A Phase I and Pharmacokinetic Study of Oral Lapatinib Administered Once or Twice Daily in Patients with Solid Malignancies

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Abstract

Purpose: This study determined the range of tolerable doses, clinical safety, pharmacokinetics, and preliminary evidence of clinical activity following once or twice daily administration of lapatinib in patients with solid malignancies.

Experimental Design: Cancer patients ($n = 81$) received oral doses of lapatinib ranging from 175 to 1,800 mg once daily or 500 to 900 mg twice daily. Clinical assessments of safety and antitumor activity were recorded and blood was sampled for pharmacokinetic assessments. The effect of a low-fat meal on lapatinib pharmacokinetics was assessed in a subset of patients.

Results: Lapatinib was well tolerated, such that dose escalation was limited at 1,800 mg once daily only by pill burden. Twice-daily dosing was implemented to further explore tolerability, and was limited by diarrhea to 500 mg twice daily. The most commonly reported adverse events with once-daily dosing were diarrhea (48%), nausea (40%), rash (40%), and fatigue (38%) and with twice-daily dosing were diarrhea (85%), rash (54%), and nausea (34%). Lapatinib serum concentrations accumulated upon repeated dosing, increasing nearly in proportion with dose, and were significantly increased when dosed with food or administered twice daily. One patient with head and neck cancer achieved a confirmed complete response and 22 patients had stable disease of ≥8 weeks including three patients with stable disease of >10 months (renal, lung, and salivary gland cancers).

Conclusion: Lapatinib was well tolerated following once and twice daily administration. Systemic exposure to lapatinib was dependent on the dose, duration and frequency of dosing, and prandial state. Clinical activity was observed. (Clin Cancer Res 2009;15 (21):6702–8)

The aberrant activation of growth factor receptors plays an important role in human cancers (1). Overexpression of epidermal growth factor receptor (ErbB1) and HER2 (ErbB2) occurs in many epithelial tumors, and clinical studies suggest that both receptors may be implicated in tumor etiology and progression (1, 2). Overexpression of erbB1 and erbB2 receptors has been reported in head and neck carcinomas (3, 4), breast cancer (5), and non–small cell lung cancer (6) and has been associated with poor prognosis and reduced survival in patients with cancer (6–8). Clinical studies have shown activity of inhibitors of erbB1 or erbB2 receptor function in patients with advanced malignancies (9–14).

ErbB receptor tyrosine kinase activation requires receptor dimerization and erbB2 is the preferred dimerization partner for all other members of the erbB family. Heterodimerization of erbB receptors leads to a more aggressive tumorigenic phenotype (15, 16). Inhibition of both erbB1 and erbB2 receptors could have significant therapeutic advantages over current therapies that target either erbB1 or erbB2.

Lapatinib (Tykerb/Tyverb; GlaxoSmithKline), a member of the 4-anilinoquinazoline class of kinase inhibitors, is a reversible inhibitor of erbB1 and erbB2 tyrosine kinases. Lapatinib abrogates phosphorylation and activation of receptor-mediated downstream signal transduction in erbB1- and erbB2-expressing tumor cell lines and xenografts (17, 18). Initial phase I studies conducted in healthy volunteers showed that lapatinib was well tolerated at the doses studied (10- to 250-mg single doses and 25- to 175-mg repeat doses; ref. 19).

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Translational Relevance

Lapatinib is an orally administrated, dual inhibitor of erbB1 and erbB2 tyrosine kinases with clinical antitumor activity in erbB2-positive, advanced breast cancer. This article describes the dose escalation, safety and tolerability, pharmacokinetics, pharmacodynamics, and clinical activity of lapatinib when administered once and twice daily in patients with advanced solid malignancies. The article also reports on the effect of food on the bioavailability of lapatinib.

Many oral chemotherapeutic agents are in clinical development. Investigators may question which dose or schedule provides the optimal pharmacokinetic profile and whether this profile results in an optimal antitumor or safety profile. Our article may prove useful to drug development groups that face such issues. This study also provides a "fusion" design where one study incorporates several objectives that may prove useful to teams wanting to accelerate the development of their compound without having to start up several studies at once.

The objectives of this study were to determine the range of tolerable doses, to evaluate clinical safety, to characterize the pharmacokinetics of oral lapatinib across a range of doses, when given once and twice daily, and administered with food, as well as to evaluate preliminary evidence of anticancer activity in patients with solid tumors.

