Adjuvant Trastuzumab for HER2-Positive Early Breast Cancer: A Review of Clinical Data With Nursing Implications

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This article reviews clinical data on adjuvant trastuzumab (Herceptin®, Genentech, Inc.) for patients with HER2-positive early breast cancer. Published articles were searched via PubMed (1985–2009), and abstracts were located from meeting books or search engines of congress Web sites (1994–2009). Search terms included breast neoplasms, breast cancer, breast tumor, or breast tumour and adjuvant plus HER2-positive plus trastuzumab. Trastuzumab improves clinical outcomes as well as disease-free and overall survival for patients with early HER2-positive breast cancer compared with adjuvant chemotherapy alone in this population. Trastuzumab has a favorable safety profile; levels of cardiac dysfunction were acceptable in all adjuvant trials, and cardiac dysfunction was manageable in most cases. Awareness of the clinical data will help nurses identify patients eligible for adjuvant trastuzumab, familiarize them with treatment and cardiac monitoring plans, and provide them with information to help advise, treat, and support patients from diagnosis through completion of therapy.

Breast cancer is the most frequently diagnosed cancer in women in the United States (Jemal et al., 2009). Among women, breast cancer was estimated to account for 27% of all new cancer cases in the United States and was expected to cause 40,170 deaths in 2009 (Jemal et al., 2009). The chances of survival are increased with early diagnosis and treatment.

Evolution of Adjuvant Therapy

Systemic adjuvant therapy is administered following surgery because it reduces the risk of disease recurrence and metastasis and increases survival, particularly among patients with node-positive disease who are at high risk for recurrence. In the United States throughout the 1970s and 1980s, the cytotoxic chemotherapy regimen of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) was the mainstay of adjuvant therapy. Anthracyclines such as doxorubicin combined with cyclophosphamide (AC) showed substantial improvements in clinical outcome compared with CMF; anthracycline-containing regimens significantly reduced the risk of disease recurrence by 12% and risk of death by 11% and became the standard of care in the 1990s (Early Breast Cancer Trialists’ Collaborative Group, 1998a). In the early 2000s, the addition of paclitaxel to standard AC provided more improvements, reducing risk of recurrence by 17% and risk of death by 18% at five years; disease-free survival at this time point was 70% versus 65%, and overall survival was 80% for AC plus paclitaxel versus 77% for AC alone (Henderson et al., 2003). More recent progress in chemotherapy has included the use of another taxane, docetaxel, and dose-dense therapy regimens.

At a Glance

❖ Nurses are crucial for educating and supporting patients throughout the treatment period to ensure that patients derive the maximum benefit from adjuvant trastuzumab therapy.
❖ Monitoring cardiac function before, during, and after trastuzumab-based adjuvant treatment is important.
❖ Nursing intervention can lead to increased individual adaptation to the psychosocial effects that occur during all phases of breast cancer diagnosis, treatment, and survivorship.
Concurrent with the development of optimum chemotherapy regimens, research into tumor biology provided insight into predictive and prognostic factors. The research has enabled treatment to be tailored, based on tumor profile. Prognostic factors such as tumor size, nodal status, and tumor grade indicate the nature of the disease, and predictive factors allow selection of patients most likely to benefit from a therapy.

Breast tumors may express estrogen receptors or progesterone receptors, making them hormone sensitive. Estrogen-receptor modulators such as tamoxifen (Early Breast Cancer Trialists' Collaborative Group, 1998b) and aromatase inhibitors such as anastrozole (Baum et al., 2003), letrozole (Coates et al., 2007), and exemestane (Coombes et al., 2004) have provided substantial clinical benefit for patients with hormone receptor-positive disease. Other predictive and prognostic factors have been discovered, including patient age, comorbidity, menopausal status, the presence or absence of detectable metastatic disease, and HER2 tumor status (National Comprehensive Cancer Network [NCCN], 2010a).

Targeting HER2-Positive Breast Cancer With Trastuzumab

HER2 is a gene amplified or overexpressed in 20%–25% of all breast cancers (Owens, Horten, & Da Silva, 2004; Sjugren, Inganas, Lindgren, Holmberg, & Bergh, 1998; Slamon et al., 1987). HER2 positivity is associated with an aggressive disease course, a poor prognosis (Paik et al., 1990), and relative sensitivity to anthracyclines (Paik et al., 1998). In a study of 292 patients with primary invasive breast cancer, those with HER2-positive primary tumors had twice the mortality rate of those with HER2-negative tumors (p = 0.0012) (Paik et al., 1990).

Trastuzumab (Herceptin®, Genentech, Inc.) is an anti-HER2 monoclonal antibody that specifically targets the HER2 protein and has five proposed cytostatic, cytotoxic, and antiangiogenic mechanisms of action. The mechanisms include activation of antibody-dependent cellular cytotoxicity, inhibition of HER2 extracellular domain cleavage, abrogation of intracellular signaling, reduction of angiogenesis, and decreased DNA repair (Baselga, Albanell, Molina, & Arribas, 2001; Izumi, Xu, di Tommaso, Fukumura, & Jain, 2002; Pietras et al., 1994).

