Increased Bioavailability of Intravenous Versus Oral CI-1033, a Pan erbB Tyrosine Kinase Inhibitor: Results of a Phase I Pharmacokinetic Study

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Abstract

Purpose: In phase I studies with oral CI-1033, dose-limiting toxicities were primarily gastrointestinal, supporting the exploration of i.v. dosing to achieve optimal drug exposures by increasing bioavailability.

Experimental Design: Fifty-three patients with advanced nonhematologic malignancies received i.v. CI-1033 via 30-minute infusions (10-500 mg) on a thrice-weekly schedule. Pharmacokinetic samples were collected on days 1 and 8 and evaluated using noncompartmental analysis.

Results: Dose levels evaluated were 10, 20, 30, 45, 67.5, 100, 150, 225, 337.5, and 500 mg. The maximum administered dose was 500 mg, whereas the maximum tolerated dose was 225 mg. The most common treatment-related grade 1 to 2 adverse events were rashes (38% of patients), nausea (17%), vomiting (17%), stomatitis (14%), and diarrhea (13%). Most common grade 3 adverse events were hypersensitivity reactions (7.5%), rashes (3.8%), and diarrhea (3.8%). No grade 4 toxicities were observed. Ten of the 53 (19%) patients had disease stabilization at their first efficacy evaluation visit (including two with minor responses). A 5- to 10-fold increase in i.v. C_{max} was noted with a 3-fold increase in AUC compared with oral CI-1033 at equivalent doses. Treatment-related gastrointestinal adverse events were notably less frequent with this i.v. regimen.

Conclusions: CI-1033 was safely given i.v. up to 225 mg/dose on a thrice-weekly schedule, with evidence of antitumor activity. At equivalent doses, the bioavailability of i.v. CI-1033 is thrice that of the oral formulation. Treatment with i.v. CI-1033 is feasible and may be warranted when increased drug exposures are desired.

The erbB receptors are a family of four closely related receptors: epidermal growth factor receptor (EGFR; ErbB-1), Her2/*neu* (ErbB-2), Her3 (ErbB-3), and Her4 (ErbB-4; ref. 1, 2). Increased erbB expression was shown to be a negative prognostic factor (3, 4) in non–small cell lung cancer (NSCLC; ref. 5), breast (6, 7), prostate (8, 9), head and neck (10), brain (11), ovary (12, 13), and stomach cancers (14, 15), providing the rationale for development of compounds inhibiting erbB signaling (7).

CI-1033 (canertinib dihydrochloride; Pfizer Global Research and Development, Ann Arbor, MI; Fig. 1) is an orally bioavailable 3-chloro,4-fluoro,4-anilinoquinazoline. It irreversibly inhibits the tyrosine kinase (TK) domain of all erbB members (7) by alkylation of the cysteine in the TK domain of the erbB receptors.

In preclinical studies, CI-1033 has two distinct advantages over the currently available oral TK inhibitors (TKI), gefitinib, and erlotinib. (*a*) The covalent binding of CI-1033 results in prolonged suppression of erbB activity (16, 17) requiring *de novo* synthesis of the receptor to maintain erbB signaling. (*b*) There is pan erbB inhibition. In essence, these features may afford a greater therapeutic advantage to CI-1033 relative to other erbB TK inhibitors, which have reversible actions and target one specific erbB subfamily (18).

In phase I studies with oral CI-1033, dose-limiting toxicities (DLT) were primarily gastrointestinal (7). Based on the mechanism of action, it was hypothesized that the gastrointestinal toxicity may be a function of local drug effects as well as systemic drug action, and that an i.v. formulation might ameliorate the gastrointestinal toxicities thus allowing for further dose escalation. Here, we report the results of a phase I trial with i.v. CI-1033 designed to increase the bioavailability of the drug beyond those achieved by using the drug orally at the maximum tolerated dose (MTD).

