

## **Dr. Andrew Seidman's Commentary**

### **I. Breast Cancer Overview**

Breast cancer remains the most common malignancy and the second leading cause of cancer mortality in women in the United States. The following resources provide an overview of risk, epidemiology, diagnosis, and treatment of breast cancer. Included are chapters from the 9th edition of CMPMedica's *Cancer Management: A Multidisciplinary Approach*—Breast cancer overview: Risk factors, screening, genetic testing, and prevention (Chapter 8); Stages 0 and I breast cancer (Chapter 9); Stage II breast cancer (Chapter 10); and Stages III and IV breast cancer (Chapter 11). These chapters provide a framework for understanding issues and trends in breast cancer management. A more focused view of progress in chemotherapy and trends in research in this area is provided by my *ONCOLOGY* review article. An overview of an important strand of current investigations in chemotherapy is provided by the *Oncology News International* supplement covering taxane trials reported at the 2006 San Antonio Breast Cancer Symposium. Finally, some perspective on how recent studies of hormonal therapy, chemotherapy, molecular targeted therapy, and biologic markers are affecting current practice and promise to shape future practice is provided by a summary of notable presentations at the 2006 American Society of Clinical Oncology

(ASCO) symposium, as featured in the breast cancer section of the *ONCOLOGY* 2006 ASCO Desk Reference supplement.

## **II. Early Breast Cancer: Surgical Management**

Mastectomy remains the standard of care in multicentric breast cancer.

Available data indicate that the frequency of residual disease and risk of local recurrence remain high with breast-conserving surgery in this setting. It is also true, however, that interpretation of results of studies of breast-conserving surgery in this setting is hindered by poor/inconsistent standardization of surgical margins, poor quality of diagnostic mammography, and small sample sizes of studies to date.

## **III. Early Breast Cancer: Adjuvant Therapy**

A number of recent reports have indicated benefits of adding taxanes to the adjuvant chemotherapy in early-stage breast cancer. The Breast International Group (BIG) 2-98 trial showed that the addition of docetaxel (Taxotere) to anthracycline-based adjuvant therapy followed by cyclophosphamide/methotrexate/fluorouracil (CMF) reduced risk of relapse and improved overall survival (OS) among women with node-positive disease, with sequential use of doxorubicin and docetaxel providing better outcomes than concomitant use. The Italian Taxit 216 trial showed marginally improved disease-free survival (DFS) with sequential epirubicin/docetaxel vs epirubicin, both followed by CMF, in node-positive patients.

A second interim analysis of the Breast Cancer International Research Group (BCIRG) 006 study continued to support the benefits of docetaxel and trastuzumab (Herceptin) in HER2-positive disease. Whereas both doxorubicin/cyclophosphamide followed by docetaxel and 1 year of trastuzumab (AC→TH) and docetaxel/carboplatin followed by trastuzumab (TCH) improved OS and DFS compared with the control regimen of doxorubicin/cyclophosphamide followed by docetaxel, the anthracycline-including AC→TH regimen was associated with greater cardiac toxicity than the TCH regimen; neither trastuzumab-containing arm caused cardiac death. Mature results of a German trial indicate that dose-dense, dose-intense approach to the delivery of epirubicin (Ellence), cyclophosphamide, and paclitaxel improved relapse-free survival (RFS) and OS compared with conventional epirubicin, cyclophosphamide, and paclitaxel dosing and scheduling. Other studies have supported the use of epirubicin in systemic therapy. The Canadian MA.21 study showed that two epirubicin-containing regimens—cyclophosphamide/epirubicin/fluorouracil and dose-dense epirubicin/cyclophosphamide/paclitaxel—were superior to every-3-weekly doxorubicin/cyclophosphamide followed by paclitaxel (as per Cancer and Leukemia Group B trial 9344) in preventing recurrence. Notably, the non-epirubicin comparator arm in this trial was not administered in a dose-dense fashion, which is known to be superior to every-3-weekly scheduling of these agents at these doses. Pooled results of the NEAT (National Epirubicin

Adjuvant Trial) and BR9601 trials showed that epirubicin followed by CMF was associated with improved OS and RFS vs CMF alone.

With regard to radiation therapy (RT), an 8-year follow-up of a Canadian study showed that the addition of RT to tamoxifen reduced ipsilateral relapse in women with node-negative disease who had undergone lumpectomy. After 15 years of follow-up in the Early Breast Cancer Trialists Collaborative Group study, RT following mastectomy continues to be associated with lower local recurrence rates and somewhat reduced mortality compared with no RT; this analysis showed benefit in patients with one to three positive nodes, in whom clear benefit previously had not been observed. Other studies continue to provide an indication of potential benefits of more-targeted RT. One study showed reduced moist desquamation and overall skin toxicity with postoperative intensity-modulated radiation therapy and smaller early-phase studies have shown benefits of accelerated partial breast irradiation (brachytherapy) in early disease and after recurrence following traditional RT.

