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ORIGINAL ARTICLE

The effects of lapatinib on cardiac repolarization: results from a placebo controlled, single sequence, crossover study in patients with advanced solid tumors

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Abstract

Purpose To evaluate the effect of lapatinib on the QTc interval and ECG parameters in patients with advanced solid tumors.

Methods This was a multicenter, placebo-controlled study in subjects with advanced solid tumors. Subjects were administered two doses of matching placebo on day 1, 12 h apart and one dose in the morning on day 2. Two doses of lapatinib 2000 mg were administered orally on day 3, 12 h apart and one dose in the morning on day 4. Twelve-lead digital ECGs were extracted from continuous Holter recordings at pre-specified time points over the 24-h period on days 2 and 4. Venous blood samples for lapatinib concentrations were obtained immediately following the ECGs.

Results A maximum mean baseline-adjusted, placebo time-matched increase in QTcF, (ddQTcF) in the evaluable, (EV) population ($n = 37$) of 8.8 ms (90% CI 4.1, 13.4) occurred approximately 10 h after the third lapatinib dose. These results were consistent with those in the pharmacodynamic, PD population, ($n = 52$) (ddQTcF = 7.9 ms; 90% CI 4.1, 11.7). No subject experienced QTcF increases from baseline of > 60 ms on lapatinib or placebo. The geometric mean lapatinib C_{max} of 3902 ng/mL was observed at 3.6 h post-dose.

Conclusions These data show a relevant, treatment-related increase in QTcF after treatment with three doses of lapatinib 2000 mg. This study confirms the need for caution in patients with solid tumors treated with lapatinib, and who are concomitantly receiving drugs that are strong CYP3A inhibitors and/or prolong the QTc.

Keywords Lapatinib · QTc effects · Advanced cancer patients

Introduction

Lapatinib (Tykerb®) is an orally administered dual inhibitor of the tyrosine kinases of the ErbB1 (EGFR) and ErbB2 (HER2) growth factor receptors which are overexpressed in a wide spectrum of solid tumors [1, 2]. Lapatinib is currently FDA approved, in combination with capecitabine, for the treatment of patients with advanced, metastatic breast cancer that overexpresses HER2 and who have received prior therapy including an anthracycline, a

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taxane, and trastuzumab. Lapatinib is also FDA approved, in combination with letrozole, for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor and for whom hormonal therapy is indicated [3]. The most common adverse events [AEs (> 20%)] reported during lapatinib plus capecitabine therapy were gastrointestinal (diarrhea, nausea, and vomiting), dermatologic (palmar-plantar erythrodysesthesia and rash), and fatigue [4].

Cardiovascular toxicity has been reported with tyrosine kinase inhibitors (TKI's) including hypertension, decrease in left ventricular ejection fraction (LVEF) and QTc prolongation [5–8]. Several TKI's inhibit the human ether-à-go-go-related gene (hERG) channel responsible for the repolarizing delayed rectifier (I_{Kr}) potassium current of the cardiac action potential, resulting in QT prolongation and predisposing to potentially fatal arrhythmias [8–10]. TKI-mediated QT prolongation may also be due to down-regulation of phosphoinositide 3-kinase (PI3K) signaling, or indirectly via tyrosine kinase inhibition affecting multiple ion channels [11]. Nevertheless, the QT prolonging and arrhythmogenic profile of TKIs varies considerably, therefore a class-related effect of TKIs, or an effect mediated by selected kinases, is not supported, [8] and the QT liability of new TKIs should be assessed individually.

The in vitro safety evaluation of lapatinib included its effect on human embryonic kidney (HEK293) cells transfected with the hERG cDNA, which showed a hERG IC_{50} of 1.11 µM [12]. Preclinical studies in isolated canine cardiac Purkinje fibers and guinea pig field-stimulated atria with lapatinib concentrations up to 2.56 µg/mL and 58.1 µg/mL, respectively, did not show treatment-related changes on action potential duration (APD), chronotropy or any other effects on cardiac parameters [13]. There were no adverse effects on the electrocardiogram including QTc interval in in vivo assessment in rats and dogs up to 500 mg/kg [12].

Human data on the effect of lapatinib on QTc is available from prior lapatinib clinical trials and observational studies. In a clinical study investigating the effect of food on lapatinib plasma concentrations, an up to three-fold increase in lapatinib exposure was observed but no subjects had QTc values exceeding 480 ms [14]. In a retrospective review of the cardiovascular safety of TKI Inhibitors focused on cardiac repolarization, lapatinib is presented as one of the QT prolonging drugs [15], whereas a retrospective assessment by another author did not identify a relevant QT effect for lapatinib [5].

