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Advances in Medical Management of Early Stage and Advanced Breast Cancer: 2015

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Standard management of early stage and advanced breast cancer has been improved over the past few years by knowledge gained about the biology of the disease, results from a number of eagerly anticipated clinical trials and the development of novel agents that offer our patients options for improved outcomes or reduced toxicity or both. This review highlights recent major developments affecting the systemic therapy of breast cancer, broken down by clinically relevant patient subgroups and disease stage, and briefly discusses some of the ongoing controversies in the treatment of breast cancer and promising therapies on the horizon.
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Introduction

Although the number of breast cancer deaths in the United States has fallen over the past 15 years, it remains the most common serious cancer and second leading cause of cancer deaths among U.S. women. The past few years have seen a number of new drug approvals and the presentation of results from large, randomized studies that have changed treatment algorithms and offer hope of substantial improvements in outcomes in both early stage and advanced breast cancer. In this review, we discuss those advances and how they have affected the standard of care for many breast cancer patients, focusing on the 3 major subtypes—hormone receptor (HR)–positive/human epidermal growth factor receptor-2 (HER2)–negative, HER2-positive, and triple-negative.

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Hormone Receptor–Positive/ HER2-Negative Breast Cancer

Stage I-III HR+/HER2− Disease

Of patients diagnosed with breast cancer in the United States, 60%-70% have HR-positive and HER2-negative (HR+/HER2−) cancers, the vast majority with stage I-II disease at presentation, especially among those whose cancers are detected by screening mammography (Fig. 1A). A major challenge in the management of these patients is to differentiate those who are at low risk for local or distant recurrence, in whom treatment should be limited and, ideally, have minimal effect on the patient's quality of life, from those at high risk for disease recurrence and death, in whom more intensive and potentially toxic treatments are warranted. Results from recent studies have addressed the duration of adjuvant endocrine therapy, assessed the role of ovarian function suppression (OFS) in premenopausal women and expanded the potential indications for neoadjuvant endocrine therapy. There has also been widespread adoption of the use of genomic assays to select patients in whom chemotherapy may, or may not, offer significant benefit over endocrine therapy alone.

Although we have long been aware that more than half of the patients with these typically less-aggressive cancers who eventually recur will do so more than 5 years after initiation of adjuvant endocrine therapy, until fairly recently the benefit of extending that treatment beyond 5 years was uncertain. Studies such as National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 failed to demonstrate improved outcomes from extending tamoxifen from 5-10 years, though this

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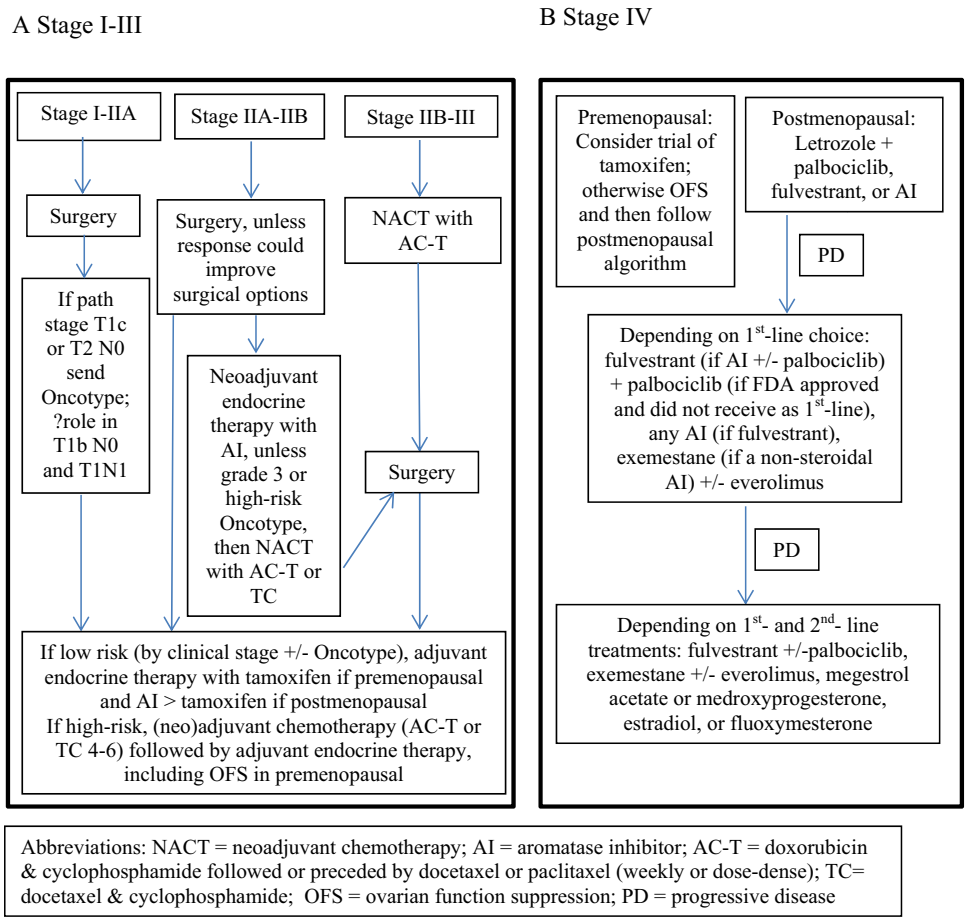

