Aromatase Inhibitors for the Treatment of Breast Cancer: Is Tamoxifen of Historical Interest Only?

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Breast cancer is the second most common cause of death from malignancy in American women (1). Although it is almost uniformly fatal, metastatic breast cancer is very treatable, and many patients will live for long periods of time with good quality of life (2). In this regard, nearly 100,000 patients are living with metastatic breast cancer in the United States (3).

There is reason to be optimistic that the life expectancy of patients with metastatic breast cancer will be extended further as novel therapies targeting growth pathways, cell signaling, and tumor microenvironment are developed. Among these therapies, the oldest and most effective are those that target the estrogen receptor pathway. Although the importance of endocrine control of breast cancer was recognized by Beatson 110 years ago (4), the field is still exploring means of optimizing endocrine therapy. Over the last 35 years, the selective estrogen receptor modulator tamoxifen has become the standard of care for patients with hormone receptor-positive breast cancer in most of the western world (5). However, several recent studies have suggested that estrogen depletion may be a slightly more effective endocrine strategy against hormone-dependent breast cancer. In postmenopausal patients, estrogen depletion is best accomplished by specific inhibition of aromatase, which converts estrogen precursors, dihydroepiandrostenedione and testosterone, respectively, to estradiol and estrone. These aromatase inhibitors were developed after the recognition that aminoglutethimide, which nonspecifically inhibits a number of critical enzymes in steroidogenesis, including the aromatase cytochrome P450 CYP19, was effective in controlling breast cancer. Subsequent translational studies have demonstrated that agents that more specifically target aromatase are equally or more effective than aminoglutethimide, yet safer (6). Aromatase inhibitors are now widely used in treating breast cancer in both the metastatic and adjuvant setting, and ongoing studies are investigating the use of the aromatase inhibitors to prevent breast cancer (7).

In this issue of the Journal, Mauri et al. (8) report a meta-analysis of published randomized controlled trials comparing aromatase inhibitors and standard endocrine therapy in patients with metastatic breast cancer. Overall, they conclude that either first- or second-line aromatase inhibitor therapy results in a moderate, but statistically significant, proportional prolongation of overall survival of approximately 10%. When compared with nonaromatase inhibitor treatments for hormone receptor-positive metastatic breast cancer, this effect predicts an increased survival of approximately 5 months among patients with an expected median survival of 40 months.

As in all good studies, these results raise several questions. First, does this study represent a reliable analysis of the situation? There are several approaches to conduct of meta-analytical studies. In this regard, Mauri et al. gathered the accumulated data for this study from published literature. Although this approach is satisfactory, the preferred strategy for meta-analysis requires access to individual patient data for all studies (9). Thus, the analysis of Mauri et al. is limited by the potential for publication bias associated with use of published-only studies and by variation in clinical trial eligibility criteria. Nonetheless, taking these limitations into account, we believe that this study was well executed and that the results are acceptable. The statistical power of this meta-analysis is high because of the large amount of compiled data, and the results support what is already a strong bias in the clinical community that aromatase inhibitors are slightly more effective than selective estrogen receptor modulators or progestational agents.

Indeed, it is our opinion that the positive effect of aromatase inhibitors in treating metastatic breast cancer is probably underestimated by this meta-analysis, given the limitations of examining only published literature and the inclusion of studies examining the older, less-effective therapy, i.e., aminoglutethimide. In fact, this study demonstrates an even larger survival advantage if the studies of aminoglutethimide are excluded, so that only the effects of third-generation agents that specifically inhibit aromatase are analyzed (relative hazard = 0.87, 95% confidence interval = 0.82 to 0.93; P < .001). We believe that this is a more appropriate analysis because these are the agents that are now in clinical use.

We propose that other biases inherent in this type of study further lead to underestimation of the beneficial effects of aromatase inhibitors in the metastatic setting. It is likely that, in several of these studies, aromatase inhibition was permitted for those patients randomly assigned to tamoxifen or progestational treatment first. This so-called crossover effect would, of course, dilute the benefit for those patients randomly assigned to aromatase inhibitor therapy initially. Therefore, we suspect that overall survival would be even greater for those patients who would be randomly assigned to aromatase inhibitor treatment in more purely conducted but ethically difficult trials preventing such crossover.