Trastuzumab was first investigated in HER2-positive metastatic breast cancer. The U.S. Food and Drug Administration (FDA) approved trastuzumab in this setting in 1998, based on its significant improvements in clinical outcomes when observed as a monotherapy and in combination with chemotherapy (Cobleigh et al., 1999; Slamon et al., 2001; Vogel et al., 2002). Trastuzumab was approved as first-line therapy in combination with paclitaxel or as monotherapy in patients who had previously received chemotherapy for their metastatic disease.

The effectiveness of trastuzumab in the metastatic setting prompted investigators to test it in the adjuvant setting to determine whether treating HER2-positive tumors at an earlier stage could improve patient outcomes. As a result, trastuzumab also is indicated for the treatment of HER2-positive breast cancer in the adjuvant setting; as part of a regimen that contains doxorubicin, cyclophosphamide, and paclitaxel (FDA approval received in 2006); or as monotherapy for HER2-positive, node-negative (estrogen receptor- or progesterone receptor-negative or with one high-risk feature) or node-positive breast cancer, following multimodality anthracycline-based therapy (FDA approval received in 2008). Trastuzumab can be used as part of a treatment regimen consisting of AC and paclitaxel or docetaxel, with docetaxel and carboplatin, or as monotherapy following multimodality anthracycline-based therapy (Genentech, Inc., 2009).

Because trastuzumab is a targeted agent, the monoclonal antibody does not produce many of the adverse effects commonly associated with cytotoxic chemotherapy. Mild infusion-related fever and chills are the most frequently observed adverse events (Cobleigh et al., 1999; Vogel et al., 2002). Cardiotoxicity in the form of left ventricular dysfunction and, occasionally, congestive heart failure also is associated with trastuzumab, particularly when it is administered concurrently with anthracyclines (Seidman et al., 2002; Slamon et al., 2001). Clinical data and nursing implications related to trastuzumab therapy for metastatic breast cancer are reviewed by Frankel (2000a, 2000b).

FDA approval of adjuvant trastuzumab use was based on data obtained from four large adjuvant trials, which are reviewed in this article with a focus on patient suitability, treatment and monitoring plans, and symptom management.

Major Adjuvant Trastuzumab Trials

Design and Treatment Regimens

Four large phase III randomized trials were initiated in 2000 and 2001 to evaluate the efficacy and safety of adding trastuzumab to adjuvant chemotherapy for HER2-positive early breast cancer. Each trial included a chemotherapy only arm (control arm) and one or two trastuzumab-containing arms, in which trastuzumab was administered concurrently or following the chemotherapy portion of treatment. Standard chemotherapy regimens were used, which differed among the trials. Because of the cardiac safety issues associated with trastuzumab and anthracycline therapy, trastuzumab and doxorubicin were not administered concurrently in any of the trials, and one trial included a nonanthracycline-containing regimen. In addition, stringent cardiac monitoring plans were part of the trial design for at least three of the four trials. In all trials, patients received hormonal therapy or radiation therapy after chemotherapy, where indicated. The main endpoints of the four trials were to assess disease-free survival and cardiac safety. Overall survival was a secondary endpoint, and other efficacy and safety endpoints varied between trials.

Trial Descriptions

Patients in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial were randomized to receive four cycles of AC given every three weeks, followed by paclitaxel given weekly or every three weeks over 12 weeks, alone (arm 1, control) or with weekly trastuzumab for 52 weeks (arm 2). Time to distant recurrence was an additional secondary endpoint (Romond et al., 2005).
Patients in the North Central Cancer Treatment Group (NCCTG) N9831 Intergroup Trial were randomized to receive AC, as in NSABP B-31, followed by weekly paclitaxel in one of three subsequent arms: paclitaxel alone for 12 weeks (arm A, control), paclitaxel for 12 weeks followed by 52 weeks of weekly trastuzumab (arm B), or concurrent paclitaxel and trastuzumab for 12 weeks, followed by trastuzumab alone for an additional 40 weeks (arm C). The concurrent paclitaxel and trastuzumab regimen was very similar to NSABP B-31. The sequential paclitaxel and trastuzumab arm was designed to compare the efficacy and safety of this strategy with the concurrent paclitaxel and trastuzumab regimen. Time to distant recurrence also was a secondary endpoint of this trial (Romond et al., 2005).

The worldwide Breast Cancer International Research Group (BCIRG) 006 trial used docetaxel instead of paclitaxel; docetaxel was active and well tolerated when given in combination with trastuzumab for the treatment of metastatic breast cancer (Extra et al., 2004). Patients were randomized to one of three arms: AC (as in NSABP B-31 and NCCTG N9831) followed by docetaxel alone for 12 weeks (arm A, control); AC followed by docetaxel and trastuzumab for 12 weeks, followed by trastuzumab alone for 40 weeks (arm B); or concurrent docetaxel, carboplatin, and trastuzumab (TCH), followed by trastuzumab alone for 34 weeks (arm C) (Slamon et al., 2005). The latter regimen was included to test a nonanthracycline chemotherapy combination and was designed based on synergy between the three agents (Pegram et al., 2004a) and the efficacy observed with the regimen in the metastatic setting (Pegram et al., 2004b). Quality of life was an additional secondary endpoint (Slamon et al., 2001).

