Breast Cancer: Targets and Therapy

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REVIEW

Role of lapatinib alone or in combination in the treatment of HER2-positive breast cancer

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Purpose: This review aims to present the preclinical and clinical data regarding efficacy and safety of lapatinib alone and in combination with other agents in the treatment of human epidermal growth factor receptor-2 (HER2)-overexpressing breast cancer.

Background: HER2-positive (HER2+) breast cancer remains a treatment challenge. It is more aggressive than other breast cancers and it is associated with a poor outcome. Targeted therapy for HER2+ breast cancer has significantly changed the clinical course of the disease. Despite advances in therapy, there remains an unmet need in the treatment of HER2+ breast cancer. Lapatinib is a novel, orally bioavailable epidermal growth factor receptor/HER2+ targeted agent. Many trials have investigated the efficacy and safety of lapatinib alone and in conjunction with other agents in the treatment of HER2+ breast cancer.

Methods and results: Preclinical and clinical trials of lapatinib have shown that it is effective in the treatment on HER2+ breast cancer. More important, studies show that it is effective in the setting of trastuzumab resistance and in the treatment of central nervous system metastases, both of which are current treatment challenges. Furthermore, lapatinib is effective in conjunction with trastuzumab in the treatment of early breast cancer. Data regarding the safety of lapatinib show that it is generally well tolerated; however, multiple studies have shown significant (grade 3 and 4) diarrhea and rash associated with lapatinib, thereby limiting its use. Carditoxicity has not been a significant adverse event associated with the use of lapatinib.

Conclusion: Lapatinib is effective alone and in conjunction with other agents in the treatment of HER2+ breast cancer. However, its use is limited by significant diarrhea and rash.

Keywords: human epidermal growth factor receptor 2, breast neoplasms, central nervous system metastases, trastuzumab

Introduction

Each year, nearly 1.4 million cases of breast cancer are diagnosed globally,[1] including over 200,000 cases in the United States.[2] While advances in both early detection and treatment have improved clinical outcomes for those diagnosed, breast cancer remains the leading cause of cancer deaths worldwide[1] and the second-leading cause of cancer deaths in women in the United States.[2] Advances in the molecular characterization of breast tumors have revealed that several distinct subtypes of breast cancer exist.[3,4] An improved understanding of the genetic changes that drive tumor biology has facilitated the development of targeted therapeutics to rationally treat this disease. One subtype that accounts for up to 25% of breast cancers is distinguished by amplification of the human epidermal growth factor receptor-2 (HER2) gene on chromosome 17, which leads to overexpression of the HER2 protein on the surface of

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tumor cells.[5,6] Tumors with the HER2 alteration have been shown to be particularly aggressive and are associated with a poorer prognosis than HER2-normal tumors.[5] Fortunately, the development and subsequent US Food and Drug Administration (FDA) approval of trastuzumab (Herceptin®; Genentech, Inc, San Francisco, CA), a humanized IgG monoclonal antibody targeted against the extracellular domain of HER2, has vastly improved outcomes for patients diagnosed with HER2-driven breast cancer.[7–10] The success of trastuzumab cannot be overstated; however, limitations of this targeted therapy do exist. Significant clinical challenges remain including de novo and acquired trastuzumab resistance, lack of central nervous system (CNS) penetration of trastuzumab, and a small but important risk of cardiotoxicity. Therefore, newer targeted agents in the treatment of HER2-positive (HER2+) breast cancer are still needed.

Lapatinib (Tykerb®; GlaxoSmithKline, Brentford, UK) is an orally bioavailable small molecule dual tyrosine kinase inhibitor of both HER2 and epidermal growth factor receptor (EGFR or HER1).[11] Inhibition of HER2 and EGFR results in blockade of downstream signaling pathways and preclinically has been shown to lead to cessation of cell proliferation and cell death.[12] In 2007, lapatinib was approved by the FDA for use in combination with capecitabine for the treatment of HER2+ locally advanced or metastatic breast cancer (MBC) in patients whose disease progressed on or after an anthracycline, a taxane, and trastuzumab.[11] Studies have also investigated the use of lapatinib as monotherapy and in combination with other chemotherapeutic and nonchemotherapeutic agents. This article will review the use of trastuzumab, including its clinical limitations, and then will focus on data relating to the use of lapatinib for HER2+ breast cancer – including evidence related to its efficacy, safety, and tolerability.

Trastuzumab

Clinical data: trastuzumab in the metastatic setting

In 1998, trastuzumab became the first targeted monoclonal antibody approved by the FDA for the first-line treatment of HER2+ MBC. This approval was based on a pivotal Phase III trial that enrolled 469 patients and showed the addition of trastuzumab to chemotherapy led to improved objective response rates (ORRs) compared with patients treated with chemotherapy alone (50% vs 32%, respectively; $P < 0.001$), time to progression (TTP) (median, 7.4 vs 4.6 months, respectively; $P < 0.001$), duration of response (median, 9.1 vs 6.1 months, respectively; $P < 0.001$), and overall survival (OS) (median, 25.1 vs 20.3 months, respectively; $P = 0.01$).[7] As a single agent in the first-line MBC setting, trastuzumab has been shown to yield response rates ranging from 19% to 26% (up to 35% in those confirmed to be HER2+ by immunohistochemistry or FISH [fluorescence in situ hybridization] testing).[13,14] Beyond the first-line setting, trastuzumab has been shown to lead to a response rate of 15%.[15]

Many Phase II and III studies have evaluated the combination of trastuzumab with chemotherapy for MBC in the first-line setting and beyond, yielding response rates ranging from 30% to 70%.[16–25] Trastuzumab has also been given in combination with hormonal manipulation. In the Phase III randomized TANDEM (Trastuzumab in Dual HER2 ER-Positive Metastatic Breast Cancer) study, 207 patients with HER2+ and hormone receptor–positive MBC were randomly assigned to receive anastrozole alone or with trastuzumab. The trastuzumab-treated patients had an improved median progression-free survival (PFS) compared with the control arm (4.8 vs 2.4 months, respectively; log-rank $P = 0.0016$; hazard ratio [HR], 0.63; 95% CI: 0.47–0.84). There was no difference in OS between the two groups; however, 70% of patients from the control arm crossed over to receive trastuzumab after progression.[26]

While use of trastuzumab in trastuzumab-naïve patients with MBC has been an accepted standard of care for over a decade, the continued use of trastuzumab after disease progression on trastuzumab-based therapy is also now gaining evidence-based support through the reporting of several studies.[27–30] The first prospective trial to address this issue randomly assigned 156 patients with HER2+ MBC who had previously progressed on trastuzumab to receive capecitabine alone or with trastuzumab. The median TTP was significantly better in the trastuzumab arm than in those receiving capecitabine alone (8.2 vs 5.6 months, respectively; $P = 0.0338$), as was the ORR (48.1% vs 27.0%, respectively; $P = 0.0115$).[27,28] While the final OS analysis did not show a significant improvement, a post hoc analysis showed women who received HER2-targeted therapy in the third-line setting (n = 88) demonstrated an improved post-progression survival compared with those who did not receive HER2-targeted treatment (18.8 vs 13.3 months, respectively; HR: 0.63; $P = 0.02$).[28]

Clinical data: trastuzumab in the early disease setting

Subsequent to its approval for MBC, trastuzumab was approved in 2005 for use in combination with chemotherapy for nonmetastatic HER2+ breast cancer based on several

large Phase III randomized clinical trials that showed the addition of trastuzumab to chemotherapy improves not only disease-free survival but also OS.[8,9,31,32] Data are now emerging that show the use of trastuzumab in early HER2+ breast cancer has altered the natural history of the disease, such that patients with HER2+ breast cancer treated with trastuzumab may have a better outcome than patients with HER2-negative (HER2–) disease.[10,33]

