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Phase I safety and pharmacokinetic study of cipatinib, an original dual tyrosine kinase inhibitor

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Abstract

Background: Cipatinib is a novel tyrosine kinase inhibitor against both *EGFR* and *HER2/neu.* This phase I trial was conducted to assess the safety, dose-limiting toxicities (DLTs), and maximum-tolerated dose of cipatinib in *HER2*-positive patients with advanced breast cancer.

Methods: Eligible adults with advanced breast cancer were administered cipatinib 200 mg/day (n = 3) as an initial dose, with escalating dosages of 400 mg (n = 4), 800 mg (n = 2), 1200 mg (n = 3), 1400 mg (n = 3), 1600 mg (n = 3), and 1800 mg (n = 2) in 21 day cycles. DLTs were monitored until the end of cycle 2. Physical examinations, vital signs, blood sampling for hematology, clinical chemistry, and pharmacokinetics were performed throughout the trial.

Results: Of the 26 subjects enrolled, 23 completed the trial. A total of 143 adverse events (AEs) were reported, of which 87 were associated with cipatinib treatment and comprised: neutropenia (38%), hypertriglyceridemia (15%), fatigue (15%), nausea (12%), fever (19%), and myocardial ischemia (19%). Six AEs were graded 3–4 (neutropenia, increases in aspartate aminotransferase, and total bilirubin, fatigue, dizziness and nodal tachycardia), but none of the AEs observed were considered to be DLTs.

Conclusion: This tolerability study revealed that despite a mild toxicity profile, cipatinib was well tolerated up to the anticipated maximum dosage of 1800 mg/m^2. Further clinical trials are warranted.

Introduction

EGFR/ErbB1 and HER2/ErbB2 are receptor tyrosine kinases (RTKs) and their ligand binding leads to homo-heterodimerization, autophosphorylation of their cytosolic tyrosine residues, and activation of their intrinsic kinase function, in which cellular proteins are phosphorylated. The signaling pathway is involved in cell growth, proliferation, differentiation, and migration.[1] Tyrosine kinase inhibitors (TKIs) compete with the ATP binding site of the catalytic domain of tyrosine kinases, with single or multiple target specificities.[2] Lapatinib, a reversible dual TKI of *HER2* and *EGFR* has shown efficacy in the treatment of patients with ErbB1-expressing and/or ErbB2-overexpressing metastatic cancers.[3] Although *HER2* targeting monoclonal antibodies have taken the leading role in targeted therapy,[4] lapatinib has its own unique advantages: it can be orally administered, crosses the blood-brain barrier, and has lower cardiac toxicity compared to trastuzumab.[5] Cipatinib is a dual TKI, which binds to the intracellular domain of both *EGFR* and *HER2* (K_i 3 nM and 13 nM, respectively) and like lapatinib, is a quinazoline. In preclinical experiments, cipatinib has been effective against human cancer cells, such as SK-OV-3, Calu-3, and BT-474, with an obvious concentration-related effect in a human tumor nude mice transplantation model that examined both *EGFR* and *HER2* overexpression (half maximal inhibitory concentrations [IC50] were 4.1 nM and 0.5 nM, respectively), and thus shows promise as a TKI. As the preclinical data strongly suggested that cipatinib should be tested in a human clinical trial, we launched this phase I trial from January to December 2012 to further clarify its clinical safety and to determine a specific safe dose.

