Lapatinib in the Treatment of Breast Cancer

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Abstract: Lapatinib is an oral dual tyrosine kinase inhibitor against epidermal growth factor receptor (EGFR) and HER-2/*neu* (HER2). The success of trastuzumab in breast cancer prompted investigations of lapatinib in breast cancer, which revealed that lapatinib has effectiveness similar to that of trastuzumab. Clinical trials showed that lapatinib is effective for patients with HER2-positive breast cancer. Furthermore, lapatinib may be effective in patients with central nervous system metastasis that developed after trastuzumab therapy. Lapatinib may have synergistic effects with trastuzumab or hormonal therapy. There are encouraging preliminary data on the efficacy of lapatinib in patients with inflammatory breast cancer. Ongoing trials may give us exciting data on lapatinib as adjuvant therapy. HER2 positivity is a strong predictor of response to lapatinib, but the predictive value of EGFR positivity is less clear. While cardiac toxic effects have been observed with lapatinib, their incidence and severity are less significant than with trastuzumab. Current data indicate that lapatinib is a promising agent with unique potential benefits in the treatment of metastatic breast cancer.

Keywords: lapatinib, targeted therapy, breast neoplasm, HER2, HER1, EGFR

Introduction

Encouraged by the success of trastuzumab, investigators have turned their attention to the dual HER-2/*neu* (HER2) and epidermal growth factor receptor (EGFR) inhibitor lapatinib, which is progressing rapidly through clinical development. Clinical development of lapatinib started less than 5 years ago with trials designed to test the efficacy and safety of lapatinib as monotherapy. On March 13, 2007, the U.S. Food and Drug Administration approved lapatinib for use in combination with capecitabine in the treatment of women with HER2-positive breast cancer previously treated with trastuzumab, an anthracycline, and a taxane. Now, at the beginning of 2009, lapatinib is heading towards trials in patients with early breast cancer.

Lapatinib (Tykerb in the United States, Tyverb in Europe, GlaxoSmithKline, North Carolina, U.S.) is a small molecule tyrosine kinase inhibitor against HER2/ErbB2 and EGFR/ErbB1. Several studies suggest that lapatinib has promise in the treatment of breast cancer and has some unique potential benefits beyond those of trastuzumab. While large-molecular-weight molecules like trastuzumab cannot effectively cross the blood-brain barrier, small-molecular-weight molecules like lapatinib can penetrate into the central nervous system (CNS). Although trastuzumab clearly has effectiveness in the treatment of HER2-overexpressing breast cancer, some tumors develop resistance to trastuzumab.[1] Lapatinib showed the effect in the patients who progressed in the treatment of trastuzumab.[1] A synergistic effect between trastuzumab and lapatinib was demonstrated in a phase I trial.[2] Furthermore, preliminary results of a phase II trial evaluating the combination of lapatinib and paclitaxel for neoadjuvant treatment in patients with inflammatory breast cancer (IBC) were encouraging.[3]

In this review, we summarize the pharmacologic characteristics of lapatinib, results of clinical trials of this agent, the unique features and potential uses of lapatinib in the treatment of breast cancer, and its toxicity and tolerability.

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Review Criteria

This information for this review was compiled in part by searching the PubMed and MEDLINE databases for articles published through 31 December 2008. Electronic early-release publications listed in these databases were included. Only articles published in English were considered. The search terms used were "lapatinib" or "GW572016". When possible, primary sources have been quoted. Full articles were obtained, and references were checked for additional material when appropriate. The specified search terms were also used to search the abstracts of the 2006, 2007, and 2008 American Society of Clinical Oncology annual meetings; the 2006, 2007, and 2008 San Antonio Breast Cancer Symposia; and the 2007 and 2008 American Society of Clinical Oncology Breast Cancer Symposia. The results of some experiments conveyed to the authors by personal communication were also included. References were chosen on the basis of the best clinical or laboratory evidence, and special weight was given to work corroborated by published work from other centers.

What is Lapatinib? Drug Description, Mode of Action and Pharmacokinetics

Drug description

Lapatinib is a small molecule tyrosine kinase inhibitor against two oncogenes, HER2/ErbB2 and EGFR/ErbB1. Lapatinib is present as the monohydrate of the distosylate salt. Its chemical name is *N*-(3-chloro-4-[(3-fluorophenyl)methyl] oxyphenyl)-6-[5-([2 (methylsulfonyl)ethyl] amino methyl)-2-furanyl]-4-quinazolinamine bis (4-methylbenzenesulfonate) monohydrate. Lapatinib has the molecular formula $C_{29}H_{26}ClFN_4O_4S$ $(C_7H_8O_3S)_2$ H_2O and a molecular weight of 943.5.

Mode of action

HER2/ErbB2 and EGFR/ErbB1 belong to the human epidermal growth factor receptor (HER) family, which also includes HER3 and HER4.[4] All members of the HER family consist of an extracellular ligand binding site, a transmembrane domain, and an intracellular tyrosine kinase domain. To activate tyrosine kinase phosphorylation requires receptor dimerization. The dimerization can be homodimerization, between two molecules of the same type, or heterodimerization, between two molecules of different types. The phosphorylated HER activates downstream cell proliferation (mitogen-activated protein kinase), cell survival (phosphoinositide 3-kinase), and signal transducer and activator of transcription pathways.[4] Although HER2 homodimers from overexpression can activate signaling without the ligand, which has not been discovered, heterodimers of EGFR and HER2 also promote signaling. Whereas trastuzumab targets HER2 by targeting the extracellular domain as a monoclonal antibody, lapatinib targets both EGFR and HER2 by binding reversibly to the intracellular adenosine triphosphate binding domain of the tyrosine kinase (Fig. 1).[5,6]

In cell growth assays, lapatinib selectively inhibited the growth of human tumor cell lines overexpressing either EGFR or HER2 compared with the growth of normal human foreskin fibroblasts, nontumorigenic epithelial cells, and non-EGFR- or HER2-overexpressing tumor cells.[7] Lapatinib inhibited the tumor growth of xenografts of head and neck cancer and breast cancer cell lines that overexpressed EGFR or HER2.[7,8] That tumor growth inhibition was associated with inhibition of activation of downstream signaling for cell proliferation and survival.[7,8] Furthermore, lapatinib induced apoptosis in HER2-overexpressing cells. This effect was more pronounced in HER2-overexpressing breast cancer cells (BT-474) than in head and neck cancer cells (HN5).[7,8] Lapatinib also induced apoptosis in HER2-overexpressing and trastuzumab-resistant cell lines.[1]

