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The Strategic Use of Antiestrogens to Control the Development and Growth of Breast Cancer

V. Craig Jordan, Ph.D., D.Sc.

Tamoxifen has become the endocrine treatment of choice for all stages of breast cancer. Its low incidence of side effects and proven survival advantage observed during adjuvant therapy in postmenopausal women with node-positive disease has encouraged the use of long-term treatment for patients to benefit fully from therapy. The drug has an appropriate level of estrogen-like effects that could be beneficial to maintain bone density and prevent development of coronary heart disease by lowering circulating cholesterol. These effects might be useful in all patients with estrogen receptor-positive breast cancer who currently are receiving no therapy. This antiestrogenic agent could be effective therapy to deter recurrence, and the estrogen-like side effects support the physiologic processes of the patient as hormone-replacement therapy. In the laboratory, a tamoxifen-stimulated breast cancer model has been described in vivo. This form of drug resistance may occur in patients after long-term or indefinite adjuvant therapy. Novel pure antiestrogenic drugs have been discovered that soon will become available as second-line therapy after tamoxifen failure. In addition, tamoxifen is being evaluated in the United Kingdom as chemosuppressive therapy to prevent the development of breast cancer in high-risk women. A similar clinical evaluation is underway in the United States.
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Key words: tamoxifen, breast cancer, prevention, drug resistance.

The clinical development of antiestrogenic drugs[1,2] has introduced a new therapeutic dimension for the physician treating patients with breast cancer. Tamoxifen (Fig. 1), a nonsteroidal compound,[3] is now established as the "gold standard" to treat selected patients with all stages of this disease.[4] The side effects generally are limited to symptoms of estrogen blockade. Nevertheless, physicians should remain vigilant to their patients' concerns and provide optimal health care during tamoxifen therapy.

In this article, a treatment strategy is designed for the 1990s to maximize the use of antiestrogenic drugs to control breast cancer. Long-term adjuvant tamoxifen therapy, a concept successfully transferred from the laboratory to the clinic,[5] provides a survival benefit for postmenopausal patients with node-positive disease.[6] This encouraging clinical finding has increased the enthusiasm to extend and broaden the use of antiestrogen therapy. This article addresses some of the issues involved and considers the potential benefits of a broader application of tamoxifen therapy.

Long-Term Adjuvant Tamoxifen Therapy

During the past 3–4 years, it has become clear that tamoxifen, an antiestrogenic agent originally introduced as a palliative treatment for advanced breast cancer in postmenopausal women,[7] is effective adjuvant therapy in both node-positive and node-negative disease. The results of numerous clinical trials recently were reviewed.[8] Therefore, it is only necessary in this report to consider the strategic issues.

Several clinical trials showed the benefit of at least 5 years of tamoxifen treatment;[9–12] however, there is currently a trend toward evaluating indefinite adjuvant tamoxifen therapy. There are two major concerns about this strategy. First, will the patient benefit from continuous therapy? It is hoped that an advantage will be observed in the analysis of current clinical trials because the prospects for patient survival are not good after there is recurrence. Any strategy to suppress the process of recurrence would be a valuable advance. However, this raises a second issue: Is indefinite tamoxifen therapy safe?

In 1977, a pilot clinical evaluation was begun of the safety and potential efficacy of long-term adjuvant ta-

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From the Department of Human Oncology, University of Wisconsin Clinical Cancer Center, Madison, Wisconsin.

Address for reprints: V. Craig Jordan,, Ph.D., D.Sc., Department of Human Oncology, University of Wisconsin Clinical Cancer Center, 600 Highland Avenue, Madison, WI 53792.

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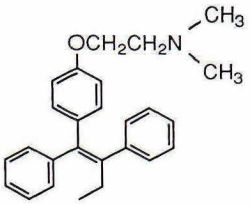

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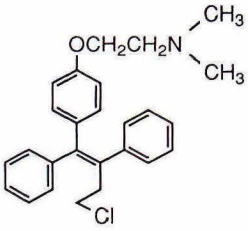

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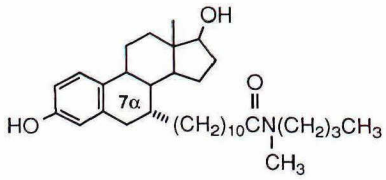

ICI 164,384

Figure 1. Formulas of antiestrogens.