In the Breast International Group Herceptin Adjuvant (HERA) trial, predefined neoadjuvant or adjuvant chemotherapy given for a minimum of four cycles or four months, with or without radiation therapy as deemed appropriate by the oncologist, was allowed. Patients were randomized after chemotherapy to observation only (arm A, control) or every-three-week trastuzumab for one year (arm B) or two years (arm C). Additional secondary efficacy endpoints were time to distant recurrence and site of first recurrence (Piccart-Gebhart et al., 2005).

**Eligibility Criteria**

HER2 testing was performed on tumor tissue by using immunohistochemistry, a staining technique evaluating overexpression of the HER2 protein, or by fluorescence in situ hybridization, which measures the number of copies of the HER2 gene. Additional information regarding HER2 testing was reviewed by Chorn (2006). In NSABP B-31, NCCTG N9831, and HERA, tumors with an immunohistochemistry 3+ score (strong overexpression) or fluorescence in situ hybridization–positive (HER2 to chromosome enumeration probe 17 [CEP17] ratio 2 or higher) status were considered HER2 positive. In NSABP B-31 and NCCTG N9831, HER2 status was determined by central laboratory testing. Tumors with an immunohistochemistry 2+ score (moderate overexpression) had HER2-positive status confirmed by fluorescence in situ hybridization. In BCIRG 006, all cases had to be fluorescence in situ hybridization positive.

Breast tumors had to be axillary lymph node positive in NSABP B-31. Patients with node-positive or high-risk (according to tumor size and hormone receptor status) node-negative disease were eligible for NCCTG N9831, BCIRG 006, and HERA. No patients had evidence of metastases in any trials.

Adequate cardiac function, defined as normal left ventricular ejection fraction (LVEF), assessed by echocardiogram or multigated acquisition scan (multigated acquisition only in BCIRG 006), and no history of congestive heart failure or current cardiac disease requiring medication was necessary for enrollment in the adjuvant trials.

Other key eligibility criteria included being aged 18 years or older; adequate organ function; no prior biologic therapy, chemotherapy, or radiation therapy for breast cancer (except in HERA, and fewer than four weeks hormonal therapy in NCCTG N9831); no prior taxanes or anthracyclines (except in HERA), and no prior platinum agents (BCIRG 006 only) for any malignancy. Institutions participating in the trials obtained the approval of their human investigations committee or institutional review board and filed assurances with the Department of Health and Human Services. All patients provided signed, informed consent.

**Cardiac Safety and Monitoring**

LVEF evaluations by echocardiogram or multigated acquisition took place at registration and at 3, 6, 9, and 18 months in NSABP B-31 and NCCTG N9831; evaluations were performed at these time points and at 12, 24, 30, 36, and 60 months in HERA. The cardiac monitoring plan for BCIRG 006 is not available.

Cardiac events were defined as severe congestive heart failure or death from cardiac causes. Severe congestive heart failure was defined as National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 grade 3 or 4 left ventricular dysfunction or New York Heart Association (NYHA) class III or IV. Table 1 describes the NCI grading criteria. To view the NYHA functional classification for congestive heart failure, visit www.americanheart.org/presenter.jhtml?identifier=1712. Grade 3 or 4 arrhythmia and cardiac ischemia or myocardial infarction also were cardiac events in BCIRG 006. A difference higher than 4% in the

<table>
<thead>
<tr>
<th>GRADE</th>
<th>CRITERIA</th>
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<tbody>
<tr>
<td>1</td>
<td>Asymptomatic decline of resting ejection fraction of 10% or higher but lower than 20% of baseline value; shortening fraction from 24%–30%</td>
</tr>
<tr>
<td>2</td>
<td>Asymptomatic but resting ejection fraction below lower limit of normal for laboratory or decline of resting ejection fraction 20% or higher than baseline value; lower than 24% shortening fraction</td>
</tr>
<tr>
<td>3</td>
<td>Congestive heart failure responsive to treatment</td>
</tr>
<tr>
<td>4</td>
<td>Severe or refractory congestive heart failure or requiring intubation</td>
</tr>
</tbody>
</table>

**Note.** Based on information from National Cancer Institute Cancer Therapy Evaluation Program, 1999.
incidence of cardiac events between the trastuzumab-containing arms and control or observation arms in NSABP B-31, NCCTG N9831, or HERA would stimulate suspension of the respective trial. This cut-off point was chosen based on metastatic breast cancer trial experience of a reported difference of 4% or lower between trastuzumab-containing and nontrastuzumab-containing treatment arms. Details of protocol-defined differences in incidences of cardiac events that would lead to suspension of BCIRG 006 are unknown.

Independent cardiac review boards monitored and reviewed the cardiac safety results. Trastuzumab was discontinued if patients developed severe symptomatic congestive heart failure. If significant decreases in LVEF occurred (without symptoms of congestive heart failure), treatment was held and cardiac function was re-evaluated after three to four weeks in NSABP B-31, NCCTG N9831, and HERA; trastuzumab was discontinued in patients with persistent substantial decreases in LVEF. Table 2 details how trastuzumab treatment was managed in patients with asymptomatic LVEF declines in NSABP B-31 and NCCTG N9831.

