Tamoxifen: the Herald of a New Era of Preventive Therapeutics

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The skeptics and naysayers will view the article by Costantino et al. in this issue of the Journal (1) as an example of the failure of tamoxifen to fulfill its promise. Some love always to criticize, but they rarely contribute constructively. By contrast, Costantino et al. (1) are systematically cataloging potential side effects of tamoxifen, in this case myocardial infarction, in an adjuvant clinical trial (entitled B14) involving women with lymph node-negative breast cancer. They state: “The average annual death rate from coronary heart disease [in their adjuvant trial] was lower for patients who received tamoxifen than for patients who received placebo, but the difference was not statistically significant.” This result is not a surprise, inasmuch as only one third of the approximately 3000 women were at an age (≥60 years old) at which the positive effects of hormone replacement therapy are profound (2). Conversely, I believe that the key finding by the National Surgical Adjuvant Breast and Bowel Project (NSABP) in this study is that tamoxifen, an antiestrogen in the breast, does not increase the risk of coronary heart disease in young patients who have breast cancer. It is reassuring that the majority (i.e., women <60 years old) are not placed at risk for another fatal disease during or after tamoxifen treatment.

Tamoxifen has revolutionized thinking about women’s health issues. These data are a piece of additional information that is driving the evolution of ideas from the systemic treatment of breast cancer toward preventive therapeutics. Laboratory concepts and clinical testing with tamoxifen have laid the foundation for a new generation of medicines that hold the promise of preventing breast and endometrial cancers, osteoporosis, and the principal killer, coronary heart disease. Without the precise and methodical investigation of tamoxifen and its ultimate success as a breast cancer treatment, the potential for advancement in preventive therapeutics would not have been possible.

Tamoxifen has been available for the treatment of advanced breast cancer in the United States since 1978. During the past 20 years, the drug has emerged from obscurity to become the endocrine treatment of choice for all stages of breast cancer (3). It is now the most prescribed cancer medicine and is described by the World Health Organization as an essential drug for the treatment of breast cancer.

Data from the clinical trials of tamoxifen as an anticancer agent are unimpeachable (4). The adjuvant use of this drug confers a survival advantage for patients with node-positive or node-negative breast cancer, and tamoxifen is the only treatment that reduces the incidence of contralateral breast cancer. More than 2 years of tamoxifen reduces this incidence by 54% (4). Similarly, 5 years of adjuvant tamoxifen is better than 2 years of tamoxifen if overall survival of patients with breast cancer is the end point (5). The concept of “longer treatment is better than shorter treatment” is also fundamental for the successful development of preventives for coronary heart disease and osteoporosis.

In October 1986, Dr. Trevor Powles at the Royal Marsden Hospital in London, England, started to recruit women at high risk to a vanguard breast cancer prevention study (6). The scientific reasons for attempting the pilot trial were based on three known facts: 1) Tamoxifen prevents mammary cancer in rats (7,8), 2) tamoxifen prevents contralateral breast cancer (9), and 3) the safety record of tamoxifen in clinical practice was excellent (10). Although there is every reason to believe that tamoxifen can prevent breast cancer, the small pilot study at the Royal Marsden Hospital, with 2012 healthy women at high risk who were randomly assigned to tamoxifen or placebo, has little prospect of answering this important question. The study is too small for accurate results over and above the play of chance. The task of proving the worth of tamoxifen as a breast cancer preventive requires enormous randomized, placebo-controlled, double-blinded clinical trials. These trials are ongoing in North America and Europe (3). Hopefully, they will answer the question posed: “Can tamoxifen prevent breast cancer in healthy women, with or without risk factors?” Each of the three trials currently in progress has set goals to recruit between 13,000 and 20,000 volunteers to have any hope of answering the question. Unfortunately, despite the desire of biostatisticians to analyze purely on the basis of “intention to treat,” this approach is pharmacologically inappropriate. Long-term compliance is the most important issue for the success and ultimate proof of the concept. If there is no drug present in a patient’s body (and tamoxifen is easy to detect with its long biologic half-life), then there can be no protection. Powles et al. (11) have noted a 20% decrease in compliance in their pilot study at 5 years, undoubtedly because of negative publicity about the tamoxifen prevention trials in the early 1990s. This figure is based on patient questioning, rather than on serum assays of the drug, and it is probably an underestimate. The problem can only be worse rather than better. After all of the investment of money, time, and effort, a phar-
macologic confirmation of treatment compliance would be advisable to avoid a nil result based on noncompliance in the treatment arm. (As the trials shrink, they cannot provide secure results if only a few events are to be expected.)

