

# Dual HER1/HER2 inhibitor lapatinib in advanced/metastatic breast cancer

*Small molecule tyrosine kinase inhibitor shows impressive results in trastuzumab-resistant cases*

## What's new, what's important

Patients with HER2-positive breast cancer have more aggressive disease and relative resistance to certain therapeutic approaches. The introduction of trastuzumab (Herceptin) over the past decade has changed the treatment and survival of this subset of patients. Recent studies have proved that trastuzumab is effective in improving disease-free survival in early breast cancer as well.

However, many patients progress while on trastuzumab and develop new lesions, including brain metastases. Usually, we change the chemotherapy agents and continue to treat such patients with trastuzumab. Studies and our clinical experience have shown that this is a reasonable approach, especially when we do not have any other therapeutic options.

Recent studies with lapatinib (Tykerb), an oral, small molecule dual tyrosine kinase (EGFR and HER2) inhibitor, have shown that treatment of this subset of patients with lapatinib, 1,250 mg/d, in combination with capecitabine (Xeloda), 1,000 mg taken twice daily on days 1–14 of a 3-week cycle, more than doubled the duration of progression-free survival compared with capecitabine therapy alone. Lapatinib is currently being tested with other combinations of drugs and in different clinical settings, including inflammatory breast cancer and in patients with metastatic disease to the brain.

Lapatinib is expected to receive US Food and Drug Administration approval in the near future. It is an exciting therapeutic option for patients with this highly aggressive form of breast cancer.

—Jame Abraham, MD  
Section Editor

**L**apatinib (Tykerb) is a small molecule reversible inhibitor of the tyrosine kinases EGFR (HER1) and HER2. The monoclonal antibody trastuzumab (Herceptin) inhibits HER2 and is effective in the treatment of HER2-overexpressing metastatic breast cancer. Dual inhibition may be useful to prevent augmented oncogenic activity resulting from the interaction of EGFR and HER2. Lapatinib has been shown to be active in trastuzumab-resistant breast cancer and currently is being evaluated for the treatment of a variety of solid tumors.

An open-label phase III trial published recently in the *New England Journal of Medicine* (EGF100151) indicates that combining lapatinib with capecitabine (Xeloda) significantly prolongs the time to disease progression and progression-free survival compared with capecitabine alone in

patients with pretreated advanced or metastatic HER2+ breast cancer.<sup>1</sup>

## Lapatinib combined with capecitabine

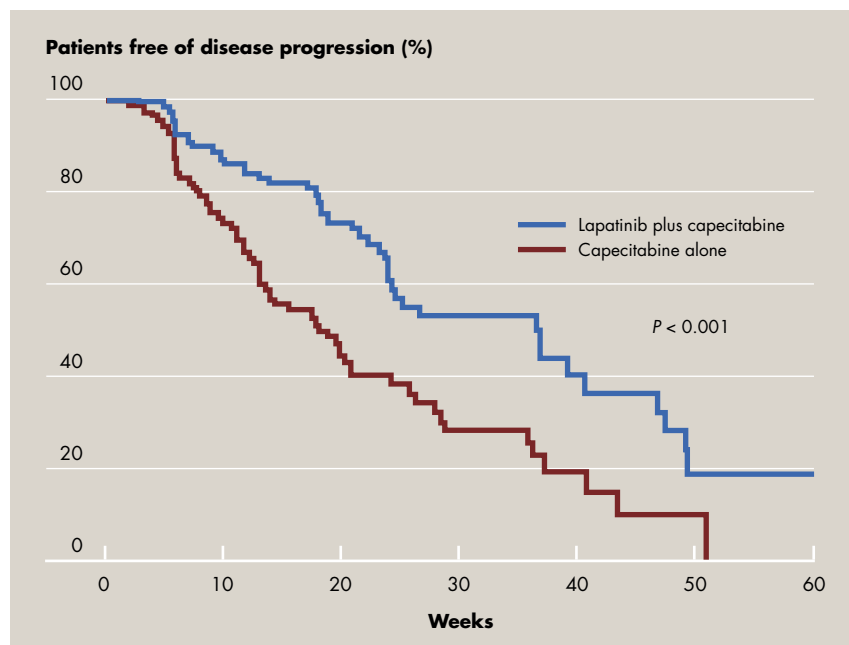
In this trial, patients with HER2+ locally advanced (a T4 tumor and stage IIIB/IIIC disease) or metastatic breast cancer were randomized 1:1 to receive oral lapatinib (1,250 mg/d) continuously plus capecitabine (2,000 mg/m<sup>2</sup> daily) or capecitabine alone (2,500 mg/m<sup>2</sup> daily) on days 1–14 of every 21-day cycle. All patients overexpressed HER2, defined as grade 3+ by immunohistochemical (IHC) staining alone or 2+ by a combination of IHC analysis with fluorescence in situ hybridization (FISH), and, for study entry, had to have been treated previously with an anthracycline, a taxane, and trastuzumab. Women who had been treated previously with capecitabine were excluded.

