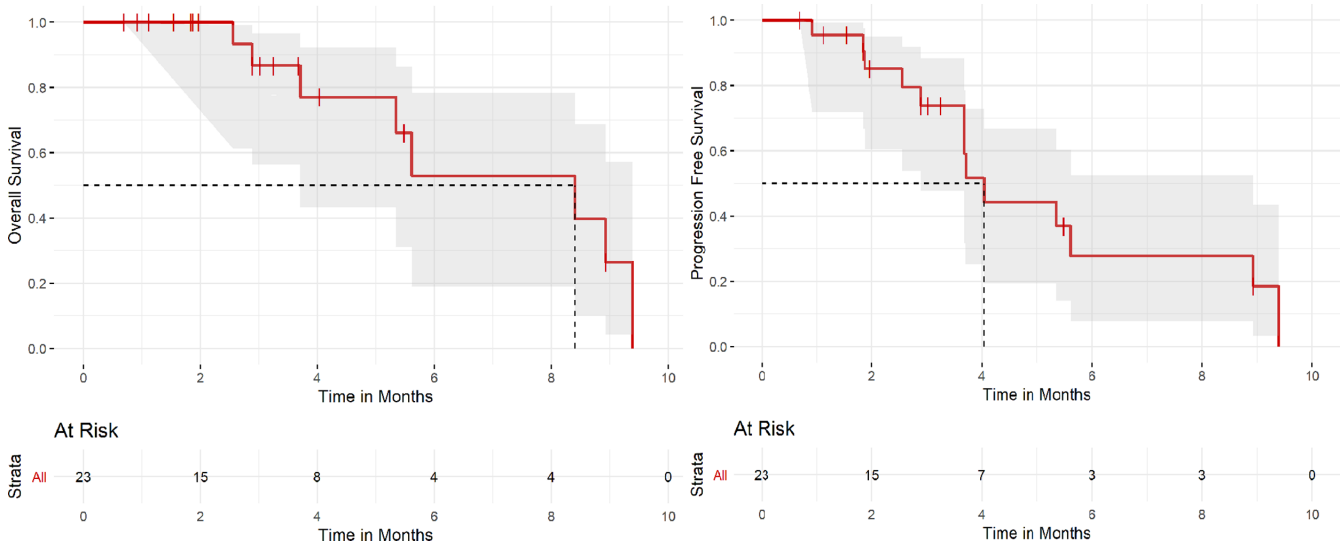

FIGURE 3 Kaplan Meier estimates of overall survival and progression free survival among the 23 evaluable participants who received one cycle of irinotecan and curcumin

compliance, without treatment-related AEs with the addition of 8000 mg of curcumin to gemcitabine-based chemotherapy.[10] Nonetheless, based on our hypothesis of the potential for competitive inhibition of UGT, we are surprised that there was no increase in irinotecan-related AEs. There was no report of grade 3 diarrhea in this study, and grade 3 neutropenia was reported in only 9% of participants, compared to historic reports of 10% and 18%, respectively, for irinotecan.[34]

The test of exposure equivalence (ratio of AUC_{0-6h} of irinotecan and its metabolites after and prior to exposure to PC) suggested that PC is unlikely to affect plasma irinotecan and SN-38 exposures. The C_{max} was attained at about 1.7 h with a rapid drop thereafter. Irinotecan and SN-38 were at or below the specified LLOQ at 24 h. Multiple studies have confirmed irinotecan C_{max} is reached at the end of a 1.5 h infusion.[18]

A strength of our study was the crossover design of the PK trial, where each participant served as their own control. Because participants received only irinotecan on day 1 and the combination on day 15 (following 5-day run-in from day 11 with curcumin) we were able to assess the effect of PC on irinotecan within the same participant, thus reducing the risk of interindividual variation in PC exposure that would occur in a two-arm study. In addition, we utilized a PC preparation that is associated with improvement in the absorption and bioavailability of curcuminoids compared to typical curcumin standardized extracts.

The ORR (22%) reported in this study is similar to an ORR of 17.5% reported in previous studies of irinotecan administered in the second line.[35,36] This is interesting considering that participants in this trial had received a median of three prior treatments. However, the small sample size and heterogeneity of the cancers in the study makes it difficult to draw any conclusions about clinical activity of the combination.

Although it is encouraging that PC does not appear to affect the PK and side effect profile of irinotecan, it is important to understand why this may be the case. Due to its poor bioavailability, the plasma concentration of orally administered curcumin is typically low.[28,37,38] In one study, free plasma curcumin was detected in only one of 12 volunteers administered 10 g and 12 g doses.[37] This has informed the push to deliver higher doses and develop newer formulations of oral curcumin.[24,28,39] Our group has previously showed detectable plasma levels of curcuminoid conjugates with 2 g daily dosing of PC. Despite this, it is possible that even the 4 g dose of PC tested in this study is insufficient to significantly competitively inhibit UGT enzymes. The lack of measured curcumin levels in this current study cannot rule out the possibility that PC was not sufficiently bioavailable to inhibit UGTs in the liver. Interestingly, and in congruence with findings from this study, Volak and colleagues, also noted that curcumin (4 g)/piperine combination did not affect the PKs of acetaminophen, another agent metabolized by UGT1A1,[40] although it is important to note that acetaminophen is metabolized by other UGT enzymes in addition to UGT1A1. Given that the bulk of curcumin glucuronidation occurs in the small intestine, it is likely that the proportion of active curcuminoids that is absorbed is insufficient to have a significant impact on hepatic UGT1A1, which contributes to SN38 metabolism.[41]

We recognize the possibility that participants in the PK study may not have been compliant with taking eight tablets of PC daily. Our previous experience with participants of trials of dietary supplements suggests participants who choose to be in these trials are highly motivated participants who maintain high treatment adherence.[28,42,43] Furthermore, all participants of this trial had already received multiple prior chemotherapy regimens; the attraction of this trial was the addition of curcumin to a standard chemotherapy regimen. However, it remains possible that we did not detect differences in irinotecan PKs due to curcumin as a result of poor compliance.

Another major limitation of our study was that we did not test PC doses beyond 4 g because of concerns about a large pill burden.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

O.B.G., B.H.O., and G.N.A. wrote the manuscript. B.H.O. and G.N.A. designed the research. B.H.O., G.N.A., A.M., H.S., J.K.F., P.C.S., and J.D. performed the research. O.B.G., B.H.O., G.N.A., A.M., H.S., J.K.F., P.C.S., and J.D. analyzed the data.

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SUPPORTING INFORMATION

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