Improvements in Tumor Targeting, Survivorship, and Chemoprevention Pioneered by Tamoxifen

Review Article [1] | May 01, 2006
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Twenty years ago, antiestrogen therapy with tamoxifen played only a secondary role in breast cancer care. All hopes to cure metastatic breast cancer were still pinned on either the discovery of new cytotoxic drugs or a dose-dense combination of available cytotoxic drugs with bone marrow transplantation. A similar strategy with combination chemotherapy was employed as an adjuvant for primary breast cancer. Simply stated, the goal was to kill the cancer with nonspecific cytotoxic drugs while keeping the patient alive with supportive care. However, medical research does not travel in straight lines, and an alternative approach emerged to solve the problem of controlling tumor growth with minimal side effects: targeted therapy. The approach of using long-term antihormone therapy to control early-stage breast cancer growth would revolutionize cancer care by targeting the tumor estrogen receptor (ER). The success of the strategy would contribute to a decrease in the national mortality figures for breast cancer. More importantly, translational research that targeted the tumor ER with a range of new antiestrogenic drugs would presage the current fashion of blocking survival pathways for the tumor by developing novel targeted treatments. But a surprise was in store when the pharmacology of "antiestrogens" was studied in detail: The nonsteroidal "antiestrogens" are selective ER modulators—ie, they are antiestrogens in the breast, estrogens in the bone—and they lower circulating cholesterol levels. This knowledge would establish a practical approach to breast cancer chemoprevention for women at high risk (tamoxifen) and low risk (raloxifene).

Mina and Sledge presented a valuable overview of the changes that have occurred during the past few decades in the treatment of breast cancer.[1] I am pleased to be invited to offer my personal observations on the changes that have occurred in the endocrine treatment of breast cancer over this period. These changes are considerable, and I will approach my task as an observer from the bottom looking up. I say this because, as a new PhD graduate in pharmacology who had studied "antiestrogens" as an academic exercise from 1969 to 1972, I was told I could now do anything I wanted. I chose to contribute to the reinvention of an orphan drug, ICI 46,474, into tamoxifen. Each generation creates and defends its own fashion in cancer research, and this concept is well illustrated by the early resistance to change in the approach to treating breast cancer. Virtually no one was interested in "another endocrine therapy," as combination cytotoxic chemotherapy was predicted to cure cancer.

In contrast, it is now clear that the approach to health care has changed in the past 20 years, not once but twice, as a result of advances in endocrine therapy. In the first case, Mina and Sledge identify tamoxifen as the first targeted treatment for breast cancer.[1] This is a reasonable assessment, as the translation work on tumor targeting ultimately was shown to be successful.[2] Perhaps equally important was the fact that tamoxifen has a beneficial therapeutic ratio that facilitated its use as a long-term adjuvant therapy. The application of the laboratory strategy of long-term antihormonal therapy targeted to the estrogen receptor (ER)[3,4] saved lives, which in turn has contributed significantly to the national reductions in mortality.[5,6]

Secondly, the knowledge gained with tamoxifen propelled the drug forward for testing as the first chemopreventive for any cancer, created a new drug group—the selective ER modulators (SERMs)—and resurrected keoxifene, a failed breast cancer drug,[7] to be the first SERM for the treatment and prevention of osteoporosis, but with the ability to reduce the risk of breast and endometrial cancer.[8]

Historical Background
The story of the discovery of tamoxifen as a "morning after pill" in the 1960s to then being reinvented as a targeted breast cancer therapy in the 1970s has been recounted recently.[3,4] Nevertheless, the tale is important to retell, as it illustrates how changing fashions in research can influence progress. The development of the oral contraceptive by Pincus and colleagues at the Worcester Foundation during the 1950s changed society forever.
enthusiasm to create new ways to manipulate reproduction, the fashion of research in reproductive biology declined steadily throughout the 1960s with a decreased investment in the development of new contraceptive methods. But, in its place, the "War on Cancer" was declared in 1971. The tale of tamoxifen also illustrates the length of time that must be taken to evaluate successful treatment strategies to effect changes in health care. Nevertheless, momentum to change the approach to the treatment of breast cancer, and, indeed, of any cancer, accelerated with tamoxifen. The drug became a ubiquitous tool to test targeting in breast cancer. More importantly, tamoxifen set the stage for the current optimism that important advances in cancer research are within our grasp and the sincere belief that clever people will solve problems and develop practical ways to kill cancer cells selectively with minimal side effects for the patient. Although it is not possible to recapture the exact mood of the clinical community during the early 1980s, it is fair to say that chemotherapy was king. It is possible, however, to illustrate the unimportance of antihormonal therapy by reference to the work of opinion leaders at the time.

