A Phase I and Pharmacokinetic Study of Lapatinib in Combination with Letrozole in Patients with Advanced Cancer

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Abstract

Purpose: The main objectives of this phase I and pharmacokinetic, open-label study were to determine the optimally tolerated regimen (OTR), safety, pharmacokinetics, and clinical activity of lapatinib in combination with letrozole in patients with advanced solid malignancies.

Experimental Design: Patients with advanced breast cancer with immunohistochemically detectable estrogen or progesterone receptors or other cancers were eligible. Doses of lapatinib were escalated in cohorts of three subjects from 1,250 to a maximum of 1,500 mg/d based on dose-limiting toxicities in the first treatment cycle. The letrozole dose was fixed at 2.5 mg/d. Additional patients were enrolled at the OTR dose level to further evaluate safety and for pharmacokinetic analyses.

Results: Thirty-nine patients were enrolled in the study: 12 in the dose-escalation group, 7 in the OTR safety group, and 20 in the pharmacokinetic group. The OTR dose level was identified as 1,500 mg/d lapatinib and 2.5 mg/d letrozole. The most common (>25% of patients) drug-related adverse events were diarrhea (77%), rash (62%), nausea (46%), and fatigue (26%). No significant differences were observed in the pharmacokinetic variables (C_{max} and AUC) of lapatinib and letrozole when coadministered compared with single-agent administration. One patient with endometrial cancer had a confirmed partial response.

Conclusions: Clinically relevant doses of lapatinib in combination with letrozole were well tolerated and did not result in a pharmacokinetic interaction, and clinical antitumor activity was observed.

The abnormal activation of growth factor receptors has been implicated in many types of cancer (1). Overexpression of epidermal growth factor receptor (ErbB1) and HER-2 (ErbB2), two members of the type 1 receptor tyrosine kinase family (ErbB), has been reported in a wide variety of malignancies including carcinomas of the breast (2), head and neck (3, 4), and lung (non-small cell; ref. 5). Overexpression of these ErbB receptors has also been linked to poor prognosis and reduced survival (5–7).

Ligand binding to ErbB receptors promotes formation of homodimers and heterodimers and activation of the intracellular kinase domain (1, 8). Kinase activation leads to interaction with other signal transduction molecules, thereby initiating an intracellular signaling cascade that results in proliferative, survival, and/or cell differentiation stimuli (9, 10). Both monoclonal antibodies and small-molecule tyrosine kinase inhibitors targeting ErbB1 and/or ErbB2 have been shown to inhibit proliferation of ErbB1 or ErbB2 receptor-expressing cancer cells, (11–16), and such therapeutics have shown significant antitumor activity in patients with a broad range of advanced malignancies (17–20).

Lapatinib (Tykerb; GlaxoSmithKline), a member of the 4-anilinoquinazoline class of kinase inhibitors, is a potent, selective, reversible inhibitor of ErbB1 and ErbB2 tyrosine kinases (21, 22). Lapatinib has shown activity against $ErbB2^+$, metastatic breast cancer in recent clinical studies. In a phase II study of lapatinib administered as a single agent in previously untreated patients with $ErbB2^+$ ($FISH^+$) breast cancer, a 26% response rate was observed (23), which is within the range of activity reported with single-agent trastuzumab (17, 24, 25). A phase III trial of lapatinib in combination with capecitabine versus capecitabine in patients with $ErbB2^+$, metastatic breast cancer whose tumors progressed on prior trastuzumab reported a longer median time to progression (8.4 versus 4.4 months) in the lapatinib-containing arm (hazard ratio, 0.49; 95% confidence interval, 0.34-0.71; log-rank $P < 0.001$; ref. 26).

