SERMs: Meeting the Promise of Multifunctional Medicines

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The successful development and clinical evaluation of the selective estrogen receptor modulators in the Study of Tamoxifen and Raloxifene trial provides an occasion to reflect on the milestone that has been achieved and the potential for further progress in the chemoprevention of breast cancer. The evolution of tamoxifen from a successful treatment for breast cancer to the first chemopreventive for any cancer took two decades. Clinicians gained an enormous amount of experience with the use of tamoxifen as a treatment, and, as a result, there were few surprises in terms of efficacy or the side effect profile when the medicine was used to prevent breast cancer in high-risk women. In contrast, raloxifene emerged via the novel path of the evidence-based hypothesis that a drug targeted at one disease, osteoporosis, could also prevent breast cancer. Changes in health care strategies to implement chemoprevention take time, but the evidence now suggests that chemoprevention has become a reality in clinical practice.


With declining investment in cancer research and reluctance by the pharmaceutical industry to address prevention, why must the chemoprevention of breast cancer remain a priority? The disease has a high incidence, with an estimated 1 million women worldwide diagnosed with breast cancer annually. Solid tumors are difficult to control, but it can be argued that substantial progress is being made with targeted therapies for breast cancer that save lives. Treatments targeting the tumor estrogen receptor (ER) (1) or the growth factor receptor HER2/neu (2) confer statistically significant survival advantages in clinical trials (3–7). In the case of tamoxifen, there is evidence that the drug has contributed to the reduction in national death rates from breast cancer (4). With the experience gained from the successful treatment of breast cancer with targeted aromatase inhibitors, it should be obvious to the casual observer that the application of the same principle—in the right women at the right time—to prevent the development of the disease would provide much needed relief for a society burdened with an overextended and overexpensive health care system.

However, it would be naïve to expect that the medical science community can prevent breast cancer at a single stroke. The lessons of the Study of Tamoxifen and Raloxifene (STAR) (8) trial show that progress is slow, often unpredictable, and, at least in the case of STAR trial, dependent on three factors: good ideas that translate from the laboratory to the clinic, fashions in research, and the development of a patenting strategy that ensures exclusivity for a company during clinical testing.

The practical application of molecular theory to the prevention of cancer requires collaborative teams from multiple disciplines to translate a concept into lives saved. Unfortunately, society has erected an artificial barrier to achieving success in chemoprevention. This is because in assessing the success of a new treatment for breast cancer, the benchmark is “lives saved”. In chemoprevention, it may take a generation to quantify “lives saved”, but if the medicine is safe and there is a dramatic reduction in the incidence of breast cancer, it follows that the treatment must ultimately reduce the death rate from breast cancer. Most importantly, the medicine used for chemoprevention should have minimal side effects to ensure compliance. To achieve the goal of chemoprevention, prospective clinical trials must demonstrate advantages over current approved therapies or the traditional “wait and see” approach with routine screening.

Once the concept of chemoprevention becomes a reality and an agent is proven to reduce the risk of breast cancer, the cost–benefit ratio to the health care system must be advantageous. Only half of the women who develop breast cancer can be identified using the Gail model (9), and identification of specific women for intervention is based on large populations with only a small percentage of women developing the disease. At present, therefore, large numbers of women must be treated to benefit the few. As a result, the preventive treatment must be of low cost, highly effective, and without serious side effects if health care is to be improved, and these qualities are critical to widespread acceptance by national managed health care systems.

The feasibility of reducing breast cancer incidence in high-risk pre- and postmenopausal women has been established by the pioneering work of Fisher et al. and the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 Study (10,11). Tamoxifen administered at a daily dose of 20 mg for 5 years reduced breast cancer incidence by about 50%. This milestone achievement in translational research was the result of a century of laboratory and clinical studies to understand the genesis of breast cancer (12). The STAR trial now establishes the practicality of chemoprevention of breast cancer, but the knockout blow has yet to be delivered. My purpose in this commentary is to explain how cancer research evolved to result in the STAR trial
and to present options available to future progress in breast cancer chemoprevention.

