Letrozole Beats Tamoxifen in Breast Cancer Trial

A switch back to tamoxifen for the remainder of their 5 years would not compromise their outcome.

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — Updated results of the landmark Breast International Group 1-98 trial suggest that overall survival in breast cancer patients is superior with 5 years of adjuvant letrozole, compared with tamoxifen.

The 13% reduction in mortality risk in the letrozole (Femara) group at a mean follow-up of 76 months in a prespecified intent-to-treat analysis fell short of statistical significance ($P = .08$), but that's clearly because the letrozole arm included 25% of all patients initially randomized to tamoxifen. These patients crossed over and spent a median of 18 months on the aromatase inhibitor after the study's unblinding in 2005. The study was unblinded for ethical reasons because of the superior disease-free survival with letrozole, Dr. Henning Mouridsen said at the San Antonio Breast Cancer Symposium.

The BIG 1-98 update also showed that sequential adjuvant hormonal therapy—2 years of either letrozole or tamoxifen followed by 3 years of the other drug—is not more effective than 5 years of letrozole, added Dr. Mouridsen, study investigator and professor and head of oncology at Copenhagen University Hospital.

The BIG 1-98 trial involved 8,010 women with endocrine-responsive early breast cancer in 27 countries. A landmark previous finding was that 5 years of adjuvant letrozole monotherapy was superior to 5 years of tamoxifen in terms of disease-free survival and time to distant recurrence (N. Engl. J. Med. 2005; 353:2747-57).

The update addressed two key outstanding questions. The first, whether aromatase inhibitor monotherapy is superior to tamoxifen monotherapy in terms of overall survival, was something that had yet to be shown to a level of statistical significance in any of the major randomized trials. The second was whether sequential therapy—the so-called switching strategy—offers advantages over aromatase inhibitor monotherapy, as some had theorized.

The overall survival analysis involved 4,922 BIG 1-98 participants. There were 303 deaths in the letrozole arm and 343 in the tamoxifen arm.

"Since we're almost at the conventional level of significance in the compromised intention-to-treat analysis, I take that as fairly strong evidence that in fact letrozole improves on overall survival," observed Dr. Alan Coates, cochair of the scientific committee of the International Breast Cancer Study Group, which coordinated BIG 1-98.

The sequential therapy analysis involved 6,182 patients at a median follow-up of 71 months. Neither 2 years of tamoxifen followed by 3 years of letrozole nor 2 years of letrozole followed by 3 years of tamoxifen proved superior to 5 years of letrozole.

Moreover, among the 42% of participants at increased risk of recurrence as reflected in their node-positive status, there was a strong trend for worse outcomes in the group randomized to sequential tamoxifen followed by letrozole. Their rate of breast cancer recurrence was 7.9% at 2 years and 14.7% at 5 years, compared with 4.7% and 12.4%, respectively, in node-positive patients assigned to 5 years of letrozole.

"Cancer recurrence is more common while patients are on early tamoxifen and that leeway is never made up after the switch. The curves remain parallel. Many people will take the message that it's better to start with letrozole, particularly for patients at high risk," added Dr. Coates of the University of Sydney.

Among patients assigned to the reverse sequence—letrozole followed by tamoxifen—the rates of disease-free and overall survival and time to distant recurrence were closely similar to those seen in the letrozole monotherapy arm.

'I take that as fairly strong evidence that in fact letrozole improves on overall survival.'

DR. COATES

"I think that's a very important message for patient care. Some women find these aromatase inhibitors really hard to take, not only because of menopausal symptoms but also arthralgia and myalgia. If they were worried about doing themselves a disservice by switching after a couple of years of putting up with this or they can't afford the greater dollar cost, I think the data are reassuring that such a switch back to tamoxifen for the remainder of their 5 years would not compromise their outcome in any way," the oncologist explained.

Asked whether he thought the routine preferential use of aromatase inhibitors over tamoxifen was justified in light of their far greater cost, substantial side effects, and modest clinical advantages, Dr. Coates replied that it's a decision belonging to the fully informed patient. And multiple surveys conducted in the United States and United Kingdom have shown that for many women with breast cancer, even very small differences in outcome are felt to justify unpleasant forms of therapy.