### Efficacy and Safety Results

Data are available for all four trials. Because of the similarities between arms 1 and A (control arms) and arms 2 and C in NSABP B-31 and NCCTG N9831, the efficacy results of the two trials were combined (joint efficacy analysis) (Romond et al., 2005). Definitions of cardiac events differed slightly between the trials; therefore, the cardiac safety results were reported separately (Perez et al., 2008; Tan-Chiu et al., 2005). The efficacy results of the AC followed by sequential paclitaxel and trastuzumab arm of NCCTG N9831 currently are under analysis and are not discussed in this article. Data are not yet available for the two-year trastuzumab arm in HERA; therefore, only the one-year trastuzumab results (versus observation) are discussed in this article.

#### Disease-Free Survival

In all trials, disease-free survival was significantly higher in the trastuzumab-containing arms than in the control or observation arms (see Table 3). In the joint analysis of NSABP B-31 and NCCTG N9831, the risk of disease progression was reduced by 52% in the trastuzumab arm compared with the control arm (hazard ratio [HR], 0.48; p < 0.00001) in the second interim analysis (Perez et al., 2007). The 52% improvement also was observed in the first interim analysis, indicating consistent significant benefit (Romond et al., 2005). Both trastuzumab-containing arms in BCIRG 006 showed improved disease-free survival relative to the control arms, with 39% and 35% reductions in risk of disease progression in the AC followed by docetaxel plus trastuzumab and TCH arms, respectively. No significant difference in disease-free survival was found between the AC followed by docetaxel plus trastuzumab and TCH arms in BCIRG 006 (three-year disease-free survival rates were 87% and 86%, respectively) (Slamon et al., 2006). A 36% reduction in the risk of disease progression was observed in the one-year trastuzumab group compared with the observation group in HERA (disease-free survival rates at three years were 80.6% and 74.3%, respectively) (Smith et al., 2007). The significant improvement in disease-free survival conferred by the addition of trastuzumab in HERA was confirmed when results from an updated analysis were published (median follow-up: 48.4 months; disease-free survival rate with trastuzumab 79% versus 73% in the observation arm, p < 0.0001) (Gianni et al., 2009). In subset analyses, improvements in disease-free survival were observed across trials in all groups assessed. Disease-free survival was similar for patients with hormone receptor-positive or -negative tumors in all patient age groups, ranging from younger than 40 years to older than 60 years of age, regardless of tumor size (Perez et al., 2007; Slamon et al., 2006; Smith et al., 2007).

#### Overall Survival

In the joint analysis of NSABP B-31 and NCCTG N9831, the addition of trastuzumab to adjuvant chemotherapy significantly reduced the risk of death by 35% (92.6% versus 89.4%; HR, 0.65; p = 0.0007) in the second interim analysis (Perez et al., 2007). Improvement in overall survival was not significant in the first interim analysis (Romond et al., 2005). Improved overall survival also was observed in both trastuzumab-containing arms compared with chemotherapy only in the BCIRG 006 trial (p values were 0.004 and 0.017 for AC to docetaxel plus trastuzumab and TCH arms, respectively) (Slamon et al., 2006). In HERA, three-year overall survival (after two years follow-up) was significantly higher in the one-year trastuzumab arm than in the observation arm (92.4% versus 89.7%; HR, 0.66; p = 0.012) (Smith et al., 2007).

#### Other Efficacy Endpoints

The combined analysis of NSABP B-31 and NCCTG N9831 had fewer recurrences in the trastuzumab-treated group (arm 2 and C) than the control group (arm 1 and A): 89.7% versus 73.7% of patients were free of distant recurrence at four years (HR, 0.47; p < 0.0001) (Romond et al., 2005). First recurrences were more frequent at distant sites than at local or regional sites in both control and trastuzumab-treated groups in both trials. In HERA, a 51% reduction was observed in the risk of distant recurrence in the one-year trastuzumab arm (arm B) (HR, 0.49; p < 0.0001), and about 70% of first recurrences in both arms were to distant sites (Piccart-Gebhart et al., 2005).

#### Cardiac Safety

All four trials had a higher incidence of protocol-defined cardiac events in the trastuzumab-containing arms than in the control or observation arms. The difference, however, was

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**Table 2. Trastuzumab Treatment Management in Patients With Asymptomatic Decreases in Left Ventricular Ejection Fraction**

<table>
<thead>
<tr>
<th>RELATIONSHIP OF LVEF TO LLN</th>
<th>ABSOLUTE LVEF DECREASE FROM BASELINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In normal limits</td>
<td>Continue</td>
</tr>
<tr>
<td>Below LLN</td>
<td>Continue Hold for 4 weeks</td>
</tr>
</tbody>
</table>

LLN—lower limit of normal; LVEF—left ventricular ejection fraction

**Note.** Based on information from Romond et al., 2005
Table 3. Primary Efficacy and Cardiac Safety Endpoints of Large Clinical Trials