Clinical data also support the use of trastuzumab in the neoadjuvant setting. The TECHNO (Taxol Epirubicin Cyclophosphamide Herceptin Neoadjuvant) trial is a Phase II clinical trial that investigated the addition of trastuzumab to chemotherapy in the neoadjuvant setting for patients with HER2+ disease.[34] Patients received four cycles of epirubicin and cyclophosphamide followed by four cycles of paclitaxel and trastuzumab before surgery. Of the 217 patients enrolled, 39% achieved a complete pathologic response (pCR) in the breast and lymph nodes. In another study, patients were randomly assigned to four cycles of paclitaxel followed by four cycles of FEC (5-fluorouracil, epirubicin, cyclophosphamide) with or without trastuzumab. The data monitoring committee closed this study early because of the superiority of the trastuzumab-containing regimen. The analysis for the 42 randomized and treated patients showed a statistically significant improvement in pCR with the addition of trastuzumab to neoadjuvant chemotherapy compared with neoadjuvant chemotherapy without trastuzumab (65.2% vs 26%, respectively; $P = 0.016$).[35]

The GeparQuattro and NOAH (Neoadjuvant Herceptin) trials are both Phase III trials that investigated the addition of trastuzumab to neoadjuvant chemotherapy in patients with HER2+ disease.[36,37] Of 445 patients treated with a neoadjuvant trastuzumab-based regimen in the GeparQuattro study, 32% achieved a pCR in breast and nodes.[22] The NOAH trial reported a statistically significant improvement in pCR with the addition of trastuzumab to neoadjuvant chemotherapy (38% vs 19%, for with and without trastuzumab, respectively; $P = 0.001$, in breast and lymph nodes). The same trial also reported a statistically significant improvement in the 3-year event-free survival rate (71% vs 56%, for with and without trastuzumab, respectively; HR: 0.59; 95% CI: 0.38–0.90; $P = 0.013$).[36]

Limitations to trastuzumab

In general, trastuzumab is well tolerated and safe. Approximately 20%–50% of patients experience mild to moderate infusion-related reactions that are usually most severe with the initial administration,[15] but this is rarely life threatening, and the majority of patients are able to receive trastuzumab subsequently.

Cardiotoxicity has emerged as the most serious side effect of trastuzumab. The mechanism of trastuzumab-induced cardiomyopathy is not fully understood; however, it is known that HER2 is expressed in cardiac myocytes and that HER2 signaling may play a role in regulating cell survival during stress.[37,38] Trials evaluating single-agent trastuzumab in the metastatic setting have reported a 2.6%–8.5% incidence of symptomatic heart failure.[38] The vast majority of these patients had received prior anthracycline-based chemotherapy. More concerning is that 27% of patients who received concurrent anthracyclines and trastuzumab in the metastatic setting developed symptomatic congestive heart failure, 16% of whom were New York Heart Association Class III/IV.[7] Therefore, subsequent studies have in general not allowed concurrent administration of anthracyclines with trastuzumab. In the adjuvant setting, trastuzumab has been reported to be discontinued because of cardiac events in 4.3% of patients,[39] and cardiac events have been reported in up to 3.8% of patients treated primarily with sequential anthracycline-based regimens.[40,41] One adjuvant study compared a nonanthracycline-based trastuzumab regimen (docetaxel, carboplatin, trastuzumab) and the standard anthracycline-based regimen (doxorubicin/cyclophosphamide followed by docetaxel and trastuzumab). This study reported congestive heart failure in 0.4% vs 2.0% of patients receiving the nonanthracycline-based trastuzumab and the standard anthracycline-based regimen, respectively, and a drop in left ventricular ejection fraction of greater than 10% in 9.4% vs 18.6% of patients, respectively.[31]

De novo and acquired resistance to trastuzumab is also common.[42] Up to 19% of patients with HER2+ early breast cancer treated with a trastuzumab-based chemotherapy regimen will have disease relapse in 5 years,[31,32] and in advanced HER2+ breast cancer, up to 50% of patients do not respond to first-line trastuzumab plus chemotherapy.[7] Several mechanisms of resistance to trastuzumab have been proposed, including, but not limited to, overexpression of truncated HER2 (p95) that does not contain an extracellular domain for trastuzumab binding,[43,44] elevated levels of insulin-like growth factor-I receptor (IGF-1R),[45,46] and increased signaling through pathways such as EGFR[47] and the phosphoinositide-3-kinase (PI3K)/activated protein kinase B (AKT) pathway.[48–50] One goal in the development of new HER2-targeted agents is to circumvent the most relevant pathways of resistance to reduce the risk of inherent or acquired resistance to treatment.

Another clinical dilemma that has not been adequately addressed by trastuzumab is the issue of CNS metastases. In a retrospective analysis of 136 patients with HER2+ MBC, the incidence of CNS metastases was found to be 31%, and the median OS after development of CNS metastases was 13 months (range, 0–60 months).[51] Lack of hormone receptor expression correlated with incidence of brain metastases (43% lack of expression vs 23% presence of expression; $P = 0.01$) and the median time from diagnosis of metastatic disease to diagnosis of brain metastasis was 14 months. Other studies have reported similar incidence rates for the development of CNS metastases in HER2+ breast cancer.[51–53] It is important to also note that retrospective data from 598 women with CNS metastases from breast cancer indicate that patients with HER2– disease and patients with HER2+ disease not treated with trastuzumab had shorter times to CNS metastases and an increased risk of death than patients with HER2+ breast cancer who received trastuzumab as first-line treatment for MBC.[54] Therefore, trastuzumab does appear to delay the diagnosis of CNS metastases and it improves survival. That said, trastuzumab does not cross the blood-brain barrier. A pilot study measured trastuzumab levels in the serum and cerebrospinal fluid of six women with HER2+ breast cancer with CNS metastases at different time points in the course of treatment.[55] The ratio of trastuzumab in the serum to that in the cerebrospinal fluid was 420:1 prior to radiotherapy, indicating that trastuzumab is unable to penetrate the blood-brain barrier. After whole-brain radiotherapy, the ratio improved to 76:1, and in patients with meningeal carcinomatosis the ratio after radiotherapy was 49:1. While the penetration of trastuzumab was improved after radiation, especially in the setting of leptomeningeal carcinomatosis, the levels achieved were still likely to be subtherapeutic. While there are observational data to suggest that patients benefit from continued use of trastuzumab after CNS progression,[56,57] the optimal treatment for brain metastases is still an area of unmet need.

Lapatinib

Preclinical data

Early in its development, preclinical evaluation of lapatinib in EGFR- and HER2-dependent tumor cell lines was shown to produce several antitumor effects including (1) a reduction in activation of both EGFR and HER2; (2) inhibition of Erk1/2, a transcription factor that stimulates tumor cell proliferation; and (3) a decline in AKT, leading to a 23-fold increase in apoptosis.[58] These inhibitory effects were not reversed by adding the epidermal growth factor ligand to cells. Moreover, these findings were reproduced in vivo in human tumor xenograft models.[58] The activity of lapatinib was further tested in a well-characterized panel of 22 human breast cancer cell lines expressing different levels of EGFR and HER2.[59] Nine of the cell lines were known to have amplification and overexpression of HER2, three were known to have high levels of EGFR, and the remaining cell lines had lower levels of expression of these two receptors. Interestingly, cells with the highest level of HER2 expression were most sensitive to lapatinib ($r = -0.61$; $P = 0.005$) but no such correlation was found for EGFR expression ($r = 0.05$; $P = 0.838$).[59] These preclinical results suggested the activity of lapatinib should be greatest in HER2-driven tumors.

