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TAMOXIFEN: Toxicities and Drug Resistance During the Treatment and Prevention of Breast Cancer

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ABSTRACT

Tamoxifen, a nonsteroidal antiestrogen, is the endocrine therapy of choice for all stages of breast cancer. There are six million women-years of experience with tamoxifen, and the drug has produced survival advantages in node-positive and node-negative patients who have had 2–5 years of adjuvant tamoxifen therapy. A low incidence of side effects has been reported with tamoxifen, resulting in the proposal to use the antiestrogen as a preventive agent for breast cancer. Three separate clinical trials are currently under way—in the United States, Italy, and the United Kingdom. Current concerns about tamoxifen are the development of rat liver tumors during long-term treatment and an increased incidence of endometrial carcinomas observed in patients. Another concern is the development of drug resistance to long-term tamoxifen therapy. There is increased interest in both determining the mechanism of drug resistance and evaluating new antiestrogens that may be more beneficial as a preventive, as an adjuvant therapy, or for the treatment of advanced breast cancer.

INTRODUCTION

Tamoxifen is a nonsteroidal antiestrogen (1–4) that exhibits antitumor properties in laboratory animals (5–9). Although many compounds were investi-

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gated in the 1960s and 70s (10), only tamoxifen was successfully developed in the laboratory for the treatment of breast cancer (10–12). The initial focus of anti–breast cancer drug development in the 1970s was as a palliative therapy for advanced breast cancer. However, adjuvant therapy and the exploration of long-term tamoxifen therapy (13, 14) has revolutionized breast cancer treatment. An overview analysis of randomized clinical trials of adjuvant tamoxifen therapy demonstrates that long-term (i.e. more than one year) adjuvant tamoxifen is an appropriate strategy to control the recurrence of both node-positive and node-negative breast cancer (15). Tamoxifen confers a survival advantage to those women with breast cancer who are treated for more than two years. Tamoxifen is the hormonal treatment of choice for all stages of breast cancer.

The use of tamoxifen as a treatment for breast cancer has over six million women-years of experience. The drug has a low reported incidence of serious side effects (16), and five years of therapy is commonplace (17).

The success of tamoxifen as a treatment for breast cancer has fueled interest in the drug as a preventive agent. Estrogen is known to promote the development of breast cancer, so it is only natural that an antiestrogenic drug that has been extensively clinically tested would be the leading candidate for evaluation. The pharmacology of tamoxifen is complex (18, 19), but the scientific rationale for testing tamoxifen has merit. An important component of the drug's pharmacology is the target-site specificity of tamoxifen; the drug can act as an antitumor agent (probably as an antiestrogen) in the breast but can also be estrogenic at physiological sites to prevent bone loss and decrease circulating cholesterol.

Animal studies demonstrate that tamoxifen prevents mammary carcinogenesis (5, 7, 20–22), and clinical studies show that adjuvant tamoxifen therapy decreases the incidence of second primary breast cancers by 40% (15). Postmenopausal bone density is maintained by tamoxifen treatment (23–25), which could ultimately lead to the prevention of osteoporosis. Tamoxifen also decreases low-density lipoprotein cholesterol levels in postmenopausal women (26–28). This positive property of tamoxifen may be responsible for the decrease in hospital visits for the treatment of any cardiac condition (29) and the significant decrease in fatal myocardial infarction for women treated for five years with tamoxifen (30, 31). These data provide a scientific basis for placebo-controlled clinical trials to test tamoxifen's ability to prevent breast cancer.

PREVENTION STUDIES

Unlike the laboratory models of mammary tumorigenesis, where all animals develop tumors and the efficacy of tamoxifen is readily demonstrated, targeting

the appropriate population at risk for breast cancer is difficult. Numerous risk factors have been identified, and these have been reviewed elsewhere (32). However, because the incidence of breast cancer is small in the general population, women volunteers with a high-risk profile must be recruited. It is essential to design a double-blind, placebo-controlled trial, but the large numbers of volunteers required and the long time period necessary to obtain a statistically significant result mandates data management, compliance monitoring, and an enormous clinical trials effort.

Three clinical trials are currently recruiting and following volunteers to test tamoxifen's ability to prevent breast cancer. The first trial was begun at the Royal Marsden Hospital in 1986 (33, 34). The initial goal was to recruit 2000 women as a Vanguard study and monitor the progress of the volunteers. Healthy women aged 30–70 are eligible provided they have a family history of breast cancer on the maternal side, with at least one first-degree relative (sister, mother, daughter) under the age of 45 years who has developed breast cancer or bilateral breast cancer or with a first-degree relative and at least one other maternal relative affected. The women are randomly assigned to receive 20 mg of tamoxifen or a placebo daily for at least eight years. At five years (by June 1993) compliance for the 2012 women assigned to the tamoxifen arm of the study was greater than 70% (35).

There is a significant increase in hot flashes (34% vs 20%), vaginal discharge (16% vs 4%), and menstrual irregularities (14% vs 9%) for tamoxifen- vs placebo-treated women. Safety monitoring shows no obvious effects on radial bone mineral density, but fibrogen, antithrombin III, and cholesterol levels decrease out to five years in the tamoxifen-treated women.