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>NSABP B-31</th>
<th>NCCTG N9831</th>
<th>BCIRG 006</th>
<th>HERA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up (years)</td>
<td>2.9</td>
<td>2.9</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>PRIMARY EFFICACY ENDPOINT: DISEASE-FREE SURVIVAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time point for evaluation (years)</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Disease free in control or observation arm (%)</td>
<td>73.1</td>
<td>73.1</td>
<td>81</td>
<td>74.3</td>
</tr>
<tr>
<td>Disease free by treatment arms (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Doxorubicin plus cyclophosphamide to taxane or trastuzumab</td>
<td>85.9</td>
<td>85.9</td>
<td>87</td>
<td>N/A</td>
</tr>
<tr>
<td>• Docetaxel, carboplatin, and trastuzumab</td>
<td>N/A</td>
<td>N/A</td>
<td>86</td>
<td>N/A</td>
</tr>
<tr>
<td>• One-year trastuzumab</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>80.6</td>
</tr>
<tr>
<td>Hazard ratio versus control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Doxorubicin plus cyclophosphamide to taxane or trastuzumab</td>
<td>0.48***</td>
<td>0.48***</td>
<td>0.61**</td>
<td>N/A</td>
</tr>
<tr>
<td>• Docetaxel, carboplatin, and trastuzumab</td>
<td>N/A</td>
<td>N/A</td>
<td>0.67*</td>
<td>N/A</td>
</tr>
<tr>
<td>• One-year trastuzumab</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0.64*</td>
</tr>
<tr>
<td>PRIMARY SAFETY ENDPOINT: PROTOCOL-DEFINED CARDIAC EVENTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence in control or observation arm (%)</td>
<td>0.9</td>
<td>0.3</td>
<td>0.38b</td>
<td>0.06</td>
</tr>
<tr>
<td>Incidence by treatment arms (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Doxorubicin plus cyclophosphamide to taxane or trastuzumab</td>
<td>3.8</td>
<td>3.3</td>
<td>1.87b</td>
<td>N/A</td>
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<tr>
<td>• Doxorubicin plus cyclophosphamide to taxane to trastuzumab</td>
<td>N/A</td>
<td>2.8</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>• Docetaxel, carboplatin, and trastuzumab</td>
<td>N/A</td>
<td>N/A</td>
<td>0.38b</td>
<td>N/A</td>
</tr>
<tr>
<td>• One-year trastuzumab</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0.62</td>
</tr>
</tbody>
</table>

* p = 0.0003; ** p < 0.0001; *** p < 0.00001

a Efficacy and safety data are shown for observation and one-year trastuzumab arms only.
b Congestive heart failure or death only

BCIRG—Breast Cancer International Research Group; HERA—Breast International Group Herceptin Adjuvant trial; NCCTG—North Central Cancer Treatment Group; N/A—not applicable; NSABP—National Surgical Adjuvant Breast and Bowel Project

Note. Based on information from Ewer et al., 2007; Rastogi et al., 2007; Romond et al., 2005; Slamon et al., 2006; Smith et al., 2007; Tan-Chiu et al., 2005.

lower than 4% in each trial, which was within the limits specified in NSABP B-31, NCCTG N9831, and HERA.

Results from NSABP B-31 and NCCTG N9831 demonstrated that congestive heart failure associated with trastuzumab generally was reversible and manageable with standard medical treatment, and cardiac function improved in most patients who experienced congestive heart failure (Rastogi, 2007; Perez et al., 2008). Investigators in both trials found that cardiac events appeared to be more frequent among older patients (older than 50 years), but no correlation was found between radiation therapy and risk of cardiac dysfunction (Halyard et al., 2006; Perez et al., 2008; Tan-Chiu et al., 2005). An association between the pretreatment LVEF level and LVEF level immediately following AC therapy and risk of cardiac dysfunction was observed in NSABP B-31 (Tan-Chiu et al., 2005).

The BCIRG 006 trial had a higher incidence of congestive heart failure in the AC followed by docetaxel plus trastuzumab arm compared with the AC followed by docetaxel (control) arm (1.9% versus 0.4%) (Slamon et al., 2006). In the TCH arm, however, the incidence of congestive heart failure was the same as that in the control arm (0.4%). The finding is significant because patients with HER2-positive early breast cancer who are at a high initial risk for cardiac dysfunction are now able to benefit from treatment with a nonanthracycline-containing, trastuzumab-based adjuvant regimen. Other patients who may benefit from treatment with the TCH regimen include those who experience a decrease in LVEF after treatment with AC or those with an LVEF that is close to or at the lower limit of normal.

Hematologic and Nonhematologic Safety

In NSABP B-31 and NCCTG N9831, the incidences of NCI-CTC noncardiac adverse events were similar between treatment groups, apart from rare cases (approximate incidence of 0.5%) of interstitial pneumonitis that appeared to be related to trastuzumab therapy (Romond et al., 2005). HERA had a significantly higher incidence of grade 3 or 4 adverse events in the one-year trastuzumab group than in the observation group (79% versus 4.4%, respectively; p < 0.001). Infection (1.3% versus 0.4%) and vascular disorder (1.2% versus 0.5%) were the only grade 3 or 4 events with an incidence higher than 1% in either group in HERA (Piccart-Gebhart et al., 2005).