Given the structural and functional differences between trastuzumab and lapatinib, a natural question is whether lapatinib is able to overcome trastuzumab resistance. Indeed, laboratory studies have shown that many trastuzumab-resistant cell lines remain sensitive to lapatinib, suggesting that the mechanisms of resistance to these two treatments differ. In one study, three HER2-overexpressing, trastuzumab-conditioned cell lines were tested to evaluate the efficacy of lapatinib in the setting of trastuzumab resistance.[59] As expected, trastuzumab retreatment yielded little to no effect; however, lapatinib demonstrated significant activity in all three cell lines compared with untreated controls. The antitumor activity of lapatinib on trastuzumab-resistant cells was further evaluated using a trastuzumab-resistant, HER2+ SKBR3 breast cancer cell line.[60] In this experiment, lapatinib was shown to inhibit not only EGFR and HER2 signaling but also IFG-I signaling. The cytotoxic effects of lapatinib were augmented by cotreatment with an IGF-1R-blocking antibody, indicating that one way lapatinib circumvents trastuzumab resistance is through blockade of IGF-1 pathway activation. Several studies indicate that activation of the PI3K-AKT pathway, via activating mutations in PI3K or downregulation of the tumor suppressor phosphatase and tensin homolog (PTEN), leads to trastuzumab resistance, but does not affect sensitivity to lapatinib.[48,50,61] To further evaluate the role of this pathway in the development of treatment resistance, O'Brien et al[49] evaluated the response of 18 HER2+ cell lines to lapatinib and trastuzumab and showed that lapatinib (but not trastuzumab) response correlated with increased phosphorylation of HER2, EGFR, and IGF-1R, and further showed that increased activation of the PI3K-AKT pathway was a marker of resistance to trastuzumab, but could be overcome by lapatinib. Collectively, these data provide support for the clinical development of lapatinib in the trastuzumab-resistant disease setting.

The effects of combining lapatinib and trastuzumab have also been studied in the laboratory. The combination of both HER2-targeted agents has demonstrated synergistic

antiproliferative effects in four HER2 overexpressing cell lines,[59] it has been shown to augment apoptosis,[62] and it has shown enhanced antitumor activity in vivo using a HER2-overexpressing (BT-474) tumor xenograft model.[63] These promising results have provided the foundation for evaluation of the combination of these two targeted approaches in the clinic. Other nonchemotherapeutic combinations have also been studied preclinically, including lapatinib plus tamoxifen[64] and lapatinib plus fulvestrant.[65]

Clinical data: lapatinib in the metastatic setting

Since the first-in-human studies of lapatinib were initiated in 2001,[12] there have been multiple trials that have evaluated lapatinib as single agent or in combination with other antitumor therapies. Table 1A and B shows the ongoing clinical trials evaluating lapatinib in the metastatic setting.

Lapatinib monotherapy

A Phase I dose escalation (increasing from 500 to 1600 mg daily) trial (EGF10004) evaluated lapatinib in 67 heavily pretreated patients with EGFR- and/or HER2-overexpressing advanced solid tumors (30 of whom had breast cancer) and reported four partial responses in trastuzumab-resistant MBC and prolonged stable disease (SD) in 10 patients. The most common drug-related adverse events (AEs) were dose-related diarrhea in 42% and rash in 31%.[66] A Phase II trial evaluating single-agent lapatinib for treatment-refractory advanced breast cancer enrolled 140 women with trastuzumab-pretreated HER2+ disease and showed that by independent review only 1.4% of patients achieved an objective response and 5.7% of patients derived clinical benefit from this therapy.[67] Another Phase II trial that evaluated single-agent lapatinib in 78 women with HER2+, trastuzumab-refractory disease showed a slightly improved ORR of 5.1%.[68] The study also reported a median PFS of 15.3 weeks and a median OS of 79 weeks. A third Phase II trial evaluated 122 Japanese women who relapsed on prior treatment with trastuzumab.[69] In the 100 women who had HER2+ disease, the ORR was 19% and OS was 58.3 weeks. These studies show a wide array of response rates for lapatinib monotherapy in the trastuzumab refractory setting, leaving the role of single-agent lapatinib in these patients unclear.

Lapatinib monotherapy has also been evaluated in the trastuzumab-naïve setting. In a Phase II clinical trial, 138 patients with HER2+ locally advanced or MBC and who were previously untreated for advanced disease were randomly assigned to be treated with either 1500 mg daily or 500 mg twice-daily lapatinib as a single agent. No patients had received prior trastuzumab. The ORR was 24% and the 6-month PFS was 43%.[70] Although active, based on cross-trial comparisons, first-line monotherapy with lapatinib does not seem to offer significant benefit over that of single-agent trastuzumab.[13] A randomized trial comparing the two in the front-line metastatic setting has not been reported to date.

Lapatinib in conjunction with other HER2-targeted agents

Synergistic activity for the combination of lapatinib and trastuzumab has been demonstrated in HER2-overexpressing

Table 1A Ongoing clinical trials of lapatinib in the metastatic setting: lapatinib plus chemotherapy

Study	Status	Patient population	Study design and treatment regimen	Phase	N
NCT00496366	Ongoing	First-line for HER2+, stage III/IV	Single-arm, open-label, capecitabine + lapatinib	II	11
NCT00721630	Ongoing	HER2+ MBC	Single-arm, open-label, capecitabine + lapatinib	II	24
NCT00903656	Ongoing	HER2+, advanced or MBC	Single-arm, open-label, doxorubicin + lapatinib	II	30
NCT00508274	Ongoing	HER2+, stage III/IV	Open label, capecitabine + lapatinib	III	52
NCT00820222	Ongoing	HER2+ MBC	Randomized, capecitabine + lapatinib or trastuzumab	III	650
NCT00667251	Ongoing	HER2+ MBC	Randomized, docetaxel or paclitaxel with lapatinib vs trastuzumab	III	600
NCT00281658	Ongoing	HER2+ MBC	Randomized, double-blind, paclitaxel ± lapatinib	III	444
NCT00709618	Ongoing	First-/second-line HER2+ MBC	Single-arm, open-label, vinorelbine + lapatinib	II	60
NCT00709761	Ongoing	First-/second-line HER2+ MBC	Single-arm, open-label, nab-paclitaxel + lapatinib	II	60
NCT00272987	Ongoing	HER2+ MBC	Open-label, paclitaxel + trastuzumab + lapatinib	III	63
NCT01128543	Ongoing	HER2+ MBC	Single-arm, open-label, vinorelbine + lapatinib	II	29
NCT00829166	Ongoing	Trastuzumab refractory, HER2+	Randomized, open-label, trastuzumab emtansine vs capecitabine + lapatinib	III	980
NCT01013740	Ongoing	First-/second-line HER2+ MBC	Randomized, open-label, vinorelbine + lapatinib vs capecitabine + lapatinib	II	105

Abbreviations: HER2+, HER2 positive; MBC, metastatic breast cancer; vs, versus.

Table 1B Ongoing clinical trials of lapatinib in the metastatic setting: lapatinib plus nonchemotherapeutic agents

Study	Status	Patient population	Study design and treatment regimen	Phase	N
NCT00558103	Ongoing	HER+ inflammatory breast cancer	Randomized, double-blind, lapatinib ± pazopanib	III	360
NCT01272141	Ongoing	Triple negative, advanced or MBC	Single-arm, open-label, everolimus + lapatinib	II	43
NCT00470704	Ongoing	HER2+ MBC	Single-arm, open-label, trastuzumab + lapatinib	III	85
NCT00390455	Ongoing	HR+, stage III/IV	Randomized, double-blind, fulvestrant + lapatinib	III	324
NCT00688194	Ongoing	HER2–, HR+ MBC	Randomized, double-blind, fulvestrant + AI + lapatinib	III	396
NCT00118157	Ongoing	HR+, tamoxifen resistant	Single-arm, open-label, tamoxifen + lapatinib	II	19
NCT01499160	Ongoing	HR+, advanced or MBC	Single-arm, open-label, letrozole + lapatinib + everolimus	II	76
NCT00968968	Ongoing	Trastuzumab-pretreated HER2+ MBC	Randomized, open-label, trastuzumab + lapatinib vs trastuzumab maintenance therapy	III	280
NCT01160211	Ongoing	First-line HER2+, HR+ MBC	Randomized, three-arm, open-label, AI + trastuzumab and/or lapatinib	III	525

Abbreviations: AI, aromatase inhibitor; HER2–, human epidermal growth factor receptor 2 negative; HER2+, human epidermal growth factor receptor 2 positive; HR+, hormone receptor positive; MBC, metastatic breast cancer.

cell lines, suggesting a potential for clinical activity with the combination of the two HER2-targeted agents.[59] A Phase I study to evaluate the safety, feasibility, and dosing of trastuzumab combined with lapatinib in 54 patients with HER2+ advanced breast cancer revealed the optimal regimen was lapatinib 1000 mg daily with standard weekly trastuzumab. There were no pharmacokinetic interactions with the two drugs, and eight patients achieved a response to this regimen (one complete response [CR], seven partial response [PR]).[71] A randomized Phase III clinical trial compared lapatinib alone or in combination with trastuzumab in trastuzumab-refractory HER2+ MBC in 296 patients.[72] The study found a statistically significant improvement in PFS (HR: 0.73; 95% CI: 0.57–0.93; $P = 0.008$), increasing from 8.1 to 12.0 weeks with the combination (Table 2). The final OS intent to treat analysis showed that, in spite of 77 patients crossing over to the combination arm at the time of progression, OS was significantly improved in the combination arm (9.5 vs 14.0 months, for lapatinib alone and with trastuzumab, respectively; HR: 0.74; 95% CI: 0.57–0.97; $P = 0.026$).[73] These studies suggest that the combination of lapatinib and trastuzumab is an effective nonchemotherapeutic regimen in patients with HER2+ MBC who have progressed on trastuzumab-containing regimens.