moxifen therapy, with initial adjuvant chemotherapy, in node-positive breast cancer.[13,14] Not only has the pilot study provided interesting therapeutic data, but also the findings in the patients treated have proved to be an invaluable resource to monitor the acceptability and safety of tamoxifen. Many of these patients were younger than 40 years of age, and they maintained their menstrual cycles after adjuvant chemotherapy. Long-term adjuvant tamoxifen therapy caused an increase in circulating estrogen levels.[15,16] Currently, there is no evidence that the observed increased estrogen levels will reverse the action of tamoxifen as an antitumor agent. However, it is known that tamoxifen is likely to be more effective in a low estrogen environment. Tamoxifen, and its metabolites, are competitive inhibitors of estrogen action.[17] Two strategies could be considered to reduce estrogen levels: ovariectomy (in node-positive disease) or the administration of luteinizing hormone-releasing hormone (e.g., depot goserelin). The latter is known to inhibit ovarian estrogen synthesis (by suppressing luteinizing hormone release),[18,19] and this may be rational therapy for node-negative, estrogen receptor-positive women who elect not to receive chemotherapy because they wish to have a family 5 or more years in the future. Clinical trials are ongoing to address both the safety and efficacy of tamoxifen–depot goserelin combinations.

One natural concern about indefinite tamoxifen therapy was the probability that an antiestrogenic drug might cause serious bone loss. Ultimately, this would limit the use of the agent in women with either node-negative disease or those surviving long term. We found (in the laboratory) that tamoxifen has a target-site specificity, i.e., tamoxifen will produce an antiestrogenic effect in the uterus (with some estrogenic actions), but it has estrogenic effects in bone and prevents decreases in density.[20] Tamoxifen does not cause any significant decreases in bone density (compared with control) in patients who have received at least a 2-year course of adjuvant tamoxifen.[21] Similarly, long-term (5-year) adjuvant tamoxifen therapy appears to stabilize bone loss.[22]

It is known that tamoxifen has a mixture of estrogenic and antiestrogenic actions,[4] and it is possible that the estrogenic actions could cause troublesome side effects. Estrogens are known to predispose individuals to thromboembolic disorders and endometrial carcinoma. Tamoxifen causes some decreases in antithrombin III during long-term adjuvant therapy,[23] but the decreases are within the clinically acceptable range. However, women with a prior history of thromboembolic disorder should not receive long-term tamoxifen therapy unless the risks are outweighed by the severity of the disease.

Tamoxifen-induced endometrial carcinoma is a much more complicated issue, and the findings deserve to be placed into perspective. As might be expected, endometrial carcinoma has been detected in patients who are being treated for breast cancer with tamoxifen.[24] Unfortunately, only approximately 33% of endometrial carcinoma is hormone responsive; therefore, most tumors would be expected to progress. However, in one study,[25] it was found that a steroid receptor-positive human endometrial tumor is stimulated to grow in athymic mice by either estradiol or tamoxifen. In fact, tamoxifen again shows target site specificity. If animals are bitransplanted with a human breast tumor (MCF-7) and a human endometrial carcinoma (EnCa 101), tamoxifen will inhibit estradiol-stimulated growth of the breast tumor but encourage the growth of the endometrial tumor.[26] These findings led to an examination of clinical-trial data to determine whether an increase in endometrial carcinoma occurs during adjuvant tamoxifen therapy for breast cancer. Currently, only one randomized clinical trial found an increase in endometrial carcinoma. This Swedish study[27] of approximately 1900 women, randomized to receive no or tamoxifen (20 mg twice a day) treatment, found an increase of 11 endometrial carcinomas in the tamoxifen treatment arm compared with control. What is particularly interesting is the association of an increased risk for endometrial carcinoma with increased duration of tamoxifen therapy. Nevertheless, it is clear from all clinical results that no patient should be denied adjuvant tamoxifen therapy for breast cancer because she might have an occult endometrial carcinoma that is encouraged to grow by tamoxifen. Physicians should, however, remain vigilant to this possibility and immediately investigate any cases of suspicious bleeding.

Failure of Adjuvant Tamoxifen Therapy

It is unrealistic to believe that indefinite tamoxifen therapy will control disease recurrence indefinitely. Failure of tamoxifen therapy usually is associated with estrogen receptor-negative clone emergence. However, based on experience with advanced disease, a significant proportion of disease will remain hormone responsive. Second-line therapies, like progestins[28] and aromatase inhibitors,[29] can be effective in some patients. The new antiestrogenic agent, toremifene,[30–35] might produce a subsequent response in some patients in whom tamoxifen therapy fails after an initial response. Toremifene currently is being evaluated in Phase III trials against tamoxifen in postmenopausal patients with advanced disease. The next step will be to evaluate this antiestrogenic drug as adjuvant therapy.