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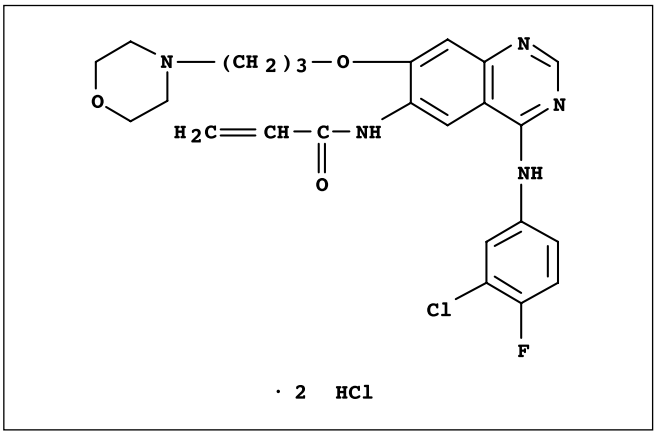

Fig. 1. CI-1033 (canertinib dihydrochloride; Pfizer Global Research and Development) is an orally bioavailable 3-chloro,4-fluoro,4-anilinoquinazoline. It irreversibly inhibits the TK domain of all erbB members by alkylation of the cysteine in the TK domain of the erbB receptors.

Materials and Methods

Study design

This was an open-label, noncomparative, single center, dose escalation trial of i.v. CI-1033 in patients with advanced solid tumors to establish the MTD and DLT of the i.v. dosing schedule and to compare the bioavailability of the i.v. preparation at its MTD with the oral formulation of CI-1033 at its MTD.

Patient selection

Patients with histologically documented, advanced-stage nonhematologic malignancies that were refractory to standard therapy, or for whom no effective therapy existed, were candidates for this study. Eligibility criteria were: (*a*) age ≥18 years; (*b*) Karnofsky performance status ≥60%; (*c*) life expectancy of at least 12 weeks; (*d*) no chemotherapy within 4 weeks before the first dose of CI-1033 and no hormonal therapy, immunotherapy, or radiotherapy within 2 weeks; (*e*) adequate hematopoietic (absolute neutrophil count ≥1,500/μL, platelet count ≥100,000/μL), hepatic (total bilirubin ≤1.5 times the institutional upper normal limit, aspartate amino transaminase, and alanine amino transaminase ≤3 times the institutional upper normal limit); and renal function (calculated creatinine clearance ≥45 mL/min; ref. 19); and (*f*) no concurrent serious infection or coexisting medical problem of sufficient severity to potentially limit full compliance with the protocol. All patients gave written informed consent before entry into the study in accordance with federal and institutional guidelines.

Dosage and drug administration

At the beginning of the study, CI-1033 was administered as a single i.v. dose over 30 minutes thrice a week with at least 1 day between doses (e.g., Monday, Wednesday, and Friday) for 4 consecutive weeks followed by 2 weeks without treatment. Before escalation to the next higher dose level, patients who did not receive all protocol-specified study medication doses during the first 4 weeks of therapy for reasons other than a DLT were replaced in order to achieve a full cohort of at least three patients per cohort.

Dose escalation started at the 10 mg dose (schedule A), with subsequent dose escalations at 20, 30, 45, 67.5, and 100 mg (see Table 1 for dose escalation schema). At the 100 mg dose, after obtaining regulatory approval, the dosing schedule was modified to a continuous regimen (schedule B), thrice a week (without the 2-week interruption). Dose escalation then continued in schedule B, with the 150, 225, 337.5, and 500 mg dose levels being explored.

At least three patients were to be treated at each dose level that did not result in a DLT during the first cycle. If one of the first three patients experienced a DLT in cycle 1, at least three additional patients were enrolled at the same dose level to verify its validity. The MTD was defined as the highest dose at which less than two of the first six patients experienced a DLT during the first cycle of treatment. DLT was defined as (*a*) any grade 4 hematologic toxicity; (*b*) an absolute neutrophil count <1,000/μL with a documented infection or fever of >38.5°C; (*c*) any grade 3 or 4 nonhematologic toxicity (excluding nausea, vomiting, or diarrhea associated with suboptimal premedication and/or management of tolerable cutaneous toxicity); and (*d*) a delay exceeding 14 days in the initiation of treatment of CI-1033 because of toxicity that did not resolve to grade ≤1 or pretreatment levels. Patients were permitted to begin successive treatments as long as drug-related toxicities had resolved to the levels specified previously, and there was no evidence of disease progression. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. (http://ctep.cancer.gov/reporting/CTC-3.html). In the event of DLT, patients could be continued on treatment with CI-1033 at the next lower dose level. Intrapatient dose escalation was not permitted.

