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Optimally tolerated dose of lapatinib in combination with docetaxel plus trastuzumab in first-line treatment of HER2-positive metastatic breast cancer

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Background: This phase IB, open-label, dose-escalation study evaluated the safety, tolerability, and optimally tolerated regimen (OTR) of lapatinib in combination with docetaxel and trastuzumab in patients with previously untreated stage IV metastatic breast cancer (MBC) tumors overexpressing human epidermal growth factor receptor 2 (HER2).

Patients and methods: Evaluated dose regimens included lapatinib (500–1500 mg/day), docetaxel (triweekly; 60–100 mg/m^2), and trastuzumab (weekly; 2 mg/kg fixed dose); prophylactic granulocyte colony-stimulating factor was included with regimens with ≥750 mg/day lapatinib. End points included OTR and safety/tolerability (primary), overall response rate (ORR), and pharmacokinetics (secondary).

Results: None of the patients ($N = 53$) experienced dose-limiting toxic effects (DLTs) at the highest dose level; thus, the OTR of lapatinib with 100 mg/m^2 docetaxel was not determined. Common adverse events included diarrhea, nausea, alopecia, fatigue, and rash; grade 3/4 (≥2 patients) were neutropenia, diarrhea, leukopenia, peripheral neuropathy, and rash. Seven patients had DLTs (cycle 1). In 45 patients with measurable disease confirmed by bone scan, investigator-assessed ORR was 31%; without bone scan, confirmation was 64%; 8 patients without measurable disease were evaluated as stable. Lapatinib/docetaxel plasma concentrations were positively associated with complete response.

Conclusions: Lapatinib/docetaxel/trastuzumab is a feasible and well-tolerated treatment of untreated HER2-positive stage IV MBC. Two lapatinib/docetaxel OTR doses were recommended (1250 mg/75 mg/m^2; 1000 mg/100 mg/m^2).

Clinical trial number: NCT00251433.

Key words: docetaxel, HER2/ERBB2, lapatinib, metastatic breast cancer, trastuzumab, tyrosine kinase inhibitor

introduction

Approximately 15%–20% of invasive breast cancers have alterations, usually amplifications, in the human epidermal growth factor receptor 2 (HER2) gene [1, 2]. Patients whose cancer exhibit this molecular lesion have an inferior prognosis compared with those patients with HER2 'normal' disease [2]. When added to conventional chemotherapy, trastuzumab, a humanized monoclonal antibody that interacts with the extracellular domain of HER2, improves the time to progression and overall survival for patients with HER2-altered metastatic disease [3]. Although a minority of these patients appear to have durable remissions, most develop progressive cancer, usually within 1 year [4].

Other HER2 antagonists have entered the clinic. Lapatinib is a small molecule that inhibits the intracellular tyrosine kinase domains of both HER2 and the epidermal growth factor (EGF) receptor [5]. In a pivotal clinical trial in patients with HER2-positive metastatic breast cancer (MBC) who had prior exposure to anthracyclines, trastuzumab, and taxanes, treatment with lapatinib and capecitabine resulted in statistically improved progression-free survival (PFS) compared with treatment with capecitabine alone ($P < 0.001$) [6]. As a result, lapatinib has been licensed in many jurisdictions in this specific clinical setting.

Preclinical studies suggested that combinations of trastuzumab and lapatinib might be superior to single HER2 antagonists. First, despite having the same target, differential mechanisms of resistance to trastuzumab and lapatinib have been described. Activation or mutation of PI3K, a downstream mediator of HER2 signaling, confers resistance to trastuzumab, but not to lapatinib in HER2-altered cells [7]. Further,

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lapatinib was synergistic with trastuzumab and with the combination of trastuzumab and chemotherapy [5, 8].

Combination therapy with lapatinib and trastuzumab produced significantly improved overall survival for heavily pretreated patients with trastuzumab-refractory HER2-positive MBC compared with lapatinib alone ($P = 0.026$), an observation that was particularly striking given the fact that trastuzumab had already failed in these patients [9, 10]. Further support for dual targeting of HER2 was provided by two studies in earlier-stage disease in the NeoAdjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NeoALTTO) and National Surgical Adjuvant Breast and Bowel Project B-41 (NSABP B-41); patients with HER2-altered disease received preoperative chemotherapy with trastuzumab and/or lapatinib. In both trials, the rate of pathologically complete response of tumor was higher for combined HER2 antagonism, although the difference reached statistical significance only in NeoALTTO ($P = 0.0001$) [11, 12].