In the early 1980s, you could refer to two bibles if you wanted to know about a particular treatment or medicine. Goodman and Gilman's *The Pharmacological Basis of Therapeutics* (7th edition), published in 1985, is where you would go first to look up the importance of tamoxifen in medicine. The book has less than a page on the anticancer uses of tamoxifen and a short discussion of antiestrogen action relevant to the induction of ovulation. What you will find is reference to a couple of review articles that were written to consolidate all the small and scattered reports about the pharmacology, clinical studies, and future potential of antiestrogens.[9,10] The second book—the *Pharmacologic Principles of Cancer Treatment*—was edited by Bruce Chabner and published in 1982. In this 443-page book, the structure of tamoxifen is shown on page 148 and descriptive information about antiestrogen therapy appears on pages 164 and 165. The absence of anything further about the agent was not an omission. There was not much optimism about the use of tamoxifen at that time. Although a preliminary study of the efficacy of ICI 46,474 (tamoxifen) first appeared in 1971, the response rates were the same as for other endocrine therapies.[11] The clinical development of tamoxifen to treat advanced breast cancer did not set the world on fire! Importantly, however, there were fewer side effects compared to other treatments. Tamoxifen was approved for the treatment of advanced breast cancer in the United States in December 1977, but how could the drug be used to its best advantage in the clinic?

Focus on Chemotherapy

In the early 1980s, most eyes were focused on the merits of combination chemotherapy and its value as a curative adjuvant therapy. Reference to the proceedings of a 4-day meeting reported in *Adjuvant Therapy of Cancer IV*, edited by Stephen Jones and Syd Salmon (1984), illustrates the quest by cooperative groups worldwide to use chemotherapy to cure cancer. Almost half of the 64 papers presented focus on the adjuvant therapy of breast cancer, with only 8 of the 26 breast cancer papers mentioning the evaluation of 1 or 2 years of tamoxifen treatment in their protocols. Away from the application of adjuvant therapy to enhance survival, the quest for cancer cure was focused on dose-dense chemotherapy and the empirical application of bone marrow transplantation. This was admirably reviewed by I. Craig Henderson in *Breast Diseases*.[12] That said, why did the process of moving from concept to changes in health care take such a long time for a novel targeted therapy with few side effects?

The Lost Decade—Tamoxifen on Life Support

In April 1972, the preliminary clinical data on ICI 46,474 was reviewed by scientists at ICI Pharmaceuticals Division (now part of AstraZeneca), near Manchester, UK, but there was reluctance to pursue the development of the drug as a short-term palliative treatment for breast cancer. Several factors were considered in the decision not to develop ICI 46,474. The compound had no patent protection in the United States; this would only be granted in 1985. Most importantly, there was estimated to be no significant market for a palliative drug that would only be effective for about a year for one out of three metastatic breast cancer patients. In the early 1970s, the total incidence of metastatic breast cancer in the United Kingdom was only a few thousand patients per year. Worldwide figures were obviously larger, but the drug was to be 10 times more expensive than the standard endocrine treatment (diethylstilbestrol). The turnover of the drug was estimated to be £500,000 per annum at most, with only £50,000 profit. It would always be an orphan drug, and clinical development was stalled.

With the wisdom of hindsight, there was also no infrastructure at ICI Pharmaceuticals to support a breast cancer program. The division was not a "cancer company," and there was no pipeline of compounds to replace ICI 46,474 should subsequent studies reveal unacceptable toxicities (as they
did with rat liver carcinogenesis). Development could not be taken seriously. In the clinical community, it was generally accepted that another endocrine therapy would add almost nothing to the medical armamentarium of breast cancer therapies. Overall, there was little initial enthusiasm for the use of a new antihormonal therapy that benefited a minority of patients for a short period.

