Journal of Cellular Biochemistry, Supplement 22:51–57 (1995)

Alternate Antiestrogens and Approaches to the Prevention of Breast Cancer

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Abstract The biological rationale and extensive clinical experience with the breast cancer drug tamoxifen make it the agent of choice for *testing* as a breast cancer preventive. However, concerns (Jordan and Morrow, *Eur J Cancer*, in press) about development of endometrial cancer in patients and liver tumors in rats with tamoxifen has encouraged the investigation of other antiestrogens. At present no compounds are available to replace tamoxifen, but two triphenylethylenes, toremifene and droloxifene, have been tested in postmenopausal women to treat advanced breast cancer. The response rates are similar to those observed with tamoxifen (*i.e.*, approximately 35% [CR + PR] in unselected patients), although dosage regimens of the new antiestrogens are higher than the 20 mg tamoxifen required daily. Doses of up to 200 mg toremifene daily are being tested and studies use up to 100 mg droloxifene daily. Side effects appear comparable, but neither droloxifene nor toremifene produce liver tumors in rats. Tamoxifen produces DNA adducts, whereas toremifene and droloxifene appear to be only weakly active. A new tamoxifen analogue, idoxifene, is entering clinical trial. The drug is designed to be metabolically stable so that there will be low carcinogenic potential.

In contrast, a novel strategy may be considered to be of value to protect women from developing breast cancer. It is known from laboratory and clinical studies that antiestrogens protect bone and prevent rat mammary cancer. One compound, raloxifene, is being tested as an agent to treat osteoporosis. If the drug becomes generally available to prevent osteoporosis in postmenopausal women, a beneficial side effect may be a reduction in breast cancer risk. This broad-based strategy may prove more effective than focusing on small groups of women with a high risk for breast cancer alone. Protection from breast cancer may be as an advantageous side effect from the successful treatment of other diseases in women. © 1995 Wiley-Liss, Inc.

Key words: Breast cancer, droloxifene, endometrial cancer, liver cancer, raloxifene, tamoxifen, toremifene

Tamoxifen (Fig. 1) is the endocrine therapy of choice for selected patients with all stages of breast cancer [1]. An overview analysis [2] demonstrates a survival advantage for both node-positive and node-negative patients who received adjuvant tamoxifen therapy. Tamoxifen can reduce the incidence of fatal myocardial infarction [3,4] and stabilize bone density in postmenopausal patients [5–7], an incentive to test its worth as a preventive in women who are only at risk for breast cancer [8,9].

Tamoxifen has a low incidence of side effects [1], but its balance of estrogenic and antiestrogenic action that is considered an advantage [9] may result in more serious complications. Concerns about endometrial carcinoma [10–13] and developing liver tumors [14,15] have resulted in new drug development programs to produce novel therapeutic agents with improved toxicological profiles.

This article will review progress in developing new antiestrogens and describe the rationale for each drug design. All of the compounds under

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investigation have their genesis in pharmacological investigations of tamoxifen. For convenience, the drugs have been divided into three main groups—tamoxifen analogues, derivatives of tamoxifen metabolites, or novel antiestrogens.

TAMOXIFEN ANALOGS

A current concern with the use of tamoxifen is development of endometrial carcinoma and the potential to induce hepatocellular carcinoma. Tamoxifen is a partial estrogen agonist; it has been suggested that hydroxylation, dealkylation of the side chain, and isomerization could produce estrogenic metabolites that stimulate tumor growth [16–18]. However, this hypothesis has recently been found untenable; stable derivatives of tamoxifen that cannot isomerize after metabolic activation also provoke growth of tamoxifen-stimulated tumors under laboratory conditions [19,20]. Nevertheless, new analogs of tamoxifen that may be metabolically resistant and reduce the potential for carcinogenicity are being evaluated in clinical trials.

