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Phase I Study of Sunitinib and Irinotecan for Patients with Recurrent Malignant Glioma

David A. Reardon, MD[1,2], **James J. Vredenburgh, MD**[3], **April Coan, MS**[4], **Annick Desjardins, MD**[3], **Katherine B. Peters, MD, PhD**[3], **Sridharan Gururangan, MD**[1,2], **Sith Sathornsumetee**[5], **Jeremy N. Rich, MD**[6], **James E. Herndon II, PhD**[3], and **Henry S. Friedman, MD**[1,2]

[1]Department of Pediatrics, Duke University Medical Center, Durham, North Carolina [2]Department of Surgery, Duke University Medical Center, Durham, North Carolina [3]Department of Medicine, Duke University Medical Center, Durham, North Carolina [4]Department of Cancer Center Biostatistics, Duke University Medical Center, Durham, North Carolina [5]Department of Medicine (Neurology), Faculty of Medicine at Siriraj Hospital, Mahidol University, Bangkok, Thailand [6]Department of Stem Cell Biology and Regenerative Medicine, Cleveland Clinic, Cleveland, Ohio

Abstract

Background—We determined the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of the oral vascular endothelial growth factor receptor (VEGFR) inhibitor, sunitinib, when administered with irinotecan among recurrent malignant glioma patients.

Methods—For each 42-day cycle, sunitinib was administered once a day for four consecutive weeks followed by a two week rest. Irinotecan was administered intravenously every other week. Each agent was alternatively escalated among cohorts of 3-6 patients enrolled at each dose level. Patients on CYP3A-inducing anti-epileptic drugs were not eligible.

Results—Twenty-five patients with recurrent malignant glioma were enrolled, including 15 (60%) with glioblastoma and 10 (40%) with grade 3 malignant glioma. Five patients progressed previously on bevacizumab and two had received prior vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy. The maximum tolerated dose was 50 mg of sunitinib combined with 75 mg/m^2 of irinotecan. Dose limiting toxicities (DLT) were primarily hematologic and included grade 4 neutropenia in 3 patients and one patient with grade 4 thrombocytopenia. Non-hematologic DLT included grade 3 mucositis (n=1) and grade 3 dehydration (n=1). PFS-6 was 24% and only one patient achieved a radiographic response.

Conclusion—The combination of sunitinib and irinotecan was associated with moderate toxicity and limited anti-tumor activity. Further studies with this regimen using the dosing schedules evaluated in this study are not warranted.

Keywords

Sunitinib; irinotecan; malignant glioma; vascular endothelial growth factor; platelet-derived growth factor

Address for reprints: David A. Reardon, M.D., The Preston Robert Tisch Brain Tumor Center, Room 047 Baker House, Trent Drive, DUMC 3624, Durham, NC 27710 USA; reard003@mc.duke.edu.

Introduction

The outcome for patients with malignant glioma remains poor. Nearly all patients recur after standard multi-modality therapy that includes maximum safe resection, radiotherapy and temozolomide-based chemotherapy. Median overall survival for glioblastoma (GBM), the most common type of malignant glioma, is only 14.6 months [1]. A contributing factor to overall poor outcome is ineffective therapies for recurrent patients [2-4].

Malignant gliomas are highly angiogenic tumors, and vascular endothelial growth factor (VEGF) is the principal angiogenic growth factor [5, 6]. Targeting VEGF in preclinical orthotopic xenograft GBM models has demonstrated anti-tumor activity [7, 8]. Recent clinical studies have confirmed that VEGF inhibiting therapies have anti-tumor benefit for recurrent GBM patients. Specifically, bevacizumab, a humanized monoclonal antibody against VEGF, was granted accelerated approval by the U.S. Food and Drug Administration (FDA) for recurrent GBM patients based on radiographic responses observed in a single-arm phase II study of bevacizumab monotherapy [9] and a phase II study that randomized patients to either single-agent bevacizumab or bevacizumab with irinotecan [10].

