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Phase I Study of Pazopanib in Patients with Advanced Solid Tumors and Hepatic Dysfunction: A National Cancer Institute Organ Dysfunction Working Group Study

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Abstract

Purpose: Pazopanib is a potent, multitargeted receptor tyrosine kinase inhibitor; however, there is limited information regarding the effects of liver function on pazopanib metabolism and pharmacokinetics. The objective of this study was to establish the maximum-tolerated dose (MTD) and pharmacokinetic profile of pazopanib in patients with varying degrees of hepatic dysfunction.

Experimental Design: Patients with any solid tumors or lymphoma were stratified into four groups based on the degree of hepatic dysfunction according to the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria. Pazopanib was given orally once a day on a 21-day cycle. A modified 3+3 design was used.

Results: Ninety-eight patients were enrolled. Patients in the mild group tolerated 800 mg per day. The moderate and severe groups tolerated 200 mg per day. Pharmacokinetic data in the mild group were similar to the data in the normal group. Comparison of the median C_{max} and area under the curve [$AUC_{(0-24)}$] in the moderate or severe groups at 200 mg per day to the values in the normal and mild groups at 800 mg per day indicated less than dose–proportional systemic exposures in patients with moderate and severe hepatic impairment. This suggests that the lower maximum-tolerated dose in the moderate and severe group is not due to a decrease in drug clearance or alteration in the proportion of metabolites.

Conclusions: In patients with mild liver dysfunction, pazopanib is well tolerated at the Food and Drug Administration (FDA)–approved dose of 800 mg per day. Patients with moderate and severe liver dysfunction tolerated 200 mg per day. *Clin Cancer Res; 19(13); 3631–9. ©2013 AACR.*

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Introduction

Pazopanib is a potent, multitargeted receptor tyrosine kinase inhibitor approved for the treatment of renal cancer (1). Pazopanib inhibits angiogenesis and lymphangiogenesis by targeting multiple receptors including VEGF receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α, PDGFR-β, and c-kit (2). The primary route of metabolism is hepatic, but there is limited information regarding the effects of liver function on pazopanib metabolism and pharmacokinetics (3).

In the initial phase I clinical trial of pazopanib in patients with advanced cancer, a total of 63 patients were treated at varying dose escalation cohorts ranging from 50 mg 3 times per week to 2,000 mg once daily and 300 to 400 mg twice daily. Patients with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 2 times the upper limit of normal (ULN) were excluded from that trial. The most common adverse events were hypertension, diarrhea, hair depigmentation, and nausea. Dose-limiting toxicities

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Translational Relevance

Pazopanib is a potent, multitargeted receptor tyrosine kinase inhibitor approved for the treatment of renal cancer and soft tissue sarcoma. Clinical activity has also been observed in urothelial, ovarian, and non–small cell lung cancer. Because patients with hepatic impairment are typically excluded from studies conducted during the clinical development of a new drug, safe dosing guidelines are usually not available at the time of approval. Hepatic dysfunction is common in patients with cancer, either as a result of comorbid conditions or because of the cancer itself. The Food and Drug Administration (FDA) has recognized this as a significant unmet clinical need, and therefore, they recently began requiring that safety and pharmacokinetic studies in patients with liver dysfunction be either completed or planned by the time of first approval. Therefore, the current study was conducted to describe the pharmacokinetics and determine the maximum-tolerated dose of pazopanib in patients with varying degrees of hepatic impairment.

observed at the 50, 800, and 2,000 mg dose levels included gastrointestinal hemorrhage, extrapyramidal involuntary movements, and fatigue. Hypertension was the most common grade 3 toxicity. Abnormal liver function tests with elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin were observed in 38%, 24%, and 13% of patients, respectively (3). In another phase I study conducted in patients with hepatocellular carcinoma, subjects with serum bilirubin less than 2.0 mg/dL (Child-Pugh A) were eligible. The maximum-tolerated dose was determined to be 600 mg per day, and the dose-limiting toxicities were grade 3 AST/ALT elevations and malaise (4). In subsequent clinical trials using pazopanib, hepatotoxicity with ALT more than 3 times the ULN was reported in 14% of patients and ALT more than 8 times the ULN was reported in 4% of patients. These studies suggest that pazopanib dosage has yet to be optimized and may affect patients differently based on their degree of clinical hepatic dysfunction (5).

Four pazopanib metabolites (GSK1268992, GSK1268997, GSK1071306, and GW700201) have been identified. Only one of these metabolites (GSK1268997) has been shown to inhibit the proliferation of VEGF-stimulated human umbilical vein endothelial cells with potency similar to pazopanib. The other metabolites show at least 10- to 20-fold less activity than the parent compound in the same cellular assay. The oxidative metabolism of pazopanib is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8 (6). *In vitro* studies also indicate that pazopanib is a potential inhibitor of CYP2C9, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 (data on file; GlaxoSmithKline). In patients with cancer, pazopanib was a weak inhibitor of CYP3A and CYP2D6 isozymes and had no effect on the pharmacokinetics of probe substrates for CYP1A2, CYP2C9, or CYP2C19 (7). Therefore, clinical liver function may affect pazopanib pharmacokinetics and its subsequent pharmacodynamics. In patients with normal liver function, previous pharmacokinetic studies showed similar area under the curve (AUC_{0-24}), C_{max}, and C_{24} values after daily administration of doses from 800 to 2,000 mg per day. This suggested that doses above 800 mg per day would not increase activity and 800 mg per day was the recommended dose for future studies. Currently, there is limited information regarding the effects of liver function on pazopanib metabolism and pharmacokinetics. This study was designed to establish the maximum-tolerated dose, dose-limiting toxicities, and pharmacokinetics profile of pazopanib in patients with varying degrees of hepatic dysfunction.