Docetaxel is the most active chemotherapeutic drug in the treatment of MBC and has demonstrated marked *in vitro* synergy with HER2 antagonists [13, 14].

Our phase IB study was designed to evaluate the safety and tolerability of lapatinib in combination with docetaxel and trastuzumab in previously untreated patients with MBC whose tumors overexpress HER2 and to determine the recommended optimally tolerated regimen (OTR) for further trials in patients with untreated HER2-positive MBC.

patients and methods

study design and objectives

EGF100161 was a phase IB, open-label, multicenter, dose-escalation study of oral lapatinib given in combination with docetaxel plus trastuzumab in patients with previously untreated HER2 overexpressing MBC (ClinTrials.gov: NCT00251433). This study was conducted in accordance with Good Clinical Practice, all applicable regulatory requirements, and the guiding principles of the 2008 Declaration of Helsinki. Ethics committees or institutional review boards at the participating institutions approved the study protocol. All patients provided written informed consent before study entry.

The primary end points were to determine the OTR of lapatinib when administered in combination with docetaxel plus trastuzumab and to assess the safety and tolerability of this triple-drug regimen. The OTR was defined as the dose level at which no more than one of six patients experience a dose-limiting toxic effect (DLT) after completing one treatment cycle. Secondary end points included the assessment of response rate (i.e. complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]) and pharmacokinetics.

patient eligibility

Eligible patients had to have histologically or cytologically confirmed stage IV metastatic MBC with documentation of HER2 overexpression (i.e. immunohistochemistry 3 + and/or fluorescent *in situ* hybridization-positive by local assessment), evaluable disease (including bone lesion–only disease), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with stable central nervous system (CNS) metastases or leptomeningeal involvement were eligible only if they were not talking oral corticosteroids or enzyme-inducing anticonvulsants. Any radiation therapy had to have been completed at least 4 weeks before enrollment and with recovery from all treatment-related toxic effects. Additional inclusion criteria included cardiac left ventricular ejection fraction (LVEF) within the institutional range of normal and adequate hematologic, hepatic, and renal function. Patients who had received adjuvant or neoadjuvant taxane treatment were eligible if disease progression occurred more than 6 months after completion of this therapy. Patients treated with HER2 inhibitors in the adjuvant setting were eligible if they had experienced a minimum 6-month disease-free interval after this adjuvant therapy.

Patients with CNS-only disease were not eligible for this study. Other reasons for study exclusion were a history of current active hepatic or biliary disease; grade 2 or higher peripheral neuropathy; prior systemic therapy for metastatic disease (except for one line of hormonal therapy); and uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure.

treatment

The study regimen consisted of weekly intravenous (IV) trastuzumab (a loading dose of 4 mg/kg followed by a fixed dose of 2 mg/kg IV), docetaxel given every 3 weeks at escalating doses (60, 75, and 100 mg/m^2), and once-daily oral lapatinib given at escalating doses (500, 750, 1000, 1250, and 1500 mg).

After a protocol amendment, which was initiated following the occurrence of cases of febrile neutropenia, prophylactic granulocyte colony-stimulating factor (G-CSF) was given to all patients enrolled in cohorts treated at lapatinib doses of 750 mg or higher.