Table 1. Dose escalation schema

Dose tier	CI-1033 dose (mg)	No. of patients	Total no. of cycles/cohort	No. of first cycle DLTs/cohort
Schedule A				
1	10	5	22	0
2	20	3	3	0
3	30	6	12	0
4	45	5	12	0
5	67.5	3	4	0
6	100	3	8	0
Schedule B				
7	100	3	7.5	0
8	150	8	8.25	1
9	225*	7	27	0
10	337.5†	7	9	2
11	500†	3	<1 cycle each	2

*Maximum tolerated dose.
†Maximum administered dose.

CI-1033 was supplied by Pfizer Global Research and Development (Ann Arbor, MI) as a solution of 2.5 mg/mL in two different vial sizes: a 75 mg vial containing 30 mL of CI-1033 in solution, and a 250 mg vial containing 100 mL of CI-1033 in solution (2.5 mg/mL × 100 mL = 250 mg). An absolute dose was administered irrespective of the body surface area and weight of the patient based on the results of previous pharmacokinetic studies that did not show a relationship between clearance with either body weight or body surface area.

Pharmacokinetic evaluations

Pharmacokinetic sampling. Plasma samples were collected on days 1 and 8 before the infusion, 10, 20, and 30 minutes after the start of the infusion and at the following times after the end of the infusion: 5, 10, 20, and 40 minutes and 1, 2, 4, and 8 hours for pharmacokinetic profiling. Plasma samples were stored and shipped at −20°C or less until the time of assay. CI-1033 stability under these conditions exceeds the retention time for all samples collected in this study.

Assay. CI-1033 was isolated from potassium EDTA/ascorbic acid–treated human plasma using a protein precipitation reaction. Internal standard [^{3}H]-CI-1033 was added to the protein precipitation reagent (acetonitrile). Analysis was conducted by liquid chromatography-tandem mass spectrometry using multiple reaction monitoring. Regression variables were estimated using a linear model with reciprocal squared response weighting and used to back-calculate QC and patient sample concentrations. The range of quantitation for CI-1033 as determined by suitable (<10% absolute error) accuracy and precision was 1.00 to 500 ng/mL in potassium EDTA/ascorbic acid–treated human plasma, based on a sample volume of 0.2 mL. QC overall precision (%CV) was 9.9%, whereas QC overall accuracy (%RE) ranged from −7.7% to −1.6% (20). Matrix effects were not observed.

CI-1033 was assayed in urine without extraction. A 50 μL aliquot of urine was diluted with 30 ng/mL of internal standard in acetonitrile and assayed directly by liquid chromatography-tandem mass spectrometry using multiple reaction monitoring. The range of quantitation for CI-1033, as determined by suitable accuracy and precision, was 10 to 500 ng/mL, based on a sample volume of 50 mL. QC overall precision (%CV) was 13.0%, whereas QC overall accuracy (%RE) ranged from −5.08% to 6.56%.

Data analysis. Plasma CI-1033 pharmacokinetic variable values were calculated for each subject for each treatment using noncompartmental analysis of concentration-time data. Samples below the limit of quantitation were reported as zero. Nominal sample collection times were used for pharmacokinetic analysis and the generation of mean profiles. Pharmacokinetic variable values were calculated using WinNonlin version 4.0.1. Plasma and urine CI-1033 concentration-time profiles were inspected visually for similarities to and difference from a typical profile following oral dosing.

Results

Fifty-three patients with advanced nonhematologic malignancies received i.v. CI-1033 via 30-minute infusions (10-500 mg) on a thrice weekly schedule (please see dose escalation schema in Table 1). Patients were initially given treatment 4 out of 6 weeks, and subsequently, the protocol was modified to allow continuous dosing without interruption. Pharmacokinetic samples were collected on days 1 and 8 and evaluated using noncompartmental analysis.

Thirty-one men and 22 women were treated (please see Table 2). The median Karnofsky performance status was 90 with the range being 70 to 100. The median age was 64 (range, 23-78). Patients with NSCLC (n = 14), colorectal cancer (10), mesothelioma (10), melanoma (5), breast cancer (2), sarcoma (2), head and neck cancer (2), carcinoma of unknown primary (2), and one each with cancers of the endometrium, thyroid, anus, kidney, round cell tumor, and bladder were enrolled. Patients were enrolled in the 10, 20, 30, 45, 67.5, 100, 150, 225, 337.5, and 500 mg dose levels. The maximum administered dose was 500 mg. Two DLTs occurred in the three patients enrolled at this dose level, a grade 3 myalgia and syncope secondary to prolonged corrected QT interval in the EKG. Three additional patients were then enrolled at the 337.5 mg dose level. Out of the seven patients enrolled in this dose level, two DLTs were encountered which were grade 3 hypersensitivity reaction and grade 3 diarrhea. Hence, the next lower dose level, i.e., 225 mg dose level, at which seven patients were previously treated, was determined to be the MTD.