Patients and Methods

Eligibility criteria

Eligible patients were 18 years or more of age with a life expectancy of more than 3 months and a Karnofsky Performance Status of 60% or more. All patients must have had a histologically or cytologically confirmed solid tumor or lymphoma except patients with hepatocellular carcinoma diagnosed by an elevated α-fetoprotein level ($\geq$500 ng/mL) and positive serology for hepatitis. Other eligibility criteria included: absolute neutrophil count (ANC) of $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L; serum creatinine $\leq$ULN; or a calculated or measured level of $\geq$60 mL/min/1.73 m^2 for creatinine levels above the institutional normal. For patients with gliomas or brain metastases, only those patients receiving a stable dose of corticosteroids and who were seizure-free for at least 1 month before enrollment were eligible. Patients taking CYP 450 enzyme-inducing anticonvulsant drugs were switched to other medications at least 7 days before the first dose of pazopanib. Patients requiring anticoagulation were required to be on a stabilized dose of low molecular weight heparin. Therapeutic anticoagulation with warfarin was not permitted. Patients with biliary obstruction were eligible if the stent had been in place for at least 10 days before study initiation and liver function was stable for at least 2 days without any categorical change in hepatic dysfunction stratum. Radiotherapy was required to be completed 4 weeks or more before entering the study; chemotherapy, targeted therapy, or biotherapy for 3 weeks or more; and nitrosoureas or mitomycin C for 6 weeks or more. Agents with longer half-lives (such as suramin and bevacizumab) required longer elimination periods. Patients were not eligible if they had received prior therapy with pazopanib, had major surgery within 28 days before treatment, or were receiving any other concurrent investigational agents. Pregnant patients and patients with human immunodeficiency virus, or uncontrolled intercurrent illness were also excluded. The following patients were not eligible for this study: patients with a serious or nonhealing wound, ulcer, or bone fracture; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days of treatment; a cerebrovascular accident, myocardial infarction, baseline QTc $\geq$480 msec, recent admission for unstable angina, cardiac angioplasty, or stenting within 6 months of entry.

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Table 1. NCI ODWG liver function classification and dosing schema

Group	Group A Normal liver function	Group B Mild liver dysfunction	Group C Moderate liver dysfunction	Group D Severe liver dysfunction
Total bilirubin (>35% direct)	≤ULN	B1: ≤ULN B2: >1.0×–1.5× ULN	>1.5×–3× ULN	>3× ULN
ALT	≤ULN	B1: >ULN B2: Any	Any	Any
Dose Level	(mg/day)	(mg/day)	(mg/day)	(mg/day)
Level 1	800 ($n = 23$)	400 ($n = 9$)	200 ($n = 13$)	100 ($n = 13$)
Level 2		800 ($n = 14$)	400 ($n = 7$)	200 ($n = 19$)
Level 3			800	400
Level 4				800

Abbreviations: ULN, upper limit of normal; ALT, alanine aminotransferase.

Drug administration

Pazopanib was given orally once a day (1 hour before or 2 hours after a meal to minimize the effects of food on absorption) on days 1 to 21 of a 21-day cycle. For days on which pharmacokinetic samples were obtained, patients were instructed to take their daily dose after the pretreatment blood draw to allow accurate timing of subsequent pharmacokinetic blood draws.

Study design

This was a multi-institutional study conducted at 16 participating sites. Institutional Review Board (IRB) approval was obtained at each participating site and the City of Hope Comprehensive Cancer Center was the coordinating center for this National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) study. Patients were stratified into 4 groups [A (normal), B (mild), C (moderate), and D (severe)], using the NCI-ODWG categories of liver dysfunction for trials involving anticancer therapeutics (Table 1; ref. 8). Both bilirubin and serum ALT were used to define each group; if the total bilirubin level and ALT level indicated different groups, enrollment was into the group with the greatest degree of liver dysfunction. No distinction was made between liver dysfunction due to metastases or other causes. All liver function tests were repeated within 24 hours before the start of treatment and patients whose degree of hepatic dysfunction changed between registration and initiation of protocol therapy were reassigned to a different dysfunction group and dose level after discussion with the principal investigator. Patients in group A (normal) were included in this study to obtain concurrent pharmacokinetics data in a subject population with normal hepatic function. Although adverse events (AE) data were recorded for group A, there were no dose escalations because the maximum-tolerated dose was defined in previous studies (7). In the other groups, patients were evaluable for the purpose of cohort dose escalations if in the first cycle they either experienced a dose-limiting toxicity (see below) or received at least 80% of the planned treatment dose and were followed for one full cycle without a dose-limiting toxicity. Group B (mild) was defined according to either of 2 criteria (B1 and B2). Groups B1 and B2 were combined for dose level allocation and all analyses. For safety reasons, patients in group D (severe) were enrolled only after it was possible to escalate the dose in groups B (mild) and C (moderate).