Pharmacokinetics

Lapatinib has been evaluated in various phase I trials conducted in both healthy individuals and those with advanced malignant tumors. The adverse symptoms most commonly observed with the drug were diarrhea and mild rash, and no grade 4 drug-related adverse events were reported.[9,10]

Absorption

Administration to healthy individuals of single and multiple doses of lapatinib of 10, 25, 50, 100, 175, and 250 mg resulted in a delayed absorption with a T_{lag} of 15–30 min. In the multiple dose study, no significant accumulation was found at the 25 mg dose on day 8 compared to day 1; however, a 50% accumulation was observed at the 100 mg and 175 mg doses. T_{max} occurred at 2.5–4 hours; the

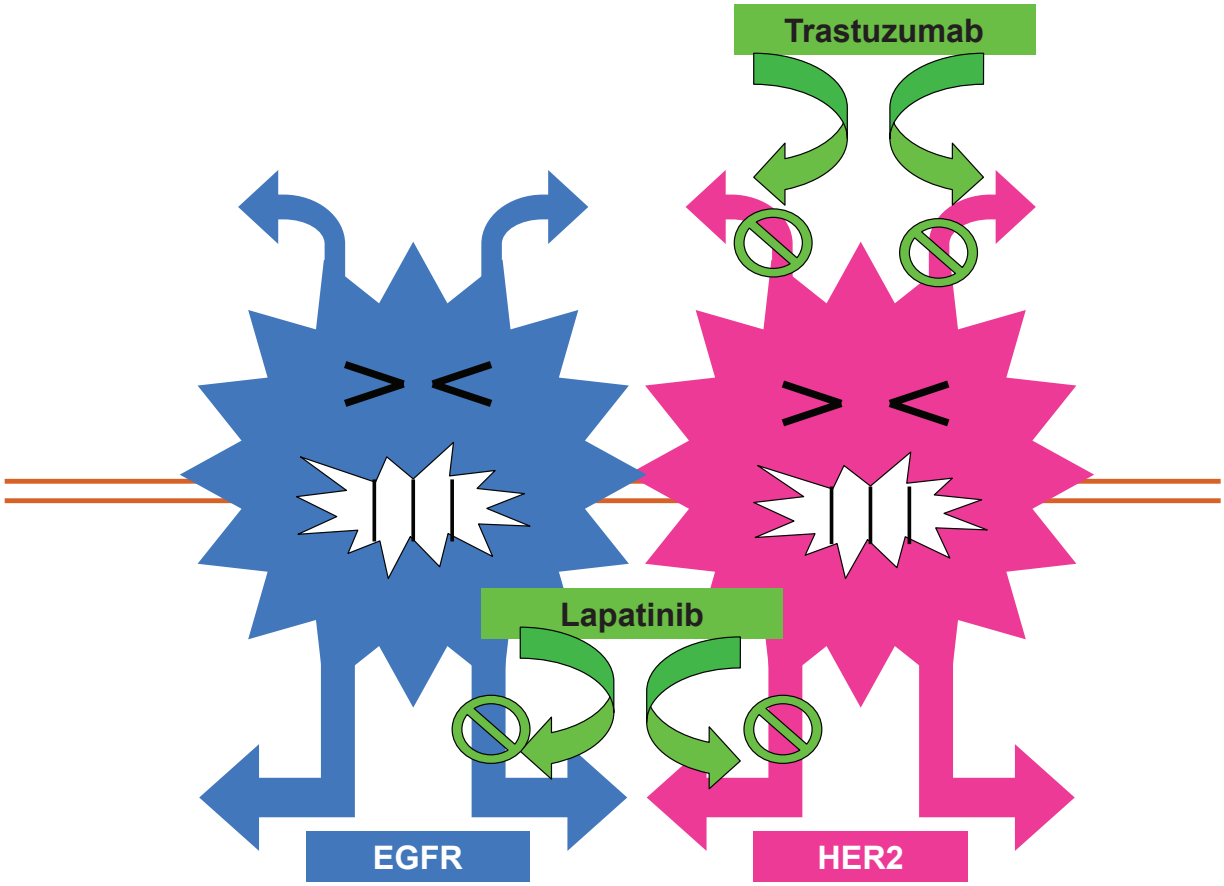

Figure 1. Mechanism of action of trastuzumab and lapatinib.

C_{max} range was 11–317 ng/ml, and there was a time-dependent increase in C_{max} and area under the curve values at higher doses only.[9]

In patients with metastatic carcinoma, doses ranging from 100 mg to 1,600 mg were administered once daily for 20 days, and these doses were well tolerated in all patients. Repeated dosing resulted in a twofold accumulation on day 20 relative to day 1. T_{max} occurred at 3–6 hours; the C_{max} range was 1.02–2.13 µg/ml, and there was a dose-dependent increase in area under the curve values (13.9–29.4 h*µg/ml).[10]

Distribution

Lapatinib is highly (more than 99%) bound to albumin and α-1 acid glycoprotein.

Metabolism

Lapatinib is metabolized to oxidated metabolites by the cytochrome P450s 3A4 (about 70%), 3A5, 2C19, and 2C8. Data from healthy volunteers receiving ketoconazole, a CYP3A4 inhibitor, showed that systemic exposure to lapatinib increased about 3.6-fold and half-life increased 1.7-fold at a ketoconazole dose of 200 mg twice daily for 7 days.[11] Data from healthy volunteers receiving carbamazepine, a CYP3A4 inducer, showed that systemic exposure to lapatinib decreased approximately 72% at a carbamazzepine dose of 100 mg twice daily for 3 days and 200 mg twice daily for 17 days.[11]

Elimination

In single-dose studies, the mean half-life of lapatinib ranged from 6 to 8 h with an apparent increase with increasing dose. Half-life increased to 7–11 h in the multiple-dose studies owing to drug accumulation.[9]

Efficacy of Lapatinib as Monotherapy

The initial phase I trial of lapatinib as monotherapy was performed in 16 healthy volunteers with lapatinib doses ranging from 10 mg to 250 mg. Median peak serum concentration was seen 3 hours

after dosing.[9] In a multiple-dose study with 27 participants, lapatinib was given daily for 8 days at doses of 25, 100, and 175 mg. Steady state occurred after 6–7 days. Only grade 1 or 2 toxic effects were reported; no grade 3 or 4 adverse events were reported. The most common adverse events were headache, diarrhea, rash, cold symptoms, gastrointestinal symptoms, and elevated liver function test results.