A Drug in Search of Applications

A.L. Walpole, Head of the Fertility Control Program at ICI Pharmaceuticals, discovered the antifertility properties of the molecule ICI 46,474 in the early 1960s. The compound was an effective "morning after pill" in rats[13] but induced ovulation in women.[14] The project did not achieve its goal. Nevertheless, the observations that ICI 46,474 had reduced side effects compared to standard endocrine therapies used to treat advanced breast cancer[11,15] convinced Walpole that the drug should be marketed at least as an option for treatment. The drug was available for experimentation but looking for applications. Although no studies were conducted by scientists at ICI, Walpole ensured that my laboratory would be supported to find those applications. Regrettably, Walpole died suddenly in 1977 and never saw the benefits that tamoxifen was to bring.[16,3]

A scientific strategy for the appropriate clinical application of tamoxifen was developed in the laboratory to target the drug to the tumors that were the most likely to respond. Tamoxifen blocked the binding of estradiol to human breast and rat mammary tumor ERs and prevented the induction and growth of ER-positive carcinogen-induced rat mammary carcinomas.[3,4] These early studies raised the question of whether tamoxifen could prevent the majority of breast cancers—ie, ER-positive breast cancer. However, the finding that long-term tamoxifen treatment in animals with early mammary cancer—ie, a low tumor burden[3]—could create a tumor-free state suggested longer would be better than shorter durations of adjuvant therapy.

The laboratory observations were to prove remarkably effective as an approach to treating women with early node-positive and node-negative ER-positive breast cancer. However, the original clinical strategy in the 1970s for the evaluation of tamoxifen was to use 1 year of adjuvant treatment after surgery. The reason for this was that tamoxifen was only effective for the treatment of advanced breast cancer for about a year, and there was a sincere concern that longer adjuvant treatment durations would result in premature drug resistance. This approach was to change. With these observations as background, all of the pieces of the puzzle were about to come together in 1986, to create a significant advance that would change health care twice.

Pieces of the Puzzle

By 1986, clinical studies were in place around the world to evaluate long-term use (3 or more years) of tamoxifen by cooperative clinical trials groups.[17-19] Michael Baum[20] was the first to report the survival advantage achieved with 2 years of adjuvant tamoxifen treatment, but regrettably there was no correlation with ER status.[21] Although alternative mechanisms of action for tamoxifen were examined for some time,[22] it is generally agreed that the original conclusions were methodically flawed.

An enormous advance in medicine is the introduction of meta-analysis or Overview analysis of small randomized clinical trials that individually show little or no benefits for agents under investigation but together provide a valid result. The Overview analysis of breast cancer clinical trials was first conducted at Heathrow Airport in 1984.[23] The results when they were published in full in 1988 demonstrated a significant advantage for postmenopausal patients receiving tamoxifen.[24] Most importantly, a Consensus Conference held in Bethesda, Md, recommended that tamoxifen should be used as an adjuvant therapy for postmenopausal ER-positive, node-positive patients with breast cancer.[25] Although the title of the summary statement was somewhat misleading ("Adjuvant Chemotherapy for Breast Cancer"), the Consensus Panel did at least point out that 2 years of adjuvant tamoxifen treatment was better than 1 year, but further studies of duration were needed.

Patent Politics

The year 1985 was a good time for ICI Pharmaceuticals to be awarded a use patent for tamoxifen from the US Court of Appeals. Although tamoxifen was approved for the treatment of advanced breast cancer in postmenopausal women in 1977 in the United States, the patent situation was unclear. In 1963, ICI Pharmaceuticals filed a broad patent in the United Kingdom that stated, "The alkene derivatives of the invention are useful for the modification of the endocrine system in man and animals and they may be useful for the control of hormone dependent tumors or for the sexual cycle or aberrations thereof. They also have useful hypocholesterolaemic activity."
Regrettably, the patent was repeatedly denied by US authorities because of the perceived primacy of existing Merrell patents (the manufacturer of clomiphene) awarded in the late 1950s. The patent examiners also required that the reference to tumors should be removed as a "fantastic claim." The award of a patent for tamoxifen in 1985 started a 17-year exclusivity use patent in the United States just at the time when the patent for tamoxifen had expired worldwide, and just at the time that tamoxifen was poised to change healthcare! Thus, the cumulative 40-year patent for tamoxifen was to be the financial engine that facilitated the development of a whole range of cancer therapies from AstraZeneca and subsequently other companies (Table 1).