The primary endpoint was time to

disease progression; secondary endpoints included overall survival, progression-free survival, overall response rate, rate of clinical benefit, and safety. The study was funded and conducted by GlaxoSmithKline.

At study end, 49 (30%) of 163 patients in the lapatinib/capecitabine arm and 72 (45%) of 161 in the capecitabine arm had disease progression or died (hazard ratio [HR] = 0.49; 95% confidence interval [CI], 0.34–0.71;  $P < 0.001$ ; Figure 1). In the intention-to-treat population, median time to disease progression was 8.4 months in the combination arm versus 4.4 months with capecitabine monotherapy (HR = 0.47; 95% CI, 0.32–0.68;  $P < 0.001$ ). Median progression-free survival was 8.4 months versus 4.1 months (HR = 0.47; 95% CI, 0.33–0.67;  $P < 0.001$ ).

Summary by Matt Stenger, MS; reviewed by Padmaja V. Mallidi, MD, Hematologist-Medical Oncologist, Blue Ridge Cancer Care, Roanoke, VA.



**FIGURE 1** Proportion of patients with pretreated advanced/metastatic breast cancer remaining disease progression free during treatment with lapatinib/capecitabine or capecitabine alone in study EGF100151.

Overall response rates were 22% in the lapatinib/capecitabine arm (including 35 partial responses and 1 complete response) and 14% in the capecitabine-alone arm (23 partial responses;  $P = 0.09$  [not significant]). Thirty-six patients (18%) in the combination-therapy group and 35 patients in the monotherapy group died (HR = 0.92; 95% CI, 0.58–1.46;  $P < 0.72$ ). Fewer women in the lapatinib-containing arm than those receiving capecitabine monotherapy developed central nervous system (CNS) metastases (4 vs 11, respectively); however, this difference was not statistically significant.

Lapatinib plus capecitabine was well tolerated. The most common adverse events were diarrhea, hand-foot syndrome, nausea/vomiting, fatigue, and rash. Of these events, only diarrhea and rash occurred more often in the group receiving combination therapy than among the group treated with capecitabine alone (for diarrhea, 60% vs 39% [ $P < 0.01$ ]; for rash, 27% vs 15% [ $P = 0.011$ ]). Decreases in left ventricular ejection fraction (LVEF) were infrequent, asymptomatic, and

reversible. There were no symptomatic cardiac events in either group of patients.

In addition to showing that lapatinib plus capecitabine produced a clinically meaningful and statistically significant 4-month increase in time to disease progression, the findings suggest that lapatinib should be investigated in earlier stages of HER2+ breast cancer.

### Other findings on lapatinib

Other findings on lapatinib reported at the 2006 meeting of the American Society of Clinical Oncology (ASCO) support potential activity in reducing brain metastases, indicate a low risk of serious cardiotoxicity, and suggest potential benefits in selected patients with relapsed/refractory inflammatory breast cancer.

#### CNS metastases

Approximately one third of patients with HER2+ metastatic breast cancer develop CNS metastases. In a phase II trial in 39 patients developing brain metastases while receiving

trastuzumab, treatment with lapatinib, 750 mg twice daily, was associated with a partial response in 2 patients (remaining on study at 23 and 49 weeks), with 23 and 8 patients remaining disease progression free at 8 and 16 weeks, respectively.<sup>2</sup> Median time to disease progression was 3.0 months, and median overall survival was 6.6 months. Volumetric analysis in 20 patients showed a 30% or greater decline in CNS lesions in 4 patients and a 10%–30% decline in 6 patients. Grade 3 toxicities of lapatinib included diarrhea in 21% of patients, fatigue in 15%, and headache in 10%.

#### Decreases in LVEF

An analysis of cardiotoxicity risk in patients receiving lapatinib showed an LVEF reduction  $\geq$  grade 3 or  $\geq 20\%$  from baseline (and below the institutional lower limit of normal) in 22 (1.3%) of 1,674 breast cancer patients (1,078 receiving lapatinib in combination regimens and 596 as monotherapy) and in 19 (1.3%) of 1,453 non-breast cancer patients, yielding a total of 41 cases (1.3%) among 3,127 patients.<sup>3</sup> The average decrease in LVEF compared with baseline was 30.2% (range, 25%–33%). Symptomatic decreases in LVEF occurred in 2 breast cancer patients (0.1%) and 2 non-breast cancer patients (0.1%), for a total of 4 cases (0.1%) among the 3,127 patients. Patients with symptomatic decreases presented with dyspnea, palpitations, and signs of heart failure, which responded to standard therapy with furosemide, corticosteroids, and diuretics or to treatment with nitroglycerin and diuretics. The investigators noted that the overall 1.3% incidence of LVEF decreases in lapatinib recipients compares well with reported rates of asymptomatic LVEF decreases of 3%–6% in the general population.