A second strategy to target angiogenesis for malignant glioma patients is inhibition of VEGF receptor (VEGFR) signaling using specific and potent VEGFR tyrosine kinase inhibitors. Sunitinib (Sutent; SU11248; Pfizer, Inc., New York, NY) is an orally-bioavailable pan-VEGFR inhibitor that also inhibits other biologically relevant growth factors in GBM including platelet-derived growth factor receptors (PDGFRα and PDGFRβ) and stem cell growth factor receptor (KIT). Sunitinib, which also inhibits ms-like tyrosine kinase 3 (FLT-3), glial cell line-derived neurotrophic factor receptor (RET) and colony stimulating factor-1 receptor (CSF1-R), is currently FDA-approved for renal cell carcinoma and gastrointestinal stromal tumors [11].

At the time this study was designed, our group had just reported highly encouraging evidence of anti-tumor activity with bevacizumab plus irinotecan (Camptosar; CPT-11), a topoisomerase-1 inhibitor, among heavily pre-treated, recurrent malignant glioma patients [12, 13]. Studies of single-agent bevacizumab had not been reported. We hypothesized that sunitinib with irinotecan may also have anti-tumor activity and designed this phase I study to evaluate the safety of this combination and determine its maximum tolerated dose (MTD) as well as dose-limiting toxicity (DLT) among recurrent malignant glioma patients.

Materials and Methods

Protocol Objectives

The primary objective of this study was to define the MTD and DLT of sunitinib when administered daily with irinotecan among adults with recurrent malignant glioma. Secondary objectives included: to define other toxicities associated with the regimen; and to document antitumor activity.

Patient Eligibility

Patients were required to have a histologically confirmed diagnosis of grade III or IV malignant glioma that was recurrent. Patients with prior low-grade glioma were eligible if histologic transformation to malignant glioma prior to enrollment was confirmed. Patients were also required to: be ≥18 years of age; have a Karnofsky performance status (KPS) ≥ 70%; be on a stable corticosteroid dose for ≥1 week; have satisfactory hematologic (hemoglobin >9 g/dl; absolute neutrophil count >1500 cells/μl; platelet count >100,000 cells/μl) and biochemical results (serum creatinine and bilirubin ≤ 1.5 × institutional upper limit of normal [ULN]; and aspartate aminotransferase [AST] and alanine aminotransferase

[ALT] ≤ 2.5 × ULN); have recovered from all expected toxicity related to previous therapy; and provide written informed consent. In addition, patients were required to be at least 2 weeks from prior surgical resection (1 week for stereotactic biopsy), and 4 weeks from either radiotherapy or chemotherapy (6 weeks for nitrosoureas).

Exclusion criteria were: prior sunitinib therapy; progressive disease or grade ≥ 3 toxicity to prior irinotecan therapy; concurrent administration of warfarin or CYP3A enzyme-inducing anti-epileptic drugs (EIAEDs; phenytoin, phenobarbital, carbamazepine, oxcarbazepine, or primidone); grade > 1 intratumoral hemorrhage on baseline imaging; homozygosity for UGT1A1; pregnancy or nursing; significant concurrent medical illness; or prior malignancy requiring active intervention. There was no restriction for eligibility based on number of prior episodes or progressive disease, degree of prior treatment or prior bevacizumab therapy.

Treatment Design

Sunitinb and irinotecan were provided by Pfizer, Inc. (New York, New York). Sunitinb was taken orally once a day without regard to food for four weeks followed by a two week rest for each 42-day treatment cycle. Patients and caregivers were carefully taught how to administer sunitinib and were asked to complete a daily dose administration diary.

Irinotecan was administered intravenously over 90 minutes on days 1, 15 and 29 of each 42 day cycle. Prior studies confirmed that the metabolism of irinotecan is significantly increased by concurrent use of CYP3A-inducing anti-epileptic drugs (EIAEDs) such as phenytoin, carbamazepine, phenobarbital, oxcarbazepine and primidone [14, 15]. Due to this pharmacokinetic interaction, combined with a decreasing frequency of EIAED use among malignant glioma patients in general, patients who required EIAEDs were excluded from the current study.

The starting dose of sunitinib was 25 mg once a day for four weeks followed by a two week rest and the starting dose of irinotecan was 75 mg/m^2. Based on the dose escalation design (Table 1), each agent was escalated in a staggered manner in successive patient cohorts. The fifth and final planned dose level included the standard, full dose of each agent. Cohorts of 3-6 patients were treated per dose level until DLT was observed.

