VOLUME 26 · NUMBER 4 · FEBRUARY 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase I and Pharmacokinetic Study of Imatinib Mesylate in Patients With Advanced Malignancies and Varying Degrees of Renal Dysfunction: A Study by the National Cancer Institute Organ Dysfunction Working Group

Joseph Gibbons, Merrill J. Egorin, Ramesh K. Ramanathan, Pingfu Fu, Daniel L. Mulkerin, Stephen Shibata, Chris H.M. Takimoto, Sridhar Mani, Patricia A. LoRusso, Jean L. Grem, Anna Pavlick, Heinz-Josef Lenz, Susan M. Flick, Sherrie Reynolds, Theodore F. Lagattuta, Robert A. Parise, Yanfeng Wang, Anthony J. Murgo, S. Percy Ivy, and Scot C. Remick

From the Developmental Therapeutics Program, Case Comprehensive Cancer Center, Ireland Cancer Center at University Hospitals of Case Medical Center and Case Western Reserve University School of Medicine, Cleveland, OH; University of Pittsburgh Cancer Institute, Pittsburgh, PA; University of Wisconsin Comprehensive Cancer Center, Madison, WI; City of Hope National Medical Center, Duarte; University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA; University of Texas Health Science Center, San Antonio, TX; Albert Einstein College of Medicine, Bronx; Kaplan Comprehensive Cancer Center, New York University, New York, NY; Wayne State University, Detroit, MI; National Cancer Institute, Medicine Branch, National Naval Medical Center, Bethesda; Center for Treatment and Evaluation Program, Division of Cancer Diagnosis and Treatment, National Cancer Institute, Rockville, MD; and Novartis Pharmaceuticals, Florham Park, NJ.

Submitted July 23, 2007; accepted September 27, 2007.

Supported by National Institutes of Health Grants No. U01 CA62502, M01 RR-000080, P30 CA43703, U01 CA099168, 5M01 RR-00056, P30 CA47904, 5 U01 CA62505, U01 CA062491, and 5U01CA069853 and Translational Research Initiative Contract No. 22XS041A.

Presented in part at the 39th Annual Meeting of the American Society of Clinical Oncology, May 31-June 3, 2003 Chicago, IL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Scot C. Remick, MD, Mary Babb Randolph Cancer Center, West Virginia University, 1801 Health Sciences South, PO Box 9300, Morgantown, WV 26506; e-mail: sremick@hsc.wvu.edu.

0732-183X/08/2604-570/$20.00

DOI: 10.1200/JCO.2007.13.3819

ABSTRACT

Purpose
This study was undertaken to determine the safety, dose-limiting toxicities (DLT), maximum-tolerated dose (MTD), and pharmacokinetics of imatinib in cancer patients with renal impairment and to develop dosing guidelines for imatinib in such patients.

Patients and Methods
Sixty adult patients with advanced solid tumors and varying renal function (normal, creatinine clearance [CrCL] ≥ 60 mL/min; mild dysfunction, CrCL 40 to 59 mL/min; moderate dysfunction, CrCL 20 to 39 mL/min; and severe dysfunction, CrCL < 20 mL/min) received daily imatinib doses of 100 to 800 mg. Treatment cycles were 28 days long.

Results
The MTD was not reached for any group. DLTs occurred in two mild group patients (600 and 800 mg) and two moderate group patients (200 and 600 mg). Serious adverse events (SAEs) were more common in the renal dysfunction groups than in the normal group ($P = .0096$). There was no correlation between dose and SAEs in any group. No responses were observed. Several patients had prolonged stable disease. Imatinib exposure, expressed as dose-normalized imatinib area under the curve, was significantly greater in the mild and moderate groups than in the normal group. There was a positive correlation between serum alpha-1 acid glycoprotein (AGP) concentration and plasma imatinib, and an inverse correlation between plasma AGP concentration and imatinib clearance. Urinary excretion accounted for 3% to 5% of the daily imatinib dose.

Conclusion
Daily imatinib doses up to 800 or 600 mg were well tolerated by patients with mild and moderate renal dysfunction, respectively, despite their having increased imatinib exposure.