Lapatinib in conjunction with endocrine therapy

Approximately half of HER2+ breast cancers coexpress estrogen and/or progesterone receptors, opening up the possibility of dual targeting of these pathways as a treatment strategy. A Phase III randomized trial compared lapatinib plus letrozole to lapatinib plus placebo as first-line therapy in patients with hormone receptor–positive MBC (Table 2).[74] In the 219 patients with HER2+ disease, the combination arm yielded a statistically significant improved PFS, increasing from 3.0 to 8.2 months (HR: 0.71, 95% CI: 0.53–0.96; $P = 0.019$); ORR, increasing from 15% to 28% (OR: 0.4, 95% CI: 0.2–0.9; $P = 0.021$); and clinical benefit rate (CBR), increasing from 29% to 48% (OR: 0.4, 95% CI: 0.2–0.8; $P = 0.003$). The difference in OS was not statistically significant. This study supports a role for lapatinib in combination with letrozole as an effective nonchemotherapeutic first-line therapy in patients with hormone receptor and HER2+ MBC. That said, no study at this time has compared dual targeting of both HER2 and hormone receptors to the combination of HER2-targeted therapy plus chemotherapy. Cross-trial comparisons, though faulty by nature, seem to suggest that the combination of chemotherapy with HER2-targeted therapy is more active than the combination of endocrine therapy plus HER2-targeted therapy.[75]

Lapatinib in combination with antiangiogenic agents

One mechanism by which HER2 overexpression mediates aggressive tumor behavior may be via expression of angiogenic factors such as vascular endothelial growth factor (VEGF). Supporting this are preclinical data that demonstrate an upregulation of VEGF in HER2+ breast cancer cell lines[76,77] and in patients with HER2+ primary breast tumors.[78] Furthermore, the combination of trastuzumab and bevacizumab reduced tumor volume in HER2-overexpressing xenografts when compared with single-agent controls, suggests a role for the combination of HER2-targeted therapy with VEGF inhibitors.[79] A Phase II trial that investigated the combination of lapatinib and bevacizumab in the treatment of 52 patients with HER2+ MBC showed a PFS of 24.7 weeks and an ORR of 13.3%.[80] A Phase II trial

Table 2 Summary of Phase III trials of lapatinib in combination with other agents

Study	N	Patients	Treatment	Outcomes
Lapatinib + nonchemotherapeutic agents				
Schwartzberg et al[108]	219*	First-line HR+, HER2+ MBC	Lapatinib ± letrozole	PFS: 3.0 vs 8.2 months; HR: 0.71; $P = 0.019$ ORR: 15% vs 28%; $P = 0.021$ CBR: 29% vs 48%; $P = 0.003$ OS: 32.3 vs 33.3 months (*P*-value not reported)
Blackwell et al[72,73]	296	HER2+, trastuzumab refractory MBC	Lapatinib ± trastuzumab	PFS: 8.1 vs 12.0 weeks; HR: 0.73; $P = 0.008$ ORR: 6.9% vs 10.3%; $P = 0.46$ CBR: 12.4% vs 24.7%; $P = 0.01$ Final OS: 9.5 vs 14.0 months; HR: 0.74; $P = 0.026$
Chemotherapeutic agents ± lapatinib				
Geyer et al[11]	399	HER2+, trastuzumab refractory MBC	Capecitabine ± lapatinib	PFS: 4.4 vs 8.4 months; HR: 0.47; $P < 0.001$ ORR: 14% vs 22%; $P = 0.09$ CBR: 29% vs 44% Death: 22% vs 22%; HR: 0.92; $P = 0.72$
Di Leo et al[84]	86**	First-line MBC	Paclitaxel ± lapatinib	PFS: 25.1 vs 36.4 weeks; HR: 0.53; $P = 0.005$ ORR: 37.8% vs 63.3%; $P = 0.023$ CBR: 40.5% vs 69.4%; $P = 0.011$ OS: 82.4 vs 104.6 weeks; HR: 0.74; $P = 0.365$
Neoadjuvant administration of lapatinib				
Baselga et al[96]	455	Invasive, operable, HER2+	Lapatinib and/or trastuzumab***	pCR: 24.7% vs 29.5% vs 51.3%; $P = 0.34$ (lapatinib vs trastuzumab); $P = 0.0001$ (lapatinib + trastuzumab vs trastuzumab) ORR: 52.6% vs 30.2% vs 67.1%; $P < 0.001$ (lapatinib vs trastuzumab); $P < 0.001$ (lapatinib + trastuzumab vs trastuzumab)
Untch et al[94]	620	Locally advanced, HER2+	Lapatinib vs trastuzumab****	pCR: 21.7% vs 31.3%; $P < 0.03$

Notes: *Study enrolled a total of 1286 patients (219 were HER2+); the outcome data presented here are from the HER2+ patients; **study enrolled a total of 579 patients (only 86 were HER2+); the outcome data presented here are from the HER2+ patients; ***therapy administered for 6 weeks followed by 12 weeks of same therapy plus weekly paclitaxel; ****therapy administered with epirubicin, cyclophosphamide, and docetaxel.

Abbreviations: CBR, clinical benefit rate; HER2+, human epidermal growth factor receptor 2 positive; HR, hazard ratio; HR+, hormone receptor positive; MBC, metastatic breast cancer; ORR, overall response rate; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; vs, versus.

comparing the combination of lapatinib plus pazopanib (an oral small molecule inhibitor of VEGFR, c-KIT, and platelet-derived growth factor receptor [PDGFR]) with lapatinib alone as first-line therapy in the treatment of HER2+ MBC is ongoing.[81] A prespecified interim analysis (N = 62) showed an improved ORR, increasing from 30% to 44%, and a reduction in the week-12 progressive disease (PD) rate, decreasing from 27% to 19%, with the combination. A Phase III trial evaluating lapatinib in conjunction with pazopanib for HER2+ inflammatory breast cancer (NCT00558103) is ongoing (Table 1B).

Lapatinib in conjunction with chemotherapeutic agents

Metastatic setting

Two Phase III studies have reported outcomes associated with lapatinib in combination with chemotherapy (Table 2). In the Phase III study[11] that led to the FDA approval of lapatinib in 2007, 399 women with HER2+ locally advanced or MBC and whose disease had progressed on regimens containing an anthracycline, taxane, and trastuzumab were randomly assigned to receive either lapatinib plus capecitabine or capecitabine alone. Patients in the lapatinib arm had a

significantly prolonged TTP compared with patients receiving capecitabine alone (6.2 vs 4.3 months, respectively; HR: 0.57, 95% CI: 0.43–0.77; $P < 0.001$), a significantly improved ORR (23.7% vs 13.9%, respectively; OR: 1.9, 95% CI: 1.1–3.4; $P = 0.017$), and a significantly improved CBR (29.3% vs 17.4%, respectively, OR: 2.0; 95% CI: 1.2–3.3; $P = 0.008$).[11,82] The final analysis of OS in this heavily pretreated patient population revealed no significant difference between the treatment arms. However, early termination of enrollment, as recommended by the independent data monitoring committee, as well as crossover from the control arm to the lapatinib arm made a survival difference difficult to detect.[83]

Another Phase III trial compared lapatinib plus paclitaxel with placebo plus paclitaxel as first-line therapy for women with MBC (Table 2).[84] For the 86 patients with HER2+ disease, there was a statistically significant improved PFS reported for those receiving the combination of lapatinib plus paclitaxel, as compared with the combination of placebo plus paclitaxel (35.4 vs 25.1 weeks, respectively; $P = 0.005$). This statistically significant improvement also applied to ORR (53.3% vs 37.8%, respectively; $P = 0.023$) and CBR (69.4% vs 40.5%, respectively; $P = 0.011$). Interestingly, no benefit was seen with the combination in patients with HER2– disease.[85] While the results of combining lapatinib with chemotherapeutic agents in the first-line setting are promising, it is not yet FDA approved for this indication.