Table 2. Patient characteristics

	No. of patients (N = 53)
Characteristics	
Gender (male/female)	31/22
Median age (range), years	64 (23-78)
Median KPS (range)	90 (70-100)
Previous therapy CT/RT/HT/IT	41/26/1/6
Median number of cycles/patient (range)	2 (1 to 20+)*
Tumor types	
NSCLC	14
Colorectal carcinoma	10
Mesothelioma	10
Melanoma	5
Breast cancer	2
Sarcoma	2
Head and neck cancer	2
Unknown primary	2
Other solid tumors	6

Abbreviations: KPS, Karnofsky performance status; CT, chemotherapy; RT, radiotherapy; HT, hormonal therapy; IT, immunotherapy.
*One patient continues on trial.

Safety. A total of 116 cycles were administered in 53 patients (median, 2; range, 1-20). The most common toxicities (all grades; regardless of causation) encountered are listed in Table 3. The most common all-grade treatment-related events were rashes (64%), nausea (26%), facial flushing and lightheadedness (23%), stomatitis (21%), dyspnea (19%), myalgia (19%), vomiting (19%), diarrhea (17%), and thrombocytopenia (15%). Grade 3 toxicities included hypersensitivity reactions (7.5%), rashes (3.8%), and diarrhea (3.8%). No grade 4 toxicities were observed (see Table 3 for a list of toxicities seen in all grades and in all cycles).

Despite the i.v. route of administration, we did encounter gastrointestinal toxicities that were most commonly stomatitis, nausea, vomiting, and diarrhea. In the majority of instances, there were other mitigating factors for nausea, most commonly, the use of concomitant narcotics and other medications, although a causal relation to CI-1033 could not be unambiguously excluded. In all situations, nausea and vomiting were controlled with routine antiemetic measures and did not require the interruption of treatment. Diarrhea was also grade 1 or 2 in the majority of the patients and easily controlled with the use of loperamide. Two patients had grade 3 diarrhea, one

Table 3. Summary of toxicities (all grades) encountered during the study with an incidence of 15% or more

	Daily dose (mg)											All patients (n = 53) no. of patients (%)
	3 days per week for 4 weeks on/2 weeks off (Schedule A)						3 days per week continuously (Schedule B)					
	10 (n = 5)	20 (n = 3)	30 (n = 6)	45 (n = 5)	67.5 (n = 3)	100 (n = 3)	100 (n = 3)	150 (n = 8)	225 (n = 7)	337.5 (n = 7)	500 (n = 3)	
Cutaneous toxicities	2	2	2		1	2	3	8	5	7	2	34 (64)
Pain	3		2	2		4		5	2	4	2	24 (45)
Asthenia	2	1		1		2	1	1	2	3	1	14 (26)
Nausea	2		3	1				2	2	3	1	14 (26)
Vasodilation*								2	2	6	2	12 (23)
Stomatitis			1			1	1	3	2	3		11 (21)
Dyspnea		1	1	2	1	1	1	1	1		1	10 (19)
Myalgia	1	2	2					1	2	1	1	10 (19)
Vomiting	1		1					3	2	2	1	10 (19)
Diarrhea	2	1	1							3	2	9 (17)
Infection			1			2	1	1	3		1	9 (17)
Thrombocytopenia							1	3	1	1	2	8 (15)

*Vasodilation implies facial flushing, lightheadedness, orthostasis, or dizziness.

of which happened during the first cycle, at the 337.5 mg dose level, and therefore was a DLT. In this patient, treatment was resumed at the 225 mg dose, and completed after a brief dose interruption without encountering further diarrhea.

The stomatitis encountered in this study was mild and palliated easily with routine measures. Interestingly the occurrence of stomatitis seemed to coincide with the presence of rashes.

Hypersensitivity reactions were seen in this trial and were the DLT at both the maximum administered doses of 500 and 337.5 mg. These reactions almost always occurred in the first cycle (although not necessarily with the first dose). Two grade 3 hypersensitivity reactions occurred with the first cycle and these patients were not rechallenged. In all other instances, patients were rechallenged after prophylaxis with steroids and/or benadryl, and/or just by doubling the time of infusion. Subsequently, in some instances, we were able to continue treatment without steroid and/or benadryl prophylaxis and were able to continue infusion at the regular rate. In some instances, patients continued to require the additional premedications and/or a slower rate of infusion but were able to continue with treatment.