Although selective estrogen receptor (ER) modulators, such as tamoxifen, have played a role in reducing breast cancer mortality, only about one-half of ER^+ breast tumors respond to antiestrogen therapy (1, 27). Unlike tamoxifen, which binds to the ER and induces receptor dimerization and DNA binding, selective aromatase inhibitors block the conversion of adrenal androgens to estrogens, thereby depriving the ER of ligand in

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target tissues (28). Differences in their pharmacologic mechanism may account for differences in clinical activity between tamoxifen and the aromatase inhibitors. Clinical studies have reported that the aromatase inhibitor letrozole (Femara; Novartis Pharmaceuticals) is superior to tamoxifen in postmenopausal women in the neoadjuvant, adjuvant, and advanced breast cancer settings (28–30).

Cross-talk between growth factors and the ER occurs at multiple levels and seems to play a crucial role in breast cancer etiology and progression (27). Recent data also suggest that endocrine resistance is linked to certain cellular kinase and growth factor pathways (27). Given the existence of cross-talk between the ER and ErbB pathways, combination therapy with letrozole and lapatinib may be a rational approach for improving response and delaying or bypassing endocrine-resistant tumor progression (1, 27, 31).

The purpose of the current study was to determine the safety, optimally tolerated regimen (OTR), pharmacokinetics, and clinical activity of lapatinib in combination with letrozole in patients with advanced breast cancer and other solid malignancies.

Patients and Methods

Eligibility criteria. Male and female cancer patients ages ≥18 years with advanced histologically/cytologically confirmed, breast cancer with immunohistochemically detectable ER or progesterone receptor (PgR) or other tumors (e.g., ovarian and endometrial) that were likely to potentially benefit from a lapatinib/letrozole combination regimen were eligible to participate. Patient's tumors were not required to be ErbB2$^+$. Female eligibility criteria also included postmenopausal status as defined by one of the following: (*a*) age ≥50 years and lack of menstrual period in the preceding 12 months, (*b*) castrate follicle-stimulating hormone level >40 IU/L, and/or (*c*) prior history of bilateral oophorectomy. Additional inclusion criteria were Karnofsky performance status ≥70, life expectancy ≥12 weeks, hemoglobin ≥9 g/dL, absolute granulocyte count ≥1,500/mm^3, platelet count ≥100,000/mm^3, estimated creatinine clearance >30 mL/min, total bilirubin <1.5 mg/dL, aspartate aminotransferase/alanine aminotransferase ≤3 times the upper limit of the normal institutional reference range, and ability to swallow and retain oral medication. All patients provided written informed consent.

Exclusion criteria included uncontrolled brain metastasis or leptomeningeal disease, other serious illness or conditions (e.g., clinically significant cardiac disease, active infection, and psychiatric disorder), known contraindication to aromatase inhibitors, known immediate or delayed hypersensitivity reaction to the study drugs or products chemically related to the study drugs, left ventricular ejection fraction (LVEF) ≤40%, poor venous access (exclusion for pharmacokinetic patients), moderate or severe hepatic impairment, pregnancy/lactation, malabsorption syndrome, disease significantly affecting gastrointestinal function, or major resection of the stomach or small bowel that could affect lapatinib absorption. Patients who had participated in any investigational study within 28 days of study enrollment were excluded as were those who had undergone major surgery, hormonal (or other replacement) therapy, chemotherapy, or radiotherapy within the previous 4 weeks and/or had not recovered from prior therapy within the previous 4 weeks. For mitomycin C or nitrosourea therapy, 6 weeks must have elapsed from prior treatment to study participation.

Because lapatinib undergoes hepatic metabolism by CYP3A4, medications or substances known to inhibit or induce this enzyme system were prohibited from study enrollment until withdrawal from the study. This included certain HIV antiretrovirals, antibiotics, antifungals, anticonvulsants, antidepressants, and other miscellaneous medications and foods (e.g., glucocorticoids, St. John's Wort, and grapefruit and its juices). Agents to control gastric acidity (antacids within 1 h of dosing, histamine 2 receptor antagonists, and proton pump inhibitors) were prohibited because the effect of their administration on lapatinib absorption was not known at the time of this study. Patients were prohibited from undergoing other anticancer therapy while on study drugs. No other investigational drug could be administered from 28 days before the first dose of the study drugs until 28 days after the last dose was administered or post-treatment blood draws were completed, whichever occurred first.

