

Surgical Oncology Forum

Tamoxifen for the Prevention of Breast Cancer in the High-Risk Woman

Monica Morrow, MD, and V. Craig Jordan, PhD, DSc

In 1998, a major landmark in the battle against breast cancer was reached when the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 prevention trial¹ demonstrated a 49% reduction in the risk of invasive breast carcinoma in high-risk women who took tamoxifen for 5 years. The significance of this result was questioned when two additional reports from the Royal Marsden² and Italy³ demonstrated no reduction in rate of occurrence of breast cancer with tamoxifen. However, these should not be viewed as one positive and two negative trials, because the European studies were not completed prospective clinical trials designed to answer the chemoprevention question. Most important, the use of tamoxifen for prevention is the culmination of more than 30 years of laboratory research that has been translated into clinical practice, and a large data base of breast cancer patients treated with tamoxifen and followed for 10 years exists to address some of the questions suggested by the initial results of the prevention studies.

Rationale for Prevention With Tamoxifen

Although the idea of breast cancer prevention with antiestrogens may seem new, it was first proposed in 1936 by Professor Antoine Lacassagne at a meeting of the American Association for Cancer Research. With remarkable foresight, Lacassagne stated “If one accepts the consideration of adenocarcinoma of the breast as a consequence of a special hereditary sensibility to the proliferative action of oestrone, one is led to imagine a therapeutic preventive for subjects predisposed by their heredity to this cancer. It would consist—perhaps in the very near future when the knowledge and use of hor-

mones will be better understood—in the suitable use of a hormone, antagonistic or excretory, to prevent the stagnation of oestrone in the ducts of the breast.”⁴

Unfortunately, at that time, there was no known antagonist to estrogen activity other than oophorectomy, and the mechanism of hormonal regulation of breast tissue was not understood. In 1962, Jensen and Jacobson⁵ described the selective binding of radiolabeled estradiol in the estrogen target tissue of the rat, and proposed the concept of an estrogen receptor (ER). The presence of the ER was subsequently shown to predict the likelihood of a breast cancer patient’s response to hormonal manipulation in the form of endocrine ablation.⁶ In the 1970s, tamoxifen was shown to block the binding of [³H]estradiol to the ER derived from rat uterus⁷ or human tumor.⁸ Thirty-five years after Lacassagne’s initial suggestion, an estrogen antagonist was available for study. Although tamoxifen’s first clinical use was for the treatment of breast cancer, the earliest animal studies with the drug provided the scientific basis for prevention. Tamoxifen was shown to prevent rat mammary carcinogenesis induced by dimethylbenzanthracene or *N*-nitrosomethylurea,^{9,10} as well as spontaneous carcinogenesis in mice infected with the mouse mammary tumor virus.¹¹ These studies established two key principles that have subsequently been validated in clinical studies. First, that longer durations of tamoxifen are more effective for prevention than short ones, and second, that tamoxifen acts through the ER, suggesting that the use of the drug for prevention will reduce the incidence of ER-containing tumors.

The first clinical observation of tamoxifen’s efficacy as a chemopreventive was made by Cuzick and Baum,¹² who reported a decrease in the incidence of contralateral breast carcinoma in women taking adjuvant tamoxifen. This has subsequently been confirmed in other clinical trials. The 1998 Oxford Overview Analysis¹³ included 37,000 breast cancer patients treated in 55 adjuvant ta-

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From the Lynn Sage Breast Program (MM, VCJ), Department of Surgery (MM), and the Robert H. Lurie Comprehensive Cancer Center (VCJ), Northwestern University Medical School, Chicago, Illinois.

Address correspondence and reprint requests to: Monica Morrow, MD, 676 N. St. Clair Street, 13th Floor, Room 13-104, Chicago, IL 60611; Fax: 312-926-1722.