Table 4. Pharmacokinetic variables averaged by dose for days 1 and 8

Dose (mg)	n	Day 1					Day 8				
		C_{max} (ng/mL)	AUC (0-∞)	$t_{1/2}$ (h)	Vd (L)	CL (L/h)	C_{max} (ng/mL)	AUC (0-∞)	$t_{1/2}$ (h)	VD (L)	CL (L/h)
10	5	121	117	3.83	686	115	118	139	3.54	496	92
20	3	203	294	2.70	270	71	325	358	3.61	301	57
30	6	545	477	2.99	283	66	727	524	3.93	426	84
45	5*	1,019	1,003	3.49	249	47	892	1,315	4.64	235	37
68	3	828	1,408	6.66	439	57	1,686	1,722	4.11	275	44
100	6	1,407	1,476	3.02	334	76	1,023	1,351	3.24	350	76
150	8	1,245	1,983	3.56	420	79	1,087	1,795	3.75	483	91
225	6*	2,084	3,533	3.64	325	68	2,188	3,387	2.89	293	70
338	7*	2,676	4,949	3.53	372	72	2,512	4,853	4.18	437	80
500	3*	6,027	10,862	2.49	180	50	4,417	8,331	2.45	214	60
Average				3.59	356	70			3.63	351	69
RSD (%)				32	39	27			18	29	28

Abbreviations: AUC, area under the curve from 0 to infinity expressed in ng × h/mL; $t_{1/2}$, half-life; VD, volume of distribution; CL, clearance; RSD, relative SD from the mean.
*Day 8 profiles missing for one patient at each of these doses.

Dyspnea was reported by 19% of the patients. In all instances they were grade 1 or 2. All patients were evaluated as the clinical situation mandated. On workup, two patients were found to have atrial fibrillation and one patient was found to have a deep venous thrombosis with a suspected pulmonary embolism. Other patients required treatment for possible infectious bronchitis or for their chronic obstructive pulmonary disease. Generalized myalgia was reported by 19% of the patients. In all instances, they were grade 1 or 2 and were well palliated with acetaminophen.

Thrombocytopenia was seen only in schedule B and was spread across all dose levels and did not seem to be dose-related. In all instances, it was grade 1 or 2 and treatment was continued without a further drop in platelets. There were no clinical manifestations associated with these episodes of thrombocytopenia. The thrombocytopenia seemed to be idiosyncratic rather than dose related.

In the majority of patients, treatment was discontinued secondary to progressive disease. Only at the maximum administered doses was treatment discontinued secondary to toxicity. At the MTD, i.v. CI-1033 was well tolerated.

Pharmacokinetics. Pharmacokinetic profiles were obtained in all patients. Four patients discontinued treatment prior to characterization of the day 8 profile. Data for these patients are included in the day 1 analysis and in both graphical and tabular study summaries. Urinary excretion of the parent drug represented a small percentage of the administered dose and will not be further evaluated.

Systemic exposure was dose-proportional and without accumulation under this thrice weekly dosing regimen (Table 4). Elimination was strongly multiphasic with an initial distribution phase apparent over the first 2 to 3 hours following infusion. Concentrations dropped to ~30% of their respective peak values within 20 minutes of stopping the infusion (see Fig. 2 for a representative pharmacokinetic graph at the 100 mg dose level). Within 2 to 4 hours of stopping the infusion, concentrations were ~10% of respective peak values and approximated those observed following oral administration of a bioequivalent dose (Fig. 3). Subsequent elimination approximated that observed following oral dosing and was characterized by an elimination half-life of ~3 to 4 hours. Total body clearance and the respective volume of distribution (CL/K_{el}) averaged 73 L/h and 371 L, respectively.

