Anastrozole Seen as First-Line Breast Ca Therapy

Anastrozole showed significant advantages over tamoxifen in time to local and distant recurrence.

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SAN ANTONIO — Five years of the aromatase inhibitor anastrozole has now replaced tamoxifen as the endocrine therapy of choice for primary adjuvant therapy of women with hormone receptor–positive early-stage breast cancer, Anthony Howell, M.D., said at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

He presented the updated results of the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial, which at a mean follow-up of 68 months continues to show superior efficacy for anastrozole (Arimidex), as has consistently been the case since the first year of follow-up.

ATAC is an AstraZeneca-sponsored, randomized, double-blind trial for which data are available on 9,366 postmenopausal women with early-stage breast cancer treated at 381 sites in 21 countries. Participants were randomized to 5 years of tamoxifen, anastrozole, or both, although the combination treatment arm was halted early because of clearly inferior results, explained Dr. Howell of the University of Manchester, England.

At 68 months, 16% of hormone receptor–positive patients in the anastrozole arm had died or developed recurrent breast cancer, compared with 19% of tamoxifen-treated patients. The anastrozole group also had significant relative advantages of 26% in time to local recurrence, 16% in time to distant recurrence, and a 53% lower rate of contralateral breast cancer.

Among hormone receptor–positive patients, there were 152 breast cancer deaths in the anastrozole arm and 172 in the tamoxifen arm, a trend that didn't reach significance but may do so with several more years of follow-up, he said.

The incidences of endometrial cancer, thromboembolic events, and ischemic stroke were significantly lower in the anastrozole group. However, the rates of osteoporosis, fractures, and arthralgias were significantly greater with anastrozole than with tamoxifen.

Despite Dr. Howell's call for anastrozole to be considered the agent of choice for first-line initial endocrine therapy, many oncologists indicated that they—and large numbers of their patients—remain unwilling to do so routinely for now.

That reservation is reflected in a recent American Society of Clinical Oncology technology assessment, which advised that adjuvant therapy for postmenopausal women with hormone receptor–positive breast cancer "should include an aromatase inhibitor in order to lower the risk of tumor recurrence," without specifying whether the agent should be used as initial therapy or after tamoxifen.

The ASCO report cited as reservations the still limited data regarding the late consequences of aromatase inhibitor therapy and how best to utilize these agents.

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DR. HOWELL

ASCO took a conservative stance—and appropriately so, Hope S. Rugo, M.D., said at a satellite symposium sponsored by Merck and Co.

In her own practice, she favors using an aromatase inhibitor from the beginning in women at increased risk for osteoporosis or thromboembolism, and in those with higher-risk breast cancer as defined by a human epidermal growth factor receptor 2 (HER2)–positive and/or estrogen receptor–positive/progesterone receptor–negative (ER+/PgR–) tumor.

"For the average woman, though, I do tend to think that maybe a couple of years of tamoxifen isn't a bad thing. I discuss the data with each patient. And I have to say, many patients are still very enthusiastic about taking tamoxifen. It's kind of gone in reverse: Whereas before nobody wanted to take tamoxifen and everybody thought it was an evil drug, now many people are saying, 'No, I want to take tamoxifen—I'm worried about the long-term side effects of the aromatase inhibitors,' " said Dr. Rugo, codirector of the breast oncology clinical trials program at the University of California, San Francisco, Comprehensive Cancer Center.

She added that a particularly intriguing finding in ATAC—albeit one derived from a secondary retrospective analysis—was that the benefits of anastrozole seemed to be concentrated in the 19% of study participants who had ER+/PgR– disease.

Their risk of recurrence was 57% less with anastrozole than with tamoxifen, compared with just a 16% advantage favoring anastrozole in patients with ER+/PgR+ tumors, who accounted for 71% of the ATAC population.

"I think we're going to be seeing a lot more about that issue in the future. It's now a bit controversial," Dr. Rugo observed. ■

Menstrual Timing of Surgery Not Seen as Prognostic Factor

SAN ANTONIO — The timing of breast cancer surgery with respect to menstrual cycle phase failed to affect prognosis in two large multicenter prospective observational studies presented at the annual breast cancer symposium sponsored by the Cancer Therapy and Research Center.

