MINIREVIEW

Tamoxifen for Breast Cancer Prevention

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The case for tamoxifen to be tested as a preventive for breast cancer has merit. Animal studies demonstrate that tamoxifen prevents mammary carcinogenesis (1–5) and clinical studies now confirm that adjuvant tamoxifen therapy is the only systemic treatment that will prevent contralateral breast cancer (6). Developing clinical studies (7–10) confirm the laboratory data (11–13) that tamoxifen will maintain postmenopausal bone density in the lumbar spine and the neck of the femur; two important skeletal sites for the ultimate prevention of osteoporosis. However, a most important target site-specific effect of tamoxifen is the decrease in low-density lipoprotein cholesterol levels in postmenopausal women (14–17). This positive property of tamoxifen may be responsible for the recorded decreases in hospital visits for the treatment of cardiac conditions (18) and the significant decrease in fatal myocardial infarction for women treated with 5 years of adjuvant tamoxifen (19, 20). These data provide the scientific basis to undertake randomized, placebo-controlled clinical trials to test the worth of tamoxifen to prevent breast cancer.

Concern has been expressed (21) about the use of tamoxifen by premenopausal women in prevention trials because there is less clinical experience in premenopausal patients. The complicating factors are an increase in ovarian steroidogenesis (22) and the possibility of pregnancy and teratogenesis (23). Each concern has theoretical merit, but the supporting data are somewhat ambiguous. It is possible that increased steroidogenesis might negate the preventive effect of tamoxifen in the developing tumor; however, animal studies indicate that it is not easy to reverse the antitumor action of tamoxifen with estradiol (24). Much higher levels of estrogen are required to reverse the actions of tamoxifen than are observed clinically. Nevertheless, some mature clinical studies (25, 26) appear to show that tamoxifen is ineffective in premenopausal women for the prevention of secondary primary breast cancers (25) and that tamoxifen is significantly inferior to chemotherapy-induced ovarian ablation in preventing breast cancer recurrence in premenopausal patients (26). However, both studies (25, 26) chose an inadequate duration of tamoxifen to use as an adjuvant therapy. Only two years of adjuvant therapy was used in both the Cancer Research Campaign Study (25) and the German Study (26). In contrast, prevention studies will employ at least 5 years of tamoxifen. This treatment duration is based on the positive reanalysis of results from the National Surgical Breast and Bowel Project B14, where node-negative patients are receiving at least 5 years of tamoxifen. Premenopausal women will require longer treatment periods to prevent estrogen from reactivating tumor development in much the same way as that found in animal models (27).

The issue with tamoxifen and pregnancy is more straightforward. Tamoxifen should not be prescribed to a pregnant patient and women who wish to become pregnant are not to be recruited to prevention trials. Women are at risk for pregnancy during tamoxifen therapy and must use barrier contraceptive methods. Tamoxifen, however, has not been associated with specific teratogenic effects.

If it is easier to avoid these issues by recruiting only postmenopausal women, why are premenopausal

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women being recruited to prevention trials? The answer is multifaceted and draws upon components from both basic and clinical research. A carcinogen is optimally effective at inducing mammary carcinogenesis in young animals (reviewed in 28), and an antihormonal therapy is most effective in preventing mammary carcinogenesis the sooner it is applied after the carcinogenic insult (29, 30). The prevention strategies in the laboratory are best targeted in young animals. We are, however, naïve about the carcinogenic process in women, but some general principles are clear. Radiation, a well-known carcinogenic insult, is more effective at inducing an elevated incidence of breast cancer if it occurs in early adolescence (reviewed in 28). On the other hand, women with nonfunctioning ovaries, or those who have an early medical oophorectomy, have a reduced incidence of breast cancer (31). This later observation is the whole basis of the Pike proposal to use luteinizing hormone-releasing hormone as a contraceptive in young women to stop ovarian function and reduce the incidence of breast cancer (31). It appears that in humans, as in the laboratory, early intervention may be best.