#### Inflammatory breast cancer (IBC)

Finally, a phase II trial of lapatinib (1,500 mg/d) reported by Spec-

tor et al<sup>4</sup> in heavily pretreated (median number of prior regimens, 4.5; range, 0–21) patients with relapsed/refractory IBC was performed on the basis of phase I study findings suggesting that IBC might be particularly sensitive to the effects of this novel agent. Seventy-nine percent of the patients had stage IV disease and 21%, stage IIIB. Patients were grouped in cohort A (n = 24) if they were HER2+ and in cohort B (n = 12) if they were HER1+/HER2-. A partial response, stable disease, and progressive disease were observed in 62%, 21%, and 17%, respectively, of cohort A and in 8%,

17%, and 58%, respectively, of cohort B (response in 17% of the latter group was not available).

In terms of safety, most (119/132 [90%]) adverse events recorded were grade 1/2 events, including 57 gastrointestinal reactions and 23 skin reactions. Grade 3/4 adverse events (n = 10) included diarrhea, anorexia, headache, anemia, and thrombocytopenia. One death related to dyspnea and fever accompanying disease progression occurred.

These results suggest a preferential effect of lapatinib in IBC in patients who are HER2+.

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*From the Community Oncologist's Perspective*

# A step forward in targeted treatment for breast cancer

Padmaja V. Mallidi, MD | Blue Ridge Cancer Care, Roanoke, VA

**T**he advent of trastuzumab (Herceptin) represented a major breakthrough in the treatment of women with HER2+ metastatic breast cancer, showing improved survival when added to chemotherapy in this subgroup of patients, who otherwise faced a disease with an aggressive natural history and short median survival.<sup>1</sup>

Lapatinib (Tykerb) is an oral, small molecule, reversible dual inhibitor of both the epidermal growth factor receptor (EGFR; ErbB1) and HER2 (ErbB2) tyrosine kinases that can penetrate cancer cells, exerting its effect intracellularly. Its site of action therefore differs from that of trastuzumab, which is a monoclonal antibody that targets the extracellular HER2 receptor.<sup>2</sup>

## Relapsed metastatic breast cancer

The phase III randomized study described in the accompanying article

compared lapatinib plus capecitabine (Xeloda) with capecitabine alone in women with advanced, progressive HER2+ breast cancer who had received multiple previous treatments, including trastuzumab.<sup>3</sup> Interim analysis of the study results showed that the addition of lapatinib to capecitabine was associated with a 51% reduction in the risk of disease progression. The median time to disease progression was 8.4 months versus 4.4 months among patients receiving capecitabine alone. Serious adverse events were similar in both arms. Treatment-related asymptomatic cardiac events occurred infrequently and were reversible.

It is too early to comment on survival, but these outcomes are impressive. Such results are rarely, if ever, seen in this patient population and support lapatinib as a promising new agent for patients whose disease has progressed on trastuzumab-based therapy.

Although brain metastases developed in a small number of women during this study, they occurred in fewer women (4) in the combination-therapy group than in the monotherapy group (11); the difference was not statistically significant.

The latest update on this study, presented by David Cameron at the San Antonio Breast Cancer Symposium (SABCS) in mid-December, also showed a correlation of response to lapatinib with HER2 positivity, as determined by both immunohistochemistry (IHC) and fluorescence in situ hybridization, but not with HER1 positivity. The results also showed a nonsignificant trend toward greater response with increased positivity for HER2, as measured by IHC.<sup>4</sup>

## Inflammatory breast cancer

Inflammatory breast cancer is a rare, aggressive subtype of breast cancer with a poor prognosis. HER2

is overexpressed in approximately 30%–50% of these cases. At the 2006 SABCS, Cristofanilli presented the latest data from an international phase II study testing a 14-week combination regimen of paclitaxel and lapatinib in newly diagnosed, HER2+ inflammatory breast cancer.<sup>5</sup>

Of the 30 patients with HER2+ tumors, 3 (10%) had a complete response (CR) and 20 (67%) had a partial response (PR), adding up to a clinical response rate of 77%. Three other HER2+ patients (10%) had stable disease. Disease status was unknown in four patients.