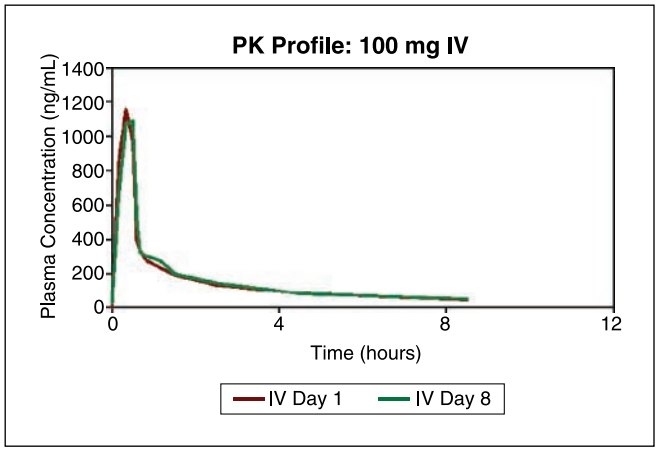

Fig. 2. CI-1033 plasma concentration-time curve after treatment with 100 mg of CI-1033 i.v. on days 1 and 8. Elimination was strongly multiphasic with an initial distribution phase apparent over the first 2 to 3 hours following infusion. Concentrations dropped to ~30% of their respective peak values within 20 minutes of stopping the infusion. Day 1 and day 8 concentration-time curves were essentially identical.

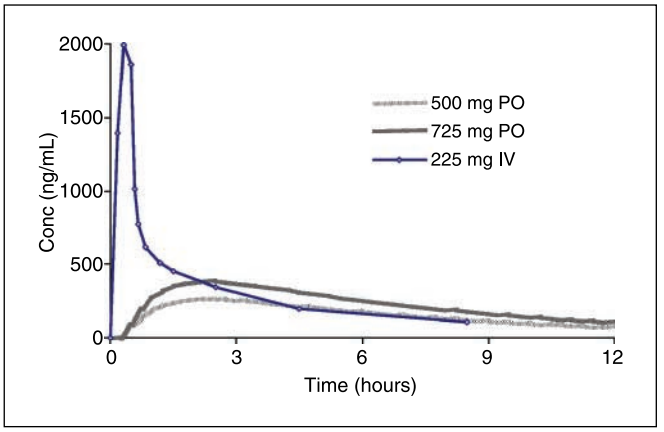

Fig. 3. Relative systemic exposure following i.v. dosing at the MTD (225 mg) as well as oral dosing at the MTD (500 mg) and at a dose (725 mg) bioequivalent to the i.v. MTD. Within 2 to 4 hours of stopping the infusion, concentrations were ~10% of respective peak values and approximated those observed following oral administration. Subsequent elimination approximated that observed following oral dosing and was characterized by an elimination half-life of ~3 to 4 hours.

Antitumor activity. Ten of the 53 (19%) patients had disease stabilization at their first efficacy evaluation visit (week 8), two of whom had minor responses. No major responses were seen. Tumors demonstrating disease stabilization were NSCLC, colon cancer, breast cancer, mesothelioma, and thyroid cancer. One patient with thyroid cancer and previously documented progression continues to enjoy stable disease and has had 20+ cycles of treatment. Two additional patients with previously documented progression (one with mesothelioma and one with NSCLC) enjoyed progression-free survival for 6 months.

Discussion

Despite an ~20-fold increase in C_{max} and 3-fold increases in AUC following i.v. administration compared with oral administration at equivalent doses, treatment-related gastrointestinal adverse events were notably less frequent with this regimen (Table 5). Although plasma CI-1033 concentrations during and shortly after a 30-minute infusion greatly exceed those achieved during oral dosing, these exposures were transient and converged with those more typical of oral regimens within a few hours (Fig. 3). The brief nature of this relatively high exposure, together with avoidance of direct exposure of the gastrointestinal tract to the drug may have facilitated achieving an MTD that, whereas lower (225 versus 500 mg), provided an almost 10-fold increase in C_{max} and ~50% increase in AUC.

This ability to increase drug exposures may be relevant in light of the recently concluded clinical trials with gefitinib and erlotinib. Gefitinib was used at its biologically effective dose (21, 22) and has been especially effective in inducing responses in patients with activating mutations in the ATP-binding pocket of its TK domain (22–25). However, it has failed to show efficacy in any malignancy other than NSCLC, presumably

Table 5. Comparison of pharmacokinetic variables between the oral and i.v. CI-1033 at the MTD and bioequivalent oral dose

Variable	Canertinib-CI-1033		
	I.v.	Oral	
	MTD	MTD	Bioequivalent
Dose	225	500	725
K_{el}	0.232	0.157	0.157
$t_{1/2}$	3.2	4.4	4.4
t_{max}	0.4	2.3	2.3
C_{max}	2233	265	384
AUC	3,518	2,385	3,458
VD	371	1,336	1,336
CL	73	210	210
F (%)		31	31