Methods

Eligibility criteria

The China Food and Drug Administration (Approval No.: 2010L04211 and 2010L04213) and the ethical committee of the Chinese Academy of Medical Sciences Tumor Hospital approved the trial. Written informed consent was obtained from all participants. Patients enrolled in the trial met the following criteria: (i) women aged 18–65; (ii) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1; (iii) a life expectancy of at least 12 weeks; (iv) histological or cytological confirmation of advanced solid breast tumor, with demonstrated expression of *HER2* (reported grade 3+ staining intensity [on a scale of 0–3] by means of immunohistochemical analysis or grade 2+ staining intensity using immunohistochemical analysis with gene amplification on fluorescence in situ hybridization);[6] (v) standard therapies were either not administered or had been unsuccessful; (vi) adequate bone marrow (a hemoglobin concentration ≥ 9 g/dL, an absolute granulocyte count ≥ 1.5×10^9/L, and a platelet count ≥ 100×10^9/L); (vii) hepatic function (total bilirubin ≤ 1.5 × upper limit of normal [ULN], aspartate transaminase [AST] or alanine transaminase [ALT] ≤ 1.5 × ULN, and blood albumin ≥ 0.5 g/dL); (viii) renal function (creatinine ≤ ULN and Cr ≥ 50 mL/min as determined by the Cockcroft-Gault formula; (ix) blood lipids (cholesterol ≤ 7.75 mmol/L, trilaurin ≤ 2.5 × ULN); (x) cardiac function (a left ventricular ejection fraction ≥ 50%, normal electrocardiography [ECG], QT adjusted by Fridericia's formula [QTcF] < 470 ms for women/450 ms for men); (xi) any previous symptoms resulting from treatments had been cured, and the patient had received radiotherapy, chemotherapy, hormonal surgery, or molecule targeted therapy within the previous four weeks or treatment with nitrosourea or mitomycin within the previous six weeks; and (xii) a normal swallow function without absorption failure in the stomach and intestine.

Safety assessments

All subjects underwent a series of safety assessments: 12-lead ECG, vital signs, and physical examinations were performed at least once a week during the medication period and one, two, and three days before the medication was administered. Blood, urine, and stool examinations were repeated after 7, 21, and 42 days of successive drug treatment. ECOG PS, hepatic and renal function, blood lipids, blood electrolytes, coagulation function, and tetraiodothyronine were examined on days 21 and 42 after the initiation of treatment. Holter monitoring, ultrasonic echocardiography, myocardial protein, and enzyme spectrums (creatinine kinase-muscle brain [CK-MB], lactate dehydrogenase [LDH]), as well as human chorionic gonadotropin [HCG] tests of urine and serum levels for childbearing women were performed on day 42. Tumor biopsies were performed on day 20.

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3 (NCI-CTCAE v3).

Study treatments

This was a dose-climbing study in patients with advanced solid tumors. In this trial, the initial dose of cipatinib was 200 mg/day with escalation to 400, 800, 1200, 1400, 1600, and 1800 mg in seven groups of patients, following previous studies with lapatinib.[3,6] Each group consisted of at least three patients (Fig 1).

If there was a case of dose limiting toxicity () within the adaption time (1–5 days), three more subjects were added to the group; otherwise they were transferred into the next experimental dose group. If two cases of DLTs were recorded in the former three or six subjects, dose escalation was ceased. Cipatinib was orally administered once daily. Single dosage began on day 1, while successive dosage started at day 5 after observation of the previous four days. After completing the initial 21 days of the study, patients resumed once-daily cipatinib until disease progression, treatment-emergent toxicities, withdrawal of consent, or two cycles were completed.

Pharmacokinetic assessments

Preliminary experiments of single doses and multi-successive doses were performed at 200 mg/day to determine the half-life ($t_{1/2}$) of cipatinib. Formal pharmacokinetic tests were performed using > 200 mg/day single doses or multi-successive doses after the preliminary tests were completed. The blood collection point was designed based on the results from preliminary tests of cipatinib in the high, moderate, and low dose groups. At 1, 4, 5, 6, 7, and 21 days, blood was analyzed 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours after cipatinib uptake for single and multiple dose pharmacokinetic studies. At each time point, 3–4 mL of venous blood was collected and centrifuged at 3500 rpm for 10 minutes until the serum was separated. Samples were then stored at −80°C for subsequent analysis.