From the Theoretical to the Practical

However, not only was treatment with tamoxifen emerging as a valuable therapeutic option, but also research on the aromatase inhibitors was slowly gaining momentum on the sound principle that creating a "no estrogen state" was a reasonable treatment strategy for breast cancer. Most research for the preceding 15 years was focused on aminogluthethimide,[26-28] but the well described toxicities of this agent prevented long-term adjuvant studies. In contrast, the pioneering translational research by Brodie[29] with 4-hydroxyandrostenedione (formestane) was poised to launch the careers of numerous targeted aromatase inhibitors to become the new "crown princes."

A revolutionary approach to cancer control was also moving from the theoretical[30] to the practical in 1986. The novel approach of using chemicals or dietary interventions to prevent breast cancer started to be taken seriously in the US with a workshop entitled "Workshop on Chemoprevention of Breast Cancer" that occurred on December 1-2, 1983, in Rye, NY.[31] The choices for chemoprevention were danazol and tamoxifen. I put forward the case for tamoxifen, based on published laboratory studies. It was possible to prevent the initiation of rat mammary[32,33] or promotion of rat mammary carcinogenesis with tamoxifen.[34,35] Clinical colleagues (Pritchard, Carbone, Wolmark) considered intervention with tamoxifen. However, chemoprevention studies were stalled because of the reasonable uncertainties about long-term toxicities with tamoxifen and the selection of an appropriate target population.

In contrast, Trevor Powles in the UK chose to make a bold move and initiated a pilot clinical study. Two hundred women with a perceived elevated risk for developing breast cancer were randomized to tamoxifen or placebo. Recruitment began in October 1986. Powles based his conviction primarily on the observation that tamoxifen was a preventive for mammary cancer in animal models[35] and the expanding clinical experience with tamoxifen as an adjuvant therapy. His preliminary study, published in 1989,[36] was intended to be the vanguard to a much larger national study.

Regrettably, events would take an ugly turn, but that is another chapter. What was clear to the medical community was that the time for talk was over and the time for action had arrived. In 1986, two concepts had converged: long-term tamoxifen therapy and chemoprevention. Results in one would support or hinder the other.
Adjuvant Advances

The pharmacology and anticancer potential of ICI 46,474 (tamoxifen) was introduced to the Eastern Cooperative Oncology Group (ECOG) in 1974[37] and the National Surgical Adjuvant Breast and Bowel Project (NSABP) in 1976.[38] The concept of long-term adjuvant therapy to treat ER-positive breast cancer was first presented at a meeting at the University of Cambridge in 1977.[39] Following presentations at the Wisconsin Clinical Cancer Center 2 weeks later, Doug Tormey initiated a trial of 5 years and then indefinite adjuvant tamoxifen therapy.[17,40] This would mature into ECOG trials E5181 and E4181.[41]

Based on the successive analysis of cumulative randomized worldwide clinical trials, it is possible to summarize the main conclusions about tamoxifen therapy. Twenty years ago, when the Overview analysis was first conducted, tamoxifen was the only universally used antihormonal agent. With no other competition, tamoxifen became the gold standard, established the principles of tumor targeting, and identified the appropriate treatment strategy to aid survivorship.[5,6,24,42] Specific conclusions at that time included the following:

• Five years of adjuvant tamoxifen enhances disease-free survival. There is a 50% decrease in recurrences observed in ER-positive patients 15 years after diagnosis.
• Five years of adjuvant tamoxifen enhances survival, with a decrease in mortality 15 years after diagnosis.
• Adjuvant tamoxifen does not provide an increase in disease-free or overall survival in ER-negative breast cancer.
• Five years of adjuvant tamoxifen alone is effective in premenopausal women with ER-positive breast cancer; tamoxifen is ineffective in ER-negative breast cancer.
• The benefits of tamoxifen in terms of lives saved from breast cancer far outweighs concerns about an increased incidence of endometrial cancer in postmenopausal women.
• Tamoxifen does not increase the incidence of second cancers other than endometrial cancer.
• No non-cancer-related overall survival advantage is noted with tamoxifen when given as adjuvant therapy.