Because treatment delays would be detrimental for patients in the eligible population and it was likely that several patients would not be evaluable for cohort dose-escalation decisions, the typical 3+3 up and down dose-escalation rules were modified to allow accrual of up to 6 patients at a level if less than 3 patients were evaluable and less than 2 had experienced dose-limiting toxicities. Dose finding was carried out independently for each of the liver dysfunction groups; however, the dose recommended for a group with greater liver dysfunction could not be greater than that for a group with a lesser dysfunction. In each of the liver dysfunction groups, 6 patients in an expansion cohort were treated at the maximum-tolerated dose (or the highest allowed dose) to obtain more extensive pharmacokinetic data. The maximum-tolerated dose was defined as the highest dose at which no more than one instance of dose-limiting toxicity was observed among the first 6 patients treated.

Dose-limiting toxicities

Toxicity was graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. First-cycle dose-limiting toxicities guided cohort dose escalations. Dose-limiting toxicities definitions from the NCI CTEP protocol template were modified for patient safety and defined as: a required dose reduction before 17 doses (80%) of pazopanib were administered in the first cycle of treatment; delays in next treatment cycle by ≥2 weeks due to treatment-related toxicity; grade 4 neutropenia, or occurrence of neutropenic fever with ANC $<1.5 \times 10^9$/L; grade 4 thrombocytopenia; grade 3 nausea

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and vomiting if it occurred despite maximal antiemetic therapy and if hydration was required for >24 hours; grade 3 diarrhea despite patient compliance with antidiarrheal therapy; grade 3 bleeding/hemorrhage; grade 4 hypertension and grade 4 proteinuria; and all other grade 4 nonhematologic toxicities (if an increase in grade above baseline), except hypersensitivity. Considering the nature of the patient populations, the changes in total bilirubin that constituted a dose-limiting toxicities were specific for each group. For group B, an increase of total bilirubin to the level defined for the group D lasting > 1 week was a dose-limiting toxicity. For patients in group C, a 1.5-fold increase from baseline total bilirubin to level defined for group D lasting >1 week was a dose-limiting toxicity. (Note: 1.5-fold increase from baseline total bilirubin which did not put a patient into group D did not constitute a dose-limiting toxicity). For patients in group D, a 1.5-fold increase from baseline without recovery to <1.2 × baseline lasting >2 weeks was a dose-limiting toxicity.

Pharmacokinetics

During the dose-escalation phase of the protocol (mild, moderate, and severe cohorts), blood samples for pharmacokinetic analysis were collected over 6 hours during a clinic visit in week 3. During the expansion phase of the protocol at the maximum-tolerated dose in each liver dysfunction cohort, blood samples for pharmacokinetic analysis were collected over 72 hours starting on day 1 and over 24 hours during a week-3 clinic visit. Pazopanib and its metabolites (Supplementary Fig. S1) were measured in plasma using high-performance liquid chromatography–mass spectrometry (HPLC–MS/MS; ref. 7. The method for pazopanib was validated over the range 0.1 to 50 μg/mL. Samples above the upper limit of quantitation were diluted with blank plasma to within the validated range before analysis. The method for the determination of the pazopanib metabolites GSK1268992, GSK1268997, and GSK1071306 in plasma was validated over the range 0.05 to 10 μg/mL. The between run assay precision (%CV) for pazopanib and all metabolites was 15% or less. C_{max}, T_{max} $AUC_{(0-6)}$ and/or $AUC_{(0-24)}$, and CL/F of pazopanib were calculated, as appropriate for each patient using noncompartmental methods and summary statistics were tabulated. A normal liver function cohort was included for comparison of pharmacokinetic parameters. In addition, the noncompartmental (trapezoidal rule) AUCs of GSK1071306, GSK1268992, and GSK1268997 were calculated to compare the exposure of metabolites as a percentage of the pazopanib exposure in hepatically impaired patients to the exposure to pazopanib metabolites observed in patients with normal hepatic function.

Results

Patient characteristics

A total of 98 patients were enrolled in the study, one of whom was not treated (Table 2). The median age of the study population was 57 years with a range between 24 and 78. A slightly higher proportion of the patients were male (54%). Colorectal cancer and liver cancer were the 2 most common types of primary tumor.

Dose-limiting toxicities

Group B (mild dysfunction). Nine patients were enrolled at 400 mg of pazopanib once daily. Of the 6 patients evaluable for dose escalation, one experienced a dose-limiting toxicity and grade 4 increased AST. Including the dose-escalation and expansion patients, 13 were treated at the Food and Drug Administration (FDA)-approved dose of 800 mg per day, with one dose-limiting toxicity (grade 5 stomach hemorrhage). One patient was accrued, but withdrew from the study before treatment.

