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Letrozole in Postmenopausal Hormone-Responsive Early-Stage Breast Cancer

A Viewpoint by Gerald M. Higa

School of Pharmacy, Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, West Virginia, USA

In recent months several groups have reported marked improvement in relapse-free survival when targeted therapy was added to chemotherapy in patients with human epidermal growth factor receptor 2 [HER-2]-positive, early-stage breast cancer. In spite of the significance of these findings, a discovery of even greater importance was the identification of the estrogen receptor (ER) and its relevance in breast cancer. Indeed, the application of hormonal therapy, and tamoxifen in particular, for patients with ER-positive tumours was one of the most important breakthroughs in oncology in the past 50 years. Although equally effective as all other endocrine strategies, tamoxifen has been long established as the endocrine therapy of choice in post-menopausal women with advanced or early hormone-dependent breast cancer. While the tolerability profile of tamoxifen was the primary basis for this distinction, it has, paradoxically, also stimulated a resurgence of interest aimed at antagonising estrogenic activity with less toxicity. A primary target is the enzyme aromatase, which catalyses the conversion of androgens to estrogens. Strategically positioned in the estrogen biosynthetic pathway, inhibition of aromatase can be selective and relatively specific.

In less than a decade, the antiaromatase agents have apparently displaced antiestrogen agents as first-line therapy for postmenopausal women with advanced and, more recently, early disease. While the data on letrozole reported in this journal support this belief, a number of unanswered questions remain. First, if estrogen deprivation is the operative mode of all endocrine therapies, what other plausible mechanism(s) of aromatase inhibition explains the improved disease-free survival (DFS)? Second, notwithstanding the importance of the DFS endpoint, patient well-being must be considered equally important. Although vaginal bleeding, hot flushes and night sweats are significantly lower with letrozole compared with tamoxifen, this favourable profile is at least partially offset by more frequent occurrences of arthralgia and bone fractures. Third, since very few patients, if any, have completed the arbitrarily determined 5-year treatment period, some small, heretofore statistically insignificant, differences could be magnified by the thousands of women who will be prescribed these agents.

The BIG (Breast International Group) 1-98 and MA-17 studies do demonstrate that DFS is significantly improved in letrozole-treated patients; the agent is also relatively well tolerated. While the issue of aromatase inhibitor or antiestrogen therapy is less contentious today, the data presented in the profile should not imply that letrozole is superior to tamoxifen. Tamoxifen became the treatment of choice primarily because of the recognised benefits in women with hormone-dependent breast cancer, regardless of menopausal status and risk or stage of the disease. Despite all the clinical data, letrozole still cannot make such a claim. ▲