moxifen trials. Overall, a 30% reduction in the risk of contralateral breast carcinoma was seen in patients taking tamoxifen. Benefit was observed for women younger than age 50, as well as their older counterparts, with risk reductions of $27\% \pm 11\%$ or $31\% \pm 7\%$, respectively. In addition, the overview analysis confirmed the laboratory observation that longer durations of tamoxifen are more effective for breast cancer prevention. One year of adjuvant tamoxifen did not significantly reduce breast cancer incidence compared with control. After two years of therapy, a 29% reduction in risk was observed, which increased to 47% with 5 years of tamoxifen treatment. In addition to confirming the importance of duration of therapy, the data from the overview provides insight into an important question raised by critics of the NSABP prevention trial; namely, was the tamoxifen benefit observed in that study the result of the suppression of established, but clinically undetected, breast cancers? If this was the case, then the reduction in breast cancer incidence would be expected to disappear with further follow-up after the discontinuation of tamoxifen. The overview data suggest that this is not true. Although patients were treated with tamoxifen for durations of 1 to 5 years, at a minimum follow-up of 10 years (i.e., at least 5 years of not receiving therapy), the curves for the incidence of contralateral breast cancer remain widely separated, without evidence of a lessening of the tamoxifen effect. As a whole, the overview analysis provides important confirmatory evidence that the observations in the NSABP P-1 trial are reproducible and unlikely to change with further follow-up.

Although the laboratory and clinical evidence that tamoxifen could reduce the incidence of breast carcinoma was compelling, there were significant concerns about giving an antiestrogen compound to healthy women, given what was known about the beneficial effects of estrogen on the cardiovascular system and on bone. However, laboratory studies demonstrated that tamoxifen caused vaginal cornification and increased uterine weight in the mouse,¹⁴ signs of estrogenic activity. Further investigations led to the concept of the target site specificity of tamoxifen, which suggested that the ER complex could be stimulatory or inhibitory at different sites.¹⁵ Animal experiments subsequently demonstrated that tamoxifen had estrogen-like activity in bone¹⁶ and in the uterus.¹⁷ These findings were confirmed in clinical investigations that confirmed that tamoxifen increases bone density¹⁸ and lowers blood cholesterol,¹⁹ alleviating concerns that the use of tamoxifen for prevention would cause significant increases in the risk of osteoporotic fractures or myocardial infarction. In addition, the potential for an increased incidence of endometrial carci-

noma caused by tamoxifen's estrogenicity in the uterus was also demonstrated clinically.^{20,21} This background of an extensive data base of both laboratory and clinical information, suggesting that tamoxifen reduces breast cancer risk and has the potential to reduce the incidence of two other major problems in postmenopausal women's health, osteoporosis and cardiovascular disease, provided a strong rationale for the study of tamoxifen to prevent breast cancer in high-risk women.

NSABP P-1 Prevention Trial

The NSABP P-1 study¹ was opened in 1992 with a primary end point of determining whether the use of tamoxifen for 5 years reduced the incidence of invasive breast carcinoma. The secondary aims of the study were to determine if tamoxifen reduced the incidence of myocardial infarction and bone fracture. Women were eligible for study entry if they were age 60 or older, or if they were between the ages of 35 and 59 years and had a history of lobular carcinoma in situ, or a 5-year predicted risk of breast cancer development of 1.66% or more. Risk was calculated by using the model of Gail et al.,²² which includes age, age of menarche, parity and age at first live birth, number of first-degree relatives with breast cancer, number of breast biopsies, and a diagnosis of atypical hyperplasia, to estimate breast cancer risk. This model has been shown to predict risk accurately in two validation studies of women undergoing annual mammographic screening,^{23,24} but is not a useful model for assessing risk in women with a strong family history of breast cancer suggestive of a genetic mutation, because it includes only first-degree relatives.

Eligible women were randomized to receive tamoxifen 20 mg daily for 5 years or placebo. A total of 13,388 women were randomized, and results were reported for 13,175 participants with a median follow-up of 54.6 months (mean, 47.7 months). A total of 368 invasive and noninvasive breast cancers occurred in the study participants, 124 in women on tamoxifen and 244 in those in the placebo group. Overall, a 49% reduction in the risk of invasive carcinoma was seen in the tamoxifen group, a figure remarkably similar to the 47% reduction in contralateral breast cancer reported in the overview analysis.¹³ A 50% reduction in noninvasive breast cancer was also observed in those receiving tamoxifen.

