HER2-Targeted Therapy for Early-Stage Breast Cancer: A Comprehensive Review

This review discusses the treatment of primary, nonmetastatic HER2-positive breast cancer in the adjuvant and neoadjuvant settings—settings in which tremendous progress has been made.

Introduction

Breast cancer is a model disease for the development of both targeted therapies and associated prognostic and predictive biomarkers. Targeted therapies have potentially greater anticancer activity and fewer side effects compared with the traditional cytotoxic chemotherapies that are used to treat breast cancer. The discovery of human epidermal growth factor receptor 2 (HER2) and its role in breast cancer, and the subsequent development of anti-HER2 therapies, have revolutionized the treatment of women with HER2-positive breast cancer and constitute a modern success story in oncology.

HER2 is a transmembrane receptor that belongs to the ErbB/HER family of receptor tyrosine kinases. In 20% to 30% of breast cancers, HER2 is amplified and the HER2 protein is overexpressed—patterns that, until the discovery of effective anti-HER2 therapies, were associated with more aggressive disease and worse outcomes. In this review, we discuss treatments for early-stage HER2-positive breast cancer in the adjuvant and neoadjuvant settings.

Defining HER2-Positive Breast Cancer

Because of its prognostic and predictive value, HER2 protein expression should be evaluated in the tumors of all patients with newly diagnosed primary invasive breast cancer either by immunohistochemistry (IHC) or in situ hybridization (ISH). The current American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines, updated in 2013, define HER2 positivity as 3+ on IHC (defined as uniform intense membrane staining of > 10% of invasive tumor cells) or amplified on ISH (a HER2:chromosome enumeration probe [CEP]17 ratio of > 2.0, or < 2.0 plus average HER2 copy number > 6 signals/cell).[1]

Although a detailed discussion of HER2 testing is beyond the scope of this paper, we would like to note that if a patient’s HER2 expression is ultimately deemed to be equivocal on both IHC and ISH, the oncologist can still consider HER2-targeted therapy, based on the patient’s history, prognosis, and comorbidities.

Adjuvant Therapy

The monoclonal antibody trastuzumab is the first and only targeted agent that has been approved for the adjuvant treatment of early-stage HER2-positive breast cancer. Trastuzumab binds to the extracellular domain of HER2, suppressing its signaling activity and inducing antibody-dependent cell-mediated cytotoxicity (ADCC). Trastuzumab was first approved for use in patients with metastatic HER2-positive disease, as monotherapy and in combination with paclitaxel or docetaxel.[2-4]

Two major North American Cooperative Group trials, published as a joint analysis in 2005, established the benefit of trastuzumab in the adjuvant setting.[5] In both studies, patients were treated with a backbone of doxorubicin plus cyclophosphamide (AC) every 3 weeks for 4 cycles, but subsequent therapies differed slightly between the two trials. The first trial, National Surgical Adjuvant Breast and Bowel Project B-31 (NSABP B-31), randomized women with HER2-positive, node-positive breast cancer to 4 cycles of single-agent paclitaxel, given every 3 weeks, with or without weekly trastuzumab (initial loading dose of 4 mg/kg, then 2 mg/kg weekly for 1 year), beginning with the first dose of paclitaxel. The second trial, North Central Cancer Treatment Group...
(NCCTG) N9831, randomized women with HER2-positive, node-positive or high-risk, node-negative disease to one of three regimens: weekly paclitaxel for 12 weeks, followed by no further treatment; weekly paclitaxel, followed by sequential trastuzumab for 52 weeks; or weekly paclitaxel with concurrent trastuzumab for 12 weeks, followed by trastuzumab alone for 40 weeks. The combined analysis compared patients who were treated with paclitaxel that was administered concurrently with trastuzumab and those who received paclitaxel alone. The primary endpoint of both trials was disease-free survival (DFS). At the first joint interim efficacy analysis, it was recommended that the trials end enrollment and that the results be released. When initially published, at a median follow-up of 2 years, the hazard ratio (HR) for a first event in the trastuzumab group (compared with the control group) was 0.48 (95% confidence interval [CI] = 0.39–0.59; P < .0001).[5] At 3 years, the absolute difference in DFS was 11.8% (95% CI = 8.1%–15.4%; P < .0001), and the absolute difference in overall survival (OS) was 2.5% (95% CI = 0.1%–5.0%; P < .015). An updated analysis confirmed that chemotherapy plus adjuvant trastuzumab resulted in superior DFS (85.7% vs 73.7%; HR = 0.52) and OS (93.0% vs 85.6%; HR = 0.61) at 4 years.[6] The results of NCCTG N9831 and NSABP B-31 established the benefit of trastuzumab in addition to anthracycline-taxane-based adjuvant chemotherapy in women with early-stage breast cancer. These findings were reconfirmed in a recent Cochrane review that evaluated the use of adjuvant trastuzumab-containing regimens in eight studies of 11,991 women with early-stage breast cancer,[7] in which the combined HRs for OS and DFS favored the trastuzumab-containing regimens (OS: HR = 0.66; 95% CI = 0.57–0.77; P < .00001 and DFS: HR = 0.60; 95% CI = 0.50–0.71; P < .00001).

