Cancer Chemother Pharmacol (2017) 79:603–610
DOI 10.1007/s00280-017-3247-3

CLINICAL TRIAL REPORT

A phase 1 trial of intravenous liposomal irinotecan in patients with recurrent high-grade glioma

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Received: 12 October 2016 / Accepted: 23 November 2016 / Published online: 23 February 2017

Abstract
Purpose Preclinical activity of irinotecan has been seen in glioma models, but only modest efficacy has been noted in clinical studies, perhaps related to drug distribution and/or pharmacokinetic limitations. In preclinical testing, irinotecan liposome injection (nal-IRI) results in prolongation of drug exposure and higher tissue levels of drug due to slower metabolism and the effect of enhanced permeability and retention. The objective of the current study was to assess the safety and pharmacokinetics (PK) of nal-IRI and to determine the maximum tolerated dose (MTD) in patients with recurrent high-grade glioma stratified based on UGT1A1 genotyping.
Methods This phase I study stratified patients with recurrent high-grade glioma into 2 groups by UGT1A1 status: homozygous WT ("WT") vs heterozygous WT/*28 ("HT"). Patients who were homozygous *28 were ineligible. The design was a standard 3 + 3 phase I design. WT patients were started at 120 mg/m^2 intravenously every 3 weeks with dose increases in 60 mg/m^2 increments. HT patients were started at 60 mg/m^2, with dose increases in 30 mg/m^2 increments. The assessment period for dose-limiting toxicity was 1 cycle (21 days).
Results In the WT cohort ($n = 16$), the MTD was 120 mg/m^2. In the HT cohort ($n = 18$), the MTD was 150 mg/m^2. Dose-limiting toxicity in both cohorts included diarrhea, some with associated dehydration and/or fatigue. PK results were comparable to those seen in other PK studies of nal-IRI; UGT1A1*28 genotype (WT vs. HT) did not affect PK parameters.
Conclusions Nal-IRI had no unexpected toxicities when given intravenously. Of note, UGT1A1 genotype did not correlate with toxicity or affect PK profile.

Keywords Glioblastoma · High-grade glioma · Chemotherapy · Irinotecan · Liposomes

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Introduction

High-grade gliomas are the most common primary malignant brain tumor in adults; approximately 15,000 new cases are diagnosed in the US each year [1]. Despite progress made using combination therapies including surgery, radiation, and/or chemotherapy, the treatment of malignant gliomas remains problematic, and patients experience nearly universal recurrence. At the time of recurrence, effective treatment options are limited.

Irinotecan liposome injection

Irinotecan, also known as CPT-11, is a topoisomerase I inhibitor used as an antineoplastic agent to treat colorectal, gastric, lung, cervical, and ovarian cancers; diarrhea and myelosuppression are the dose limiting toxicities. Liposomal encapsulation of chemotherapeutic agents is an approach used to improve the therapeutic ratio of antineoplastic agents; several anti-cancer drugs such as doxorubicin and vincristine have been encapsulated in liposomes, and have demonstrated therapeutic benefits over their unencapsulated counterparts. Nanoliposomal irinotecan (nal-IRI) is a proprietary liposomal formulation of irinotecan hydrochloride [2] that is approved in combination with 5-fluorouracil and leucovorin for the treatment of pancreatic cancer in patients who have previously been treated with gemcitabine.

Preclinical development

Studies of human breast, colon, Ewing's sarcoma, and brain cancer xenograft rodent models have evaluated the efficacy of nal-IRI when administered intravenously, most using 4- or 7-day dosing regimens [3–5]. Results showed that nal-IRI enhanced anti-tumor efficacy, including inhibition of tumor growth and regression, over unencapsulated irinotecan without increasing irreversible toxicity (loss of body weight). The results of pharmacokinetic and metabolism studies in mice and rats demonstrated that encapsulation not only increased overall plasma concentrations of the parent drug (irinotecan) and its active metabolite, SN-38, but also prolonged its circulation in the blood, as well as increased and sustained exposure in tumors [2]. In glioma mouse models, nal-IRI has been tested both intravenously and with local delivery using convection-enhanced delivery (CED). Both routes of delivery demonstrated efficacy, but CED appeared particularly promising [3–6].