Tamoxifen will be used to block estrogen-stimulated promotion in women over the age of 35, selected with the highest risk of developing breast cancer. Of the current 11,000 women already randomized in the National Surgical Adjuvant Breast Project/ National Cancer Institute (NSABP/NCI) prevention trial, the relative risk of the volunteers is elevated between 4- and 10-fold in the 35- to 50-year-old age group. Any concerns that young women at risk would not volunteer for the clinical trial are not substantiated by the population distribution; about one-third of the volunteers are 35–50 years old. Furthermore, the inclusion of younger women is a strategic necessity, as there is no possibility that a second trial could be started a decade from now if only postmenopausal women had been recruited in the first study. The purpose of this single study, which is complimentary to studies in Britain (32) and Italy (33), is to evaluate the benefits for women of all ages who are concerned about their risk of developing a fatal disease.

The goal of a well-controlled clinical trial is to weigh without emotion the advantages and disadvantages of a therapy. Naturally, it is impossible to predict every eventuality, but continued monitoring of clinical and laboratory research is the best safeguard. The double-blind, placebo-controlled clinical trial mechanism is the only method capable of answering the questions about the safety and efficacy of tamoxifen. The alternative is to ignore the established methods for clinical evaluation and condone the random prescribing of tamoxifen by physicians, who are responding to requests from their high-risk patients.

What are the toxicities that are most quoted to be caused by tamoxifen? These include macular degeneration, clotting, endometrial carcinoma, hepatocellular carcinoma and now, colorectal cancer. The first two are easily dispensed with, as they are protocol exclusions for the prevention trial. Macular degeneration has been reported as a side effect of tamoxifen in a Greek study (34), but no women with this condition are to be entered in the prevention trial. There are no adequate data linking tamoxifen to ocular problems from placebo-controlled clinical trials. Nevertheless, clinicians should be ready to evaluate volunteers on the prevention trial who raise the issue of changes in visual acuity. Tamoxifen causes an increase in thromboembolic events (1%) when used as a single agent to treat breast cancer. However, none of the participants in these trials were screened for clotting disorders. Women with a history of clotting disorders are excluded from participation in the prevention trials.

In contrast, considerable concern has been raised about the association between tamoxifen and the development and growth of endometrial carcinoma. In the laboratory (35), tamoxifen can stimulate the growth of human endometrial carcinoma while blocking the growth of a breast carcinoma transplanted in the same athymic mouse. The laboratory principle was first illustrated in patients by the Stockholm group (36) who observed a 40% decrease in the development of second primary breast cancers but a 5-fold increase in endometrial carcinoma. The current total of endometrial tumors observed is 17 in the tamoxifen-treated group (2–5 years) versus three in the control (37). There are approximately 1000 patients in each arm of the study. A review of the world literature reveals a total of more than 100 cases (38) in the 5 million women-years of experience with tamoxifen. Overall, the approximate rate in endometrial carcinoma for patients taking tamoxifen is 2–3/1000 women/year compared with about 1/1000 women who do not.

The increase in endometrial carcinoma is to be expected, because tamoxifen has an estrogen-like effect on the uterus and, like estrogen, can encourage the growth of occult or silent tumors. The stimulatory effect that tamoxifen has on some (but not all) uteri leads to increased gynecological investigations and therefore higher detection. It is known that there is five times the level of endometrial carcinoma found in autopsy specimens compared wtih the detected populations (39); therefore, the results with estrogen or tamoxifen are naturally biased.

The fact that deaths from endometrial carcinoma occur during or after tamoxifen treatment does, however, create uncertainty for participants in prevention trials. Nevertheless, the apparent risks must be placed in perspective. A report from the Yale/New Haven

tumor registry suggested that women receiving tamoxifen as treatment for breast cancer, and who subsequently develop uterine cancer, are "at risk for high-grade endometrial cancers that have a poor prognosis" (40). They base their conclusions on 15 patients who had been treated with tamoxifen for breast cancer in a 10-year survey period. However, every patient with endometrial carcinoma (40) in the registry, apparently from the surrounding area in Connecticut, received 40 mg tamoxifen daily, rather than the standard 20 mg daily. This unusual finding is further complicated by the fact that some patients were given tamoxifen for only a few months before death from endometrial carcinoma, so a cause and effect cannot be made in patients with preexisting metastatic disease.