Clinical activity has been suggested by two subsequent phase I trials performed in patients with multiple types of solid tumors.[10,12] In the first of these phase I studies, a dose escalation study for cancer patients,[12] 39 patients received 175–1800 mg daily, and 25 patients were assigned to receive either 500, 750, or 900 mg twice daily. One patient with an EGFR-overexpressing head and neck tumor experienced a complete response that lasted for 16 months. Twenty-two patients with various types of cancer, most of whom had EGFR- or HER2-overexpressing tumors, had stable disease with a median duration of 4 months (range, 1–13 months). The subsequent phase I study[10] was performed in 67 patients with heavily pretreated EGFR-expressing (positive by immunohistochemical analysis [IHC]) and/or HER2-overexpressing (2+ or 3+ by IHC) metastatic solid tumors, who were randomly assigned to one of six lapatinib daily doses (500, 650, 900, 1000, 1200, or 1600 mg) for 21 days.[10] Among the 59 patients whose disease activity was assessable, four patients had a partial response. All four patients had HER2-positive breast tumors (3+ by IHC) and had received trastuzumab previously. Two of the four partial responders had recurrent IBC.

Both preclinical findings and findings from phase I trials suggested the clinical activity of lapatinib in breast cancer. Lapatinib monotherapy was tested in patients with advanced breast cancer in phase II studies. Lapatinib monotherapy at two different dosages (1500 mg daily or 500 mg twice daily) was investigated as first-line therapy in 138 patients with HER2-positive locally advanced or metastatic breast cancer.[13] Thirty-three of the 138 patients (24%) had a partial response, and 71 of the 138 patients (51%) had stable disease. This response rate was similar to that observed in a phase II trial of trastuzumab monotherapy as first-line therapy for HER2-positive metastatic breast cancer (complete response, 2%; partial response, 17%; stable disease, 51%).[14] There was no significant difference in efficacy between the two dosing regimens. The authors noted some responses at the first assessment at 8 weeks, and the median duration of response was more than 6 months.

Results from these phase I and II studies confirmed the safety and efficacy of lapatinib in clinical settings and led to phase III trials.

Efficacy of Lapatinib in Combination with other Drugs for Treatment of Breast Cancer

On the basis of the interim results of a phase III trial of lapatinib in combination with capecitabine, lapatinib was approved by the U.S. Food and Drug Administration in March 2007 for use in combination with capecitabine in the treatment of patients with HER2-positive advanced breast cancer.[15] This trial was conducted in patients with HER2-positive advanced or metastatic breast cancer (3+ by IHC or 2+ by IHC and amplified by fluorescence in situ hybridization [FISH]) that had progressed after treatment with an anthracycline, a taxane, and trastuzumab. A total of 339 women were randomly assigned to receive either lapatinib 1,250 mg daily in combination with capecitabine 2,000 mg/m^2 in two divided doses or capecitabine 2,500 mg/m^2 in two divided doses on days 1–14 every 3 weeks. The primary endpoint of this study was time to disease progression (TTP), which was defined as the time from randomization to disease progression or death due to breast cancer and assessed independently.

The interim analysis of this trial demonstrated that median TTP was 4 months longer in the 163 patients receiving lapatinib in combination with capecitabine than in the 161 patients receiving capecitabine monotherapy (8.4 months vs. 4.4 months; $p < 0.001$). The treatment assignment was the only significant predictor of TTP in a Cox regression model. On the basis of these results, an independent data safety monitoring committee recommended termination of accrual after 339 patients had been randomly assigned to treatment.

In an updated analysis of those 399 patients,[16] 198 patients received the combination regimen while 201 received capecitabine alone. The median TTP was 6.2 months for the patients receiving the combination regimen compared to 4.3 months for the patients receiving capecitabine alone

(hazard ratio, 0.57; $p < 0.001$). Overall response rate (24% vs. 14%; $p = 0.017$) and clinical benefit rate (29% vs. 17%; $p = 0.008$) were better in the combination group than in the capecitabine-alone group.

Lapatinib has also been tested in combination with taxanes. In a phase III, double-blind study, 580 patients were randomly assigned to paclitaxel and lapatinib or paclitaxel and placebo as a first-line treatment for HER2-negative or uncharacterized metastatic breast cancer.[17] No patient had previously received trastuzumab therapy. In the intent-to-treat population ($n = 579$), no significant differences were observed in TTP, event-free survival, or overall survival between the treatment arms. HER2 positivity was confirmed in 49 of 291 patients (17%) in the combination therapy group and 37 of 288 patients (13%) in the monotherapy group, by centralized IHC or FISH analysis. In the analysis of this subset with confirmed HER2-positive tumors, the addition of lapatinib to paclitaxel was associated with better overall response rate (63.3% vs. 37.8%; $p = 0.023$), better clinical benefit rate (69.4% vs. 40.5%; $p = 0.011$), and longer median TTP (36.4 vs. 25.1 weeks; $p = 0.005$).

Currently, a phase III study is ongoing to evaluate lapatinib in combination with weekly paclitaxel versus paclitaxel plus placebo in patients with HER2-positive advanced breast cancer.[18]

Efficacy of Lapatinib for CNS Metastases

Recently, CNS metastases have been receiving increasing attention as an important target for cancer treatment. While many therapies have been developed for cancer, few are able to cross the blood-brain barrier. As improved cancer treatments have led to better control of systemic disease, patients are surviving long enough that cancer cells may have time to reach the brain. We are starting to see more and more patients who are suffering from CNS metastases.