Impact on Clinical Practice

Because of the significant impact that trastuzumab has on clinical outcomes, all patients who are likely to benefit must be identified. The American Society of Clinical Oncology (ASCO), College of American Pathologists (CAP), and NCCN recommend tumor
HER2 testing at the time of breast cancer diagnosis (NCCN, 2010a; Wolff et al., 2007). ASCO and CAP recently published new HER2 testing guidelines to address issues regarding HER2-testing accuracy and provided recommendations for the standardization of testing procedures (Wolff et al., 2007). Guidance regarding tissue collection, fixation, and storage are detailed, and new criteria for HER2-positive status have been established. Immunohistochemistry 3+ is now defined as uniform staining in more than 30% (previously 10%) of invasive cancer cells. Immunohistochemistry 2+ is considered an equivocal result and should be confirmed by fluorescence in situ hybridization. For entry into the adjuvant trials, a fluorescence in situ hybridization—positive result was a ratio of HER2 gene copies to CEP17 of 2 or higher. The new guidelines require a HER2 to CEP17 ratio of 2.2 or higher. A ratio of 1.8–2.2 is considered equivocal and should be confirmed by assessing more cells by fluorescence in situ hybridization, repeating the fluorescence in situ hybridization assay, or using immunohistochemistry. The guidelines state that both tests are equally appropriate for determining HER2 status if performed properly. In addition, the FDA has recently approved a chromogenic in situ hybridization testing kit for the determination of HER2 status in breast tumor samples. Maintaining high standards of HER2 testing is paramount, and quality assurance via a standardized testing process to both accurate and reproducible results is desirable.

Patients eligible for trastuzumab therapy also need to have adequate baseline cardiac function before starting treatment. Adequate function includes no history of congestive heart failure, no current cardiac disease requiring medication, and an LVEF measurement in the normal range for the treating institution (institutional ranges = 45%–55%). Patient age should also be considered, as one study found that patients aged 50 years or older with low baseline LVEF were more likely to develop cardiac dysfunction; however, another large adjuvant study found no increase in cardiac dysfunction in that age group and virtually no increased incidence in patients aged 60 years or older (3.75% versus 3.61%, respectively) (Perez, 2008). Patients should undergo cardiac monitoring (LVEF measurements) before, during, and after treatment. NCCN (2010a) guidelines recommend monitoring before and during adjuvant trastuzumab therapy; in the case of the regimen of four cycles of AC followed by paclitaxel plus trastuzumab, NCCN (2010a) recommends LVEF evaluation at baseline and at three, six, and nine months after treatment initiation. A cardiac guidelines consensus committee composed of renowned cardiologists from the United States, Spain, Australia, Belgium, France, Poland, and Switzerland has provided guidance for managing cardiac events in patients treated with adjuvant trastuzumab (Ewer, Perez, & Baselga, 2007). Similar to the trial protocols of the four large adjuvant trials, the consensus committee recommends that trastuzumab should be discontinued in patients who develop NYHA class III or IV congestive heart failure (Ewer et al., 2007). Consensus committee guidelines regarding management of asymptomatic declines in LVEF are summarized in Table 4.

Noninvasive approaches to measuring LVEF have demonstrated accuracy and reproducibility. Table 5 compares features of multitigated acquisition and echocardiogram, noninvasive methods used in the adjuvant trials. Importantly, a single and consistent measurement method used throughout the treatment period allows for correct comparative serial measurements of LVEF.

BCIRG 006 investigated the use of two trastuzumab-containing treatment regimens: AC followed by docetaxel and trastuzumab, and TCH. Compared with the control arm, the regimens significantly improved both disease-free and overall survival at the three-year follow up (Slamon et al., 2006), and as a result, they are both recommended by NCCN (2010a) for the adjuvant treatment of HER2-positive breast cancer. Importantly, the TCH regimen was not associated with an increase in congestive heart failure compared with the control arm. The regimen could, therefore, be used to avoid potential cardiac complications in patients who would otherwise not be eligible to receive trastuzumab as part of an anthracycline-based regimen. TCH also may be the regimen of choice for particular patient groups, such as younger patients who may be at risk for developing anthracycline-related cardiac dysfunction in the long term. Other patients who may benefit from TCH include older adults, who are likely to have comorbidities, and those who would be suited to receiving a shorter, 12-month treatment regimen rather than a 15-month regimen (with AC followed by docetaxel and trastuzumab).

The optimal duration of trastuzumab treatment has yet to be elucidated. Each of the large trials incorporated a one-year period of trastuzumab treatment, as patients are at highest risk of relapse in the first year after surgery. Regulatory approval was granted for one year of adjuvant trastuzumab therapy as a result. Findings from the two-year trastuzumab arm in HERA are not yet available. A shorter duration of adjuvant trastuzumab

<table>
<thead>
<tr>
<th>CHANGE IN LVEF</th>
<th>STEP 1</th>
<th>STEP 2</th>
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<tbody>
<tr>
<td>40%–50%</td>
<td>Continue trastuzumab and monitor LVEF every month.</td>
<td>If LVEF remains higher than 40%, continue trastuzumab, monitor LVEF every three months, and administer cardiac medication at discretion of cardiologist. If LVEF decreases to lower than 40%, hold trastuzumab, consult cardiologist, and monitor LVEF every month.</td>
</tr>
<tr>
<td>Lower than 40%</td>
<td>Hold trastuzumab, consult cardiologist, and monitor LVEF every month.</td>
<td>If LVEF returns to higher than 40%, restart trastuzumab, monitor LVEF every three months, and administer cardiac medication at discretion of cardiologist. If LVEF remains below 40%, consider restarting trastuzumab only if or when appropriate, and administer cardiac medication at discretion of cardiologist.</td>
</tr>
</tbody>
</table>

*Decline of 15% or higher or a decline of 10% or higher and below the lower limit of normal of 50%*  
*Note. Based on information from Ewer et al., 2007.*
Fatigue associated with breast cancer treatment adds to the severity of other symptoms of chemotherapy, diminishing quality of life and adversely affecting the patient’s ability to manage self-care (NCCN, 2010b; Williams & Schreier, 2004).

