Original Article

Novel Approaches to Advanced Breast Cancer: Bevacizumab and Lapatinib

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Key Words

Metastatic breast cancer, biologic therapy, bevacizumab, lapatinib, vascular endothelial growth factor, angiogenesis inhibitor, HER2

Abstract

New biological therapies continue to emerge in breast cancer. Recent advances with anti-angiogenesis therapies and anti-HER2 therapies highlight the next generation of treatments that will be entering clinical practice. Important questions regarding these targeted treatments remain, however. There are uncertainties as to how best to integrate new drugs into existing treatment algorithms, whether to use monotherapy or combination therapy with chemotherapy, and how to manage novel side effects seen with these agents. This review highlights recent advances with the anti-vascular endothelial growth factor antibody, bevacizumab, and the dual-kinase inhibitor, lapatinib, in the treatment of metastatic breast cancer. (*JNCCN* 2007;5:314–323)

Breast cancer treatment is increasingly based on biologic therapies. For decades, antiestrogen therapy has been a mainstay of breast cancer care for patients with hormone-receptor positive tumors. Over the past 10 years, trastuzumab has emerged as a tremendously important drug for women with tumors overexpressing HER2. These agents target growth factor pathways known to be critical in the transformation and persistence of malignant breast cells and have proven worthy in managing both early- and late-stage breast cancer.

More novel therapeutic agents continue to be explored in breast cancer. This article provides an update on 2 of the more promising targeted therapies: bevacizumab, the anti-vascular endothelial growth factor (VEGF) antibody, and lapatinib, a dual kinase inhibitor of both epidermal growth factor receptor (EGFR) and HER2 signaling. The clinical trials that are the foundation of drug development for these agents highlight both the opportunities and challenges in creating new therapies. First, traditional concerns exist, such as establishing the safety and dosing of drugs. As with many biologic agents, bevacizumab and lapatinib lack traditional side effects such as nausea, vomiting, and myelosuppression. The determination of the maximally tolerated dose is often based on side effects that are less familiar to medical oncologists, such as rash or hypertension.

Second, the crucial matter exists of patient selection based on tumor biology. For bevacizumab, the search continues to identify markers that show which patients are more (or less) likely to benefit from therapy. For lapatinib, careful work continues to assess which tumors, based on EGFR and HER2 expression, are most likely to be suitable targets.

Another prominent challenge is the integration of novel agents into established treatment paradigms. Breast cancer is a complex disease with multiple treatment options and many therapeutic choices, especially in advanced disease. Clinical trials attempt to explore novel agents in different contexts, where their benefits might most be realized and where the commercial and regulatory markets allow for introduction of new products. Bevacizumab has proven most useful in first-line treatment of metastatic breast cancer. By contrast, the available phase III data for lapatinib are in the second-line setting. Additional trials now underway explore these agents as treatment for early-stage breast cancer, wherein the potential for changing the natural history of this disease is even more profound.

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Finally, the success of these new therapies will quickly stimulate development of similar drugs that target related growth factor and signaling pathways. Just as the mature arsenal of antiestrogen treatments includes multiple effective drugs, the markets for anti-HER2 and antiangiogenesis agents, now in their infancy, will continue to evolve. The experiences with bevacizumab and lapatinib provide guideposts for the ongoing development of the next generation of treatments.

Angiogenesis in Breast Cancer

Angiogenesis, the process of new blood vessel formation, plays a crucial role in both local and metastatic tumor growth. This complex, highly regulated process is characterized by intricate cross-talk between tumor and endothelial cells mediated by pro- and antiangiogenic factors, leading to stimulation of vascular recruitment and neovascularization.[1,2] One of the most potent of these angiogenic factors, VEGF, plays a pivotal role in tumor angiogenesis. Several members of the VEGF family exist, and 3 receptors, including VEGF receptor 1 (VEGFR-1/Flt-1), VEGFR-2 (KDR/Flk-1), and VEGFR-3 (Flt-4), are found on endothelial cells. VEGF-mediated receptor stimulation leads to vascular hyperpermeability, formation of a plasma-derived matrix, endothelial cell proliferation, and growth of neovasculature.[3]

