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Pilot Study Comparing Systemic and Tissue Pharmacokinetics of Irinotecan and Metabolites following Hepatic Drug Eluting Chemoembolization

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Abstract

Differences in drug metabolism associated with UGT1A1 polymorphism could result in individualized local response to hepatic chemoembolization with irinotecan-eluting beads (DEBIRI) or predictable toxicities. Five patients with inoperable hepatic metastases from colorectal or anal malignancies treated with DEBIRI were assessed for UGT1A1 mutations, No difference in AUC for SN38 in normal liver and tumor tissue samples was noted with variant (VAR) or wild-type (WT) UBT1A1 ($p = 0.16$ and $p = 0.05$ respectively). Plasma SN-38 AUC was significantly lower in WT compared to VAR patients ($p<0.000l$). UGT1A1 genotype may not be predictive of hematological toxicity following DEBIRI.

Introduction

Although improved progression free survival and overall survival has been reported with chemoembolization with DEBIRI as salvage therapy for colorectal hepatic metastases compared to FOLFIRI[l], concentrations of irinotecan and active metabolite achieved within hepatic metastases following fixed-dose chemoembolization are unknown. Differences in drug metabolism associated with UGT1A1 polymorphism potentially could result in individualized local therapeutic response to or toxicity from DEBIRI. The aim of the present study was to estimate and compare the influence of UGT1A1 phenotype on plasma and tumor drug and metabolite concentrations and pharmacokinetics following hepatic DEBIRI.

Materials and Methods

This study was an institutional review board-approved prospective pilot performed under an FDA-approved investigational device exemption for irinotecan-eluting embolization beads. Five patients with inoperable hepatic metastases were recruited between March, 2011 and November, 2014. Inclusion criteria included hepatic metastatic burden less than 60% of the total liver volume determined by comparison of manual segmentation of tumors to whole liver on CT, disease refractory to (or intolerant of) approved systemic chemotherapy, ECOG ≤2 and life expectancy >3 months, age <85 years, ALT/AST ≤ three times the institutional upper limit of normal, and INR <1.5. Exclusion criteria included severe cardiac or pulmonary insufficiency, portal vein occlusion, prior radio- or chemoembolization, or requirement for medications considered CYP3A inducers or inhibitors. Patient demographic, tumor, and prior treatment characteristics are summarized in Table 1.

Preprocedurally patients received dexamethasone 8mg iv, ondansetron 16–24mg iv, and antibiotics consisting of metronizdole 500mg with cefazolin 1gm, ciprofloxacin 400mg, or piperacillin/tazobactam 2.25mg intravenously. Procedures were performed under general anesthesia in all but one case. All patients received a total of 2ml of 100–300 μm DC Bead® preloaded with 100mg irinotecan (Paragon Bead® an investigational device provided by Biocompatibles UK Ltd, a BTG International group company, Farnham, UK) injected through a microcatheter (2.8F Progreat, Terumo Medical, Somerset, NJ or 2.8F Maestro, Merit Medical, Jordan, UT] with the tip positioned in the proximal lobar (four of six procedures) and/or segmental artery (two of six procedures). Each vial of beads was reconstituted into a final dilution of 1:30 with a 50:50 mixture of sterile water and iodinated contrast agent (Isovue 300®, Bracco Diagnostics, Sirgen, Germany). Embolization progressed until complete stasis was achieved and/or all beads had been injected. Seven treatments were administered to the five patients. In two of seven treatments, an additional volume of bland microspheres (Embozene® 250 μm, CeloNova Biosciences Inc./Boston Scientific, San Antonio, TX) was administered to achieve complete stasis. Treatment was repeated in 4–6 weeks in the absence of serious adverse events or radiographic evidence of target tumor progression. Adverse events were recorded according to CTCAE v.4 and followed until resolution or return to baseline value. Patients were hospitalized until the last serum sample was collected at 96 hours. Follow-up CT and/or MRI examinations were obtained four weeks after each DEBIR1.

Plasma and liver tissue concentrations of irinotecan (CPT-11), its active metabolite SN38, and the glucuronic acid metabolite of SN38, SN38-G, were measured using a previously published LC-MS/MS assay [2]. Plasma samples were obtained on day 1 of each treatment cycle (C1D1) pre-dose, half-way through the infusion, end of infusion, and 15-min, 30 min, 60 min, 90 min, 120 min, 2-hr, 3-hr, 4-hr, 6-hr, 12-hr, 18-hr, 24-hr, 36-hr, 48-hr, and 78-hr post-end of infusion. Tissue biopsy samples were obtained with ultrasound guidance immediately after, at 90 minutes and 24 hr (±3 hrs) after embolization. Each time point was sampled twice, once at the chemoembolized target tumor, the other at a remote portion of nonneoplastic liver tissue in the untreated lobe. Two patients had pharmacokinetic data available from a repeat (second) chemoembolization (C2D1) as well, yielding seven total cycles from five patients. An effort was made to quantitate the amount of irinotecan that

remained bound to the beads in the liver tissue biopsy samples, although no beads were identified by gross inspection in the tissue prior to homogenization.