It is increasingly recognized that CNS metastases are more common in patients with HER2-positive tumors than in patients with HER2-negative disease especially after treatment with trastuzumab. The hypothetical causes of this phenomenon include the inability of trastuzumab to cross an intact blood-brain barrier. Unlike trastuzumab, lapatinib is small enough to cross the blood-brain barrier, as confirmed in a preclinical model.[19] Lapatinib inhibits the formation of brain metastasis colonization from HER2-overexpressing breast cancer cells by 50%–53%.[19]

In an exploratory analysis of the aforementioned pivotal phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone for patients with advanced breast cancer, the rate of CNS metastasis was lower in the combination therapy group than in the capecitabine alone group (4 of 198 patients [2%] vs. 13 of 201 patients [11%]; $p = 0.045$).[16] Those findings have prompted further investigations of the efficacy of lapatinib for CNS metastases.

One phase II clinical trial evaluated lapatinib monotherapy for brain metastases.[20] Thirty-nine patients who had HER2-positive breast cancer, progressive brain metastases while receiving trastuzumab treatment, and at least one measurable metastatic brain lesion were enrolled. One patient experienced a partial response in a brain lesion according to the Response Evaluation Criteria in Solid Tumors. Seven patients remained free of progression at both CNS and non-CNS sites at 16 weeks. In addition, by exploratory analysis, some patients experienced reduced brain tumor burden.

On the basis of this observation, the investigators designed a larger trial with response defined as a 50% volumetric reduction of CNS lesions without development of a new lesion, need for an increased dose of steroid, progressing neurologic signs and/or symptoms, or progressing nontarget lesions.[21] Fifteen of the 242 patients (6%) had an objective response, and the median absolute volumetric reduction was 3.2 cm^2 (range, 0.7–29.7 cm^2).

As an extension of this trial, enrolled patients who experienced disease progression while receiving lapatinib monotherapy were treated with a combination of lapatinib and capecitabine. Results from 51 patients were reported in abstract form.[21] Ten patients (20%) had more than 50% volumetric reduction of CNS metastases, and 18 patients (35%) had more than 20% volumetric reduction. This study suggested that the combination of lapatinib and capecitabine might be effective for the treatment of CNS metastases of breast cancer, even metastases developing after lapatinib monotherapy.

Further trials are ongoing to investigate combinations of lapatinib with other therapies—including topotecan and temozolomide—in patients with CNS metastases.[22,31] In summary, clinical trials have shown that lapatinib has activity against CNS

disease, a finding not generally observed with trastuzumab.

Efficacy of the Combination of Lapatinib and Trastuzumab for HER2-Positive Breast Cancers

Trastuzumab-based monotherapy for the treatment of HER2-positive breast cancer has shown clinical benefits over standard chemotherapy alone. In spite of these advances, however, 70%–80% of HER2-positive breast cancers either are intrinsically resistant to trastuzumab or acquire resistance within 1 year of treatment initiation. Preclinical studies have suggested a therapeutic advantage of combining two HER2-targeting agents, lapatinib and trastuzumab, for the treatment of advanced, HER2-positive breast cancers. However, studies to further elucidate the mechanism of this interaction are a necessity.

Primary resistance to trastuzumab is presumed to be due, in part, to the presence of an amino terminally truncated receptor, p95HER2, that maintains kinase activity (Fig. 2). Preclinical studies investigating the sensitivity of cell lines expressing full-length HER2 or truncated p95HER2 to lapatinib and trastuzumab have shown growth inhibition in p95HER2-expressing cells when they are treated with lapatinib but not when they are treated with trastuzumab. In contrast, cell lines expressing full-length HER2 are sensitive to both anti-HER2 agents.[23] In addition, results of a retrospective analysis of clinical data supported these findings. This retrospective study included 46 patients with HER2-positive advanced breast cancer treated with trastuzumab. Of the 46 patients, nine had tumors expressing p95HER2 as evaluated by immunofluorescence, while the remaining 37 had tumors expressing full-length HER2. Only one (11.1%) of the nine patients with truncated p95HER2 had a response to trastuzumab therapy, compared with 19 (51.4%)of the 37 patients with full-length HER2.[23] This study highlights the need for alternative or additional anti-HER2 targeting