Smaller studies have also evaluated lapatinib in combination with other chemotherapies, including a Phase I study that evaluated lapatinib with docetaxel in 52 patients with advanced solid malignancies.[86] The optimally tolerated dosing regimen was defined as 1250 mg daily of lapatinib with 75 mg/m^2 of docetaxel every 3 weeks. Two out of 43 assessable patients had confirmed partial responses and there was no pharmacological interaction observed with the two drugs. Lapatinib has also been combined with a less traditional regimen of "1 week on/1 week off" of capecitabine (flat dose of 2000 mg orally twice daily) in a Phase II study that enrolled 23 patients with trastuzumab-pretreated HER2+ MBC.[87] This study reported a PR in 23% of patients and SD in 27%, as well as a median PFS of 9.4 months, and trastuzumab was shown to be well tolerated with respect to gastrointestinal toxicity. Another Phase I study evaluated two different dosing schedules of lapatinib in combination with vinorelbine in 52 patients; this study showed the regimen to be safe and well tolerated, with some clinical activity in two patients with HER2+ breast cancer.[88] Other Phase II and III trials are further examining the use of lapatinib with capecitabine (NCT00496366), vinorelbine (NCT00709618), and nab-paclitaxel (NCT00709761) in the first-line setting (Table 1A).

Early breast cancer setting: focus on neoadjuvant

Because of the ability to serially biopsy primary breast tumors before and after treatment, neoadjuvant clinical trials provide a unique opportunity for evaluating the molecular activity of a given therapy and grant scientists an opportunity to better understand mechanisms of response and resistance to this therapy. A window-of-opportunity, tissue-acquisition, randomized, placebo-controlled study evaluated lapatinib (1500 mg/day) for 3 weeks between biopsy and surgery in 60 women with HER2+ operable breast cancer in order to evaluate molecular changes (including Ki67) as well as clinical activity in the invasive tumor and adjacent ductal intraepithelial neoplasia. Lapatinib treatment was associated with a greater reduction of Ki67 in ER-negative tumors than placebo treatment (35% reduction; $P = 0.01$), and it resulted in a significantly decreased tumor diameter at the time of surgery (18 vs 24 mm, for lapatinib and placebo, respectively; $P = 0.009$); however, the prevalence of adjacent ductal intraepithelial neoplasia was not significantly different (70% vs 76%, for lapatinib and placebo, respectively; $P = 0.8$).[89] A Phase II study of lapatinib monotherapy (1500 mg daily) enrolled 45 patients with recurrent inflammatory breast cancer. As one end point of the study was to investigate a molecular signature that would predict response to lapatinib, fresh pretreatment tumor samples were taken from all patients.[90] Fifty percent of the patients with HER2+ breast cancer had clinical responses; in these patients, pHER3 and lack of p53 expression predicted for lapatinib sensitivity ($P < 0.05$). Moreover, prior trastuzumab and loss of PTEN did not rule out a response to lapatinib.

Several neoadjuvant studies have also compared the clinical activity and/or molecular outcomes of lapatinib and trastuzumab in HER2+ primary breast cancer. A Phase II neoadjuvant trial with serial biopsies for molecular analyses evaluated a 14-day run-in of single-agent lapatinib (1500 mg/daily) followed by 12 weeks of lapatinib plus weekly paclitaxel (80 mg/m^2) in 42 patients with HER2+ inflammatory breast cancer. A pCR was achieved in 18.2% of patients, but grade 3 diarrhea was reported in 55% of patients.[91] Two parallel-run Phase II neoadjuvant clinical trials with serial biopsies built into the study design investigated the molecular activity of HER2-targeted therapy.[92] In the first study, 35 patients were treated with a 3-week run-in of trastuzumab monotherapy followed by docetaxel (every 3 weeks for 12 weeks); in the second study, 49 patients received a run-in of single-agent

lapatinib for 6 weeks followed by trastuzumab plus docetaxel for 12 weeks prior to definitive surgery. Molecular markers including Ki67, phosphorylated mitogen-activated protein kinase, phosphorylated AKT, and PTEN were evaluated using immunohistochemistry and tumors were also evaluated for PI3K mutations (PIK3CA). Patients whose tumors had low PTEN or activating mutations of PI3K tended to be resistant to trastuzumab; however, low PTEN was associated with a higher rate of pCR.[92] Another Phase II trial examined the correlation between molecular changes and clinical outcomes in early-stage HER2+ disease treated with lapatinib, trastuzumab, and their combination.[93] In this trial, 100 patients with stage II or III HER2+ breast cancer received a 2-week run-in of trastuzumab and/or lapatinib with pre- and post-run-in biopsies taken, followed by chemotherapy (FEC-paclitaxel) plus trastuzumab and/or lapatinib. pCR in breast and lymph nodes was achieved in 74% of patients who received both trastuzumab and lapatinib, 54% of patients who received trastuzumab alone, and 45% of patients who received lapatinib alone. Nonresponders appeared to have more autophagy and stem cell-related pathways activated as well as intact PI3K signaling, and responders showed more disruption of HER2-HER3 linkages as well as downstream pathways such as PI3K.[93]

Two large studies have compared outcomes with neoadjuvant use of lapatinib and trastuzumab (Table 2). In the GeparQuinto trial, 620 patients with HER2+ early or locally advanced primary breast cancer were randomly assigned to receive chemotherapy (epirubicin and cyclophosphamide followed by docetaxel) with either lapatinib (1000–1250 mg daily) or trastuzumab. The rate of pCR (invasive and non-invasive cancer) in the breast and lymph nodes was significantly higher in the trastuzumab arm (31.3% vs 21.7%, for trastuzumab and lapatinib, respectively; $P < 0.05$).[94] Additionally, 34.5% of patients in the lapatinib arm discontinued treatment because of toxicities, necessitating a dose reduction in lapatinib.[95] The three-arm, Phase III Neo-ALTTO (Neo-Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) trial[96] randomly assigned 455 patients with invasive, operable HER2+ breast cancer to receive a 6-week run-in of neoadjuvant lapatinib (1500 mg/day), trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly) or the combination of lapatinib (1000 mg/daily, dose reduced to 750 mg/daily in a third of patients) plus trastuzumab followed by 12 weeks of paclitaxel (80 mg/m^2 weekly) in conjunction with lapatinib and/or trastuzumab. In its first results, the study reported a statistically significant improvement in pCR rate in the combination arm when compared with trastuzumab alone (in breast only: 51% vs 30%, combination arm and trastuzumab alone, respectively; $P = 0.0001$; in breast and lymph nodes: 47% vs 28%, combination arm and trastuzumab alone, respectively; $P = 0.001$). The pCR rate in the trastuzumab arm was not statistically different from the lapatinib arm ($P = 0.34$). Of note, an incidence of grade 3 or higher diarrhea was seen in over 20% of patients in both the lapatinib and lapatinib plus trastuzumab arms, compared with 2% in the trastuzumab arm. These studies do not suggest a benefit of lapatinib over trastuzumab in the neoadjuvant setting. Although the combination of the two agents may have a clinical advantage, this must be balanced with the increased incidence of toxicity.

