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Managing the Early and Locally Advanced Breast Cancer Patient at High Risk for Recurrence: Recent Advances and Nursing Implications

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Abstract

OBJECTIVES—To identify breast cancer patients at high risk for recurrence.

To describe current evidence for clinical management of early and locally advanced breast cancer and integrate this knowledge into nursing practice.

DATA SOURCES—Articles, abstracts, and practice guidelines.

CONCLUSION—Recent clinical trials have integrated the biology of breast cancer into individualized systemic therapy. Risk-adjusted treatment is driven by the addition of taxane therapy to systemic therapy, aromatase inhibitors and perhaps most markedly, trastuzumab into adjuvant therapy strategies.

IMPLICATIONS FOR NURSING PRACTICE—The decision to initiate systemic adjuvant therapy requires knowledge of risk of relapse, integration of evidence from clinical trials, and facilitation of patient decision making.

Breast cancer is the most frequently diagnosed form of cancer among women in the United States (U.S.), with more than one million women diagnosed each year. It is expected that 41,000 deaths will occur among women in the U.S. in 2006 and more than 200,000 will die on a yearly basis worldwide¹. Ten percent of newly diagnosed patients have locally advanced or metastatic disease. Additionally up to 75% of patients diagnosed with early breast cancer eventually relapse and develop metastatic disease². The likelihood of survival is increased with early diagnosis, made possible by the optimization of screening and diagnostic tools and the identification of better local and systemic treatments³. The focus of this review is to highlight new data from adjuvant clinical studies in the early breast cancer setting, including subtypes based on biological classifications, and the nursing implications associated with them.

Current Treatment of Early Breast Cancer Patients

Surgical Intervention

Appropriate local therapy remains the basis of treatment for patients with early stage breast cancer. Adjuvant systemic chemotherapy with or without hormonal therapy and anti-HER2 therapy, based on the biological characteristics of the tumor, is the current standard of treatment for patients who have undergone surgery and are deemed to be at high risk for breast cancer

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recurrence. High risk is defined as a risk of recurrence of greater than 10% at 5 years, and is associated with node-positive breast cancer as well node-negative disease that includes invasive tumors measuring greater than 1cm.⁴ Neoadjuvant systemic therapy is indicated for tumors that are greater than 5 cm, sometimes called locally advanced, or to decrease tumor size to diminish the extent of surgery itself. This may allow for lumpectomy or other breast conserving surgery instead of mastectomy.

Systemic therapy

Systemic adjuvant therapy is typically administered following surgery, as it reduces the risk of disease recurrence and metastasis and increases survival. One of the key reports of the benefit of adjuvant combination chemotherapy was from the Early Breast cancer Trialists' Collaborative Group (EBCTCG), meeting at five year intervals to perform meta-analysis on all mature randomized clinical trials focusing on women with early-stage breast cancer.⁵ Trials must have a minimum of five years' follow-up to be included in the analysis, and to date greater than 15 years of follow-up have been reviewed.⁶ Prior to the 1990's, the cytotoxic chemotherapy regimen of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) was the standard adjuvant therapy. Anthracyclines, doxorubicin or epirubicin, combined with cyclophosphamide and/or 5-fluorouracil (AC, FAC, CEF, FEC) showed improvements in clinical outcome compared with CMF, and became a standard of care. The benefits of adjuvant anthracyclines have persisted for 15 years, with a 26% reduction in breast cancer death. Optimal duration of adjuvant chemotherapy is 3–6 months.⁶ The addition of paclitaxel to standard doxorubicin and cyclophosphamide (AC) in the CALGB C9344 trial supported by the North American Breast Intergroup, provided further improvements in disease-free survival (DFS) of 70 % and overall survival (OS) of 80% at five years compared to 65% and 77% respectively for doxorubicin and cyclophosphamide alone, with modest differences in the rate of toxic effects. More recent progress in chemotherapy has included the use of another taxane, docetaxel, in combination with AC therapy (TAC) that allowed for increased efficacy versus FAC.⁸ Dose-dense therapy regimens (C9741) that built on previous studies of chemotherapy sequencing and schedules, demonstrated that combined AC followed by paclitaxel chemotherapy administered every two weeks instead of every three weeks provided increased efficacy.⁹ Subset analysis of these data demonstrate that the DFS benefit of this so-called dose dense approach (every two week chemotherapy with growth factor support) appears to benefit only patients with estrogen receptor negative breast cancer. The 5 year DFS for patients with ER-positive disease was the same whether the chemotherapy was given every two or every three weeks. One of the most recent reported adjuvant trials is the Eastern Cooperative Oncology Group (ECOG) E1199 trial, supported by the North American Breast Intergroup, in which patients with stage II breast cancer received six months of adjuvant chemotherapy: AC followed by a taxane.¹⁰ The taxane was either paclitaxel every three weeks or weekly, or docetaxel every three weeks or weekly. The trial demonstrated similar DFS for either taxane, but with a trend for improved outcome for those patients with ER negative disease treated with the weekly paclitaxel. The docetaxel regimens were associated with increased toxicity, but in terms of efficacy, any of these treatments could be considered appropriate. Further studies of chemotherapy schedules are ongoing.