J Clin Oncol 26:570-576. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Imatinib mesylate (Gleevec; Novartis Pharmaceuticals, Florham Park, NJ), is an orally administered, highly selective inhibitor of the tyrosine kinase family containing ABL, the platelet-derived growth factor receptor (PDGFR), c-KIT, and the receptor for stem-cell factor.[1-4] Imatinib has become standard treatment for chronic myeloid leukemia and other hematologic malignancies that express a constitutively active form of the *BCR-ABL* fusion gene.[5,6] Imatinib has also become standard treatment for gastrointestinal stromal tumors and other less common malignancies that have rearrangement of the *PDGFRα* and *PDGFRβ* genes.[7-18] The daily imatinib dose ranges from 400 to 800 mg.

Although safety and pharmacokinetic data for imatinib are available for healthy volunteers and patients with cancer who have acceptable renal function, there are currently no data regarding the safety and disposition of imatinib in patients with renal dysfunction. Characterizing the safety and pharmacokinetics of imatinib in patients with impaired renal function is important because renal dysfunction is regularly encountered among patients with cancer, and fluid retention and electrolyte abnormalities occur in patients receiving imatinib. Therefore, this study and one in patients with liver

dysfunction[19] were conducted by the National Cancer Institute Organ Dysfunction Working Group.

PATIENTS AND METHODS

Patient Eligibility

Eligible patients were required to meet the following criteria: pathologically confirmed malignancy that was no longer curable by standard surgical or medical therapy, age ≥16 years; Eastern Cooperative Oncology Group performance status ≤ 2; life expectancy ≥ 3 months; leukocytes ≥ 3,000/μL or absolute granulocytes ≥ 1,500/μL; platelets ≥ 100,000/μL; total bilirubin within institutional normal limits; and AST/ALT ≤ 1.5 × the institutional upper limit of normal. Because imatinib is metabolized by CYP3A, patients requiring therapeutic anticoagulation with warfarin were excluded. The institutional review board at each participating institution approved the protocol. Written informed consent was obtained from all patients before study treatment.

Study Design

Ten institutions enrolled patients into four groups on the basis of measured creatinine clearance (CrCL). Group A (normal renal function) had CrCL ≥ 60 mL/min; group B (mild dysfunction) had CrCL 40 to 59 mL/min; group C (moderate dysfunction) had CrCL 20 to 39 mL/min; and group D (severe dysfunction) had CrCL less than 20 mL/min. Two separately measured 24-hour urine CrCL determinations, not deviating from each other by more than 25%, were required, with the most recent performed within 1 week of treatment. Stratification was based on the most recent measurement. Laboratories at each institution performed CrCL measurements, and no cross-site standardization was performed. Patients were seen for safety evaluations and examination weekly during cycle 1, biweekly during cycle 2, and every 4 weeks thereafter. CBCs and serum chemistries were performed weekly for the first 12 weeks and biweekly thereafter.

Drug Formulation and Administration

Imatinib was supplied as hard gelatin capsules of 100-mg dosage strength by the Cancer Therapy and Evaluation Program, National Cancer Institute (Rockville, MD), under a Collaborative Research and Development Agreement with Novartis Pharmaceuticals. Imatinib was ingested with 8 ounces of water. Doses ≤ 600 mg were given as a single dose. The 800-mg dose was administered as 400 mg bid to avoid local irritant effects on the gastric mucosa, except on day 1, when an 800-mg single dose was given to facilitate pharmacokinetic studies (Table 1). To permit single-dose pharmacokinetic profiling, therapy was started on day 1, held on days 2 and 3, and resumed on day 4. Imatinib was ingested daily without interruption thereafter.

A cycle of therapy consisted of uninterrupted daily dosing for 28 days (except for the first cycle). Participants who completed one cycle of therapy and had pharmacokinetic studies completed were considered assessable. Response was evaluated using Response Evaluation Criteria in Solid Tumors Group criteria after every two cycles.[20] Doses were escalated separately in each group (Table 1). Intrapatient dose escalation by one level was permitted for patients who failed to respond or who experienced disease progression at their starting dose level, provided they did not experience any dose-limiting toxicity (DLT). Dose modifications were prescribed in the protocol. For grade 3 or worse toxicity, imatinib was reduced by one dose level on recovery.