Therefore, to accurately determine the effect of lapatinib on cardiac repolarization, we conducted a dedicated multicenter, single sequence, placebo-controlled, crossover study in patients with advanced solid tumors (NCT01328054) treated with multiple high doses of lapatinib to formally evaluate its effect on the Fridericia-corrected QTc interval (QTcF) and other ECG parameters.

Materials and methods

Patient recruitment and eligibility

Subjects were recruited at four clinical centers in the United States. Subjects were eligible for study entry if they were 18 years of age or older with a histology- or cytology-confirmed diagnosis of metastatic breast cancer that overexpressed ErbB2, or with recurrent, advanced or metastatic solid tumor malignancy (including breast cancer that does not over-express ErbB2), were Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 with LVEF of at least 50% on an echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan, adequate baseline organ function including hemoglobin ≥ 9 g/dL, neutrophils ≥ 1500/mm^3, and platelets ≥ 75,000/mm^3, serum albumin ≥ 3 g/dL, bilirubin ≤ 1.5× ULN, AST and ALT ≤ 3× ULN (with or without liver metastasis), and serum creatinine ≤ 1.5 mg/dL or estimated creatinine clearance of ≥ 50 mL/min. Eligible females were enrolled if they were of non-childbearing potential, or had a negative serum pregnancy test and agreed to predefined methods of contraception prior to starting treatment. All patients provided written informed consent prior to study participation, and the protocol was approved by the local Institutional Review Boards at all participating study centers. All procedures and the experiments done respected the ethical standards in the Helsinki Declaration of 1975, as revised in 2000 (5), as well as the national law.

Key study exclusion criteria were baseline QTcF > 480 ms, PR interval > 240 or < 110 ms, sinus bradycardia < 50 beats per minute, or significant cardiac conduction abnormalities. Patients on medication known to prolong QT/QTc, or with clinically significant gastrointestinal abnormalities that would adversely affect drug absorption were also excluded. A 7–14 day washout period was applied for medication known to be CYP3A4 inducers and/or strong inhibitors, including grapefruit juice and dietary or herbal supplements. These concomitant medication restrictions applied for the duration of the study.

Study objectives

The primary objective of the study was to assess the effects of lapatinib on the baseline-adjusted, time-matched Fridericia-corrected QT interval compared with placebo (ddQTcF). Secondary objectives were to estimate the effects of lapatinib on the Bazett-corrected QTc interval (QTcB), the individual-corrected QT (QTci), and on heart rate. Tertiary

exploratory study objectives included characterizing the relationship between the lapatinib plasma concentrations and QTcF and QTci.

Study design and treatment

This was a multicenter, single-blind, placebo-controlled, single sequence crossover study to evaluate the effects of lapatinib on the QTcF interval in patients with advanced solid tumors. Subjects were screened within 14 days prior to start of study treatment, to which the study participant was blinded. Lapatinib 2000 mg was selected as the suprathera-peutic dose as a three-dose ¨pulse dosing¨ regimen with fixed dose loperamide to achieve high lapatinib exposure levels while avoiding the known gastrointestinal adverse events that start after 48 h. The maximum tolerated dose (MTD) for lapatinib is 5250 mg/day [16].

During the study treatment period, three doses of matched placebo were administered, in the morning and evening on day 1, 12 h apart, and in the morning on day 2. Lapatinib 2000 mg (eight 250 mg tablets) was administered orally for three doses, in the morning and evening on day 3, 12 h apart, and on the morning of day 4 (see Fig. 1 for study schema). Patients received loperamide 4 mg daily on all study days. Subjects who completed the QTc study were able to continue lapatinib treatment in a continuation study, provided they met the study entry criteria and the investigator assessed that the benefits of continuing lapatinib outweighed the risks.

QT interval measurements and analysis

Continuous 24 h digital Holter recordings were used to extract 12-lead ECGs at protocol defined time points. Mean values were calculated for triplicate ECGs for each time point. QT intervals were corrected for heart rate based on the Fridericia (QTcF), Bazett (QTcB) and individual–corrected methods. To calculate QTci, $QTi/(RRi)^{\beta i}$ was calculated with βi being individually determined, based on the estimated slope of log-transformed QT versus log-transformed RR interval for the patient [17, 18]. Baseline QT measurements were extracted from ECGs collected at 30, 15, and 0 min before the first placebo dose on study day 1, and before the first dose of lapatinib on study day 3. On study days 2 and 4, ECGs were extracted at time points detailed in Fig. 1. Venous blood samples to determine lapatinib concentrations were obtained prior to the first dose on days 1 and 3, prior to the third dose of each treatment on study days 2 and 4 and immediately following each pre-specified QT interval measurement. Loperamide 4 mg, an anti-diarrheal without QT liability when used at standard, low doses, was administered daily in the morning on study days 1–5 to counteract treatment-related diarrhea.