Prior clinical experience

A phase 1 clinical study of nal-IRI administered every 3 weeks in patients with advanced solid tumor was conducted at 3 sites in Taiwan [7]. A total of 11 patients were recruited at 3 different dose levels (1 at 60 mg/m^2, 6 at 120 mg/m^2, and 4 at 180 mg/m^2). The dose-limiting toxicities (DLT) that occurred in the study were grade 3 diarrhea and grade 4 leucopenia/neutropenia, and the maximum-tolerated dose (MTD) of single-agent nal-IRI found in the study was 120 mg/m^2. Among the 11 patients treated, the most common types of adverse events were gastrointestinal, such as diarrhea. However, these events were mostly categorized as National Center Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 1 or 2, while most grade 3 and 4 adverse events were hematological toxicities. UGT1A1 genotyping was not prospectively performed prior to therapy for patients in that study.

Since initiation of the study we report here, plasma pharmacokinetics of nal-IRI have been compared with those of non-liposomal irinotecan in a phase 2 study of patients with gastric cancer [8]. Re-analysis of the supplementary data in this study showed that compared with irinotecan 300 mg/m^2 every 3 weeks ($n=27$), nal-IRI 100 mg/m^2 every 3 weeks ($n=37$) had a total irinotecan (tIRI) maximum concentration (C_{max}) that was 13.4 times higher, a half-life ($t_{1/2}$) that was 2.0 times longer, and an area under the concentration–time curve extrapolated to infinity (AUC0-∞) that was 46.2 times greater (D.C. Drummond, PhD, unpublished data). The $t_{1/2}$ and AUC0-∞ of SN-38, the active metabolite of irinotecan, were also increased relative to non-liposomal irinotecan (3.0-fold and 1.4-fold, respectively), while maintaining a 5.3-fold lower SN-38 C_{max}.

Furthermore, in a separate clinical trial, nal-IRI–mediated tumor delivery of irinotecan and SN-38 were evaluated in tumor biopsies from 13 patients [9]. In this study, 70 mg/m^2 nal-IRI was administered and biopsies collected 72 h thereafter. The ratio of total SN-38 (tSN38) to total irinotecan (tIRI; a measure of the extent of conversion) was observed to be 8 times higher in tumor lesions than in plasma, providing evidence that the liposomal formulation of irinotecan increases delivery and conversion of irinotecan to SN-38 in the tumor.

Finally, the results of an open-label phase 3 clinical trial testing nal-IRI alone or in combination with fluorouracil and folinic acid in patients with metastatic pancreatic cancer after prior treatment with gemcitabine were recently published [10] and demonstrated improvement in overall survival for the combination, leading to FDA approval of the combination for this indication.

Of note, all nal-IRI doses in this manuscript are expressed as the irinotecan hydrochloride trihydrate salt, which was the convention at the time the study was written (120 mg/m^2 irinotecan trihydrate salt is equivalent to approximately 100 mg/m^2 irinotecan free base). Since approval in the US on October 22, 2015, per FDA guidance, the dose in the US is now expressed as the irinotecan free base. Conversion of a dose based on irinotecan salt to a dose based on irinotecan free base is accomplished by substituting the molecular weight of the salt (677.19 g/mol) with the molecular weight of the free base (586.68 g/mol), resulting in a conversion factor of 0.866.