Toremifene

Chlorination of the ethyl side chain of tamoxifen to produce toremifene (Fig. 1) reduces antiestrogenicity and decreases potency as an antitumor agent. However, toremifene appears to possess an advantage over tamoxifen because it has a reduced ability to induce rat liver tumors [21,22]; unlike tamoxifen, toremifene does not produce DNA adducts in the rat liver [22–24]. There is currently no evidence that tamoxifen does increase the incidence of hepatocellular carcinoma (at least above the ten-fold increased risk observed with oral contraceptives [24]). However, if hepatocarcinogenicity becomes an issue in humans, toremifene could replace tamoxifen in prevention studies. The issue of endometrial carcinoma is unresolved because there is no experience with long-term toremifene therapy. Conversely, there is no reason to believe that toremifene will not produce an identical risk for endometrial carcinoma as tamoxifen, *i.e.*, 2–3 fold [13].

Toremifene has been extensively tested for the treatment of advanced breast cancer [25–28]. The dose range is between 60–280 mg daily, but the response rate is similar to tamoxifen, *i.e.*, approximately 30% of unselected patients. Initial reports that high dose toremifene (>100 mg) will produce responses in patients with tamoxifen-resistant disease [29] are unsupported; current clinical studies demonstrate cross-resistance. A crossover study from Denmark that compared 40 mg tamoxifen daily with 240 mg toremifene daily found cross-resistance with both therapies [30]. No subsequent responses were observed at crossover. Similarly, an American study found only a 5% response in 105 patients who had failed tamoxifen but were then treated with 200 mg toremifene daily [31]. A major clinical trial of tamoxifen *versus* toremifene to treat advanced breast cancer in postmenopausal women has been completed in the United States. An analysis of the results is anticipated and FDA approval will be sought in 1995.

Idoxifene

Hydroxylation of tamoxifen to produce 4-hydroxytamoxifen increases antiestrogenic potency [32]. However, this metabolic activation is an advantage, but not a requirement, for antiestrogenic activity. Blocking 4-hydroxylation with halogen substitutions results in compounds of weaker antiestrogenic potency [33], but does not reduce partial agonist activity. It has been reasoned that a compound with reduced 4-hydroxylation and a stable alkylaminoethoxy side chain may have less carcinogenic potential. Idoxifene (Fig. 1) is a weak antiestrogen in the rat but exhibits antitumor activity in rat mammary carcinoma models [34]. Idoxifene is resistant to metabolic degradation in laboratory tests and is detected as the principal compound in the serum of treated patients. The compound is currently undergoing Phase I/II clinical trials in England.

DERIVATIVES OF TAMOXIFEN METABOLITES

TAT 59

This antiestrogen is a derivative of 4-hydroxytamoxifen. Although 4-hydroxytamoxifen is a potent antiestrogen *in vitro* [35,36] and can exhibit antitumor activity in both carcinogen-induced rat mammary carcinoma models [37] and athymic mice inoculated with MCF-7 breast tumors [38], higher doses are required to produce

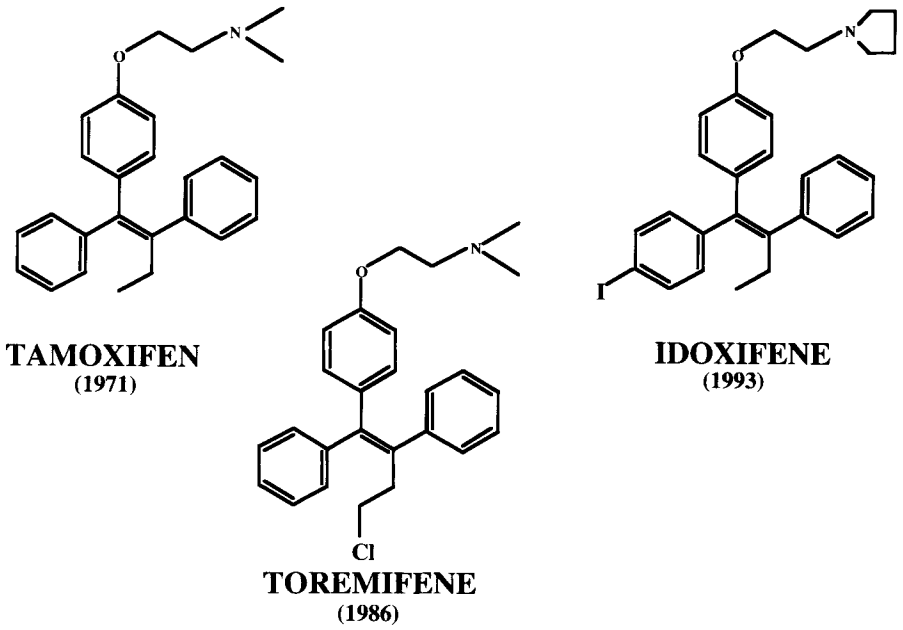

Fig. 1. Tamoxifen analogues that are in clinical trial. The date in parentheses indicate the year breast cancer studies were reported.