Conclusions Reconsidered

Since then, all data have remained consistent except that initially (in the 1980s), tamoxifen was considered ineffective in premenopausal patients.[24] Any conclusions as to tamoxifen's efficacy in premenopausal patients were quite perplexing to endocrinologists, because the randomized clinical trials were done with a ubiquitous background of combination cytotoxic chemotherapy. It was well known at the time that combination cytotoxic chemotherapy induced an early menopause in women from 40 to 50 years of age, and studies had shown that chemotherapy destroys the ovarian capacity for steroidogenesis.[43] Thus, combination cytotoxic chemotherapy is an indirect way of performing an oophorectomy. In other words, the early analysis of adjuvant clinical trials did not show a difference between a "chemical oophorectomy" plus short-term tamoxifen (1 or 2 years) and a "chemical oophorectomy" alone.

Today it is recognized that tamoxifen alone is an effective long-term adjuvant treatment for premenopausal women,[5] and this can be enhanced by a chemical oophorectomy using a luteinizing hormone-releasing hormone (LHRH) superagonist. The reason for tamoxifen alone being suboptimal is that long-term adjuvant treatment with tamoxifen increases and maintains ovarian steroidogenesis in women with intact ovaries.[44,45] Thus, the question arises: Should women without ovarian failure following chemotherapy receive antihormonal therapy? The evidence suggests that this is a reasonable course of action.[46,47]

Prevention Strategies

The trend throughout the 1980s was to use tamoxifen to its best advantage to treat earlier and earlier stages of the disease. In the case of node-negative ER-positive breast cancer, this meant that for every 1 out of 10 women who might obtain some benefit from tamoxifen, 1 or 2 would not benefit because of aberrations in the ER system, and about 70% of women would be receiving tamoxifen who had actually been cured of their disease, for the foreseeable future, by surgery. The clinical experience with tamoxifen was therefore enormous and ever-expanding in the cancer patient population.

However, issues of patient compliance and safety are clearly different if you have had a diagnosis of a fatal disease compared to those women who might or, more likely, will not develop breast cancer. Issues of toxicology are completely different for well women, and testing must be more rigorous. The challenge to action by Powles in 1986[36] prompted a reexamination of the toxicology and safety of tamoxifen. As a result, the research would ultimately have broad implication for the accelerated development of two entirely new drug groups—SERMs and aromatase inhibitors.
Twenty years ago, tamoxifen was classified as a nonsteroidal antiestrogen.[9] In pharmacologic terms, tamoxifen was described as a partial agonist (estrogen-like) in target tissues such as the immature rat uterus, but it was antiestrogenic because it blocked the full action of estradiol alone. In 1986, it was plausible that if estrogen was necessary to fend off osteoporosis and coronary heart disease, the long-term administration of an antiestrogen to node-negative women could eventually have a deleterious effect on bone density and produce a potential increase in the incidence of coronary heart disease for the majority of women. The potential side effects would be even worse for women who were only at high risk of developing breast cancer. A small minority of women would have a reduced risk of breast cancer, but all women would be exposed to potential "antiestrogenic" toxicities. However, the classification of nonsteroidal antiestrogens was to change just after 1986. Today the concept is known as selective ER modulation.