This has been a longstanding controversy. Since 1989, roughly two dozen surgical studies have examined the issue. Close to half have reported a survival advantage for breast cancer patients who undergo their surgery during the luteal phase of the menstrual cycle. The remaining studies concluded timing of surgery had no impact upon disease-free or overall survival.

But most prior studies involved a few hundred patients or less, many were single-center retrospective series, and nearly all relied upon patient recall of the last menstrual period, which has the potential for inaccuracy. To shed new light on the issue, investigators from the North Central Cancer Treatment Group conducted a study in which 842 patients undergoing breast cancer surgery at 103 sites were categorized as to menstrual cycle phase both by biochemical determination at time of surgery and by recall of last menstrual period, explained Clive S. Grant, M.D., professor of surgery at the Mayo Clinic, Rochester, Minn.

Five-year disease-free survival in 231 women operated on during the luteal phase was 81.9%, not significantly different than the 82.2% rate among 364 women in the follicular phase or the 79.1% rate in women in an indeterminate menstrual phase.

Nor did overall survival differ between the groups, Dr. Grant said.

Biochemical determination of menstrual phase based upon hormone levels at the time of surgery demonstrated that reliance upon last reported menstrual period would have resulted in misclassification of 29% of women, a finding that casts doubt upon the validity of much of the prior work in this area.

In a separate presentation, Richard Sainsbury, M.D., reported on 412 women followed for a median 59 months after undergoing breast cancer surgery in a multicenter British study. The 3-year overall survival of 90.7% wasn't affected by timing of surgery in relation to menstrual cycle.

The initial data analysis relied upon patient report of last menstrual period. Hormone levels at the time of surgery were also measured, however, and in the near future the data will be reanalyzed using those measurements to categorize patient menstrual status, according to Dr. Sainsbury, professor of surgery at the University of Leeds (England). ■

Soy Isoflavones Did Not Cause Breast Proliferation in Postmenopausal Women

SAN ANTONIO — Consumption of soy isoflavones by postmenopausal breast cancer survivors doesn't appear to stimulate epithelial proliferative activity in the contralateral breast, according to a small pilot study.

This is an important and reassuring, albeit still preliminary, observation. The great majority of breast cancer patients are postmenopausal, either because of their age at diagnosis or as a consequence of their cancer therapy.

They are discouraged from using hormone therapy to manage their menopausal symptoms, which can be quite severe. Soy supplements, which are rich in phytoestrogens, are growing in popularity as a nonpharmacologic alternative, Melanie R. Palomares, M.D., noted at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Because preclinical work had shown conflicting stimulatory and inhibitory effects of soy isoflavones on breast tissue, Dr. Palomares and her coinvestigators launched the University of Washington/Seattle Cancer Care Alliance Phytoestrogen Trial.

Participants were randomized to 100 mg/day of isoflavone tablets or placebo. Ultrasound-guided core biopsies of the contralateral breast were taken with a 14-gauge needle at baseline and after 6 and 12 months of therapy, explained Dr. Palomares of City of Hope National Medical Center in Duarte, Calif.

She reported on the results seen for 23 postmenopausal disease-free women previously diagnosed with and treated for in situ or early-stage invasive breast cancer who have completed the year-long randomized trial.

The primary study end point was change in Ki-67 index, a widely used measure of epithelial proliferation. Ki-67 levels were elevated in both treatment and control groups at baseline, which was to be expected in light of the known elevated risk of contralateral breast cancer in women with a history of breast cancer.

The Ki-67 index dropped steadily throughout the 12 months of follow-up, indicative of a decline in breast epithelial proliferation. The decline was greater in soy isoflavone-treated women, although not significantly so.

Hyperplasia was present in the contralateral breast tissue samples of 10 patients at baseline and 5 patients after a year.

The treatment groups were too small to show significant differences in serial histology. Similarly, there was a trend toward decreased estrogen receptor expression over time in both the soy isoflavone- and placebo-treated groups, but no significant differences between the two study arms. ■