The relative value of hormonal and chemotherapy approaches in early breast cancer is a matter of great importance, and current data indicate that chemotherapy appears to work better (at least in the short term) in patients whose tumors are ER-negative compared to those that are ER-positive.¹¹ Moreover, the debate of whether to use only hormonal instead of combination chemotherapy is a strategy for patients with low risk of recurrence, not the high-risk population reviewed herein. In the setting of node-positive breast cancer, there is excellent evidence of

improved patient outcome using combined chemotherapy-hormones vs. hormone therapy alone.¹²

Risk Assessment in Early Breast Cancer: Definition of High Risk and Individualization in Treatment

Earlier research into tumor biology provided insight into predictive and prognostic factors that has enabled treatment to be tailored, or individualized, based on the tumor profile. Prognostic factors such as tumor size, nodal status, and tumor grade can indicate the natural history of the disease, and predictive factors permit the selection of patients most likely to benefit from a therapy. We have used hormone receptors for therapeutic decisions for many years and this standard has been recently validated by the National Institutes of Health (NIH) Consensus Conference and National Comprehensive Cancer Network (NCCN) Guidelines.^{13, 14}

Adjuvant Therapy Based on Hormonal Status

Concurrent with the development of optimum chemotherapy regimes, a large group of randomized controlled adjuvant trials allowed for significant advances in understanding endocrine responsiveness. A meta-analysis of these trials led to an estimation of both relative and absolute average treatment benefits associated with the adjuvant use of tamoxifen, ovarian ablation and chemotherapy.^{6, 15, 16} Reduction in the relative risk for recurrence and death is greater than 50% when using these therapies in sequence or in combination, with long-term benefits extending for 15 years.⁶ Breast tumors are considered hormone-sensitive if they express estrogen receptors (ER) and/or progesterone receptors (PgR). ER modulators such as tamoxifen¹⁵ and more recently, aromatase inhibitors such as anastrozole¹⁷, letrozole¹⁸, and exemestane¹⁹ have provided substantial clinical benefit for patients with hormone receptor-positive disease in the adjuvant setting. One of the most important recent findings include the incorporation of gene profiling such as the Oncotype-DX^{TM} and Mammaprint® in defining prognosis and prediction of the group of patients most likely to benefit from hormone therapy or chemotherapy plus hormones in the setting of ER-positive disease.²⁰ The Mammaprint® technology includes a 70 gene profile assayed in fresh tumor specimens. The Oncotype-DX^{TM} is a 21 gene profile (16 genes and 5 reference genes) performed in paraffin embedded tissues, that has demonstrated that tamoxifen benefits patients with ER-positive disease and low reference scores (based on the aggregate expression of those 15 genes). On the other hand, patients with ER-positive disease but high recurrence scores do not appreciably benefit from tamoxifen, but will primarily benefit from chemotherapy. Major trials are being launched in Europe (MINDACT) and the United States (TAILORx) to further understand the potential role of these gene profiles in the clinic.

