Questions about Tamoxifen and the Future Use of Antiestrogens

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ABSTRACT

Tamoxifen is the most widely prescribed anticancer drug in the world. It not only improves overall survival and decreases recurrence from breast cancer, but has beneficial effects on bone density and lipid profiles. Unfortunately, tamoxifen carries disadvantages such as unpleasant side effects and a questionable connection to endometrial carcinoma. However, after intense debate, the general consensus among the medical community is that the benefits of tamoxifen far outweigh the risks. Nonetheless, resistance to tamoxifen has been seen both in the clinic and in the laboratory prompting investigators to look for new antiestrogens in the treatment and prevention of breast cancer. We report on three agents: toremifene (Fareston®), ICI 182,780 (Faslodex®), and raloxifene (Evista®). Unfortunately, clinical studies comparing tamoxifen and toremifene in the treatment of breast cancer have not shown a clear advantage of toremifene over tamoxifen. ICI 182, 780 is a “pure antiestrogen” that carries a low incidence of side effects and may hold promise as an effective agent for patients who have failed tamoxifen therapy or even as primary adjuvant therapy. Raloxifene displays beneficial bone and cardiovascular effects without uterine stimulation. It is being used as an agent to prevent osteoporosis and holds promise as an agent for advanced breast cancer. We hope that these new antiestrogens will revolutionize the way we treat breast cancer.

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INTRODUCTION

Tamoxifen (Nolvadex®) [1] is an excellent example of a drug that started development unsuccessfully in one area but was then successfully developed in another area of medicine. Tamoxifen originally started drug development in the 1960s as an agent to regulate fertility. Today, tamoxifen is the most widely prescribed anticancer drug in the world. Tamoxifen has improved overall survival and decreased recurrence from breast cancer and has decreased the risk from contralateral disease. Although tamoxifen has revolutionized the way we look at breast cancer treatment, it has also uncovered some key issues regarding the exact mechanisms of antiestrogen action. Tamoxifen exhibits site-specific actions; the drug has antiestrogenic activity in the breast but estrogen-like activity in the endometrium and bone and on lipids. Uterine stimulation is evident in some patients by endometrial proliferation and thickening which may increase the risk of endometrial carcinoma. The exact mechanism of target-site specificity is not known, but discovery of this principle has opened the door to new applications of new drugs and an understanding of drug resistance. It is now clear that prolonged tamoxifen therapy may result in resistant tumors that have either lost their estrogen receptor (ER) or retain their ER to become dependent on tamoxifen for growth. This discovery brings into question the appropriate duration of therapy for tamoxifen and the ultimate development of resistant disease. As a result of these findings, there has been intense interest in developing new antiestrogens that may avoid the perceived detrimental effects of tamoxifen but still preserve the beneficial effects. We will discuss the advantages of tamoxifen, the gold standard for the treatment of all stages of breast cancer, and place the side effects of the drug in perspective. Finally, we will consider the new antiestrogens that are currently available and describe their potential uses for the treatment and, ultimately, the prevention of breast cancer.

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ADVANTAGES OF TAMOXIFEN

Tamoxifen was first approved for the treatment of metastatic breast cancer in postmenopausal patients in the United Kingdom in 1973 and subsequently in the United States in 1977. Over the years, the medical community has expanded the use of tamoxifen to encompass pre- and postmenopausal women, node +/- women, and ER+ women for adjuvant therapy alone or in combination with chemotherapy for early breast cancer. Tamoxifen is now used as a first-line agent for male breast cancer as well.

Tamoxifen benefits the breast cancer patient with an increase in overall survival, decreased time to recurrence, and decreased risk of contralateral disease (Table 1). The results of the Nolvadex Adjuvant Trial Organization (NATO) trial [2] and the Scottish trial [3] published between 1983 and 1987 both suggested improvement in overall survival regardless of menopausal status, nodal status, or ER positivity. The NATO trial used two years of adjuvant tamoxifen therapy, while the Scottish trial used five years of adjuvant therapy. Likewise, the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial [4] demonstrated in 1989 that women, with receptor-positive node-negative disease had improved overall survival with five years of adjuvant tamoxifen. Today it is known that five years is superior to two years of adjuvant tamoxifen [5]. In 1992, the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) reported, in an overview analysis of all clinical trials, that tamoxifen reduced annual rates of recurrence and death in women on tamoxifen alone [6]. However, women greater than 50 years old benefited to a greater extent than the women less than 50 years old, as did receptor-positive women. Nevertheless, in a new analysis soon to be published, there appears to be equal benefit for pre- and postmenopausal women with receptor-positive tumors taking tamoxifen. In addition, the EBCTCG showed a decrease in the risk of contralateral cancer by 39% over an average follow-up period of 5.6 years for those on tamoxifen versus those on no adjuvant therapy.