Trial design and study drug administration. The study protocol was approved by the institutional review board at the study sites and was conducted in accordance with "Good Clinical Practice" and the Declaration of Helsinki. Patients were enrolled in three groups: (*a*) a dose-finding group to determine the OTR, (*b*) an OTR expansion group to further evaluate the safety of lapatinib and letrozole at the OTR dose, and (*c*) a pharmacokinetic group to determine the pharmacokinetic variables of each agent alone and in combination. With the exception of the pharmacokinetic group (discussed below), patients received oral daily lapatinib and oral daily letrozole beginning on the first day of treatment period 1 (treatment period = 1 month) continuing for the duration of the study. Lapatinib could be taken with a light, low-fat breakfast. On pharmacokinetic sampling days only, patients in the pharmacokinetic group were required to fast 4 h before lapatinib dosing and 2 h afterwards on pharmacokinetic sampling days. All patients continued on study until disease progression, unacceptable toxicity, or withdrawal of consent.

Study drug dose modification and dose intensity analysis. Lapatinib was reduced by 250 and 500 mg for grade 3 and 4 diarrhea, respectively. For other toxicities and their causality with lapatinib, dose modification was made following discussions among the study investigators. Percent of prescribed dose intensity was calculated by dividing the administered dose intensity/prescribed dose intensity and multiplying by 100%. Administered dose intensity calculations included dose reductions, treatment interruptions, and compliance as assessed by the study investigators.

Dose-escalation and OTR expansion group. At least 3 patients were initially enrolled in the first dosing cohort [lapatinib, 1,250 mg/d once daily continuous; letrozole, 2.5 mg/d once daily continuous (dose level 0)] and monitored for toxicity for one treatment period. The starting dose of lapatinib represented a lower dose than the highest doses administered in phase I studies of monotherapy lapatinib (1,600-1,800 mg/d; refs. 32, 33) or the typical monotherapy dose used in phase II trials (1,500 mg/d; ref. 23). The starting dose of letrozole was 2.5 mg/d, the Food and Drug Administration–approved monotherapy dose, and remained fixed during the study. If no dose-limiting toxicity (DLT) was observed, 3 additional patients were entered at the next higher dose level [lapatinib, 1,500 mg/d; letrozole, 2.5 mg/d (dose level +1)] and evaluated for DLT in the first treatment period or the maximum lapatinib dose of 1,500 mg/d was reached in the absence of DLT. If 1 of 3 patients experienced a DLT at a given dose, 3 additional patients were entered at that dose level; however, if ≥2 patients at any given dose level involving 2 to 6 total patients experienced DLT, a lower dose was explored to more precisely determine the OTR.

DLT was defined as evidence of at least grade 3 toxicity with "suspected" or "probable" relationship to investigational product during the first treatment period. Additionally, any grade 2 non-hematologic toxicity persisting beyond treatment period 1 was considered a DLT if deemed dose limiting in the judgment of the study investigators. The OTR was defined as the dose level of lapatinib and letrozole at which no more than 1 of 6 patients experienced a DLT in the first treatment cycle.

After determination of the OTR, up to 15 patients were to be enrolled in the OTR expansion group to evaluate the safety and efficacy of lapatinib at the dose level identified as the OTR.