New Findings Related to the Biology of Breast Cancer

Although the definition of breast risk recurrence has traditionally been made based on the tumor size, node involvement, tumor grade and hormonal status, new gene profiling technology promises to modify this strategy. New subtypes of breast cancer include luminal A & B, basal and HER2 positive.^{20, 21} Although more studies are needed, luminal A & B tumors appear to be ER-positive, with luminal A having a better prognosis than luminal B. The basal subtype has sometimes been called “triple negative,” as these tumors have negative expression for ER, PR and HER2. Although these patients appear to have worse prognosis after standard adjuvant chemotherapy, they are still managed with these standard agents (such as alkylating agents, anthracyclines and taxanes). However, new strategies are being evaluated in the metastatic setting, including platinum and anti-EGFR agents, as these tumors appear to have increased endothelial growth factor receptor (EGFR) gene expression. It is estimated that 15%–20% of all breast cancers are “triple negative,” thus it will be important to complete these studies to

determine whether we will have novel adjuvant recommendations for study in the next few years.

Adjuvant Therapy Based on HER2 Status

More recently, other predictive and prognostic factors have been investigated. HER2 is gene amplified or overexpressed in approximately 25% of all breast cancers,²² and HER2-positivity is associated with a poor prognosis, more aggressive clinical behavior^{23, 24} and an increased sensitivity to anthracyclines.^{25, 26, 27} The anti-HER2 monoclonal antibody trastuzumab specifically targets the HER2 protein, and has exhibited cytostatic, cytotoxic, and anti-angiogenic modes of action.^{28, 29, 30} Trastuzumab was shown to be effective as a single agent.^{31, 32} In 1998, the Food and Drug Administration (FDA) approved trastuzumab for first-line therapy in combination with paclitaxel or as second- or third-line monotherapy for HER2-positive metastatic breast cancer (MBC). The addition of trastuzumab to standard chemotherapy (AC or paclitaxel) for HER2-positive MBC showed that trastuzumab significantly improves clinical outcomes in this patient population compared with chemotherapy alone in a pivotal trial.³³

The American Society of Clinical Oncology (ASCO) and the NCCN advise that tumor HER2 testing be performed at the time of breast cancer diagnosis to identify all patients eligible for trastuzumab therapy.^{14, 34} Because trastuzumab is a targeted agent, the antibody does not produce many of the adverse effects commonly associated with cytotoxic chemotherapy, such as alopecia, significant myelosuppression, nausea or vomiting. Mild infusion-related fever and chills are the most frequently observed adverse events.^{31, 32} Cardiotoxicity, in the form of left ventricular dysfunction and infrequently, congestive heart failure (CHF), is also associated with trastuzumab, particularly when it is administered concurrently with anthracyclines.^{33, 35}

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. The current adjuvant trial data are reviewed with a focus on patient suitability, treatment and monitoring plans, and symptom management.

The Large Adjuvant Trastuzumab Trials: Trial Design and Treatment Regimens

Four large phase III randomized trials, two U.S.-based studies; NCCTG N9831 and NSABP31 (which formed the joint analysis);³⁶ and two international studies; HERA³⁷ and the BCIRG 006,³⁸ were planned and initiated in 2000 and 2001 to evaluate the efficacy and safety of adding trastuzumab to adjuvant chemotherapy for early breast cancer (Table 1). Each trial included a chemotherapy-only arm, followed by either one or two trastuzumab-containing arms, in which trastuzumab was administered either concurrently with or following the chemotherapy portion of treatment. Trastuzumab and doxorubicin were not administered concurrently in any of the trials due to cardiac safety issues, and the BCIRG trial included a non-anthracycline-containing regimen (docetaxel, trastuzumab and carboplatin). In addition, stringent cardiac monitoring plans were part the trial design. In all of the trials, patients received hormonal therapy and/or radiation therapy after chemotherapy, where indicated. The main objectives (primary endpoints) of the four trials were to assess DFS and cardiac safety. OS was a secondary endpoint, and other efficacy and safety objectives varied between trials.