Pharmacogenetics of nal-IRI

It is now recognized that inherited differences in the metabolism and excretion of an agent or its metabolites can have a significant impact on toxicity and efficacy [11–13], and

this is particularly relevant for irinotecan. In humans, the ester bond of irinotecan is cleaved to form a primary pharmacologically active metabolite, SN-38, which is inactivated by the UGT enzyme system to its ß-glucoronic acid conjugate, SN-38G. The metabolism of irinotecan is substantially influenced by a nucleotide polymorphism in the TATA-box sequences of *UGT1A1* [11–13]. This gene encodes the enzyme UGT1A1, which is responsible for the glucuronidation of SN-38. An extra (7th) repeat in 1 allele (designated UGT1A1*28) results in an approximately 70% reduction in transcriptional activity compared with wild-type *UGT1A1*. The allelic frequency of UGT1A1 in Caucasians is approximately 45% homozygous wild-type, 45% heterozygous wild-type/*28, and 10% homozygous *28. Patients with either a 6/7 heterozygous or 7/7 homozygous UGT1A1*28 have a reduced ability to metabolize SN-38, and as a result are at increased risk for significant drug-related toxicities [10–12]. However, the association between UGT1A1*28, SN-38 concentrations, and hematologic toxicity is also dependent on the dose of irinotecan [13–15].

In the prior solid tumor phase 1 study of nal-IRI, the single patient who died from toxicity related to the agent had genotyping performed and was a heterozygote for the UGT1A1 *28 allele [7]. As shown in the plasma concentration–time profile of SN-38 for this patient, there was prolonged elevation of the plasma concentration compared to the other patients. UGT1A1 genotyping was not performed in all patients in that study, however, so the relationship of UGT1A1 genotyping and the pharmacokinetic results remained unclear. Several years ago, UGT1A1 genotyping was made commercially available, and the available information regarding the role of UGT1A1 genotype as a predictor of toxicity of irinotecan was felt to warrant prospective evaluation and stratification in this phase 1 trial of nal-IRI.

Materials and methods

Study design

The primary objective of this study was to assess the safety and pharmacokinetics of nal-IRI in patients with recurrent malignant glioma stratified based on UGT1A1 genotype. The primary efficacy endpoint was 6-month progression-free survival (PFS-6). Eligibility criteria for this phase 1 clinical trial included unequivocal radiographic or pathologic confirmation of recurrent high-grade glioma (glioblastoma, gliosarcoma, anaplastic astrocytoma, anaplastic oligoastrocytoma, anaplastic oligodendroglioma, or malignant astrocytoma NOS); age ≥18; Karnofsky Performance Status score of ≥60; adequate organ and bone marrow function; lack of other cancer, infection, or serious medical problem; and patients could not be on any enzyme-inducing drugs including enzyme-inducing anticonvulsants. There were no limits on number of prior recurrences or prior treatments aside from exclusion of patients who had previously been treated with irinotecan. Patients were stratified by UGT1A1 genotype; patients who were homozygous wild-type were enrolled in the wild-type (WT) cohort, while patients who were heterozygous wild-type/*28 were enrolled into the heterotype (HT) cohort. Patients who were homozygous 7/7 *28 were not eligible for study enrollment. Starting dose for the WT cohort was 120 mg/m^2, the MTD from the unselected phase 1 solid tumor study. Starting dose for the HT cohort was 60 mg/m^2, due to concern for potentially increased toxicity in these patients. Planned dose levels were as outlined in Table 1, with the plan to continue escalation if the MTD had not been reached at the highest dose levels.

Because the starting dose for the WT cohort was the MTD from the prior phase 1 study, enrollment was initially restricted to the WT cohort, and 6 patients were to be enrolled at dose level 0 before any dose escalation was attempted. If there were 0 or 1 DLTs in those patients, then the WT cohort could be escalated and the HT dose level 0 enrollment could begin.

Aside from the initial 6 patients enrolled within the WT cohort, the study was a standard 3 + 3 design. Drug was given on D1 of each 21-day cycle, for up to 12 months in the absence of progression or intolerable toxicity, and the DLT period was defined as the first 21-day cycle. The MTD was defined as the dose level at which 0 of 3 or 1 of 6 patients experienced DLT, with the next higher dose having at least 2 of 3 or 2 of 6 patients encountering DLT. Table 2 shows definitions for DLTs and recommended dose modifications; CTCAE v3.0 was used for this study. Informed consent was obtained from all individual participants included in the study.

