Adjuvant therapy with aromatase inhibitors following tamoxifen improves disease-free survival in women with early-stage, hormone-responsive breast cancer. A meta-analysis presented at the San Antonio Breast Cancer Symposium in December suggests that anastrozole (Arimidex) also improves overall survival in these patients. Moreover, new data show that adjuvant therapy with letrozole (Femara) improves disease-free survival and shows a trend toward improved overall survival even after a substantial gap between completion of tamoxifen and start of letrozole therapy. Interim results from several trials showed improved event-free survival and a trend for improved overall survival in women who switched to aromatase inhibitor therapy after 2–3 years on tamoxifen compared with those who took tamoxifen for 5 years. However, overall survival data are not statistically significant in individual trials. To determine whether the decrease in recurrence translates into improved overall survival, Walter Jonat, M.D., director of the Gynecology and Maternity Unit at the University of Kiel in Germany, and colleagues performed a meta-analysis of three European trials that tested the efficacy of anastrozole.

The trial designs were generally similar. Arimidex-Nolvadex (ARNO) 95 trial included 979 women who were randomly assigned after 2 years of tamoxifen to either 3 additional years of tamoxifen or 3 years of anastrozole. The Italian Tamoxifen Arimidex (ITA) trial included 448 women who were randomly assigned after 2–3 years on tamoxifen to either tamoxifen or anastrozole for 2–3 years. The Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial, 2579 women were randomly assigned immediately after their primary surgery to receive 5 years of tamoxifen therapy or 2 years of tamoxifen followed by 3 years of anastrozole. Only the women who were event free at the 2-year point were included in the meta-analysis.

With a median follow-up of 30 months for all patients in the meta-analysis, 92 (4.6%) of 2009 patients treated with anastrozole had disease recurrence, as did 159 (8.0%) of 1997 patients in the tamoxifen arm (a 41% relative decrease in risk of recurrence). There was also a 29% relative reduction in mortality with anastrozole (66 [3.3%] deaths in the anastrozole arm and 90 [4.5%] in the tamoxifen arm).

“We all know survival is the important endpoint. It is what patients want to get from us,” Jonat said. “These data confirm that postmenopausal women currently receiving tamoxifen should be switched to anastrozole.”

A major question, however, is who should take aromatase inhibitors and for how long. New data from MA.17, a large randomized trial run by the National Cancer Institute of Canada, partially answers that question. The trial, which was designed to test the efficacy of 5 years of letrozole following 5 years of tamoxifen therapy, was unblinded in October 2003 when a preplanned interim analysis with a median follow-up of 2.4 years showed a 4.6% absolute reduction in recurrence with letrozole therapy. (See article, Vol. 97, No. 17, p. 1262.) In a new analysis of recurrences that occurred prior to the unblinding, MA.17 researchers found that increasing time on letrozole was associated with an increasing benefit in terms of the risk of local and distant
recurrence. The analysis “confirmed that longer is better at least up to 48 months,” said James N. Ingle, M.D., professor of medical oncology at the Mayo Clinic in Rochester, Minn., who presented the data at the San Antonio meeting. “This [finding] is important because there is no information on the optimal duration of therapy.” The results suggest that research looking at the duration of therapy beyond 5 years is important because 5 years was chosen somewhat arbitrarily for this trial.

Although the early unblinding may have compromised the researchers’ ability to determine the overall survival benefit associated with extended letrozole therapy (see News, Vol. 95, No. 23, p. 1738, “Critics Question Price of Success in Halted Clinical Trial of Aromatase Inhibitor Letrozole”), it provided a unique opportunity to determine whether letrozole therapy was effective after a treatment hiatus. Of the 2594 women originally assigned to placebo, 2268 were event free when the trial was unblinded. Those women were all offered 5 years of letrozole therapy, and 1655 chose to take the drug and 613 declined. By comparing what has happened to those two groups of women, Paul E. Goss, M.D., Ph.D., professor of Medicine at Massachusetts General Hospital in Boston, and colleagues have been able to determine that letrozole therapy is effective even when a woman who has completed tamoxifen therapy one has been off any treatment for 1–5 years.

There were differences between the groups of women who opted to take letrozole and those who chose not to, Goss said during his presentation at the San Antonio meeting. Women who opted for therapy tended to be younger, tended to have more advanced disease at the time of diagnosis, were more likely to have had adjuvant chemotherapy, and had worse ECOG performance status relative to women who opted not to take letrozole. Yet, when the team analyzed the number of events in the two groups from the time of unblinding, they saw that the women on letrozole had statistically significantly better outcomes. They had lower rates of local recurrence, distant recurrence, and contralateral breast cancer than did the no-treatment group. Overall survival was better among women on letrozole—15 deaths (0.9%, with seven due to breast cancer) in the letrozole arm versus 11 deaths (1.8%, with seven due to breast cancer) in the placebo arm—but the results just reached statistical significance.

“So often when we stop studies and we worry that we are going to lose something,” said Eric P. Winer, M.D., director of the Breast Oncology Center and chief of Ambulatory Services at the Dana-Farber Cancer Institute in Boston. “What I found to be very positive was that from MA.17 they turned around a study that had been stopped early from which we might have learned very little, and we really learned something from after it stopped.”

The team plans to do further analysis to see if there was a drop in letrozole efficacy with increasing duration off of therapy, but Goss does not think so. “I think we are dealing with a biological metronome that is just ticking every year with a recurrence risk, and we come in with an effective tool and effectively close it down.”

Goss, Ingle, and Winer conclude that because patients with estrogen-responsive cancers have a chronic risk of relapse, they likely could benefit from this therapy at any time, even if they have been off therapy for several years.

—Rabiya S. Tuma

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