

Tamoxifen vs the Aromatase Inhibitors: News From San Antonio, 2001

Perhaps the key data presented at the 26th Annual San Antonio Breast Cancer Symposium in December 2001 related to the initial outcomes of the ATAC adjuvant trial, since it forces thousands of oncologists and patients to make decisions about whether or not to change a time-honored, comfortable, reliable, reassuring, relatively safe, and effective option for the adjuvant therapy of breast cancer — tamoxifen.

Adjuvant Therapy

The ATAC trial (Arimidex, Tamoxifen, Alone or in Combination) evaluated two new approaches for adjuvant therapy in postmenopausal women: the aromatase-inhibitor anastrozole (Arimidex) and a combination of anastrozole plus tamoxifen and compared outcomes to treatment with tamoxifen alone. This well-balanced, double-blind study included 9,366 patients from 21 countries. Approximately two thirds of the patients had small, node-negative tumors. The first analysis was presented after a median follow-up of 34 months.

The preliminary results showed that 5 years of adjuvant therapy with anastrozole was associated with approximately a 17% better disease-free survival compared with

either tamoxifen alone or the combination approach. These effects included both loco-regional recurrence and distant failure.

Anastrozole also significantly decreased the incidence of new contralateral breast cancer (relative risk reduction 58%) when compared to tamoxifen or the combination. Anastrozole was generally well tolerated with a significantly lower frequency of hot flashes, weight gain, vaginal bleeding and discharge, as well as fewer cerebrovascular and venous thromboembolic and endometrial cancer events. However, there was an excess of musculoskeletal disorders and bone fractures in the anastrozole group.

While this trial has not yet reached maturity and has not been scrutinized by peer review, the data are nonetheless intriguing. However, several factors should be considered. The new data pertain only to postmenopausal women. An aromatase inhibitor should not be offered to premenopausal patients. Currently, there is no evidence that aromatase inhibitors are safe and/or beneficial for premenopausal women with breast cancer. Effects on metabolism and cognitive function may be adversely affected. Taking into account that the data are immature, it might be reasonable to consider anastrozole for those post-

menopausal patients who are at risk for tamoxifen-related complications such as vascular events or endometrial cancer, especially if they do not have undue concerns about osteopenia. Patients who are currently being treated with tamoxifen should not generally have the treatment changed to anastrozole. The ATAC trial did not address the benefits or the timing of a sequential exposure to tamoxifen and an aromatase inhibitor. This question is currently being studied. Clinicians should use their judgment when considering an alternative in cases where tamoxifen negatively affects a patient's quality of life or safety.

While the toxicity profile of hormonal therapy favors the aromatase inhibitor, the increased risk of fractures in this population of postmenopausal women is of concern. Many women in this age group require prevention or treatment for osteoporosis. When choosing a modality to prevent or treat osteoporosis, the clinician should keep in mind that in the ATAC trial the benefits in disease-free survival were eliminated when anastrozole was combined with tamoxifen. A combination of raloxifene with an aromatase inhibitor also may not be beneficial.

Clinical research groups and investigational review boards will

have to address how to approach these issues for the large volume of patients who are entered on clinical trials that include adjuvant tamoxifen treatment.

Advanced/Metastatic Breast Cancer

An additional important presentation was the update on the randomized, double-blind study evaluating first-line therapy for metastatic breast cancer. This trial comparing letrozole (Femara) with tamoxifen included 907 patients and was initially reported in May 2001. The data demonstrated that letrozole was superior to tamoxifen with regards to time to progression and objective response rate. However, at that time of publication, the study had not sufficiently matured to comment on survival. This later assessment of the trial (33 months of follow-up) was presented in San Antonio. While letrozole remained superior to tamoxifen in time to progression, response rate, and toxicity profile, the overall survival did not differ significantly, regardless of whether letrozole or tamoxifen was given first (34 vs 30 months, respectively). The data were further analyzed for survival at earlier timepoints, which suggested a superiority of letrozole only during the first 2 years.

While the data presented suggest that an aromatase inhibitor may be the drug of choice for first-line therapy, it also endorses the continuation of tamoxifen in patients who are currently taking

tamoxifen. These patients appear to benefit from letrozole upon progression on tamoxifen. Furthermore, for the next few years, the majority of the patient with hormone-receptor positive tumors will have been exposed to adjuvant tamoxifen. Therefore, an aromatase inhibitor as first-line endocrine therapy in postmenopausal patients is the most likely choice, and the question will be which aromatase inhibitor to use — an answer that cannot be found yet.

Ductal Carcinoma In Situ (DCIS) and Breast Cancer Prevention

There is currently no indication to change the hormonal approach for the prevention of breast cancer or the treatment of DCIS. These questions are currently being addressed, but may take some years to be answered. It is tempting to extrapolate a potential superiority of aromatase inhibitors over tamoxifen from the findings in the metastatic and adjuvant setting. Nonetheless, their empirical use contradicts the principles of evidence-based medicine and may obstruct future trials addressing this question. It would be a pity to find out that we prevented breast cancer in a few women but lessened the cognitive function in many.

Conclusions

While the data on the aromatase inhibitors in the adjuvant setting are certainly promising, it is

prudent to await maturation of this trial before globally changing a management practice that has been established for over 2 decades.

Pamela N. Munster, MD
John Horton, MB, ChB

Comprehensive Breast Cancer Program
H. Lee Moffitt Cancer Center &
Research Institute
Tampa, Florida