Angiogenesis is believed to play a central role in the development and progression of breast cancer. Examination of invasive and noninvasive breast tumor tissue shows increased expression of VEGF in tumor cells compared with benign cells, and increases in VEGF receptor expression in the endothelial cells of small vessels adjacent to malignant tumor cells.[4] Increased VEGF expression has also been associated with increased microvessel density, a surrogate marker of angiogenic activity, both in tumor tissue and the surrounding stroma.[5,6] Increased microvessel density and VEGF expression in breast tumor tissue are independent predictors of axillary node status, metastatic disease, and both relapse-free and overall survival.[7–9] Given the overexpression of VEGF in breast tumor cells and the association with an inferior clinical outcome, VEGF has become a target of interest for breast cancer therapy.

Bevacizumab: Clinical Development

Significant efforts have been made to inhibit tumor-induced angiogenesis and subsequent tumor growth through interruption of the VEGF–VEGFR interaction using targeted drug therapy. Bevacizumab is a humanized monoclonal antibody developed to specifically target VEGF. Treatment with bevacizumab leads to reductions in tumor microvessel density, normalization of tumor vasculature, decreases in interstitial fluid pressure, and possibly more efficient delivery of cytotoxic agents.[10] Large randomized trials have shown that bevacizumab has clinical activity in several tumor types, including colorectal, lung, and renal, leading to approval by the U.S. Food and Drug Administration (FDA) as a first-line agent in the metastatic setting.[11–14]

Bevacizumab has been studied extensively in metastatic breast cancer. Early study of bevacizumab monotherapy in anthracycline- and taxane-refractory metastatic breast cancer showed modest evidence of single-agent activity, with response rates within 5% to 15%.[15] Subsequently, bevacizumab has been evaluated in combination with several different types of chemotherapy. At the Dana Farber/Harvard Cancer Center, a phase II study of bevacizumab (10 mg/kg intravenously every 2 weeks) combined with vinorelbine (25 mg/m^2 weekly) in 56 patients with metastatic disease showed moderate activity with a response rate of 31%.[16] Bevacizumab has also been combined with docetaxel in the first- or second-line setting, with an observed response rate of 52%.[17] Bevacizumab has been studied in combination with metronomic chemotherapy (CM): continuous, oral, low-dose cyclophosphamide and methotrexate, a regimen believed to exert activity through an antiangiogenic mechanism. In a phase II study, 55 women who underwent no more than one prior chemotherapy regimen were randomized to undergo CM alone or CM in combination with bevacizumab. Those in the CM arm showed a response rate of 10%, improving to 29% with the addition of bevacizumab. Approximately 40% of women in each arm showed stable disease as their best response.[18]

Bevacizumab also has been evaluated with hormonal therapy. In a phase II feasibility study of bevacizumab in combination with letrozole, the treatment was well tolerated, with evidence of clinical activity.[19] A small phase I study of trastuzumab and bevacizumab has shown tolerability of the combination therapy with clinical responses observed in 5 of 9 patients studied. A phase II trial is ongoing.[20]

In the first phase III trial of bevacizumab for metastatic breast cancer, 462 women with anthracycline- and taxane-treated breast cancer were randomized to treatment with capecitabine alone or capecitabine in combination with bevacizumab. Final results from this study showed a significant improvement in response rate from 9.1% to 19.8% with combination treatment. However, the responses were not durable enough to translate into an improvement in the primary end point of progression-free survival.[21] Researchers have hypothesized that the apparent lack of benefit reflected the highly refractory nature of the patient population. In late 2005, Miller et al.[22] presented updated results from the Eastern Cooperative Oncology Group (ECOG) 2100 trial, a phase III randomized trial of paclitaxel alone (90 mg/m^2 given days 1, 8, and 15, every 28 days) versus paclitaxel plus bevacizumab (10 mg/kg given days 1 and 15) as first-line therapy for metastatic breast cancer. Because of patient selection factors, this study of 722 patients included very few women with HER2-overexpressing breast cancer. In ECOG 2100, combination therapy significantly increased the response rate (28.2% vs. 14.2%; $P < .0001$) and progression-free survival (11.4 vs. 6.11 months; hazard ratio = 0.498, $P < .001$); data were still too immature for full survival analyses.[22] Based on these data, bevacizumab paired with paclitaxel seems to have clinically significant activity as first-line therapy for patients with metastatic breast cancer, and is increasingly considered a treatment option.