Table 1 Planned dose levels

Dose level	WT (mg/m^2)	HT (mg/m^2)
−1	60	30
0 (starting)	120	60
1	180	90
2	240	120
3		150

Dose expression of nal-IRI here is in the form of the trihydrate salt; as described in the manuscript text, the conversion factor from the trihydrate salt dose to the currently used free base dose is 0.866

Table 2 Dose-limiting toxicities and recommended dose modifications

Dose-limiting toxicity		
Hematological	Grade 3+ thrombocytopenia persisting >5 days	
	Grade 4 neutropenia persisting >5 days	
	Grade 4 anemia of any duration	
Non-hematological	Any grade 3 or greater toxicity[b] except for grade 3 alopecia	
Other	Failure to recover from toxicities to be eligible for re-treatment with nal-IRI within 35 days of the first dose of nal-IRI	
Recommended dose modifications: hematological toxicity		
ANC Nadir	Platelet Nadir	Subsequent dose to be given
≥1000	≥75,000	Full dose (no dose reduction)[a]
750–999	50,000–74,000	Held, then single dose level reduction[a]
<750	<50,000	Held, then two-dose level reduction[a]
Recommended dose modifications: non-hematological toxicity		
Grade 0–2+		Full dose (no dose reduction)[c]
Grade 3		Hold, then single dose level reduction[d]
Grade 4		Hold, then two-dose level reduction[e]

Defined according to NCI CTCAE version 3.0

[a]To be given only once there had been recovery to ANC ≥1000 and platelets ≥100,000

[b]For nausea, vomiting or diarrhea, only if grade 3 or greater despite optimal medical management

[c]For intolerable Grade 2 toxicity, the dose could be held until recovery to CTCAE Grade 0–1, then resumed at one dose lower, at the investigator's discretion

[d]To be held until recovery to CTCAE Grade 0–1 (or to within 1 grade of starting values for pre-existing laboratory abnormalities), and then resumed at one dose level lower, unless toxicity was nausea/vomiting and patients were not on optimal antiemetic therapy

[e]To be held until recovery to CTCAE Grade 0–1 (or to within 1 grade of starting values for pre-existing laboratory abnormalities), and then resumed at two dose levels lower

Pharmacokinetic analyses

Pharmacokinetics samples were to be drawn prior to the first dose of drug, and then immediately post-infusion, at 2, 4, 6, and 24 h post-infusion, and, if possible, at 48 h post-infusion. Samples were drawn again prior to the second infusion. Study samples (human plasma) were analyzed for 3 analytes [irinotecan (CPT-11), SN38, and SN38 glucuronide (SN38G)] using a modified version of a validated ultra performance liquid chromatographic (UPLC) assay. Authentic standards of CPT-11, SN38, and SN38G were obtained from Toronto Research Chemicals Inc. (Toronto, Ontario, Canada) and camptothecin, the internal standard (IS), was obtained from Sigma Aldrich (St. Louis, MO). Study samples were quantitated using calibration standards and quality control (QC) samples prepared by spiking CPT-11, SN38, and SN38G into human lithium heparin plasma (Bioreclamation, LLC, Westbury, New York). Calibration ranges were 0.200–1000 ng/mL for all analytes, and plasma QCs were prepared at 1.00, 100, and 750 ng/mL for all analytes.

Study samples were analyzed undiluted for SN38 and SN38G, but diluted for CPT-11 prior to extraction so the concentrations were within the range of the standard curve. Study samples were extracted by mixing a 200-µL aliquot of a calibrator, QC, plasma blank, or study sample with 800 µL of ice cold, acidified methanol containing the IS camptothecin at 20 ng/mL in a 1.5-mL microcentrifuge tube. The tubes were capped, vortexed, and centrifuged at 14,000 rpm and 4 °C for 10 min. After centrifugation, 700 µL of the supernatant was transferred to a clean 16 × 100-mm glass culture tube, and the supernatant evaporated at 37 °C under nitrogen. The residue was reconstituted with 200 µL of a mixture of 85% mobile phase A (80.0% water containing 3.00% trimethylamine (TEA)/20.0% acetonitrile, pH 5.5) and 15% mobile phase B (100% acetonitrile). The suspension was centrifuged at 14,000 rpm and 4 °C for 10 min to separate insoluble materials. A 100-µL aliquot of the supernatant was transferred to a glass insert in an amber autosampler vial and a 15-µL aliquot injected.