**Tamoxifen, the First Selective Estrogen Receptor Modulator**

The story of the “reinvention” of tamoxifen—at one time a failed contraceptive discovered in the fertility control department at ICI Pharmaceuticals Division (now AstraZeneca)—as the first targeted therapy for the treatment of ER-positive breast cancer has recently been described (13,14). The scientific approach to cancer drug development used in the 1960s and 1970s is adequately summarized elsewhere (13), but the clinical focus at that time was directed exclusively to breast cancer therapy rather than chemoprevention. The scientific principles established in the laboratory—of targeting ER-positive tumors for treatment, while coupleing the treatment with long-term adjuvant treatment regimens—produced a substantial increase in patient survivorship. It has been estimated that 500,000 women are alive today because of long-term adjuvant therapy being appropriately administered to patients with ER-positive tumors (13).

However, the transition of tamoxifen from a treatment to chemopreventive was already occurring in the 1970s and 1980s during the era of breast cancer treatment. The discovery that tamoxifen could prevent the initiation and promotion of rat mammary carcinogenesis (15–18), coupled with the clinical finding that tamoxifen treatment reduced the anticipated increase of contralateral breast cancer (19), acted as a catalyst for consideration of tamoxifen as a potential chemopreventive in women at elevated risk (20–22). The major obstacles to progress through the 1980s were in deciding whom to treat and when to deploy a chemopreventive agent, along with safety concerns. Up until the early 1980s, tamoxifen was classified as a nonsteroidal antiestrogen (23), which created a dilemma: if estrogen was essential to maintain bone density and could possibly protect women from coronary heart disease, how could women at risk for breast cancer be treated to reduce that risk if the result would be increases in osteoporotic fractures and deaths from coronary heart disease? The recognition of selective ER modulation during the 1980s ultimately propelled selective estrogen receptor modulators (SERMs) to center stage in efforts to improve women’s health and to the testing of two of them in the STAR trial.

**Selective Estrogen Receptor Modulation**

The recognition of SERM activity in the target tissues of laboratory animals resulted in several successes in women’s health. Paradoxically, while tamoxifen was being recognized as an “antiestrogen” that blocked breast or mammary cancer growth (15,16,24,25), it also was found to maintain bone density in ovariectomized rats (26–28). The concept of target tissue–specific effects of tamoxifen was extended further with the discovery that in the same athymic mouse tamoxifen prevented estrogen-stimulated human breast tumor growth while increasing uterine weight and stimulating the growth of endometrial carcinoma (29,30). This concept translated immediately to improvements in health care (31,32) with the observation that tamoxifen increased the risk of endometrial cancer but decreased the incidence of contralateral breast cancer in postmenopausal patients (33). This observation was subsequently confirmed in other randomized clinical trials using tamoxifen as a treatment (34), with the results that patient care was improved and gynecologists were involved in the health care of breast cancer patients. Most important, the new knowledge about the SERM action of tamoxifen allowed measures to be put in place to detect increases in early-stage, low-grade endometrial cancer in the NSABP P-1 chemoprevention trial (10,11).

Data showing that bone density was maintained in rats treated with tamoxifen (26) were used to support the evaluation of the actions of tamoxifen on postmenopausal bone density in the Wisconsin Tamoxifen Study. A secondary endpoint in this trial was the levels of circulating lipids because it had been established that tamoxifen reduces circulating cholesterol levels in the ovariectomized rat (35). In fact, the drug already possessed a patent in the United Kingdom for use as a hypocholesterolemic agent (13). The Wisconsin Tamoxifen Study demonstrated that tamoxifen maintained bone density in postmenopausal women (36) and reduced the circulating levels of low-density lipoprotein (LDL) cholesterol, but did not reduce the levels of beneficial high-density lipoprotein cholesterol (37,38). Thus, there were grounds to conclude that bone density would be maintained in postmenopausal women treated with tamoxifen and to suggest that the drug might reduce the risk of coronary heart disease (39).