It is now clear that a rigorous examination of the side effects of tamoxifen has opened the door to new therapeutic opportunities. More than two decades ago, the main focus of clinical trials in breast cancer was testing the efficacy of long-term adjuvant tamoxifen therapy. However, a decade ago, the concern became focused on whether tamoxifen, an antiestrogen, would predispose the majority of patients with node-negative disease cured by surgery alone to subsequent early osteoporosis and myocardial infarction. Without this knowledge, prevention trials in healthy women would have been unacceptable. However, after a decade of clinical study, it is now clear that tamoxifen maintains bone density and lowers circulating cholesterol levels in postmenopausal patients [reviewed in (12)]. Tamoxifen has estrogen-like actions in bones and in the control of liver functions. We now appreciate that the drug has target-site specificity in tissues throughout a woman’s body. The actions of nonsteroidal antiestrogens appear to be selective, and there is intense interest in discovering the molecular basis for this observation (13). Knowledge of the mechanisms of action in different tissues would undoubtedly be instrumental in the immediate design of targeted preventives. In the meantime, as we anticipate the marriage between molecules and medicine, we must examine the clinical database and continue advances with opportunities in other directions.

Costantino et al. (1) argue that additional data on myocardial infarction can be derived only from the ongoing NSABP tamoxifen prevention trial. The recruitment goal is 13,000 women, of whom one third are 60 years old or older at recruitment, providing a sample size of fewer than 2000 women in each of the tamoxifen and placebo arms if there is 80% compliance. It is not clear, however, whether the sample size will again be insufficient for a definitive answer. On the one hand, it is true that risk factors for coronary heart disease are very different from those for breast cancer, and the women were selected to be in good health. On the other hand, it is impressive that any positive findings for cardioprotection have been noted with tamoxifen. However, the findings cited (14-16) in the article by Costantino et al. (1) are tantalizing but cannot be considered proof.

In the Stockholm study (14), tamoxifen protected women from first hospital admissions from any cardiac condition as long as treatment was continued; i.e., 5 years was more effective than 2 years. However, as in the NSABP study (1), the decrease that was observed in fatal myocardial infarction was not statistically significant. What I found particularly interesting in the article by Costantino et al. (1) was their observation that definite and possible coronary heart disease-related deaths increased dramatically after tamoxifen was stopped [see Fig. 2, B, in (1)]. Only the Scottish Trial (15) demonstrated a clear-cut decrease in fatal myocardial infarction if at least 5 years of tamoxifen was given. In a follow-up report (16), the Scottish Trial group provided a further analysis and concluded that current users of tamoxifen were less likely to develop myocardial infarction than either never users or former users. One is tempted to speculate whether the Scottish results reflect the high risk of heart disease in Scotland or differences in emergency medicine.

There is agreement (1,14-16) that the mechanism of tamoxifen’s cardioprotective effect is based on its estrogen-like properties, since estrogen replacement therapy produces an impressive reduction in the rate of myocardial infarction (2,17,18). However, these data are derived from large epidemiologic studies rather than from prospective clinical trials.