North Central Cancer Treatment Group (NCCTG) N9831 Intergroup Trial

Patients were randomized to receive AC, followed by weekly paclitaxel in one of three subsequent arms; paclitaxel alone for 12 weeks, paclitaxel for 12 weeks followed by 52 weeks of weekly trastuzumab, or concurrent paclitaxel and trastuzumab for 12 weeks, followed by

trastuzumab alone for an additional 40 weeks. The sequential paclitaxel and trastuzumab arm was designed to compare the efficacy and safety of this strategy with the concurrent paclitaxel and trastuzumab regimen.³⁶

National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 Trial

Patients were randomized to receive four cycles of AC given every 3 weeks, followed by paclitaxel given weekly or every 3 weeks over 12 weeks, alone or with weekly trastuzumab for 52 weeks. The concurrent paclitaxel and trastuzumab regimen was very similar to NCCTG N9831.³⁶

Breast International Group Herceptin Adjuvant (HERA) Trial

In the non-U.S. HERA trial, any neoadjuvant or adjuvant chemotherapy regimen (for a minimum of four cycles or 3 months) with or without radiation therapy, as determined to be appropriate by the treating oncologist, was allowed. Patients were randomized after chemotherapy to every-3-week trastuzumab for 1 or 2 years, or for observation only.³⁷

Breast Cancer International Research Group (BCIRG) 006 Trial

This worldwide trial used docetaxel instead of paclitaxel. Patients were randomized onto three arms: AC followed by docetaxel alone; AC followed by docetaxel plus trastuzumab; or docetaxel, carboplatin, and trastuzumab (TCH). The latter regimen was included to test a non-anthracycline chemotherapy combination.³⁸

Eligibility Criteria

For all four trials, patients had to have HER2-positive early breast cancer. HER2 testing was performed on tumor tissue using immunohistochemistry (IHC), a staining technique evaluating overexpression of the HER2 protein, or by fluorescence in situ hybridization (FISH), which measures the number of copies of the HER2 gene. 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, but had to be axillary lymph node-positive in NSABP B-31. Further eligibility included adequate cardiac function, defined as normal left ventricular ejection fraction (LVEF), assessed by echocardiogram (ECHO) or multigated acquisition (MUGA) scan (MUGA only in BCIRG 006), and no history of CHF or current cardiac disease requiring medication. Other key eligibility criteria were standard for adjuvant therapy trials.

Cardiac Safety and Monitoring

LVEF evaluations by ECHO or MUGA took place at registration, and at three, six, nine, and 18 months in NSABP B-31 and NCCTG N9831; evaluations were performed at these timepoints and at 12, 24, 30, 36, and 60 months in HERA. Trastuzumab was discontinued for patients who developed CHF. If significant decreases in LVEF were observed, treatment was held and cardiac function re-evaluated after 3–4 weeks in NSABP B-31, NCCTG N9831, and HERA; trastuzumab was discontinued for patients with persistent substantial decreases in LVEF in these three trials.

Efficacy and Safety Results

Interim results are available for all four trials. Because of the similarities between the control arms and the AC followed by concurrent paclitaxel and trastuzumab arms in NSABP B-31 and NCCTG N9831, the efficacy results of these two trials were combined (joint efficacy analysis)³⁶. Definitions of cardiac events differed slightly between the trials; therefore, the cardiac safety results were reported separately.^{39, 40} The efficacy results of the AC followed

by sequential paclitaxel and trastuzumab arm of NCCTG N9831 and the 2-year trastuzumab arm in HERA are not yet available.

Disease-Free Survival

In all trials, DFS was significantly higher in the trastuzumab-containing arms than in the control or observation arms. In the joint efficacy analysis, DFS was 52% higher in the trastuzumab arm than in the control arm. A 46% improvement in DFS was observed in the 1-year trastuzumab group compared with the observation group in HERA. Both trastuzumab-containing arms in BCIRG 006 showed higher DFS than the control arm, with 51% and 39% improvements in the AC followed by docetaxel plus trastuzumab and TCH arms, respectively. There was no significant difference in DFS between the AC followed by docetaxel plus trastuzumab and TCH arms in BCIRG 006.³⁸

Overall Survival

The trastuzumab-containing arms in the joint analysis of NSABP B-31 and NCCTG N9831 showed a trend toward increased OS at 4 years compared with the control arm (91.4% versus 86.6%; hazard ratio [HR], 0.67; $P=0.015$), equating to a 33% reduction in the risk of death in the trastuzumab arm. In HERA, OS at 2 years was not significantly different between the 1-year trastuzumab and observation arms (96.0% versus 95.1%; HR, 0.76; $P=0.26$); however the follow-up period was short at the time of analysis.