To evaluate the performance of the formulas used to correct for changes in the heart rate (RR,) the adequacy of the QTcF, QTcB and QTci methods were assessed using pre-treatment ECG data. The placebo and time-matched QTcF change from baseline, dQTcF and ddQTcF were subsequently calculated per time point. Plots were then created of ddQTcF versus time-matched mean lapatinib concentrations, and a regression line and 90% confidence interval (CI) added and geometric mean and 95% CI of C_{max} estimated from the non-compartmental pharmacokinetic data analysis. Bootstrap analysis of the ddQTcF, ddQTci, dQTcF and dQTci versus lapatinib concentration regression was also performed and the 95% percentile for the regression slope and geometric mean C_{max} obtained.

Lapatinib pharmacokinetic sampling schedule and analysis

Two mL of venous blood was collected in EDTA-K2 tubes to determine lapatinib plasma concentrations at pre-dose on days 1 and 2 (placebo) and days 3 and 4 (lapatinib), and at 1, 2, 3, 4, 6, 8, 10, 12 and 24 h post-dose on the profile days

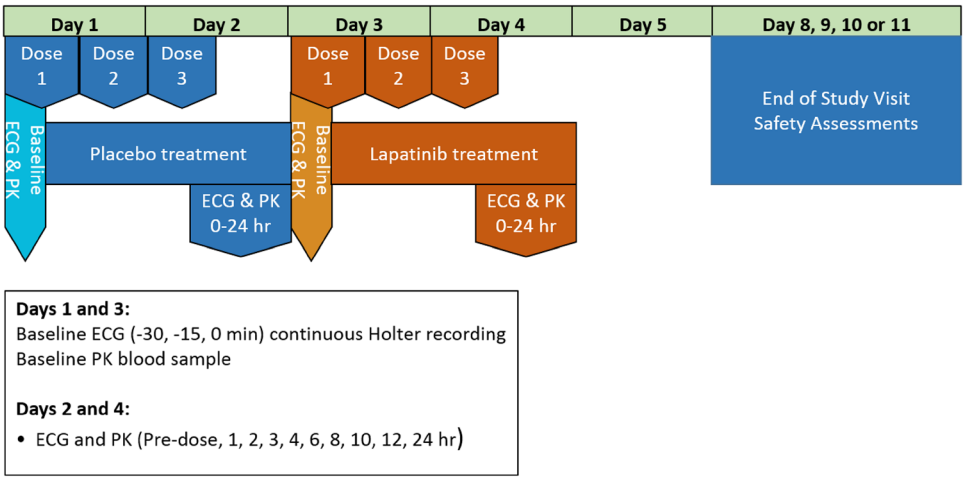

Fig. 1 Schema of the study design

2 and day 4. Blood was drawn directly after time-matched ECG collection and immediately spun in a refrigerated centrifuge. Plasma was separated, and frozen at − 70 °C or below and stored until analysis.

Lapatinib plasma concentrations were determined in 50 µL plasma samples by a validated high performance liquid chromatographic (HPLC) tandem mass spectrometry (LC/MS/MS) method with automated extraction [19], and the analyses validated using internal standards (Lapatinib-^{13}C2,^{15}N). The lower limit of quantification (LLQ) for lapatinib was 100 ng/mL and the upper limit of quantification (HLQ) was 10 µg/mL. Reanalysis of 57 test samples met the criteria for assay reproducibility (100%). The within-run and between-run accuracy and precision of lapatinib quality control samples showed a bias of − 1.1% to 1.9%, and coefficients of variation between 3.1 and 4.0%.

Pharmacokinetic analysis

Non-compartmental analysis of the lapatinib plasma concentration vs time data was conducted by ICON® (Marlow, UK) in Phoenix Build 6.3.0.395 and WinNonlin 6.3 (Pharsight Corporation, St. Louis, MO) using Model 200 (for extravascular administration). The values for primary pharmacokinetic parameters—C_{max}, T_{max} were observed and the $AUC_{0–24\,h}$ was estimated. The summary statistics (mean, standard deviation, median, minimum and maximum) were obtained using SAS 8.02 for UNIX under the HARP environment. Nominal blood sampling collection times were used to calculate summary statistics.