Evaluation of the role of bevacizumab in the adjuvant and neoadjuvant settings is ongoing. Treatment of locally advanced disease with preoperative docetaxel with or without bevacizumab has been shown to be feasible with evidence of clinical response.[23] In inflammatory breast cancer, the National Cancer Institute studied a brief exposure to preoperative bevacizumab followed by combination therapy with bevacizumab, doxorubicin, and docetaxel. Of the 21 patients studied, 14 showed a partial clinical response, indicating an overall response rate of 67%. Evaluation of tissue after bevacizumab monotherapy showed a significant decrease in tumor VEGFR2 activation, an increase in tumor apoptosis, and a decrease in endothelial proliferation. Dynamic contrast-enhanced magnetic resonance imagery (DCE-MRI) was also performed before and after bevacizumab administration and showed decreases in tumor perfusion.[24] In patients with triple negative disease (i.e., estrogen receptor–negative, progesterone receptor–negative, HER2-negative), an upcoming phase II study will evaluate the role of bevacizumab in combination with cisplatin chemotherapy (Paula D. Ryan, MD, PhD, personal communication, 2006).

Ongoing studies will also explore the role of bevacizumab in the adjuvant setting. A multicenter pilot study through Dana-Farber/Harvard Cancer Center offers 1 year of either bevacizumab monotherapy (15 mg/kg every 3 weeks) or bevacizumab with CM to women with residual disease after the completion of neoadjuvant chemotherapy. ECOG 2104 is a phase II feasibility study exploring the incorporation of bevacizumab into standard dose-dense doxorubicin/cyclophosphamide and paclitaxel adjuvant therapy. Data from this study are expected to lead to a subsequent randomized phase III trial to further evaluate the contributions of bevacizumab in the adjuvant setting.

In general, treatment with bevacizumab has been well tolerated. In the phase III trial of capecitabine with or without bevacizumab, common side effects included hypertension requiring treatment (17.9% vs. 0.5%) and proteinuria (22.3% vs. 7.4%).[21] Hypertension (15% vs. 2%) and proteinuria (2% vs. 0%) were also observed with increased frequency in the combination arms in ECOG 2100.[22] Cessation of bevacizumab therapy generally leads to resolution of these events, although whether long-term cardiovascular or renal sequelae might occur is unknown. Thromboembolic events were noted in the early phase I and II trials of bevacizumab; however, rates in the phase III studies have been essentially less than 5%. Bleeding events in general have been rare. Grade 3/4 congestive heart failure was seen in 7 versus 2 patients in the capecitabine trial. Ongoing investigation seeks to further evaluate potential cardiovascular toxicity of bevacizumab.

Next-Generation Antiangiogenesis Agents

Inhibition of angiogenesis using small molecule tyrosine kinase inhibitors of VEGFR, such as sunitinib and sorafenib, has proven successful in several malignancies, including renal cell carcinoma and gastrointestinal stromal cell tumors.[25–27] These agents also interfere with various other membrane receptors, including c-kit, platelet-derived growth factor receptor (PDGFR), Raf, and fms-like tyrosine kinase 3 (FLT3),

leading to inhibition of several downstream signal transduction pathways. Data reflecting the role of VEGFR antagonists in breast cancer have been limited, consisting of early-phase studies in heavily pretreated patients. Studies with sunitinib and sorafenib in breast cancer have shown limited activity in heavily pretreated patients, with controllable toxicity.[28,29] Other agents being actively evaluated include AZD2171, ZD6474, PTK787, axitinib, and pazopanib. Ongoing investigations will study these agents in less heavily pretreated populations and in combination with cytotoxic chemotherapy.