We believe that this study further underestimates the clinical value of aromatase inhibitor therapy because of the chosen endpoint: prolongation of overall survival. By nature of the design of

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the published trials that were included in the meta-analysis, this study cannot address other clinically important endpoints in treatment of metastatic breast cancer: quality of life and cost-effectiveness (10). In many of the studies, surrogate measures of quality of life, such as comparisons of side effects, suggest that the aromatase inhibitors have fewer side effects than older second-line endocrine treatments, such as the progestational agents (6). Furthermore, the aromatase inhibitors appear to be cost-effective when compared with tamoxifen for first-line hormonal therapy in advanced breast cancer in health systems in the United States, the United Kingdom, and Canada (11).

Does this paper change clinical practice? We think probably not. Indeed, the conclusions of Mauri et al. are welcome confirmation of common clinical practice in the United States. Surveys of patterns of care of American medical oncologists indicate that 90%–96% of clinicians would treat a postmenopausal woman with an aromatase inhibitor as first-line therapy when selecting a hormonal treatment at progression of disease on adjuvant tamoxifen (12).

So, do the above considerations suggest that all postmenopausal patients with hormone receptor–positive metastatic breast cancer should receive an aromatase inhibitor preferentially instead of other endocrine treatments? Has tamoxifen become anachronistic, to be placed on the shelf with diode-tube television sets and rotary-dial phones? We think not. Practice patterns surveys indicated that, in 2005, as many as 50% of postmenopausal patients with hormone receptor–positive breast cancer received aromatase inhibitor therapy in the adjuvant setting (13). However, optimal adjuvant treatment for such patients has not yet been established. Even though a recent statement by the American Society of Clinical Oncology has recommended that all patients with estrogen receptor–positive breast cancer should receive an aromatase inhibitor at some point in their adjuvant therapeutic course, the committee did not recommend when or whether an aromatase inhibitor should be administered in sequence with tamoxifen (14). For those who do develop metastases, there are little data to guide subsequent endocrine treatment. Tamoxifen or fulvestrant, which disrupts estrogen receptor signaling, are presumably reasonable choices.

In either setting, we believe that the therapeutic risk benefit ratio for the aromatase inhibitors versus tamoxifen will be influenced by our growing knowledge of tumor biology and pharmacogenomics. Emerging data suggest that tumor-associated predictive biomarkers may aid the clinician’s choice of endocrine therapy. For example, tumor progesterone receptor status and HER-2 status might indicate a better response to an aromatase inhibitor than to tamoxifen in the adjuvant setting (15), although these findings have not been confirmed in all studies (16). Although gene expression profiling of breast tumors has suggested that two subtypes of hormone receptor–positive disease may exist (luminal A and B) (17), and a multiplex reverse transcription–polymerase chain reaction assay appears to be associated with outcome for patients treated with adjuvant tamoxifen (18), it is unclear how results of these types of assays may be used to assess potential response to a particular hormonal therapy, but we believe that the progress in identifying prognostic and predictive factors through tissue analysis should be able to guide decisions on therapy in the future. We await similar analysis of studies comparing multigene expressions for patients treated with endocrine therapies.

Perhaps more intriguing, the field of inherited genetic polymorphisms that affect drug response and toxicity, designated pharmacogenomics, offers promise of further individualization of treatment. Preliminary studies suggest that women who are slow metabolizers of tamoxifen to its active metabolite, endoxifen, may have a worse outcome in the adjuvant setting than those who are fast metabolizers of tamoxifen, suggesting that these patients might be better treated with an aromatase inhibitor (19–21). Recently opened clinical trials are similarly addressing the inherited genetic differences that may influence metabolism or response to the newer aromatase inhibitors. Such studies may permit patient-specific selection of therapy (e.g., aromatase inhibitor, selective estrogen receptor modulator, or fulvestrant) that based on both efficacy and toxicity.

In conclusion, aromatase inhibitors appear to be the present drug of choice for endocrine-responsive metastatic breast cancer, if the tumor has not previously become resistant to this therapy. Patients with hormone receptor–positive metastatic breast cancer are often candidates for serial hormonal manipulations. Will the use of an aromatase inhibitor be the first choice in all situations? It is unlikely that we can be that dogmatic. One hundred and ten years after Beatson’s extraordinary observation, we continue to optimize our approach to endocrine therapy. Depletion of estrogen in postmenopausal patients by inhibition of aromatase is clearly a step forward, but there is much to be done and much to be learned.

References


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