Assessment of adverse events

Adverse events (AEs) were monitored by history and during physical examination, and in ECG and clinical laboratory assessments from day 1 until the final study visit and subsequent follow-up visit. AEs were graded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events, NCI-CTCAE version 4.0.

Study sample size justification statistical methods

Based on the results of a Phase I, dose escalation study of lapatinib, where a within-subject variability for QTcF of 17 ms was evident [20], a sample size of 36 evaluable subjects was estimated to provide a 90% CI equal to the estimated mean difference ± 6.8 ms when the estimated standard deviation is 17 ms. We estimated that up to sixty eligible subjects needed to be enrolled in the study to ensure that approximately 36 subjects completed the study and were evaluable for the primary study endpoint.

Repeated measures analysis of variance (MANOVA), was used to calculate the treatment effect difference on QTcF between placebo and lapatinib at the predefined time points that included PK sampling. A linear mixed effect model was used to explore the relationship between lapatinib plasma concentration and ddQTcF duration.

Definition of analysis populations

The following subject populations definitions were applied for data reporting and analysis.

The "All Treated" population used for the safety analysis included all subjects who received one or more doses of the study treatment. The pharmacokinetic (PK) population included all subjects who received treatment, and for whom a PK sample was obtained. The evaluable (EV) population included the "all treated" patient population who received consecutive doses of study drug, with adequate ECG data especially at baseline, for placebo and lapatinib. The pharmacodynamic (PD) population includes all subjects who received one or more doses of study treatment and had Holter ECG data on all four study days.

Results

Patient enrollment and demographics

The study population consisted of 58 subjects, 21 males and 37 females that were enrolled across the four participating study centers in the United States during the period December 2011 to April 2015. Five subjects withdrew prior to completing the study, 2 subjects due to adverse events, and physician-investigator decision for 1 subject, and patient decision for 2 subjects. Detailed patient demographics are shown in Table 1.

Lapatinib pharmacokinetic profile

Data on the lapatinib plasma concentration versus time profile was available in 56 study participants in the PK population. The geometric mean $AUC_{0–24}$ was 59,200 (15,400–188,000) ng h/mL. The geometric mean lapatinib C_{max} of 3920 (1370–10,000) ng/mL was observed at a median T_{max} of 3.6 (0–24.1) h. The mean concentration observed at 4 h post-dose was 3948.8 (95% CI 3495.7–4401.9) ng/mL; thereafter, the mean concentration decreased to 3456.6 (3015.4–3897.7) ng/mL at 6 h, 3297 (2820.2–3775.8) ng/mL at 8 h, 3049.1 (2547.1–3551.1) ng/mL at 10 h, 2804.5 (2317.6–3291.4) ng/mL at 12 h, and 1838.6 (1450.6–2226.7) ng/mL at 24 h after the last dose of lapatinib.

Table 1 Patient demographics

Total number of patients; [male (female)]	$N=58$; [21 (37)]
Median age (range) years	56 (24–81)
Ethnicity *n* (%)	
Hispanic/Latino	5 (9)
Non-Hispanic/Latino	53 (91)
Baseline ECOG performance status *n* (%)	
0	27 (47)
1	31 (53)
Type of cancer *n* (%)	
Colon/rectum	6 (10)
Breast, endometrial/uterine, non-small cell lung	Each 5 (9)
Bladder, esophageal, ovarian, salivary gland	Each 4 (22)
Cervical, head and neck, skin	Each 2 (3)
Acrine cell (parotid gland), adenoid cystic, anus, bile ducts, bile duct, chondrosarcoma, chordoma, gallbladder, intrahepatic cholangiocarcinoma, liver, lung, parotid adenoid cystic, salivary, synovial, testicular, urothelial	Each 1 (2)
Number prior cancer therapies *n* (%)	
Chemotherapy	49 (98)
Biologic therapy	12 (24)
Hormonal therapy	6 (12)
Small molecule targeted therapy	5 (10)
Median baseline laboratory values, (range)	
ANC (per mm^3)	2400 (1500–8570)
Platelets (per mm^3)	262 (252–510)
ALT (IU/L)	25.9 (8–94)
Serum creatinine (mg/dL)	0.8 (0.4–1.9)
Serum bilirubin (mg/dL)	0.6 (0.2–1.3)

Adequacy of QT correction formulas

The adequacy of the QT correction formulas for heart rate changes was tested for the QTcF, QTcB and QTci formulas. Based on the results of the QT-RR data sets for the placebo profile days (Days 1 and 2), the slope of the regression lines for males and females were calculated, and were 0.008 and 0.007 for QTcF, −0.088 and −0.053 for QTcB and −0.102 and 0.078 for QTci, respectively. The Fridericia correction method was, therefore, superior to the Bazett and individual correction methods to control for heart rate changes.