Group C (moderate dysfunction). Three patients were enrolled at 200 mg of pazopanib once daily without experiencing a dose-limiting toxicity. Seven patients were enrolled at a dose of 400 mg. Of the 4 patients evaluable for dose escalation, 2 experienced a dose-limiting toxicity, one patient had a grade 4 AST, and the other patient had grade 4 AST, grade 4 ALT, and grade 3 hyperbilirubinemia. In each case, elevations in AST and ALT decreased in grade after discontinuation of the pazopanib. The dose was de-escalated to 200 mg and 3 additional patients were accrued without a dose-limiting toxicity, establishing the maximum-tolerated dose. One dose-limiting toxicity, grade 3 hyperbilirubinemia, was observed in the expansion cohort of 6 patients. Altogether, 1 of 12 patients experienced a dose-limiting toxicity at the maximum-tolerated dose.

Group D (severe dysfunction). At the 100 mg dose level, 1 of 6 evaluable patients experienced a dose-limiting toxicity, grade 4 bilirubin. This patient with metastatic colon cancer initiated therapy with a total bilirubin of 7.4 mg/dL. After 2 weeks of treatment, the bilirubin increased to 11.5 mg/dL. Despite a metal stent placement, the bilirubin remained greater than 1.5 times the baseline value. Relationship to pazopanib could not be excluded and this was considered a dose-limiting toxicity. However, even after pazopanib was discontinued, the bilirubin continued to rise likely due to progressive disease. One of the first 6 evaluable patients experienced a dose-limiting toxicity at the 200 mg dose level, grade 3 diarrhea. On the basis of the study design and the maximum-tolerated dose established in group C, higher doses were not tested in group D, making 200 mg per day the recommended dose. Five evaluable patients were accrued to the expansion cohort without dose-limiting toxicity.

Toxicity data for all cycles. The most frequently occurring treatment-related adverse event across all groups, dose levels, and cycles were fatigue, diarrhea, nausea, and increased AST, events known to be associated with pazopanib. Frequently occurring AEs were similar among all groups and dose levels. Table 3 summarizes grade 3 and 4 toxicities observed on trial across all cycles and Supplementary Table S1 summarizes the most frequently reported adverse events (all grades).

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Table 2. Patient demographics by study group and treatment cohort

	Group A	Group B		Group C		Group D	
	Normal liver function	Mild liver dysfunction		Moderate liver dysfunction		Severe liver dysfunction	
Starting dose of pazopanib (mg)	800	400	800	200	400	100	200
Number of patients	23	9	14	13	7[a]	13	19
Median Age (range)	58 (24–78)	56 (51–66)	57 (47–78)	58 (36–76)	65 (52–73)	56 (31–70)	51 (39–78)
Gender (number and %)							
Male	10 (43%)	3 (33%)	8 (57%)	4 (31%)	7 (100%)	9 (69%)	12 (63%)
Female	13 (57%)	6 (67%)	6 (43%)	9 (69%)		4 (31%)	7 (37%)
Race (number and %)							
White	22 (96%)	7 (78%)	12 (86%)	11 (84%)	2 (29%)	10 (76%)	11 (58%)
Black	1 (4%)	1 (11%)		1 (8%)	1 (14%)	1 (8%)	5 (26%)
Asian		1 (11%)	2 (14%)	1 (8%)	4 (57%)	1 (8%)	2 (11%)
Native Hawaiian or other Pacific Islander						1 (8%)	
Unknown							1 (5%)
Ethnicity (number and %)							
Not Hispanic or Latino	22 (96%)	9 (100%)	13 (93%)	9 (69%)	5 (72%)	13 (100%)	15 (79%)
Hispanic or Latino			1 (7%)	4 (31%)	1 (14%)		4 (21%)
Unknown	1 (4%)				1 (14%)		
KPS[b] Score (number and %)							
60	1 (4%)	1 (11%)	2 (14%)	1 (8%)	1 (14%)	3 (23%)	5 (26%)
70–80	9 (39%)	5 (56%)	2 (14%)	6 (46%)	5 (72%)	10 (76%)	13 (68%)
90–100	13 (57%)	3 (33%)	10 (72%)	6 (46%)	1 (14%)		1 (6%)
Baseline abnormalities (AEs; number and %)							
Grade 1	95 (63%)	44 (60%)	72 (64%)	106 (67%)	39 (47%)	81 (50%)	133 (65%)
Grade 2	48 (32%)	22 (30%)	32 (28%)	44 (28%)	33 (40%)	57 (35%)	45 (22%)
Grade 3	7 (5%)	7 (9%)	9 (8%)	9 (5%)	11 (13%)	20 (12%)	21 (10%)
Grade 4		1 (1%)				5 (3%)	5 (3%)
Type of primary tumor/hematologic malignancy (*n*)							
Bile duct				1		1	1
Breast		4				1	
Colon/rectum	6	2	6	9	3	5	10
Liver	1	2	3	1	2	2	2
Lung	1			1		2	
Pancreas	1		2	1		1	1
Other ($n = 26$)							

[a]One patient was not treated; there is no weight information for this patient.
[b]Karnofsky Performance Status.

