Drugs 1999 Oct; 58 (4): 681-682
0012-6667/99/0010-0681/$02.00/0


# Exemestane

## A Viewpoint by W.R. Miller

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The strategy of using drugs to inhibit estrogen biosynthesis in the treatment of hormone-sensitive breast cancer is attractive, particularly in postmenopausal women in whom sites of aromatase activity (the key enzyme step) are peripheral. These agents fall into 2 classes: Type I inhibitors (such as formestane, atamestane and exemestane) compete with the substrate, are steroidal and inhibit the enzyme irreversibly; Type II inhibitors interfere with the cytochrome p450 prosthetic group of aromatase, are nonsteroidal and inhibit the enzyme reversibly.

Although early Type II inhibitors lacked specificity, newer agents such as anastrozole, letrozole and vorozole are highly potent and selective. They have been shown to reduce circulating estrogens to virtually undetectable levels in postmenopausal women. In addition, in large clinical trials in patients with advanced breast cancer, this endocrine regulation has translated into antitumour effects.

These powerful effects of Type II inhibitors raise the question as to the role of a Type I drug, such as exemestane, that is less potent than the most effective Type II inhibitor and is steroidal and therefore may have hormonal adverse effects. However, of all the Type I inhibitors, exemestane probably has the most favourable profile since it is at least as potent as other Type I inhibitors, may be administered orally (unlike formestane) and is well tolerated with few or no androgenic adverse effects. Further, and most importantly, exemestane in common with other Type I inhibitors has an irreversible mechanism of action and an apparent lack of cross-resistance with Type II inhibitors. Thus, exemestane has shown clinical efficacy in patients who had relapsed on Type II inhibitors.

Paradoxically, letrozole and anastrozole treatment may enhance aromatase activity as a consequence of either induction of aromatase messenger RNA or enzyme stabilisation. Prolonged therapy with Type II inhibitors could therefore potentially increase aromatase activity, which in turn may result in breakthrough estrogen biosynthesis. In this scenario, substitution of a Type I inhibitor, such as exemestane, may theoretically produce further beneficial antitumour effects. This, plus the promising results from clinical trials in postmenopausal women, suggest that exemestane may play a role in the treatment of hormone-sensitive breast cancer. ▲