Relationship between lapatinib PK and QT interval parameters

The results of the PK/PD linear and local regression smoothing (LOESS) regression analyses presented in Fig. 2 show a positive relationship between lapatinib plasma concentration and QTcF change from baseline ddQTcF. The relationship between lapatinib exposure and the mean ddQTcF per time point after the third dose are presented in Fig. 3. This shows a residual QTcF increase after two previous doses of lapatinib of 6.3 ms, and a maximum mean ddQTcF of 8.8 ms (4.1, 13.4) at 10 h post-dose.

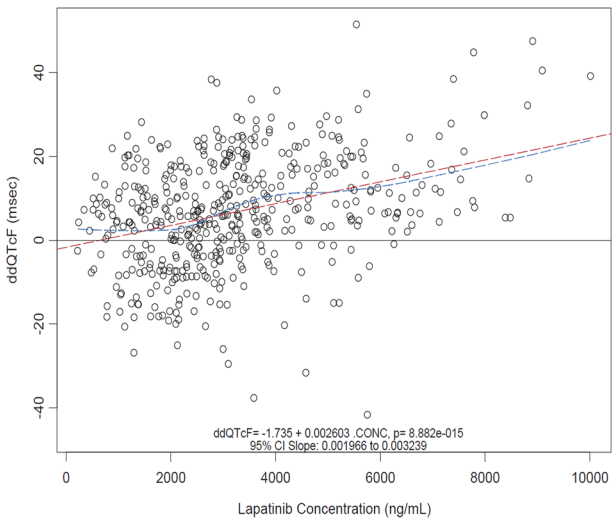

Fig. 2 Plot of mean baseline-adjusted, placebo time-matched increase in QTcF, ddQTcF vs lapatinib concentration. *x*-axis: actual lapatinib concentration (ng/mL). *y*-axis: mean baseline-adjusted, placebo time-matched increase in QTcF, ddQTcF (ms)

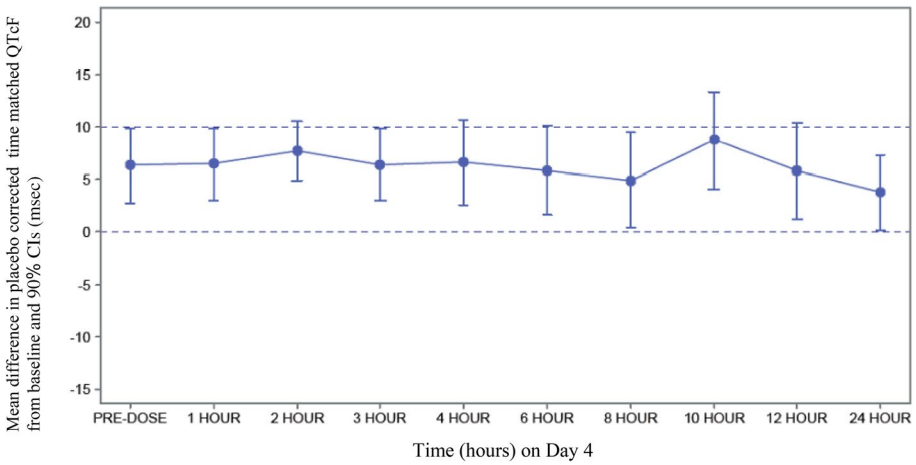

Fig. 3 Plot of mean difference in baseline-adjusted, placebo time-matched increase in QTcF, ddQTcF (90% CI) at each time point (evaluable population—EV population). *x*-axis = time (h) day 4. *y*-axis = mean baseline-adjusted, placebo time-matched increase in QTcF,ddQTcF (ms). Reference lines denote 0 and 10 ms

Table 2 Summary of results of repeated measures analysis of variance on QTcF change from baseline ($N = 52$), (evaluable population)

Planned time	Least square mean (ms)		Treatment difference (SE) (90% confidence interval)
	Placebo	Lapatinib	Lapatinib–placebo
Pre-dose	− 3.71	2.60	6.31 (2.15)–(2.72, 9.89)
1 h	0.66	7.09	6.43 (2.06)–(3.00, 9.87)
2	0.49	8.20	7.71 (1.73)–(4.82, 10.60)
3	2.78	9.19	6.42 (2.09)–(2.94, 9.89)
4	3.18	9.78	6.60 (2.43)–(2.54, 10.65)
6	-4.50	1.36	5.86 (2.57)–(1.57,10.14)
8	-5.09	-0.18	4.91(2.74)–(0.35,9.47)
10	-4.53	4.22	8.75 (2.8)–(4.08,13.42)
12	-1.49	4.27	5.76(2.76)–(1.16,10.36)
24	-1.25	2.51	3.75(2.16)–(0.15,7.36)

Effect of lapatinib on QTcF

The ddQTcF least square mean change was analyzed in the EV and PD populations, $N = 37$ and $N = 52$, respectively, after the third dose of lapatinib 200 mg. Table 2 and Fig. 4 present the mean placebo-corrected QTcF change from pre-treatment baseline compared to placebo (ddQTcF) in the EV population by time point. A residual ddQTcF of 6.3 ms was present at predose on the last treatment day due to the presence of lapatinib accumulation (Table 2). The maximum mean ddQTcF (90% CI) of 8.8 ms (4.1, 13.4) in the EV population and 7.9 ms (4.1-11.7) in the PD population were observed 10 h after the third dose of 2000 mg of lapatinib. In both populations, no subject had an increase in QTcF > 60 ms from baseline after receiving placebo or lapatinib. An increase over baseline in QTcF interval of > 30 ms

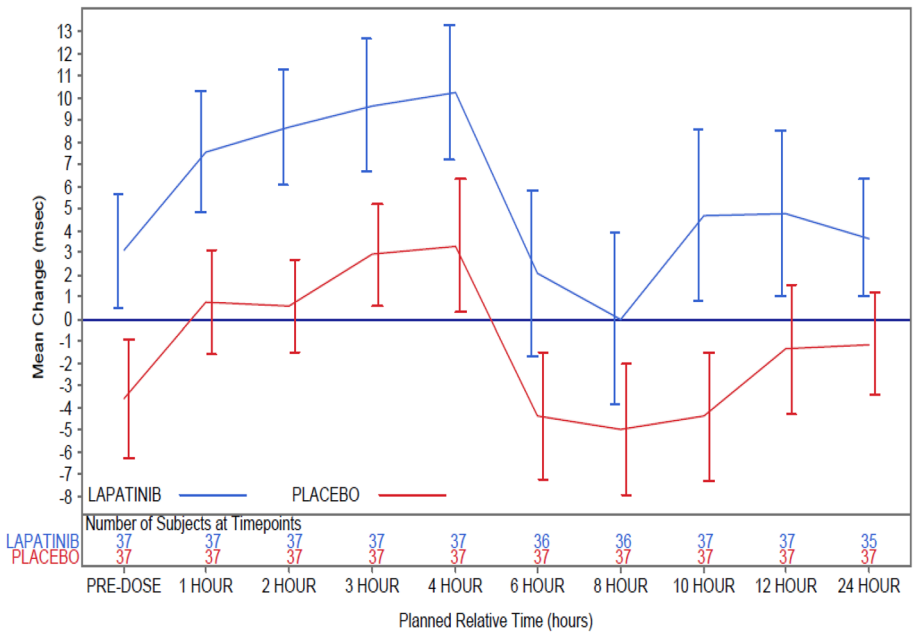

Fig. 4 Plot of mean change in baseline dQTcF interval by time in evaluable population. *x*-axis = relative time (h). *y*-axis = mean change in baseline QTcF (90% CI) ms

was reported for 2 subjects (4%) on placebo and for 5 subjects (10%) after receiving lapatinib in the PD population, and for 1 subject (3%) after receiving placebo and 2 subjects (5%) after receiving lapatinib in the EV population.

Effect of lapatinib on QTcB interval

Maximum mean (± SD) change in QTcB interval compared to baseline was 12.9 (± 8.5) ms after placebo and 19.9 (± 9.2) ms after treatment with lapatinib in the EV population. In the PD population, mean (± SD) maximum change in QTcB interval compared to baseline was 12.7 (± 8.1) ms after placebo and 20.0 (± 10.4) ms after treatment with lapatinib.

Effect of lapatinib on QTc*i*

Mean (± SD) maximum change in QTci (Individual) interval compared to baseline was 6.9 (± 10.9) ms after placebo and 16.0 (± 12.0) ms after treatment with lapatinib in the EV population. In the PD population, mean (± SD) maximum change in QTci interval compared to baseline was 7.5 (± 11.5) ms after placebo and 16.2 (± 11.9) ms after treatment with lapatinib.

Effect of lapatinib on other ECG parameters

The mean (± SD) maximum change in PR interval was 5.4 (± 5.5) ms after placebo and 9.4 (± 7.7) ms after treatment with lapatinib in the evaluable population. In the PD population, the mean (± SD) maximum treatment-related change in PR interval was 5.6 (± 5.9) ms after placebo and 9.6 (± 7.5) ms after treatment with lapatinib.

The mean (± SD) maximum change in QRS interval in the Evaluable population was 4.4 (± 3.7) ms after placebo and 4.2 (± 3.7) ms after treatment with lapatinib. In the PD population, the mean (± SD) maximum on-therapy change in QRS interval was 4.4 (± 3.7) ms after placebo and 5.2 (± 4.5) ms after treatment with lapatinib.

Effect of lapatinib on heart rate

The mean (± SD) of subjects' maximum on-therapy change in heart rate from baseline was 12.5 (± 9.5) beats per minute after placebo and 11.9 (± 10.2) beats per minute after treatment with lapatinib in the evaluable population. In the PD population, the mean (± SD) maximum on-therapy change in heart rate from baseline was 11.8 (± 8.8) beats per minute after placebo and 11.7 (± 9.6) beats per minute after treatment with lapatinib.

Adverse event and drug safety data

Forty-four of 58 subjects (76%) experienced at least one adverse event (AE), with 27 subjects (47%) experiencing AEs during lapatinib treatment that were assessed to be treatment-related. AEs leading to permanent discontinuation of study treatment occurred in 3% of subjects and were assessed as not treatment related. At least one AE was reported in 16 subjects on placebo (28%). The most frequently reported AE was diarrhea (4% of subjects on placebo and 29% of subjects during treatment with lapatinib), followed by anemia (16% of subjects during treatment with lapatinib), constipation (4% of subjects on placebo and 10% of subjects during treatment with lapatinib), nausea (7% of subjects on placebo and 9% of subjects during treatment with lapatinib) and fatigue (10% of subjects during treatment with lapatinib). The most frequently reported grade 3 AE with lapatinib dosing was hypokalemia (5%). The remaining grade 3/4 AEs include anemia, diarrhea, dyspnea, hyperbilirubinemia, hyponatremia, insomnia, esophagitis, and syncope, each reported in 1 subject (2%), a grade 4 AE (bacteremia) was reported for 1 subject (2%). Table 3 provides greater detail of the adverse events with a frequency greater than or equal to 3%, by maximum grade. There were no study treatment-related SAEs including arrhythmias or treatment-related deaths. One subject died during the study (18 days after last lapatinib dose), due to disease progression.

Discussion

The cardiovascular safety profile including the proarrhythmic potential of oral chronically administered tyrosine kinase inhibitors, as for other potent drugs in clinical development, is an important safety concern. The normative ICH E14 guidance to industry on QT liability was first published in 2005 but has been most recently updated in 2015 to guide industry in the evaluation of drugs under clinical development to characterize a drug's potential effects on arrhythmogenicity using QT/QTc interval as a surrogate [21, 22]. This study evaluated the effect of lapatinib on cardiac repolarization in patients with advanced solid malignancies. Definitive QT assessment with oncology drugs poses a challenge, therefore, a single sequence, placebo controlled high-dose crossover design was selected, but a positive control arm was omitted. The results show that after three doses of oral lapatinib 2000 mg 12-hourly, the maximum mean baseline-adjusted, placebo time-matched corrected QTcF was prolonged by 8.8 ms (90% CI 4.1, 13.4). The upper bound exceeds the 10 ms threshold of potential concern cited in the International Conference on Harmonization (ICH) E14 guideline [22]. The study findings are in agreement both

Table 3 Number of patients experiencing adverse events with an overall frequency greater than or equal to 3%, by MedDRA preferred term and maximum CTCAE grade

Adverse event	Maximum CTCAE grade					Total
	1	2	3	4	3+4	
Any event	20 (34%)	16 (28%)	7 (12%)	1 (2%)	8 (14%)	44 (76%)
Diarrhea	12 (21%)	4 (7%)	1 (2%)	0 (0%)	1 (2%)	17 (29%)
Anemia	2 (3%)	6 (10%)	1 (2%)	0 (0%)	1 (2%)	9 (16%)
Constipation	5 (9%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	6 (10%)
Fatigue	3 (5%)	3 (5%)	0 (0%)	0 (0%)	0 (0%)	6 (10%)
Nausea	5 (9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (9%)
Decreased appetite	2 (3%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	4 (7%)
Dyspepsia	3 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (5%)
Dyspnea	2 (3%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)	3 (5%)
Hypoalbuminemia	2 (3%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	3 (5%)
Hypokalemia	0 (0%)	0 (0%)	3 (5%)	0 (0%)	3 (5%)	3 (5%)
Hypomagnesaemia	3 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (5%)
Edema peripheral	2 (3%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	3 (5%)
Rash	3 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (5%)
Vomiting	3 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (5%)
Abdominal pain	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Anxiety	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Back pain	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Dizziness	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Dry skin	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Hyperbilirubinemia	1 (2%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)	2 (3%)
Hypertension	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Hypocalcemia	1 (2%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Hyponatremia	1 (2%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)	2 (3%)
Hypotension	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Pain in extremity	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)

