

AROMATASE INHIBITORS FOR BREAST CANCER

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1 INTRODUCTION

The continued evolution of endocrine therapy has contributed to many therapeutic options for patients with breast cancer. In 1998, Oxford overview demonstrated that the selective estrogen receptor modulator (SERM) tamoxifen (TM) was equally effective in pre- and postmenopausal breast cancer patients. Development of aromatase inhibitors (AIs) added a new option in addition to SERMs for the treatment of breast cancer.

The landmark study of anastrozole (Arimidex), tamoxifen alone, or TM in a combination (ATAC) trial by Michael Baum presented at the San Antonio Breast Cancer Symposium in 2001 marked a turning point in breast cancer therapy. In the ATAC trial anastrozole had a better disease-free survival rate compared to TM when used in postmenopausal patients. Since the publication of the ATAC trial [1], several other trials have looked at the role of aromatase inhibitors such as letrozole [Breast International Group (BIG 98)] and exemestane [Intergroup Exemestane Study (IES)] in adjuvant therapy for postmenopausal breast cancer patients. All these studies have confirmed that AIs are superior to tamoxifen and have fewer side effects.

2 BIOCHEMISTRY

The two main circulating estrogens in the body are estrone and estradiol, derived from cholesterol. By inhibiting the enzymes, which act on earlier steps in the

branching pathway of steroidogenesis, it is possible to have consequences of undesirable impact on the production of other physiologically necessary and important hormones such as aldosterone and cortisol. The conversion of androgens to estrogens occurs at peripheral sites such as in muscle, fat, liver, and also in breast tumor cells. Aromatase is a cytochrome P450 enzyme that has both a steroid-binding and iron-containing site.

Androstenedione is the substrate for aromatase and it is linked to the enzyme's steroid-binding site. Based on this structural relationship, there are two reasonable and effective ways to inhibit aromatase, either by occupying the steroid-binding site of the enzyme with a compound or by binding the iron with nitrogen-containing compounds such as aminoglutethimide. Since aromatase catalyzes the last step in estrogen production, it makes an ideal target for the development of selective and potent inhibitors.

The comparative efficacy of AIs may be assessed in two ways. The conversion measurement of androgens into estrogens provides direct evidence of enzymatic activity. On the other hand, measurement of suppression of plasma estrogens provides indirect evidence of enzymatic aromatase activity. Drug metabolism (half-life) and tissue distribution are the two main factors for in vivo measurements of the biochemical efficacy of a compound. Intergeneration and intrageneration significant differences have been reported in the time to reach steady-state plasma levels, half-life, elimination, and in the interaction with several cytochromes (CYP) of the P450 superfamily. Aromatase inhibition and estradiol