UPLC analysis of the extracted samples was performed using an Acquity® UPLC System with fluorescence detection (Waters Corporation, Milford, MA, USA). Chromatographic separation was achieved using a Waters® Acquity® RP18, 2.1 mm × 100 mm, 1.7 µm column (part number 186002854) preceded by a Waters® Acquity® BEH Shield RP18, 2.1 mm × 5.0 mm, 1.7 µm guard column (part number 186003977). The HPLC column was maintained at 40 °C and a flow rate of 500 µL/min using a biphasic gradient (Mobile Phase A: 80.0% water containing 3.00% TEA/

20.0% acetonitrile pH 5.5; and Mobile Phase B: 100% acetonitrile).

Analytes were analyzed by fluorescence detection controlled by Waters® Empower™ 3 software, build 3471. Excitation wavelength was set at 370 nm for all three analytes with emission wavelengths at 510, 530, and 420 nm for CPT-11, SN38, and SN38G, respectively. Calibration curves were generated using analyte/IS peak area response ratios versus nominal concentrations (ng/mL) and weighted linear regressions with a weighting factor of 1/concentration^2. Back-calculated concentrations were generated using the formula $x = (y - b)/m$ where x is the back-calculated concentration, y is the analyte/IS peak area ratio, b is the y intercept, and m is the slope. Calibrator and QC acceptance criteria required all acceptable concentrations to have accuracy deviations of 15% or less from the nominal concentration with coefficients of variations (% CV) of 15% or less, except at the lower limit of quantitation, which was allowed a 20% deviation for both parameters.

The standard non-compartmental method was used to estimate the pharmacokinetic parameters of total irinotecan, SN-38, and SN-38G from the analyzed plasma concentration data in patients. The estimated pharmacokinetic parameters included maximum plasma concentrations (C_{max}), areas under the plasma concentration time curve (AUC_{0-t}) and terminal half-life ($t_{1/2}$).

Results

Patient demographics

Patients in the two groups had similar baseline characteristics. In the WT cohort, mean age was 50 years (range 28–65 years) and median Karnofsky Performance Status (KPS) was 80 (range 60–90); in the HT cohort mean age was 48 years (range 28–75 years) and median KPS was 90 (60–100). Of the 16 patients in the WT cohort, 12 patients had GBM and 4 had grade III oligoastrocytoma. Of the 18 patients in the HT cohort, 14 had GBM, 1 had grade III oligoastrocytoma, and 3 had grade III astrocytoma. The median number of relapses was 3 in both groups (WT, range 1–8; HT, range 1–5).

Safety results

The MTD for the WT cohort was 120 mg/m^2 every 3 weeks. Six patients were enrolled at that dose, without any DLTs. Four patients were enrolled at 180 mg/m^2 without DLTs (patients #3 and #4 were consented and screened, including testing of UGT1A1 genotype, simultaneously, and an exception was granted to allow both patients to enroll when their genotypes were both WT). Three patients were then enrolled at 240 mg/m^2, but DLTs occurred in 2 of the 3 patients (diarrhea and dehydration). As a result, the dose was de-escalated to 180 mg/m^2, and 3 additional patients were enrolled. Within these 3 patients, there were 2 DLTs (diarrhea in one patient, and diarrhea and fatigue in the other). As such, the MTD for the WT cohort was declared to be 120 mg/m^2, to which 6 patients had already been enrolled without any DLTs.

In the HT cohort, 3 patients were treated at 60 mg/m^2, with no DLTs. Six were treated at 90 mg/m^2 with 1 DLT. Three were treated at 120 mg/m^2 with no DLTs, and then 6 patients were treated at 150 mg/m^2 with 1 DLT (dehydration/diarrhea). Given the above-described experience with the WT cohort, further dose escalation to 180 mg/m^2 was not felt advisable, and as such, the MTD for the HT cohort was declared to be 150 mg/m^2. Table 3 lists all grade 3 or greater toxicities that were possibly, probably or definitely related to the study medication.

Efficacy results

PFS-6 was 2.9% for the intent-to-treat (ITT) cohort. Median PFS (Fig. 1a) was 42 days (95% CI 40–45 days), while median overall survival (Fig. 1b) was 107 days (95% CI 87–198 days).

Pharmacokinetic analysis results

The pharmacokinetic parameters of nal-IRI were analyzed by each dose level for total irinotecan and the metabolites SN-38 and SN-38G (Table 4). Due to the limited sampling schedule, only C_{max} was reported for SN-38 and SN-38G. The maximum concentration and AUC_{0-t} for total

Table 3 Grade 3 or greater toxicities possibly related to drug

Toxicity	Grade[a]	Number of patients
Neutropenia	3	1
	4	1
Leukopenia	3	5
	4	1
Lymphopenia	3	4
	4	1
Fatigue (asthenia, lethargy, malaise)	3	2
Nausea	3	1
Dehydration	3	3
Diarrhea	3	3
Elevation of creatinine	3	1
Hypokalemia	4	1