Of the five HER2– patients, none had a CR, but four (80%) had a PR. An additional exciting finding from this study was the 30% response rate seen after 2 weeks of treatment with lapatinib alone in HER2+ patients.

Despite the intriguing nature of these new findings, we need to keep in mind that these results are preliminary and from a very small study. They need to be reproduced before treatment with lapatinib can be embraced as the standard of care in the community.

## Brain metastases

We have all seen in our practice that once breast cancer patients develop brain metastases, the prognosis is exceedingly poor, with a reported 1-year survival of 20%. Patients with HER2+ breast cancer, including those who have been treated with trastuzumab, have been found to have a significantly higher risk of developing brain metastases.<sup>6</sup> This observation suggests that the blood-brain barrier prevents trastuzumab from reaching adequate concentrations in the central nervous system (CNS).<sup>7,8</sup> Because lapatinib is a small molecule HER2 tyrosine kinase inhibitor—and therefore may be able to penetrate the blood-brain barrier better than trastuzumab—clinical trials have been carried out with lapatinib for the treatment

of brain metastases.

Results from a phase II trial of lapatinib in HER2+ breast cancer patients with new or progressive brain metastases were presented at the 2006 Annual Meeting of the American Society of Clinical Oncology.<sup>9</sup> The median time to disease progression was 3.02 months, and overall survival was 6.57 months. Lapatinib was well tolerated in this patient population, and there was some evidence of CNS clinical activity.

## Cardiac safety of lapatinib

Because of the cardiac toxicity associated with trastuzumab therapy, Perez and colleagues analyzed cardiac function in patients treated with lapatinib in 18 phases I–III lapatinib clinical trials.<sup>10</sup> The 1.3% incidence of symptomatic and asymptomatic decreases in left ventricular ejection fraction (LVEF) in patients treated with lapatinib was less than the 3%–6% incidence of asymptomatic decreases in LVEF seen in the general population and, moreover, was less than that observed in breast cancer patients treated with trastuzumab. Thus, there is currently no firm evidence that lapatinib causes cardiac toxicity. These cardiac safety results further support the rationale for studying lapatinib in the adjuvant setting.

## Ongoing trials

Presently, several studies of lapatinib in metastatic breast cancer, including combinations of this novel agent with trastuzumab, conventional chemotherapy, and hormonal therapies, are actively recruiting patients. Several trials, including the ongoing phase III Tykerb Evaluation After Chemotherapy (TEACH) trial, are evaluating the safety and efficacy of lapatinib in the adjuvant setting.

## Conclusion

The striking clinical benefits of HER2-targeted therapy with agents

such as trastuzumab are offset by their nearly inevitable failure in the metastatic setting. The efficacy and safety data on lapatinib presented so far are exciting. GlaxoSmithKline, the company developing lapatinib, filed for US Food and Drug Administration approval of the drug in September 2006.

A full appreciation of the potential sources of resistance to these novel therapies for breast cancer should allow for stronger predictive power and more individualized patient care with less toxicity, which is what we all have been looking forward to.

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*Dr. Mallidi can be reached at padmaja.mallidi@usoncology.com.*

*From the Nurses' Station*

# The role of lapatinib in the treatment of breast cancer

Trish Tarpley, RN, BSN | Blue Ridge Cancer Care, Roanoke, VA

**I**n general, the role of the oncology nurse has expanded to include the addition of oral chemotherapeutic agents to treatment regimens for a growing number of cancer patients. The addition of these drugs, as well as drugs in the pipeline, such as lapatinib (Tykerb) for patients with metastatic breast cancer, has added several hurdles to the already complex oncology nurses' role in the outpatient clinic. Despite the many benefits that oral therapy brings to patients, the ability of nurses to effectively manage these patients is becoming more and more challenging.

From the patients' perspective, oral therapies are infinitely easier to manage and less time consuming than coming into the clinic for treatment. Moreover, patients feel more in charge of a disease that is known for its ability to control their lives. The perception of coming into an infusion center for therapy instills fear in the majority of patients, whereas the mere act of taking a pill seems entirely benign.

The downside of oral therapies for patients is concern for the lack of effective reporting and management of side effects, compliance with the prescribed regimen, the safe handling of potentially toxic drugs in the home environment, and the increased out-of-pocket expense patients face because of these agents' cost.

## Education is key to providing quality care

Oncology nurses are instrumental in the education that is needed for patients to receive the full benefit of oral therapies. The challenge begins with the physicians, as they are accustomed to writing prescriptions for patients, giving a brief explanation of what to expect, and then sending patients to their local pharmacy to obtain the medication. It is imperative for outpatient clinics to maintain an open line of communication between physicians and nurses to close this gap in providing quality patient care.