Dose escalation followed a classic 3 + 3 design, whereby DLTs were assessed during the first treatment cycle (Table 1). If no DLTs were observed with the first three patients during the first cycle at a particular dose level, recruitment started at the next dose level. If one patient experienced a DLT, an additional three patients were enrolled at that dose level. DLTs were defined as grade 4 granulocytopenia for at least 5 days, or grade 3 or 4 granulocytopenia with fever (38.5°C) or documented infection; grade 4 thrombocytopenia; grade 3 or higher diarrhea with maximal antidiarrheal therapy; grade 3 or higher nonhematologic systemic toxic effect (excluding alopecia and grade 3 nausea); grade 3 left ventricular cardiac dysfunction or a 20% decrease from baseline in LVEF that is also below the institution's lower limit of normal (LLN); inability to begin the next course of treatment within 2 weeks of scheduled dosing due to unresolved toxic effect; and any grade 2 toxic effect considered to be a DLT.

assessments

Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used to evaluate response in terms of CR, PR, SD, and PD [15]. Tumor assessments were carried out every two treatment cycles (i.e. every 6 weeks). The same diagnostic method, computed tomography or magnetic resonance imaging, was used throughout the study to evaluate a specific lesion. Bone scans were used to confirm CR or PR.

Adverse events (AEs) and changes from baseline laboratory values were evaluated throughout the study to assess safety and tolerability. Toxic effect assessments were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3. Cardiac monitoring (by echocardiogram or multigated acquisition scan) was carried out at screening, weeks 3 and 9, and then every 9 weeks. Patients with a minimum 20% relative decrease from baseline in LVEF and below the institution's LLN had to have a repeat evaluation of ejection fraction 1–2 weeks later, with results reviewed by an independent board.

pharmacokinetic analyses

Patients who agreed to pharmacokinetic sampling were asked to withhold lapatinib until arrival to the clinic on day 1 of cycles 1 and 2. In this subset of patients, blood samples were obtained before lapatinib dose, immediately before termination of docetaxel infusion, 4-h post-lapatinib dose, and 4-h

Table 1. Dosing schedule

Dose level	Patients ($N = 53$)	Lapatinib (mg/oral/OD)	Docetaxel (mg/m^2/IV/q3 weeks)	Trastuzumab	Growth factor
0	6	500	60	4 mg/kg first week followed by 2 mg/kg once a week	no
1	3	500	75	4 mg/kg first week followed by 2 mg/kg once a week	no
1A	12 (6 + 6)[a]	750	75	4 mg/kg first week followed by 2 mg/kg once a week	no → yes[b]
1B	5	1000	75	4 mg/kg first week followed by 2 mg/kg once a week	yes
1C	4	1250	75	4 mg/kg first week followed by 2 mg/kg once a week	yes
1D	3	1500	75	4 mg/kg first week followed by 2 mg/kg once a week	yes
2	5 (2 + 3)[c]	500	100	4 mg/kg first week followed by 2 mg/kg once a week	no → yes[b]
3	6	750	100	4 mg/kg first week followed by 2 mg/kg once a week	yes
4	6	1000	100	4 mg/kg first week followed by 2 mg/kg once a week	yes
5	3	1250	100	4 mg/kg first week followed by 2 mg/kg once a week	yes

[a]Six patients without prophylactic growth factor.
[b]After protocol amendment.
[c]Two patients without prophylactic growth factor.
OD, once daily; IV, intravenous.

post-docetaxel infusion. Relationships between these intervals of exposure and measures of therapeutic or toxicologic response were explored. This sampling scheme was designed to provide plasma concentrations representing the peak of exposure to each agent to explore possible correlation with any AEs that might occur. Any incidence of neutropenia was characterized by pharmacodynamic modeling for a relationship to plasma concentrations, using nonlinear regression (WinNonlin 5.2 software, Pharsight Corporation, Mountain View, CA) to fit a sigmoidal E_{max} model relating decreases in neutrophils to drug concentrations.

statistical analysis

All analyses were carried out on the safety population, which comprised patients who received at least 1 dose of study treatment. No specific hypotheses were tested in this phase IB study. There were no safety or efficacy comparisons. The primary efficacy analysis was to evaluate overall response rate (ORR), defined as the percentage of patients achieving a confirmed CR or PR, based on confirmed responses from the investigator assessment of best overall response. Exact 95% confidence intervals for tumor response rates were calculated. PFS, clinical benefit response rate, duration of response, time to response, and overall survival were not calculated because of the limited sample size within dose levels and because the OTR was not achieved.

results

patient population

Between January 2006 and June 2010, 53 patients were recruited into 10 dose levels from five sites in three countries (France, Ireland, and United States). None of the patients experienced a DLT at the highest dose level tested; thus, the OTR dose regimen of lapatinib with the higher docetaxel dose (100 mg/m^2) was not determined.