Dose Escalation and Statistical Considerations

Three patients were accrued in successive cohorts at each dose level as long as DLT did not occur. If one instance of DLT was observed among the initial three evaluable patients, an additional three patients were treated at that dose level. Dose escalation then continued as long as no DLT occurred in these additional patients. If two instances of DLT were observed at a dose level, the MTD was surpassed, and a total of six patients were treated at the previous level to assure its tolerability. MTD was defined as the highest dose causing DLT during cycle 1 in no more than one of six patients.

Non-hematologic DLT included ≥ grade 3 attributable toxicities, except for alopecia, nausea, vomiting or diarrhea that responded to standard medical therapy. Hematologic DLT included either grade 4 neutropenia or grade 3 thrombocytopenia. Any toxicity resulting in a >14-day delay to re-treat was also considered DLT.

Time to progression (TTP) and overall survival (OS) were measured from treatment initiation and analyzed by the Kaplan-Meier method including 95% confidence intervals (CIs).

Toxicity Evaluation

Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. Patients were evaluated by physical examination before each cycle. In addition, blood pressure was measured every other week. A complete blood count with differential was obtained weekly, and serum electrolytes, BUN/creatinine and liver function tests as well as urinalysis were obtained before every cycle. A beta human chorionic gonadotropin test was performed prior to the first cycle in women with reproductive potential. Patients who experienced DLT or unacceptable toxicity were followed weekly until toxicity resolved.

Response Evaluation

Response was evaluated by neurologic examination and contrast-enhanced MRI prior to the start of every treatment cycle and was graded using modified Macdonald criteria [16]. Radiologic assessment in neuro-oncology (RANO) criteria [17]were not used because they were not defined prior to the execution of this study.

Dose Modification and Retreatment Criteria

Re-treatment required adequate hematologic and biochemical parameters (defined in eligibility criteria) and resolution of any treatment-related grade ≥ 3 toxicity to grade ≤ 1. Dose reduction of both sunitinib and irinotecan by one dose level were instituted for DLTs during study drug administration. The dose of irinotecan was planned to be decreased to 50 mg/m^2 for patients who experienced DLT in dose level one.

Study therapy was discontinued for unacceptable toxicity despite appropriate dose modification, progressive disease or withdrawal of consent.

Pharmacokinetic Analysis

The study protocol included an optional dose expansion of six patients to determine pharmacokinetics of sunitinib and irinotecan at the MTD. However, due to limited evidence of anti-tumor activity observed during the performance of the dose escalation portion of this trial, the sponsor and study investigators determined that further investigation of this study regimen was unlikely to be considered. Hence, the dose expansion portion of this protocol to evaluate pharmacokinetics of the study agents was electively not pursued, and therefore there are no results of the pharmacokinetic of the study regimen.

Results

Patient Characteristics

Twenty-five patients with recurrent malignant glioma were enrolled at Duke University Medical Center between April, 2008 and April, 2010 (Table 2). Fifteen patients had GBM (60%), 8 had anaplastic astrocytomas (AA) (32%) and 2 patients had anaplastic oligodendroglioma (8%). None of the patients had debulking surgery prior to study enrollment. All patients had progressive disease after at least radiotherapy and chemotherapy including temozolomide. Fourteen patients (56%) enrolled after their first episode of progressive disease, while 11 enrolled after 2 or more progressions. The median time from original diagnosis to study enrollment was 18.8 months (range, 5.0-1274.8 months). Five patients had received prior bevacizumab and two patients had been treated with an alternative VEGFR tyrosine kinase inhibitor (vandetanib). Four patients (16%) had received prior irinotecan.

As of April 1, 2011, 9 patients (36%) remain alive and 16 have died of progressive tumor. All patients have discontinued study therapy.

Dose-Limiting and Non-Dose-Limiting Toxicities

Fifty-seven courses of sunitinib and irinotecan were administered. Table 3 summarizes the frequency of attributable grade ≥ 2 adverse events. Neutropenia was the most common grade ≥ 2 adverse event and affected 13 patients (52%), while fatigue was the next most common toxicity and affected 9 patients (36%), but was grade 2 in seven. The frequency of grade ≥ 3 hematologic adverse events was unexpected and affected 12 patients (48%) including eight patients with neutropenia, three patients with thrombocytopenia and one patient with anemia. Grade ≥ 2 electrolyte abnormalities were also fairly common and affected 10 patients (40%), and included hypophosphatemia (n=4), hypocalcemia (n=2) and hypokalemia (n=2). Grade ≥ 3 amylase/lipase occurred in two patients. Both patients were symptomatic but the event reversed with appropriate medical management.