Effect on Bone Density
In 1986, virtually nothing was known about the actions of nonsteroidal antiestrogens on bone density. A single report from NASA scientists showed that clomiphene, a drug used for the induction of ovulation, would preserve bone density in ovariectomized rats.[48] Clearly efforts were made to prevent osteoporosis during space flight, but the choice of experimental compound was flawed and, frankly, a little bizarre. (Given that nonsteroidal antiestrogens such as tamoxifen reduce libido in men, perhaps that was the rationale!) However, interpretation of the NASA results was not that simple. Clomiphene is an impure mixture of estrogenic and antiestrogenic isomers. Which isomer was affecting bone? The consistent laboratory finding that tamoxifen, the pure antiestrogenic isomer of a triphenylethylene, maintained bone density in ovariectomized rats[49-51] seemed to translate to postmenopausal women,[52] but would prospective clinical studies really show benefit? The Wisconsin Tamoxifen Study was started in 1986 to explore the potential toxicity of tamoxifen on bone density. Led by Richard Love, the double-blind placebo-controlled clinical trial demonstrated that tamoxifen could preserve bone in the postmenopausal woman.[53] Bone-building would clearly be an advantage for chemoprevention studies, thereby enhancing the possibility that the worth of tamoxifen in preventing breast cancer could be tested safely. In the same studies, tamoxifen lowered low-density lipoprotein levels and, by inference, would appear not to increase the risk of coronary heart disease. On the other hand, although tamoxifen prevented the estrogen-stimulated growth of human breast cancers, the drug stimulated the growth of human endometrial cancers grown in the same athymic mouse.[54] This again reflected selective ER modulation, stimulating one target site to produce growth while blocking another.

Risk of Endometrial Cancer
There was a very quick response from the clinical community to the warnings[54] that long-term tamoxifen treatment could be associated with an increase in the incidence of endometrial cancer,[55-57] but not all reported studies[58,59] found increases in endometrial cancer associated with tamoxifen treatment. These studies were either too small or data was simply not collected. There was also a question as to whether the high dose of tamoxifen (40 mg/d) used by Forander and coworkers[57] was responsible for their findings, but the report by Fisher[60] neutralized the argument with data because NSABP studies all used 20 mg/d of tamoxifen. Endometrial cancer again became an issue during recruitment to the pioneering P-1 chemoprevention study by Fisher and the NSABP, when it was suggested that extremely dangerous endometrial cancer could be caused by tamoxifen treatment.[61] Nevertheless, results from the prospective P-1 chemoprevention study with tamoxifen actually showed that only postmenopausal women developed an excess of early-stage low-grade endometrial cancers. No fatalities from endometrial cancer were associated with tamoxifen in the study.[62,63]

Other Negative Findings
Events were about to take an ugly turn at the beginning of the 1990s with new findings that tamoxifen was a complete carcinogen in rat liver.[64] These new data created justifiable concern, but the world literature on tamoxifen did not[5]—and has not to this point[6]—shown an increase in second cancers other than endometrial carcinoma. By the 1990s, it was clear that the revelations about tamoxifen were not going to be helpful in bringing a proven agent, which reduces the risk of breast cancer in pre- and postmenopausal women by 50%,[63,62] to a broad constituency of high-risk women. However, a chemopreventive strategy was already in place by the end of the 1980s. The definitive proof of the new strategy is about to become center stage when a STAR is born—ie, the Study of Tamoxifen and Raloxifene—in April 2006.

Selective ER Modulators
The recognition that the so-called nonsteroidal antiestrogens had estrogenic and antiestrogenic actions at different sites in the ovariectomized female rat, and that these data translated in women to the prevention of osteoporosis and breast cancer, created a new dimension in drug development. The fact that tamoxifen and the failed breast cancer drug keoxifene (LY156,758) both prevented the development of carcinogen-induced rat mammary carcinomas and maintained bone density in ovariectomized rats indicated that this was a class effect. The significance of these observations for public health and chemoprevention of breast cancer was immediately recognized.

At the first International Chemoprevention Meeting hosted by Dr. Ezra Greenspan, a group of scientists and clinicians were invited to New York in 1987 to share their vision of the possibilities and potential of chemoprevention. In my opinion, the future of drug development was clear: The majority of breast cancer occurs unexpectedly and from unknown origin. Great efforts are being focused upon the identification of a population of high-risk women to test "chemopreventive" agents. But are resources being used less than optimally? An alternative would be to seize upon the developing clues provided by an extensive clinical investigation of available antiestrogens. Could analogs be developed to treat osteoporosis or even retard the development of atherosclerosis? If this proved to be true then a majority of women in general could be treated for these conditions as soon as menopause occurred. Should the agent also retain anti-breast tumor actions then it might be expected to act as a chemosuppressive. A bold commitment to drug discovery and clinical pharmacology will potentially place us in a key position to prevent the development of breast cancer by the end of this century.