Several other neoadjuvant trials have been performed to clinically evaluate lapatinib in combination with different chemotherapy agents. One such study investigated the neoadjuvant administration of nab-paclitaxel and lapatinib in 30 patients with HER2+ disease[97] and reported a pCR rate of 17.9% and a CBR in 82.8% of patients (CR: 20.7%, PR: 62.1%; SD: 17.9%). This study did not report a significant toxicity profile. A Phase Ib trial investigating the administration of neoadjuvant lapatinib in combination with paclitaxel and capecitabine in 13 patients with HER2+ disease reported tumor and nodal pCR in 25% of patients.[98] Again, lapatinib was dose reduced or discontinued in 33.3% of patients because of toxicity. Ongoing adjuvant (including the large Phase III ALTTO study, a companion study to NeoALTTO) and neoadjuvant clinical trials evaluating lapatinib are listed in Table 3.

Lapatinib in CNS metastases

Patients with HER2+ breast cancer are at increased risk of developing brain metastases.[99,100] This finding is likely due to multiple factors including an underlying biological propensity of HER2+ cells to penetrate the CNS,[101] as well as the fact that trastuzumab has extended the amount of time patients live with HER2+ MBC;[54] thus more patients are alive long enough to develop CNS metastases. Furthermore, trastuzumab is unable to penetrate the blood-brain barrier,[55] thus allowing metastatic foci to proliferate in that unprotected environment. The current standard of care for CNS metastases includes surgery with or without whole-brain radiation or stereotactic radiosurgery. Unfortunately, the blood–brain barrier prevents the entry of most chemotherapeutic agents effective against breast cancer, limiting the effectiveness of chemotherapy. Thus, optimal treatment of brain metastases remains an unmet need in breast cancer.

Preclinical studies of lapatinib in mouse models transfected with brain-seeking breast cancer cells showed

Table 3 Ongoing clinical trials of lapatinib in the neoadjuvant and the adjuvant setting

Study	Patient population	Study design and treatment regimen	Phase	N
NCT00499681	HER2+ and HR+, operable	Randomized, double-blind, neoadjuvant letrozole ± lapatinib	II	6
NCT00769470	HER2+, operable	Randomized, open-label, neoadjuvant TC + lapatinib and/or trastuzumab	II	140
NCT00486668	HER2+, operable	Randomized, open-label, neoadjuvant AC-T + trastuzumab and/or lapatinib	III	529
NCT00206427	HER2+, stage III/IV	Nonrandomized, open-label, neoadjuvant lapatinib	II	55
NCT00548184	HER2+, locally advanced	Randomized, neoadjuvant trastuzumab ± lapatinib and endocrine therapy	II	64
NCT00422903	HER2–, HR+, operable	Randomized, double-blind, neoadjuvant letrozole ± lapatinib	II	91
NCT00756470	HER2+ inflammatory breast cancer	Single-arm, open-label, neoadjuvant paclitaxel-FEC + lapatinib	II	60
NCT00429299	HER2+, locally advanced	Randomized, open-label, neoadjuvant chemotherapy + lapatinib and/or trastuzumab	IIb	120
NCT00770809	HER2+, operable	Randomized, neoadjuvant paclitaxel + lapatinib and/or trastuzumab	III	400
NCT00490139	HER2+, operable	Randomized, open-label, adjuvant chemotherapy + lapatinib and/or trastuzumab	III	8381
NCT01309607	HER2+, stages I–III	Single-arm, open-label, neoadjuvant paclitaxel + carboplatin + lapatinib	II	34
NCT01485926	HER2+, locally advanced	Randomized, open-label, neoadjuvant TC + lapatinib and/or trastuzumab	II	120
NCT01205217	HER2+, stages I–III	Randomized, open-label, neoadjuvant EC-T + lapatinib vs trastuzumab	II	164
NCT00374322	HER2+ early stage	Randomized, double-blind, adjuvant lapatinib	III	3000
NCT01275859	HER2+, HR+, locally advanced	Single-arm, open-label, neoadjuvant letrozole + lapatinib	II	32
NCT00841828	HER2+, locally advanced	Randomized, open-label, neoadjuvant EC-docetaxel + lapatinib vs trastuzumab	II	102
NCT00553358	HER2+, locally advanced	Randomized, open-label, neoadjuvant paclitaxel + lapatinib and/or trastuzumab	III	455
NCT00999804	HER2+, locally advanced	Randomized, open-label, neoadjuvant lapatinib + trastuzumab + letrozole	II	96
NCT00524303	HER2+, locally advanced	Randomized, open-label, FEC-paclitaxel + lapatinib and/or trastuzumab	II	100
NCT01104571	HER2+, operable	Randomized, open-label, neoadjuvant and adjuvant trastuzumab vs lapatinib	III	250

Abbreviations: AC-T, doxorubicin, cyclophosphamide, paclitaxel; EC, epirubicin, cyclophosphamide; EC-T, epirubicin, cyclophosphamide, paclitaxel; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; HER2–, human epidermal growth factor receptor 2 negative; HER2+, human epidermal growth factor receptor 2 positive; HR+, hormone receptor positive; TC, docetaxel, carboplatin; vs, versus.

promising results.[102] In mice transfected with HER2– and HER2+ cells, treatment with lapatinib 100 mg/kg resulted in a statistically significant reduction in large CNS metastases 24 days after initiation of treatment when compared with the control ($P < 0.001$ for both groups), whereas treatment with lapatinib 30 mg/kg resulted in a statistically significant reduction in large CNS metastases in the HER2+ group only ($P < 0.001$). In the aforementioned registration trial of lapatinib with capecitabine, an exploratory analysis revealed a statistically significant reduction in symptomatic CNS progression as part of the first progression event in patients receiving the combination regimen (13% in patients in the capecitabine arm vs 4% in patients in the combination arm; $P = 0.045$).[82] Subsequent to this observation, the use of lapatinib 750 mg twice daily for patients with established CNS metastases from HER2+ breast cancer was evaluated in a Phase II clinical trial,[103] which reported an ORR of the CNS metastases in 6% of patients. Furthermore, a ≥20% volumetric reduction of CNS lesions was experienced by 21% of patients. The study was expanded to allow patients whose systemic disease progressed on lapatinib (with no progression in the brain) to receive lapatinib plus capecitabine. Of the patients who received the combination, 20% experienced an objective response and 40% experienced a ≥20% volumetric reduction of their CNS lesions.[103]

Several retrospective analyses have also reported on the activity of lapatinib for CNS metastases. The combination of lapatinib and capecitabine was evaluated in a survey of sites that were allowed access to lapatinib prior to commercial availability.[104] The survey assessed 138 patients who had progressive CNS metastases upon entry and reported an unconfirmed CR in 2% of patients, PR in 16% of patients, SD in 47% of patients, and PD in 14% of patients. Furthermore, improvement in neurological signs and symptoms was reported in 25% of patients. Another retrospective study evaluated 30 patients with CNS metastases due to HER2+ disease who were treated with lapatinib plus capecitabine in two Italian institutions.[105] In this study all patients had received prior trastuzumab, no patient had received prior lapatinib or capecitabine, but 87% of patients had received prior brain radiotherapy. Of the 22 patients with response-evaluable disease, seven achieved a PR and six displayed SD. Brain-specific PFS was

5.6 months. Furthermore, OS from the time of development of CNS metastases for the lapatinib-treated patients was statistically significantly improved when compared with 23 patients who received only trastuzumab-based therapy beyond CNS progression (27.9 vs 16.7 months, for lapatinib and trastuzumab, respectively; $P = 0.01$).[105] Another retrospective analysis compared patients with HER2+ MBC involving the brain treated with trastuzumab- and lapatinib-containing regimens to controls not treated with any HER2-targeted agents after local treatment of CNS metastases.[106] Although the results from retrospective analyses are limited, the study reported a median survival of 3 months in patients treated with radiotherapy alone, 9 months in patients treated with chemotherapy without HER2-targeted agents, 13 months in patients treated with trastuzumab-containing regimens, and >24 months in patients treated with lapatinib-containing regimens. The addition of trastuzumab to therapy resulted in a statistically significant improvement in OS ($P < 0.001$), and the addition of lapatinib to therapy led to a statistically significant improvement in OS when compared with the addition of trastuzumab ($P = 0.002$).