ADDITIONAL BENEFITS OF TAMOXIFEN

The extensive use of tamoxifen over the past 25 years has resulted in a systematic study of its clinical pharmacology. The target-site-specific effects produced by tamoxifen are now well documented. Careful clinical studies have found that tamoxifen has beneficial effects on bone density and lipid profiles because it displays estrogen-like effects in the relevant organs and tissues (Table 2). Several studies have shown that patients on tamoxifen have an average 13% decrease in total cholesterol and a 19% decrease in LDL levels [7]. Apparently, HDL levels are not affected. Consequently, these effects translate into a decreased cardiovascular mortality [8, 9]. Tamoxifen not only holds promise for the prevention of cardiovascular disease, but it may help prevent bone loss as well [10]. A series of studies shows that tamoxifen will preserve bone density in postmenopausal women [7], and overall tamoxifen could be viewed as a physiologic support for postmenopausal women with a diagnosis of breast cancer [11]. However, all the news is not good. The estrogen-like actions of tamoxifen can produce some troublesome side effects. Nevertheless, it is now possible to place these problems in perspective.

PERCEIVED DRAWBACKS OF TAMOXIFEN

For the most part, tamoxifen is very well tolerated, with only 5% of patients discontinuing therapy because of side effects (Table 3). Patients most commonly complain of hot flashes first and vaginal bleeding, water retention, mood swings, and headache second. Tamoxifen has also been associated with thromboembolic episodes; a 1.7% incidence in treated patients versus 0.3% incidence in non-treated patients is reported in an NSABP trial [12]. However, the story concerning hepatic cancer has been confusing, primarily because the clinical risks have been inappropriately linked to laboratory studies of rat liver cancer. In rats, tamoxifen has been shown to form DNA adducts and cause hepatic tumors (at doses much higher than those used in women), but there is no increase in hepatic tumors over the 20 years that tamoxifen has been used clinically [13]. By contrast, the most publicized side effect is the link between tamoxifen and endometrial cancer. Tamoxifen has been shown to encourage the growth of established endometrial carcinoma transplanted into athymic mice and to cause endometrial proliferation in 30%-40% of postmenopausal women. Whether these observations translate into a significant clinical outcome is the subject for debate; however, several important facts have emerged after intense investigation during the past decade. The Stockholm study in 1989 [14] concluded that women randomized to five years of tamoxifen are at a much higher risk of endometrial carcinoma than women randomized to two years of treatment. A re-analysis of this study found, however,
that a majority of the endometrial cases occurred in women who received less than two years of therapy [15]. In addition, a study from the Yale registry claimed that if a woman did develop endometrial carcinoma on tamoxifen it tended to be a high-grade, poor-prognosis tumor [16]. The NSABP B-14 trial evaluated women who received 20 mg/day of tamoxifen for five and eight years [17]. The incidence of endometrial carcinoma in these groups compared favorably with surveillance, epidemiology, and end results (SEER) data—that is, approximately one to two of 1,000 women per year [18]. Additionally, the endometrial carcinomas were found to be low-grade tumors, unlike those seen in the Yale registry report. They concluded that the benefits of tamoxifen in the treatment of breast cancer far outweigh the risks. Similarly, the NSABP B-14 trial did not find any increased incidence of liver, gastrointestinal, urinary tract, or nonuterine genital tumors [12]. During the past two years, we have reviewed the world database concerning the association between tamoxifen and endometrial carcinoma and concluded that the benefits far outweigh the risks [19]. Similarly, the International Agency for Research on Cancer, an agency of the World Health Organization, has concluded that no woman stop taking tamoxifen for the treatment of breast cancer because of concerns about endometrial cancer (http://www.iarc.fr/preleases/111e.htm).