Challenges in Development of Antiangiogenesis Agents for Breast Cancer

Many questions have been generated from ongoing investigations into the role of bevacizumab in breast cancer. Substantial effort has been made to identify appropriate biomarkers of activity of and response to antiangiogenic therapy. Despite valiant efforts measuring serum VEGF levels, circulating tumor cells, circulating endothelial cells, and other possible targets, results have been inconclusive and variable. Novel markers of effect, whether serologic, pathologic, or radiologic, are needed for further investigations.

Whether a target population of breast cancer patients exists for angiogenesis inhibitor therapy is currently unknown, and efforts to identify which patients will benefit are ongoing. Increased microvessel density has been observed in triple-negative tumors with a basal-like phenotype, suggesting a novel target for angiogenesis inhibitors.[30] Subset data from ECOG 2100 showed comparable activity of bevacizumab regardless of hormone-receptor status. Additionally, improved efficacy of antiangiogenic therapy may be achieved through multi-level angiogenic blockade, a strategy that could also overcome resistance to single-agent therapy. The concept of concomitant antiangiogenic blockade pairing bevacizumab with small-molecule VEGFR-targeted agents is being evaluated in multiple phase I/II studies in different tumor types. In summary, antiangiogenesis therapy is a rational approach to breast cancer management and seems to be a promising treatment at all stages of breast cancer therapy.

Rationale for HER2-Targeted Therapy

HER2 (Her-2/*neu*, c-*erb*B-2) is a transmembrane tyrosine kinase with extensive homology to the EGFR.[31,32] In both cell lines and animal models, overexpression of HER2 confers a malignant phenotype, suggesting a central role in tumorigenesis.[33] Because of its centrality for breast cancer tumorigenesis, HER2 has been an inviting target for antineoplastic therapy.

Trastuzumab is a humanized, monoclonal antibody directed against the extracellular domain of *HER2*. In the first-line setting, trastuzumab produces objective responses in 34% of patients whose tumors show *HER2* gene amplification.[34] In women with advanced breast cancer, adding trastuzumab to cytotoxic chemotherapy causes significant improvements in disease-free and overall survival compared with chemotherapy alone.[35] Randomized trials incorporating trastuzumab and chemotherapy in the adjuvant setting have shown striking reductions in the risk for recurrence and improvements in overall survival with the addition of *HER2*-directed therapy.[36–39] Thus, HER2 seems to be a highly relevant target in this subtype of breast cancer.

Despite the established efficacy for trastuzumab, significant challenges persist for patients with HER2-positive breast cancer. In most patients with advanced breast cancer, tumor growth eventually progresses despite trastuzumab-based therapy. In a pivotal study in advanced breast cancer, the median time to disease progression was approximately 7 months for patients treated with trastuzumab in combination with paclitaxel.[35] Despite the great success of the adjuvant trials that used trastuzumab, approximately 15% of women with early stage breast cancer experienced recurrence within 4 years after diagnosis.[36] Therefore, in addition to the need for multiple lines of antiestrogen therapy, regimens must be developed that can overcome trastuzumab resistance, and further targeted treatment options for HER2-overexpressing breast cancer must be provided.

Lapatinib

Lapatinib (GW592106; GlaxoSmithKline, Philadelphia, PA) is an orally bioavailable inhibitor of both EGFR and HER2.[40,41] Like other small-molecule EGFR inhibitors, lapatinib binds reversibly to the ATP-binding cleft, leading to inhibition of downstream signaling pathways, but it has a slower off-rate compared with geftinib or erlotinib.[42] Lapatinib

inhibits the proliferation of primary human breast cancer cell lines in vitro and has activity against human breast cancer xenografts in animal models.[43–45] Inhibition of EGFR and HER2 occur in the nanomolar range (IC_{50} ~10.8 and 9.2 nmol/L, respectively), making the agent attractive for further study in humans.[46]