Dr. Virginia Kaklamani of Northwestern University, Chicago, who wasn't involved in BIG 1-98, put the results of this and the other major aromatase inhibitor/tamoxifen randomized trials in perspective.

"The studies show that the aromatase inhibitors are a little bit better than tamoxifen. But you're talking about more than 10,000 women in these trials, and we're still very hard-pressed to find a survival advantage for the aromatase inhibitors. So we are talking about a great drug in tamoxifen that's been available for the last 30 years. Still, it would seem that for whoever can go on the aromatase inhibitor, that would probably be the best option," she said.

Dr. Peter Ravdin, who also was not involved in BIG 1-98, commented that the new results have "dulled the enthusiasm" for sequential therapy. A key remaining question about adjuvant hormonal therapy is whether it's worthwhile to extend it beyond the now-standard 5 years to reduce late recurrences. That issue should be settled by ongoing trials in a few more years, added Dr. Ravdin of M.D. Anderson Cancer Center, Houston.

Dr. Mouridsen disclosed that he has received lecture fees from and is on the advisory board for Novartis, which financed BIG 1-98. ■

Gail Model Inaccurate in Women With Atypical Hyperplasia

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — The widely used Gail model proved no better than a coin toss in predicting breast cancer risk in individual women with atypical hyperplasia on a benign breast biopsy, a case-control study has shown.

'The Gail model couldn't separate who was going to go on to breast cancer.'

DR. HARTMANN

"The Gail model couldn't separate who was going to go on to breast cancer. We found that the accuracy of the model for individual women with atypia was essentially a flip of the coin, with a concordance statistic of 0.50 for predicted versus observed outcomes," Dr. Lynn C. Hartmann reported at the San Antonio Breast Cancer Symposium.

The findings of this case-control study underscore the need for physicians to exercise great caution when using the Gail model to counsel individual women with atypia. The Gail model was designed to assess risk in populations of women, yet it's increasingly being applied in an effort to identify the risk in individuals. And as this study shows, when those women already have atypia on a benign breast biopsy, the Gail model greatly underestimates their breast cancer risk, according to Dr. Hartmann, a professor of oncology at the Mayo Clinic, Rochester, Minn.

Among 9,376 women prospectively followed in the ongoing Mayo Benign Breast Disease Cohort, 3.5% had atypia. During a mean 13.7 years of follow-up after biopsy, 58 of these 331 women (17.5%) were diagnosed with invasive breast cancer. Yet application of the Gail model predicted there would be only 34.9 breast cancers during the same period. In other words, 66% more breast cancers occurred in women with atypia than predicted by the Gail model.

"I think the take-home message here is if you have access to the tissue and you see the phenotype of atypia, the tissue has already integrated the risks featured in the Gail model, both the endogenous risks like family history and the exogenous exposures. Adding them back in is not going to help you further," the oncologist said.

Dr. Hartmann said the Gail model and most other risk models work best in the setting of hereditary breast cancer. Better screening tools are needed for the broad population of 150 million American women over age 40 who should be getting screened for breast cancer; physicians would then be able to identify within that vast pool of healthy women the 1-2 million who are truly at high risk.

Dr. Hartmann and her Mayo colleagues are developing a tissue-based risk stratification system applicable to the 1 million women per year who undergo breast biopsy showing benign disease.

"If you look at where we do best in predicting cancer risk, it's where we can actually examine the tissue at risk: cervix, colon, esophagus, bladder. We're trying to apply this principle to breast cancer," Dr. Hartmann explained.

Atypia and other standard histologic findings are incorporated in the evolving Mayo model because they have demonstrated utility in stratifying level of risk. Molecular markers are also of value in this regard, she said. And recent studies conducted in the Mayo Benign Breast Disease Cohort have identified a novel indicator of breast cancer risk: the extent of lobular involution in a biopsy specimen.

The Mayo Clinic's prospective studies of benign breast disease are funded by the Department of Defense. ■