Patients and Methods

Eligibility criteria. Male and female cancer patients ages ≥18 y with a histologically confirmed solid tumor that was amenable to treatment were eligible for the study. Additional inclusion criteria were Karnofsky performance status of ≥60, life expectancy of ≥12 wk, hemoglobin of ≥9 g/dL, absolute granulocyte count of ≥1,500/mm^3, platelet count of ≥100,000/mm^3, and ability to swallow and retain oral medication. All patients provided written informed consent.

Exclusion criteria included malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel; history of psoriasis or moderate to severe acne; history of drug or other allergy that would contraindicate participation; known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study drug; New York Heart Association class III/IV heart failure; left ventricular ejection fraction (LVEF) of <40% by multigated angiogram; total bilirubin of >2.0 mg/dL; aspartate aminotransferase or alanine aminotransferase of greater than thrice the upper limit of normal; or participation in a study with a new molecular entity within the previous 30 d. Pregnant or lactating women were excluded, as were sexually active males or females not using adequate contraception. Patients were prohibited from taking other medications or substances known to inhibit or induce CYP3A4, and other anticancer therapies while taking lapatinib, as well as any investigational drug <4 wk before starting or stopping lapatinib.

The study protocol was reviewed and approved by institutional review boards at the institutions of participating investigators. The study was conducted in accordance with "Good Clinical Practice" and the Declaration of Helsinki. All patients provided signed informed consent.

Trial design and study drug administration. This phase I, open-label, repeat-dose-escalation study was conducted to investigate the safety and tolerability, pharmacokinetics, and clinical activity of lapatinib in patients with solid tumors. Lapatinib (lapatinib ditosylate) was supplied as oral capsules (5, 25, and 100 mg) and tablets (100 and 250 mg). Three groups of patients were evaluated: the first received once-daily lapatinib administration, the second received twice-daily administration, and the third received single doses with and without a low-fat breakfast.

In the once-daily lapatinib dose-escalation group, lapatinib was administered to a minimum of three patients at a starting dose of 175 mg once daily for 14 d using a standard 3 + 3 design. Patients were observed for safety before a higher dose was evaluated in a new cohort of patients. If a dose-limiting toxicity (DLT) was observed during the first 14 d, three additional patients were entered at that dose level. DLT was defined as any grade 3 or 4 toxicity in the 14-d dosing period based on National Cancer Institute-Common Toxicity Criteria version 2.0. The doses administered once daily for 14 d were 175, 375, 675, 900, 1,200, 1,600, and 1,800 mg.

The study was amended to evaluate the safety, tolerability, and pharmacokinetics of lapatinib following twice daily administration (900 mg) for 14 d when pill burden limited further escalation of once-daily dosing (see Results). Following the administration of 900 mg twice daily using a standard 3 + 3 design, the study was further amended to evaluate lower doses of lapatinib (750 and 500 mg) administered twice daily. Initially three patients were to be enrolled and administered 750 mg of lapatinib twice daily for 14 d. If no DLT was seen in these patients, an additional three patients were to be entered at this same dose level. If less than or equal to one of these six patients had a DLT, an additional six patients were to be entered at this same dose level. If 3 or less of these 12 subjects experienced a DLT, enrollment was to be complete. If greater than or equal to two of the first six had DLT, the next lower dose (500 mg) was to be evaluated in the same manner as the 750 mg dose.

A third group of patients was given a single 1,250-mg dose of lapatinib on day 1 and day 8 in an open-label, randomized, crossover fashion to assess the effect of a low-fat breakfast on lapatinib pharmacokinetics.

After the completion of the 14-d study period in the once-and twice daily dose escalation cohorts and the 8-d study period in the food-effect

Table 1. Patient characteristics

Characteristic	No. (%)
No. of Subjects	81 (100%)
Age (y)	
Median (range)	61 (25-80)
Sex	
Female	37 (46%)
Male	44 (54%)
Median prior antitumor regimens (range)	3 (1-7)
Tumor type	
Colon	26 (32%)
Lung	9 (11%)
Adenocarcinoma of unknown primary	7 (9%)
Head and neck	7 (9%)
Breast	6 (7%)
Kidney	6 (7%)
Ovarian	4 (5%)
Mesothelioma	3 (4%)
Cervix	2 (2%)
Pancreas	2 (2%)
Sarcoma	2 (2%)
Other*	7 (9%)

*Includes one each of anus, esophageal, gastrointestinal stromal, melanoma, prostate, skin, stomach.