Pharmacokinetic group. Additional patients were enrolled at OTR dose level and randomly assigned to one of four treatment sequences in a randomized crossover to determine the potential for drug-drug interaction affecting either letrozole or lapatinib at steady state. In sequence 1, lapatinib was dosed on days 1 to 8, letrozole was dosed on day 8, and blood was sampled for lapatinib analysis on days 7 and 8. In sequence 2, lapatinib was dosed on days 1 to 23, letrozole was dosed on day 8, and blood was sampled for lapatinib assay on days 8 and 23. In sequence 3, letrozole was dosed on days 1 to 28, lapatinib was dosed on day 28 and blood was sampled for letrozole analysis on days 21 and 28. In sequence 4, letrozole was dosed on days 1 to 28, lapatinib was dosed on day 21, and blood was sampled for letrozole analysis on day 21 and 28. Blood samples (2 or 4 mL) were collected before dosing and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 h after dosing. Samples were anticoagulated with EDTA and centrifuged at 1,000 × *g* for 15 min, and the plasma was separated and stored at -20°C until assayed.

Sample and pharmacokinetic analyses. Plasma concentrations of lapatinib were measured by an online extraction, liquid chromatography/tandem mass spectroscopy method described previously (34). The limit of quantification was 5 ng/mL. Plasma concentrations of letrozole were measured by liquid chromatography/tandem mass spectroscopy after solid-phase extraction using an electrospray interface with multiple reaction monitoring in the positive ion mode. The limit of quantification was 0.5 ng/mL. Precision and accuracy for both methods were within 15%.

Plasma concentration data were analyzed by standard noncompartmental methods using WinNonlin Professional software version 4.1 (Pharsight). Area under the plasma drug concentration-time curve within a steady-state dosing interval (AUCτ), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), and plasma concentration at the end of a dosing interval ($C\tau$) were calculated for lapatinib and letrozole for each patient in each treatment period in the pharmacokinetic phase of the study. AUCτ, C_{max}, and $C\tau$ were analyzed by ANOVA; t_{max} and t_{lag} were analyzed using nonparametric statistical methods. ANOVA of both AUC and C_{max} were done using a mixed model to estimate a point and a 90% confidence interval estimate of the true difference in least squares means between the test and reference treatments. Nonparametric methods were used to evaluate paired differences between treatments for t_{max}.

Safety assessments. Safety assessments were done at all clinic visits and throughout the study. Measurements used to assess safety included vital signs, clinical laboratory tests (hematology and chemistry), 12-lead electrocardiogram, Karnofsky performance status, and multiple gated acquisition scan or echocardiogram. Adverse events/serious adverse events were monitored at each visit, each scheduled assessment, and at 28-day poststudy follow-up.

Adverse events and toxicities were graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 (35). Patients who presented with decreased LVEF were graded according to the New York Heart Association classification system (36).

Assessment of clinical activity. Antitumor response and disease status were determined using the Response Evaluation Criteria in Solid Tumors guidelines (37). The number of patients with complete response, partial response, stable disease, and progressive disease was determined.

Results

Patient characteristics and disposition. Thirty-nine patients, whose pertinent demographic characteristics are listed in Table 1, were enrolled in the study. The most common tumor types were breast (46%) and ovarian cancer (41%; Table 1). The majority of patients were heavily pretreated with previous cytotoxic and hormonal therapy (Table 1). Five patients had received prior trastuzumab and 4 patients had received prior letrozole. Twelve patients were enrolled in the dose-escalation phase, 7 patients were enrolled in the OTR expansion phase, and 20 patients were enrolled in the pharmacokinetic phase. Estrogen, progesterone, and ErbB2 status are provided in Table 1. Four patients received starting doses of lapatinib of 1,250 mg and letrozole of 2.5 mg. Thirty-four patients received starting doses of lapatinib of 1,500 mg and letrozole of 2.5 mg. An additional patient in the pharmacokinetic cohort was assigned to receive a starting dose of lapatinib of 1,500 mg and letrozole of 2.5 mg, received letrozole, but discontinued before receiving lapatinib due to deterioration in performance status.