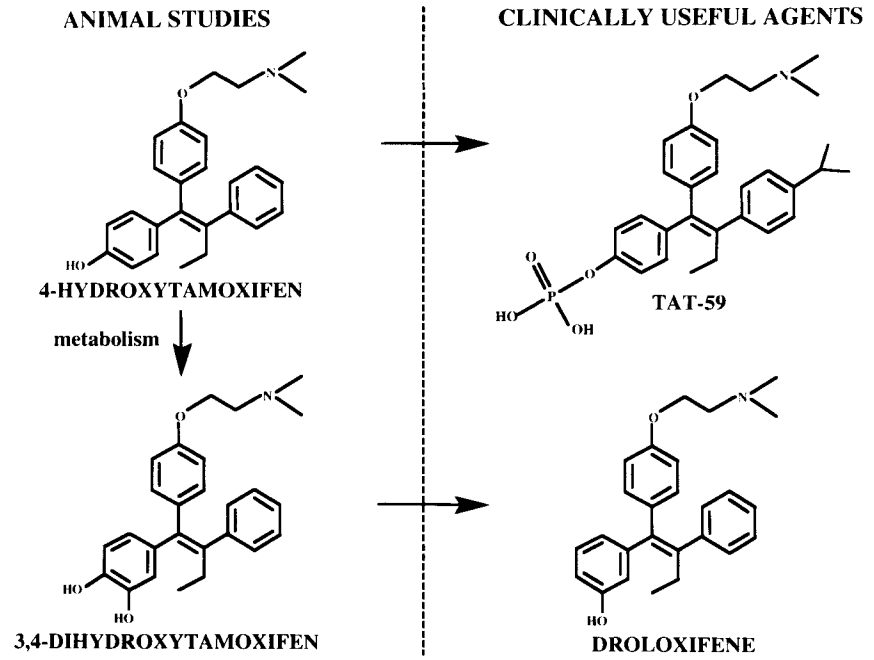

Fig. 2. The derivatives of tamoxifen that have used metabolite mimicry to design an antibreast cancer agent.

equivalent effects because the drug is vulnerable to phase II metabolism. TAT 59 is phosphorylated (Fig. 2) at the 4-hydroxy position, which could protect it from phase II metabolism, but the drug probably needs to be dephosphorylated to produce the active agent. Animal studies demonstrate antitumor activity [39]; the drug is in clinical trial in Japan.

Droloxifene

4-Hydroxytamoxifen and 3,4-dihydroxytamoxifen are metabolites of tamoxifen [40]. Both have high binding affinity for the estrogen receptor and both exhibit antiestrogenic activity in rats [40]. Interestingly, 3,4-dihydroxytamoxifen has only weak estrogen agonist properties and is an antiestrogen in mouse uterine weight-tests [32, 40]. This contrasts with tamoxifen and 4-hydroxytamoxifen, both estrogens in mouse assays. Droloxifene (Fig. 2), the 3-hydroxylated analog of tamoxifen, has a high binding affinity for the estrogen receptor and blocks the growth of MCF-7 breast cancer cells in culture [41,42]. It does not produce DNA adducts in laboratory models of genotoxicity [23].

Droloxifene has had extensive clinical testing throughout the world. Phase I testing found few side effects [43], but as anticipated, human pharmacokinetics demonstrate a rapid excretion, with low circulating blood levels [44]. Droloxifene has been used at daily doses up to 100 mg; response rates for unselected postmenopausal patients are between 30–40% [45]. Clinical trials in postmenopausal women with advanced disease are being planned in the United States.