This blueprint to improve health care was subsequently restated at the 1989 annual meeting of the American Association of Cancer Research in San Francisco. Compounds of the keoxifene class (LY117018 and LY156758) were obvious candidates for study despite the fact that the program to develop these drugs to treat breast cancer had been abandoned by Eli Lilly in 1988. The compounds were known to be less uterotrophic than tamoxifen in rodents but they were short-acting, which could explain their poor antitumor properties compared with tamoxifen. Interestingly, keoxifene was already known to partially inhibit the growth of tamoxifen-stimulated human endometrial tumors under laboratory conditions.

Keoxifene, the failed breast cancer drug was reinvented in the early 1990s as raloxifene (Evista), a SERM. A use patent for the treatment and prevention of osteoporosis was filed by Eli Lilly in 1992. Raloxifene has now been available for the treatment and prevention of osteoporosis in postmenopausal women since 1999, based on prospective clinical trials demonstrating an approximately 40% decrease in spinal fractures with the advantage over hormone-replacement therapy of causing a 70% decrease in the incidence of breast cancer.

The anticipated result in reducing the risk of breast cancer as a beneficial side effect of treating osteoporosis propelled raloxifene into a clinical trial vs tamoxifen, with the prevention of breast cancer as the primary endpoint. Results of the STAR trial in high-risk postmenopausal women will be released in mid-2006. As would be expected, raloxifene also causes decreases in circulating low-density lipoprotein cholesterol and for this reason is currently being evaluated as a preventive for coronary heart disease in the study named Raloxifene Use for The Heart (RUTH). These data will also be released in 2006.

Overall, raloxifene is positioned to realize the predicted promise of the SERMs as multifunctional medicines. Indeed, there are now numerous new SERMs (eg, lasofoxifene, Basedoxifene, arzoxifene, etc) being evaluated. Additionally, the concept is being applied throughout the steroid receptor superfamily, and the impact on medicine in the years to come, with selective androgens, glucocorticoids, or progestins, will be considerable.

No Estrogen At All

The treatment strategy of blocking estrogen synthesis in postmenopausal women followed rapidly on the heels of tamoxifen therapy. However, unlike tamoxifen as the gold standard with ubiquitous applications in breast cancer treatment and prevention, aromatase inhibitor development was initially slow until the clear advantages of long-term antihormonal therapy were being demonstrated 15 years ago. The path to development of effective aromatase inhibitors was not easy. The standard, aminoglutethimide/hydrocortisone was too toxic for long-term treatment but the new agent 4-hydroxyandro-stenedione was an injectable steroid that was unlikely to replace an orally active antiestrogen for 5 years of adjuvant therapy. A number of different agents (eg, vorozole) were examined but rejected during the 1990s because of toxicity issues, but the "bad and ugly" problems with tamoxifen as a carcinogen created an urgency for the three "crown princes"—all orally active drugs—to compete.

Fortunately, by the mid 1990s, there was a proven and expanding market developed by tamoxifen,
so risks were minimized for the pharmaceutical industry as the kingdom was divided. Anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin) have all shown important medical advantages as an adjuvant after 5 years of tamoxifen,[78,79] after a few years of tamoxifen,[80,81] or, indeed, instead of tamoxifen.[82-84] The advance in the reduction of side effects is consistent with each of the aromatase inhibitors; there are fewer endometrial cancers noted compared to tamoxifen and fewer thromboembolic events. Advances in the control of osteoporosis with bisphosphonates during the past 20 years has placed these important bone-building agents in the hands of the medical oncologist just at the right moment to neutralize one of the side effects of aromatase inhibitors—reduction in bone density. Remarkably, research conducted over the past 20 years has identified the value of bisphosphonates in the control of boney metastases.[85]

Steps have already been taken to advance aromatase inhibitors into the chemoprevention setting. The winner of STAR will be pitted against letrozole in the NSABP P4 study, and anastrozole is already being pitted against placebo in IBIS II.