Four patients with normal renal function and three in each renal dysfunction group could accrue to each dose level. If a patient's second CrCL indicated that patient qualified for a different group than indicated by the first CrCL, then the eligible patient was added to the safest known level in the appropriate group.

Assessment of DLT was limited to the first cycle of therapy, which was defined as any drug-related grade 3 or 4 nonhematologic toxicity or worse (excluding alopecia and renal abnormalities); grade 4 neutropenia; occurrence of fever with absolute neutrophil count less than 1,500/μL; grade 4 thrombocytopenia; grade 3 or worse nausea and/or vomiting occurring despite antiemetic therapy and requiring hydration for more than 24 hours; grade 3 or worse diarrhea occurring despite loperamide therapy; or treatment delay lasting more than 4 weeks. Elevation of γ-glutamyltransferase was not considered a DLT. Assessment of renal toxicity was conducted per previously published guidelines.[21] Elevations in creatinine or decreases in CrCL that moved a patient to a more advanced renal dysfunction group were considered DLT. If CrCL worsened by ≥ 30%, the patient was removed from the study. No dosing changes were made for improvements in renal function. The National Cancer Institute Common Toxicity Criteria, Version 2.0, were used to assess all toxicities.[22] The maximum-tolerated dose (MTD) for each group was defined as the highest dose tested in which one patient or fewer experienced DLT when at least six patients had been treated at that dose.

Pharmacokinetic Studies

On day 1, 7-mL heparinized venous blood samples were obtained before and at 0.5, 1, 2, 3, 4, 8, 12, 24, 36, 48, and 72 hours after imatinib ingestion. On day 15, blood samples were obtained just before and at 0.5, 1, 2, 3, 4, 8, 10, 12, 13, 16, and 24 hours after imatinib ingestion. Plasma was prepared by centrifugation and stored at −20°C until analyzed for drug content. Imatinib protein binding on the day 15, 24-hour sample was determined by equilibrium dialysis.[23] Alpha-1 acid glycoprotein (AGP) concentrations in serum obtained before therapy and on day 15 were measured by immunonephelometry (Dade Behring nephelometer; Covance CLS, Indianapolis, IN). On day 1, urine was collected for 24 hours after imatinib ingestion, and an aliquot was stored at −20°C until analyzed for drug content.

Plasma and urinary concentrations of imatinib and its active metabolite *N*-desmethyl-imatinib (CGP74588) were determined by a validated liquid chromatography/mass spectrometry assay.[24] Concentration versus time data for imatinib and CGP74588 were modeled noncompartmentally using the Lagrange function as implemented by the LAGRAN computer program.[25,26]

Statistical Methods

Statistical methods are described in detail in the Appendix (online only).[27]

Table 1. Imatinib Dose Administration and Dose-Escalation Schema

	Group A		Group B		Group C		Group D	
Dose Level	Dose (mg)	No. of Patients	Dose (mg)	No. of Patients	Dose (mg)	No. of Patients	Dose (mg)	No. of Patients
1	400	4	400	4	200	8	100	2
2	600	4	600	9	400	4	200	0
3	800*	6	800*	9	600	10	400	0
4	—		—		800*	0	600	0
5	—		—				800*	0
Total patients		14		22		22		2

NOTE. Imatinib dose is shown in milligrams per day administered orally in 28-day cycles.
*Given in divided daily dose (400 mg bid) except for day 1, when given as a single dose.

RESULTS

Patient Demographics

Sixty patients were enrolled between September 2001 and February 2005 (Table 2). Fourteen patients were entered in group A, 22 patients were entered in group B; 22 patients were entered in group C, and two patients were entered in group D. One group B patient had incomplete data; only registration and safety data were analyzed. No patients requiring dialysis were enrolled, and it was deemed expeditious not to delay closure of the study for purposes of recruiting only this cohort. Causes of renal insufficiency (groups B through D) were identified retrospectively for 34 (74%) of the 46 patients.

Safety Profile

A total of 182 imatinib cycles were administered. The cumulative experience of clinical toxicity occurring in all 60 patients during the first cycle of therapy is summarized in Table 3. The MTD of imatinib was not reached for any group. Group A had a higher proportion of assessable patients (13 of 14 patients) than did group B (14 of 22 patients) or group C (14 of 22 patients). Both group D patients were assessable.