A Phase II trial compared lapatinib plus capecitabine with lapatinib plus topotecan in patients with progressive CNS metastases after trastuzumab and radiotherapy.[107] The lapatinib plus topotecan arm was terminated after 22 patients were enrolled, as toxicity and a lack of efficacy were shown. In the lapatinib plus capecitabine arm, PR was seen in 38% of patients, SD in 46% of patients, and PD in 15% of patients. These results suggest a role for lapatinib-based therapy in the treatment of CNS metastases. However, further and ongoing studies will better evaluate the role of lapatinib in the prevention and treatment of brain metastases (Table 4).

Safety and tolerability of lapatinib

Early on, Phase I studies evaluating lapatinib revealed that the most frequent toxicities imparted by this therapy are diarrhea (42% of patients) and rash (31% of patients).[66] In a Phase II trial of lapatinib as first-line therapy in patients with locally advanced or metastatic HER2+ disease, diarrhea (36%), rash (27%), pruritus (18%), and nausea (10%) were reported as the most frequent lapatinib-related toxicities.[70] These toxicities are likely due to the EGFR-inhibitory effects of the molecule. Based on the National Cancer Institute Common Terminology Criteria for Adverse Events, the majority of the toxicities experienced were from grade 1 to 3; grade 4 toxicities were rare. These rates of AE have been corroborated in later clinical trials of lapatinib in combination with chemotherapy or trastuzumab.[11,70,72,74] Because the effectiveness of lapatinib is greatest in combination with other agents, it is important to examine how the frequency and grade of common AEs changes when lapatinib is used in conjunction with various agents.[11,70,72,96,108] This section will focus on skin, gastrointestinal, and cardiac toxicity reported in larger clinical trials of lapatinib.

Skin toxicity

The characteristic rash of lapatinib consists of inflammatory papules and pustules occurring most often on the face, chest, and back.[109] In addition to the discomfort caused by the rash, its apparent nature causes significant morbidity for the patient. As mentioned, lapatinib-associated rash occurred in 27% of patients (26% were grade 1 or 2, 1% were grade 3) in a Phase II trial of lapatinib monotherapy as first-line therapy.[70] Pruritus is another common dermatological toxicity associated with lapatinib, reported in 18% of patients.[70] In a Phase III trial investigating lapatinib and trastuzumab in 296 trastuzumab-refractory patients, an increased frequency of rash was not seen with the combination (29% lapatinib vs 22% lapatinib/trastuzumab).[72] However, increased frequency of rash was seen in a Phase III trial investigating the combination of lapatinib and letrozole as first-line therapy in 219 patients with HER2+, HR+ disease (46% lapatinib/letrozole vs 8% letrozole).[108] In spite of this, no grade 3 or 4 rash was reported. The prevalence of pruritus was also greater with the combination (13% vs 5%). The incidence of rash (27% combination vs 15% single agent; $P = 0.011$) but not hand-foot syndrome (49% combination vs 49% single agent; $P = 1.00$) was increased with the combination of lapatinib and capecitabine

Table 4 Ongoing clinical trials of lapatinib in patients with central nervous system (CNS) metastases

Study	Status	Patient population	Study design and treatment regimen	Phase	N
NCT00263588	Ongoing	HER2+ with CNS metastases after trastuzumab-based regimen and WBRT	Single-arm, open-label, lapatinib	II	242
NCT00470847	Ongoing	HER2+ with CNS metastases	Single-arm, open-label, WBRT + lapatinib	II	39
NCT00614978	Ongoing	HER2+ with CNS relapse	Single-arm, open-label, temozolomide + lapatinib	I	18
NCT00967031	Ongoing	HER2+ with CNS metastases	Single-arm, open-label, capecitabine + lapatinib	II	45
NCT01218529	Ongoing	Lung or breast cancer with CNS metastases	Single-arm, open-label, WBRT + lapatinib	II	81

Abbreviations: HER2+, human epidermal growth factor receptor 2 positive; WBRT, whole-brain radiotherapy.

in 324 women with pretreated disease in the Phase III registration trial.[11] Again, no incidence of grade 4 rash was reported, and the prevalence of grade 3 rash was the same in both arms (1%). The combination of lapatinib and paclitaxel resulted in a significant increase in the incidence of rash (43% rash combination paclitaxel/lapatinib vs 21% paclitaxel alone; $P < 0.0001$) when used as first-line therapy in a Phase III trial enrolling 579 women.[84] The incidence of grade 3 rash was 4% in the lapatinib arm compared with 0% in the placebo arm, but there was no grade 4 rash reported.

Toxicity of lapatinib has also been evaluated in the neoadjuvant setting. The Neo-ALTTO trial – the aforementioned Phase III trial enrolling 455 patients and investigating the neoadjuvant addition of lapatinib, trastuzumab, and their combination with paclitaxel – reported an incidence of grade 3 or 4 skin disorder of 7% in the lapatinib group vs 3% in the trastuzumab group vs 7% in the combination group.[96] The GeparQuinto trial – the aforementioned Phase III trial investigating the neoadjuvant addition of lapatinib vs trastuzumab to chemotherapy in 620 patients – reported a nonsignificant increase in the incidence of grade 3 or 4 rash in the lapatinib arm compared with the trastuzumab arm (8.0% vs 0.0%, respectively; $P = 0.202$).[94]

Gastrointestinal toxicity

Diarrhea is the most frequent gastrointestinal toxicity associated with lapatinib; however, nausea, vomiting, and anorexia are also often reported. Although the majority of diarrhea experienced by patients is from grade 1 to 3 (with grade 3 defined as an increase in up to nine stools per day, incontinence, or severe cramping), it is important to realize that even milder grades of diarrhea can cause significant discomfort and decline in quality of life (QoL) for patients. In a Phase II trial that evaluated lapatinib monotherapy as first-line treatment for locally advanced or metastatic HER2+ breast cancer in 138 patients, diarrhea due to lapatinib occurred in 36% of patients (33% were grade 1 or 2, 3% were grade 3, 0% were grade 4), and nausea occurred in 10% of patients.[70]

Three Phase III studies comparing a lapatinib-containing regimen to a chemotherapy or endocrine agent alone have shown that the rates of diarrhea are increased in lapatinib-containing regimens. The Phase III trial that evaluated letrozole and lapatinib compared with letrozole plus placebo reported diarrhea in 68% of patients (7% were grade 3) in the lapatinib arm compared with 8% in the placebo arm.[108] The severity of the diarrhea led to a dose reduction of lapatinib in 2% of patients and dose interruption in 4% of patients. The incidence of nausea (27% vs 18%, for lapatinib and placebo, respectively) and vomiting (17% vs 7%, for lapatinib and placebo, respectively) was also increased with the combination. Before clinical trials of lapatinib and capecitabine were carried out, concern for significant diarrhea with the combination was raised, as both drugs commonly cause diarrhea.[109] In the Phase III registration trial of the combination of lapatinib and capecitabine compared with capecitabine alone, interim analysis of 324 pretreated patients revealed a statistically significant increase in diarrhea with the combination (60% vs 39%, for lapatinib plus capecitabine and capecitabine alone, respectively; $P < 0.001$).[11] Although most of the diarrheal events in the combination group were grade 1 or 2, 12% were grade 3 and 1% were grade 4. Rates of treatment discontinuation because of AEs were similar between the two arms (13% in the combination group, 12% in the monotherapy group). Likewise, the incidence of nausea, vomiting, stomatitis, abdominal pain, constipation, mucosal inflammation, and anorexia were not significantly different between the two groups. However, the incidence of dyspepsia was significantly increased with the combination (11% vs 3%, for combination and monotherapy, respectively; $P = 0.014$). The Phase III trial comparing paclitaxel plus lapatinib with paclitaxel plus placebo as first-line therapy in 579 patients reported a statistically significant increase in the incidence of diarrhea with the combination (58% vs 26%, respectively; $P < 0.0001$).[83] Furthermore, the incidence of diarrhea that met protocol-defined serious AE criteria was also significantly increased with the combination (8% vs <1%, for lapatinib and placebo, respectively; $P < 0.0001$). The incidence of vomiting (25% vs 17%, for lapatinib and placebo, respectively; $P = 0.01$) but not nausea (34% vs 30%, for lapatinib and placebo, respectively) was significantly increased with the combination. In contrast to the registration trial,[84] this study reported that AEs led to treatment discontinuation in 16% of patients in the lapatinib-containing arm compared with 7% of patients in the paclitaxel-alone arm.