One of the most remarkable findings of the P-1 trial is the consistent benefit of tamoxifen across all groups studied. Tamoxifen was found to be of benefit in all age groups, with relative risks ranging from 0.56 in women age 49 and younger, 0.49 for women age 50 to 59, and 0.45 for those age 60 and older. Although all women included in this study were defined as being at an in-

creased risk of breast cancer, a benefit was seen for all levels of risk within the study. Those at the lowest level of increased risk ($\leq 2\%$ during 5 years) had a 63% reduction in breast cancer risk, compared with 66% for those at the highest level of increased risk ($\geq 5.01\%$ during 5 years). Women at risk on the basis of a family history of breast cancer, as well as those at risk because of other factors were found to benefit from treatment. A particular benefit was observed in women at risk on the basis of lobular carcinoma in situ or atypical hyperplasia. In an updated analysis of this subgroup,²⁵ treatment with tamoxifen reduced risk by 65% in those with lobular carcinoma in situ and 86% in those with atypical hyperplasia. In addition, the benefits of tamoxifen were consistent over time, with no evidence of diminution as the length of follow-up increased. Thus, the reduction in breast cancer incidence was 55% in year 2 of the study, 49% in year 4, and 55% in year 6.

Regarding the secondary aims of the study, a 19% reduction in the incidence of fractures was noted, and this almost reached statistical significance. The tamoxifen benefit was most notable for hip fractures, where a 45% reduction was observed. No reduction in any type of ischemic cardiac event was noted in the tamoxifen group.

Other Studies of Tamoxifen for Prevention

Although the results of the P-1 trial were strongly positive and consistent with the laboratory data and findings from the overview, the publication of two other studies that showed no decrease in breast cancer incidence in women taking tamoxifen^{2,3} suggested significant questions regarding its efficacy. The Italian prevention trial³ randomized 5,408 of the proposed 20,000 women, aged 35 to 70, to tamoxifen 20 mg daily or placebo. There was no requirement for an increased level of breast cancer risk to enter the study, and participants were required to have had a hysterectomy. Those women who had a premenopausal bilateral oophorectomy and hysterectomy (47% of participants) were actually at a reduced risk of breast cancer development. The relatively low risk of these women is evident from the breast cancer incidence in the placebo arm of the study, 2.3 per 1000 (compared with 6.7 per 1,000 in the NSABP trial), and the small number of total cancers in the study, 41. In addition, although 5408 women were randomized, 1,422 withdrew from the study and only 149 completed 5 years of treatment. The failure of this study to demonstrate a benefit of tamoxifen is readily explained by its lack of statistical power because of small sample size, high dropout rate, and low level of baseline risk in the population studied.

The other report that failed to demonstrate a benefit of tamoxifen was from the Royal Marsden Hospital.² This study recruited 2484 women, aged 30 to 70, who took tamoxifen 20 mg daily, or placebo, for up to 8 years. Risk was primarily determined on the basis of a family history of breast cancer. Although the trial was initially described as a pilot study to evaluate toxicity,²⁶ it was subsequently analyzed for incidence of breast cancer. After a median follow-up of 70 months, 70 breast cancers had occurred, with no difference in incidence between the tamoxifen and placebo arms. This study differed from the NSABP trial in that participants were younger and were allowed to use hormone replacement therapy during the study. The authors suggest that they may have a high proportion of BRCA1 and 2 mutation carriers in their population based on pedigree analysis, and that the negative study results indicate that tamoxifen chemoprevention is ineffective in this subgroup. This seems unlikely, because the incidence of breast cancer, in the placebo arm of the study, was only 5.5 per 1000, lower than that seen in the NSABP trial, and not suggestive of a study population enriched with carriers of a genetic mutation. Overall, the NSABP trial with its 46,858 women years of follow-up and 264 malignancies is considerably more robust than the Royal Marsden and Italian studies, which together have only 103 malignant events. The NSABP trial is the only one of the three studies that was designed to be a definitive prevention trial, and the study results are completely consistent with data from the laboratory and the overview analysis.

Other Concerns in Tamoxifen Prevention

The use of tamoxifen for prevention has prompted several concerns, many of which can be addressed with currently available data. The first of these is that because tamoxifen reduces the incidence of ER-positive breast cancer, its use will increase the amount of poor prognosis, ER-negative breast cancer. Although the NSABP study confirms that tamoxifen reduces the annual rate of ER-positive breast cancer by 69%, it shows no difference in the incidence of ER-negative tumors.¹ In addition, there was no increase in the number of cancers with positive axillary nodes or those more than 2.0 cm in size in the tamoxifen-treated group. Thus, although the proportion of ER-negative tumors will be higher in a population of women treated with tamoxifen, the absolute number will be unchanged.