Efficacy

Of 98 enrolled patients, there were no complete responses. There were 4 (4.1%) partial responses (PR): 3 in group A, and 1 in group B (all at the 800 mg dose level). The partial responses were seen in patients with fibrosarcoma, leiomyosarcoma, poorly differentiated germ cell tumor and hepatocellular carcinoma with duration of treatment ranging from 7 to 22 cycles. The patients with fibrosarcoma and germ cell received 7 cycles of chemotherapy before coming off trial for progressive disease. The patient with hepatocellular carcinoma received 16 cycles of treatment but came off trial due to the development of an abdominal fistula. The patient with uterine leiomyosarcoma received 22 cycles of treatment but required a dose reduction after 19 cycles from 800 mg per day to 400 mg per day due to grade 2 proteinuria. Treatment was stopped due to progressive disease. At the 800 mg per day dose, stable disease was seen in 19 patients with the following diagnosis: colon, fibromyxoid, osteosarcoma, bronchoalveolar, esophageal, rectal, ovarian, leiomyosarcoma, hepatocellular, breast, neuroendocrine, and gastric. The duration of treatment ranged from 3 to 27 cycles. In summary, percentage of best responses in patients evaluated for response were 18% PR, 47% stable disease (SD), and 35% progressive disease (PD) in group A; 6% PR, 61% SD,

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Table 3. Grade 3 and 4 adverse events at least possibly related to pazopanib[a]

	Group A	Group B		Group C		Group D		Total
	normal	mild		Moderate		severe		
Dose of pazopanib (mg)	800	400	800	200	400	100	200	
Number of patients (%)	23 (100)	9 (100)	14 (100)	13 (100)	6 (100)	13 (100)	19 (100)	97 (100)
Hematologic								
Lymphopenia	1(4)		2 (14)		1 (17)	1 (8)		5 (5)
Neutrophil count decreased			1 (7)					1 (1)
Platelet count decreased				1 (8)				1 (1)
Gastrointestinal disorders								
Abdominal Pain				1 (8)				1 (1)
Colitis			1 (7)					1 (1)
Diarrhea							2 (11)	2 (2)
Fistula–Abdomen NOS			1 (7)					1 (1)
Nausea		1 (11)	1 (7)	1 (8)				3 (3)
Vomiting	1 (4)		1 (7)	1 (8)				3 (3)
Coagulation								
Partial thromboplastin time						1 (8)		1 (1)
Constitutional								
Anorexia		1 (11)			1 (17)			2 (2)
Dyspnea	1 (4)							1 (1)
Fatigue	3 (13)			1 (8)	1 (17)	4 (31)	1 (5)	10 (10)
Muscle weakness				1 (8)				1 (1)
Liver dysfunction								
Alanine aminotransferase increased		1 (11)		1 (8)	2 (33)			4 (4)
Alkaline phosphatase increased		2 (22)		1 (8)		1 (8)	1 (5)	5 (5)
Aspartate aminotransferase increased		3 (33)		1 (8)	2 (33)	2 (15)	3 (16)	11 (11)
Blood bilirubin increased		1 (11)		4 (31)	1 (17)	2 (15)	2 (11)	10 (10)
Metabolic and other								
Hypokalemia							1 (5)	1 (1)
Hyponatremia		1 (11)				2 (15)		3 (3)
Hypophosphatemia		1 (11)				1 (8)	1 (5)	3 (3)
Hyperkalemia		1 (11)						1 (1)
Hypertension	1 (4)	1 (11)	1 (7)	2 (15)				5 (5)

[a]Maximum grade for all cycles in a given patient.

and 33% PD in group B; 18% SD and 82% PD in group C; and 12% SD and 88% PD in group D.

Pharmacokinetics

Steady-state pazopanib pharmacokinetics data were available in 69 patients and the results are summarized in Table 4. In addition, the average concentration versus time plots at steady-state for each of the groups are depicted in Fig. 1. The median steady-state C_{max} in groups A and B at a dose of 800 mg were 52.0 and 33.5 μg/mL, respectively, whereas the median $AUC_{(0-24)}$ were 888.2 and 774.2 μg/mL × hour, respectively. The median steady-state C_{max} at the maximum-tolerated dose level in patients in groups C and D (200 mg once daily) were 22.2 and 9.4 μg/mL, respectively, and the median $AUC_{(0-24)}$ were 256.8 and 130.6 μg/mL × hour, respectively. Therefore, at the maximum-tolerated dose in group C, the median steady-state C_{max} was 44% and the median $AUC_{(0-24)}$ was 39% of the values in the normal group at full dose. At the maximum-tolerated dose in group D, the median steady-state C_{max} was 18% and the median $AUC_{(0-24)}$ was 15%, of the values in the group A at full dose, even lower than in group C patients at the same dose. The median trough concentration ($C_{(0)}$) for patients in groups C and D were 16.2 and 5.7 μg/mL, respectively. As shown in Fig. 1, pazopanib plasma concentrations at steady-state were highly variable in all of the groups. There were no significant differences in the average systemic exposures in patients in groups A and B treated at a dose of 800 mg. Likewise, there were no significant differences in subjects in groups C and D treated with 200 mg,