Phase I Clinical Development

In the initial studies in healthy volunteers, repeated dosing of lapatinib was well-tolerated up to doses of 175 mg/d.[47] Subsequently, 2 phase I studies (EGF100003, EGF10004) of monotherapy lapatinib were conducted in patients with multiple tumor types.[48,49] Doses of up to 1800 mg once daily were reached. Pharmacokinetic analyses indicated that steady state was achieved in 6 to 7 days, with peak levels occurring approximately 3 to 6 hours after each dose, and an effective half-life of 24 hours.[49] Serum concentrations exceeded 90% of the in vitro IC_{50}.[46] Furthermore, as part of EGF10004, pre- and post-treatment tumor biopsies were obtained in a subset of 33 patients (including 12 patients with HER2-positive breast cancer), showing effects on p-ErbB2, p-Akt, and p-Erk1/2 in target tissues among a proportion of patients.

In these studies, the most commonly reported adverse events were diarrhea and rash; nausea and fatigue were also reported. Significant myelosuppression was not seen. In terms of clinical activity, approximately half of patients in EGF10004 (30 of 67) had a primary diagnosis of breast cancer. Of these patients, 4 women, all with trastuzumab-refractory, HER2-positive breast cancer, experienced a partial response. An additional 10 patients with breast cancer experienced prolonged stable disease.

Phase II Studies in Breast Cancer: Efficacy

Based on results of the phase I trials, lapatinib was brought forward in phase II studies in breast cancer, and the recommended phase II dose was set at 1500 mg orally once daily. Two studies were conducted in patients with refractory breast cancer. The first study (EGF20002) enrolled 80 patients with HER2-positive metastatic breast cancer that had progressed after first- or second-line trastuzumab-based therapy.[50,51] The objective response rate was 5% (1 complete response, 3 partial response). The second study (EGF20008) enrolled 2 separate cohorts: HER2-positive and HER2-negative. The study enrolled a refractory population and required that patients have previously undergone treatment with an anthracycline, taxane, and capecitabine. Prior trastuzumab was required for patients with HER2-positive tumors. No objective responses occurred in the cohort of patients with HER2-negative tumors. In the HER2-positive cohort, 3 partial responses were observed, for an overall response rate of 7.5%.

Lapatinib was subsequently studied in the first-line setting in patients with HER2-positive, locally advanced, or metastatic breast cancer (EGF20009).[52] At the first interim analysis (n = 40), 35% of patients experienced a confirmed partial response and 2 unconfirmed partial responses were also reported. A high response rate was also noted in a phase II study in relapsed/refractory inflammatory breast cancer (EGF103009).[53] In that study, 62% of patients with HER2-overexpressing tumors experienced response. Interestingly, although one postulated mechanism of trastuzumab resistance is loss of *PTEN*, in both EGF20009 and EGF103009 *PTEN* loss did not seem to preclude response to lapatinib.[54–55]

Lapatinib also was evaluated in the specific setting of HER2-positive breast cancer metastatic to the brain.[56] Approximately one third of women with HER2-positive advanced breast cancer will develop clinically evident brain metastases, often in the setting of continued control of systemic cancer.[57,58] Researchers have hypothesized that one reason for this finding is that trastuzumab does not easily penetrate the blood–brain barrier.[59] In a phase II study of lapatinib in this setting, the observed objective response rate was 5%, similar to that seen in the phase II studies in refractory systemic disease. Based on these results, a multicenter phase II study is currently being conducted, and accrual was expected to be complete by December 2006. In addition, because of preclinical work suggesting that lapatinib may act as a radiosensitizer,[43] a phase I study of lapatinib in combination with cranial radiotherapy is currently being developed.

Phase II Studies in Breast Cancer: Toxicity

Across the phase II studies, the most commonly observed drug-related adverse events have been rash, diarrhea, nausea, and fatigue. Although rash was noted in 30% to 50% of patients, grade 3 rash was uncommon (2.5%–5%). Similarly, nausea was observed in 25% to 35% of patients, generally minor. Diarrhea

seems to be dose- and schedule-related. At the 1500-mg-daily dose, 10% to 17% of patients experienced grade 3 diarrhea. In contrast, when given in divided doses (750 mg twice daily), as in the phase II brain metastases study, 21% of patients reported grade 3 or higher diarrhea.