In HER2-negative breast cancer, AC is often given on a dose-dense schedule with granulocyte colony-stimulating factor support, based on improved outcome data, particularly in patients with hormone receptor-negative breast cancer.[8] Morris et al, in a phase II trial, assessed the feasibility and cardiac safety of incorporating trastuzumab into a dose-dense AC regimen. At a median follow-up of 84 months, the cumulative incidence of congestive heart failure (CHF) was 1.4% (95% CI = 1.36%–7.7%), which is comparable to rates seen in other major adjuvant trastuzumab trials (Table 1).[9] Outcome results were similarly favorable. However, there are no data to suggest that a dose-dense AC regimen is superior in this setting, and the additional toxicity and cost that are associated with granulocyte colony-stimulating factor support should be considered. National Comprehensive Cancer Center (NCCN) guidelines do suggest that dose-dense AC is an acceptable option as part of trastuzumab-based adjuvant therapy.[10]

Data on non-anthracycline-based adjuvant therapy in combination with trastuzumab come from the Breast Cancer International Research Group 006 (BCIRG-006) trial, in which women with HER2-positive, node-negative breast cancer were randomized to one of three regimens: A) AC every 3 weeks for 4 cycles, followed by docetaxel every 3 weeks for 4 cycles (AC-T); B) AC-T plus trastuzumab for 1 year (weekly beginning with the first dose of docetaxel, then every 3 weeks) (AC-TH); and C) docetaxel plus carboplatin every 3 weeks for 6 cycles, with concurrent weekly trastuzumab during chemotherapy, then every 3 weeks for 1 year of total trastuzumab therapy (TCH).[11]

At a median follow-up of 65 months, both trastuzumab-containing arms experienced a significant improvement in estimated 5-year DFS (81% with TCH and 84% with AC-TH vs 75% with AC-T) and OS (91% with TCH and 92% with AC-TH vs 87% with AC-T). The differences in DFS and OS between AC-TH and TCH were not statistically significant, although the study was not powered to detect equivalence. Compared with AC-TH, TCH resulted in significantly lower rates of severe (grade 3/4) neutropenia and leukopenia, CHF, and sensory neuropathy but significantly higher rates of severe anemia and thrombocytopenia. TCH is the most common non-anthracycline-based adjuvant chemotherapy regimen in the United States for patients with HER2-positive breast cancer. Because of the increased risk of cardiotoxicity (see Table 1), the decision of whether to treat with an anthracycline-containing or a non-anthracycline-containing regimen should be based on clinical stage, hormone receptor status, and comorbid conditions. It is our practice to administer anthracycline-based therapy in patients without cardiac risk factors, particularly in the setting of node-negative or hormone receptor-negative disease (Figure). The presence of cardiac risk factors alone (hypertension, known baseline cardiac dysfunction, age > 50 years) should not exclude patients from receiving HER2-directed therapy if otherwise indicated. However, such patients should be monitored closely.

Cardiac function should be assessed in all patients prior to starting trastuzumab. In the adjuvant setting, when administration of trastuzumab follows the use of an anthracycline, left ventricular ejection fraction (LVEF) should be measured after completion of the anthracycline and prior to the
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initiation of trastuzumab. The optimal surveillance schedule for trastuzumab-related cardiotoxicity has not been defined. At a minimum, patients should undergo a baseline evaluation for cardiac function, with a repeat study at 6 months. Early adjuvant trials employed more frequent monitoring—with evaluation of cardiac function at baseline; on completion of AC; and at 6, 9, and 18 months following initiation of trastuzumab.[12,13] In addition, new signs or symptoms that are suggestive of CHF warrant further evaluation.