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Table 4. Steady-state pazopanib pharmacokinetics measured in all patients at week 3 (medians and ranges)

Group	Dose (mg)	*n*	C_{max} (μg/mL)	T_{max} (hour)	$C_{(0)}$[a] μg/mL	$AUC_{(0–6)}$ (μg/mL × hour)	$AUC_{(0–24)}$ (μg/mL × hour)	CL/F[b] (L/hour)
A	800	18	52.0 (17.1–85.7)	2.8 (1.0–24.2)	29.8 (10.3–750.)	260.5 (92.0–475.9)	888.2 (345.5–1482)	0.9 (0.5–2.3)
B	300[c]	1	32.9	3.0	17.3	170.5	n/a	n/a
	400	5	22.7 (14.6–39.8)	3.0 (2.0–4.1)	19.3 (6.8–36.6)	125.1 (78.3–205.8)	467.6	0.9
	800	12	33.5 (11.3–104.2)	3.0 (0.5–24.4)	24.0 (8.3–74.6)	176.5 (41.4–518.1)	774.2 (214.7–2034.4)	1.0 (0.4–3.7)
C	200	11	22.2 (4.2–32.9)	2.0 (0.0–4.0)	16.2 (3.1–24.2)	122.2 (21.2–182.9)	256.8 (65.7–487.7)	0.8 (0.4–3.0)
	400	3	17.6 (13.0–42.5)	4.0 (3.0–5.9)	16.5 (11.8–28.9)	94.1 (74.7–220.0)	n/a	n/a
D	100	5	2.3 (0.7–12.6)	4.0 (1.1–6.0)	4.2 (2.3–9.4)	12.8 (3.0–69.1)	n/a	n/a
	200	14	9.4 (2.4–24.3)	3.0 (1.0–8.0)	5.7 (1.5–18.4)	49.2 (9.5–134.5)	130.6 (46.9–473.2)	1.7 (0.4–4.3)

[a]$C_{(0)}$ is the predose plasma concentration and is equivalent to the trough level following the previous dose.
[b]CL/F calculated as dose/$AUC_{(0–24)}$ at steady-state for the 24-hour dosing interval.
[c]Patient was dose-reduced per protocol before week 3.

although there was a trend toward lower average plasma levels in group D.

The data for the 3 pazopanib metabolites measured at steady-state are summarized in Supplementary Tables S2 and S3. Although the median values of each of the metabolites decreased with increasing severity of liver impairment, the ratios of the $AUC_{(0–6)}$ for each of the metabolites to the $AUC_{(0–6)}$ for the parent drug showed no apparent differences across all of the liver function cohorts.

First-dose pazopanib pharmacokinetics data, which were obtained in the expansion and normal cohorts, are available in 50 patients and the results are summarized in Table 5. The median first-dose C_{max} in groups A and B at a dose of 800 mg were 30.8 and 23.8 μg/mL, respectively, whereas the median $AUC_{(0–24)}$ were 563.1 and 462.9 μg/mL × hour, respectively. The median first-dose C_{max} at the maximum-tolerated dose level in groups C and D (200 mg) were 4.1 and 3.7 μg/mL, respectively, and the median $AUC_{(0–24)}$ were 42.1 and 56.4 μg/mL × hour, respectively. As in the case of the steady-state pazopanib pharmacokinetics data, systemic exposures to pazopanib following a single dose at the maximum-tolerated dose level in patients in groups C and D were less than the systemic exposure to pazopanib after administration of 800 mg once daily in patients in groups A and B. Univarate analyses of various steady-state and first-dose pazopanib pharmacokinetics parameters versus total bilirubin, ALT, and albumin revealed no significant correlations. Although the AUCs of the metabolites were lower after the first dose than at steady state, the patterns across hepatic dysfunction groups and metabolites were similar to those at steady state (Supplementary Table S4).

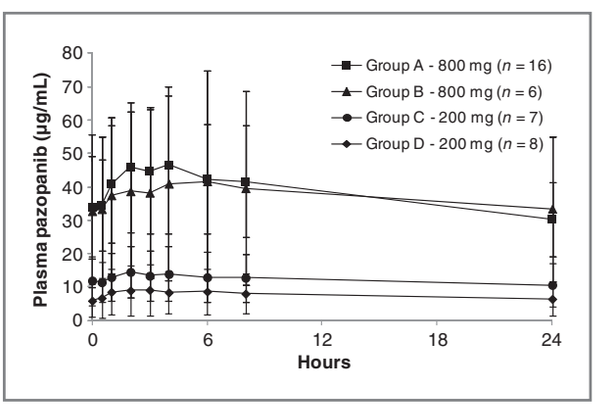

Figure 1. Average steady-state pazopanib plasma concentration versus time plots measured during the week 3 expansion phase.