Table 4 summarizes DLTs by dose level. Three out of four DLTs were hematologic. One out of six patients experienced DLT at both dose levels two and three, respectively, while two out of six patients treated at dose level four experienced DLT. These results confirmed the MTD of sunitinib to be 50 mg daily for four consecutive weeks when combined with irinotecan administered at 75 mg/m2 every other week.

Outcome

The median follow-up for all patients was 100.1 weeks (95% CI, 58.1-126.7 weeks). The 6-month PFS rate, median PFS and median OS for all patients were 24% (95% CI: 9.8, 41.7%), 6.9 weeks (95% CI: 5.7, 17.7 weeks), and 53.1 weeks (95% CI: 30.3, 87.9 weeks). All patients were evaluable for response. One patient (4%) achieved a radiographic PR and 9 (36%) patients achieved SD. Progressive disease was noted at initial evaluation in 15 patients (60%).

Discussion

This study was designed just after the regimen of bevacizumab and irinotecan was reported to be associated with a radiographic response rate of approximately 57% and PFS-6 of 46% among recurrent GBM patients [13]. These results contrasted strikingly with those of recent meta-analyses of salvage therapies from the pre-bevacizumab era that reported radiographic response and PFS-6 rates less than 10%, respectively [2-4]. We hypothesized that sunitinib and irinotecan may have clinical activity similar to that initially reported for bevacizumab and irinotecan among recurrent malignant glioma patients and designed the current study to determine the MTD and DLT of this regimen in this patient population.

Sunitinib is an attractive therapeutic option for GBM because it targets several biologically relevant tyrosine kinases. First, it is a pan-VEGFR inhibitor. Second, it blocks PDGFRα and PDGFR-β, which are overexpressed in a subset of GBM and linked with gliomagenesis in neural stem cell models [18-21]. PDGFRs are also important mediators of pericyte activation and stabilization of tumor vasculature [22, 23]. Third, sunitinib also inhibits c-KIT, a growth factor receptor that has been shown to be overexpressed and amplified in a subset of GBM tumors [24, 25].

Sunitinib is currently FDA approved for renal cell carcinoma as well as gastrointestinal stromal tumors [11] and has shown encouraging activity in several other solid tumors [26-29]. Effective penetration into the CNS has been inferred by reports of brain metastases undergoing regression following sunitinib therapy [30-32].

Preclinical studies suggest that sunitinib has activity against malignant glioma. In an organotypic malignant glioma brain slice model, sunitinib therapy enhanced apoptosis and decreased tumor cell proliferation, angiogenesis and invasion, while treatment of U87MG intracranial xenografts resulted in growth delay and diminished microvessel density [33]. Chahal and colleagues demonstrated that sunitinib decreased proliferation and survival of MGMT-transfected U87MG cells treated with radiotherapy alone, temozolomide alone or the combination, but did not affect U87MG MGMT negative cells [34]. Sunitinib has also been shown to augment the cytotoxicity of chemotherapy in a flank xenograft GBM model [35]. Finally, sunitinib therapy can enhance the intratumoral delivery of temozolomide in intracranial malignant glioma models, consistent with vascular normalization [36].

Only one clinical study of sunitinib among recurrent malignant glioma patients has been reported to date [37]. In a series of 21 patients, single-agent sunitinib administered at 37.5 mg continuous, once daily oral dosing, was well tolerated but failed to achieve any objective radiographic responses and was associated with a median PFS of only 1.6 months.

In the current study, we evaluated sunitinib administered at the conventional once daily schedule for four weeks followed by a two week rest, in combination with irinotecan administered every other week. Although the MTD included sunitinib at 50 mg/day, which is the established single-agent dose, irinotecan was only able to be escalated to 75 mg/m^2. The regimen was associated with an increased rate of grade ≥3 hematologic toxicity than reported with single-agent Sunitinib [37], which included neutropenia or thrombocytopenia in 11 patients (40%). Grade 2 or 3 electrolyte deficiencies, including hypocalcemia, hypokalemia and hypophosphatemia were also common and occurred in 8 patients (32%). The etiology of these adverse events is unclear but may be related to the multi-targeted activity of sunitinib or to its combination with irinotecan. Although pharmacokinetic evaluations were not performed, detrimental interactions with increased accumulation of metabolites may have contributed to the observed toxicity given the shared pathways of metabolism of sunitinib and irinotecan.