Table 2. Summary of adverse events in ≥10% of patients overall: once-daily dosing cohort

Adverse events	175 mg (*n* = 3)	375 mg (*n* = 3)	675 mg (*n* = 4)	900 mg (*n* = 4)	1,200 mg (*n* = 6)	1,600 mg (*n* = 4)	1,800 mg (*n* = 9)	1,250 mg (*n* = 7)	Total (*n* = 40)
Any event	3 (100%)	3 (100%)	4 (100%)	4 (100%)	5 (83%)	3 (75%)	9 (100%)	7 (100%)	38 (95%)
Diarrhea	0	2 (67%)	0	2 (50%)	2 (33%)	3 (75%)	6 (67%)	4 (57%)	19 (48%)
Nausea	1 (33%)	3 (100%)	2 (50%)	2 (50%)	3 (50%)	1 (25%)	3 (33%)	1 (14%)	16 (40%)
Fatigue	1 (33%)	2 (67%)	2 (50%)	0	3 (50%)	0	5 (56%)	2 (29%)	15 (38%)
Rash	0	0	2 (50%)	1 (25%)	4 (67%)	1 (25%)	6 (67%)	2 (29%)	16 (40%)
Constipation	1 (33%)	1 (33%)	0	0	2 (33%)	1 (25%)	3 (33%)	1 (14%)	9 (23%)
Anorexia	2 (67%)	1 (33%)	1 (25%)	1 (25%)	0	0	3 (33%)	1 (14%)	9 (23%)
Vomiting	0	1 (33%)	1 (25%)	1 (25%)	1 (17%)	0	2 (22%)	1 (14%)	7 (18%)
Headache	0	0	1 (25%)	1 (25%)	1 (17%)	2 (50%)	1 (11%)	1 (14%)	7 (18%)
Abdominal pain	0	0	0	0	1 (17%)	1 (25%)	3 (33%)	1 (14%)	6 (15%)
Pyrexia	0	0	0	0	2 (33%)	1 (25%)	2 (22%)	0	5 (13%)
Dyspnea	1 (33%)	0	0	1 (25%)	0	0	3 (33%)	1 (14%)	6 (15%)
Dyspepsia	0	1 (33%)	0	2 (50%)	0	1 (25%)	0	0	4 (10%)
Depression	0	0	1 (25%)	1 (25%)	0	0	2 (22%)	0	4 (10%)

group, patients could continue on daily doses of lapatinib until disease progression, unacceptable toxicity, or withdrawal of consent. In the dose-escalation cohorts, patients could increase to the next dose level if that dose had been shown not to cause DLT.

Patients in the once-daily and twice daily dose escalation cohorts were required to fast from 2 h before to 4 h after the dose on days 1 and 14, and from 2 h before to 1 h after the dose on days 2 to 13. In the food-effect group, doses were administered with 240 mL of water following an overnight fast of at least 10 h. These patients continued fasting for 4 h after the dose in one period, and consumed a standard low-fat breakfast that was completed within 5 min before dosing in the other period. Following the day 14 dosing in the dose-escalation cohorts, or day 8 in the food-effect cohort, patients were given the option of taking their morning dose with a light breakfast.

Pharmacokinetic assessment. Blood samples for analysis of lapatinib serum concentrations were collected throughout the 24-h and two 12-h dosing intervals (τ) on days 1 and 14 of once daily and twice-daily dosing, respectively, and throughout 24 h in the food-effect group. The serum was stored at -20°C until analyzed for lapatinib concentration by a liquid chromatography/tandem mass spectroscopy (LC-MS/MS) method (20).

Noncompartmental analysis using WinNonlin Professional software version 4.1 (Pharsight) was used to determine peak concentration (Cmax), the time of peak concentration, and the lag in appearance of measurable concentration. Area under the concentration versus time curve within a dosing interval (AUCτ) was calculated using linear (absorptive phase) and log-linear (postabsorptive phase) trapezoidal methods. Accumulation ratio (R) was calculated as AUCτ-day 14/AUCτ-day 1.

Safety assessments. Safety assessments were done at all clinic visits throughout the study. Safety evaluations included blood pressure and heart rate measurements, clinical laboratory tests (hematology, clinical chemistry, and urinalysis), continuous electrocardiogram monitoring (not performed in food-effect group), and 12-lead electrocardiogram on day 1 and 14 (day 1 and day 8 for food-effect group). Multigated angiogram was done at baseline. Adverse events were monitored throughout the study (from the start of lapatinib until 28 d after the last dose) and were graded using National Cancer Institute-Common Toxicity Criteria (version 2.0). Patients who continued on therapy after day 14 underwent study assessments every 4 wk and multigated angiogram was done every 8 wk. Follow-up safety assessments were also done 4 wk after the last dose of study medication.