Discussion

Pazopanib is a multitargeted tyrosine kinase inhibitor that is approved for the treatment of advanced renal cell carcinoma and soft tissue sarcomas. However, treatment of patients with advanced disease can be challenging due to impaired liver function from metastasis. Pazopanib's package insert has a black box warning due to severe and fatal hepatotoxicity observed in clinical trials and currently there is limited information regarding pazopanib in patients with liver dysfunction. In a phase I study of pazopanib in patients with advanced hepatocellular carcinoma, the maximum-tolerated dose was determined to be 600 mg per day. Evidence of antitumor activity was seen at this dose; however, the 800 mg per day dose was not tolerable due to dose-limiting toxicities of grade 3 malaise and grade 3 AST/ALT elevation. Liver abnormalities were seen in a majority of the patients with hepatocellular carcinoma treated with pazopanib. AST elevation was seen in 63% of the patients. ALT elevation occurred in 41% of patients and hyperbilirubinemia in 63% of patients. We therefore conducted this clinical trial with the primary objective of determining the optimal dose of pazopanib in cancer patients with varying degrees of liver dysfunction as determined by the NCI ODWG classification system.

Steady-state pazopanib pharmacokinetics data were available for 69 patients. The median steady-state C_{max} and

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Table 5. First-dose pazopanib pharmacokinetics in expanded cohorts and the maximum-tolerated dose (medians and ranges)

Group	Dose (mg)	*n*	C_{max} (μg/mL)	T_{max} (hour)	$AUC_{(0–6)}$ (μg/mL × hour)	$AUC_{(0–24)}$ (μg/mL × hour)
A	800	20	30.8 (4.2–66.2)	4.0 (1.0–24.0)	120.6 (10.8–271.3)	563.1 (74.4–1107)
B	200	1	9.4	6.5	41.8	179.8
	400	1	13.6	2.0	62.0	223.1
	800	6	23.8 (6.1–127.5)	4.6 (2.0–8.3)	103.0 (11.2–403.3)	462.9 (102.0–2147)
C	200	7	4.1 (0.4–13.5)	2.0 (2.0–3.1)	19.7 (1.6–67.1)	42.1 (6.1–231.2)
D	100	3	2.9 (1.8–3.1)	3.0 (2.0–24.2)	13.1 (0.5–13.3)	33.6 (19.5–43.4)
	200	12	3.7 (0.5–13.1)	3.5 (2.0–8.3)	17.2 (1.8–57.3)	56.4 (6.3–208.4)

AUC in groups A and B at 800 mg are similar to the corresponding values previously reported in patients with cancer with normal hepatic function (3). Therefore, patients with mild liver dysfunction would most likely derive the same benefit from this dose as patients with no hepatic impairment. However, the median steady-state C_{max} and $AUC_{(0–24)}$ values after administration of 200 mg pazopanib once daily to patients in group C were approximately 44% and 39%, respectively, of the corresponding median values after administration of 800 mg/day in patients with normal hepatic function. Although interpretation of the data across doses is complicated by the fact that the pharmacokinetics of oral pazopanib are not linear in patients with normal hepatic function, the plasma concentrations at the maximum-tolerated dose in group C are clearly lower than the concentrations at the maximum-tolerated dose in groups A and B. Administration of 200-mg pazopanib once daily to patients in group D resulted in median steady-state C_{max} and $AUC_{(0–24)}$ values of only 18% and 15%, respectively, compared with the 800 mg daily dose in patients with no liver dysfunction. While the median trough concentration for patients in group C was within the range of plasma concentrations associated with clinical and biologic effects consistent with VEGFR inhibition of 15 to 20 μg/mL in patients with renal cell carcinoma (3), the median trough levels in group D was less than the desired level. These data suggest that the systemic exposure of pazopanib in group D at the highest dose tested (200 mg/day) may not provide a therapeutic benefit to these patients.

Pazopanib has been reported to exhibit nonlinear pharmacokinetics behavior, such that steady-state plasma levels increase in a less than dose-proportional manner (3, 4). As a result, the mean plasma AUC plateaus at doses above 800 mg. The most likely explanation for pazopanib's nonlinear pharmacokinetics behavior is saturable oral absorption. Interestingly, recent studies have shown that by either taking pazopanib with food (9) or crushing the tablet (10), one can increase the oral bioavailability by as much as 2-fold. On the current trial, patients were instructed to take pazopanib on an empty stomach in accordance with the current FDA recommendations and to minimize the variable effect of food. In contrast to previously published pharmacokinetics in patients with normal liver biochemistry and mildly impaired liver function, our results from patients with severe hepatic impairment show a greater than dose-proportional increase in AUC. There were no differences between the groups with respect to the metabolite to pazopanib ratios, suggesting that hepatic metabolism of pazopanib was not affected by the severity of liver dysfunction. There are limited published data at a dose of 200 mg from the initial dose finding studies. Previous steady-state pharmacokinetics results in patients with normal or Child-Pugh A liver function receiving 200 mg show trough levels of 12.4 and 15.4 μg/mL, respectively (3, 4). The average steady-state trough pazopanib concentration from the current study in subjects with severe hepatic dysfunction treated with 200 mg was 5.7 μg/mL, suggesting reduced oral absorption. The pharmacokinetics results following a single dose of pazopanib were consistent with the steady-state data.

