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Letrozole in Postmenopausal Hormone-Responsive Early-Stage Breast Cancer

A Viewpoint by Laura B. Michaud

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While the benefits of the antiaromatase agents (letrozole, anastrozole and exemestane) have been known for nearly a decade in the setting of metastatic breast cancer, data in patients with early-stage breast cancer are only now coming to light and appear to indicate an advantage over the previous gold-standard adjuvant endocrine therapy, tamoxifen. Not only are these agents apparently more effective, they also appear to circumvent some of the serious adverse events associated with tamoxifen therapy (e.g. endometrial cancer and venous thromboembolism). However, secondary to the extreme estrogen deprivation experienced with antiaromatase therapy, these agents are associated with an increased incidence of osteoporosis and possibly cardiovascular complications. Other long-term consequences are relatively unknown and will only be determined through continued monitoring of all participants in the adjuvant trials.

In addition to the data with letrozole, anastrozole and exemestane have data indicating similar advantages. Currently, no clinical trials have directly compared the antiaromatase agents with each other in the adjuvant setting. While there may be differences in the incidence of cardiovascular events in individual trials, it is difficult to draw conclusions from indirect comparisons due to differences in patient populations and lack of detailed information regarding underlying risk factors for cardiovascular disease.

In clinical practice, menopausal status is often difficult to determine. For many women, menses cease during adjuvant chemotherapy and may or may not return for several months. Serum follicle-stimulating hormone, luteinising hormone and estradiol levels have become important tools in determining menopausal status in this setting. While these serum tests are fairly reliable, some women may still have their menses return after initiation of an antiaromatase agent. The antiaromatase agent should be discontinued if menses return. Data with the antiaromatase agents in premenopausal women (with functional ovaries) are sparse, but appear to indicate an induction in ovulation secondary to the loss of negative feedback on the pituitary gland. While the clinical consequences of this effect on breast cancer have not been examined, lack of estrogen deprivation is likely and potential benefits would be lost.

Many questions regarding the adjuvant use of antiaromatase agents remain. What is the optimal duration of an adjuvant antiaromatase agent? Is there an advantage to upfront antiaromatase agent over sequential therapy after initial tamoxifen? What is the long-term safety of these agents utilised in this setting? These questions among many others will hopefully be answered through continued research efforts. ▲