These predictions were addressed in the results of the NSABP P-1 study (10,11): tamoxifen reduced the risk of breast cancer by 50%, elevated the risk of endometrial cancer in postmenopausal women fivefold, and reduced (though not to a statistically significant extent) the incidence of fractures. However, it did not reduce the incidence of coronary heart disease. In the P-1 trial, tamoxifen also reduced the incidence of breast cancers in women with hyperplasia by 80% and reduced ductal carcinoma in situ by 50%. Tamoxifen also increased the risk of deep-vein thrombosis and pulmonary emboli, and these results were confirmed subsequently in the first International Breast Intervention Study, in which Cuzick et al. (40,41) found an increase in deep-vein thrombosis with tamoxifen and an increase in the death rate caused by pulmonary emboli as a result of elective surgical procedures. The results of the NSABP P-1 trial are summarized in Fig. 1, which shows the incidence of recorded endpoints in the control and treatment arms at 48 and 74 months of follow-up. Tamoxifen was approved by the US Food and Drug Administration (FDA) for reduction of the risk of breast cancer in high-risk women in 1998.

**Raloxifene as a Multifunctional Medicine**

The development of raloxifene to its current status as a treatment for osteoporosis and a preventive treatment for breast cancer is summarized in Fig. 2. The findings that the failed breast cancer drug keoxifene (LY156758) (42,43) could preserve bone density in ovariectomized rats (26), could prevent rat mammary carcinogenesis (44), and was less effective than tamoxifen in stimulating the growth of human endometrial carcinomas implanted into athymic mice (45) demonstrated that the target tissue–selective actions of tamoxifen (now called selective ER modulation) were common to other drugs in the group previously referred to as nonsteroidal antiestrogens. These laboratory findings resulted in the publication of a strategy by which nonsteroidal antiestrogens related to tamoxifen such as keoxifene could be used to simultaneously prevent osteoporosis in postmenopausal women and reduce the incidence of breast cancer in the general population (46,47). It was as a
result of this strategy, supported by the data from animal models (26,44,45), that keoxifene (LY156758) was reinvented as raloxifene (LY139481 HCL). When the previous laboratory findings that raloxifene maintained bone density in the rat, lowered circulating cholesterol, and possessed low activity as an estrogen in the rodent uterus were confirmed (48), clinical studies were initiated to evaluate raloxifene as a novel agent to preserve bone density in osteoporotic women.

Clinical trials demonstrated that raloxifene treatment maintained bone density in women at risk for osteoporosis (49) and reduced LDL cholesterol (50) to the same degree as tamoxifen (36,37). The success of the SERM concept was underscored by the observation that raloxifene reduced spinal fractures in women at high risk for such fractures (51) and reduced the risk of breast cancer by 75% without measurable increases in endometrial cancer (52,53). Raloxifene was approved by the FDA for the treatment and prevention of osteoporosis in 1998.

The confirmation that SERMs are multifunctional medicines suggests two opportunities for chemoprevention of breast cancer. One is based on an indirect approach, i.e., introducing a novel modality to prevent osteoporosis and reduce the risk of breast cancer as a beneficial side effect (46,47). The other is a direct approach, namely reducing the risk of breast cancer in women at elevated risk by treating them with raloxifene, the feasibility of which was determined by the STAR trial. Both approaches can now be evaluated.

The Indirect Approach to Breast Cancer Risk Reduction

It is estimated that half a million women are currently taking raloxifene for the treatment and prevention of osteoporosis (8). To preserve and build bone density, the medicine must be taken continuously, and in practice, the treatment regimen could last for 10 years or more. The pivotal antiosteoporosis trial—the Multiple Outcomes of Raloxifene Evaluation (MORE)—was extended for an additional 4 years as a safety vanguard study; this study evolved
into the Continuing Outcomes Relevant to Evista (CORE) study. The results from this long-term trial of raloxifene now provide an invaluable database to estimate reductions in age-related incidence of breast cancer. The breast cancer incidence rates among postmenopausal women at risk for osteoporosis have been estimated to be 1.4 and 4.2 cancers per 1000 women per year for women taking 60 mg raloxifene daily or placebo, respectively (54).