Finally, the National Cancer Institute–supported Eastern Cooperative Oncology Group-coordinated TAILORx trial (Trial Assigning Individualized Options for Treatment [Rx]) is underway to assess whether the Oncotype DX gene expression profile can be used to clarify the role of chemotherapy in addition to antiestrogen therapy for patients with estrogen receptor–positive, lymph node–negative breast cancer who have an intermediate Recurrence

Score by this assay. The trial has a target accrual of > 10,000 patients at sites in the United States, Canada, and Peru.

#### **IV. Early Breast Cancer: Adjuvant Hormonal Therapy**

This section includes articles exploring the implications of the recently reported STAR (Study of Tamoxifen and Raloxifene) trial comparing the selective estrogen-receptor modulators tamoxifen and raloxifene (Evista) in chemoprevention of breast cancer; the drugs were similar in preventing invasive breast cancer in high-risk postmenopausal women, with raloxifene being somewhat less effective at preventing noninvasive breast cancer but also being associated with reduced risk of thromboembolic events. Recent data from adjuvant therapy trials include: follow-up of the Intergroup Exemestane Study indicating that switching to the aromatase inhibitor exemestane after several years of tamoxifen treatment reduces risk of relapse and death; and the finding in the BIG 1-98 trial that initial treatment with the aromatase inhibitor letrozole (Femara) reduced early relapse and distant recurrence compared with tamoxifen. Other articles in this section discuss the loss of bone density observed with aromatase inhibitor treatment.

#### **V. Management of Advanced Breast Cancer: First-Line Therapy**

Recent trials in first-line therapy of advanced breast cancer included those examining taxane-based combination regimens. A European noninferiority

trial showed that capecitabine (Xeloda)/paclitaxel and epirubicin (Ellence)/paclitaxel were associated with similar progression-free survival (PFS), overall survival (OS), and objective response rates; leukopenia and neutropenia were more common in the epirubicin arm, and diarrhea and hand-foot syndrome were more common in the capecitabine arm.

Another European trial found that three taxane-containing regimens, consisting of paclitaxel/carboplatin, gemcitabine (Gemzar)/docetaxel (Taxotere), and paclitaxel alone, were associated with similar time to progression (TTP), OS, response rate, and overall toxicity; myelotoxicity was more common with gemcitabine/docetaxel and peripheral neuropathy was more common in the paclitaxel arms.

In the BCIRG 007 trial for patients with HER2-positive disease, docetaxel/trastuzumab (Herceptin) and docetaxel/carboplatin/trastuzumab (TCH) produced similar response rates and TTP; the docetaxel/trastuzumab regimen (which included a higher docetaxel dose compared with the triple-drug regimen) was associated with more neuropathy, myalgia, and rash, while the triple-drug regimen caused more thrombocytopenia, nausea, and vomiting.

Phase II trials of interest included a European study indicating improved TTP with docetaxel/capecitabine/trastuzumab vs docetaxel/trastuzumab. Interim analysis of a randomized phase II trial indicated that weekly

nanoparticle albumin-bound (nab) paclitaxel (Abraxane) was associated with a markedly improved response rate compared with every-3-week docetaxel and every-3-week nab-paclitaxel; nab-paclitaxel regimens were associated with markedly reduced severe neutropenia.

## **VI. Management of Advanced Breast Cancer: Targeted Therapy**

The oral dual HER1-HER2 kinase inhibitor lapatinib (Tykerb) was recently approved for use in combination with capecitabine (Xeloda) for treatment of locally advanced or metastatic HER2-overexpressing breast cancer in patients who have previously received anthracycline, taxane, and trastuzumab (Herceptin) treatment. The phase III trial supporting approval was stopped after interim analysis showed that lapatinib/capecitabine significantly improved time to progression vs capecitabine alone in this setting; response rates were higher in the combination group and toxicities were comparable.

Other recent reports indicate benefit of lapatinib and lapatinib/paclitaxel in inflammatory breast cancer. An open-label phase III trial indicated that the addition of trastuzumab to anastrozole (Arimidex) significantly improved progression-free survival in patients with both hormone receptor and HER2-positive metastatic breast cancer. A phase II study suggested a high response rate with the combination of trastuzumab and bevacizumab (Avastin) in first-line treatment.

