Aromatase inhibitor development for treatment of breast cancer

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Summary

Inhibition of estrogen production provides effective therapy for patients with hormone-dependent breast cancer. The source of estrogens in premenopausal women is predominantly the ovary, but after the menopause, estradiol is synthesized in peripheral tissues through the aromatization of androgens to estrogens. Uptake from plasma is the primary mechanism for maintenance of estradiol concentrations in breast cancer tissue in premenopausal women, whereas several steps may be operant in postmenopausal women. These include enzymatic synthesis of estradiol via sulfatase, aromatase, and 17β-hydroxysteroid dehydrogenase in the tumor itself. Aromatization of androgens secreted by the adrenal to estrogens in peripheral tissues and transport to the tumor via circulation in the plasma provides another means of maintaining breast tumor estradiol levels in postmenopausal women. These various sources contribute to the high tissue estrogen levels measured in breast tumor tissue.

To effectively suppress tissue concentrations of estrogens and circulating estradiol in postmenopausal patients, various aromatase inhibitors have been developed recently. These include steroidal inhibitors such as 4-hydroxy-androstenedione as well as non-steroidal compounds with imidazole and triazole structures. The most potent of these, CGS 20267, is reported to suppress levels of active estrogens (i.e., estrone, estrone sulfatase, and estradiol) by more than 95%. This compound can suppress both serum and 24-hr urine estrogens to a greater extent than produced by the second generation inhibitor, CGS 16949A. CGS 20267 is highly specific since it does not affect cortisol and aldosterone serum levels during ACTH stimulation tests nor sodium and potassium balance in 24-hr urine samples. These data suggest that CGS 20267 can be expected to bring improved response rates in the treatment of metastatic hormone-dependent breast cancer without substantial side effects.

Introduction

A subpopulation of human breast cancers are dependent upon estradiol for cellular proliferation. Studies to elucidate the mechanism of estradiol stimulated growth have been ongoing for two

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decades. Several hormonally related strategies have been developed for treatment of human breast cancer which are based upon the principle that estrogens are mitogenic for these tumor cells. Initial methods involved surgical ablative therapies such as oophorectomy, adrenalectomy, and hypophysectomy. These procedures eliminate ovarian estrogen synthesis, adrenal steroid synthesis, and the stimulatory effects of the gonadotropins on estrogen production in the ovaries, respectively. The rates of response to these therapies range from 30-40% [1].

Adrenalectomy and hypophysectomy, because they involve major surgery, are infrequently employed currently, whereas oophorectomy continues to be selected. Pharmacologic methods to alter the hormonal milieu eliminate the need for major surgery and have generally replaced surgical ablative therapies. Agents currently used are the antiestrogen tamoxifen, the progestins medroxyprogesterone acetate and megestrol acetate, gonadotropin releasing hormone analogs such as goserelin, and inhibitors of estrogen biosynthesis such as the aromatase inhibitors. Surprisingly, inhibition of aromatase, which blocks the conversion of androgens to estrogens, is effective therapy in patients with breast cancer even after they relapse from responses to antiestrogen or progestin (medroxyprogesterone acetate or megestrol acetate) therapy. Several second- and third-generation aromatase inhibitors are now available which are highly potent and associated with few side effects. Their role in the therapy of breast cancer will probably become increasingly important. In this review, the current status of aromatase inhibitors will be discussed.

**General role of aromatase**

Fat, liver, muscle, and hair follicles contain the aromatase enzyme which catalyzes the conversion of androgens to estrogens [2,3]. In postmenopausal women, the major source of circulating estrogens is the peripheral conversion from androgens in fat tissue and in muscle [2]. Androstenedione, the major precursor androgen, and testosterone, a minor substrate, are secreted primarily from the adrenal glands and are converted in peripheral tissues to estrone and estradiol, respectively, through the catalytic action of the enzyme aromatase. The major aromatized product, estrone, is then enzymatically reduced to estradiol by the enzyme 17β-hydroxysteroid dehydrogenase. These enzymatic activities result in measurable amounts of circulating estrogen in the range of 10-20 pg/ml in the plasma of postmenopausal women.

Despite relatively low serum concentrations, the levels of estradiol in breast tumors of postmenopausal women are almost equivalent to those in premenopausal women [4]. The tumor tissue levels are much higher than the values predicted from calculations of serum concentrations and the affinity ($K_d$) of tissue receptors for estradiol. One of the explanations for maintenance of high tissue estradiol concentrations is the in situ synthesis of estradiol catalyzed by the various enzymatic activities present in breast tumor tissue itself. These include sulfatase which catalyzes the conversion of estrone sulfate to estrone, aromatase which mediates androgen to estrogen conversation, and 17β-hydroxysteroid dehydrogenase which allows formation of estradiol from estrone. The absolute levels of aromatase activity in human breast cancer tissues are low (5-100 pg/gm tissue/hr) when compared to those of sulfatase and 17β-hydroxysteroid dehydrogenase [5]. However, it is difficult to quantitate experimentally the amount of estradiol synthesized locally by each enzymatic pathway and the amount concentrated in tissue via uptake from plasma. Nonetheless, tissue enzymes such as sulfatase, 17β-hydroxysteroid dehydrogenase, and aromatase are likely to be involved in the production of at least some of the estrogen present in situ in tumor tissue. As another possible source of estrogens in breast tumors, lipoidal estradiol is reported to accumulate in estrogen receptor (ER) positive as well as ER negative breast cancer cells and can be hydrolyzed to free estradiol by esterase or lipase in tissues [6,7].

Androstenedione is the major circulating