Table 1. Patient characteristics

Assessment variable	*n* (%)
No. subjects	39 (100)
Age (y), median (range)	57 (31-73)
Sex	
Female	38 (97)
Male	1 (3)
Ethnic origin	
Caucasian	34 (87)
American Hispanic	3 (8)
Asian	1 (2.5)
African American	1 (2.5)
Karnofsky performance status, median (range)	90 (70-100)
Prior therapy	
Hormonal therapy, median (range)	1 (0-5)
Cytotoxic therapy, median (range)	3.5 (0-12)
Primary tumor site	
Breast	18 (46)
Ovary	16 (41)
Endometrium	2 (5)
Bladder	1 (3)
Cervix	1 (3)
Fallopian tube	1 (3)
ER/PgR status	
All patients	
ER^+	23 (100)*
PgR^+	15 (79)†
Breast cancer patients	
ER^+	18 (100)
PgR^+	12 (75)‡
HER-2 status (breast cancer patients)	
$IHC3^+$ and/or $FISH^+$	3 (20)§

*ER status was unknown in 16 patients.
†PgR status was unknown in 20 patients.
‡PgR status was unknown in 2 breast cancer patients.
§ErbB2 status was unknown in 3 breast cancer patients.

Determination of the OTR. Four patients were enrolled at dose level 0 (1,250 mg lapatinib and 2.5 mg letrozole) and no DLT were reported in the first treatment cycle and the next dose level (dose level 1) was opened for enrollment. The third patient at dose level 1 (1,500 mg lapatinib + 2.5 mg letrozole) had a DLT of grade 2 diarrhea that was considered dose-limiting by the investigator. The diarrhea developed 2 days following the start of lapatinib therapy and resolved 4 days later. Lapatinib was temporarily interrupted and restarted at a reduced dose on resolution of the diarrhea. Five additional subjects were enrolled (8 total subjects at dose level 1) and there were no other DLT in the first treatment cycle. The OTR was defined as 1,500 mg/d lapatinib and 2.5 mg/d letrozole.

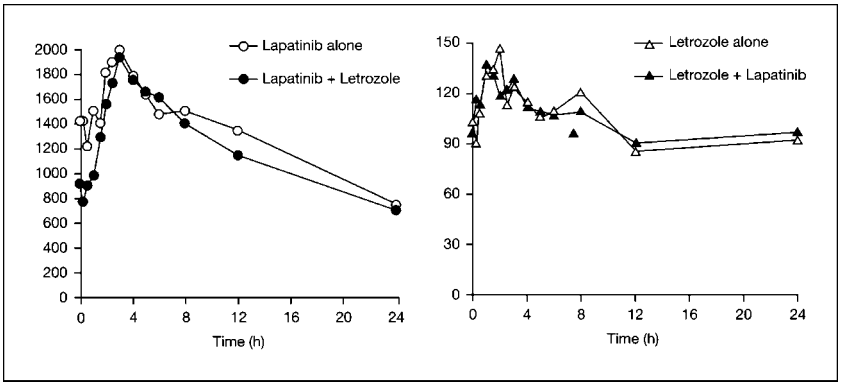

Fig. 1. Median steady-state plasma concentrations versus time for lapatinib (*left*) and letrozole (*right*) alone and in combination.

Dose administration and modification. The median percent of prescribed dose intensity was 100% (range, 63.6-100%) for lapatinib and 100% (range, 54-100%) for letrozole. Four patients required lapatinib dose reductions: 3 patients with grade 3 diarrhea and 1 patient with grade 2 diarrhea. Letrozole was not dose reduced during the study.

Safety. The safety population consisted of all 39 study participants: 4 patients received 1,250 mg lapatinib plus 2.5 mg letrozole and 35 patients received 1,500 mg lapatinib plus 2.5 mg letrozole. One patient in the pharmacokinetic group assigned to receive 1,500 mg lapatinib plus 2.5 mg letrozole only received 2.5 mg letrozole before discontinuing therapy due to clinical deterioration due to disease progression. Lapatinib was generally well tolerated in combination with 2.5 mg letrozole at doses up to 1,500 mg. The most frequently (≥10%) reported drug-related adverse events were diarrhea (77%), rash (62%), nausea (46%), fatigue (26%), vomiting (23%), anorexia (23%), and mucositis (13%; Fig. 1). No grade 3 or 4 drug-related adverse events were reported in the 1,250 mg lapatinib plus 2.5 mg letrozole group. Nine patients receiving 1,500 mg lapatinib plus 2.5 mg letrozole experienced a drug-related grade 3 adverse events [diarrhea (n = 6), rash (n = 1), anemia (n = 1), and clostridium colitis (n = 1)], but no drug-related grade 4 adverse events were reported in this group.