Patients had a median age of 51 years and 83% had an ECOG performance status of 0 (Table 2). The majority of patients presented with infiltrating ductal carcinoma (83%) and with visceral disease (70%); 74% were estrogen/progesterone receptor positive. The median number of metastatic disease sites was 3 and the most common metastatic disease sites at baseline were the lymph nodes (60%), bone (55%), lung (38%), liver (36%), and breast (23%). Most patients (62%) received prior adjuvant treatment, including chemotherapy (51%), radiation therapy (51%), hormonal therapy (47%), and prior trastuzumab (17%). The median time since initial diagnosis of breast cancer was 144.7 weeks.

The median time of exposure to lapatinib ranged from 18.4 to 123.6 weeks (supplementary Table S1, available at *Annals of Oncology* online). Most patients (83%) discontinued lapatinib treatment, with the most common reasons being disease progression (51%) and AEs (17%). AEs leading to treatment discontinuation included diarrhea in three patients (6%) and one patient (2%) each with colitis, vomiting, fatigue, general physical deterioration, cardiac failure, pustular rash, decreased LVEF, dehydration, hyperkalemia, hyponatremia, renal failure, pulmonary fibrosis, onycholysis, and hypotension. The median number of docetaxel cycles ranged from 6 to 9; the median number of trastuzumab cycles ranged from 6 to 41.

Table 2. Patient characteristics

Characteristic	All patients ($N = 53$)
Age, median (years)	51.0
Range	22–67
Race, *n* (%)	
White	52 (98)
Asian	1 (2)
ECOG performance status, *n* (%)	
0	44 (83)
1	9 (17)
Histology, *n* (%)	
Adenocarcinoma	5 (9)
Infiltrating ductal not otherwise specified	44 (83)
Lobular invasive	3 (6)
Other	1 (2)
Estrogen/progesterone receptor status, *n* (%)	
Positive	39 (74)
Negative	14 (26)
Metastatic sites, median (range)	3.0 (1–5)
Visceral disease, *n* (%)	37 (70)
Time since initial diagnosis, median (range) (weeks)	144.71 (1.4–670.6)
Prior adjuvant treatment, *n* (%)	
Any therapy	33 (62)
Chemotherapy	27 (51)
Trastuzumab	9 (17)
Hormonal therapy	25 (47)

ECOG, Eastern Cooperative Oncology Group.

safety

The most common all-grade AEs observed at all dose levels were diarrhea (87%), nausea (72%), alopecia (70%), fatigue (55%), and rash (51%) (Table 3). The most common grade 3 and 4 AEs that occurred in two or more patients included neutropenia, diarrhea, leukopenia, peripheral neuropathy, and rash. The most common grade 4 event was neutropenia, which was experienced by one patient at dose level 1, five at dose level 1A, and three at dose level 2. The incidence of neutropenia was lower at the higher dose levels after the introduction of prophylactic growth factors. One patient at dose level 2 had leukopenia, which was the only other grade 4 toxic effect.

A total of seven patients had DLTs during cycle 1 (supplementary Table S2, available at *Annals of Oncology* online). Three had febrile neutropenia (two at dose level 1A; one at dose level 2), one had neutropenic sepsis (dose level 2), two had diarrhea (one each at dose levels 0 and 3), and one had rash (dose level 1A).

All cases of decreased LVEF were toxic effect grade 1 or 2. Relative decreases of at least 20% in LVEF that were also below the LLN were seen in four patients (one each at dose levels 1 and 1A; two at dose level 3), with no apparent increase in occurrence with higher doses of lapatinib. One patient (dose level 3) experienced a grade 4 cardiac failure and was withdrawn from the study; the event resolved with sequelae after ~1 year. The investigator reported that there was a reasonable possibility that the event was related to the treatment regimen. One patient (dose level 1D) died because of chronic respiratory disease, an AE that was not considered to be treatment related.