Evaluation of clinical activity. Tumor response and disease status were assessed every 8 wk using Response Evaluation Criteria in Solid Tumors guidelines (21).

Results

Patient characteristics. Eighty-one patients were enrolled in the study. Patient characteristics are provided in Table 1. Thirty-three patients were assigned to once-daily dosing, 41 patients to twice-daily dosing, and 7 patients to the food effect group.

Dose escalation and determination of the tolerable dose range. In the once-daily group, no DLT was observed during the dose escalation phase, which continued until reaching a limit due to pill burden at 1,800 mg (18 × 100 mg capsules). Twice daily dosing of 900 mg was then initiated in three patients to further explore the tolerable dose range. One of the three patients developed a DLT (grade 3 diarrhea) in the first cycle and an additional four patients were enrolled at this dose level. One of these additional patients had DLT (grade 3 diarrhea) that required temporary interruption in therapy. As noted in Patients and Methods, the study was amended to evaluate lower doses of lapatinib administered twice daily.

In the next lower dose level cohort, 750 mg was administered to three patients, with no DLTs observed in the first cycle. An additional six subjects were enrolled with one subject developing grade 2 diarrhea on day 6 resulting in a dose reduction to 500 mg twice daily. The dose level was expanded to 15 patients with grade 1 and 2 diarrhea the most frequently reported adverse event. Another subject required a dose reduction to 500 mg twice daily due to grade 2 diarrhea that began on day 7. Seven additional subjects were added to evaluate the pharmacokinetics of lapatinib 750 mg twice daily. Because of the intermittent grade 2 diarrhea and two subjects requiring dose reduction, the 500 mg dose level was evaluated with 13 patients at this dose level and the pharmacokinetics evaluated. None of these subjects required dose reduction during the first cycle.

Dose administration and modification. Thirty-two patients in the once-daily cohort and 39 patients in the twice-daily cohort continued treatment after the day 14 assessments. Six patients in the food-effect cohort continued after the day 8 assessments.

In the once-daily cohort, six patients (one at 175, three at 675, and two at 1,200 mg dose cohorts) had their doses escalated following evidence of tolerability at their starting doses. One patient (1,800 mg) had their dose reduced to 1,200 mg due to grade 2 rash then had their dose escalated to 1,600 mg.

In the twice-daily cohort, two patients at 900 mg had their dose reduced during therapy (one due to grade 1 diarrhea reduced to 800 mg twice daily, one due to grade 3 diarrhea reduced to 600 mg twice daily). Five patients in the 750 mg dose cohort had their dose reduced during therapy (four due to grade 2 diarrhea reduced to 500 mg twice daily, one unspecified toxicity reduced to 500 mg twice daily). None of the patients at 500 mg twice daily had dose reductions.

In the food-effect part of the study, none of the patients required dose reduction.

Safety and Tolerability. All patients enrolled in the study received at least one dose of lapatinib and were included in the safety population.

Once-daily dose group and food-effect group. Thirty-eight of 40 patients (95%) in the combined once-daily dose escalation and food-effect group reported at least one adverse event regardless of causality. The most commonly reported adverse events (Table 2) were diarrhea (48%), nausea (40%), rash (40%), and fatigue (38%). The most frequently reported grade 3 adverse events were dyspnea (8%), small intestinal obstruction (8%), nausea (6%), vomiting (6%), and dehydration (6%); the only grade 4 adverse event was hyponatremia (3%). One patient in the food-effect cohort had grade 3 diarrhea (2.5%). One patient (1,800 mg) prematurely discontinued the study due to grade 3 abdominal pain, grade 3 hyperkalemia, and grade 4 hyponatremia, and these events were not attributed to lapatinib (the only grade 4 event in patients receiving once daily lapatinib)). A patient in the food-effect group discontinued lapatinib due to small bowel obstruction not attributed to lapatinib. One patient died during treatment due to progressive disease.

Twice daily dose-escalation group. Forty of 41 patients (98%) in the twice-daily cohort reported at least one adverse event regardless of causality. The most commonly reported adverse events (Table 3) were diarrhea (85%), rash (54%), and nausea (34%). Four grade 4 adverse events (two patients with dyspnea, one patient with dehydration, and one patient with pulmonary embolism) were reported. The most frequent grade 3 adverse events were diarrhea (17%) and deep vein thrombosis (5%). The frequency of grade 3 diarrhea in the 500, 750, and 900 mg cohorts was 15%, 14%, and 33%, respectively. Seven patients prematurely discontinued the study due to adverse events; one patient at 900 mg (grade 2 diarrhea attributed to lapatinib), three patients receiving lapatinib 750 mg twice daily (one patient with grade 2 nausea attributed to lapatinib, one with grade 3 chest wall pain and failure to thrive, one with grade 3 diarrhea attributed to lapatinib), and three patients receiving lapatinib 500 mg twice daily (one patient with failure to thrive, and two with grade 3 diarrhea attributed to lapatinib). Three patients died during treatment due to disease progression.