Two patients in the 1,500 mg lapatinib plus 2.5 mg letrozole group discontinued study drug due to adverse events. One patient discontinued treatment because of drug-related grade 3 rash, and the other patient discontinued treatment because of non-drug-related grade 4 respiratory failure. The latter patient died, but the investigator did not attribute the toxicity to drug treatment.

Four patients (3 in the 1,500 mg lapatinib + 2.5 mg letrozole group and 1 in the 1,250 mg lapatinib + 2.5 mg letrozole group) had ≥20% decrease in LVEF relative to their pretreatment values. In only one of these patients did the post-treatment ejection fraction decline to a value of <50%. In this patient, the baseline LVEF value of 70% decreased to a 48% value after 2 months of therapy (31% decline relative to their pretreatment value). The patient remained on study drug until disease progression and had a LVEF measurement of 64% (9% decline relative to their pretreatment value) at their post-study assessment.

Antitumor activity. Thirty-four patients (4 receiving 1,250 mg lapatinib + 2.5 mg letrozole and 30 receiving 1,500 mg lapatinib + 2.5 mg letrozole) had at least one available disease assessment after baseline evaluation and were analyzed for clinical activity. Five patients were removed from the study before their initial disease assessment for the following reasons: (*a*) ulcerative colitis, (*b*) drug-related grade 3 rash, (*c*) decreased performance status, (*d*) non-drug-related pneumothorax, and (*e*) noncompliance.

Two patients, one with endometrial cancer and the other with breast cancer, experienced partial response. The endometrial cancer patient (ER/PgR status unknown) who responded

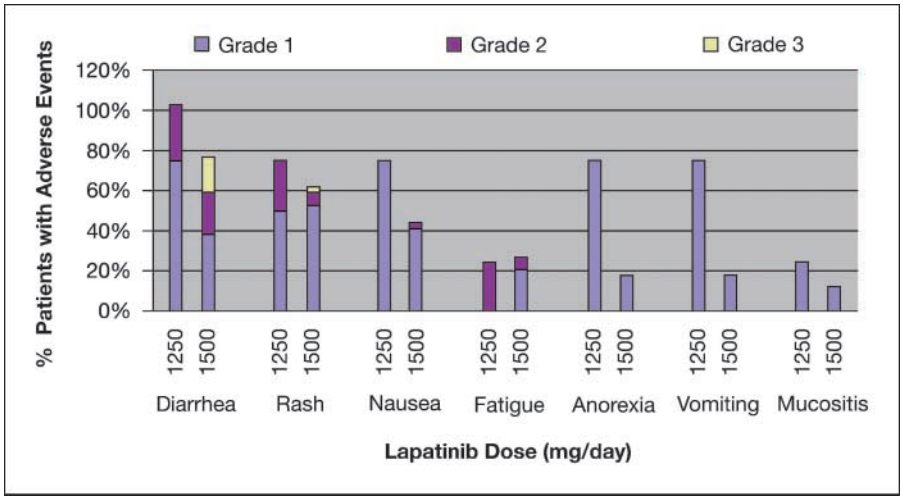

Fig. 2. Drug-related adverse events in >10% of all patients by toxicity grade.