Pharmacokinetic analyses were performed using WinNonlin software (Pharsight, Mountain View, CA, USA). Non-compartmental standard methods were used to calculate the area under the serum concentration versus time curve within the dosing interval (AUCτ), peak serum concentration (C_{max}), the time of C_{max} and the trough

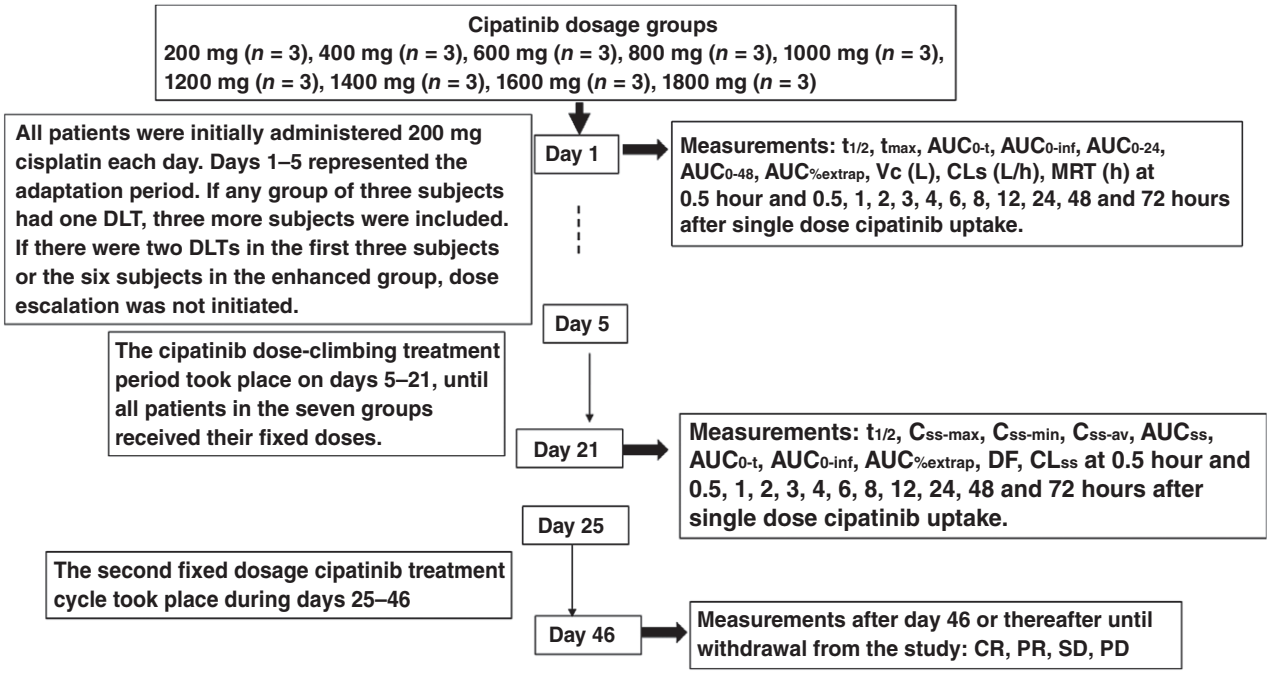

Figure 1 Scheme of therapy and outcome measurements. AUC, area under the curve; CLs, clearances; Cmax, peak serum concentration; CR, complete response; Css, steady-state concentration; DLT, dose limiting toxicity; MRT, mean residence time; PD, progressive disease; PR, partial response; SD, stable disease; Vc, volume of distribution.

concentration at steady-state (C_{min}). The drug concentration time curve (AUC), T_{max}; minimum, maximum, and average steady-state clearances (C_{ss_min}, C_{ss_max}, C_{ss_av}); and the mean residence time (MRT) in addition to apparent volume of distribution (V_c) were calculated for each time point.

Evaluation of clinical activity

Response Evaluation Criteria in Solid Tumors (RECIST) was used to assess disease status before treatment and after two cycles (each comprising three weeks cipatinib application until withdrawal from the study) in time intervals of four weeks.[7]

Results

Patient characteristics

The study population consisted of women with *HER2*-positive advanced breast cancer. Twenty-six patients enrolled in the trial were administered cipatinib between January 2011 and September 2012; 23 (88.5%) completed the dosage course. Patients were randomly assigned to one of seven daily dose cohorts (200 mg [n = 3], 400 mg [n = 7], 800 mg [n = 3], 1200 mg [n = 3], 1400 mg [n = 4], 1600 mg [n = 3], and 1800 mg [n = 3]). Patient characteristics are presented in Table 1. The dosage of cipatinib was ultimately calculated according to body surface area.