Pharmacokinetic results. Lapatinib pharmacokinetic parameters (at steady state) are summarized by dose and (after a single dose) by prandial state in Table 4. Serum concentrations appeared after a median lag in appearance of measurable concentration of 15 minutes and peaked at a median time of peak concentration of 4 hours independent of dose. Once- and twice-daily dosing for 14 days achieved steady-state concentrations with mean accumulation ratios of 1.9 and 4.7, respectively. AUCτ increased nearly in proportion with dose, independent of dosing frequency (Fig. 1). However, dose-normalized AUCτ was 1.86-fold higher at doses administered twice daily compared with once-daily administration of similar doses (900-1,800 mg/day). Administration of a single 1,250 mg dose with a low-fat breakfast resulted in 3.0-fold (2.2- to 4.2-fold) higher 24-hour AUC and 3.2-fold (1.9- to 5.3-fold) higher Cmax compared with fasting. Variability in pharmacokinetics was high. Coefficients of variation for dose-normalized AUC were 50% for once-daily dosing, 43% for twice-daily dosing, and 59% and 43% for the fasted and fed states, respectively.

Dose and concentration-toxicity relationships. The frequency and severity of diarrhea seemed to be more closely related to increasing dose (Fig. 2) than to plasma concentration. Conversely, the frequency and severity of rash seemed to be more closely related to increasing AUC (Fig. 2), Cmax, or Cmin than to dose. The time to onset of rash seemed to be inversely related to plasma concentration.

Tumor response. Seventy-seven patients continued therapy beyond day 14 and were evaluable for response. One confirmed complete response was observed in a patient in the food-effect group (1,250 mg once daily) with erbB1-overexpressing head and neck squamous cell carcinoma and metastatic disease to the lymph nodes. The patient had previously been treated with surgery and chemotherapy (fluorouracil and cisplatin). The patient continues to receive lapatinib and remains in complete remission >5 years after beginning lapatinib therapy. Twenty-two patients had stable disease of ≥8 weeks (once daily: two patients at 900 mg, one patient at 1,200 mg, one patient at 1,250 mg, five patients at 1,600 mg, three patients at 1,800 mg; twice daily: five patients at 500 mg and five patients at 750 mg). One patient with renal cancer (at 750 mg twice daily), one patient with non–small cell lung cancer (originally at 675 mg then dose escalated to 1,600 mg once daily), and one patient with salivary gland cancer (originally at 1,200 mg then dose escalated to 1,600 mg once daily), had stable disease for 301, 384, and 400 days, respectively.

Discussion

In this phase I study, lapatinib was generally well tolerated without a need for adjustment of doses up to 1,800 mg once daily and 500 mg twice daily in both the 14-day evaluation phase and the treatment continuation phase in patients with a variety of solid tumors. The range of tolerability for once-daily dosing was limited by pill burden rather than toxicity. Twice daily dosing indicated the limiting toxicity to be grade 3 diarrhea.

Both the frequency and severity of diarrhea were increased in patients receiving twice daily lapatinib compared with patients receiving once daily lapatinib. Although 1,800 mg once daily

Table 3. Summary of adverse events reported in ≥10% of patients overall: twice-daily dosing cohort

Adverse events	500 mg (*n* = 13)	750 mg (*n* = 22)	900 mg (*n* = 6)	Total (*n* = 41)
Any event	12 (92%)	22 (100%)	6 (100%)	40 (98%)
Diarrhea	11 (85%)	18 (82%)	6 (100%)	35 (85%)
Rash	6 (46%)	12 (55%)	4 (67%)	22 (54%)
Nausea	3 (23%)	8 (36%)	3 (50%)	14 (34%)
Anorexia	3 (23%)	4 (18%)	2 (33%)	9 (22%)
Fatigue	1 (8%)	5 (23%)	2 (33%)	8 (20%)
Cough	3 (23%)	5 (23%)	0	8 (20%)
Vomiting	1 (8%)	5 (23%)	0	6 (15%)
Dyspnea	2 (15%)	1 (5%)	2 (33%)	5 (12%)
Pain	1 (8%)	4 (18%)	0	5 (12%)
Pyrexia	2 (15%)	3 (14%)	0	5 (12%)
Abdominal pain	0	4 (18%)	0	4 (10%)
Bronchitis	2 (15%)	2 (9%)	0	4 (10%)
Headache	1 (8%)	2 (9%)	1 (17%)	4 (10%)