Table 3. Adverse events reported in more than 30% of all patients

Adverse event	All patients ($N = 53$)	
	All grades, *n* (%)	Grades 3 and 4, *n* (%)
Diarrhea	46 (87)	8 (15)
Nausea	38 (72)	2 (4)
Alopecia	37 (70)	0 (0)
Fatigue	29 (55)	2 (4)
Rash	27 (51)	3 (6)
Nail disorder	26 (49)	2 (4)
Epistaxis	25 (47)	0 (0)
Dysgeusia	23 (43)	0 (0)
Vomiting	23 (43)	1 (2)
Arthralgia	22 (42)	0 (0)
Headache	22 (42)	0 (0)
Neutropenia	22 (42)	20 (38)
Peripheral neuropathy	20 (38)	5 (9)
Asthenia	19 (36)	1 (2)
Cough	17 (32)	0 (0)
Rhinorrhea	17 (32)	0 (0)

efficacy

The majority of patients (85%) had measurable disease at baseline. Investigator-assessed responses without bone scan confirmation included 5 CRs (11%) and 24 PRs (53%), for an ORR of 64% (supplementary Table S3, available at *Annals of Oncology* online). The ORRs without bone scan confirmation of dose level 1C ($n = 3$) and dose level 4 ($n = 6$) were 100% and 83%, respectively. Among the 45 patients with bone scan confirmation, there were no CRs and 14 PRs, for an ORR of 31%. The eight patients without measurable disease at baseline were all evaluated as having SD with bone scan confirmation.

pharmacokinetics

Lapatinib and docetaxel plasma concentration data were available from 14 patients enrolled at dose levels 0–2. These data are graphically summarized in Figure 1. The relationship between the severity of neutropenia and plasma concentrations of docetaxel and lapatinib described previously was assessed in this study [16]. Patients with grades 2–4 neutropenia were included in the analysis, based on a model that quantifies the maximum decrease in neutrophils presumably directly due to docetaxel antimitotic effect in granulocytes and lapatinib inhibition of P-glycoprotein (Pgp)-mediated efflux of docetaxel from those cells. In this study, neutropenia was related to docetaxel peak concentration (Figure 2) with a half maximal inhibitory concentration (IC_{50}) of 1.60 ± 0.07 μM. Expanding the model to describe enhancement by lapatinib had no impact. Lapatinib plasma concentrations were all below its 4-μM IC_{50} for inhibition of ABCB1 (Pgp). The effect of growth factors was evident above 1.60 μM.

An association between plasma concentrations of both lapatinib and docetaxel with categorical clinical response was also observed (Figure 3). CRs were associated with 24-h

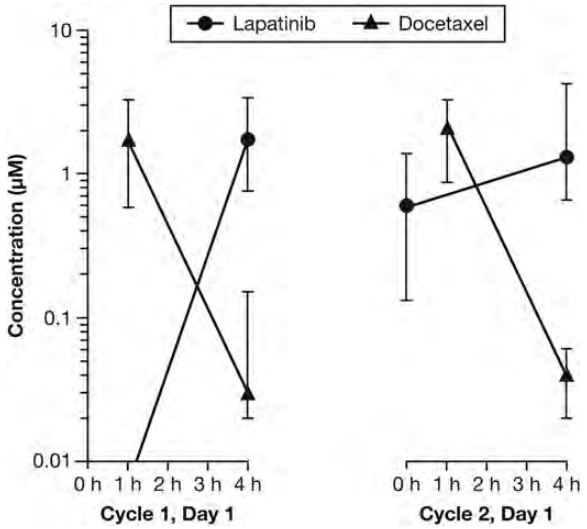

Figure 1. Median and range plasma concentrations of lapatinib and docetaxel in samples taken at the times of peak concentration.

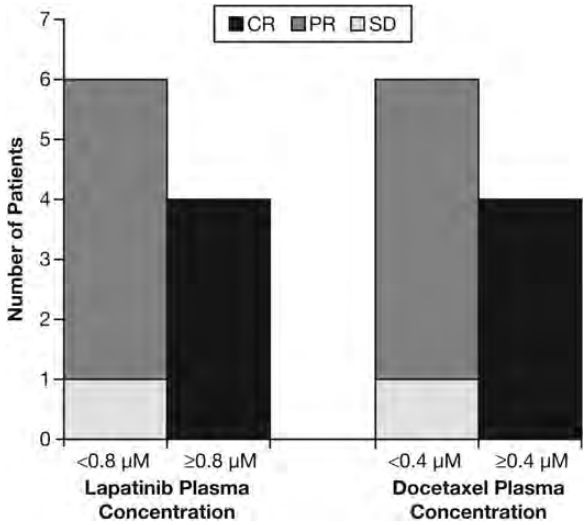

Figure 3. Association between categorical clinical response (CR, complete response; PR, partial response; SD, stable disease) and minimal systemic exposure (steady-state predose trough).