Other Efficacy Endpoints

In the combined analysis of NSABP B-31 and NCCTG N9831, there were fewer recurrences in the trastuzumab-treated group than the control group: 89.7% versus 73.7% of patients were free of distant recurrence at 4 years (HR, 0.47; $P<0.0001$). 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, TTDR was significantly higher in the trastuzumab arm (HR, 0.49; $P<0.0001$) and approximately 70% of first recurrences were to distant sites in both arms.

Hematologic and Nonhematologic Safety

In NSABP B-31 and NCCTG N9831, the incidences of NCI-CTC non-cardiac adverse events were similar and tolerable between treatment groups. In all four trials, there was a higher incidence of protocol-defined cardiac events in the trastuzumab-containing arms than in the control or observation arm. The difference was <4% in each trial, which was within the limits specified in three of the four trials (NSABP B-31, NCCTG N9831, and HERA). There was no significant difference in the incidence of cardiac events between the anthracycline-containing and non-anthracycline-containing trastuzumab arms in BCIRG 006.³⁸ Results of NSABP B-31 and NCCTG N9831 showed that CHF associated with trastuzumab was generally reversible and manageable with standard medical treatment; the cardiac function improved in the majority of patients who experienced CHF.^{36, 39}

Impact of Trial Results on Clinical Practice

The high efficacy observed with adjuvant trastuzumab compared with that of chemotherapy alone has stimulated the NCCN to update current guidelines to recommend that adjuvant trastuzumab be given weekly or every three weeks with or following paclitaxel after AC for HER2-positive early breast cancer and recommends that one year of trastuzumab be given in the adjuvant setting.¹⁴

The availability of this targeted therapy mandates that appropriate HER2 testing of all invasive breast cancer is conducted, either to evaluate the HER2 protein (by immunohistochemistry – IHC) or the HER2 gene (typically by fluorescence in situ hybridization - FISH).⁴¹

Nursing Implications Summary: Symptom Management and Education

Clinical outcomes are improved significantly with the addition of trastuzumab to standard adjuvant chemotherapy, and the benefits outweigh the risk of cardiac dysfunction. Further follow up of patients enrolled in the four large trials will provide long-term outcomes data, such as duration of trastuzumab therapy. Use of trastuzumab has shifted the poor prognosis paradigm to a better prognosis in HER2-positive early breast cancer; therefore, it is important to identify all patients who could benefit from trastuzumab therapy. Nurses play a pivotal role in patient education and support and those who are aware of trastuzumab's cardiac safety profile will be better able to manage these critical issues with the patient. Discussions include the importance of frequent cardiac monitoring, and identification of the signs and symptoms of cardiac dysfunction, such as shortness of breath, peripheral edema, and unexplained or sudden weight gain. Nurses can be instrumental in educating patients to successfully manage distressing chemotherapy and trastuzumab treatment induced symptoms.⁴² This may include a discussion of the pathophysiology and treatment options associated with cardiac dysfunction, such as suspending trastuzumab treatment, cardiac re-evaluation, and trastuzumab re-initiation or discontinuation. Following completion of therapy, patients require regular overall health surveillance with an emphasis on breast health and ongoing cardiac and bone health evaluations.

Key nursing-focused questions that call for ongoing study include successful strategies in the assessment and management of cardiac dysfunction, QOL associated with current modes of adjuvant therapy and the collaboration in adverse event and symptom management by nurses, patients, and caregivers.

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Table 1**Large Adjuvant Trastuzumab Trial Schemas Trial**

NCCTG N9831 ³⁶ n=3505	AC x 4 followed by:	T T → H alone for a total of one year TH → H alone for a total of one year
NSABP B31 ³⁶ n=2403	AC x 4 →	T TH → H
Joint Analysis N9831 and B31 ³⁶	AC x 4 →	T TH → H
HERA ³⁷ n=5090	≥ 4 cycles/3 mos of neo/adjuvant chemo →	Observation 1 year H 2 years H
BCIRG 006 ³⁸ n=3222	AC x 4 → DCH →	D DH → H H

AC= doxorubicin + cyclophosphamide; T= paclitaxel; H= trastuzumab; D= docetaxel; DH= docetaxel + trastuzumab; DCH= docetaxel + carboplatin + trastuzumab