was tolerated, dividing the total daily dose and administering it twice daily resulted in more frequent and severe diarrhea. This was unexpected because smaller amounts were administered comprising the same total daily dose. However, as this toxicity is manifest in the small intestine, it is possible that more frequent, albeit lower doses, produce a greater insult mediated locally in the gut. This notion is supported by the data suggesting that the frequency and severity of diarrhea are more closely related to the dose than to plasma concentration, a finding consistent with a previous report (22).

One patient receiving once-daily lapatinib (1,250 mg) developed grade 3 diarrhea versus 17% of patients receiving twice daily lapatinib. Grade 3 diarrhea was more frequent at the higher twice daily doses (900 mg, 33%; 750 mg, 14%; and 500 mg, 15%). None of the patients receiving once daily lapatinib required dose reduction due to diarrhea, whereas six patients (two at 900, four at 750 mg) required dose reduction due to diarrhea In addition, four patients (all receiving twice daily lapatinib) discontinued lapatinib due to diarrhea.

As with other small molecule inhibitors of ErbB1 (23), lapatinib use was associated with the development of skin rash. Rash was more frequent in twice daily administration (54%) than once daily (40%). No patients developed grade 3 rash. The frequency of patients developing grade 2 rash was similar in the once and twice daily groups (8% and 10%, respectively). Fifty percent of patients at the 900 twice daily dose developed grade 2 rash. All once daily patients developing grade 2 rash received lapatinib doses of 1,250 mg or higher. Despite these observations, the frequency and severity of rash seemed to be more closely related to increasing concentrations than to dose (Fig. 2). A previous report did not show a relationship between lapatinib dose or concentration and frequency of rash (22).

Two patients experienced asymptomatic relative LVEF decreases of >20% from baseline and ejection fraction of <50% during the continuation phase of the study. In one patient, with a pretreatment LVEF of 50%, the LVEF declined to 24% ~6 weeks after starting lapatinib (1,200 mg once daily). The patient was asymptomatic. Lapatinib was interrupted and 2 weeks later, the patient developed progressive disease and was removed from study. Approximately 5 weeks later, the patient was noted to have an LVEF of 43%. A second patient with a pretreatment LVEF of 56% had an LVEF of 39% ~8 weeks after starting lapatinib (500 mg twice daily). The patient was asymptomatic. No additional LVEF evaluations were undertaken. The patient was removed from study ~21 weeks after starting lapatinib due to progressive disease. In a recent analysis of 3,689 cancer patients receiving lapatinib (24), a 1.6% incidence of decreased LVEF was reported (National Cancer Institute-Common Toxicity Criteria grade 3 or 4 or asymptomatic LVEF decline of ≥20% relative to baseline and below the institution's lower limit of normal). These cardiac events were usually asymptomatic and reversible and occurred at a similar frequency in patients who were or not previously treated with anthracyclines and trastuzumab. Only 0.2% of patients had symptomatic LVEF dysfunction.

The pharmacokinetics of lapatinib at the higher doses given to patients in this study were consistent with data at lower doses (up to 250 mg) in healthy individuals (19). Previous data indicated achievement of steady state in 7 days and up to 2-fold accumulation, consistent with an effective accumulation half-life of 24 hours. In this study, once-daily and twice-daily dosing exhibited accumulation consistent with this previous data. However, twice-daily dosing resulted in ~2-fold higher serum concentrations than once-daily dosing at an equivalent total daily dose. The increase in exposure, but not in relative accumulation, indicates that increasing the frequency of dosing increased bioavailability, rather than decreasing clearance. The mechanism underlying this difference is unknown.

