THE ROLE OF TAMOXIFEN IN THE TREATMENT AND PREVENTION OF BREAST CANCER

ABSTRACT.—Tamoxifen is a nonsteroidal antiestrogen that has found successful applications for each stage of breast cancer in the treatment of selected patients. Tamoxifen was originally introduced for the treatment of advanced disease in postmenopausal women; however, the drug is now also available for the palliative treatment of premenopausal women with estrogen receptor (ER) positive disease. The proven efficacy of tamoxifen and the low incidence of side effects made the drug an ideal agent to test as an adjuvant therapy for women with node-positive breast cancer. Laboratory studies indicate that long-term treatment schedules may provide maximal benefit in preventing recurrence, and recent analysis of clinical trials demonstrates that between 2 and 5 years of adjuvant tamoxifen therapy provides a survival advantage for postmenopausal women with node-positive disease. Similarly, adjuvant studies in node-negative breast cancer have demonstrated an increase in the disease-free survival of both pre- and postmenopausal patients with ER-positive tumors. However, the extended use of tamoxifen has raised questions about the long-term safety of antiestrogen therapy. Of special concern is the impact of tamoxifen on ovarian function in premenopausal women and the potential risks to the fetus if pregnancy occurs. Fortunately, there are no reports about the teratogenicity of tamoxifen in the human, but it is important that physicians counsel women about the risk of pregnancy. Tamoxifen should not be used if a patient is pregnant.

Initial concerns that the long-term administration

of an antiestrogen would increase bone loss and increase the risks of coronary heart disease appear to be unwarranted. Tamoxifen has some estrogen-like activities in postmenopausal women and causes a preservation of bone in the lumbar spine and a decrease in circulating cholesterol. Indeed, a reduction in fatal myocardial infarction (MI) has been noted during 5 years of tamoxifen therapy, possibly the direct result of a prolonged reduction in circulating cholesterol.

However, the estrogen-like qualities of tamoxifen that could be valuable as a hormone replacement therapy for all postmenopausal women following a diagnosis of breast cancer may also increase the risk for developing endometrial carcinoma. To date, there are only a few reports of endometrial carcinoma being diagnosed during adjuvant therapy with tamoxifen; however, any instances of uterine bleeding or spotting should be followed up with an endometrial biopsy.

There are some concerns about large doses of tamoxifen promoting liver cancer in rats. These results are of particular concern if tamoxifen is to be used as a preventive in normal women. However, tamoxifen is acting as a weak estrogen in the rat model, and other estrogens (eg, conjugated estrogens and estrogens used in oral contraceptives) are much more potent promoters of liver cancer. There are no reports of an increased incidence of hepatocellular carcinoma during long-term tamoxifen therapy; in fact, there is a report of the use of tamoxifen to treat the disease successfully.

The estrogen-like properties of tamoxifen may encourage clones of breast cancer cells to grow in response to the drug. This form of drug resistance has been described in the laboratory, and a new pure antiestrogen is being evaluated for use as a second-line agent following the failure of long-term adjuvant tamoxifen therapy.

The extensive clinical experience with tamoxifen has encouraged its evaluation as a preventive in women at risk of developing breast cancer. Several clinical studies are being positioned in different countries to address this question. All the laboratory studies demonstrate that tamoxifen will prevent or suppress mammary cancer, and clinical experience has

shown a 40% reduction in the incidence of second primary breast cancers.

The completion of randomized prevention trials with tamoxifen will place a valuable medical option in the hands of the physician who treats women at risk for breast cancer.

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INTRODUCTION

It has been known since the turn of the century[1,2] that about one-third of patients with advanced breast cancer will respond to some form of additive or ablative endocrine therapy. However, the reason for the apparently arbitrary responses remained unclear until the estrogen receptor was described[3–5] and utilized in selecting patients with a high probability of responding to endocrine therapy.[6] Approximately 60% of ER-positive patients will have an objective response to endocrine therapy.[6]

Tamoxifen (ICI 46,474; Nolvadex®) is the *trans* isomer of a substituted triphenylethylene that has antiestrogenic activity in laboratory animals[7] and causes the regression of carcinogen-induced rat mammary tumors.[8–11] Tamoxifen is a competitive inhibitor of estrogen action and blocks the binding of [^{3}H]estradiol to the ER.[12,13] Although a whole range of different nonsteroidal antiestrogens were described in the 1960s,[14] only tamoxifen was developed successfully for the treatment of breast cancer.[15,16] The first preliminary clinical evaluation of tamoxifen to treat advanced breast cancer was conducted by Cole and colleagues[17] at the Christie Hospital in Manchester. The efficacy of tamoxifen was equivalent to either androgen or high-dose estrogen therapy in postmenopausal patients, but the side effects noted with tamoxifen were modest. Several reports[18,19] subsequently confirmed the efficacy of tamoxifen in producing palliation in postmenopausal women with advanced breast cancer.

In 1973, Nolvadex®, the ICI brand of tamoxifen (as its citrate salt), was approved in the United Kingdom for the treatment of advanced breast cancer by the Committee on the Safety of Medicines. Similar approval was given in the United States by the Food and Drug Administration (FDA) on December 30, 1977. Nolvadex® is now available in more than 110 countries as first-line endocrine therapy for

the treatment of advanced breast cancer in postmenopausal women.

Tamoxifen was initially used in premenopausal women to treat menometrorrhagia[20] and to induce ovulation in infertile women.[21, 22] Although tamoxifen causes an increase in circulating estrogen levels during the treatment of advanced disease in premenopausal women,[23, 24] it causes an objective response in about one-third of patients. Evidence has been accrued to demonstrate that tamoxifen produces a response rate similar to oophorectomy;[25, 26] however, the reported studies are small and do not possess the statistical power to detect significant differences. Nevertheless, the FDA has approved the use of tamoxifen to treat ER-positive advanced breast cancer in premenopausal women.

During the past 20 years, a dramatic change has occurred in the strategic application of antiestrogen to treat breast cancer. Approximately 170,000 new cases of breast cancer will be diagnosed annually in the United States, but less than 20% will be advanced disease. The rest will be node-positive and node-negative breast cancers with no detectable distant metastatic spread. Twenty years ago, patients would have waited for disease recurrence before treatment. The use of adjuvant therapy (ie, treatment following mastectomy) is now accepted as a useful strategy for destroying micrometastases (Fig 1). Tamoxifen has found a valuable place in the medical armamentarium because it has been shown to have proven efficacy as an adjuvant therapy[27] and has a low incidence of side effects. Indeed tamoxifen has been so successful that clinical trials are planned to study the use of tamoxifen in healthy women for preventing the development of breast cancer.[28, 29]

During the next decade, up to 2 million women in the United States will have a diagnosis of breast cancer. It is hoped that tamoxifen therapy will produce a beneficial effect in a significant proportion of these patients. The ubiquitous use of tamoxifen now mandates a serious evaluation of both the strategic use of antiestrogens in the clinic and the potential consequences of long-term antihormonal therapy.

ADJUVANT TAMOXIFEN THERAPY

CONCEPTS

A variety of *in vivo* laboratory models have been used to support the development of clinical trials that assess the efficacy of long-term or indefinite adjuvant therapy with tamoxifen in stages I and II disease. Unfortunately, these models do not precisely replicate the clinical situation, but their results clearly demonstrate the advantages of extended therapy in suppressing the appearance of palpa-

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