Conducting a liver dysfunction clinical trial with a hepatotoxic drug can be challenging, but the information obtained from our study is critical for the management of many patients. The primary indication for pazopanib is for patients with advanced renal cell carcinoma. Since many of these patients may have had nephrectomies, there is concern for potential hepatorenal syndrome. In our study, 98 patients were treated and 7 patients had elevated creatinine (3—grade 1; 1—grade 2; 2—grade 3; and 1—grade 4). In our assessment, the grade 3 and 4 creatinine elevations were not related to treatment, but to disease progression. Overall, the pharmacokinetics data suggest that the lower maximum-tolerated dose in patients with moderate or severe liver dysfunction, compared with those with no or mild liver dysfunction is not due to a decrease in drug clearance or an alteration in the metabolic pattern of pazopanib. Multiple factors are likely to have contributed to the poorer outcome for patients in the moderate and severe liver impairment groups. Concurrent with their hepatic dysfunction, the patients may have had more extensive disease when they entered the study. Therefore, they may have been less likely to have an objective response or stable disease even if they had tolerated the same drug exposure. It is not surprising that patients with baseline hepatic dysfunction did not

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tolerate a hepatotoxic agent well, leading to overall lower exposure to the drug and reducing further the likelihood of clinical benefit. Patients with mild hepatic dysfunction, as evidenced by total bilirubin in the range of 1.0 to 1.5 times the ULN or an ALT above the ULN, tolerated full-dose pazopanib, and should be considered for therapy with this agent if otherwise appropriate. Patients with moderate or severe hepatic dysfunction tolerated a 200 mg daily dose. Furthermore, our pharmacokinetic data do not support the use of dose individualization for patients with impaired liver function. This study was not designed, and does not have the statistical power, to determine whether or not this reduced dose is efficacious. However, based on the low drug exposure in patients with severe hepatic dysfunction, both the FDA package insert and the European Commission Summary of Product Characteristics do not recommend pazopanib for patients with severe hepatic dysfunction.

Disclosure of Potential Conflicts of Interest

A.B. Suttle has ownership interest (including patents) in GlaxoSmith-Kline. L.H. Ottesen is employed (other than primary affiliation; e.g., consulting) as a medical director by GSK and has ownership interest (including patents) in GSK Stocks. H.J. Lenz has a commercial research grant from GSK. A. Hamilton is a consultant/advisory board member of GSK. M.A. Rudek's husband is employed by Amplimmune as a scientist. No potential conflicts of interest were disclosed by the other authors.

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References

1. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28:1061–8.
2. Kumar R, Knick VB, Rudolph SK, Johnson JH, Crosby RM, Crouthamel MC, et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. Mol Cancer Ther 2007;6:2012–21.
3. Hurwitz HI, Dowlati A, Saini S, Savage S, Suttle AB, Gibson DM, et al. Phase I trial of pazopanib in patients with advanced cancer. Clin Cancer Res 2009;15:4220–7.
4. Yau T, Chen PJ, Chan P, Curtis CM, Murphy PS, Suttle AB, et al. Phase I dose-finding study of pazopanib in hepatocellular carcinoma: evaluation of early efficacy, pharmacokinetics, and pharmacodynamics. Clin Cancer Res 2011;17:6914–23.
5. GlaxoSmithKline RTP, NC 27709. Pazopanib [package insert].
6. van Geel RM, Beijnen JH, Schellens JH. Concise drug review: pazopanib and axitinib. Oncologist 2012;17:1081–9.
7. Goh BC, Reddy NJ, Dandamudi UB, Laubscher KH, Peckham T, Hodge JP, et al. An evaluation of the drug interaction potential of pazopanib, an oral vascular endothelial growth factor receptor tyrosine kinase inhibitor, using a modified Cooperstown 5+1 cocktail in patients with advanced solid tumors. Clin Pharmacol Ther 2010;88:652–9.
8. Patel H, Egorin MJ, Remick SC, Mulkerin D, Takimoto CHM, Doroshow JH, et al. Comparison of Child-Pugh (CP) criteria and NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction (HD): implications for chemotherapy dosing. J Clin Oncol 22:14s, 2004 (suppl;abstr 6051).
9. Heath EI, Chiorean EG, Sweeney CJ, Hodge JP, Lager JJ, Forman K, et al. A phase I study of the pharmacokinetic and safety profiles of oral pazopanib with a high-fat or low-fat meal in patients with advanced solid tumors. Clin Pharmacol Ther 2010;88:818–23.
10. Heath EI, Forman K, Malburg L, Gainer S, Suttle AB, Adams L, et al. A phase I pharmacokinetic and safety evaluation of oral pazopanib dosing administered as crushed tablet or oral suspension in patients with advanced solid tumors. Invest New Drugs 2012;30:1566–74.

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