Of the 26 patients included in the trial, 23 finally received one response evaluation. Three patients (11.5%) discontinued the study: transaminase elevation did not meet the requirements of the experimental protocol; grade 3 arrhythmia associated with fever; and disease progression. One subject (3.8%) exhibited a partial response (PR) but none achieved a complete response (CR), leading to an overall response rate (ORR) of 3.8%. Four subjects (15.4%) had stable disease (SD) and 18 (69.2%) developed progressive disease (PD) (Table 2).

Safety and tolerability

Twenty-six subjects (100%) experienced AEs, 11 of which suffered grade 3 or 4 AEs (Fig 2). The total number of AEs was 143; 87 were associated with cipatinib. Drug-related AEs occurred in 20 patients (200 mg [n = 3], 400 mg [n = 4], 800 mg [n = 2], 1200 mg [n = 3], 1400 mg [n = 3], 1600 mg [n = 3], and 1800 mg [n = 2]). The most frequently reported drug-related AE was neutropenia (38%), followed by hypertriglyceridemia (15%) and fatigue (15%). Other treatment-related AEs included nausea (12%), fever (19%), myocardial ischemia (19%), coughing (12%), dizziness (27%), skeletal muscle pain (42%), upper

Table 1 Patient characteristics after different cipatinib dosages

Characteristics	Cipatinib dose (mg/day) cohorts						
	200 mg	400 mg	800 mg	1200 mg	1400 mg	1600 mg	1800 mg
No. of patients	3	7	3	3	4	3	3
Age, years (median)							
Median	50	44	47	57	46	52	48.5
Range	37–52	27–56	44–52	48–64	42–54	38–59	27–64
Body surface area (median, range)	1.58 (1.54–1.70)	1.69 (1.51–1.91)	1.78 (1.77–1.79)	1.75 (1.64–1.79)	1.61 (1.60–1.72)	1.60 (1.52–1.78)	1.70 (1.61–1.91)
Prior treatment							
Chemotherapy	10	24	20	10	19	8	14
Hormonal therapy	2	1	2	2	2	3	4
Targeted therapy	0	5	0	0	2	1	1
Radiotherapy	3	6	3	1	1	1	3
Median administration period (months)	1.5	1.4	5	2.3	4.3	1.3	1
HER2-overexpression, n (%)	100%	100%	100%	100%	100%	100%	100%

Table 2 The baseline anti-tumor outcomes of advanced breast cancer patients after different dosages of cipatinib

Dose level (mg/day)	No. of patients	Median treatment duration (weeks), range	Response by RECIST, *n* (%)				
			CR	PR	SD	PD	Not evaluated
200	3	4				3 (11.5)	
400	7	4		1 (3.8)		4 (15.4)	2 (7.7)
800	3	8			1 (3.8)	2 (7.7)	
1200	3	8			2 (7.7)	1 (2.8)	
1400	4	12				3 (11.5)	1 (3.8)
1600	3	4			1 (3.8)	2 (7.7)	
1800	3	4				3 (11.5)	
Total	26		0 (%)	1 (3.8)	4 (15.4)	18 (69.2)	3 (11.5)

CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

respiratory tract infection (35%), urine occult blood (12%), urinary tract infection (15%), peripheral nerve toxicity (12%), pruritus (12%), leukopenia (38%), and decreased hemoglobin (12%). Eleven AEs graded 3 or 4 included neutropenia (3.9%), increases in AST (3.9%) and total bilirubin (TBIL; 3.9%), fatigue (3.9%), dizziness (3.9%), and nodal tachycardia (3.9%). Two serious AEs (SAEs), right arm cellulitis without neutropenia and increases in grade