Although this was a phase I study, and therefore not designed to evaluate efficacy, we noted that the regimen of sunitinib and irinotecan was associated with limited evidence of anti-tumor activity. As described above, single-agent sunitinib was also associated with minimal anti-tumor activity among recurrent GBM patients [37]. Other VEGFR TKIs have also noted disappointing results among recurrent malignant glioma patients [38-40], although the reason underlying their apparent inferior anti-tumor activity relative to bevacizumab remains unclear. A factor that may have contributed to the low level of anti-tumor activity noted in this study was that 28% of the enrolled patients had received prior VEGF/VEGFR-directed therapy.

In conclusion, we established the MTD of sunitinib and irinotecan in this phase I, dose escalation study. The regimen was associated with moderate toxicity and limited anti-tumor activity. An elective dose expansion at the MTD to evaluated pharmacokinetics and potential correlative biomarkers of response was not pursued due to toxicity and limited anti-tumor activity observed during the dose escalation portion of this study. Further evaluation of this regimen utilizing this dose schedule among malignant glioma patients is not warranted.

Acknowledgments

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Abbreviations List

AA	anaplastic astrocytoma
CI	confidence interval
CR	complete response
DLT	dose-limiting toxicity
EIAEDs	enzyme-inducing antieptileptic drugs
GBM	glioblastoma
ITT	intent-to-treat
KPS	Karnofsky performance status
MG	malignant glioma
MTD	maximum-tolerated dose
OS	overall survival
PD	progressive disease
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PFS	progression-free survival
PR	partial response
SD	stable disease
TTP	time to progression
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

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Table 1

Dose escalation schema

Dose Level	Sunitinib[1] (mg)	Irinotecan[2] (mg/m^2)
1	25	75
2	37.5	75
3	50	75
4	50	100
5	50	125

[1] Given once a day for four weeks followed by a two week rest.

[2] Given on days 1, 15 and 29 of each 42-day cycle.

Table 2

Patient Characteristics (% unless otherwise indicated)

CHARACTERISTIC	ALL
Median age (years)	45.9
Range	24.5 – 69.6
Male (%)	17 (68)
Histology (%)	
GBM	15 (60)
AA	8 (32)
AO	2 (8)
KPS (%)	
90-100	13 (52)
80	9 (36)
70	3 (12)
Number prior progressions (%)	
1	14 (56)
2	7 (28)
3	2 (8)
≥4	2 (8)
Time from original diagnosis (months)	
Median	*18.8*
Range	*5.0-1274.8*
Prior bevacizumab	5 (20)
Prior VEGFR TKI	2 (8)

Abbreviations: AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; GBM, glioblastoma; KPS, Karnofsky performance status; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor

Table 3

Summary of grade ≥ 2adverse events (numbers in parentheses indicate percent of affected patients)

	Grade		
ADVERSE EVENT	***2***	***3***	***4***
Amylase/lipase		1 (4)	1 (4)
Anemia	3 (12)	1 (4)	
Anorexia	1 (4)		
Dehydration	1 (4)	1 (4)	
Diarrhea	4 (16)	1 (4)	
Fatigue	7 (28)	2 (8)	
Hypertension	1 (4)	1 (4)	
Hypocalcemia	2 (8)		
Hypokalemia		2 (8)	
Hypophosphatemia	2 (8)	2 (8)	
Infection	2 (8)	1 (4)	1 (4)
Mucositis	3 (12)	1 (4)	
Nausea	1 (4)	1 (4)	
Neutropenia	5 (20)	6 (24)	2 (8)
Rash	3 (12)	1 (4)	
Thrombocytopenia	1 (4)	2 (8)	1 (4)
Transaminase elevation	1 (4)	1 (4)	

Table 4

Dose limiting toxicities by dose level

Dose level	Number of patients	Number of DLTs	DLT type (grade)
1	7	0	-
2	6	1	Neutropenia (4)
3	6	1	Nausea/emesis (3)
4	6	2	Neutropenia (4) Thrombocytopenia (4)