In patients who experience cardiotoxicity while taking trastuzumab, it is reasonable to follow the dose adjustment guidelines from NSABP B-31 and NCCTG N9831.[5] If the LVEF declines 16 percentage points or more from baseline, or 10 to 15 percentage points from baseline, yet to below the lower limits of normal, trastuzumab should be held for 4 weeks and cardiac function should be re-evaluated. If the LVEF remains below these levels at the 4-week re-evaluation or if the patient has signs or symptoms of CHF, trastuzumab should be discontinued permanently and standard therapy for heart failure should be initiated. Similarly, trastuzumab should be permanently discontinued if it is held for three nonconsecutive doses because of declines in LVEF.

The recommended duration of adjuvant trastuzumab treatment remains a total of 12 months. This is based on the studies above, plus the results of the HERA trial, which found no difference in DFS or OS between 12 and 24 months of trastuzumab, and the results of the PHARE trial, which demonstrated that 6 months of adjuvant trastuzumab resulted in worse DFS rates and increased the number of deaths and more distant recurrences compared with 12 months.[14,15] The use of concurrent cytotoxic chemotherapy and trastuzumab vs sequential trastuzumab following chemotherapy was evaluated in several trials, including HERA and NCCTG N9831.[14,16] While sequential therapy appears to have benefit compared with non-trastuzumab-containing regimens, better outcomes were observed with the concurrent approach (ie, trastuzumab combined with a taxane). Based on these findings, concurrent adjuvant trastuzumab in combination with chemotherapy is preferred.

In an attempt to improve outcomes further, novel agents have been combined with trastuzumab in the adjuvant setting. The results of the BETH trial were reported at the 2013 San Antonio Breast Cancer Symposium.[17] In this trial, the anti–vascular endothelial growth factor monoclonal antibody bevacizumab was combined with chemotherapy plus trastuzumab in approximately 3,000 women with node-positive and high-risk, node-negative HER2-positive breast cancer. After a median follow-up of 38 months, there was no improvement in invasive disease–free survival (primary endpoint) with the addition of bevacizumab (HR = 0.99; 95% CI = 0.79–1.25; \( P = .96 \)).

Other agents that target HER2 have been developed since the introduction of trastuzumab, including lapatinib, pertuzumab, and ado-trastuzumab emtansine, all of which are under investigation in the adjuvant setting. To date, trastuzumab remains the only agent that has a known survival benefit in the adjuvant setting.

The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial is evaluating the combination of trastuzumab plus lapatinib in early-stage breast cancer in more than 8,000 patients (clinicaltrials.gov identifier, NCT00490139). A planned interim analysis of early data from ALTTO has resulted in the closing of the lapatinib-only arm[18]; the data monitoring committee has indicated that this arm is unlikely to meet the prespecified criteria of noninferiority to trastuzumab. This trial is the second study to suggest a lack of benefit from lapatinib alone in the adjuvant setting.[19] The other three trial arms are continuing without modification. The APHINITY trial is a phase III study enrolling over 4,000 patients that is comparing 1 year of adjuvant trastuzumab plus placebo with trastuzumab plus pertuzumab following the investigators’ choice of chemotherapy (clinicaltrials.gov identifier, NCT01358877). The first patients were enrolled in 2011.

To date, HER2 overexpression is the only predictive marker for HER2-targeted therapy. However, the tremendous improvement in outcomes seen with anti-HER2 therapy in both early-stage and metastatic breast cancer has led to interest in identifying patients who are HER2-negative by conventional IHC/ISH but who might still benefit from anti-HER2 therapy. For example, in a study of patients with hormone receptor–positive metastatic breast cancer who were treated with letrozole plus lapatinib, on initial analysis, only patients with centrally confirmed HER2 amplification seemed to benefit from the addition of lapatinib.[20] However, a subsequent retrospective analysis demonstrated that among HER2-negative patients, those with low estrogen receptor (ER) expression experienced significant improvement in progression-free survival, suggesting an interaction between hormone receptor signaling and HER family signaling.[21]

Additional prospective studies are underway. NSABP B-47 is a randomized phase III trial that is currently recruiting patients and is comparing adjuvant chemotherapy alone vs adjuvant chemotherapy plus trastuzumab in women with node-positive or high-risk, node-negative, HER2-low
invasive breast cancer (clinicaltrials.gov identifier, NCT01275677). Several correlative studies are planned, including an evaluation of HER2 mRNA levels; these hope to identify predictive markers for improved outcomes in women who have been diagnosed with HER2-negative breast cancer per ASCO/CAP guidelines.