Cardiac and Pulmonary Toxicity

Cardiac toxicity remains a concern with HER2-targeted agents as a class, given the clinical experience with trastuzumab.[60,61] Among 2812 patients enrolled in all lapatinib trials up to the date of analysis, the rate of grade 3 left ventricular ejection fraction decline was 1.3%.[62] In 57% of cases, the findings resolved or improved. Whether a true difference exists in cardiac toxicity between trastuzumab and lapatinib is unknown, given differences in patient characteristics and prior treatment exposure compared with patients in the initial trastuzumab studies.

Because lapatinib also targets EGFR, data regarding pulmonary toxicity have also been collected. Thus far, the rate of interstitial pneumonitis seems low, with only 3 cases of interstitial pneumonitis and 2 cases of interstitial pneumonia reported across all studies as of January 2005 (Lapatinib investigator brochure).

Phase III Studies

At the 2006 American Society of Clinical Oncology (ASCO) meeting, Geyer et al.[63] presented the results of a phase III study (EGF100151) comparing capecitabine versus the combination of capecitabine plus lapatinib in patients with HER2-positive, advanced breast cancer previously treated with an anthracycline, taxane, and trastuzumab. In March 2006, the study was closed early after an interim analysis showed an improvement in the primary end point of time to progression (TTP) that crossed the prespecified O'Brien-Fleming stopping boundaries. With 114 events recorded, the median TTP was extended from 4.5 months to 8.5 months (P = .00016) in the intent-to-treat analysis. Numerically, more objective responses also occurred in the combination arm, but this difference did not reach statistical significance (22% vs. 14%; P = .113). This result suggests that numerically fewer patients treated with lapatinib experienced central nervous system progression (4 vs. 11), although definitive conclusions cannot be made given the small number of events. No difference in overall survival was seen. The combination of capecitabine and lapatinib was generally well-tolerated. The addition of lapatinib increased the incidence of the more common adverse events including diarrhea, palmar–plantar erythrodysesthesia, and rash.

This study explored the use of continuing anti-HER2 therapy in second-line treatment. Previous attempts to define the significance of trastuzumab treated beyond progression have been made. However, randomized trials of trastuzumab continuation in the second-line setting did not accrue in the United States because of patient and clinician preference. Thus, whether similar results would have been seen if trastuzumab had been substituted for lapatinib in trials with a design similar to EGF100151 is unclear. In small retrospective studies, results have suggested that continuing trastuzumab beyond progression may be useful, but the studies were not prospectively conducted and the results could have been caused by selection bias.[64] Nevertheless, the observed improvements in TTP with the addition of lapatinib add to the options for treating patients who have experienced progression on trastuzumab.

Ongoing Studies and Future Directions

In addition to capecitabine, various other combinations of lapatinib with chemotherapy or hormonal therapy are being explored, including paclitaxel, docetaxel, trastuzumab, and letrozole.[65–67] Cross-talk between the estrogen receptor and growth factor receptor pathways is postulated to lead to diminished sensitivity to hormonal therapy.[68,69] Results of neoadjuvant studies and of a larger meta-analysis of hormonal therapy for advanced breast cancer seem to support this hypothesis.[70,71] Great interest has been shown in determining whether blockade of growth factor signaling can restore sensitivity to hormonal therapy. Cancer and Leukemia Group B (CALGB) 40302 is a randomized, double-blind phase III study of fulvestrant with or without lapatinib in postmenopausal women with tumors that are hormone receptor–positive and have some degree of HER2 overexpression.

In addition, the concept of "vertical blockade" of the HER2 receptor has been explored in preclinical models[72] and in a phase I trial of combined lapatinib with trastuzumab.[67] A randomized phase III study of lapatinib with or without trastuzumab in patients whose

disease is refractory to trastuzumab is ongoing. In addition, a phase II study of the combination in less heavily pretreated patients (0–2 prior lines) is slated to open by early 2007.