Adding another agent to lapatinib also appears to increase the rate of diarrhea. The Phase III study that compared the combination of lapatinib plus trastuzumab with lapatinib alone reported an increased frequency of diarrhea with the combination (60% in the combination group vs 48% in monotherapy group).[72] The increased incidence of grade 1 or 2 diarrhea in the combination arm was statistically significant ($P = 0.03$); however, the incidence of grade 3 or higher diarrhea was similar between the two arms (7%). The incidence of nausea, vomiting, and anorexia was also similar between the two arms.

Additional evidence of the increased incidence of diarrhea with lapatinib is seen in the Neo-ALTTO and GeparQuinto trials, both of which investigate the use of lapatinib in the neoadjuvant setting.[94,96] The Neo-ALTTO trial reported an incidence of grade 3 or 4 diarrhea of 23% in the lapatinib group vs 2% in the trastuzumab group vs 21% in the combination group.[96] The significant increase in diarrhea in the lapatinib-trastuzumab combination arm necessitated a protocol-driven amendment to reduce the dose of lapatinib. The GeparQuinto trial reported an incidence of grade 3 or 4 diarrhea in 6.9% of patients receiving lapatinib vs 3.2% of patients receiving trastuzumab ($P = 0.606$).[94] Because of toxicity, 34.5% of patients in the lapatinib arm, compared with 3.2% of patients in the trastuzumab arm, discontinued treatment.

These data underscore the need to closely monitor patients for diarrhea, especially when lapatinib is being given in combination with other therapies. It is imperative to provide patients with upfront education about diarrhea and to provide them with aggressive management when needed with antidiarrheal agents; instructions regarding diet modification (avoidance of dairy products), dose delays, and reductions; and in some cases hospitalization for intravenous fluids and antibiotics.

Cardiotoxicity

One of the disadvantages associated with trastuzumab is its small but significant risk of cardiotoxicity. Trials of the combination of trastuzumab and chemotherapy, specifically anthracycline-containing regimens, have shown an elevated incidence of cardiotoxicity.[38] Interestingly, significant cardiotoxicity has not been seen in studies of lapatinib. In the Phase II trial of lapatinib as first-line monotherapy,[70] no symptomatic reductions of left ventricular ejection fraction were reported; however, four asymptomatic reductions of >20% were observed. Interestingly, all of these patients had received anthracycline treatment prior to enrollment.[70]

A prospective pooled analysis of 3689 patients, including 2275 breast cancer patients, enrolled in 18 Phase I–III clinical trials and who received lapatinib was conducted to assess for cardiotoxicity of lapatinib.[110] The analysis reported that 60 patients had cardiac events (53 asymptomatic and seven symptomatic). Of the 60 patients, 25 (42%) received lapatinib as monotherapy and 35 (58%) received lapatinib in combination regimens. Included in the 60 patients with cardiac events were 41 breast cancer patients; of these patients, twelve had received prior anthracycline therapy, 14 had received prior trastuzumab therapy with chemotherapy or after anthracycline therapy, and 15 had received neither anthracycline nor trastuzumab therapy. The analysis reported that cardiotoxicity resolved in all but one of the seven symptomatic patients.

These results suggest that cardiotoxicity due to lapatinib is rare and usually asymptomatic, and that when symptomatic it is often reversible. However, it is worth noting that clinical trials evaluating HER2-targeted agents generally exclude patients with any baseline cardiac dysfunction. Furthermore, most of the patients enrolled in lapatinib studies have previously tolerated trastuzumab and anthracycline therapy without reduction in left ventricular ejection fraction (EF) and have thus essentially proven that they are able to tolerate these therapies without cardiac compromise. Therefore, clinical trials are reporting on a healthy, highly selected population of patients who have, for the most part, passed the "trastuzumab/anthracycline stress test." In the aforementioned pooled analysis, only three of the 60 patients who experienced cardiotoxicity had a baseline EF of <50%.[110] Further monitoring of cardiac safety of lapatinib will be prudent as the use of lapatinib becomes more widespread in nonclinical trial patient populations.

Patient-focused perspectives

Although the toxicities associated with lapatinib are generally mild, some of these toxicities can be severe enough to cause significant distress for the patient. For many of the studies mentioned in this review, toxicities resulted in dose reduction or interruption of lapatinib. In addition to diarrhea and rash, other toxicities frequently associated with lapatinib include nausea and fatigue, both of which also diminish QoL.[109] When evaluating the efficacy of lapatinib, it is important to weigh increased disease-free survival against the change in QoL as a result of the therapy. Unfortunately, because of the subjective nature of this dilemma, it is difficult to find data relating to how QoL is affected by toxicity of therapy. Some Phase III trials have included a QoL assessment throughout the course of therapy.

The Phase III trial assessing the addition of lapatinib to trastuzumab in 296 trastuzumab-refractory patients reported no significant change in QoL in either arm compared with baseline using the FACT-B (Functional Assessment of Cancer Therapy – Breast) questionnaire.[111] In the Phase III registration trial of lapatinib and capecitabine compared with capecitabine alone, QoL was assessed with two questionnaires (FACT-B and EQ-5D) during scheduled patient visits.[112] Based on these questionnaires, the changes in QoL from baseline were not significantly different between the two groups, but were in

fact consistently in favor of the lapatinib plus capecitabine arm. Furthermore, patients with tumor response or SD had improved QoL scores compared with patients with PD. The Phase III trial investigating lapatinib plus paclitaxel compared with placebo plus paclitaxel as first-line therapy included a QoL assessment using a FACT-B questionnaire and a Q-TWiST (Quality-Adjusted Time Without Symptoms or Toxicity) assessment to investigate the trade-off between toxicity and delayed progression.[113] The QoL scores did not significantly change from baseline in the lapatinib-containing arm ($P = 0.99$), while they decreased in the placebo arm ($P = 0.01$). The Q-TWiST differences between the two arms ranged from 2 to 15 weeks, favoring the combination arm. While many studies report toxicity due to diarrhea, rash, and other symptoms from lapatinib therapy, limited data do not show a change in QoL due to these toxicities. However, further investigation is needed in this realm before conclusions can be drawn regarding QoL with lapatinib therapy.

One aspect of lapatinib that makes it a favorable therapy for patients is that it is an orally bioavailable molecule. This is especially appealing when administered in an entirely oral regimen, such as capecitabine plus lapatinib. An oral regimen mitigates the need for frequent visits to the doctor for infusions. However, compliance with therapy is difficult to gauge with oral therapies and toxicity may be more challenging to follow with fewer visits to the treatment center. An open communication between doctor and patient in addition to visits to the office each cycle may improve compliance and may reduce the risk of severe toxicities for the patient.

Conclusion

Targeted therapies have changed the clinical outcome of HER2+ breast cancer. Trastuzumab has been extensively studied alone and in combination with various chemotherapeutic and nonchemotherapeutic agents in the treatment of HER2+. Despite its efficacy in these settings, it has its limitations, including de novo and acquired resistance, cardiotoxicity, and inability to penetrate the blood–brain barrier. Therefore, newer agents in the treatment of HER2+ breast cancer are needed. Lapatinib is an orally bioavailable small molecule that is safe and has demonstrated efficacy when used alone and in combination for HER2+ breast cancer. It has especially promising activity in combination with trastuzumab; however, the risk of diarrhea limits the dose that can safely be used. Ongoing studies evaluating the use of trastuzumab in the front-line and adjuvant settings will define this drug's role in the management of HER2+ breast cancer.

Disclosure

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