**Adjuvant Treatment for Low-Risk HER2-Positive Breast Cancer**

The major adjuvant trials with trastuzumab included predominantly women with high-risk/node-positive breast cancer, all of whom demonstrated a strong survival advantage with the addition of trastuzumab to adjuvant chemotherapy. However, data from the pre-trastuzumab era suggest that even women with lower-risk, node-negative disease had a significantly higher risk of relapse if their tumor was HER2-positive.[22] Thus, most women with HER2-positive tumors > 5 mm are treated with adjuvant trastuzumab-based therapy, regardless of their nodal status.

A recent meta-analysis evaluated the prognosis of small HER2-positive breast cancers in completed randomized adjuvant trastuzumab trials.[23] For patients with tumors < 2 cm and 0 or 1 positive lymph nodes, the 5-year DFS in hormone receptor–positive disease was 91% (95% CI = 89%-93%) and 84% (95% CI = 81%-87%) in hormone receptor–negative disease. Similarly, the OS at 5 years was 97% (95% CI = 96%-98%) and 95% (95% CI = 93%-96%), respectively. These data suggest that this subset of low-risk patients might be excluded from studies that evaluate new HER2-directed adjuvant therapies, because they are unlikely to contribute significantly to improved study outcomes. However, because all of these patients received standard adjuvant regimens, we do not know in which patients we should omit or limit therapy.

A recently published phase II trial sheds some light on this issue. Tolaney et al administered weekly doses of paclitaxel plus trastuzumab followed by trastuzumab alone to complete 1 year in 406 women with HER2-positive, node-negative breast cancer and tumors < 3 cm.[24] At a median follow-up of 3.6 years, the 3-year DFS was 98.7% (95% CI = 97.6%-99.8%), with only 10 DFS events observed. Toxicity was limited; symptomatic CHF developed in 2 patients (0.5%), and asymptomatic declines in LVEF were observed in 13 patients (3.2%). These results are encouraging, suggesting that a simplified adjuvant regimen with significantly less toxicity may be sufficient for many women (see Figure).

Ongoing studies are evaluating additional ways to safely reduce the toxicity of adjuvant therapy in women with early-stage, low-risk HER2-positive breast cancer. For example, the ATEMPT trial is evaluating adjuvant ado-trastuzumab emtansine every 3 weeks for 1 year compared with 12 weeks of paclitaxel plus trastuzumab followed by trastuzumab to complete 1 year in women with stage I HER2-positive breast cancer (clinicaltrials.gov identifier, NCT01853748).

**Neoadjuvant Chemotherapy**

Neoadjuvant chemotherapy has traditionally been used in breast cancer to treat patients with locally advanced/inoperable disease to facilitate surgical resection and to allow breast-conserving surgery in women with larger tumors who are not candidates for such surgery at presentation. Further, the complete eradication of invasive tumor in the primary breast lesion and/or lymph nodes (pathologic complete response, or pCR) in response to neoadjuvant chemotherapy is a known prognostic factor. Kuerer et al retrospectively evaluated 372 patients with locally advanced breast cancer who were treated with anthracycline-based neoadjuvant chemotherapy and demonstrated that the 5-year OS and DFS rates were significantly higher in patients who achieved a pCR in the breast and lymph nodes (89% and 87%, respectively) than in those with less than a pCR (64% and 58%, respectively; P < .01).[25]

Similar results were seen prospectively in the NSABP B-18 trial, in which 1,523 women with early-stage breast cancer were randomly assigned to preoperative vs postoperative anthracycline-based chemotherapy. There was no difference in DFS or OS at 5 years between the two groups. However, among the 683 women who received neoadjuvant treatment, outcomes were significantly better in the women who achieved a pCR than in those without a pCR (5-year OS, 87.2% vs 76.9%-78.4%; P = .06; DFS, 83.6% vs 60.3%-71.7%; P = .0004).[26] These and similar results have led to significant interest in the use of neoadjuvant chemotherapy as a research tool in breast cancer, because as a primary endpoint, pCR can be evaluated faster than endpoints traditionally used in adjuvant trials, such as DFS and OS. This has been particularly true in HER2-positive breast cancer.