Most importantly, the Marsden study demonstrates an increased incidence of uterine fibroids and benign ovarian cysts as a result of tamoxifen treatment. An in-depth study (36) of the postmenopausal women demonstrated that tamoxifen causes potentially malignant changes in the endometrium, but transvaginal ultrasonography can be used to identify those women who should be monitored. These findings resulted in approval by the Department of Health (July 1993) to recruit an additional 15,000 women volunteers from sites around the United Kingdom. Recruitment of additional volunteers has also been conducted for more than a year in Australia.

The second prevention trial began recruiting volunteers from throughout North America in May 1992. The study, funded by the National Cancer Institute, will recruit 16,000 women who will be randomly assigned to be treated with tamoxifen (20 mg daily) or a placebo for five years. Those eligible for entry into the study include any woman over the age of 60 or women between the ages of 35 and 59 years whose five-year risk of developing breast cancer, as predicted by the Gail model (37), equals that of a 60-year-old woman. Any woman over 35 years of age, with a diagnosis of lobular carci-

noma in situ (LCIS) treated with biopsy alone, is eligible for entry. In the absence of LCIS, the risk factors for entry vary with age, so a 35-year-old woman must have a relative risk of at least 5, while a 45-year-old woman's relative risk must be 1.8 to be eligible for entry.

Seven thousand women were recruited in the first year. Pretrial concerns that younger women at risk would not volunteer for the trial are not substantiated by the population distribution. About one third of the volunteers are 35–50 years old, with relative risks ranging on average between 10 for the youngest participants to 4 for the 50-year-olds.

By December 1993, 11,000 women had been recruited to the prevention trial. Administrative concerns about the development of uterine carcinoma during tamoxifen treatment halted recruitment to National Surgical Adjuvant Breast Project (NSABP) trials for several months during 1994, but recruitment was reinitiated in June 1994 after the Food and Drug Administration had reviewed the concerns.

The final tamoxifen prevention trial was initiated in Italy (38) by the European Institute of Oncology and the Milan Cancer Institute. Up to 20,000 volunteers who are over the age of 45 but who have already had a hysterectomy will be recruited. The aim of these restrictions is to avoid the complications of both pregnancy and endometrial cancer. Volunteers are being randomly assigned to tamoxifen (20 mg daily) or a placebo for five years. There were more than 3000 volunteers recruited by July 1993.

For the first time, the clinical trials community is evaluating a therapy to prevent breast cancer. Although the majority of women recruited to the trials will not develop breast cancer, they will experience symptoms and side effects from tamoxifen. The evaluation of the toxicity of tamoxifen in the trials is extremely important, not only to determine the therapeutic value of the intervention but also to assess whether compliance can be maintained by the study population. Extra attention is being paid to chronic toxicities.

TOXICITIES OF TAMOXIFEN

Considerable concern has been expressed about the potential toxic effects of tamoxifen that could become critical in any evaluation of the drug given to women without breast cancer. These concerns are listed in Table 1 and have been the subject of a recent commentary (39). Ocular problems and the small increase in thromboembolic disease has been adequately reviewed (16), but the potential of tamoxifen to be carcinogenic is a serious risk.

In the laboratory, tamoxifen can stimulate the growth of human endometrial carcinoma but can block the growth of a breast tumor transplanted in the same immune-deficient mouse (40). This possibility was demonstrated in patients when a 40% decrease in second primary breast cancers but a threefold increase

Table 1 Potential long-term toxicities from tamoxifen therapy

Ocular problems
Thromboembolic disorders
Endometrial cancers
Liver cancer

in endometrial cancer was observed in an adjuvant clinical trial of tamoxifen (41). Seventeen endometrial cancers were reported for the 1000 patients taking tamoxifen after eight years of evaluation. The rate of detection is two per thousand per year (42). A similar rate is reported by the NSABP (43). However, the NSABP study reports 6 deaths out of the 23 patients who developed endometrial carcinoma over the 6 years of evaluation for the 2639 women (43). The causes of death and the association with the duration of tamoxifen treatment are shown in Table 2. It is clear that women must be monitored for the development of endometrial carcinoma, but perhaps most importantly, patients must be screened before therapy to ensure that preexisting endometrial carcinoma is not present.

Investigators are currently interested in determining whether tamoxifen produces a higher-grade, more aggressive endometrial carcinoma. Initial reports from the Yale–New Haven tumor registry suggested that women were "at risk for high-grade endometrial cancers that have a poor prognosis" (44). Current comparisons of histological grade and stage in patients treated with tamoxifen (42, 43, 45) demonstrate the same proportions noted for the general population.

Table 2 Patients randomly assigned to the tamoxifen arms of NSABP B_{14} who died of EC[a]

Patient	Age	Time on tamoxifen (months)	Diagnosis of EC after tamoxifen (months)	Cause of death
1	66	Never took tamoxifen	—	EC
2	68	5	0	CV disease[b]
3	63	9	0	EC
4	58	22	73	EC
5	54	42	23	EC
6	68	65	0	Pulmonary embolism

[a] Endometrial cancer
[b] Cardiovascular disease

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