A similar situation pertains to the report from the NSABP study B_{14} (41). Of the 2639 tamoxifen-treated women monitored for more than 6 years, there are 23 cases of endometrial carcinoma and six deaths. One woman never took tamoxifen at all and one woman died of cardiovascular disease 5 years after diagnosis of endometrial carcinoma (challenged by the NSABP pathologists). She originally received only five months of tamoxifen. One women died 28 months after diagnosis of endometrial carcinoma but only took tamoxifen for 9 months. Two other women only took tamoxifen for 22 and 42 months before choosing to discontinue the drug. Diagnosis of endometrial carcinoma was made 60 and 23 months, respectively, after stopping tamoxifen. The last patient received tamoxifen for 65 months and died of a pulmonary embolus at the time of hysterectomy.

These statistics paint a complex picture of competing causes of death but do not demonstrate that tamoxifen causes a more aggressive disease. In fact, a comparison of histological grade and disease stage in patients treated with tamoxifen (39, 41, 42) demonstrates the same proportions noted for the general population. It is, therefore, essential to establish that a patient does not have preexisting endometrial carcinoma, or indeed, preneoplastic changes caused by long-term estrogen replacement therapy. Postmenopausal women should be educated by physicians to report any spotting or bleeding so that a gynecological examination can be made immediately. Endometrial carcinoma is not a disease with high incidence, and there are effective methods of curative treatment.

Concerns about the development of hepatocellular carcinoma with tamoxifen are based solely upon laboratory experiments. Many studies have demonstrated that very large doses of tamoxifen produce liver tumors in rats (43–45). Of greatest concern is the observation that tamoxifen produces DNA adducts in rat liver (45–47) and protein adducts have been noted *in vitro* (48). It is suggested that tamoxifen becomes metabolically activated through selective hydroxylation to form an alkylating species (49). Although recent studies demonstrate, in principle, that DNA adducts can be formed *in vitro* by human liver microsomes (50), adduct formation has not been demonstrated from patients taking long-term tamoxifen treatment. Indeed, there are doubts that adduct formation and tumorigenesis are always related. Tamoxifen can produce DNA adducts in some animal species that do not produce tumors (46). The inconsistencies may be explained because metabolic activation *in vivo,* adduct formation and DNA repair are potentially species and drug dose related.

Hepatocellular carcinoma has not been reported in patients receiving 20 mg tamoxifen daily (250 μg/kg) and only in two patients receiving 40 mg daily (36). Hepatocellular carcinoma is, however, a very rare disease with an incidence of only 5/100,000 persons/year in the Western world. In contrast, most rats given 12 mg/kg or more of tamoxifen daily for half their lifetime (i.e., rats receiving 40 times the daily therapeutic dose of tamoxifen [250 μg/kg]) produce liver tumors (45). However, it is argued that the blood levels of tamoxifen in the rat and human are comparable with these dosing schedules; therefore, the results are clinically significant (45). I believe this is untrue because the rat is metabolizing tamoxifen 40 times faster than the human to obtain equivalent blood levels and the excessive doses of tamoxifen in the rat are now overwhelming the capacity of the liver. Unique metabolic routes are being employed to cope with an overdose of a xenobiotic in the rat.

A reasonable toxicological comparison would be to study the same relative treatment designs. Tamoxifen is an effective antitumor agent in the rat at 250 μg/kg (27) (i.e., the same relative dose [250 μg/kg, 20 mg daily] used to treat human disease and being used for prevention trials. The drug is used for 5 years or about 6%–8% of a woman's lifetime. The real question is, Do animals produce liver tumors if given 250 μg/kg/day for 8% of their lifetime (i.e., 2–3 months)? This would be an important laboratory study, as no woman will be taking 800 mg tamoxifen daily for 40 years.

The alternative approach is to survey the tamoxifen-treated population. However, it is going to be difficult to assess the increased incidence in hepatocellular carcinoma. As mentioned previously, the tumor is extremely rare and epidemiologic studies may have to wait for many decades. However, after a decade of tamoxifen use, there are no reports of an increase in hepatocellular carcinoma from SEER data collection sites. In the future, one could pose the question, How much of an increase will be acceptable to drug regulatory authorities to invoke restrictive action? The parallel with oral contraceptive use can provide some guidance. Oral contraceptives produce increases in rat liver tumors by promoting carcinogenesis (51, 52). Ta-

moxifen is also reported to be a liver tumor promoter in rat models (53). It is estimated that Western women have a 10-fold elevation in the relative risk of developing hepatocellular carcinoma if they have taken oral contraceptives for 5–8 years (54). The elevation in risk is fully accepted by society (and drug regulatory authorities) for the convenience of preventing pregnancy. If the risk of developing hepatocellular carcinoma with tamoxifen is only increased 10-fold, but the drug cannot be used in selected women to prevent a fatal disease, then society has no alternative but to consider the restriction of oral contraceptives. Naturally, this is unacceptable because epidemiologists maintain that a 10-fold elevation of the risk of hepatocellular carcinoma is insignificant. A 10-fold elevation of risk for hepatocellular carcinoma was calculated into the deficit column of the prevention trial with tamoxifen at the outset.

