Guideline: Use Aromatase Inhibitor as Adjuvant

BY DIANA MAHONEY
New England Bureau

HOLLYWOOD, FLA. — An aromatase inhibitor, either alone or after tamoxifen therapy, is better than tamoxifen alone for the long-term prevention of breast cancer in postmenopausal women with invasive breast cancer, according to updated treatment guidelines from the National Comprehensive Cancer Network.

Several recent clinical trials have shown that adjuvant endocrine therapy with the aromatase inhibitors anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin) can significantly improve disease-free survival in postmenopausal women, compared with tamoxifen as a single agent.

Consequently, "tamoxifen alone [in this patient population] has fallen off the radar screen," said Robert Carlson, M.D., chair of the NCCN panel that revised the guidelines, which were last updated in 2004. The network's 19 member institutions are designated as comprehensive cancer centers by the National Cancer Institute.

The updated guidelines recommend that women who are postmenopausal when they begin adjuvant therapy receive one of the following treatment regimens:

► Anastrozole for 5 years.

► Tamoxifen for 2-3 years, followed by exemestane or anastrozole to complete 5 years of therapy.

► Tamoxifen for 4.5-6 years, followed by letrozole for 5 years.

► Tamoxifen for 5 years for women with contraindications for, or who decline, aromatase inhibitors.

The new recommendations are based primarily on findings from three large randomized controlled studies of aromatase inhibitors in postmenopausal women, he said at the annual conference of the NCCN.

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial compared anastrozole, alone or used with tamoxifen, with tamoxifen alone as 5-year adjuvant treatment for women with early breast cancer following primary treatment with surgery, radiotherapy, and/or chemotherapy. The combination arm was stopped following initial analysis showing it to have similar efficacy to the tamoxifen alone arm.

The ATAC cohort included approximately 9,300 breast cancer patients from 381 medical centers worldwide who had good prognoses: 61% had lymph node–negative disease and 64% had tumors smaller than 2 cm in diameter. The most recent outcome analysis of the ATAC data, representing a median 68 months of follow-up, showed highly significant improvements in disease-free survival, recurrence-free survival, and distant disease-free survival in patients receiving anastrozole.

"In essence, the data showed that anastrozole prevents one in four of the relapses experienced by patients on tamoxifen," said Dr. Carlson of Stanford (Calif.) University.

Another study, the MA-17 trial coordinated by the National Cancer Institute of Canada Clinical Trials Group at Queen's University, Kingston, Ont., compared the outcomes of nearly 5,200 women whose adjuvant therapy included 5 years of tamoxifen followed by 5 years of letrozole or placebo. At the median 2.5-year follow-up, patients in the letrozole group had a 40% overall reduction in their risk of metastases, compared with those in the tamoxifen/placebo group.

In the Intergroup Exemestane Study (IES) of more than 4,700 women with estrogen-receptor–positive breast cancer, patients who switched to exemestane after 2 or 3 years of taking tamoxifen for the remainder of 5 years total treatment experienced a 32% reduction in the risk of recurrence of the disease at 3 years, compared with those continuing tamoxifen for 5 years.

Because the three selective aromatase inhibitors appear to have similar antitumor efficacy and toxicity profiles, the revised guidelines do not recommend one regimen over another. When making treatment decisions, physicians should try to gauge how well the patient fits the criteria of the clinical trials on which the recommendations are based and use the regimen that most closely approximates the clinical situation, he advised.

The guidelines for adjuvant hormonal therapy in premenopausal women have been updated as well, Dr. Carlson reported. Women who are premenopausal when adjuvant hormonal therapy is initiated should receive 2-3 years of treatment with tamoxifen with or without ovarian supplementation or ablation, according to the guidelines.

"If, after the first round of adjuvant therapy with tamoxifen, a woman becomes postmenopausal, she should complete the 5 years of tamoxifen, followed by 5 years of letrozole because of the success of this regimen in postmenopausal women," Dr. Carlson said.

Because the ovarian function of some women who appear to become postmenopausal while on tamoxifen resumes when the drug is discontinued and treatment with an aromatase inhibitor begins, serial monitoring of plasma estradiol and FSH levels should be ongoing. ■

ISO a Standard Definition of Menopause

Critical to the appropriate clinical application of the updated NCCN breast cancer treatment recommendations is a standardized definition of menopause.