Figure 1 Treatment algorithm for hormone receptor–positive, HER2-negative breast cancer (HR+/HER2− BC). AC-T, doxorubicin and cyclophosphamide followed or preceded by docetaxel or paclitaxel (weekly or dose dense); NACT, neoadjuvant chemotherapy; PD, progressive disease; TC, docetaxel and cyclophosphamide. (Color version of figure is available online.)

was a relatively small study ($n = 1172$).[1] However, the National Cancer Institute of Canada (NCIC) MA.17 trial, which compared 5 years of the aromatase inhibitor (AI) letrozole with placebo in postmenopausal women who were free of disease after 5 years of tamoxifen, demonstrated a 48% improvement in disease-free survival (DFS) and a 39% improvement in overall survival (OS), taking into account crossover from placebo to letrozole when the initial results of the study were announced, illustrating the potential benefit of extended adjuvant endocrine therapy.[2,3] Further analysis revealed that younger patients, those who were premenopausal when they started tamoxifen but postmenopausal 5 years later when they transitioned to the AI, received the largest benefit from this treatment.[4]

The dilemma was how to treat women who were either still premenopausal after 5 years of tamoxifen or unable to tolerate an AI owing to side effects, most often joint stiffness and pain, vaginal dryness and atrophy, and mood swings. The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) and adjuvant Tamoxifen—To offer more (aTTOM) trials, which were initiated in 1996 and included more than 22,000 women, assessed the benefits and risks of extended adjuvant therapy with tamoxifen.[5,6] Results reported in 2012-2013 demonstrated that although patients with HR+ cancers ($n = 9600$) assigned to continue tamoxifen had minimal reductions in recurrences and breast cancer–attributed deaths during their additional 5 years of treatment, their risks of recurrence and death from breast cancer were significantly (25%-30%) lower in years 10-15 and beyond, reflecting the indolent and insidious nature of these cancers. The only major side effect of extended treatment with tamoxifen was a doubling of the incidence of endometrial cancer, from 1.2%-2.4%.

The benefit of extending adjuvant endocrine therapy beyond 5 years in patients treated with an AI—either alone or after 2-3 years of tamoxifen—are less clear; reports from 2 studies that address this matter—NSABP B-42 and MA.17 R—are eagerly awaited. Pending those findings, oncologists may recommend extending treatment with an AI to 5 years in patients who started it after 2-3 years of tamoxifen or, in higher risk patients who are tolerating it well, simply continuing the AI until these study results become available. Patients whose oncologist recommends stopping the AI (for now) may be comforted by the knowledge that, in both MA.17 and the recently reported LATER trial, patients who started an AI after a break of up to several years still benefited from this treatment.[7,8]

Despite its potential advantages, the decision to recommend extending adjuvant endocrine therapy should take into