[a]Defined according to NCI CTCAE version 3.0

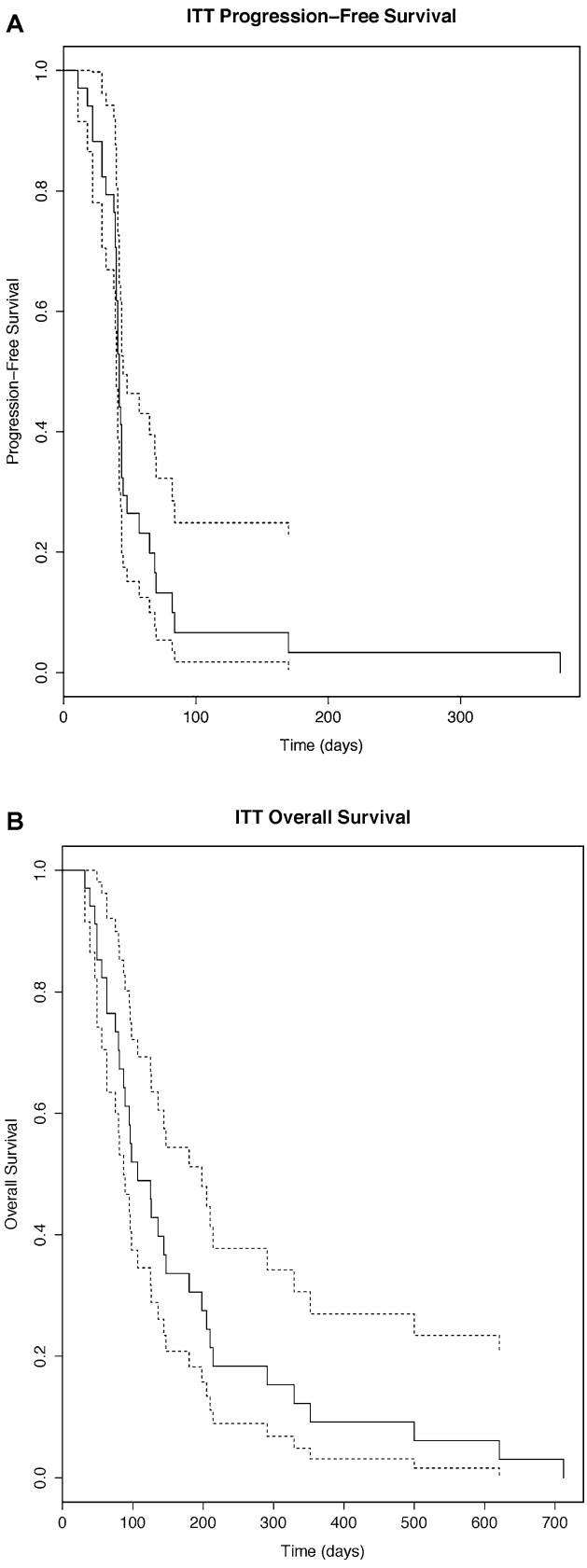

Fig. 1 **a** Kaplan–Meier estimate (*solid line*) of progression-free survival for the intent-to-treat (ITT) cohort. 95% confidence interval bands are represented using *dashed lines*. **b** Kaplan–Meier estimate (*solid line*) of overall survival for the intent-to-treat (ITT) cohort. 95% confidence interval bands are represented using *dashed lines*

irinotecan proportionally increased with dose (Table 4). The terminal half-life for nal-IRI did not change with dose and was comparable to a prior study [8] (also D.C. Drummond, PhD, unpublished data). Interestingly, UGT1A1*28 WT or HT genotype had no clear effect on nal-IRI PK parameters (Fig. 2a). In addition, the ratio of SN-38G to SN-38, the indicator of UGT1A1 activity did not show any difference (Fig. 2b).

Discussion

In this phase 1 study, nal-IRI did not demonstrate any unexpected toxicities. The DLTs were diarrhea, dehydration and fatigue, all known toxicities of the parent drug irinotecan. Contrary to expectations, there was no clear difference in the pharmacokinetic parameters between the WT cohort and the HT cohort, and the clinical tolerability, as measured by the MTD achieved in the two cohorts, was not superior in the WT cohort. Moreover, these results are consistent with recent findings that similar SN-38 concentrations were observed for both 7/7 homozygous and non-7/7 homozygous UGT1A1*28 (D.C. Drummond, MD, unpublished data). One limitation of the current study is the fact that the PK sampling time point in this study was limited to the first 24 h; therefore, the clearance of SN-38 cannot be estimated.

Although 150 mg/m^2 was not tested in the WT cohort within this study, given that the MTD in the prior (unselected genotype) phase 1 study was 120 mg/m^2 and that it was 120 mg/m^2 (WT cohort) and 150 mg/m^2 (HT cohort) in this study, we would suggest that 120 mg/m^2 be the recommended phase 2 dose going forward for glioma patients with either WT or HT genotype.

Preclinical testing of CED of nal-IRI has demonstrated efficacy in intracranial rodent models as a montherapy [16], in combination with PEGylated liposomal doxorubicin [17], and in combination with radiation [6]. Antitumor activity was also observed in spontaneous canine brain tumors treated with nal-IRI administered by CED [18]. The study we report here on intravenous delivery of nal-IRI was required by the FDA prior to testing CED of nal-IRI in patients with gliomas, and the toxicity profile of the drug was acceptable to move forward. As such, we have initiated a phase 1 clinical trial testing CED of single-agent nal-IRI in humans with recurrent malignant glioma [NCT02022644], with the goal of moving to CED

Table 4 Mean pharmacokinetic parameters of nal-IRI

	Dose, mg/m^2	60	90	120	150	180	240
Total irinotecan ($N=33$)	C_{max}, μg/mL	31.8 (2.3)	171.6 (61.6)	91.8 (12.7)	194.0 (57.0)	169.7 (14.5)	253.5 (70.5)
	AUCt, h·μg/mL	360.0 (117.1)	1848.6 (628.1)	1782.4 (409.6)	4152.2 (1341.2)	3786.2 (795.5)	9418.2 (7237.2)
	$t_{1/2}$, h	11.5 (–)	13.4 (0.2)	28.4 (14.1)	32.1 (9.2)	42.2 (13.8)	37.2 (–)
SN-38 ($N=11$)[a]	C_{max}, ng/mL	15.5 (5.2)	3.6 (–)	11.8 (4.0)	(–)	3.2 (1.4)	(–)
SN-38G ($N=33$)	C_{max}, ng/mL	15.0 (1.2)	96.0 (63.6)	25.7 (5.1)	28.0 (7.4)	28.4 (5.6)	38.5 (26.0)