These data from the CORE trial (54) permit a rough calculation of the impact of raloxifene on public health. With hormone replacement therapy currently considered as a final option for the treatment and prevention of osteoporosis, the “at-risk” population is usually treated initially with a variety of formulations of bisphosphonates that have no impact on breast cancer incidence. Thus, based on the results of the CORE trial (54), if 500,000 postmenopausal women took bisphosphonates for 10 years to prevent osteoporosis, there would be an accumulation of 21,000 (500,000 women × 10 years × 4.2 breast cancers per 1000 women per year) breast cancers requiring surgery and adjuvant therapy with radiation, chemotherapy, and/or antihormone therapy. If these same women received raloxifene to prevent osteoporosis, there would be, based on current estimates, 7000 (500,000 women × 10 years × 1.4 breast cancers per 1000 women per year) breast cancers. Thus, there would be 14,000 fewer breast cancers and 14,000 fewer women who require surgery and adjuvant therapy, not to mention a 40% decrease in the number of fractures experienced by the 500,000 high-risk women (51). This advance in public health must be viewed as a clear success for the SERM concept.

### Conclusions of the Study of Tamoxifen and Raloxifene

Building on this advance, the recent results of the STAR trial now promise to offer additional opportunities for successful use of SERMs to treat women in the general population, specifically women who are at elevated risk for breast cancer but are not osteoporotic. The STAR trial is part of an ongoing exploration of the potential of medicines to reduce breast cancer incidence in populations of women at high risk, and therefore, its results cannot be considered in isolation but must be assessed based on the prior experience with the NSABP P-1 trial. However, the NSABP P-1 and the STAR trials have important differences in their populations and designs. For example, the STAR trial participants are at a higher risk for breast cancer than the women who participated in the NSABP P-1 prevention trial (8, 10). Both the STAR and NSABP P-1 trials recruited women ascertained to be at elevated risk using the Gail model (55), but the STAR trial only recruited postmenopausal women. (Raloxifene has not been evaluated appropriately in premenopausal women and should not be used to treat premenopausal women at risk for breast cancer.) Thus, only relative trends can be identified in lieu of exact comparisons.

The broad conclusions of the STAR (NSABP P-2) trial are summarized and compared with the two evaluations of the NSABP P-1 trial (10, 11) in Fig. 1. The incidence rates of the various endpoints in the NSABP P-1 trial are only the results for women more than 50 years of age, and, therefore, valid comparisons can be made with incidence rates in the NSABP P-2 trial. However, the data pertaining to noninvasive breast cancer in the P-1 trial were not broken down into women above or below 50 years and were represented only as cumulative rates and not as an annual rate (10, 11). These data are therefore omitted from Fig. 1. The most promising results of STAR trial are, first, that raloxifene is equivalent to tamoxifen at reducing the incidence of invasive breast cancer and, second, that it is associated with a lower incidence of endometrial cancer, endometrial hyperplasia, hysterectomies, cataracts and cataract surgery, and total thromboembolic events (pulmonary embolism or deep venous thromboses) than tamoxifen. The controversial aspect of the trial appears to be the failure of raloxifene to control completely the development of noninvasive breast cancer after 2 years of treatment (8).

Examination of the breast cancer endpoints of invasive and noninvasive diseases and comparison of STAR trial data with CORE/MORE trial data shows that raloxifene actually caused a reduction in invasive breast cancer by between 65% and 75% in osteoporotic women and not the estimated 50% decrease observed in STAR trial (8, 52, 54). STAR trial results (8) cannot be compared with previous studies of noninvasive breast cancer (10) because there are no reported data on the effectiveness of treatment in postmenopausal women alone in these studies and numbers are too small in CORE/MORE trial (52, 54) for valid comparisons. Possible explanations for the good but suboptimal performance of raloxifene in preventing breast cancer in STAR trial are the differing pharmacologies of raloxifene and tamoxifen and the different populations of CORE/MORE and STAR trials.

The pharmacologic properties of tamoxifen and the group of benzothiophene nonsteroidal antiestrogens that include raloxifene are very different. Tamoxifen exhibits more estrogen-like properties in the rodent uterus than do benzothiophene-related compounds (43, 56), and the biologic properties of the tamoxifen–ER complex are more similar to the estrogen–ER complex than the complex formed by raloxifene binding (57, 58). Studies in vivo demonstrate that raloxifene-like compounds have an extremely short duration of action compared with that of tamoxifen (44, 59, 60). This is because the polyphenolic benzothiophene derivatives have poor bioavailability (2%) and undergo rapid phase II metabolism in the intestines and liver (61, 62). In contrast, 40% of tamoxifen absorption is from the gastrointestinal tract, and the drug has a long biologic half-life so that its levels persist for up to 6 weeks after therapy stops. Tamoxifen is also metabolized to active phenolic derivatives with high affinity for the estrogen–ER (23). Thus, compliance may be critical to maintain the optimal antiestrogenic actions of raloxifene and tamoxifen, but the effectiveness of tamoxifen, the suboptimal SERM with more estrogenic properties compared to raloxifene in target tissues, will be less dependent on optimal compliance. Failure to maintain adequate raloxifene levels in noncompliant STAR trial patients would allow for promotion of breast tumor growth by endogenous estrogen.