DLT occurred in two patients with mild renal dysfunction and two patients with moderate dysfunction (Table 4). A patient with mild renal dysfunction having grade 3 dyspnea (not treatment-related) had the dose reduced from 800 mg/d to 600 mg/d per protocol beginning on day 5 of cycle 1. After receiving 600 mg/d from days 5 through 15, the patient experienced drug-related grade 3 hypophosphatemia. Another patient with mild renal dysfunction at the 800-mg/d dose level experienced grade 3 dyspnea owing to imatinib-related fluid retention. One patient with moderate renal dysfunction at the 200-mg/d dose level had a DLT of grade 3 vomiting that resulted in Mallory-Weiss tears, and another, at the 600-mg/d dose level, experienced dose-limiting grade 3 hypophosphatemia and fatigue.

Imatinib was generally well tolerated (Table 3). The most frequently reported adverse events over the course of the entire study across all cohorts and dose levels were primarily mild to moderate in

Table 2. Patient Demographics and Causes of Renal Insufficiency

Characteristic	No. of Patients	%
Sex		
Male	29	48
Female	31	52
Age, years		
Median	63	
Range	16-84	
Race/ethnicity		
White	54	90
African American	5	8
Unknown	1	2
ECOG performance status		
0	17	28
1	36	60
2	7	12
Tumor type		
c-kit (CD117), status unknown	53	88
Renal	10	
Colorectal	5	
Lung	4	
Ovarian cancer	4	
Sarcoma	5	
Melanoma	3	
Other	22	
c-kit (CD117)-positive	7	12
GIST	2	
Endometrial stromal tumor	1	
Other (thymus, Ewing's sarcoma, colon, pancreas)	4	
Normal renal function	14	
Cause of renal insufficiency, retrospectively identified in 34 (74%) of 46 patients		
Multi-factorial	20	59
Age-related	5	15
Atherosclerotic cardiovascular disease	3	9
Prior chemotherapy	3	9
Cisplatin based	2	
Non–cisplatin based	1	
Other	3	9

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumor.

Table 3. Cumulative Toxicity Experience for All 60 Patients During Cycle 1

Toxicity	Grade* 1	2	3	4	5	Total
Nausea	30	7	4	0	0	41
Vomiting	16	8	3	0	0	27
Fatigue	17	7	2	0	0	26
Hemoglobin	11	6	7	0	0	24
Creatinine	9	8	5	0	0	22
Edema	16	6	0	0	0	22
Hyperglycemia	11	3	2	1	0	17
Anorexia	12	4	0	0	0	16
Diarrhea	14	1	1	0	0	16
Hypoalbuminemia	8	4	4	0	0	16
Lymphopenia	0	10	6	0	0	16
Abdominal pain	11	3	1	0	0	15
Rash/desquamation	11	4	0	0	0	15
Dyspnea	0	9	3	0	0	12
Hypocalcemia	9	1	2	0	0	12
Alkaline phosphatase	8	3	0	0	0	11
Constipation	7	2	2	0	0	11
Headache	10	0	1	0	0	11
Hyponatremia	9	0	2	0	0	11
Hypophosphatemia	2	3	4	0	0	9

*Dose-limiting toxicity was assessed during this cycle. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0).[22] Baseline abnormalities such as anemia and renal dysfunction were not ascribed relation to study drug at study entry; change in these or any other abnormalities or toxicity are captured in Table 3.

Table 4. Summary of Dose-Limiting Toxicity Encountered in the Study

Group	Dose (mg)	No. of Patients	Description
B	600	9	Grade 3 hypophosphatemia
B	800	9	Grade 3 dyspnea
C	200	8	Grade 3 nausea and vomiting with Mallory-Weiss tears
C	600	10	Grade 3 hypophosphatemia and fatigue

severity, and the majority were toxicities known to be associated with imatinib (see Appendix).