The large increase in bioavailability observed with a low-fat meal was also unexpected because preclinical studies showed a decrease in bioavailability with food and an earlier study in healthy volunteers showed only a 60% increase in bioavailability from 100 mg dosed with a high-fat meal (25). The discordance of these observations indicates the complexity of processes that determine lapatinib bioavaiability, which include low solubility and permeability, intestinal efflux

Table 4. Summary of lapatinib pharmacokinetic parameters

Dose	Cmax (mg/L)*		Cmin (mg/L)*		AUCT (h*mg/L)*	
	Geo. Mean†	Mean (SD)‡	Geo. Mean†	Mean (SD)‡	Geo. mean†	Mean (SD)‡
175mg QD (*n* = 3)	0.37	0.41 (0.25)	0.17	0.17 (0.05)	5.48	5.86 (2.74)
375mg QD (*n* = 3)	0.41	0.44 (0.21)	0.19	0.21 (0.13)	5.74	6.23 (3.20)
675mg QD (*n* = 4)	1.06	1.14 (0.43)	0.3	0.35 (0.18)	13.7	14.34 (5.04)
900mg QD (*n* = 4)	1.05	1.06 (0.19)	0.31	0.33 (0.10)	12.7	12.8 (1.94)
1,200 mg QD (*n* = 5)	1.39	1.55 (0.87)	0.4	0.48 (0.31)	17.3	20.0 (12.3)
1,600 mg QD (*n* = 4)	1.92	1.97 (0.58)	0.45	0.45 (0.08)	22.7	23.0 (4.1)
1,800 mg QD (*n* = 9)	1.89	2.02 (0.78)	0.74	0.82 (0.41)	27.7	29.6 (11.8)
500mg BID (*n* = 6)	2.2	2.37 (0.87)	0.96	1.10 (0.58)	18.1	19.6 (8.2)
750mg BID (*n* = 6)	1.87	2.11 (0.90)	0.92	1.15 (0.76)	15.4	18.0 (9.4)
900mg BID (*n* = 5)	3.27	3.57 (1.57)	1.77	2.04 (1.10)	28.5	31.5 (14.5)
1,250 mg fasted	0.76	0.91 (0.52)	—	—	9.07	10.7 (6.4)
1,250 mg fed	2.44	2.54 (0.84)	—	—	27.3	29.5 (12.0)

*Day 14 steady-state data for all but fasted/fed (single dose).
†Geometric mean.
‡Arithmetic mean (SD).

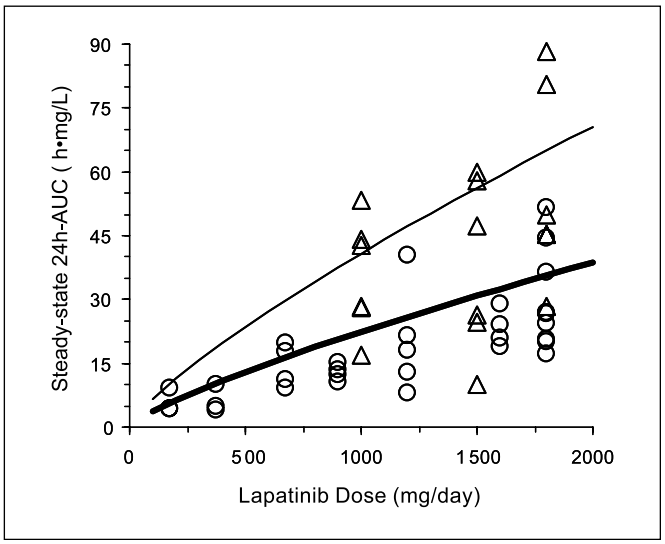

Fig. 1. Lapatinib steady-state 24-h AUC in relation to total daily dose following once (○) and twice (Δ) daily administration, showing the best-fit curves describing the once daily and twice daily data.

transporters (ABCB1 and ABCG2), and first-pass metabolism dominated by CYP3A4 (26). In the current study, the percent coefficient of variation in AUC was slightly lower in patients administered lapatinib in the fed state but the number of patients (n = 7) under investigation was small. A larger lapatinib food-effect study (n = 27) was conducted and recently reported (27). This study noted that the lapatinib AUC following administration with a low-fat or high-fat meal was increased 2.67- and 4.25-fold, respectively compared with the fasting state. In this larger study, increased bioavailability in the fed state did not decrease relative variability in lapatinib systemic exposure.

Dosing lapatinib with food and twice-daily dosing have been discussed in recent editorials in an oncology medical journal. Ratain and Cohen (28), noting the increased systemic exposure of lapatinib when dosed with food, suggested that administration of lapatinib with food may reduce the frequency and/or severity of diarrhea. Seruga and Tannock (29) suggested that dosing lapatinib with food or dosing twice daily may increase drug exposure and make the pharmacokinetics of lapatinib more predictable. In a larger lapatinib food-effect study noted above, a 24-fold variability in systemic exposure was noted among patients administered lapatinib with a high-fat meal (27). Such variability is of obvious clinical concern and data indicating that such an approach can be done safely with chronic lapatinib administration are lacking. In addition, requiring a specific type of meal to be administered with lapatinib may not be practical because cancer patients may be unable or unwilling to consistently adhere to such a dietary regimen. Day-to-day variability in the composition of a meal consumed with lapatinib could result in significant intrapatient heterogeneity in lapatinib systemic exposure thus impacting safety and clinical activity (30, 31), Thus, the current product label for lapatinib advises that lapatinib be dosed 1 hour before or after a meal.