Standard error is reported within parenthesis

[a]Not all patients have SN-38 concentration data due to assay failure

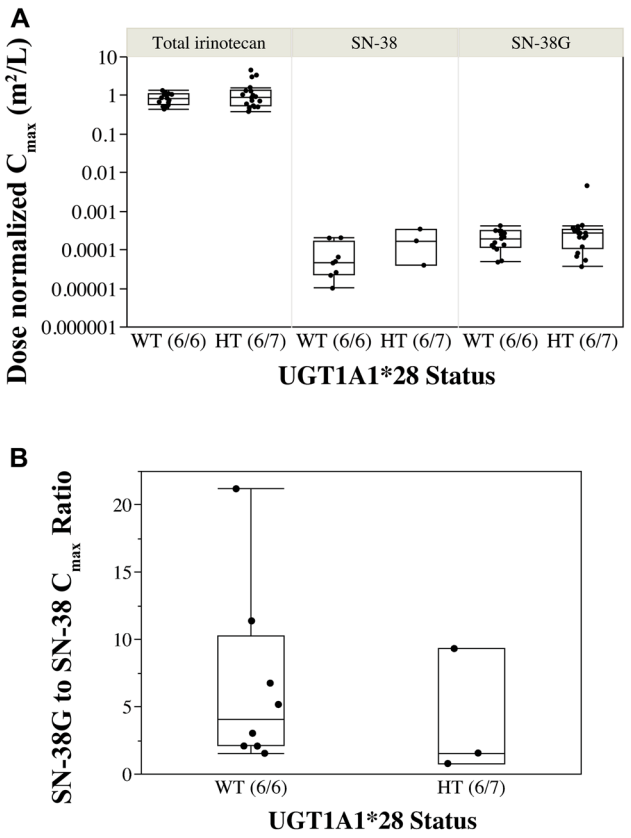

Fig. 2 **a** Comparison of dose normalized C_{max} in patients with different UGT1A1*28 genotypes. **b** Comparison of SN-38G to SN-38 C_{max} ratio in patients with different UGT1A1*28 genotypes

of combination therapy if it is tolerated as a single-agent. Further development of intravenous delivery of nal-IRI in glioma patients is not planned at this time.

In this study, the patients with UGT1A1 heterozygosity showed similar pharmacokinetic properties for SN-38 and SN-38G relative to WT patients following the administration of nal-IRI. While the plasma levels of SN-38 can be affected by the activity of UGT enzymes, they also rely on the incoming load of SN-38 (ie, the amount of irinotecan conversion to SN-38). Indeed, the associations between UGT1A1*28 7/7 homozygosity and hematological toxicity were observed only in patients treated with higher irinotecan doses [15]. Furthermore, the plasma SN-38 concentrations from UGT1A1*28 7/7 homozygous patients were higher only in patients administered with higher dose of irinotecan (300 mg/m^2), not in patients with a low daily dose (15–75 mg/m^2 for 5 days) of irinotecan [13, 14]. Therefore, the lack of significant pharmacokinetic difference in our HT cohort relative to the WT cohort could be attributed to the fact that nal-IRI can lower the amount of SN-38 to be metabolized by UGT enzymes by preventing the rapid conversion of irinotecan to SN 38.

Acknowledgements The authors would like to thank Ms. Ilona Garner (UCSF) for her expert assistance with manuscript preparation and editing.

Compliance with Ethical Standards

Funding This clinical trial was funded by the UCSF Brain Tumor Research Center's Specialized Program of Research Excellence (SPORE) Grant from the NCI: P50 CA097257.

Conflict of interest Daryl C. Drummond is both an employee and stockholder in Merrimack, and is the inventor of Onivyde (liposomal irinotecan). Jonathan B. Fitzgerald is an employee of Merrimack. Charles Noble is a stockholder in Merrimack.

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