"Just about all studies that have been done in postmenopausal women define [menopause] differently," Dr. Carlson said.

Menopause is generally the permanent cessation of menses. "As the term is used in breast cancer management, it includes a profound and permanent decrease in ovarian estrogen synthesis," the revised guidelines state. Reasonable criteria for determining menopause include any of the following:

► Prior bilateral oophorectomy.

► Age 60 years or older.

► Age younger than 60 years and amenorrheic for at least 12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression, and FSH and estradiol in the postmenopausal range.

► Age younger than 60 years and FSH and plasma estradiol level in postmenopausal range in women taking tamoxifen or toremifene.

It is not possible to assign menopausal status to women receiving an LHRH agonist or antagonist, the guidelines state. Amenorrhea is not a reliable indicator of menopausal status in women who are premenopausal at the outset of adjuvant chemotherapy.

"Women who undergo chemotherapy treatments that permanently stop menses may still produce estradiol at levels that are premenopausal," said Dr. Carlson, stressing that premenopausal estrogen levels can influence treatment with aromatase inhibitors.

Newer Radiotherapy Curbs Local Breast Cancer Recurrences

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — The improved local control of breast cancer achieved via radiotherapy translates into a significant reduction in mortality due to the malignancy that becomes apparent only late, at 10 and 15 years' follow-up, Sir Richard Peto, Ph.D., reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

That's the good news regarding radiotherapy from a new meta-analysis of the world's total randomized clinical trial experience in early breast cancer. The bad news: This reduction in breast cancer mortality is essentially canceled out—and in some subgroups outweighed—by a radiotherapy-induced excess in late deaths due to cardiovascular disease.

Radiotherapy "causes deaths from heart disease not in the first decade after treatment but in the second," said Dr. Peto, professor of medical statistics and epidemiology at the University of Oxford (England).

Still, the central point remains: Local control of breast cancer matters. And if preliminary evidence turns out to be correct in suggesting modern radiotherapy achieves it with less cardiotoxicity than the radiotherapy of the 1980s, then physicians can expect to see a further decline in overall breast cancer mortality in the decade beginning in 2010, he said.

"Breast cancer is a disease where you've really got to think of what you're achieving on a time scale of decades, not years," he said. "The question for a middle-aged woman is what is the 20-year survival?"

Dr. Peto presented a meta-analysis of data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) involving 24,000 women randomized to radiotherapy or no radiotherapy in 46 clinical trials that enrolled patients in the mid-1980s.

The overall improvement in breast cancer outcomes since the 1980s is 'a brilliant success.'

DR. PETO

The 15-year rate of isolated local recurrence was 10% in women who received radiotherapy and 31% in those who did not. And 15-year mortality due to breast cancer was 44% in radiotherapy recipients and 48% in controls.

With trials stratified based on the magnitude of difference in local control, it became apparent that the greater the difference in local control in a given study, the bigger the long-term difference in breast cancer mortality, he said.

Looking more narrowly at the impact of radiotherapy after breast-conserving therapy in a series of randomized trials involving 6,097 women with node-negative disease, he found that the 10-year rate of isolated local recurrence was 10% in those who got radiotherapy and 29% in controls. Ten-year breast cancer mortality was 17% in radiotherapy-treated women and 20% in controls.

The EBCTCG data show that besides the increase in late cardiovascular deaths associated with radiation therapy as practiced in the 1980s, treated women face smaller but significant increases in risk of death due to lung, esophageal, and contralateral breast cancer.

Nevertheless, he characterized the overall improvement in breast cancer outcomes since the 1980s as "a brilliant success." It's estimated that in 2010, mortality in middle age due to breast cancer in the United Kingdom will be just half of what it was in 1980, and a similar trend applies in the United States.

That's a success story unrivaled in oncology. Only the reduction in lung cancer deaths even comes close—and that's not due to medical advances but to smoking cessation efforts.

"The changes in breast cancer treatment during the 1980s produced changes in mortality in the 1990s. The improvements in treatment and in screening in the 1990s are going to produce continuing reductions in mortality in this decade. And the improvements coming now in treatment are going to keep those reductions in mortality going in the 2010s," Dr. Peto predicted. ■