A noncompartmental analysis was used to assess plasma and tissue pharmacokinetic parameters of all three compounds (except for SN38-G in tissue) using Phoenix 6.3 software (Certara, Princeton, NJ). The maximum plasma concentration (C_{MAX}) and the time to C_{MAX} (T_{MAX}) were recorded as observed values and the area under the plasma concentration vs time curve extrapolated to infinity (AUC_{inf}) was calculated using the Linear Trapezoidal method. Tissue pharmacokinetics were simplified compared to plasma pharmacokinetics due to the limited number of sample time points and target organ system isolation. Tissue C_{MAX} and T_{MAX} were recorded as observed values. The AUCall (includes all three time points) was determined using the linear trapezoidal rule in a noncompartmental analysis. Half-life was measured by the natural log of 2 divided by the slope of terminal line, (aka k_{EL} or the elimination rate) through log-linear regression. Means for C_{max},, $T_{1/2}$;and AUC_{ALL} were compared with unpaired parametric t tests using GraphPad Prism, v6 (GraphPad Software, San Diego, CA). Significance was defined as $p < 0.05$.

Results

All embolization procedures were successfully completed. In one case, biopsy of the normal untreated left lobe was considered challenging due to minimal sagittal dimension and retrosternal location, and was not performed. Adverse events observed are listed in Table 2. One death was observed forty days following a single DEB1RI treatment which was attributed to rapid progression of hepatic metastatic disease despite treatment Lymphocytopenia achieved the greatest CTCAE severity and was observed in three out of five patients. The lymphocyte count nadir was observed within twenty four hours of the embolization in these three patients, grade.

Data from all five patients and seven cycles were available for pharmacokinetic analysis. There was one CPT-11 tissue concentration (>600,000 pg/mg) that was excluded from statistical and pharmacokinetic analysis because it was considered an outlier (> ±2 SD). Three of our patients had wild type UGT1A1 genotypes (6/6, WT), while two had variants (VAR). Significant differences were observed in the *plasma* CPT-11 C_{max} (higher for WT), and lower SN-3B C_{max} AND AUC for WT vs VAR (Table 3). Although a trend for lower *plasma* SN-38G C_{max} and AUC is seen for VAR, these differences were *not* statistically significantly different. No differences in tissue pharmacokinetic parameters were observed between VAR and WT patients. (Table 4).

Discussion

We observed > 4 times the exposure (AUC_{inf}) of irinotecan delivered to the tumor with DEBIRI than from reported systemic exposure, as well as a greatly reduced AUC for both systemic irinotecan as well as SN-38 from DEBIRI compared with the intravenous administration of 100mg/m^2 irinotecan daily × 3 days (1000–10,000 times greater for systemic administration) [3]. The most commonly observed adverse events in our study were lymphopenia and anemia. Myelosuppression has been documented in patients receiving

systemic irinotecan, and is associated with UGT1A1*28 genotype [4,5]. Lymphocytopenia has been described following systemic irinotecan therapy, although concomitant administration of dexamethasone as an anti-emetic may contribute to this condition [6]. Neutropenia from irinotecan is thought to occur due to presumed elevated SN-38 levels in VAR patients and is irinotecan dose-related [5]. VAR genotype has previously been associated with higher SN-38 AUC in lower-dose *systemic* CPT-11 regimens, but may *not* correlate with "severe" gastrointestinal and hematological toxicity among different UGT1A1 genotypes [7]. All three of our WT patients developed lymphopenia, while one of two VAR patients demonstrated this abnormality. The occurrence of lymphopenia is somewhat surprising as serum CPT-11 C_{max} for our patients was approximately one sixth to one third of the CPT-11 C_{max} and one-half of the AUC reported for patients receiving intravenous CPT-11 at a dose of 100mg/m^2 [8]. While plasma irinotecan AUC tended to be lower in WT patients ($p=0.070$), the plasma SN-38 AUC from DEB1RI was significantly lower in WT compared to VAR patients ($p<0.0001$). Our pilot study findings suggest that UGT1A1 genotype may not be predictive of hematological toxicity following DEBIRI, but a larger study sample size is required. Eichler et al [9] also evaluated a possible relationship between administered dose and observed adverse events in their patients and found no association. Conversion of SN-38 to the inactive form SN-38G occurs by glucuronidation. If glucuronidation occurs primarily in normal liver tissue, AUC for SN-38 could be expected to be greater in patients with variant UGT1A1 genotypes treated with DEBIRI. Our study showed slightly greater SN-38 tissue AUC for 5/5 and 6/7 variants than wild type (6/6), but definitive analysis with a larger cohort is required. While speculative, burst release of irinotecan from the embolic agent as well as tumor tissue sampling error could contribute to the apparent lack of difference in CPT-11 and SN-38 levels between tumor and normal liver.