Several forms of drug resistance to antiestrogens have been described in the laboratory.[4] However, the observation that tamoxifen can encourage the growth of endometrial carcinoma in athymic mice naturally raised the question of whether a model could be developed for tamoxifen-stimulated breast cancer growth.

Long-term tamoxifen therapy eventually can cause the growth of MCF-7 breast tumors in athymic mice.[33,34] These tumors can be retransplanted but will grow only if tamoxifen treatment is maintained.[35] It is possible that tamoxifen-stimulated growth has been described in the clinic.[36] However, a withdrawal response may be difficult to define because tamoxifen has a long half-life,[37] and up to 6 weeks is required to eliminate all traces of the drug and its metabolites.

In the laboratory model of tamoxifen-stimulated growth, estradiol also stimulated tumor growth.[35] This suggests that cessation of tamoxifen therapy will not be sufficient clinically because the patient's circulating estrogen ultimately may support tumor growth. For this reason, significant numbers of patients may respond to second endocrine treatment after the failure of successful tamoxifen treatment. The tumor has a withdrawal response to tamoxifen, and the existing estrogen receptor system cannot be activated. This is achieved by either limiting the amount of endogenous estrogen (aromatase inhibitors) or perturbing the regulation of the estrogen receptor system (progestins). An alternate therapeutic strategy would be to develop antiestrogenic drugs that do not have the estrogen-like properties of tamoxifen.

Pure Antiestrogens

Several pharmaceutical companies are attempting to develop a pure antiestrogenic agent for clinical use. Currently, there is only information available about the efficacy of the lead compounds in various laboratory tests. It is therefore possible to formulate an application because the pharmacologic principle (i.e., can one synthesize a compound with pure antiestrogenic properties?) has been established.

The steroidal compound, ICI 164,384 (Fig. 1),[38] has been evaluated by numerous investigators[17,39,40] and found to be an effective pure antiestrogen. However, its systemic potency is low, and there is significant loss of potency if the compound is given to animals orally. ICI 164,384 probably will not be used clinically, but nonsteroidal agents with a higher potency could be targeted for development. An orally active agent should be an essential component of any strategy to introduce a new antiestrogen. Oral tamoxifen is so well tolerated that patients would be reluctant to consider injections or sustained-release implants as an alternative.

How could a pure antiestrogenic drug be used to its best advantage in the clinic? The finding that pure antiestrogens can inhibit tamoxifen-stimulated growth in laboratory models[34] identifies their use as second-line therapy in advanced disease or at first recurrence in patients with node-positive or node-negative breast cancer who do not respond to long-term adjuvant tamoxifen therapy.

It is likely that, early in the evolution of breast cancer, the disease is significantly more hormonally responsive than later. Early treatment of node-negative disease with an antiestrogen could provide an advantage for patients. However, this might not be true if therapy with a pure antiestrogenic drug is used early. One advantage of long-term adjuvant tamoxifen therapy is that the drug appears to have an appropriate level of estrogenic side effects.[4] Its estrogenicity might be beneficial to bone[22] and is responsible for lowering circulating cholesterol.[41] This might be important for most postmenopausal women with node-negative disease who are denied hormone replacement therapy because only a minority will have a recurrence. A pure antiestrogenic drug might produce deleterious effects on the physiologic actions of estrogen in such patients that might preclude early evaluation in these women. By contrast, it might be advisable to evaluate adjuvant therapy in women with extensive nodal metastases. Ultimately, tamoxifen therapy followed by pure antiestrogen therapy at recurrence might be more acceptable to patients if orally active pure antiestrogenic drugs are not available.

It is likely that the next decade will see the evaluation of several new agents that should provide clinicians with other valuable antiestrogenic agents with different properties. Nevertheless, the success of tamoxifen, and its balance of estrogenic and antiestrogenic actions, has encouraged a consideration of its wider clinical application to prevent breast cancer.