Trastuzumab has been combined with chemotherapy in the neoadjuvant setting, conferring benefits similar to those observed in the adjuvant setting. For example, the NOAH trial compared...
neoadjuvant chemotherapy (doxorubicin plus paclitaxel given every 3 weeks × 4 cycles, followed by cyclophosphamide, methotrexate, and fluorouracil on days 1 and 8 every 3 weeks × 3 cycles) vs the same regimen with concurrent trastuzumab followed by adjuvant trastuzumab to complete 1 year; NOAH involved 235 women with locally advanced/inflammatory HER2-positive breast cancer.[27] In this study, trastuzumab significantly improved the event-free survival (EFS) rate (HR = 0.59; 95% CI = 0.38–0.90; P = .013), the in-breast pCR rate (43% vs 22%; P = .001), and the pCR rate in the breast and lymph nodes. Follow-up results after a median of 5.4 years confirmed the EFS benefit in the trastuzumab arm (5-year EFS, 57.5% vs 43.3%; HR = 0.64; P = .016).[28] The difference was particularly notable in patients who achieved a pCR: the 5-year EFS in these patients was 86.5%. There was also a trend toward an OS benefit with the addition of trastuzumab (5-year OS, 73.5% vs 62.9%; HR = 0.66; P = .055).

The recently reported American College of Surgeons Oncology Group (ACOSOG) Z1041 trial evaluated neoadjuvant trastuzumab, given concurrently throughout chemotherapy, vs the taxane portion of the regimen only. Concurrent trastuzumab and paclitaxel followed by concurrent trastuzumab and FEC (fluorouracil, epirubicin, cyclophosphamide), with epirubicin given at an attenuated dose of 75 mg/m^2 (FEC-75), was compared with FEC-75 followed by paclitaxel and trastuzumab.[29] The in-breast pCR rate (the primary endpoint) was 54.2% in the concurrent arm compared with 56.5% in the arm in which trastuzumab was given with paclitaxel only, suggesting there was no added benefit of concurrent administration of trastuzumab with an anthracycline in the neoadjuvant setting. Asymptomatic decrease in LVEF was seen in a similar proportion of patients in the two groups, and grade 3/4 cardiac toxicity was rare (see Table 1).

There is also significant emerging data on the use of combined HER2-targeted therapy in the neoadjuvant setting. Several phase II and phase III trials have evaluated the combination of trastuzumab plus lapatinib in the neoadjuvant setting. The neoadjuvant ALTTO (NeoALTTO) trial was designed to answer questions that were similar to the questions addressed in the ALTTO study. In NeoALTTO, 455 patients with HER2-positive breast cancer and tumors > 2 cm were randomized to receive trastuzumab alone, lapatinib alone, or the two agents in combination.[30] The anti-HER2 agents were given for 6 weeks alone, followed by concurrent weekly paclitaxel for 12 weeks prior to surgery. Adjuvant therapy consisted of 3 cycles of FEC and the same anti-HER2 therapy to which the patient had previously been randomized to complete 1 year.

In the NeoALTTO trial, the pCR rate in the breast (the primary endpoint) was significantly higher with the combination of lapatinib and trastuzumab compared with trastuzumab alone (51.3% vs 29.5%; P = .0001); the pCR rate was 24.7% with lapatinib alone. Patients in the lapatinib arms experienced more grade 3 diarrhea (21.1%–23.4%) than did patients in the trastuzumab arm (2.0%). There was no excess cardiac toxicity with combined anti-HER2 therapy (see Table 1). The similarly designed NSABP B-41 trial also reported a higher (although not statistically significant) pCR rate with the combination of chemotherapy, trastuzumab, and lapatinib compared with either individual agent alone.[31]

Although NeoALTTO was not powered to evaluate long-term outcomes, a follow-up analysis of the trial, with a median clinical follow-up of 3.8 years, was recently presented.[32] In the analysis of all patients, there was no improvement in 3-year EFS or OS with the combination of trastuzumab plus lapatinib compared with trastuzumab alone (HR = 0.78; P = .33 and HR = 0.62; P = .19, respectively). However, the 3-year EFS and OS rates were significantly higher in patients who achieved a pCR (86% and 94%, respectively) than in those who did not (72% and 87%, respectively; P = .0003 and P = .005, respectively). For the subgroup of patients who achieved a pCR, the improvements seen in EFS and OS were driven by those patients who had hormone receptor-negative disease, reinforcing the notion that the hormone receptor-positive/HER2-positive and hormone receptor-negative/HER2-positive subgroups represent distinct disease subtypes. Although this study confirms the prognostic power of a pCR in an individual patient, it raises further questions regarding the use of pCR as a primary endpoint for the approval of new agents and new combinations.[33]