## **VII. Breast Cancer Screening and Diagnosis**

Resources in this section include articles discussing recently updated guidelines for magnetic resonance imaging (MRI) in breast cancer diagnosis and articles discussing screening issues in underserved United States populations. With regard to imaging studies, recent MRI studies include an American College of Radiology Imaging Network study of 969 women showing that MRI of the contralateral breast in women with newly diagnosed breast cancer revealed disease missed by mammography and breast exam in 3.1% (30 otherwise occult tumors found: 18 invasive carcinomas, 12 ductal carcinomas in situ).

In other recent imaging studies, use of elasticity imaging software for ultrasonography was associated with 100% sensitivity, 99% specificity, 94% positive predictive value, and 100% negative predictive value in distinguishing malignant from benign breast lesions. A new subgroup analysis from the Digital Mammographic Imaging Screening Trial indicated that digital mammography was significantly better than film mammography at detecting disease in pre- or perimenopausal women with dense breast tissue, but not in other subgroups examined in the analysis. A preliminary study of dual-headed cadmium-zinc-telluride gamma camera imaging showed that the technique had 88% sensitivity for detecting tumors < 10 mm (98% for tumors > 10 mm), including 75% sensitivity for those < 5 mm and 93% for those 6 to 10 mm. A large screening study showed that computer-aided

detection in interpreting routine mammograms was associated with no apparent benefit in identifying breast cancer and resulted in an increased rate of unnecessary biopsies.

### **VIII. Breast Cancer Risk**

Recent studies have supported a link between increased vitamin D intake (both dietary and through exposure to sunlight) and increased soy intake in earlier life and reduced risk of breast cancer in later life. For example, one study showed that working in an outdoor job between the ages of 10 and 19 reduced breast cancer risk by about 40% and frequent outdoor activities between ages 10 and 29 reduced the risk by 35%. Asian-American women who ate the most soy from ages 5 to 11 reduced their risk of breast cancer by 58%, compared with the women who ate the least amount, and reductions associated with greater consumption during adolescence and adulthood were about 25%. The recently opened Environmental and Genetic Determinants of Puberty study is attempting to enroll approximately 1,200 girls aged 6 to 8 years with the aim of examining whether there are vulnerable periods during mammary gland development when exposure to environmental agents may influence risk of breast cancer in later life.

Recent studies of interventions to reduce risk of disease include a large prospective study showing that salpingo-oophorectomy in high-risk women reduced risk of BRCA-associated gynecologic cancer in both BRCA1 and

BRCA2 mutation carriers and breast cancer risk in BRCA2 mutation carriers.

An early-phase study showed that a preventive vaccine consisting of the E75 peptide from the HER2 protein combined with granulocyte-macrophage colony-stimulating factor is showing promise in HLA-A2 allele-bearing women with node-positive, HER2-positive cancer and no evidence of disease after multimodality treatment; the vaccine has entered phase III evaluation.

Other articles in this section include reports of experimental studies identifying an investigational drug combination that prevents estrogen receptor–negative tumors in mice and a potential viral etiology for breast cancer.

## **IX. Psychosocial Issues**

Recent studies on the psychologic/emotional effects of cancer and cancer treatment include a study in women with stage IV breast cancer and clinical depression showing that cognitive therapy (8 weekly sessions and 3 “booster” sessions) significantly improved depressive symptoms. Another study in women undergoing large core needle breast biopsy, of whom all received standard intravenous sedation, showed that a self-hypnotic relaxation technique plus a structured attention/empathy approach reduced anxiety, compared with no change in anxiety with structured attention/empathy alone and increased anxiety with standard sedation alone; pain increased with all approaches but less markedly with the self-hypnosis and empathy techniques.

Another study in patients with different types of cancer showed that making a 2-hour videotaped interview of the patient focusing on the patient's personal and family history, life philosophy, and cancer experience significantly improved patient's functional and overall quality of life scores.

## **X. Additional Information About Breast Cancer**

This section is a miscellany of recent findings and reports of interest to the breast cancer community. Included are articles on the changing incidence of breast cancer and breast cancer mortality. Between 2002 and 2003, there was a 7% reduction in incidence of invasive breast cancer, with the decrease being confined to women aged 50 years or older (12% reduction in 50- to 69-year age group) and primarily reflecting a decrease in incidence of estrogen receptor (ER)-positive tumors. Data from 2004 indicate that this reduction has been maintained. Although no direct causality can yet be attributed, the reduction appears to be temporally associated with the dramatic decline in use of hormone replacement therapy following the mid-2002 report from the Women's Health Initiative indicating increased breast cancer risk with use of estrogen/progestin therapy. Another study has shown that breast cancer mortality decreased by 24% between 1990 and 2003, including decreases of 38% and 19% in women aged < 70 years with ER-negative and ER-positive tumors, respectively.