The safety and clinical activity of twice-daily (500 mg) and once-daily (1,500 mg) lapatinib were recently evaluated in a phase II study in patients with ErbB2-positive breast cancer previously untreated in the metastatic setting (32). Clinical activity and safety were similar in the two treatment regimens. Lapatinib (1,250 mg, once daily) is currently approved in combination with capecitabine. The safety and clinical activity of twice-daily lapatinib in combination with capecitabine have not been evaluated to date although twice-daily dosing of lapatinib deserves further investigation.

In summary, lapatinib administration was well tolerated in this phase I study. Grade 3 and 4 toxicities were infrequent

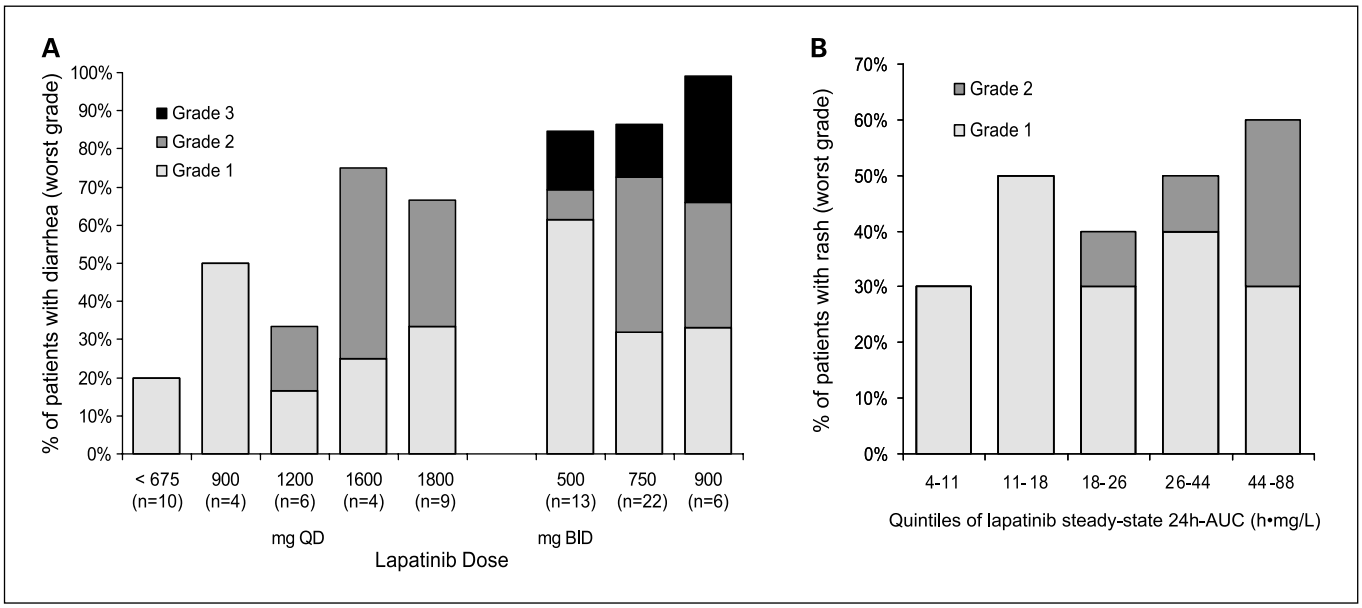

Fig. 2. *A,* frequency of diarrhea in relation to lapatinib dose following administration once (*QD*) and twice (*BID*) daily doses. *B,* frequency of rash in patients with pharmacokinetic data in quintiles (n = 10) of lapatinib steady-state 24-h AUC following administration of once and twice daily doses, showing the worst grade reported for each patient.

except at the highest twice daily administration schedule. Clinical activity was observed.

Disclosure of Potential Conflicts of Interest

K. Koch, M. Versola, N. Arya, R. Fleming, D. Smith, L. Pandite, employment, GSK. S. Jones, commercial research grant, consultancy, GSK. N. Spector, employment, commercial research grant, consultancy, honoraria, GSK. H. Burris, consultancy, GSK, Genentech.

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