Compounding the distress and severity of fatigue symptoms, patients with breast cancer are more likely to suffer from sleep and depressive symptoms compared with healthy people (Payne, Piper, Rabinowitz, & Zimmerman, 2006). Systemic chemotherapy and hormonal therapy in early breast cancer therapy is known to contribute to weight gain, menopausal-like symptoms, and issues with bone health. Gentle exercise, such as walking, is an effective intervention for such symptoms (Stricker, Drake, Hoyer, & Mock, 2004; Wilmoth, Coleman, Smith, & Davis, 2004). Psychosocial distress can be experienced at numerous times through the disease continuum, associated with changes in disease or treatment status (NCCN, 2010c). Distress can influence treatment outcomes and survival rates (Madden, 2006). Healthcare professionals may fail to assess for and effectively treat distress by focusing on the physical aspects of patients’ disease.

Nurses can be instrumental in educating patients in symptom self-management strategies (Williams & Schreier, 2004) and identification and treatment of distress, leading to improved quality of life (Boyle, 2006), particularly within the first six months after breast cancer diagnosis (Ritz et al., 2000). Following completion of therapy, patients require regular surveillance to assess breast and overall health, including physical examinations, breast awareness examinations, mammograms, cardiac and bone evaluations, and coordination of survivorship care as appropriate (ASCO, 2006). The longer treatment duration associated with trastuzumab compared with chemotherapy alone may mean that patients develop a stable support system over a prolonged period. Long after completion of therapy, patients may require additional support to promote optimal quality of life. Survivor education includes addressing common potential psychosocial challenges (e.g., long-term treatment effects, sexual dysfunction, fear of cancer recurrence), and oncology nurses are a critical influence on patients’ ability to transition through the cancer continuum (Boyle, 2006).

### Table 5. Comparison of Noninvasive Methods to Evaluate Left Ventricular Ejection Fraction

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>MULTIGATED ACQUISITION SCAN*</th>
<th>ECHOCARDIOGRAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of technique</td>
<td>The scan measures a patient’s red blood pool. A radioactive tracer is injected via IV, and radioactivity is measured with a gamma camera located over the anterior chest. The scan produces images and measurements throughout the cardiac cycle.</td>
<td>Ultrasound technique; two- or three-dimensional real-time imaging of the heart and its various structures; uses a transducer to detect ultrasonic waves</td>
</tr>
<tr>
<td>Nursing considerations</td>
<td>–</td>
<td>Inform the patient that the test lasts 15–30 minutes and does not cause pain or pose risks. Two recordings will be made (one while patient is on her back and one while on her left side). The patient must remain still during recording to avoid distorting the results. Other tests may be necessary (e.g., electrocardiogram) (Springhouse Corp., 2002).</td>
</tr>
<tr>
<td>Technical considerations</td>
<td>May be more suitable than echocardiogram for patients with poor acoustic windows (e.g., obese patients, patients with lung disease, or those who cannot be properly positioned for a thorough study during echocardiogram) (Daniel et al., 2001).</td>
<td>Requires an experienced sonographer and echocardiographer to accurately evaluate regional wall motion and various indices of diastolic left ventricular function and all cardiac structures (Thomson et al., 2001).</td>
</tr>
</tbody>
</table>

* Also known as radionuclide ventriculography

was investigated in the pilot Finnish FinHer trial (Joensuu et al., 2009). At five year follow-up, no statistically significant differences were found in distant disease-free survival (HR, 0.65; p = 0.12) or overall survival (HR, 0.55; p = 0.094) in HER2-positive patients who had received trastuzumab plus chemotherapy compared with chemotherapy alone; however, only a small number of patients (n = 115) received the shortened duration of trastuzumab therapy in the trial, so no clear conclusions can be made. Additional evaluation of this shorter trastuzumab duration will be made in the ongoing SOLD (Synergism or Long Duration) trial (NCT00593697).

### Patient Education and Support

Growing evidence indicates that patients with cancer require more information about their disease and its consequences. Nurses must understand the various education and support needs of patients with early breast cancer, as interventions can have a positive effect on numerous patient outcomes. Providing patients with information before they begin treatment may give them realistic expectations about how treatment may affect them physically and mentally (Osoba, Slamon, Burchmore, & Murphy, 2002). Useful information could include differences between trastuzumab and chemotherapy, with discussion of mode of action (targeted versus nontargeted), toxicities or adverse events (reversible versus nonreversible cardiotoxicity, infusion reactions, alopecia, and neutropenia), and duration of treatment (one year versus three months).