Prevention of Breast Cancer

One of the current goals of laboratory and clinical research is to devise a strategy to prevent the development of breast cancer. An effective plan ultimately could prevent more than 40,000 deaths annually. A successful strategy would intervene in those women in whom the disease could develop. Such an intervention must have significantly less risk to the patient than death from breast cancer and preferably be given precisely and for a short period. Regrettably, we cannot identity unequivocally the population of women in whom breast cancer will develop. Therefore, there is the immediate problem of who to treat. Although we know that women who have two or more first-degree relatives with breast cancer are at increased risk for the disease, these women are in a minority (10%) of those who subsequently have the disease. Most women have breast cancer for apparently arbitrary reasons. Because we do not know who will have breast cancer and can only identify women with an increased risk (e.g., nulliparous women, women bearing a child after age 30 years, and women who have multiple breast biopsies for suspicious lesions), the application of an intervention to prevent the disease must have negligible risk for the vast majority of women who will never have breast cancer. To prevent the disease, the timing of disease initiation should be known. However, we do not know either the timing or the nature of the carcinogenic insult in women. Therefore, currently, precise intervention therapy to prevent breast cancer seems unlikely.

An ovarian influence in the control of breast cancer growth has been known since the turn of the century.[42] In the laboratory, ovariectomy prevents the development of mammary cancer in high-incidence strains of mice[43] and mammary carcinogenesis in rats.[44] In both models, mammary carcinogenesis is initiated in young pubescent females, but all animals will have tumors unless prophylactic ovariectomy is done. It would be clearly unacceptable to do indiscriminate oophorectomies on teen-age girls to avoid the possibility of breast cancer! Nevertheless, there is epidemiologic data to support the view that early oophorectomy dramatically reduces the incidence of breast cancer.[45] Recently, one study[46] suggested the extensive use of luteinizing hormone-releasing hormone agonists as contraceptives. This reversible approach to ovarian suppression would reduce, not only the incidence of breast cancer, but also that of ovarian and endometrial carcinoma. This innovative suggestion has merit although there is currently little public enthusiasm to sponsor research in reproductive endocrinology.

An alternative approach would be to administer antiestrogenic drugs to block estrogen action. Tamoxifen reduces the incidence of second primary breast cancers that develop during adjuvant tamoxifen therapy[10,27] and prevents mammary tumorigenesis in animal models.[47,48] The strategy to use tamoxifen to prevent breast cancer has a strong scientific rationale for further evaluation. However, such a strategy will succeed only if there is a low incidence of iatrogenic disorders in the women who will never have breast cancer. The side effects that occur with tamoxifen recently were reviewed.[49] Therefore, only the major concerns will be mentioned in this report. The administration of tamoxifen to young women (as yet unidentified) of reproductive age might be unacceptable because of (1) the postmenopausal symptoms, (2) the risks for teratogenesis, and (3) the unknown effects of long-term ovarian hyperstimulation, i.e., ovarian carcinoma in the postmenopausal years.

An alternative strategy would be to study the ability of tamoxifen to prevent the appearance of breast cancer in postmenopausal women. However, the process of initiation and promotion of breast cancer almost certainly will have occurred before this age, and tamoxifen will suppress the growth of malignant cells. This concept would be considered chemosuppression, i.e., to prevent the development of occult disease. Figure 2 describes the various strategic approaches to control the development of breast cancer.

Chemosuppression

In London, a pilot clinical study was begun of tamoxifen therapy in normal women at risk for breast cancer.[50–52] Currently, the only concern of significance is the declining compliance (80% at 2 years) that occurs in both the tamoxifen and control treatment arms. Close volunteer supervision and support will be essential to achieve success in a major study.

There is the question of the duration for tamoxifen therapy. Although tamoxifen is an effective agent for the treatment of breast cancer and long-term adjuvant therapy is effective, it may be prudent to consider a 5-year regimen rather than indefinite treatment. We have considerable information about 5 years of treatment, and additional long-term studies will produce results during the next few years. An analysis of adjuvant

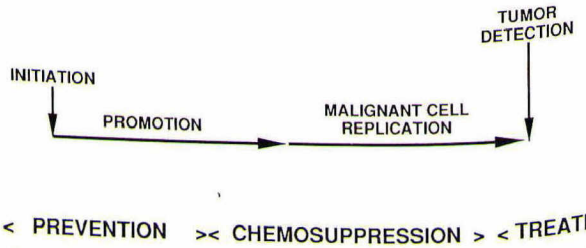

Figure 2. Concepts for the strategic use of antiestrogens to control the development of breast cancer.

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