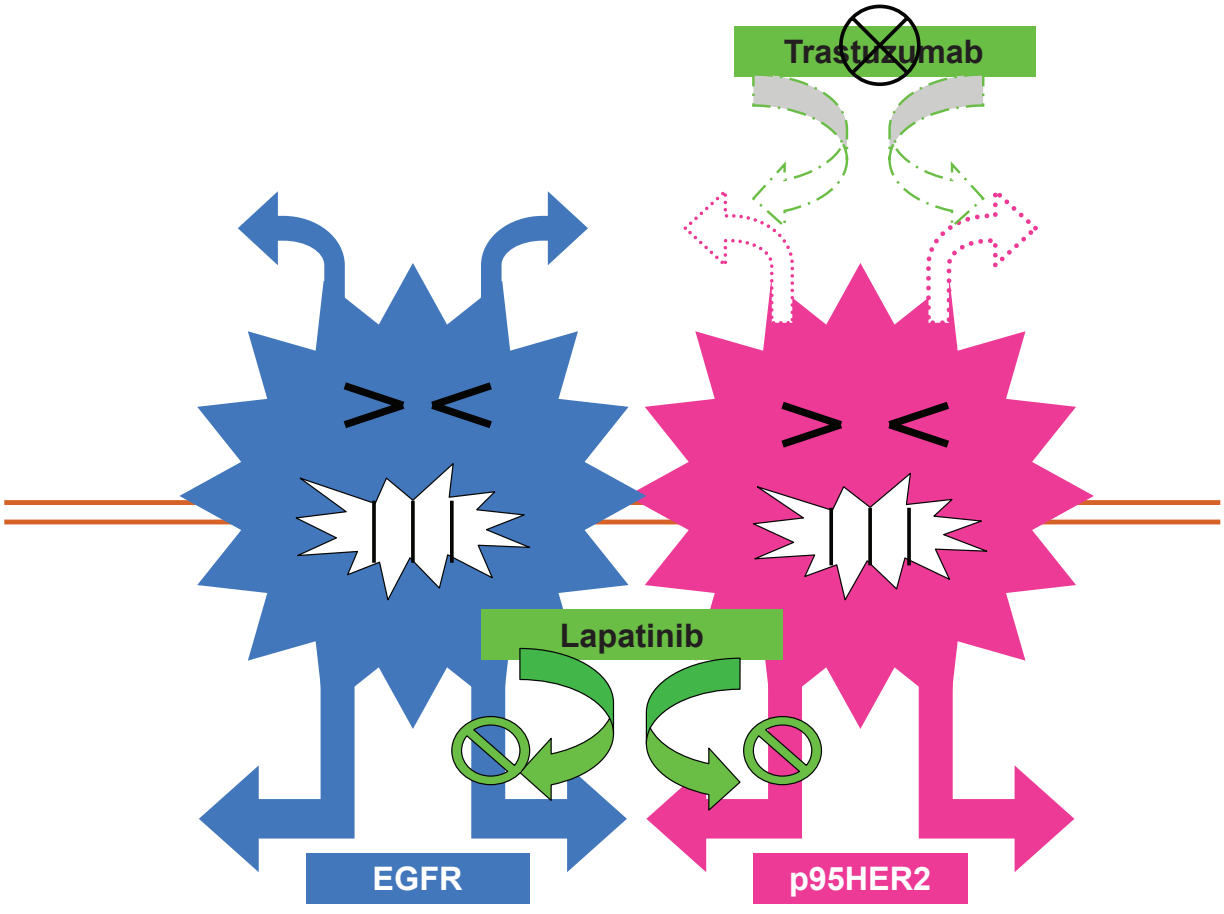

Figure 2. The truncated receptor p95HER2 is associated with resistance to trastuzumab but not resistance to lapatinib.

modalities and may be a good argument for testing the combination of trastuzumab and lapatinib for treatment of HER2-positive breast cancers. However, the role of p95HER2 in breast cancer remains to be clarified.

Studies investigating the combinatory effect of trastuzumab and lapatinib have suggested a synergistic therapeutic potential in HER2-overexpressing breast cancers. In vitro multiple-drug-effect analysis was performed in four HER2-overexpressing established human breast cancer cell lines: SKBr3, MDA-MB-453, MDA-MB-361, and BT-474. Results showed a consistent synergistic interaction of the two agents in all four breast cancer cell lines.[5] In an attempt to understand the mechanism of this synergistic interaction, studies have been performed to look at the effects of lapatinib and trastuzumab on HER2 receptor expression and signaling. A proposed mechanism of action for the observed synergistic interaction is a lapatinib-induced accumulation and stabilization of inactive HER2 receptors at the cell surface, which leads to enhanced trastuzumab-dependent, immune-mediated cytotoxicity.[24]

On the basis of the evidence from preclinical studies, the combination of lapatinib and trastuzumab has been tested in the clinical setting. A phase I study was performed to determine the safety, clinical feasibility, pharmacokinetics, and preliminary clinical activity of this combination, as well as the optimally tolerated regimen, in patients with HER2-positive advanced breast cancer.[2] A total of 54 patients were enrolled, 50 of whom (93%) had previously received trastuzumab-containing regimens. Eight patients had a response (complete response in one patient and partial response in seven), for an overall response rate of 16%. Out of these eight patients, seven were enrolled in the dose-escalation group (one complete response and six partial responses), and one was enrolled in the pharmacokinetic group (partial response). Six patients had stable disease for longer than 6 months.

Preliminary results were recently published from a randomized study of lapatinib alone versus lapatinib in combination with trastuzumab in 296 women with heavily treated HER2-positive metastatic breast cancer that had progressed during prior trastuzumab-containing therapy.[25] Combination treatment improved progression-free survival and the clinical benefit rate significantly compared with lapatinib alone (progression-free survival: 12.0% vs. 8.4%, $p = 0.029$; clinical benefit rate: 25.2% vs. 13.2%, $p = 0.020$), but there were no significant differences between groups in the response rate (10.3% for combination vs. 1.5% for monotherapy, $p = 0.46$) or overall survival rate (51.6 weeks for combination vs. 39 weeks for monotherapy, $p = 0.016$).

An ongoing trial, the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial, is comparing the activity of lapatinib alone versus trastuzumab alone versus trastuzumab followed by lapatinib versus lapatinib concomitantly with trastuzumab as adjuvant treatment for patients with HER2-positive breast cancer.[26]

To assess the activity of lapatinib in combination with standard chemotherapy, the National Surgical Adjuvant Breast and Bowel Project is conducting a double-blind, placebo-controlled, phase III study to compare the combination of doxorubicin and cyclophosphamide followed by (1) paclitaxel plus trastuzumab, (2) paclitaxel plus lapatinib, or (3) paclitaxel, trastuzumab, and lapatinib as neoadjuvant therapy for patients with palpable and operative HER2-positive breast cancer (National Surgical Adjuvant Breast and Bowel Project trial B41).[27] The primary endpoint is pathologic complete response, defined as the absence of microscopic evidence of invasive tumor cells in the postchemotherapy surgical breast specimen. A correlative study will be performed to determine whether gene expression profiles in the tumor tissue can predict pathologic complete response. These studies will provide insight into the therapeutic efficacy of trastuzumab and lapatinib combination therapy for the treatment of advanced, HER2-positive breast cancer.

Efficacy of Lapatinib Combined with Hormonal Therapy for Treatment of Breast Cancer

Preclinical studies have provided evidence that the combination of lapatinib and tamoxifen may effectively inhibit estrogen-dependent breast cancer. The cross-talk between downstream pathways of HER2 and/or EGFR and estrogen receptor has been considered to be responsible for resistance to antiestrogen therapies. Lapatinib can restore tamoxifen sensitivity in estrogen receptor-positive, tamoxifen-resistant breast cancer models.[28] A combination of tamoxifen and lapatinib showed strong antitumor activity in breast cancer cell lines

and mouse xenograft. Patients are currently being recruited for a National Cancer Institute-sponsored ongoing phase II trial to study the rate of response to the combination of lapatinib with tamoxifen in patients with locally advanced or metastatic breast cancer that did not respond to previous tamoxifen therapy.[29]

Lapatinib has also been investigated in combination with aromatase inhibitors. Based on encouraging results of a phase I and pharmacokinetic study of lapatinib in combination with letrozole, a phase III study of this combination is ongoing and has recently closed to accrual.[30,51] The preliminary results were presented at the San Antonio Breast Cancer Symposium in December 2008. A total of 1,286 postmenopausal women with hormone receptor-positive, untreated metastatic breast cancer were randomly assigned to either lapatinib with letrozole or letrozole with placebo. In patients with centrally confirmed HER2-positive tumors, adding lapatinib to letrozole significantly improved median progression-free survival, the overall response rate, and the clinical benefit rate.[32] A phase III randomized trial comparing the efficacy of a combination of lapatinib and fulvestrant with that of fulvestrant and placebo has been recruiting postmenopausal women with stage III or IV hormone receptor-positive breast cancer.[33]

The known cross-talk between HER2/EGFR and hormone receptors supports high hope for a possible combination effect. Further, the aforementioned clinical trials will define whether there is any synergism between lapatinib and hormonal therapy.