Pertuzumab is a monoclonal antibody that is similar to trastuzumab but that targets a different extracellular domain of the HER2 receptor—specifically, the dimerization region. Its binding inhibits ligand-induced heterodimerization of HER2 with other members of the HER family, while retaining the ability to induce ADCC. Although trastuzumab is active against HER2 homodimers, it is ineffective against HER2 heterodimers. These heterodimers, particularly HER2-HER3, are thought to be important in driving breast cancer cell proliferation. In the preclinical setting, dual HER2 targeting with trastuzumab and pertuzumab demonstrated enhanced blockade of the HER2 signaling network compared with either antibody alone.[34] These findings have led to several clinical trials designed...
to assess the value of pertuzumab in combination with trastuzumab, taxanes, anthracyclines, and other chemotherapeutics.

In the phase II NeoAdjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation (NeoSPHERE) trial, patients with HER2-positive breast cancer with tumors > 2 cm were randomized to one of four treatment arms: A) docetaxel plus trastuzumab and pertuzumab, B) docetaxel plus trastuzumab, C) docetaxel plus pertuzumab, or D) pertuzumab plus trastuzumab alone (without chemotherapy)—all of which were given every 3 weeks for 4 cycles.[35] Patients then received adjuvant FEC for 3 cycles and trastuzumab to complete 1 year. A statistically significant difference in the in-breast pCR rate (the primary endpoint) was noted in patients who received trastuzumab and pertuzumab plus docetaxel compared with the combination of trastuzumab and docetaxel (45.9% vs 29%; \( P = .014 \)). As reported in prior studies, pCR rates were higher in patients with hormone receptor-negative tumors (63.2% in those receiving the dual anti-HER2 regimen with docetaxel). Notably, even in the absence of cytotoxic chemotherapy, 16.8% of patients in the pertuzumab-plus-trastuzumab-alone arm achieved a pCR. During the neoadjuvant phase of the trial, the most common grade 3 or worse events were neutropenia, febrile neutropenia, and leukopenia, which were seen only in patients in the docetaxel-containing arms. No significant excess cardiac toxicity was detected with the addition of pertuzumab to trastuzumab; there was a mean maximum decrease in LVEF of 4% to 5% that was balanced across treatment groups (see Table 1).

Similarly, TRYPHAENA, a phase II study, evaluated the neoadjuvant use of pertuzumab in patients with operable, locally advanced, or inflammatory breast cancer with primary tumors > 2 cm. Patients were randomized to three arms: A) FEC for 3 cycles followed by docetaxel for 3 cycles, with trastuzumab and pertuzumab given concurrently throughout; B) FEC for 3 cycles followed by docetaxel with concurrent pertuzumab and trastuzumab for 3 cycles; and C) docetaxel plus carboplatin with concurrent pertuzumab and trastuzumab for 6 cycles.[36] All patients then received trastuzumab to complete 1 year. The primary objective was safety and tolerability. The incidence of serious adverse events was highest in arm C (35.5%), followed by arm A (27.8%) and arm B (20.0%); neutropenia, febrile neutropenia, and leukopenia were the most common grade 3 or worse adverse events. Left ventricular systolic dysfunction of all grades was seen during neoadjuvant treatment in 5.6%, 4.0%, and 2.6% of patients in arms A, B, and C, respectively. Symptomatic decline in LVEF was noted during neoadjuvant treatment in 2.7% of patients in arm B and in no patients in arm A or arm C (see Table 1). In-breast pCR was achieved in 61.6%, 57.3%, and 66.2% of patients in arms A, B, and C, respectively. These two trials, along with the CLEOPATRA study in the metastatic setting, provide evidence that pertuzumab does not compound the cardiac toxicity seen with trastuzumab.[37] However, cardiac function should be monitored, as in patients who receive adjuvant trastuzumab-based therapy.