Oncology nurses must now find time to educate patients receiving oral chemotherapy about side effects and the necessity of reporting them, the best process by which patients can obtain the medication (which will often require preauthorization by insurance companies), and the importance of adherence to the regimen to ensure the best outcome.

The impact of oral chemotherapy on oncology nursing has another downside too—the loss of part of the nurse's ability to communicate directly with patients and develop the rapport that one is accustomed to in working with patients who are seen in the clinic and treated intravenously. With oral therapy, the relationship between patients and nurses

becomes more of an “over the phone” relationship, as opposed to a face-to-face interaction.

The patients in our clinic sites are given an information sheet that contains general information about the office and how to contact the nursing staff and on-call physician, as well as how to obtain prescription refills. Our largest office site has a dedicated nurse who functions as a phone call triage nurse, which helps provide continuity of care to those patients who are requesting assistance from home.

The majority of pharmaceutical companies that manufacture oral agents offer a starter kit for patients. The packets include drug information, explain side effects, have a tracking tool or pill sorter, and offer suggestions for how to monitor side effects. Compliance is also stressed in the information about the medication. These tools are provided free of charge and are excellent resources for the patients and the staff. Our nursing staff will be fine-tuning our process to ensure that all patients have a one-on-one teaching session with a nurse prior to beginning oral therapy.

As new oral agents, such as lapatinib, enter the oncology world, the challenge will involve the use of combination oral chemotherapy versus single-agent therapies that are more commonly administered today. The use of lapatinib in clin-

ical trials indicates that the most common side effects encountered include moderate rash, fatigue, diarrhea, nausea, anorexia, and vomiting. Grade 3 and 4 events are limited to rash, fatigue, and diarrhea. Lapatinib is on the fast track for US Food and Drug Administration approval when used in combination with capecitabine (Xeloda) in the treatment of patients with meta-

static breast cancer who are HER2+ and have failed to respond to prior therapy, including treatment with trastuzumab (Herceptin).

The addition of targeted therapies in oral form to the treatment of advanced breast cancer will certainly provide many alternatives to patients in the future. The role of the oncology nurse will continue to broaden with these changes, and processes

must be developed to provide the quality of care and support that are essential to the oncology patient's care. It is important to continue providing the same quality of support to patients who are receiving oral therapies as to those receiving intravenous therapies.

*Ms. Tarpley can be reached at [trish.tarpley@usoncology.com](mailto:trish.tarpley@usoncology.com).*

*From the Administrator's Desk*

# Can community-based oncology practices (or patients) afford lapatinib?

Nicky Dozier, PharmD | US Oncology, Inc., Norfolk, VA

**I**t will be interesting to see how community-based practices respond to a drug like lapatinib (Tykerb) once it is marketed. Lapatinib is one of the first oral agents with the potential to compete directly with an IV drug that is both a high-volume and high-revenue part of office-based practice. Early use of lapatinib will likely be limited to patients whose breast cancer is refractory to trastuzumab (Herceptin); longer term, however, it could supplant or perhaps find a place in combination with trastuzumab. These questions will await the clinical evidence.

Of more immediate concern will be lapatinib's cost, payors' response to it, and patients' ability to afford the portion of its cost left to them.

Lapatinib's price has not yet been announced, but it might be expected to exceed the cost of trastuzumab (Herceptin) or to approximate or exceed the price of other recently released tyrosine kinase inhibitors, such as erlotinib (Tarceva) or sorafenib (Nexavar). These novel agents tend to be prescribed as chronic medications, the costs for which can be annualized; the average wholesale price of trastuzumab is approximately \$45,000/year; of erlotinib, \$40,000/year; and of sorafenib, \$60,000/year.

If the cost of lapatinib exceeds these levels, commercial payors may increase the portion patients will be forced to pay. Many patients today struggle to pay even 20% of a \$50,000/year drug charge. Medicare

Part D does little to solve the problem for eligible patients. A Medicare beneficiary would face an out-of-pocket expense of \$3,800 for the first 30-day supply, including annual deductibles plus the "donut hole." Thereafter, coverage would be at 95%, but this first month is difficult for most Medicare beneficiaries to handle, particularly when coupled with Part A or B co-payments.

This problem is not unique to lapatinib, but when the goal of treatment is to increase survival or the chance of cure, patients and payors value the treatment differently than they do a drug that delays disease progression.

*Dr. Dozier can be reached at [nicky.dozier@usoncology.com](mailto:nicky.dozier@usoncology.com).*