Abbreviations: K_{el}, elimination rate constant expressed in hours^{-1}; $t_{1/2}$, plasma half-life hours; t_{max}, time the maximum concentration occurs in hours; C_{max}, maximum concentration expressed as ng/mL; AUC, area under the curve expressed as ng $\times$ Hr/mL; VD, volume of distribution expressed in liters (L); CL, clearance expressed as ng/h; F, fraction of drug absorbed expressed as a percentage.

because activating mutations have not been detected in tumors other than NSCLC. Additionally, in a phase III randomized trial with previously treated patients with advanced stage NSCLC, unselected for the presence of activating mutations, gefitinib failed to show a statistically significant advantage in survival when compared with placebo (26).

Erlotinib, on the other hand, is used at its MTD and has shown statistically significant improvement in survival of unselected patients with previously treated NSCLC. Erlotinib is currently being evaluated in several malignancies other than NSCLC.

Hence, oral EGFR-TKIs have only found a limited role in the clinic, despite the demonstrable overexpression of EGFRs in a wide variety of epithelial tumors. Currently, its use is confined to previously treated advanced-stage NSCLC. The gefitinib/erlotinib experience suggests the wider clinical applicability of EGFR-TKIs if used at its MTD. We therefore speculate that increasing the bioavailability of EGFR-TKIs by its i.v. use may further extend their clinical application(s). Here we show that i.v. CI-1033 increases drug exposures, with very little variability between doses, versus the oral preparation.

Patients with NSCLC that harbor EGFR mutations activate the phosphatidylinositol-3 kinase (PI3K)/Akt survival pathway. This pathway is also a major effector of mutant K-ras signaling. Therefore, in tumors bearing EGFR mutations, treatment with EGFR-TKIs leads to tumor regression owing to brisk tumor apoptosis. In contrast, the wild-type EGFR is a weak activator of PI3K/Akt. In these tumors, the PI3K/Akt pathway may be predominantly activated by other signaling inputs (i.e., K-ras, etc.). Hence, in tumors with wild-type EGFR, treatment with EGFR-TKIs may not have a major inhibitory effect on PI3K/Akt, potentially explaining the lack of antitumor activity in NSCLC with K-ras mutations (27). This would argue against obtaining improved benefit by increasing drug exposures.

However, other markers associated with sensitivity to EGFR inhibitors have been described (28). Increased EGFR gene copy numbers based on fluorescence *in situ* hybridization analysis may be a good predictive marker for response, stable disease, time to progression, and survival. The optimal paradigm for selection of patients for treatment with EGFR-TKIs is yet to be determined and validated in prospective clinical trials (29–31). Designing clinical trials with i.v. EGFR-TKIs in a selected population of patients who do not have the activation mutations but who overexpress EGFR by fluorescence *in situ* hybridization may be a prudent strategy.

Based on this phase I experience, we conclude that the i.v. formulations of EGFR-TKIs CI-1033 allows for increased drug exposures that may be of clinical relevance in select group of patients. The oral bioavailability of CI-1033 is about one-third of that observed following i.v. dosing. Additionally, with respect to CI-1033, variability in drug exposure is reduced through i.v. administration. Day 1 and day 8 profiles in this study showed remarkable similarity within individual patients (Fig. 2). Hence, disease-specific phase II trials, in a well-selected population of patients, may be warranted with i.v. formulation of CI-1033. It is likely that this paradigm could be extended to other EGFR-TKIs as well.

Nevertheless, the inconvenience of continuous i.v. use of CI-1033 is a significant deterrent to widespread clinical use and may not be justified secondary to the rapid lowering of peak concentrations to approximate those observed following oral administration at a bioequivalent dose a few hours after the conclusion of the infusion. Therefore, a loading dose followed by an oral maintenance may be an alternative strategy that is both practical and backed by pharmacokinetic observations. Studies exploring weekly or 3-weekly cycles may therefore be justified with the EGFR-TKI being given i.v. initially followed by daily oral doses for the rest of the cycle. At the very least, the clearly shown decrease in gastrointestinal toxicity by the i.v. preparation may allow for the continued use of CI-1033 in patients who are unable to tolerate the drug owing to gastrointestinal toxicities.

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