Finally, there is a recent report that antiestrogens may cause an increased incidence of colorectal cancer.[2] Although there will be a natural temptation for rival pharmaceutical companies to suggest that tamoxifen is having a carcinogenic effect on the colon, it is essential to evaluate many studies before forming a premature conclusion about one drug versus another. Although the colon has never been considered to be an estrogen target tissue, are there any clues that should now be considered linking female hormones and colon cancer? Emerging data suggests that colorectal cancer risk is reduced in postmenopausal women by hormone replacement therapy (55–57). This unexpected observation comes at a time that an association of estrogen receptors and age has been observed in human colon (58). Apparently, advancing years result in a "silencing" of the estrogen receptor, and it is interesting that the authors note that colonic tumors have "silenced" estrogen receptors compared with surrounding normal colon. Clearly, much new work needs to be done in understanding the estrogen regulation of colonic cells, but the implication could be that *all antiestrogens* will produce a negative effect. This hypothesis and these supporting data are only a few fragments that need to be rigorously evaluated over the next decade. It is most important that these research results are analyzed unemotionally by regulatory authorities who can draw upon qualified individuals to produce a balanced view.

The fact that tamoxifen is both the most successful and the most studied anticancer drug has both positive and negative effects. On the positive side, it is essential that every attempt is being made to ensure the safety and monitoring of legitimate placebo-controlled prevention trials. Clinical trials organizations and regulatory authorities are responding rapidly to new data. It must be stressed though, that tamoxifen is not for everyone as a preventive. The goal of the prevention trials is only to provide answers to some of the questions posed. The primary questions are, Will tamoxifen prevent the development of breast cancer? What are the toxicities to be balanced against the gains? and Will women at risk be willing to take tamoxifen for the 5-year regimen? In response to these concerns, a major monitoring effort is in place to protect the interests of the volunteers. In contrast, the skewed focus on the negative aspects of tamoxifen has a disconcerting effect on those women with breast cancer who are being treated with tamoxifen. Thousands of women who benefit from the treatment are distressed because of new "revelations" in the scientific literature that find their way into the press. The implication of the reports is that women should stop tamoxifen treatment. This is wrong.

Twenty years ago when the first studies were being completed in the laboratory to formulate strategies for clinical applications (1, 2, 27), there was no serious interest in tamoxifen as a therapeutic agent and no other antiestrogens were being considered for development. If the focus of research 20 years ago had only been liver tumors in rats, tamoxifen would not have been developed and the hundreds of thousands of women with breast cancer would not have benefited from treatment. Tamoxifen is the only single-agent therapy with modest side effects that produces a survival advantage for women with primary breast cancer. The benefits of tamoxifen for a woman with breast cancer far outweigh *all* of its risks.

The prevention trials with tamoxifen are a natural extension of the clinical strategy to control breast cancer. No alternative theories to prevent breast cancer have as firm a scientific basis and can be tested as easily in clinical trial. No other antiestrogens are immediately waiting to replace tamoxifen tomorrow. At least a decade of testing of any new agent will be required to provide the same clinical assurances that we now have with tamoxifen. It must, however, be stressed that tamoxifen is not the sole answer to defeating breast cancer, but it is one important weapon to understand the control mechanisms of breast cancer development. It has taken 25 years to develop tamoxifen from a laboratory curiosity to the most successful treatment for breast cancer. For the future, a whole range of different antiestrogens could be developed to prevent osteoporosis and coronary heart disease in women. The prevention of breast cancer would be an important side effect (59). The tamoxifen prevention trials are an essential first step in a new era for therapeutics.

[2] Lars Rutqvist. MRC toxicology meeting, Leicester, 1994.

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