Efficacy of Lapatinib as Rescue Therapy for Patients with IBC

Lapatinib has shown potential for the treatment of IBC, a rare but aggressive form of breast cancer with a rate of HER2 positivity higher than that of non-IBC.[34] A number of potential molecular targets have been identified for the treatment of IBC.[35] Targeted therapy against HER2—trastuzumab and lapatinib—is a promising strategy for treatment of IBC.

The preliminary results from a phase II trial of lapatinib and paclitaxel as neoadjuvant therapy in patients with newly diagnosed IBC showed that 95% of the HER2-positive patients had clinical response.[3] In a phase II trial of lapatinib monotherapy for heavily treated patients with IBC,[36] the response rate was 50% among the 30 patients with HER2-positive tumors but only 7% among the 15 patients with HER2-negative, EGFR-positive tumors.

Currently, the European Organization for Research and Treatment of Cancer is conducting a randomized phase I/II trial of docetaxel and lapatinib as neoadjuvant therapy in patients with HER2-positive locally advanced breast cancer, IBC, or resectable breast cancer.[37] At The University of Texas M.D. Anderson Cancer Center, a phase II study of neoadjuvant lapatinib plus chemotherapy (sequential FEC75 and paclitaxel) in patients with HER2-positive IBC is in progress.[38] It remains unknown the mechanism of the effects of lapatinib to IBC.

Does Adjuvant Lapatinib Improve Clinical Outcomes for Patients with Early-Stage Breast Cancer?

The evidence of lapatinib's effectiveness in advanced breast cancer, lapatinib's ability to cross the blood-brain barrier, and a lower incidence of cardiac side effects with lapatinib than with trastuzumab have raised expectations regarding lapatinib as adjuvant therapy. Two trials are under way that test the benefit of lapatinib in patients with early-stage breast cancer.

The Tykerb Evaluation after Chemotherapy (TEACH) trial is an ongoing phase III trial that is no longer recruiting participants.[39] In this trial, women with HER2-positive early-stage breast cancer who have completed their adjuvant therapy but not received trastuzumab and who have no clinical or radiographic evidence of disease are randomly assigned to either 1 year of adjuvant lapatinib or 1 year of placebo. This trial was opened for women who had completed adjuvant chemotherapy before trastuzumab was approved by the Food and Drug Administration and might have benefited from anti-HER2 therapy but were not eligible for trastuzumab because it must be delivered concurrently with chemotherapy.

The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial is currently recruiting patients with HER2-positive breast cancer.[26] This is a randomized, open-label, phase III study comparing the activity of lapatinib alone versus trastuzumab alone versus trastuzumab followed by lapatinib versus lapatinib concomitantly with trastuzumab as adjuvant therapy.

Total estimated enrollment is very large—8,000 women—and estimated completion time is June 2010. The results of this trial will reveal the relative efficacy of lapatinib and trastuzumab and indicate the best sequence and combination of trastuzumab and lapatinib.[40]

Should HER2 Positivity or EGFR Positivity be Used to Predict Responsiveness to Lapatinib?

Since lapatinib targets HER2 and EGFR, the value of those markers in predicting the efficacy of lapatinib has been investigated in clinical trials.

The correlation between HER2 status and clinical biological effects were investigated in sequential tumor biopsy samples from patients with metastatic cancer participating in a phase I clinical trial of lapatinib monotherapy.[10,41] Among patients with breast cancer, overexpression of HER2 and higher expression of phosphorylated HER2 were observed in all four partial responders in breast cancer, whereas rates of EGFR and phosphorylated EGFR expression were not different between responders and nonresponders.[41,42]

Other investigators evaluated potential predictors of response to lapatinib in a phase II study of lapatinib monotherapy as first-line therapy in patients with HER2-amplified advanced or metastatic breast cancer. Preliminary reports showed that HER2 extracellular domain levels at baseline and during treatment were associated with response to lapatinib monotherapy.[43] In another study, an elevated ERRB2 mRNA level in breast tumors was significantly correlated with better response ($p = 0.02$) and longer time to disease progression ($p < 0.0025$).[44]

In an exploratory analysis of a the aforementioned pivotal phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone for patients with advanced breast cancer, tissue samples from 320 of the 399 patients (80%) were analyzed for EGFR by IHC and HER2 by IHC and FISH.[16] Although one of the eligibility criteria for this trial was that tumors be HER2 positive, defined as 3+ by IHC or 2+ by IHC and positive by FISH, only 241 of the 315 patients (77%) met these HER2 criteria on central evaluation. Among those 241 patients, patients in the combination group had better progression-free survival than did patients in the capecitabine-alone group (hazard ratio, 0.0446; 95% confidence interval, 0.308–0.647; $p < 0.0001$). In contrast, no benefit form the addition of lapatinib was observed in the 74 patients with tumors that did not meet the HER2 eligibility criteria on central evaluation (hazard ratio, 0.772; 95% confidence interval, 0.386–1.543; $p = 0.46$). Forty-four of 320 patients (14%) had EGFR-positive tumors, defined as IHC 2+ or 3+, and the addition of lapatinib was not observed with improved progression-free survival in this subset (hazard ratio, 0.77; $p = 0.418$).

Baseline serum samples also were investigated for levels of circulating extracellular domain of HER2 from 367 patients (92%) in the same phase III trial. Elevated serum levels of the extracellular domain of HER2 were associated with a shorter progression-free survival in the capecitabine-alone group ($p < 0.001$) but not in the combination therapy group ($p = 0.12$). This suggests that the baseline level of extracellular domain of HER2 did not predict for the efficacy of lapatinib. Furthermore, tissue status of HER2 by IHC and/or FISH predicted response to lapatinib therapy.

In a phase II trial of lapatinib monotherapy in heavily treated patients with IBC, the response rate was much higher in patients with HER2-positive tumors than in those with HER2-negative and EGFR-positive tumors (50% vs. 7%).[35] The authors also found that co-expression of phosphorylated HER2 and phosphorylated HER3 was associated with better response.