This pilot study is limited primarily by the small sample size and gender bias, inability to quantify the amount of bound CPT-11 in biopsy specimens, as well as the marked variability in tissue measurements. In conclusion, the pilot study findings suggest that lobar DEBIRI results in similar exposure of target tumor and remote normal liver tissue to irinotecan and active metabolite regardless of UGT1A1 mutation status. Additionally the incidence of lymphocytopenia with DEBIRI may not be influenced by UGT1A1 mutation status.

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Table 1:

Patient Characteristics

Patient	Age	Sex	Primary Tumor	Prior Treatment	Max Lesion Diameter (cm)	# Liver Lesions	UGT1A1 Status
1	60	M	Colon	Folfox Avastin+Folfiri Xelox Cetuximab+capecitabine Irinotecan + bevacizumab	20	1	5/5 VAR
2	56	M	Rectal	Avastin+Folfox Folfiri MEK 1/2 inhibitor	10	2	6/7 VAR
3	54	M	Colon	Avastin+Folfox Avastin+Folfiri	5	8	6/6 WT
4	70	M	Rectal	Folfox Irinotecan+cetuximab Erbitux+Irinotecan	4	5	6/6 WT
5	42	F	Anal	5FU+Mitomycin 5FU+Cisplatin Taxol	8	>20	6/6 WT

Table 2:

Adverse Events Ranked by Observation Frequency

Adverse Event	Max CTCAE grade	No. of Patients (VAR,WT)
Lymphopenia	4	3 (2,1)
Anemia	3	3 (1,2)
Abdominal Pain	3	2 (1,1)
Anorexia	2	2 (2,0)
Elevated Transaminases	3	2 (1,1)
Fever	2	2 (2,0)
Pruritis	2	1 (1,0)
Vomiting	2	1 (0,1)
Weight Loss	2	1 (1,0)
Thromboembolic Event	3	1 (1,0)
Death	5	1 (0,1)

Table 3:

CPT, SN38, and SN38G Plasma Pharmacokinetics according to UGT1A1 Phenotype

CPT-11			
	VAR	WT	p value
C_{max} [1] (ng/ml)	200.0±40.0	405.2±30.5	0.0006
AUC_{All} (hr*ng/ml)	1998.5±345.3	3227.7±857.7	0.70
$T_{1/2}$ (hr)	16.0±8.2	12.4±6.2	0.54
SN38			
	VAR	WT	p value
C_{max} [1] (ng/ml)	39.7±13.1	20.5±2.5	0.032
AUC_{All} (hr*ng/mg)	558.6±52.6	165.4±11.7	<0.0001
$T_{1/2}$ (hr)	25.6±15.5	13.6±4.8	0.19
Sn38G			
	VAR	WT	p value
C_{max} [1] (ng/ml)	34.8±4.3	86.4±51.3	0.15
AUC_{All} (hr*ng/mg)	927.0±132.1	1667.0±1026.7	0.28
$T_{1/2}$ (hr)	22.5±2.8	15.7±4.7	0.08

[1] *Abbreviations:* C_{MAX} (maximum plasma concentration), AUC (area under the plasma concentration vs time curve extrapolated to infinity), $t_{1/2}$ (half-life), CL/F (apparent oral clearance)

Table 4:

CPT and SN38 Pharmacokinetics in Tumor and Normal Tissue according to UGT1A1 Phenotype

CPT-11 Tumor issue			
	VAR	WT	p value
C_{max} [1] (pg/mg)	4003±5868	9354±13551	0.56
AUC_{All} (hr*pg/mg)	52388±72082	112784±158544	0.57
$T_{1/2}$ (hr)	24±6	21±28	0.90
CPT-11 Normal Tissue			
	VAR	WT	p value
C_{max} [1] (pg/mg)	1848±298	5870±9392	0.52
AUC_{All} (hr*pg/mg)	21005±9847	18964±13139	0.83
$T_{1/2}$ (hr)	13±3	13±6	0.99
SN-38 Tumor Tissue			
	VAR	WT	p value
C_{max} [1] (pg/mg)	112±13	109±168	0.56
AUC_{All} (hr*pg/mg)	1887±416	621±894	0.16
SN-38 Normal Tissue			
	VAR	WT	p value
C_{max} [1] (pg/mg)	196±72	201±235	0.97
AUC_{All} (hr*pg/mg)	3985±1596	1181±1289	0.05
$T_{1/2}$ (hr)	60±4	32±42	0.33

[1] *Abbreviations:* C_{MAX} (maximum tissue concentration), AUC (area under the tissue concentration vs time curve extrapolated to infinity), $t_{1/2}$ (half-life), CL/F (apparent oral clearance)