Assessment of quality of life in the adjuvant setting is ongoing; however, overall quality of life in metastatic breast cancer is significantly improved for patients who receive trastuzumab plus chemotherapy compared with those who receive chemotherapy alone (Osoba et al., 2002). Among factors affecting quality of life are those related to disease burden, treatment, and long-term follow-up or surveillance. The most common (and often distressing) side effect of cancer and cancer treatment in both early and metastatic breast cancer is fatigue (Keller, 2006), which has a major impact on a patient’s ability to perform normal daily tasks.
Nurses who are aware of trastuzumab’s cardiac safety profile will be better able to educate patients about the importance of frequent cardiac monitoring and identifying and reporting signs and symptoms of cardiac dysfunction. Cardiac dysfunction with trastuzumab often is asymptomatic and has to be identified with multigated acquisition or echocardiogram. Cases of symptomatic cardiac dysfunction can be identified and monitored with the NYHA functional classification system. The system is divided into four classes of severity, in which class I is the most mild and class IV the most severe. Patients with class I heart failure would be able to perform everyday activities without exhibiting symptoms of cardiac dysfunction, whereas patients with class IV heart failure would be severely limited and would exhibit symptoms even while resting (Heart Failure Society of America, 2006). Clinical symptoms of heart failure may include some or all of the following: dyspnea, fatigue, palpitations, peripheral edema, unexplained or sudden weight gain, insomnia, and loss of appetite. In addition to monitoring patients for the presence or changes in severity of the symptoms, nurses also can explain treatment processes and options for cardiac dysfunction (e.g., suspending or holding trastuzumab treatment, cardiac re-evaluation, trastuzumab re-initiation or discontinuation).

Nurses also can remind patients of lifestyle interventions that can decrease the risk for cardiovascular disease. According to patients’ abilities, they can be counseled on the American Heart Association’s diet and lifestyle recommendations to reduce the risk for cardiovascular disease, such as consuming an overall healthy diet; maintaining a healthy body weight; achieving recommended levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides; striving to achieve healthy blood pressure; aiming for a healthy blood glucose level; being physically active; and avoiding the use of and exposure to tobacco products (Lichtenstein et al., 2006).

Clinical trial data have shown the benefit of giving a full year of trastuzumab therapy in combination with chemotherapy. Based on clinical experience in NCCTG N9831, early patient-related discontinuation of trastuzumab treatment occurred frequently (unpublished observation). Patients’ reasons for discontinuation included quality of life issues related to dosing convenience and fears regarding cardiac safety. Therefore, support is necessary throughout treatment to encourage patient adherence to therapy so that maximum benefit from treatment is achieved. Nurses can discuss more convenient trastuzumab dosing schedules (e.g., every three weeks instead of weekly) with the physician if compliance could be improved with a different dosing schedule, which was successful in the NCCTG N9831 trial (unpublished observation). Every-three-week dosing of trastuzumab also was applied in the HERA and BCIHG 006 trials. In addition, nurses can assure concerned patients of the low incidence of cardiac dysfunction (4% or less) seen in clinical trials and reassure patients that frequent cardiac monitoring should identify changes in heart function; decreased cardiac function generally is manageable and reversible with appropriate medical treatment and often does not warrant trastuzumab discontinuation. A clinical trial telephone hotline, set up and monitored by the first author, was a successful nursing intervention used to educate and support patients regarding cardiac safety in the NCCTG N9831 trial. Patients who enrolled or wished to enroll in the trial were notified about the hotline. About 550 calls were received, with most related to cardiac safety concerns (unpublished observation). The intervention provided education above and beyond usual care and may be reproduced in clinical practice.

Future Directions

Key nursing-focused questions still to be addressed include quality of life associated with adjuvant trastuzumab therapy, treatment adherence, and adverse event and symptom management by nurses, patients, and caregivers. The benefits or effectiveness of education provided by nurses could be explored in relation to improvements in quality of life, successful management of cardiac dysfunction, and potential reduction in cost of care.

Additional follow-up of patients enrolled in the four large trials will provide long-term outcomes data. Ongoing research will investigate various combinations, including trastuzumab with other targeted and nontargeted therapies and trastuzumab-based regimens with a better cardiac safety profile, such as regimens that do not include anthracyclines. The BCIRG 006, NSABP B-31, and NCCTG N9831 investigators are assessing factors for predicting response to therapy (such as topoisomerase II-α and c-Myc) or cardiac dysfunction (such as troponins). Future research will aim to identify additional predictive and prognostic biomarkers.

Conclusions

Clinical outcomes are improved significantly with the addition of trastuzumab to standard adjuvant chemotherapy in HER2-positive breast cancer, and the benefits are believed to outweigh the risk for cardiac dysfunction. HER2-positive disease is aggressive, and patients with this type of breast cancer have a worse prognosis than do those with HER2-normal disease. Use of trastuzumab has shifted the paradigm to yield a better prognosis in HER2-positive early breast cancer; therefore, identifying all patients who could benefit from trastuzumab therapy is important. Nurses play a pivotal role in patient education and support. Knowledge of trastuzumab therapy in the adjuvant setting enables them to guide patients throughout their treatment and provide ongoing survivorship support.

The authors take full responsibility for the content of the article but thank Natalie Barker, BS, formerly of Gardiner-Caldwell London, supported by Genentech, Inc., for medical writing support. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers or editorial staff.

The authors gratefully acknowledge the editorial support provided by Deborah G. Feigel, PA-C, of the Multidisciplinary Breast Clinic at Mayo Clinic.

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