The other major concern regarding tamoxifen is its toxicity. Is the net result of using tamoxifen for prevention simply trading breast cancer death for death from endometrial carcinoma or thromboembolic disease? The toxicity of tamoxifen is of real concern. The relative risk

of endometrial cancer was 2.53 times higher in the tamoxifen group than the placebo group, although a significant increase in risk was seen only in women age 50 and older. The total number of endometrial cancer events was 51, compared with 264 breast cancer events, emphasizing that endometrial carcinoma is a much less frequent occurrence than breast cancer in a population of women selected for breast cancer risk. In addition, there were no deaths because of endometrial carcinoma in the tamoxifen-treated women. A review of the world's literature²¹ has demonstrated that the endometrial cancers seen in tamoxifen-treated women do not differ in stage and grade from those that occur spontaneously. The risk of mortality because of endometrial cancer can be minimized by ensuring that women have a normal pelvic examination and Pap smear before beginning tamoxifen therapy, and counseling them regarding the significance of spotting and bleeding and the need for regular gynecological follow-up.

The increased risk of deep vein thrombosis and pulmonary embolism in the tamoxifen arm of the P-1 study is also a cause for concern, although, again, a significant excess risk was observed only in women aged 50 and older. The presence of these competing risks emphasizes the need for a complete assessment of a woman's health status before making a decision about the appropriateness of tamoxifen as a breast cancer preventive. Clearly, there will be individuals whose breast cancer risk levels would have made them eligible for the P-1 trial, but who are not likely to achieve an overall benefit from tamoxifen because of the presence of comorbid conditions. Patient education, with discontinuation of tamoxifen during periods of prolonged immobility, will also help to decrease the risk of thromboembolic problems. Ultimately, a properly informed individual must weigh the risks of benefits of tamoxifen chemoprevention against her personal level of breast cancer risk, and the available alternatives of close observation and prophylactic mastectomy, to make a decision that meets her individual needs.

Future Directions

The publication of the NSABP prevention trial was the culmination of three decades of laboratory and clinical investigation, and it provides a valuable option for women at an increased risk for breast cancer. However, many questions remain to be answered. These include the duration of benefit from a 5-year course of tamoxifen for prevention. Clearly, the overview analysis indicates that benefit lasts for at least 5 years after the drug is stopped, and 10-year data will be available shortly. Does tamoxifen "imprint" the breast permanently? Is ongoing

exposure to estrogen (i.e., menopausal status) a factor in determining the duration of benefit? What is the optimal time in a woman's life to give tamoxifen? Serious side effects are less frequent in younger women, but does this leave them at risk later in life when the baseline incidence of breast cancer is higher? Are we giving the optimal dose of tamoxifen or are we giving too much? The dose used in the chemoprevention trial (20 mg daily) was based on experience with the use of tamoxifen as a breast cancer therapy; but could a much lower dose, say 10 mg 3 times per week, be just as effective in postmenopausal women? Finally, are there more effective agents than tamoxifen? A decade ago, when selective ER modulation was first recognized,^{10,15,16} a paradigm shift occurred for drug development that has had important implications for breast cancer prevention in postmenopausal women whose major risk factor for breast cancer is age. If tamoxifen, an anti-breast cancer drug, could maintain bone density and lower circulating concentrations of cholesterol, why not develop a drug to prevent osteoporosis that would prevent breast cancer as a beneficial side effect.²⁷ Raloxifene is the result of this strategy. Raloxifene is approved for the prevention of osteoporosis,²⁸ but an evaluation of the incidence of breast cancer in study participants shows a decrease in women taking raloxifene compared with placebo.²⁹ However, breast cancer incidence was a secondary end point of this study, and the breast cancer risk status of the participants is unknown. The Study of Tamoxifen and Raloxifene (STAR) trial³⁰ will provide a definitive comparison of the risks and benefits of both drugs in a population of high-risk postmenopausal women. Results will be available in 2006.

Conclusions

The development of tamoxifen over the past 30 years has resulted in not only the widespread use of a drug for the effective treatment of breast cancer, but also the first drug to prevent the development of a major cancer, breast cancer.³¹ The pharmacology of tamoxifen has proved to be fascinating³² and has provided an invaluable insight into the target site specificity of the drugs now called selective estrogen-receptor modulators (SERMs) or designer estrogens.³³ If the 20th century saw the development of chemotherapy as a practical approach to the treatment of disease through the synthesis of targeted drugs, then the 21st century holds the promise of being the era of chemoprevention. Tamoxifen has fulfilled its promise of being a targeted chemotherapy and it is now proven to be the first chemopreventive and the herald of a new era of preventive therapeutics.

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