Endocrine therapy has long been a mainstay in the therapy of metastatic breast cancer and in the adjuvant setting. The introduction of anastrozole (Arimidex) to the market in 1996 has provided another option for such treatment. Drs. Goss and Tye provide a thorough review of anastrozole and outline its advantages over other aromatase inhibitors as adjuvant therapy for breast cancer and its potential use in the treatment of early breast cancer. The authors delineate many important issues regarding the use of anastrozole; an understanding of these issues is imperative for the optimal utilization of this therapy. The paper has two shortcomings: (1) It focuses almost solely on aromatase inhibitors, to the neglect of other endocrine therapies. (2) Many references are unconventional and represent data on file with various drug manufacturers, which are not easily accessible to readers.

Other Endocrine Therapies
Currently available endocrine therapies for the treatment of breast cancer include the antiestrogens, progestins, aromatase inhibitors and luteinizing hormone-releasing hormone (LHRH) agonists. Androgens and high-dose estrogens are also part of the armamentarium used to fight breast cancer; however, these agents have undesirable side effect profiles compared to the other agents and are not as widely utilized.

Anastrozole is not the first aromatase inhibitor to be used in this patient population. Aminoglutethimide, while an effective aromatase inhibitor, is unselective in its enzyme inhibition, poorly tolerated, and must be administered with corticosteroid supplementations. Testolactone (Teslac) is an androgen that acts as an aromatase inhibitor. It is commercially available in the United States but is not commonly used due to its undesirable side effects. A third product formestane, has been available in Europe for some time. Anastrozole is thought to be better tolerated secondary to formestane[1]'s administration requirements (intramuscular injection); however, these agents have never been directly compared.

In patients with metastatic breast cancer, available endocrine therapies have similar response rates and are therefore chosen based on side effect profile. Historically, the front-line agent has been tamoxifen (Nolvadex). With the introduction of anastrozole, this designation may be challenged in the future through appropriately designed studies. Ongoing trials comparing tamoxifen and anastrozole would better delineate the differences in efficacy and tolerability between these agents, and trials may show that combination therapy with tamoxifen and anastrozole is more effective than either agent singly.

Results of Anastrozole Therapy to Date
Anastrozole is indicated as second-line therapy for patients with metastatic breast cancer who progress while on adjuvant tamoxifen. Patients whose disease responds to first-line endocrine therapy have a higher likelihood of responding to a second hormonal therapy; however, the proportion of responses decreases and responses are shorter in duration with each additional therapy.[1] Generally, agents with a differing mechanism of action are chosen next in the hope of avoiding cross-resistance.

The trial data on anastrozole are limited to relatively early therapy of metastatic breast cancer; however, everyday clinical practice also utilizes endocrine therapies much later in the disease...
process, primarily for palliation of symptoms, with the potential benefit of disease control or stabilization. Many patients with bone metastases have indolent disease that is responsive to hormonal therapy. These patients often live a long time with stable disease and achieve control of symptoms through the use of endocrine therapies.

At The M.D. Anderson Cancer Center, we performed a retrospective review of the first 117 consecutive patients who received anastrozole for metastatic breast cancer. Response to therapy was defined as improvement, stabilization of disease (≥ 8 weeks), or progression of disease. Patients with three or more prior endocrine therapies and two or more prior chemotherapies had a substantial response to therapy (60% and 55%, respectively). A group of 10 patients who had estrogen-receptor (ER)-negative tumors were also treated with this drug, and it is interesting that half of them achieved stabilization of disease. The activity seen in ER-negative tumors may be due, in part, to the aromatase enzyme present in approximately two-thirds of all breast cancer cells, but further investigation is warranted in this area. The role of this drug in ER-negative patients and patients who have had prior endocrine therapies needs to be evaluated in prospective studies.

Cross-Resistance

The issue of cross-resistance between the different aromatase inhibitors is not discussed in this review. While there are few data available to date, this is an interesting concept to investigate. In the retrospective review mentioned previously, 26 patients had received aminogluthethimide prior to the introduction of anastrozole. While the analysis of these patients is ongoing, anecdotal information regarding their response is promising. While these data are retrospective and lack strict scientific analysis, they do provide some evidence of a lack of cross-resistance between anastrozole and aminogluthethimide. This is not surprising, considering the difference in selectivity and potency of the two agents. More data are needed regarding this issue before any conclusions can be made; however, a trial of anastrozole may be warranted even in light of aminogluthethimide resistance. While male breast cancer is rare, most of these tumors are hormonally responsive, and there are limited data that these tumors respond to all endocrine therapies for breast cancer; however, there are no data regarding the efficacy of anastrozole in this setting.

A Major Concern

The use of anastrozole in premenopausal patients is of great concern. As mentioned in the article, surges in gonadotropins are seen with anastrozole administration in premenopausal women and subsequent increases in serum estradiol may be detrimental to breast cancer patients. However, combining anastrozole with LHRH agonists, causing medical castration, may be advantageous. This combination would result in a complete estrogen ablation, blocking both the hypothalamic/pituitary axis and the peripheral conversion as sources of estrogen. Studies investigating this concept are currently ongoing.

Conclusions

Anastrozole is only one of several new aromatase inhibitors. Other compounds that have recently been approved or in clinical trials are letrozole (Femara) and vorozole. With these additional options available for therapy of metastatic breast cancer, choosing therapy is challenging and requires an intimate knowledge of the safety and efficacy profile of each agent. Comparative information regarding tolerability and efficacy of these agents is crucial to the decision-making process. Aromatase inhibitors are a new and valuable asset in the treatment of breast cancer and discovering their full potential has yet to be accomplished.

References:


