Tamoxifen Alone Discouraged as Adjuvant Tx

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.

'Anastrozole prevents one in four of the relapses experienced by patients on tamoxifen.' The anastrozole patients also had fewer hot flashes.

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 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 who had good prognoses: 61% had lymph-node negative disease and 64% had tumors smaller than 2 cm in diameter.

The most recent analysis of the ATAC data, representing a median 68 months of follow-up, showed significant improvements in disease-free survival, recurrence-free survival, and distant disease-free survival in those receiving anastrozole.

"Anastrozole prevents one in four of the relapses experienced by patients on tamoxifen," said Dr. Carlson of Stanford (Calif.) University. The anastrozole patients also had fewer diagnoses of endometrial cancer, thromboembolic and cerebrovascular events, and hot flashes. Women with hormone-receptor–positive disease benefitted the most from adjuvant therapy with anastrozole.

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. The exemestane group had fewer local and distant tumors as well as a reduced incidence of new cancer in the other breast.

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. "The optimal use of these [aromatase inhibitors] as adjuvant therapy, either instead of or sequenced with tamoxifen, has yet to be determined through ongoing trials," Dr. Carlson said.

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 suppression or ablation.

After this round of treatment, women who continue to be premenopausal should complete 5 years of tamoxifen therapy, Dr. Carlson said. "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," he 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. "If ovarian function resumes, the aromatase inhibitor should be discontinued and tamoxifen therapy reinitiated," Dr. Carlson said. ■

Guidelines Define Menopause

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

"You wouldn't think a definition of menopause would be needed, but just about all studies that have been done in postmenopausal women define [menopause] differently," Dr. Carlson said. This can cause problems and confusion, particularly with respect to treatment with aromatase inhibitors, which are most effective in postmenopausal women.

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 levels 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," commented Dr. Carlson, stressing that premenopausal estrogen levels can influence treatment with aromatase inhibitors.

Study Identifies Novel Breast Cancer Prognostic Markers

BY PATRICE WENDLING
Chicago Bureau

Atlanta — New data suggest that the *Notch* signaling genes—*Notch1* and *Jagged1*—are potential novel prognostic markers for breast cancer, Michael Reedijk, M.D., FACS, reported at a symposium sponsored by the Society of Surgical Oncology.

"Patients expressing high levels of *Jagged1* or *Notch1* demonstrated significantly poorer overall survival than patients expressing low levels," said Dr. Reedijk of University Health Network, Princess Margaret Hospital in Toronto.

Abnormal *Notch* signaling has been observed in a number of malignancies, but this is the first report of direct evidence linking high-level *Notch1* and *Jagged1* expression with poorer outcomes in women with breast cancer.

The data also suggest a mechanism by which *Notch* is activated in aggressive breast cancer that may be targeted with drugs currently under development for Alzheimer's disease, Dr. Reedijk said.

Dr. Reedijk and colleagues at Toronto's Hospital for Sick Children and the University Health Network analyzed tumor samples from 184 breast cancers using in situ hybridization. One-third of the cancers were node-positive, one-third were node-negative, and one-third had metastasized at presentation. *Notch2* was expressed at high levels in most tumors.

In contrast, high levels of *Notch1*, *Jagged1*, and *Notch3* were found in the tumors of a subset of patients with poor prognostic pathological features.

Patients with tumors expressing high levels of these genes showed lower overall survival than those expressing low levels of these genes, although the association was not statistically significant for *Notch3*.

The 5-year survival rate for women expressing high levels of *Jagged1* was 42%, with a median survival of 50 months, compared with 65% and 83 months for patients with low levels of *Jagged1*.

The 5-year survival rate was 49% for women expressing high levels of *Notch1*, with a median survival of 53 months, compared with 64% and 91 months for patients with low levels of *Notch1*, he said at the meeting.

For patients coexpressing high levels of both *Jagged1* and *Notch1*, the 5-year survival rate and median survival time were approximately half of those seen for tumors without *Jagged1* and/or *Notch1* expression. The 5-year survival rate was just 34%, with a median survival of 43 months.

"This suggests that there is a ligand and receptor circuit that is functioning in these tumors and may identify a signaling pathway that can be therapeutically targeted using newly developed γ-secretase inhibitors, which block *Notch* signaling," Dr. Reedijk said. ■