**TAMOXIFEN RESISTANCE**

Despite these drawbacks, tamoxifen remains the hormonal therapy of choice for breast cancer. However, tamoxifen should not be seen as a cure because drug resistance can eventually occur. Animal studies evaluating long-term tamoxifen treatment in athymic mice have found that implanted breast tumors eventually become resistant to tamoxifen. Osborne et al. [20] discovered that MCF-7 tumors derived from an ER+ breast cancer cell line implanted into athymic mice remained dependent on estrogen for growth demonstrating that tamoxifen is cytostatic rather than cytotoxic. However, tumors eventually begin to regrow after three to four months despite continued tamoxifen treatment. In parallel studies, we developed transplantable tumors from the MCF-7 cell line that were dependent on tamoxifen or estradiol for growth [21, 22]. Interestingly, the tumors contain double the ER content of tumors not exposed to tamoxifen. Currently, there is intense interest in discovering the mechanisms of tamoxifen-stimulated growth. In contrast, Pink et al. [23] showed that T47D breast cancer cells can lose the ER when they are deprived of estrogen. Clearly, there are two independent routes of resistance: tumor dependence on tamoxifen with retention of the ER, or tumor insensitivity to tamoxifen with loss of the ER. These studies in the laboratory highlight the need to determine the appropriate duration of tamoxifen therapy—two versus five versus ten years versus indefinite treatment. Would ten years of tamoxifen therapy promote tamoxifen resistance? The NSABP has addressed this issue in ER-positive node-negative patients and found no advantage in extending therapy past five years [12]. Indeed, an NCI clinical alert has recommended stopping tamoxifen at five years in node-negative breast cancer patients [24]. In contrast, ECOG in a small study found that ER-positive patients benefited from longer than five years of treatment [25]. Be that as it may, in the absence of clear-cut clinical trials data, most clinicians give tamoxifen for five years despite the controversy. To resolve the issue, Professor Richard Peto at Oxford has called for large clinical trials. There are now two clinical studies, adjuvant tamoxifen to offer more (aTTom) and adjuvant tamoxifen long against short (ATLAS), each recruiting 20,000 patients to define the precise duration of tamoxifen for node-positive and node-negative breast cancer. Nevertheless, concerns about drug resistance have prompted investigators to look for new antiestrogens for breast cancer treatment and prevention.

**NEW APPLICATIONS FOR ANTIESTROGENS**

The clinical potential for new antiestrogens in the treatment and prevention of breast cancer holds great promise. There are several new agents under development, some with a safer toxicity profile than tamoxifen and others having no cross-resistance with tamoxifen. For example, new agents under investigation do not have a stimulatory effect on the uterus, nor do they form DNA adducts in the rat liver, thus abolishing the concern over endometrial cancer and possible hepatocarcinogenesis in women without breast cancer. However, some of these agents still possess the beneficial effects of tamoxifen, such as preservation of bone density and decreasing LDL and total cholesterol. Indeed, one agent, raloxifene, has been evaluated for the prevention of osteoporosis, and there are emerging data from the clinical trials that raloxifene prevents primary breast cancer. Additionally, the class of antiestrogens called pure antiestrogens which are not cross-resistant with tamoxifen would be ideal as second-line agents after tamoxifen failure or as a first-line treatment for metastatic breast cancer.
Classes of Antiestrogens

There are three broad classes of antiestrogens which are of interest: the triphenylethylenes, of which tamoxifen is the primary member; the pure antiestrogens, which are either steroidal or nonsteroidal analogs, and the benzothiophenes, which carry a nonsteroidal ring structure but are referred to as selective ER modulators (SERMS). We will discuss the three most promising agents for use in practice: toremifene; ICI 182, 780 and raloxifene.

The Triphenylethylenes: Toremifene

Toremifene (Fareston®) began development in 1978 in Finland and was approved by the FDA for the treatment of metastatic breast cancer in 1997. In the laboratory, toremifene has been found to be an estrogen antagonist, but at high doses it is oncolytic [26, 27]. At these high doses, the addition of estrogen will not reverse toremifene’s effects. Like tamoxifen, toremifene stimulates uterine proliferation in rats and produces the same estrogenic effects on the histology of the postmenopausal endometrium [28]. Perhaps more significant, toremifene does not produce DNA adducts in the rat liver [29], but its hepatocarcinogenic potential at high doses is questionable. The drug is a promoter of carcinogenesis [30]. Additionally, like tamoxifen it increases the growth of endometrial cancer in laboratory models [31]. Several studies have evaluated the use of toremifene treatment in metastatic breast cancer and have found response rates comparable to tamoxifen [32, 33]. When compared with tamoxifen as first-line hormonal therapy, no study demonstrated a significant advantage of toremifene over tamoxifen. An international trial conducted in 1995 looked at tamoxifen versus toremifene in the treatment of ER+ or unknown, previously untreated metastatic breast cancer. Toremifene showed only a slightly (but not statistically significant) better response rate and comparable median survival [33]. However, in patients who were previously treated with tamoxifen, toremifene displays poor response rates, showing that toremifene carries cross-resistance with tamoxifen. Toremifene, like tamoxifen, demonstrates a much higher response rate in ER+ patients. At this time, toremifene is available in the treatment of advanced breast cancer in patients who have not recently failed adjuvant tamoxifen therapy.