Table 2. Pharmacokinetic variables for lapatinib and letrozole

Variables	Lapatinib alone (n = 9)*	Lapatinib + letrozole (n = 10)*	Comparison †
AUCτ (h μg/mL)	31.9 (17.2-59.2)	27.0 (13.3-54.8)	0.84 (0.62-1.13)
C_{max} (μg/mL)	2.47 (1.47-4.13)	1.94 (1.13-3.34)	0.78 (0.57-1.06)
t_{max} (h)	3.00 (0.00-12.2)	3.00 (2.50-12.0)	0.02 (-0.37-1.75)
C_τ (μg/mL)	0.78 (0.37-1.66)	0.72 (0.30-1.73)	0.90 (0.63-1.28)
Variables	**Letrozole alone (n = 8)***	**Letrozole + lapatinib (n = 8)***	**Comparison †**
AUCτ (h μg/mL)	2.23 (1.34-3.71)	2.09 (1.30-3.34)	0.94 (0.79-1.11)
C_{max} (μg/mL)	0.14 (0.08-0.22)	0.12 (0.08-0.19)	0.90 (0.79-1.02)
t_{max} (h)	1.75 (1.50-24.0)	1.25 (0.00-6.00)	-1.75 (-12.0-1.00)
C_τ (μg/mL)	0.09 (0.05-0.17)	0.08 (0.05-0.13)	0.86 (0.71-1.05)

*Geometric mean (95% confidence interval), except median (range) for t_{max}.
† Geometric least-squares mean ratio (90% confidence interval), except median difference and 90% confidence interval for t_{max}.

had stable disease until a partial response was noted after 225 days of therapy. The partial response, confirmed by repeat radiologic assessments, lasted for 161 days. This patient had not received prior hormonal therapy or chemotherapy. The responding patient with breast cancer (ER^+/PgR^-, $ErbB2^-$), an unconfirmed partial response, achieved partial response at initial disease assessment (day 53) but had progressive disease at the next assessment (day 106). This patient had received prior adjuvant chemotherapy and tamoxifen and three cytotoxic chemotherapy and two hormonal regimens for metastatic disease. Twenty patients had stable disease as their best response (range, 32-289 days); of the patients with stable disease, 2 patients with breast cancer (both patients were ER^+/PgR^+ and $ErbB2^-$) experienced stable disease lasting 247 and 289 days. One of the patients had received prior adjuvant tamoxifen therapy and five cytotoxic and two hormonal regimens for metastatic disease and the second patient had received prior adjuvant chemotherapy and hormonal therapy and two cytotoxic and two hormonal regimens for metastatic disease.

Pharmacokinetics. The pharmacokinetic phase of the study involved 20 patients. Letrozole pharmacokinetic data were obtained from 8 patients that completed their assigned treatment sequence. Lapatinib pharmacokinetic data were obtained from 9 patients that completed their assigned treatment sequence. Plasma concentration versus time profiles are shown in Fig. 2 and pharmacokinetic variables are shown in Table 2. Lapatinib plasma concentrations (C_{max}, AUC, and C_{min}) tended to be lower on average (22%, 16%, and 10%, respectively) in the presence of letrozole. Letrozole plasma concentrations also tended to be lower on average (10%, 6%, and 14%, respectively) in the presence of lapatinib. For both drugs, the associated confidence intervals included 1.0.

Discussion

The extensive bidirectional cross-talk that occurs between growth factor pathways and the ER, now well recognized, may play a critical role in breast cancer etiology and progression (27). Munzone et al. reported that in 10 patients whose tumors overexpressed ErbB2 but not ER or PgR, 3 of 10 patients showed expression of ER after 9, 12, and 37 weeks after the initiation of trastuzumab. One of the 3 patients subsequently received letrozole for 3 years without evidence of progression (38).

Endocrine resistance in ER^+ breast cancer is correlated with enhanced expression of ErbB1 and ErbB2 pathways (39). ER^+ tumors resistant to endocrine therapy use these pathways to circumvent endocrine response, (40, 41), thus combining inhibitors of membrane growth factor pathways with endocrine therapy may increase responsiveness to hormone receptor directed therapy.