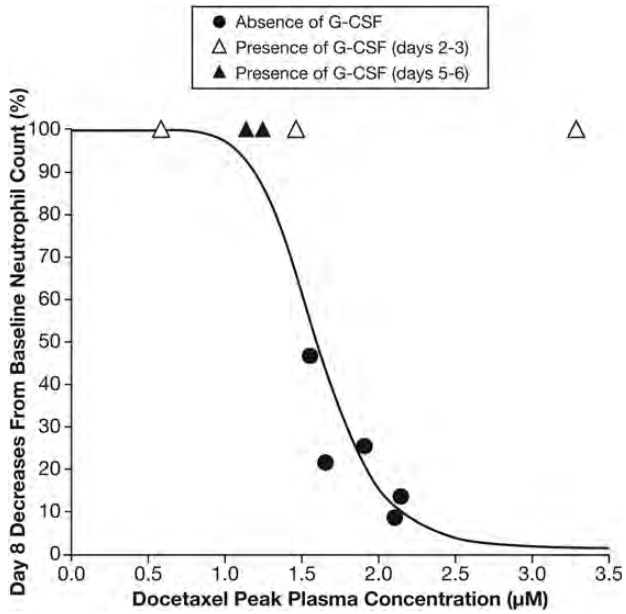

Figure 2. Magnitude of neutropenia in patients with grade 2–4 events after the first week of treatment in relation to peak (end of infusion) plasma docetaxel concentrations in the absence (circles) and presence (triangles) of growth factor started on days 5–6 (solid, fit) or 2–3 (open, not fit).

concentrations above 0.8 μM lapatinib and 0.4 μM docetaxel. Although the relevance of these values cannot be determined from these data, the pattern is consistent with positive exposure–response relationships. The exploratory nature and small samples size of these analyses should be interpreted with caution.

discussion

The availability of specific molecularly targeted agents has transformed the therapeutic outlook for patients with HER2-positive metastatic and early-stage breast cancer. One study has suggested that the prognosis for HER2-altered MBC may now be superior to that of patients with HER2-negative disease [17]. The occurrence of individual cases with very prolonged remissions of HER2-positive metastatic disease has been published, and, more recently, Gullo et al. [4] reported that a meaningful minority of patients achieved durable CRs, prompting speculation that they might be cured [18]. This observation, together with the activity of lapatinib in trastuzumab-resistant disease and *in vitro* synergy data, prompted us to investigate this combination in the clinic.

To our knowledge, this is the first completed phase I study of the triple combination of lapatinib, trastuzumab, and docetaxel. The purpose of the study was to evaluate the safety and tolerability of concomitant treatment of lapatinib and trastuzumab with two docetaxel doses (75 and 100 mg/m^2).

Both regimens with docetaxel were clinically feasible with manageable toxic effects when administered with prophylactic growth factor. No new safety signals were observed. Neutropenia, which is a prominent side-effect of docetaxel, was the most common grade 3 and 4 toxic effect, occurring in 36% of patients. However, all of these occurred during the initial phase of the study when prophylactic growth factors were not routinely administered.

The observed neutropenia rate is similar to the 32% that has been previously reported in a study combining trastuzumab and docetaxel, suggesting that there is no or only a minimal increase of hematologic toxic effect when lapatinib is added [3]. When compared with AEs previously reported with docetaxel and trastuzumab combination treatment, increases in nausea, vomiting, diarrhea, and rash were observed [3, 19]. However, the majority of events in the present study were grade 1 or 2.