The question could therefore be asked: “Is tamoxifen really an estrogen with an anomalous pharmacology in the breast?” No. There are distinct differences between estrogen and tamoxifen on circulating lipids and cholesterol, and additional mechanisms should be sought to exploit clues to explain cardioprotection. Wise- man (19) has focused research on low-density lipoprotein (LDL) peroxidation, and she has proposed that tamoxifen, estrogen, and related compounds may protect LDL by stabilizing the molecular structures. Alternatively, estrogen is known to lower circulating cholesterol and fibrinogen levels but to raise high-density lipoprotein levels, each of which is associated with a lowered risk of coronary heart disease. By contrast, tamoxifen does not affect high-density lipoprotein levels but causes a 19% decrease in LDL cholesterol levels (12). What is interesting is that tamoxifen lowers elevated cholesterol levels but has only a modest effect on lowering normal cholesterol levels, i.e., those of less than 200 mg/dL (20). Unfortunately, there are few comparative data on the effects of estrogen and tamoxifen in postmenopausal women. However, a small recent study from the Royal Marsden Hospital group is rather intriguing (21). Tamoxifen produced a 13% and 14% decrease in circulating cholesterol and fibrinogen levels, respectively, whereas estrogen produced only nonsignificant decreases in both parameters. The differences between the nonsteroidal antiestrogens and estrogen may have important implications for long-term preventive therapeutics.

Although tamoxifen has proved to be an invaluable breast cancer therapy, during the past half decade there has been a change in the therapeutic goal for new antiestrogens. This paradigm shift has its origins in the laboratory in 1986. On the basis of findings with tamoxifen and raloxifene, it was suggested that the drugs could be used to prevent osteoporosis in healthy women but that, at the same time, the antiestrogens would also prevent breast and endometrial cancers in a broad population (22). However, we subsequently found that tamoxifen would selectively encourage the growth of endometrial cancer but inhibit the growth of breast cancer under laboratory conditions (23). These conclusions focused concerns on a link between tamoxifen and endometrial cancers during adjuvant therapy. After extensive evaluation of the clinical literature, it is now clear that tamoxifen causes only a modest increase in endometrial cancer (24). However, although this disease is usually of the same stage and grade as endometrial cancer in the general population, it is a troublesome side effect for healthy women. The International Agency for Research on Cancer has recently described tamoxifen as a carcinogen, based on laboratory and clinical data, but the agency emphatically stated that the benefits of tamoxifen as a breast cancer therapy far outweigh its risks. No woman should be denied the benefits of tamoxifen to treat breast cancer because of concerns about endometrial cancer. Be that as it may, the discovery of the carcinogenic potential of tamoxifen in animals caused us to call for new drugs to be developed for the prevention of osteoporosis and atherosclerosis but with the beneficial side effect of preventing breast and endometrial cancers (25). Raloxifene was left as a possible candidate.
The challenge of 1990 has now become a reality. Raloxifene is being tested in clinical trials around the world for the prevention of osteoporosis. Eleven thousand women are participating in these studies aimed at proving that raloxifene can maintain postmenopausal bone density. Since raloxifene is known to exert little or no estrogenic activity in the rodent uterus compared with tamoxifen (26,27), extrapolation of these findings to humans would be a fundamental advance in preventive therapeutics. We have already shown that raloxifene prevents mammary carcinogenesis in the rat (28), and other investigators have reported that raloxifene also decreases circulating cholesterol levels in rats (27) and in patients (29). Plans are well advanced to realize the goal of developing a new therapeutic option for women to prevent osteoporosis; however, the eventual promise is that targeted antiestrogens will prevent coronary heart disease as well as breast and endometrial cancers. The pieces of the puzzle are rapidly falling into place.

It should therefore come as no surprise that a number of tamoxifen analogues (30), e.g., idoxifene and droloxifene, are already being tested in the laboratory and the clinic. At a time when the population is aging, the goal of designing a prevention maintenance therapy becomes a major priority in drug discovery. In its initial drug development in the 1960s, tamoxifen was investigated as a potential "morning after pill" but with the additional prospect of being a palliative agent in the treatment of advanced breast cancer (3). The application of tamoxifen as a contraceptive was ultimately shown to be inappropriate, but a firm commitment to breast cancer clinical trials has resulted in a safe and effective therapeutic option (3). It is truly remarkable that progress in understanding the basic and clinical pharmacology of tamoxifen as an adjuvant therapy should now become the herald of a new era of preventive therapeutics that could revolutionize women's health.

References


Note

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