The relationship between EGFR status and sensitivity to lapatinib has been examined in vitro and in clinical trials. When HER2-overexpressing breast cancer cells were depleted of EGFR by knockdown with EGFR small-interfering RNA, sensitivity to lapatinib was not affected. In contrast, when HER2 was knocked down in these cells, they became more resistant to lapatinib.[45] These results verified that HER2 positivity, but not EGFR positivity, is a strong predictor of response to lapatinib. The role of EGFR targeting by lapatinib requires further investigation.

Side Effects, Safety and Tolerability of Lapatinib

Cardiotoxicity

To investigate the cardiotoxicity of lapatinib, investigators collected data from 25 phase I studies, 13 phase II studies, and six phase III clinical studies of lapatinib conducted between January 5, 2001,

and September 30, 2006, in which 3,689 patients received lapatinib.[46]

Those 3689 patients included 376 healthy volunteers (10%), 2,275 patients (69%) with breast cancer, and 1,038 patients (31%) with renal, colorectal, lung, or head and neck cancer. Left ventricular ejection fraction was prospectively evaluated by multiple-gated acquisition scan or echocardiography at the time of screening for trial eligibility, every 8 weeks during treatment, and at withdrawal. A symptomatic cardiac event was defined as grade 3 or 4 left ventricular systolic dysfunction according to the National Cancer Institute Common Terminology Criteria for Adverse Events. An asymptomatic cardiac event was defined as a decrease in left ventricular ejection fraction of more than 20% relative to baseline and below the institution's lower limit of normal without symptoms. Of the 3,689 evaluated patients, 60 (2%) had a cardiac event, and in 53 of these 60 patients (88%), the event was asymptomatic. Twenty-five of the patients with a cardiac event (42%) were enrolled in lapatinib monotherapy trials, and 35 (58%) were enrolled in trials of combination regimens. Twelve patients (20%) had previously been treated with anthracyclines, and 14 patients (23%) had previously been treated with trastuzumab. Outcomes data were available for 40 of the 60 patients who had a cardiac event. Of these, 35 (88%) recovered partially or fully. No cardiac deaths were observed in patients who received lapatinib. Of note, patients who were enrolled in these trials but received nonlapatinib therapy were also evaluated for cardiac events. Among 1,301 patients who did not receive lapatinib, nine cardiac events (0.7%) were noted. This analysis indicated that lapatinib has effects on cardiac function but that these effects are not severe and are reversible.

Trastuzumab is the first targeted biologic agent for which there is evidence of cardiotoxicity. The incidence of congestive heart failure in the pivotal adjuvant trastuzumab trials ranged from 0.4% to 3.8%.[47] Thus, the incidence of cardiac events with lapatinib is not higher than the incidence of cardiac events with trastuzumab (Fig. 3). In light of the cardiotoxicity observed with trastuzumab, all trials of lapatinib have included careful planning to minimize the risk of cardiotoxicity and careful monitoring to evaluate lapatinib's cardiac safety.

One study, reported in abstract form, investigated the cardiac effects of the combination of lapatinib and trastuzumab.[48] The authors analyzed cardiac function in a total of 393 patients with HER2-positive metastatic breast cancer who were treated with lapatinib plus trastuzumab (351 patients) or lapatinib plus trastuzumab with concurrent weekly taxanes (42 patients) in four independent trials. Of the 393 patients in the trial, 313 patients (80%) had previously received trastuzumab and anthracyclines, and 20 patients (5%) had previously received anthracyclines without trastuzumab. The definitions of cardiac events and the method of detection of cardiac events were similar to those used in the previous study described at the beginning of this section.[46] Cardiac events were detected in 12 patients (3.1%) and were asymptomatic in 10 (2.5%) and symptomatic (congestive heart failure) in 2 (0.5%). Nine of the 12 patients with cardiac events had received trastuzumab with anthracyclines, and 2 had received trastuzumab without anthracyclines. Only one of the 12 patients with cardiac events had not received either trastuzumab or anthracyclines.

While trastuzumab is known to carry a risk of cardiac events, adding lapatinib to trastuzumab has not raised the cumulative risk of such events. It is recommended that patients treated with lapatinib undergo the same screening and follow-up testing used for patients treated with trastuzumab. Additional ongoing studies will give us more information on the cardiotoxicity of lapatinib, including lapatinib used for adjuvant or neoadjuvant therapy.

Dermatologic events

To characterize the dermatologic events associated with lapatinib, a pooled analysis was conducted of all patients enrolled in nine lapatinib clinical trials.[49] A total of 2,093 patients were included: 1417 patients who actually received lapatinib, and 676 patients who were enrolled in the trials but did not receive lapatinib (control group). Lapatinib was given as monotherapy (n = 926, 65%) or in combination with paclitaxel or capecitabine (n = 491, 35%). Dermatologic events were classified in eight categories: hand-foot syndrome, rash, hair disorder, dry skin, pruritus/urticaria, skin disorder, skin infection, and nail disorder. Dermatologic events were observed in 58% of patients who were treated with lapatinib monotherapy, 74% of patients who were treated with lapatinib in combination with paclitaxel or capecitabine, and