### Raloxifene Use for the Heart

The demonstrated effectiveness of SERM treatments in lowering circulating cholesterol levels (37, 38, 50) and the presumed ability of hormone replacement therapy to lower the risk of coronary heart disease prompted the initiation of a prospective clinical trial to evaluate the ability of raloxifene to reduce the risk of coronary heart disease. The Raloxifene Use for the Heart (RUTH) trial (63) randomly assigned 10,101 postmenopausal women...
with coronary heart disease or multiple risk factors for coronary heart disease to either 60 mg raloxifene (5044 women) or placebo (5057 women). The two primary outcomes, a coronary event (death, myocardial infarction, or hospitalization for an acute coronary syndrome) and invasive breast cancer, were evaluated after a median follow-up of 5.6 years. There was no evidence that raloxifene had a statistically significant effect on the risk of coronary heart disease (63) despite the previous tantalizing indications that both raloxifene (64) and tamoxifen (39) might have some benefit. The result, however, is consistent with conclusion of the Oxford Overview Analysis that tamoxifen does not improve survival from causes of death other than breast cancer (4). In contrast to what was observed in the MORE trial (52), death from stroke in the RUTH trial was elevated to a statistically significant extent in women taking raloxifene, with 59 deaths from stroke in those taking raloxifene compared to 39 deaths from stroke in controls (64).

Despite this apparent setback, the RUTH trial has provided additional important information about cancer incidence in a placebo-controlled trial of raloxifene. Endometrial cancer was not elevated in women treated with raloxifene. There were 21 endometrial cancers in 3900 nonhysterectomized women receiving raloxifene and 17 endometrial cancers in 3882 placebo-treated controls. These data clarify the results of the STAR trial where the numbers of endometrial cancers in women treated with tamoxifen increased but not to a statistically significant extent compared with the numbers among women treated with raloxifene. It is possible that the higher hysterectomy rate in women treated with tamoxifen resulted in a lower endometrial cancer rate.

The second planned outcome of the RUTH trial was the incidence of invasive breast cancer. The rate for the placebo-treated women was 2.7 per 1000 women per year, whereas the rate for raloxifene-treated women was 1.5 per 1000 per year. This 44% decrease in invasive breast cancer is consistent with the STAR trial but, again, not as impressive as that observed in the CORE/MORE trial (52,54).

**Progress in Prevention**

The success for the two SERMs, tamoxifen and raloxifene, has depended on good ideas based on effective translational research, changes in the fashions of research for the past 40 years, and the development of a patenting strategy that permits a company to test an idea during the period of exclusivity. The fashions in research changed from a focus on contraception in the 1950s and 1960s to breast cancer treatment in a period that extended from the 1970s through 1990s and finally to the current focus on chemoprevention of breast cancer and the prevention of osteoporosis. Preexisting ideas about the potential of breast cancer chemoprevention (20–22) and use of SERMs to prevent osteoporosis and breast cancer (46,47) flourished as opportunities for the broad applications of SERMs were advanced, but these advances only occurred because of delays in patenting that permitted commitment by the pharmaceutical industry. Tamoxifen was not patented for breast cancer treatment in the United States until 1985, despite the fact that FDA approval was obtained in December 1977 (13). Similarly, raloxifene was patented as a potential cancer treatment in the early 1980s, but the patent for osteoporosis did not occur until 1992 (65). It is unlikely that any progress in women’s health and chemoprevention would have occurred without patent protection. But what of future progress? The academic community cannot advance women’s health without optimal medicines to test. Despite the advances noted with tamoxifen and raloxifene, these were not optimal agents designed to perform the tasks they were called upon to perform. The truth is that there was nothing else available from the pharmaceutical industry.