A NOVEL ANTIESTROGEN: RALOXIFENE

The initial report [46] that raloxifene (originally named keoxifene) preserves bone density in laboratory animals has been confirmed [47], and studies are being set up to evaluate the worth of raloxifene as an agent to prevent osteoporosis. Raloxifene has almost complete antiestrogenic activity in high doses in the rat and mouse uterus [48] and exhibits antitumor action in the rat [49]. In contrast, it has an estrogen-like action to lower circulating cholesterol and preserves bone density in the rat [47].

Large doses will be used in clinical trials because raloxifene is rapidly cleared from the circu-

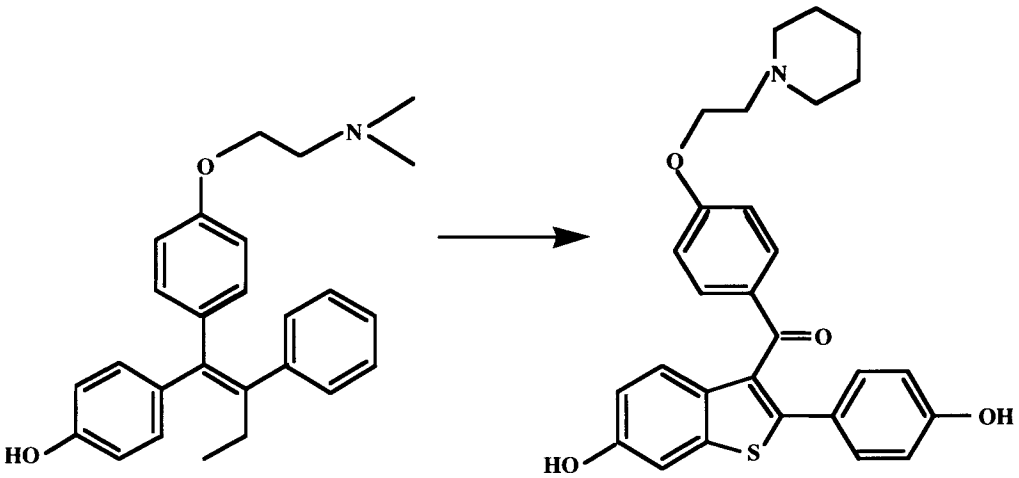

Fig. 3. A new clinical concept that is being developed to exploit the high affinity binding of antiestrogens to the estrogen receptor (ER) to produce a compound targeted to maintain bone density but block breast tumor development. Raloxifene is a high affinity antiestrogen that employs the principle first discovered with 4-hydroxytamoxifen.

lation. The hydroxyl groups make raloxifene (Fig. 3) vulnerable to phase II metabolism. Preliminary clinical studies using 200 and 600 mg raloxifene daily in several hundred postmenopausal women demonstrate that the higher daily dose will effectively lower cholesterol and reduce circulating osteocalcin levels [50].

The novel use of raloxifene opens up an exciting therapeutic opportunity. Rather than selecting women to treat with an antiestrogen to prevent breast cancer (with the added advantage of reducing their risk for osteoporosis and coronary heart disease), it is now possible to consider using safe agents to treat all postmenopausal women to prevent osteoporosis and coronary heart disease, but with the added advantage of preventing breast cancer [cf review 51]. The national impact of the new strategy on women's health may ultimately be greater than defining a narrow targeted population of women at risk only for breast cancer.

SUMMARY

The development of tamoxifen during the past 25 years has revolutionized the treatment of breast cancer. There are now an estimated six million woman-years of experience worldwide with tamoxifen, and each year in the United States an estimated 80,000 women diagnosed with breast cancer plan to start a course of long-term tamoxifen therapy.

The clinical evaluation of tamoxifen as a breast cancer preventive in high-risk women has opened the door to new therapeutic opportunities. Pharmacological studies over the past two decades have predicted not only the value of tamoxifen as a therapeutic agent with positive effects on bones and lipids, but also predicted concerns with endometrial carcinoma and the potential for hepatocellular carcinoma. Numerous compounds have been screened, and several agents with improved toxicology are waiting for extensive clinical testing. A new range of antiestrogens with different properties and potentially different applications will soon be available to treat estrogen-regulated diseases in women.

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