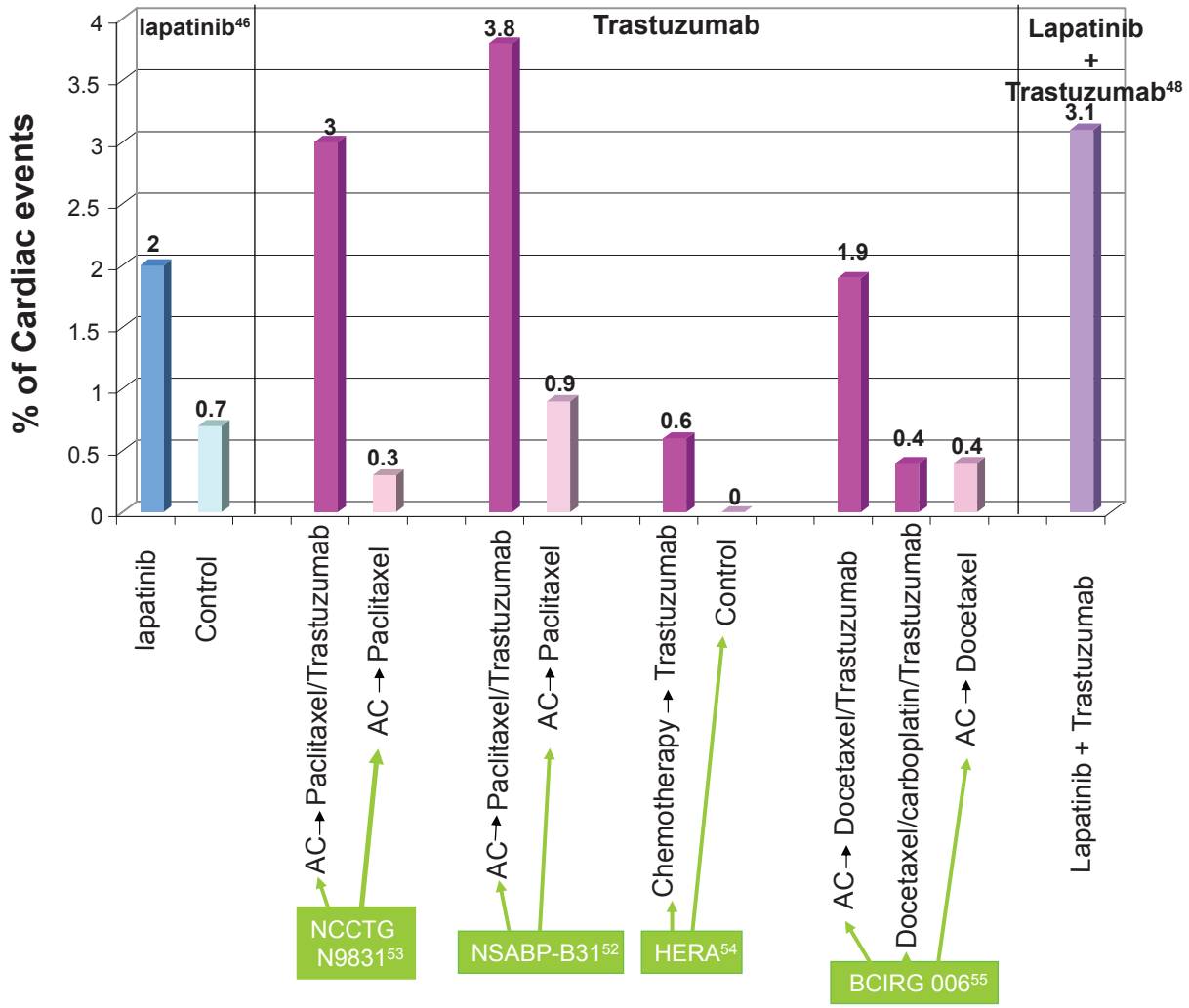

Figure 3. Comparison of cardiac events in clinical trials of lapatinib and trastuzumab.

53% of patients in the control group who did not received lapatinib. In patients who received lapatinib, grade 1 or 2 dermatologic events occurred in 55% of patients, and grade 3 in 3%; there were no grade 4 events. Rash was the most common dermatologic event with lapatinib. Most of those events were observed between days 1 and 14 after treatment initiation. The median duration of dermatologic events was 29 days in lapatinib-treated patients and 18 days in the control group. Dose reductions of lapatinib were required in 3% of cases of dermatologic events, dose interruptions in 7%, and drug discontinuation in 1%.

Patients must be educated about the possibility of these adverse dermatologic events and proactively treated with skin moisturizer without alcohol; patients should also be counseled to avoid sun exposure. Rash can be treated with a short course of oral steroids. Pruritis can be treated with topical agents or oral antihistamines. Careful monitoring is always important to prevent infections. If any significant grade dermatatologic events are noted, the interruption of therapy is recommended.

Diarrhea

Diarrhea is commonly reported with lapatinib therapy and is the adverse event that most commonly causes discontinuation of lapatinib therapy. Data from 11 clinical trials were analyzed to investigate diarrhea events with lapatinib in a total of 2093 patients, including 1417 patients who received lapatinib and 676 who did not receive lapatinib.[50] Lapatinib was given as monotherapy (n = 926) or in combination with capecitabine (n = 198) or taxanes (n = 687). Diarrhea was observed in 51% of the lapatinib-treated patients

versus 24% of the patients who did not receive lapatinib. Most of the patients with diarrhea experienced only grade 1 or 2 diarrhea; fewer than 10% had grade 3 diarrhea, and fewer than 1% had grade 4 diarrhea. Diarrhea was noted early in the treatment course (within 6 days after initiation of therapy) in most of the cases, and the median duration was 7–9 days. Most events did not required treatment discontinuation and resolved.

Of note, this study showed significant reductions in the incidence and severity of diarrhea after the introduction of supportive strategies, indicating that proactive measures to prevent and treat diarrhea are essential. Diarrhea can be managed according to the American Society of Clinical Oncology treatment guidelines. Dietary modification should be started for most uncomplicated cases; lapatinib and other chemotherapeutic agents should be withheld if grade 2 or higher diarrhea is noted. Loperamide or octreotide can be used to control diarrhea. In the case of severe and refractory symptoms, the patient needs to be hospitalized to receive intravenous medications such as octreotide and intravenous hydration.

Summary and Future Directions

Lapatinib has emerged as a promising second-generation (after trastuzumab) targeted therapy for patients with HER2-positive breast cancer. Studies show that lapatinib is not only as effective as trastuzumab but also has unique indications not shared with trastuzumab. In contrast to trastuzumab, a large molecule, lapatinib can cross the blood-brain barrier to treat CNS metastases effectively. Preliminary data on the efficacy of lapatinib against IBC are exciting, but further elucidation of its mechanism of action against IBC is required. Lapatinib in combination with hormonal therapy may be able to overcome resistance to hormonal therapy. Furthermore, lapatinib may act synergistically with trastuzumab to increase response and decrease resistance. The side effects of lapatinib are tolerable and manageable, especially in terms of cardiotoxicity, which has been monitored very carefully in light of the experiences with trastuzumab. Current ongoing clinical trials will further provide insight into the potential clinical uses of lapatinib. Further, the importance of EGFR targeting in the efficacy of lapatinib against breast cancer needs to be further investigated in clinical studies.

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