Destroying the Estrogen Receptor

Twenty years ago, there was no fulvestrant (Faslodex) or ICI 182,780 but there was a related compound, ICI 164,384, which had been discovered in the laboratories of ICI Pharmaceuticals by Alan Wakeling and Jean Bowler.[86] The finding that this new class of drugs was not cross-resistant in tamoxifen-resistant breast and endometrial cancers[87,70] made the testing of the improved agent ICI 182,780 known as fulvestrant[88,89] a first priority for women with tamoxifen-resistant breast cancer. Fulvestrant is as effective as aromatase inhibitors in second-line treatment for advanced breast cancer.[90,91] However, the intriguing fact about fulvestrant is its novel mechanism of action, which was discovered by serendipity. Fulvestrant binds to the ER but creates an unusually shaped complex that is rapidly destroyed by the cell.[92,93] This process of protein ubiquitination and destruction by proteosomes was first noted by Rose, Hershko, and Ciechanover at Fox Chase Cancer Center in 1979. These investigators were subsequently awarded the Nobel Prize in Chemistry in 2004.

Progress and Lessons Learned

Patents produce progress, and the stories of tamoxifen and raloxifene are prime examples of this principle. Both drugs failed in their primary application but were successfully reinvented with wide clinical usage once the appropriate use patents were in place. Tamoxifen did not break into the headlines one day, but rather, sneaked up on the cancer community and was established as the "standard of care" for endocrine treatment by the early 1980s. Indeed, the World Health Organization declared tamoxifen an essential drug for the treatment of breast cancer. It is cheap, remarkably nontoxic, easily administered, and saves lives. Progress is measured by the hundreds of thousands of women who are alive today who would have died if they had been diagnosed with breast cancer in the 1970s. The principle of long-term antihormonal therapy targeted to the ER has dramatically improved survivorship in breast cancer. But the tamoxifen phenomenon might not have happened. There was no program or pipeline to replace tamoxifen at the beginning. Without progress in the use of tamoxifen during the 1970s—ie, with no lead agent to pioneer targeted antihormonal therapy and develop the market—how long would it have been before aromatase inhibitors were developed? Lives would have been lost[94] and it might have been another decade before another approach of receptor targeting was shown to save lives. The obvious example of such an approach is the use of adjuvant trastuzumab (Herceptin) in patients with HER2/neu-amplified tumors.[95-97] This affects a smaller group of women, but even so it should be noted that the development of this agent from target[98] to completed adjuvant trial[95-97] has taken 20 years—the same as tamoxifen but for the "lost decade."

Numerous nonsteroidal antiestrogens tried and failed to depose tamoxifen over the past 20 years. Toremifene (Fareston) survived primarily because it did not produce liver tumors in rats,[99] but testing as an adjuvant therapy now shows equivalence with tamoxifen and the same incidence of endometrial cancers.[100] The lesson is that all SERMs are cross-resistant with tamoxifen, so initial clinical testing became an insurmountable problem under current regulations. Reinvention became the path to progress.

The reinvention of keoxifene to become raloxifene reinforces the lesson that "observations in one field of science become major discoveries in another."[67] The SERM field is following closely on the heels of raloxifene with many new medicines, but will we need a long-acting raloxifene (arzoxifene) to achieve optimal chemoprevention? STAR may give the first clues if raloxifene does not deliver the knockout blow against tamoxifen.

Overall, it is clear that there are no short-term solutions to therapeutic changes in health care. Drug targeting, clinical trials, and advances in chemoprevention require decades of dedicated effort.
However, the lessons learned from endocrine therapy demonstrate the principle that there are also consequences to the patient when new treatments are introduced, and constant reexamination of clinical results and persistent challenge to dogma are required. Laboratory research is currently defining the evolution of long-term antihormonal therapy\[101\] with the remarkable discovery that minute concentrations of estrogen can kill breast cancers following years of antihormone treatment.\[102,103\] Learning to use our new knowledge of estrogen action in clinical trials may be an unanticipated bonus of antihormone therapy.

**Disclosures:**
Dr. Jordan is supported by SPORE in Breast Cancer CA89018, R01 GM061756, The Avon Foundation, and the Weg Fund of the Fox Chase Cancer Center.

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Improvements in Tumor Targeting, Survivorship, and Chemoprevention Pioneered by Tamoxifen

Published on Physicians Practice (http://www.physicianspractice.com)