Pure Antiestrogens

In an effort to completely separate the estrogenic and antiestrogenic properties of tamoxifen, the “pure antiestrogens” were developed by Alan Wakeling and Jean Bowler at Zeneca Pharmaceuticals. These “pure antiestrogens” include ICI 164, 384 and ICI 182, 780 (Faslodex®). Since ICI 164, 384 shows reduced bioavailability in in vivo studies, we will focus this review on ICI 182, 780, which is being evaluated in clinical trials as a second-line endocrine agent following the failure of tamoxifen. Apparently, the pure antiestrogens bind to the ER in the cytoplasm and cause destruction of the ER [34]. As a result, breast cancer cells which are ER-negative are not affected by the pure antiestrogens. In the laboratory, pure antiestrogens inhibit tamoxifen-stimulated endometrial and breast cancers. This provides the scientific rationale for treating patients who have recurrences while on tamoxifen or who develop tamoxifen-dependent tumors. In a phase I trial by Howell et al. [35], 19 women with advanced breast cancer had no night sweats or hot flashes, nor was vaginal dryness noted. In addition, no endometrial effects were seen and no significant changes in total cholesterol, LDL, or HDL levels were found. They did see a 37% partial response rate, and 32% of patients maintained stable disease status. In another study of ICI 182, 780 by DeFriend et al. [36], 56 women with primary breast cancer were treated with ICI 182, 780 for four weeks, but no serious adverse side effects were noted. The most common complaint among the study subjects was headache. ICI 182, 780 did produce a significant decline in ER levels as determined by immunohistochemistry performed on tumor samples. ICI 182, 780 holds promise as an effective agent for patients who have failed tamoxifen therapy [37] or even primary adjuvant therapy with its low incidence of side effects, but further studies are needed to demonstrate its true clinical potential.

The Benzothiophenes: Raloxifene

A member of the benzothiophene family, raloxifene (Evista®) displays beneficial bone and cardiovascular effects without uterine stimulation. Raloxifene binds to the ER with an affinity equal to estradiol [38], but it targets tissues with different effects. In rats, it maintains bone density and carries little agonist activity on the uterus [39, 40]. Furthermore, no reports have shown the formation of DNA adducts in the liver or hepatocarcinogenic potential. Raloxifene does lower serum cholesterol and LDL, but has no effect on HDLs [41]. To investigate the role of raloxifene in the treatment of advanced breast cancer, the MD Anderson Hospital conducted a phase II trial of raloxifene in patients with metastatic breast cancer refractory to tamoxifen [42]. Unfortunately, no significant responses were seen. However, these data are inconsistent with the known action of raloxifene to prevent mammary cancer in rats [43, 44]. Current studies in advanced breast cancer do, however, show benefit for women receiving raloxifene [45]. It should be stressed that raloxifene is being used as an agent to prevent osteoporosis because of the beneficial effect on bone density [41]. However, unlike hormone replacement therapy, raloxifene is anticipated to reduce the incidence of breast cancer.
CONCLUSION

The development of tamoxifen has revolutionized the treatment of breast cancer. However, the clear advantages of tamoxifen in the treatment of breast cancer may become secondary to the ultimate quest to prevent the disease. The drawbacks of tamoxifen, namely hot flashes, risk of endometrial carcinoma, thromboembolic episodes, and the eventual development of drug resistance, have stimulated intense investigation into other antiestrogens. The goal is to develop agents that still have the beneficial effects of tamoxifen but avoid the perceived drawbacks. Our progress can be measured by comparing and contrasting the properties of new agents (Tables 4-6). Although a primary use of these agents could be as adjuvant therapies, there is little clinical evidence to suggest improvement compared with tamoxifen. The time needed to evaluate a new adjuvant therapy with the hopes of detecting an advantage often exceeds the patent life of a new drug. By contrast, ICI 182, 780 is an ideal agent for the treatment of advanced breast cancer because it is not cross-resistant with tamoxifen and may prove beneficial for cases of advanced breast cancer resistant to tamoxifen. In contrast, the discovery of the additional beneficial hormonal effects of tamoxifen such as preservation of bone density and lowering of cholesterol levels are, in fact, the main focus of current clinical investigations. Raloxifene is the first of a new series of drugs designed to prevent osteoporosis, but by comparison with hormone replacement therapy, it may be protective against breast cancer. It is clear, however, that the main focus of interest in raloxifene...
will not be osteoporosis, but the prevention of breast cancer in postmenopausal women. The idea that the pharmaceutical industry could exploit the beneficial side effects of tamoxifen to develop a new agent to prevent breast cancer in the general population is poised to become a reality by the 21st century.

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