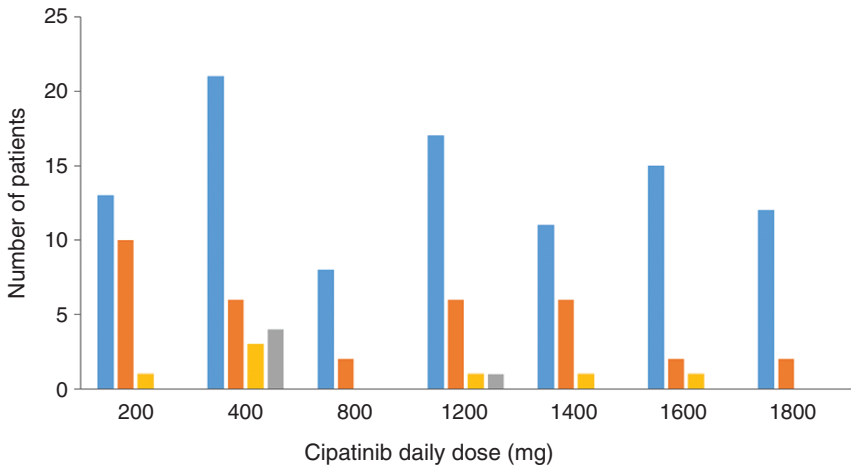

Figure 2 Distribution of adverse events (AEs) within the treatment groups. Grade 1 AE, Grade 2 AE, Grade 3 AE, Grade 4 AE.

Table 3 Adverse events in the different dose level groups

Adverse event	Dose level (mg/day)							Total	Incidence
	200	400	800	1200	1400	1600	1800		
Number of patients	3	7	3	3	4	3	3	26	
Nausea	1 (1/3)	1 (1/7)	0	1 (1/3)	0	0	0	3	12% (3/26)
Coughing	1 (1/3)	1 (1/7)	0	0	0	0	1 (1/3)	3	12% (3/26)
Myocardial ischemia	1 (1/3)	2 (2/7)	0	1 (1/3)	0	1 (1/3)	0	5	19% (5/26)
Dizziness	1 (1/3)	3 (3/7)	0	0	2 (2/4)	1 (1/3)	0	7	27% (7/26)
Fatigue	1 (1/3)	1 (1/7)	0	0	1 (1/4)	0	1 (1/3)	4	15% (4/26)
Skeletal muscle pain	2 (2/3)	2 (2/7)	2 (2/3)	1 (1/3)	0	2 (2/3)	2 (2/3)	11	42% (11/26)
Upper respiratory tract infection	1 (1/3)	0	2 (2/3)	2 (2/3)	3 (3/4)	1 (1/3)	0	9	35% (9/26)
Urine occult blood	1 (1/3)	2 (2/7)	0	0	0	0	0	3	12% (3/26)
Urinary tract infection	2 (2/3)	1 (1/7)	0	0	0	1 (1/3)	0	4	15% (4/26)
Fever	1 (1/3)	1 (1/7)	1 (1/3)	1 (1/3)	0	1 (1/3)	0	5	19% (5/26)
Peripheral nerve toxicity	0	1 (1/7)	0	2 (2/3)	0	0	0	3	12% (3/26)
Pruritus	0	0	0	1 (1/3)	1 (1/4)	0	1 (1/3)	3	12% (3/26)
Leukopenia	2 (2/3)	1 (1/7)	0	3 (3/3)	2 (2/4)	1 (1/3)	1 (1/3)	10	38% (10/26)
Neutropenia	2 (2/3)	0	0	3 (3/3)	2 (2/4)	2 (2/3)	1 (1/3)	10	38% (10/26)
Decreased hemoglobin	0	1 (1/7)	0	1 (1/3)	0	1 (1/3)	0	3	12% (3/26)
Hypertriglyceridemia	1 (1/3)	0	0	0	0	2 (2/3)	1 (1/3)	4	15% (4/26)
AEs related to drug	17	17	5	16	11	13	8	87	60.8% (87/143)
AEs not related to drug	7	17	5	9	7	5	6	56	39.2% (56/143)
Total	24	34	10	25	18	18	14	143	

AE, adverse event.

4 TBIL occurred in two patients in the 200 mg/day and 1200 mg/day groups, respectively, but improved after interrupting cipatinib and administering appropriate symptomatic treatment (Table 3).