There was a significant difference in cycle 1, day 1 (baseline) albumin among the four patient groups ($P = .025$; Appendix Table A1, online only). The pair-wise comparison showed no significant difference in baseline albumin between groups A and B, groups B and C, groups B and D, and groups C and D. However, there were significant differences in baseline albumin between groups A and C ($P = .0009$) and groups A and D ($P = .0126$). Edema was considerably more frequent among patients with normal renal function (64%) than among those patients with mild (27%) or moderate (27%) dysfunction over the course of study treatment. There was no significant association between renal function group and edema grade or the presence or absence of edema when the analysis was restricted to cycle 1 (data not shown). Similarly, there was no significant association between edema grade and dose level during the first cycle (data not shown). However, when edema was classified as absent or present, logistic regression indicated that dose level was significantly related to edema ($P = .033$). Specifically, with every 200-mg increase in imatinib dose, the odds of having edema at any time during the study increased 1.87-fold (Appendix Table A2, online only).

Serious adverse events (SAEs) were more common in patients with renal impairment than in patients with normal renal function. SAEs were reported in two (14%) of 14 patients with normal renal function, 13 (59%) of 22 patients with mild dysfunction, nine (43%) of 21 patients with moderate dysfunction, and two (100%) of two patients with severe dysfunction ($P = .0096$). There was no correlation between imatinib dose and SAEs in any group. All 13 patient deaths that occurred on this study were related to disease progression; none were considered to be treatment-related.

Time on Study and Efficacy Evaluation

The median duration of treatment was 52 days (range, 8 to 588 days; 95% CI, 43 to 59 days). No objective responses were observed. Fourteen patients had stable disease, several of which were longstanding: a group A patient with gastrointestinal stromal tumor (c-kit+) treated with 600 mg/d (511 days), a group C patient with liposarcoma treated with 200 mg/d (224 days), a group C patient with invasive thymoma (c-kit+) treated with 600 mg/d (203+ days), and a group D patient with non–small-cell lung cancer treated with 100 mg/d (143 days). The median duration of treatment of patients with c-kit+ tumors (n = 7) was 105 days, whereas that of patients with c-kit status unknown tumors was 50.5 days ($P = .108$). Group A patients remained on the study longer than did those in groups B and C ($P = .025$; Appendix Fig A1, online only).

Pharmacokinetics

Pharmacokinetic data after the first dose of imatinib (day 1) and at steady-state (day 15) were available for 51 and 47 patients, respectively (Table 5). The rate of imatinib absorption, as reflected by time to maximum serum concentration, was similar in all groups, although there was considerable interpatient variability. After the first imatinib dose, the imatinib elimination half-lives were similar among the four groups, with mean values of approximately 19 hours on day 1 and 28 hours on day 15. On days 1 and 15, the dose-normalized maximum serum concentration (C_{max}) was approximately 1.6- and 2.2-fold greater in the mild and moderate renal dysfunction groups, respectively, than in the normal group; however, there was large variability within each group. As with C_{max}, imatinib exposure, as expressed by dose-normalized $AUC_{0-\infty}$ (area under the curve from 0 to infinity) on day 1 and AUC_{0-24} (AUC from 0 to 24 hours) on day 15, was

Table 5. Pharmacokinetic Parameters of Imatinib and CGP74588 and Summary of AGP Levels