Based on the above studies, pertuzumab received accelerated approval by the US Food and Drug Administration in 2013 as part of several neoadjuvant regimens: 1) 4 preoperative cycles of pertuzumab, trastuzumab, and docetaxel, followed by 3 postoperative cycles of FEC; 2) 3 preoperative cycles of FEC (alone), followed by 3 preoperative cycles of pertuzumab, trastuzumab, and docetaxel; and 3) 6 preoperative cycles of pertuzumab, trastuzumab, docetaxel, and carboplatin. Based on the benefits and safety observed for these regimens, the NCCN guidelines and other recommendations (Table 2) state that it is reasonable to substitute 4 cycles of AC for FEC.[10] Similarly, paclitaxel may be substituted for docetaxel. However, these substitutions have not been evaluated in a clinical trial.

Unlike with the addition of lapatinib, the addition of pertuzumab to trastuzumab-based neoadjuvant regimens appears to contribute little increased toxicity. However, there is significant additional cost: the estimated monthly cost of trastuzumab is $4,090, compared with $8,980 for the combination of trastuzumab and pertuzumab.[38] Because there are no long-term outcome data on the neoadjuvant use of pertuzumab plus trastuzumab, this combination should not be the standard of care for all patients, particularly those who are clinically node-negative with small primary tumors, as the prognosis of these patients is excellent with a trastuzumab-based regimen alone. Several clinical trials are currently underway to further evaluate the value of neoadjuvant dual HER2 blockade. Based on the hypothesis that the ER pathway provides an escape mechanism by which tumor cells can evade HER2-targeted therapy, NSABP B-52 will begin enrollment in 2014 and evaluate multiagent anti-HER2 therapy (docetaxel plus carboplatin in combination with trastuzumab and pertuzumab) with concurrent endocrine therapy in ER-positive/HER2-positive breast cancer (clinicaltrials.gov identifier, NCT02003209).
Treatment Algorithm and Comparison With National Guidelines

A treatment algorithm for the management of stage I–III HER2-positive breast cancer, based on the above discussion, is shown in the Figure. For comparison, the current NCCN guidelines for the adjuvant/neoadjuvant treatment of HER2-positive breast cancer are shown in Table 2.[10]

There are several ongoing clinical trials in patients with HER2-positive breast cancer, and clinical trial participation should be encouraged where feasible. Outside of a clinical trial setting, we recommend the use of adjuvant paclitaxel plus trastuzumab in patients with early-stage, node-negative, HER2-positive breast cancer and tumors < 2.0 cm, based on a recently reported phase II trial by Tolaney.[24] Although long-term follow-up data for this combination are not yet available, such patients have an excellent prognosis, and the benefits of a more aggressive regimen must be weighed against the added toxicity.

For patients with node-positive and/or locally advanced and inflammatory breast cancer, we prefer an anthracycline-based regimen. Neoadjuvant chemotherapy is recommended, because it provides significant prognostic information, most notably in those with hormone receptor-negative disease. Further, based on available data, it is reasonable to consider dual anti-HER2 therapy with trastuzumab plus pertuzumab in this population—particularly in patients with symptoms from local disease—given the > 85% response rate seen with such combinations.[35] We prefer dual therapy with pertuzumab rather than lapatinib, based on the reported side effect profiles, although these regimens have not been compared head to head.

Conclusions

In the management of patients with breast cancer, selecting the most efficacious therapy remains a challenging but achievable goal. Improved understanding of the targets for therapy has made possible an unprecedented level of insight into the individual patient’s cancer genome and biology. Concurrent development of predictive biomarkers along with targeted therapies is the new paradigm for achieving optimal care and sparing patients unnecessary toxicity and expense. The treatment of HER2-positive breast cancer is at the forefront of this endeavor. For patients with early-stage, node-negative disease, the prognosis is excellent with current therapies, and future research should focus on limiting toxicity and cost. Patients with more advanced disease, particularly those with hormone receptor–negative tumors who do not achieve a pCR with current neoadjuvant therapies, remain at high risk for relapse, and novel treatment approaches are needed for such patients. We eagerly await the outcomes of the multiple trials underway in both the adjuvant and neoadjuvant settings. These trials will identify biomarkers that predict both the benefits and toxicity of various therapeutic combinations, further advancing the goal of personalized patient care.

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Table 2: NCCN Guidelines: Neoadjuvant/Adjuvant Chemotherapy Regimens f...

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