with the in vitro hERG ion channel findings and an earlier uncontrolled open label observational study of lapatinib that reported a maximum QTcF increase of 8.6 ms [13, 15].

Our patient study did not include a positive control treatment arm, such as moxifloxacin, to establish assay sensitivity, neither could it be performed in healthy volunteers due to safety considerations. However, the study incorporated time-matched ECGs, triplicate ECG data, a placebo control, a higher than the approved lapatinib therapeutic dose, lapatinib pharmacokinetic sampling and a single sequence crossover design incorporating other established standards for rigorous prospective QTc studies. The geometric lapatinib mean C_{max} of 3920 ng/mL, (95% CI 3450, 4460) observed after the administration of supratherapeutic lapatinib doses and BID scheduling frequency selected for this study exceeds the C_{max} of 2430 ng/mL (95% CI 1570–3770 ng/mL) observed during therapeutic dosing of 1250 mg lapatinib daily [3]. However, pre-treatment baseline QTc interval of > 480 ms, and QTcF intervals > 500 ms or increases of > 60 ms from pre-treatment values during treatment should prompt therapeutic intervention including lapatinib dose reduction or, if ineffective, stopping lapatinib treatment [23, 24].

While QTc prolongation is considered a surrogate marker for a drugs potential to cause Torsades de Pointes and other tachyarrhythmias, individual QTc interval prolonging drugs do not all have the same arrhythmogenic potential [25]. Currently lapatinib is considered to have a possible risk of causing Torsades de Pointes [26].

As lapatinib is metabolized mainly by CYP3A, with minor contribution by CYP2C19 and CYP2C8 [27, 28], there is the potential concern that concomitant use of strong CYP3A inhibitors in particular, especially in the presence of CYP2C19 and CYP2C8 inhibitors, may increase lapatinib systemic exposure and potentially predispose to arrhythmias. Caution should, therefore, be exercised when prescribing lapatinib to patients also on concomitant medication that inhibit these CYP P450 iso-enzymes or is known to prolong the QTc. Since this study restricted the use of CYP3A4 inducers and inhibitors during the study period, the magnitude of such drug–drug interactions and the impact on QTcF, during standard oncology practice remains unknown.

Several studies and reviews of the cardiac repolarization effects of the small molecule tyrosine kinase inhibitors and their arrhythmogenic potential have been published [29–31]. Some agents (e.g., pazopanib, ddQTcF = 4.4 ms) having no clinically significant QT effect while treatment with others such as nilotinib are associated with Torsades de Pointes, and the FDA approved drug label carries a black box warning for QT prolongation and reports of sudden cardiac death. In each case, the benefit-risk profile for the particular TKI should be assessed with due care.

In conclusion, three doses of lapatinib 2000 mg administered 12 h apart has a relevant effect on the QT interval as defined by the threshold of potential concern outlined by the ICH E14. The data from this study support the recommendation that caution is needed in administering lapatinib to patients with electrolyte abnormalities such as hypokalemia or hypomagnesemia, to patients concomitantly taking strong CYP3A4 inhibitors, or patients using treatments known to prolong QT.

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Compliance with ethical standards

Conflict of interest SAC: Has declared no conflicts of interest regarding the conduct of this clinical trial or drafting the manuscript. HIH: Received research funding from GlaxoSmithKline, paid through Duke University Medical Center at the time of this work and drafting the manuscript. He is currently employed by Genentech/Roche and owns Roche stock. SS: Received research funding from GlaxoSmithKline/Novartis at the time of this work and has served on GlaxoSmithKline and Novartis Advisory Boards. DW: Has declared no conflicts of interest regarding the conduct of this clinical trial or drafting the manuscript. JPZ: Is employed by Novartis. LDL: Received research funding from GlaxoSmithKline/Novartis, paid through Dartmouth College to support the costs of this study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the participating institutional and/or national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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