	Normal				Mild Renal Dysfunction				Moderate Renal Dysfunction				Severe Renal Dysfunction			
	Day 1 (n = 13)		Day 15 (n = 12)		Day 1 (n = 20)		Day 15 (n = 18)		Day 1 (n = 16)		Day 15 (n = 15)		Day 1 (n = 2)		Day 15 (n = 2)	
Plasma pharmacokinetics	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Imatinib																
T_{max}, hours	4.4	3.1	4.7	3.3	3.0	1.5	3.3	1.6	3.2	1.6	3.0	1.1	3.5	0.7	2.5	0.7
C_{max}, ng/mL/mg	5.13	1.98	6.52	2.11	8.29	3.42	10.59	4.77	11.42	5.79	14.62	8.08	6.91	6.49	13.32	6.10
AUC, (ng/mL × h)/mg	108	35*†	114	42‡	213	119†	173	77‡	269	166†	229	119‡	124	86†	190	70‡
CL/F, L/h	10.1	2.7	10.3	5.5	6.5	4.6	7.5	4.7	4.8	2.1	5.6	2.8	10.6	7.3	5.8	2.1
$t_{1/2}$, hours	17.2	6.6	26.8	10.7	19.3	6.7	30.5	24.1	20.7	6.7	25.2	17.8	21.3	7.9	40.1	23.8
V/F, L	234	62.4	355.7	137.1	164.4	93.0	308.0	290.1	139.0	71.2	229.2	235.7	366.7	345.0	290.0	73.3
Percentage free			6.2	2.4			6.1	4.1			4.7	3.0				
			(n = 10)				(n = 12)				(n = 5)					
CGP 74,588																
T_{max}, hours	4.2	2.8	5.0	3.1	3.9	2.3	4.0	2.4	4.4	2.7	3.9	1.8	6.0	2.8	3.0	1.4
C_{max}, ng/mL/mg	0.72	0.37	1.39	0.44	1.35	0.71	2.68	1.44	1.56	1.31	3.2	2.14	0.45	0.015	5.71	6.39
AUC, (ng/mL × h)/mg	24.6	14.8	25.7	9.2	53.4	32.2	45.2	24.2	55.7	40.9	54.5	37.6	Could not calculate		26.3	11.7
$t_{1/2}$, hours	29.5	12.2	48.3	64.7§	35.2	16.4	39.3	52.7	41.7	26.6	36.6	24.4	Could not calculate		33.6	3.3
CGP74599/imatinib AUC ratio	0.238	0.162	0.242	0.090	0.261	0.102	0.255	0.055	0.212	0.062	0.230	0.048	Could not calculate		0.136	0.011
Urinary excretion	(n = 7)		—		(n = 13)		—		(n = 9)		—		(n = 2)		—	
% of dose excreted as imatinib and CGP74588	4	2	—		3	2	—		3	1	—		2	2	—	
AGP, mg/dL	99.5	53.0	112.4	46.5	170.9	87.4	183.9	91.5	162.0	71.4	163.5	70.9	132.0	73.5	147.8	52.0
					(n = 18)		(n = 16)		(n = 13							

Abbreviations: AGP, α1-acid glycoprotein; T_{max}, time to maximum serum concentration; C_{max}, maximum concentration; AUC, area under the curve; CL/F, apparent clearance; $t_{1/2}$, terminal half-life; V/F, apparent volume.
*Mean ± SD.
†Dose-normalized area under the plasma concentration versus time curve from time 0 to ∞.
‡Dose-normalized area under the plasma concentration versus time curve from time 0 to 24 hours.
§Precision of estimated $t_{1/2}$ was compromised by daily dosing, which limited pharmacokinetic sampling to 24 hours after day 15 dose.

significantly greater in patients with mild or moderate dysfunction than in those with normal renal function. In that apparent clearance is defined as dose/area under the curve (AUC), there was a corresponding significant decrease in imatinib clearance as renal function worsened (Table 5 and Fig 1). The apparent volume of distribution on days 1 and 15 was significantly lower for patients with mild and moderate dysfunction than for patients with normal renal function. The percentage of unbound imatinib ranged between 2.1% and 14.5% (Table 5).

In all groups, the half-life of CGP74588 was longer than that of imatinib and, although there was great interpatient variability, there was a trend for the CGP74588 half-life assessed after the day 1 dose to increase as renal function worsened (Table 5). The limit of pharmacokinetic sampling to 24 hours after the day 15 dose precluded accurate assessment of the half-life after that dose. The day 1 and 15 dose-normalized CGP74588 C_{max} was approximately 1.9-fold and 2.2-fold greater in the mild and moderate dysfunction groups, respectively, than in the normal group. As with C_{max}, CGP74588 exposure, expressed by dose-normalized $AUC_{0-\infty}$ on day 1 and AUC_{0-24} on day 15, was approximately two-fold greater in patients with mild or moderate renal dysfunction than in those with normal renal function. The CGP74588/imatinib AUC ratio was comparable in patients with renal dysfunctions and normal controls, with the mean value ranging between 0.21 and 0.26, except for the two patients in the severe renal dysfunction group averaging 0.14 (Table 5).

There was a positive correlation between AGP concentration and dose-normalized imatinib $AUC_{0-\infty}$ on day 1 and AUC_{0-24} on day 15, inverse correlation between AGP concentration and imatinib apparent clearance, and an inverse relationship between AGP concentrations and CrCL (Fig 1, Table 5). Urinary excretion of imatinib and CGP74588 accounted for less than 10% of the imatinib dose and was not significantly different among the various groups (Table 5).