Finally, lapatinib is being explored in the neoadjuvant and adjuvant settings. CALGB is planning a trial of neoadjuvant paclitaxel, paired with either trastuzumab, lapatinib, or the combination, to assess the impact of these agents on the incidence of complete pathologic response. A global adjuvant trial will compare trastuzumab versus lapatinib versus the combination versus a sequenced approach of these agents in the adjuvant setting.

Lapatinib: Summary

Lapatinib is a promising addition to the suite of targeted agents for HER2-positive breast cancer. When combined with capecitabine in patients with progressive disease on trastuzumab, lapatinib leads to a significant improvement in TTP. Based on the results presented by Geyer et al.[63] it seems reasonable to consider the combination of lapatinib and capecitabine in patients who fit the eligibility criteria for that study. Beyond this point, however, exactly how and when to integrate lapatinib into existing treatments is not entirely clear. To this end, developing predictive markers to weigh the relative benefits of trastuzumab versus lapatinib in individual patients with metastatic disease would be helpful. In terms of the adjuvant setting, given the marked and highly significant improvements in disease-free survival seen with trastuzumab, lapatinib should not be given outside of a clinical trial. The planned trials evaluating trastuzumab, lapatinib, and the combination will be critical in evaluating the relative benefit of each agent in the adjuvant setting, and to evaluate whether vertical blockade of the HER2 receptor achieves additional gains over either agent alone. Finally, although lapatinib is the furthest in clinical development of the small-molecule HER2-targeted agents, several other dual kinase inhibitors are in early-phase clinical trials.

Implications for Current Practice

The recent data on bevacizumab and lapatinib present a challenge to patients, to clinicians who are eager to do the right thing for patients, and to expert guideline panels, such as those of the National Comprehensive Cancer Network (NCCN), that must decide how to integrate these findings into treatment algorithms. Practical considerations of use also must take into account regulatory approval of drugs as being a limiting step in drug availability, and reimbursement because oncologists and patients will probably be unable to reliably access products that have no insurance coverage. As clinical studies with novel agents evolve, additional data on the optimal timing, use of combination therapy, and duration of treatment emerge to guide clinicians. Currently, because of the limited data for bevacizumab and lapatinib in breast cancer—essentially one positive phase III trial for each drug and supporting phase II data—these drugs should probably be limited to the clinical circumstances that defined the protocol eligibility and treatment in the seminal trials for each agent.

For bevacizumab, this practice generally implies using it in first-line chemotherapy with paclitaxel. For patients with true contraindications to taxane therapy, alternative uses of bevacizumab in the first-line setting may be considered based on reported phase II data with vinorelbine or other chemotherapy combinations. No clinical reason currently exists to continue extended bevacizumab therapy beyond progression or to endorse treatment in patients with heavily refractory advanced breast cancer. Similarly, no data exist for using bevacizumab in combination with trastuzumab or in patients with HER2-overexpressing tumors, although data on such patients are anticipated soon. The NCCN guidelines endorse various chemotherapy regimens, including paclitaxel plus bevacizumab for palliation of advanced breast cancer.[73]

The available data suggest that treatment of HER2-overexpressing disease that has progressed on trastuzumab therapy may be enhanced through use of capecitabine and lapatinib. This would appear to be the appropriate patient population and treatment regimen for using lapatinib if it receives FDA approval and becomes commercially available based on these data. The limited response rate activity in patients with central nervous system metastases is a provocative finding of unclear clinical significance for most of these patients. As with bevacizumab, little reason seems to exist for continuing lapatinib therapy beyond tumor progression. Whether lapatinib will have clinically meaningful activity as a single agent in refractory tumors, how it compares with trastuzumab in treating advanced or early-stage disease, whether it is important as first-line treatment for recurrent breast cancer, or whether it is most active when paired with

different chemotherapy or other biologic therapies all remain to be determined.

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