Exposure to docetaxel is associated with neutropenic toxic effect; therefore, G-CSF support is warranted. Data from the LoRusso study [16] indicate that administration of pegfilgrastim during combination therapy of lapatinib and docetaxel is well tolerated. The most common drug-related toxic effects were

diarrhea, rash, fatigue, and nausea, and the majority of events were grade 1 or 2, with few grade 3 or 4 events [16].

The higher incidence of nausea, diarrhea, and vomiting observed in this study may be due to the additive effects of the triple-drug combination, the advanced disease stage of the patients, and the small sample size.

Relevance of the pharmacokinetic values cannot be determined from the limited data, although the pattern is consistent with positive exposure-response relationships. The exploratory nature and small sample sizes of these analyses should be interpreted with caution.

The combination of lapatinib with trastuzumab as well as the combination of lapatinib with docetaxel have synergistic activity to inhibit growth of HER2-positive breast cancer cells *in vitro* and to significantly reduce tumor growth in *in vivo* tumor models [5, 8, 16]. Other studies of trastuzumab (2 mg/kg weekly) combined with docetaxel (100 mg/m^2) demonstrated similar ORRs of 61%–72% in patients with HER-positive MBC [3, 19].

In conclusion, lapatinib in combination with docetaxel and trastuzumab with growth factor support is a feasible treatment option. Two dose levels of lapatinib with docetaxel and trastuzumab can be recommended as the OTR: lapatinib 1250 mg/docetaxel 75 mg/m^2 (dose level 1C) or lapatinib 1000 mg/docetaxel 100 mg/m^2 (dose level 4) with weekly trastuzumab administration including prophylactic use of G-CSF. The preliminary ORR of the present study is 64%, similar to the efficacy data obtained in other clinical trials evaluating combination therapy with lapatinib and trastuzumab [11, 12].

The data presented here support combinations of two HER2 antagonists in the treatment of MBC. We are currently pursuing this strategy by comparing lapatinib with trastuzumab and taxane to trastuzumab and taxane alone in the first-line treatment of MBC in an international random-assignment phase III trial.

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disclosure

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Predictors of recovery of ovarian function during aromatase inhibitor therapy

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Background: Aromatase inhibitors (AIs) may cause a rise in estrogen levels due to ovarian function recovery in women with clinical chemotherapy-induced ovarian failure (CIOF). We carried out a prospective registry trial to identify predictors of ovarian function recovery during AI therapy.
Patients and methods: Women with hormone receptor (HR)-positive breast cancer who remained amenorrheic and had hormonal levels consistent with ovarian failure after adjuvant chemotherapy were enrolled in a multi-institutional clinical trial of anastrozole. Subjects underwent frequent assessment using an ultrasensitive estradiol assay. Multivariable analysis was used to evaluate clinical and biochemical predictors of ovarian function recovery within 48 weeks.
Results: Recovery of ovarian function during AI therapy was observed in 13 of 45 (28.9%) assessable subjects after a median 2.1 months (range 0.6–11.9). Median age at chemotherapy initiation was statistically significantly different between those who regained ovarian function (43 years, range 40–51) and those who remained postmenopausal (49 years, range 44–52; $P < 0.0001$).
Conclusions: A significant proportion of women with CIOF recover ovarian function during AI therapy, including a woman over age 50 at initiation of chemotherapy. Tamoxifen remains the standard of care for women with CIOF. If an AI is used, patients should be monitored frequently with high-quality estradiol assays.
Clinicaltrials.gov: NCT00555477.
Key words: aromatase inhibitor, breast cancer, chemotherapy-induced ovarian failure, estradiol, ovarian function

introduction

Mortality from hormone receptor (HR)-positive breast cancer has been declining, in part because of adjuvant endocrine therapy [1]. Tamoxifen was the standard adjuvant endocrine therapy for decades in all women with HR-positive disease [1]. More recently, data from large, prospective, randomized, controlled trials have demonstrated superior progression-free and overall survival of aromatase inhibitor (AI) therapy compared with tamoxifen in postmenopausal women [2]. Despite this superiority, the standard of care for premenopausal women remains tamoxifen, because the AIs are ineffective in women with functional ovaries.

Patients with HR-positive disease at higher risk of disease recurrence are often treated with adjuvant chemotherapy

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