Preclinical studies investigating the effect of tamoxifen therapy combined with the ErbB1 inhibitor gefitinib have shown promise for enhancing the benefit of endocrine therapy (1, 42, 43). Results of a phase II clinical trial in patients with ER^+ and $ErbB2^+$ metastatic breast cancer showed that combination therapy with letrozole and trastuzumab was well tolerated, showed clinical activity, and produced durable responses (44). Other phase II trials assessing the efficacy of aromatase inhibitors in combination with ErbB1/ErbB2 or mammalian target of rapamycin antagonists have been conducted in neoadjuvant and advanced breast cancer settings, and phase III trials using these treatment approaches are now under way (39, 40, 45, 46).

In the current study, coadministration of lapatinib and letrozole in patients with advanced breast cancer or other solid tumors was generally well tolerated. The most frequently reported drug-related adverse events were diarrhea, rash, nausea, fatigue, vomiting, anorexia, and mucositis with few drug-related grade 3 adverse events and no drug-related grade 4 adverse events. The OTR was defined as 1,500 mg/d lapatinib in combination with 2.5 mg/d letrozole, which represent the typical monotherapy doses of lapatinib and letrozole, respectively.

The toxicities of the drugs in combination were similar to that reported previously for each drug individually although diarrhea and rash were more frequent (33, 47). Drug-related diarrhea in the current study (77%; grade 3, 15%) was more frequent than in phase II studies of monotherapy 1,500 mg/d lapatinib (36-54%; grade 3, 3%; ref. 23). Diarrhea was typically managed with dose delays, antidiarrheal medications, and occasionally dose reductions. Likewise, rash was more frequent (62%; grade 3, 3%) in the current study than reported previously with 1,500 mg/d lapatinib (27-30%; grade 3, 1%; ref. 23), although this increase was primarily due to an increase

in grade 1 rash. It is unclear why diarrhea and rash were increased. No pharmacokinetic interaction was observed (as noted below). Whether this increase is evidence of a pharmacodynamic interaction or due to the small sample size is unclear. No increase in adverse events was reported in a recent combination trial of gefitinib and anastrozole in breast cancer patients (46).

No clinically significant cardiotoxicity was observed in the current study. In a recent analysis of 3,127 cancer patients receiving lapatinib, a 1.3% incidence of decreased LVEF was reported (National Cancer Institute Common Toxicity Criteria grade 3 or 4 or asymptomatic LVEF decline of $\geq$20% relative to baseline and below the institutions lower limit of normal). Only 0.1% of patients had symptomatic LVEF dysfunction and this was generally reversible or nonprogressive (48).

The potential for a metabolic drug-drug interaction between these agents was considered because letrozole is a substrate of CYP3A4 (49) and lapatinib has been shown to inhibit this enzyme *in vitro* (50). The results of this study suggest that coadministration of these agents is unlikely to produce a clinically significant alteration in the pharmacokinetics of either drug.

The results of this study indicate that the combination of lapatinib and letrozole is safe, does not have a pharmacokinetic interaction, and has clinical activity. A current phase III trial of lapatinib plus letrozole versus letrozole plus placebo (EGF30008) in previously untreated, postmenopausal patients with ER/PgR$^+$ breast cancer is ongoing. This study will provide important answers about the clinical feasibility of inhibiting membrane growth factor pathways and ER cross-talk.

Disclosure of Potential Conflicts of Interest

Q.S.C. Chu has a commercial research grant from GlaxoSmithKline. M.E. Cianfrocca has a commercial research grant from GlaxoSmithKline and has received honoraria from GlaxoSmithKline and Novartis. E. Paul, L. Pandite, K.M. Koch, R.A. Fleming, and J. Loftiss are employed by GlaxoSmithKline. E.K. Rowinsky is employed by and has an ownership interest in ImClone Systems. L.J. Goldstein has received honoraria from GlaxoSmithKline.

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