Otherwise, vital signs and physical examinations were normal and no meaningful changes during the treatments were observed in chest X-rays and ultrasound images or adverse impacts on stool, blood coagulation function, serum urea nitrogen, serum creatinine, or blood electrolytes.

Changes of t_{max} and $t_{1/2}$ of cipatinib plasma concentrations in the different dosage treatment cohorts

After the administration of single doses, successive administration of cipatinib commenced for 21 days as a first cycle.

The concentration of cipatinib reached a peak (t_{max}) at 1.67–9.33 hours after single oral doses of 200, 400, 800, 1200, 1400, 1600, and 1800 mg at day 1, and then declined in a monophasic manner as a result of elimination. The average t_{max} values after 200 mg (2.33 hours), 400 mg (2.57 hours), 800 mg (3.00 hours), 1200 mg (1.67 hours), and 1400 mg (5.00 hours) were similar, while the average t_{max} after 1600 mg and 1800 mg was 9.33 hours, clearly longer than the other doses, which was likely caused by the t_{max} values of subject No. 22 in the 1600 mg cohort and subject No. 26 in the 1800 mg cohort of 24 hours (Table 4). The t_{max} values after successive administrations had almost the same profile as a single oral dose of cipatinib (Table 5).

For a single dose, the average $t_{1/2}$ values of 200, 400, 800, 1200, and 1800 mg were 12.0, 11.2, 12.8, 10.9, and 13.9 hours, but the average $t_{1/2}$ times of 1400 mg and 1600 mg were 22.6 and 33.1 hours, likely caused by poor absorption in two patients (No. 17 and No. 20) in the 1400 mg cohort, and three patients in the 1600 mg cohort, which suggested that these patients probably exhibited enterohepatic circulation and indicated that cipatinib concentrations can be easily accumulated in the body (Table 4). After successive cipatinib applications, $t_{1/2}$ values also varied between 12.9 and 29.8 hours, but were slightly higher than in the initial single cipatinib application period at day 1 (Table 5).

Pharmacokinetics of different dosages of cipatinib treatments

For the single dose-levels of cipatinib at day 1 with 200, 400, 800, 1200, 1400, 1600, and 1800 mg, C_{max} was 23.4, 79.5, 85.9, 276, 68.1, 33.5, and 136 ng/mL, respectively. Apparent oral clearance (CL/F) was 954, 1730, 1770, 1140, 2990, 3800, and 3830 L/h respectively, and the apparent volume of distribution (Vc/F) was 14 900, 26 800, 31 100, 16 900, 90 000, 228 000, and 68 100 L. MRT was 12.2, 11.5, 10.5, 11.1, 20.0, 23.6, and 15.9 hours. The CL/F and Vz/F values suggested that

Table 4 Pharmacokinetics of single dose cipatinib on study day 1

Dose level (mg/day)	$t_{1/2}$ (h)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	AUC_{0-48} (h*ng/mL)	$AUC\%_{extrap}$ (%)	Vc/F (L)	CL/F (L/h)	MRT (h)
200	12.0	2.3	23.4	239	244	199	230	2.0	14 900	954	12.2
400	11.2	2.6	79.5	539	548	437	513	3.3	26 800	1730	11.5
800	12.8	3.0	85.9	548	556	488	538	1.7	31 100	1770	10.5
1200	10.9	1.7	276.0	1590	1600	1310	1530	1.3	16 900	1140	11.1
1400	22.6	5.0	68.1	537	570	390	500	7.0	90 000	2990	20.0
1600	33.1	9.3	33.5	639	752	276	508	18.1	228 000	3800	23.6
1800	13.9	9.3	136.0	2180	2270	1090	2010	2.7	68 100	3830	15.9

AUC, area under the curve; CL/F, apparent oral clearance; Cmax, peak serum concentration; MRT, mean residence time; Vc/F, apparent volume of distribution.

cipatinib has a low degree of biological availability (< 10%), as well as an in vivo distribution < 24.8 L/kg (Table 4). After successive daily oral dosages of cipatinib at 200, 400, 800, 1200, 1400, 1600, and 1800 mg, the steady-state AUC of cipatinib was greater than after a single administration of AUC0-24 (day 1) after 21 days, a result which indicated that it took time to reach a steady-state serum concentration and suggested that drug accumulation occurred in the body (Tables 4–5).