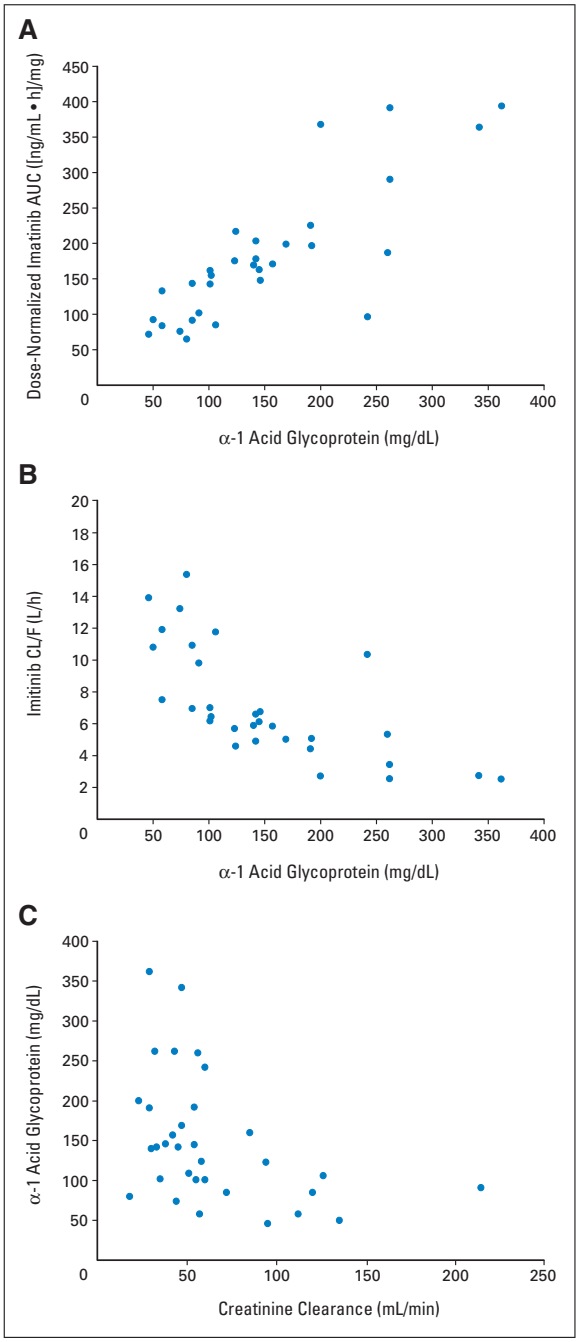

Fig 1. Relationship between creatinine clearance and imatinib apparent clearance. Points represent individual patients. (A) Alpha-1 acid glycoprotein (AGP) concentration and dose-normalized imatinib area under the curve (AUC); (B) AGP concentration and imatinib clearance (CL/F); (C) AGP concentration and creatinine clearance.

DISCUSSION

This study is the first systematic, prospective investigation of the safety and pharmacokinetics of imatinib in patients with renal dysfunction. Initial pharmacokinetic studies of imatinib were done primarily in patients with chronic myeloid leukemia and demonstrated rapid absorption; approximately 100% bioavailability; a plasma half-life of 10 to 23 hours; a two- to three-fold accumulation at steady-state; no effect of food on pharmacokinetic parameters; mainly hepatic metabolism, primarily by CYP3A; binding to AGP; and ≤ 10% renal excretion.[28-32] Earlier-phase studies of imatinib also identified electrolyte abnormalities, fluid retention and edema as toxicities, and the potential for significant drug-drug interactions, all of which provided the rationale to explore dosing in patients with renal dysfunction.[5-10]

The overall safety, side effect profile, and tolerability of imatinib in patients with renal dysfunction are similar to those in patients with acceptable renal function. An MTD was not reached in either the minimal or moderate renal dysfunction groups. Only two patients with severe renal dysfunction and no patients on renal dialysis were treated, which precludes any firm conclusion on dosing of such patients.

Despite comparable toxicity across normal, mild, and moderate renal dysfunction groups, an unexpected observation was that imatinib pharmacokinetics were altered significantly in patients with renal dysfunction. Although Pappas et al[33] reported that imatinib pharmacokinetics parameters in a patient on hemodialysis were not different than those in patients with normal renal function, the imatinib

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.