For the moment, raloxifene is proving to be an important advance in chemoprevention because it is a multifunctional medicine that can target women at low risk for breast cancer with osteopenia and healthy women with a high risk of breast cancer. Nevertheless, new SERMs are necessary for clinical testing in postmenopausal women. The SERM concept (46) clearly works, but a long-acting SERM is required to replace raloxifene, a drug that does not appear to perform optimally in a high-estrogen environment. The long-acting drug arzoxifene is superior to raloxifene in laboratory studies for chemoprevention (66), but its development has been stalled because raloxifene has proved to be financially beneficial to treat and prevent osteoporosis.

And what of tamoxifen, the first SERM? Twenty years ago, tamoxifen was noted to increase the risk of endometrial cancer in postmenopausal women (33) but not in premenopausal women. Additionally, there are reasonable concerns about deep venous thromboses and pulmonary emboli, although these concerns do not extend to the premenopausal women who are at elevated risk for breast cancer (10). The future use of tamoxifen for chemoprevention may well be restricted to high-risk women who will develop breast cancer during their premenopausal years. The risk–benefit ratio for tamoxifen is favorable (67) in premenopausal women. However, perhaps more importantly, the antitumor actions of 5 years of adjuvant tamoxifen persist and increase for at least 10 years after treatment stops (4). The posttreatment protective effect of tamoxifen is noted in animal models (fewer tumors developed) (17), adjuvant clinical studies [decreased mortality (4) and decreased contralateral breast cancer] (3), and continuing decreases in primary breast cancer in the NSABP P-1 trial (11). A prevention strategy using tamoxifen in high-risk premenopausal women will continue to prevent tumor development after tamoxifen treatment is stopped and when side effects and quality-of-life issues disappear. However, it must be stressed that raloxifene and aromatase inhibitors cannot be used to block estrogen synthesis to reduce breast cancer risk in this patient population. Raloxifene has not been tested in premenopausal women, and the manufacturer recommends against this indication. Aromatase inhibitors are only effective in blocking the constitutive synthesis of estrogen in postmenopausal women. Ovarian estrogen synthesis in premenopausal women is regulated by a pituitary-controlled feedback system, so the blockade by an aromatase inhibitor is reversed by enhanced gonadotropin secretion. Therefore, tamoxifen remains the only proven intervention in premenopausal women.

Tamoxifen and raloxifene both specifically reduce the incidence of ER-positive breast cancer. However, as the testing of chemopreventive agents targeted to the ER progresses and evolves, cost-effectiveness issues are being addressed. A recent study by Melnikow et al. (68) illustrates the dilemma for health care management posed by the price of treatment. The authors concluded that tamoxifen-pricing differences between different health care
systems in the United States and Canada are important and that tamoxifen’s use as a chemopreventive becomes cost-effective only for women at the highest risk in places where the cost of the drug is extremely low. The issue of cost-effectiveness is now even more timely as the cost of switching from tamoxifen to the more expensive aromatase inhibitors for the treatment of breast cancer has become a major issue for National Health Services in Europe. The next round of chemoprevention trials will compare SERMs with the aromatase inhibitors. The issue of osteoporosis induced by aromatase inhibitors remains a health care concern because the cost of treating large populations of women with expensive agents, monitoring them with dual energy x-ray absorptiometry, and providing them with supplementation with bisphosphonates and Vitamin D only to benefit the few may ultimately be an unreasonable public health care burden. In contrast, the proven promise of raloxifene, a safer SERM targeted specifically to women for the treatment and prevention of osteoporosis but one that also reduces the incidence of breast cancer, is a major first step in developing multifunctional medicines to improve health care.

References


Notes

Dr V. C. Jordan is supported by the Department of Defense Breast Program under Center of Excellence award number BC50277, SPORE in Breast Cancer CA 89018, R01 GM067156, Fox Chase Cancer Center (FCCC) Core Grant NIH P30 CA006927, the Avon Foundation, and the Weg Fund for FCCC. Views and opinions of and endorsements by the author(s) do not reflect those of the US Army or the Department of Defense.

Funding to pay the Open Access publication charges for this article was provided by the Weg Fund of Fox Chase Cancer Center, Philadelphia, PA.

Manuscript received August 8, 2006; revised December 21, 2006; accepted January 18, 2007.