Discussion

In the present trial, the dose levels were chosen with reference to previous studies of lapatinib.[3,6] The clinical dose with effective anti-tumor activity was 650 mg/day and the therapeutic dose in combination with capecitabine was 1250 mg/day. The loading (200 mg/day) and peak doses (1800 mg/day) of cipatinib were set up according to preclinical experimental and safety data.

In all patients (n = 26) 143 cases of AEs were detected, of which 87 were drug-related (60.8%). AEs were mostly grade 1 or 2, but two SAEs were recorded at the 400 mg and 1200 mg doses, which were cellulitis without neutrophils and grade 4 elevated TBIL, respectively, but were improved by symptomatic treatment. No DLTs were observed at doses ranging from 200 mg to 1800 mg daily in patients with ErbB2-overexpressing advanced breast cancer.

In phase I studies of lapatinib (EGFl0004),[3] 67 patients with *EGFR* or *HER2* overexpression were offered this drug at doses ranging from 500 mg to 1600 mg over 20 days. The most frequently reported AEs in 44 patients were diarrhea (42%), rash (31%), nausea (13%), and fatigue (10%). In the present trial, the most frequently observed AEs were neutropenia (38%), fever (19%), myocardial ischemia (19%), hypertriglyceridemia (15%), fatigue (15%), and nausea (12%). Apparently, there is a small distinction between the side effects of lapatinib and cipatinib. The rate of dermal toxicity was higher with lapatinib, whereas hematotoxicity was milder (31% vs. 8%). Additionally, digestive tract reactions were obviously more intense after lapatinib treatment (55% vs. 7.7%).

It should be noted that a potential effect on lipid metabolism and the cardiovascular system is predicted to occur during long-term treatment. However, all toxicities could be ameliorated by symptomatic treatment and did not constitute DLTs. No anaphylaxis was observed during the trial. Detrimental effects were not detected at the injection site or in liver and renal function tests. Although a high concentration was administered to the large dose group of patients, the subjects exhibited good tolerance to the drug and roughly identical incidences of AEs.

Briefly, consecutive administrations of cipatinib are a safe and feasible treatment regimen in patients with advanced breast cancer. Phase II studies are being planned to assess the anti-tumor efficacy of this regimen, and additional preclinical studies are ongoing to develop even more

Table 5 Pharmacokinetics of successive cipatinib doses evaluated on study day 21

Dose level (mg/day)	$t_{1/2}$ (h)	t_{max} (h)	C_{ss-max} (ng/mL)	C_{ss-min} (ng/mL)	C_{ss-av} (ng/mL)	AUC_{ss} (h*ng/mL)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	$AUC\%_{extrap}$ (%)	DF (%)	CL_{SS} (L/h)
200	21.5	4.7	58.3	7.8	18.9	453	609	639	10.0	293	730
400	12.9	2.2	151.0	15.3	44.6	1070	1330	1350	1.3	377	760
800	16.2	1.5	363.0	28.3	92.6	2220	2720	2800	2.9	343	393
1200	16.3	2.7	361.0	58.5	126.0	3020	4120	4280	3.7	236	430
1400	14.7	3.3	358.0	30.0	141.0	3400	4310	4410	3.0	202	656
1600	29.8	3.7	530.0	56.4	208.0	4980	6700	7560	9.2	233	344
1800	25.1	2.0	306.0	52.8	106.0	2550	3670	4190	12.5	169	949

AUC, area under the curve; CLss, steady-state clearance; Css, steady-state concentration; DF, coefficient of fluctuation; MRT, mean residence time.

effective approaches to enhance chemo-delivery into tumor tissues. The clinical effectiveness of anti-tumor activity will be further investigated in the near future.

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Disclosure

No authors report any conflict of interest.

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