EDITORIALS

Is Low-Dose Tamoxifen Useful for the Treatment and Prevention of Breast Cancer?

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Many studies have demonstrated the utility of tamoxifen for the treatment of estrogen receptor (ER)-positive breast cancer *(1)* and more recently for the prevention of breast cancer in women at increased risk *(2–4)*. However, the toxicities of tamoxifen such as thromboembolic events and endometrial cancers still pose a clinically significant problem. To reduce the risk of these adverse events, effective, yet safe drugs are being sought that could replace tamoxifen. Indeed, new endocrine agents such as selective ER modulators (SERMs) and aromatase inhibitors are being evaluated as alternatives to tamoxifen for the treatment *(5–9)* and prevention *(10)* of breast cancer. In this issue of the Journal, Decensi et al. *(11)* propose a different strategy to reduce the side effects of tamoxifen. They suggest that, by using a lower dose of tamoxifen, it may be possible to reduce tamoxifen's side effects while retaining its therapeutic and preventive efficacy.

To investigate the biologic effect of low doses of tamoxifen, Decensi et al. *(11)* measured biomarkers associated with breast cancer, cardiovascular disease, and bone fracture risk. They conducted a randomized, double-blind, three-arm study to investigate the ability of different doses of tamoxifen (1 mg/day, 5 mg/day, or 20 mg/day) to modulate these biomarkers in women with ER-positive breast cancer. They also compared these results to results obtained in two control groups: women with ER-negative breast cancer and women with ER-positive breast cancer. None of the women in the control groups received preoperative tamoxifen.

The results of their study show that tamoxifen decreased the expression of the proliferation marker Ki-67 in breast tissue at all doses tested and that there was no difference in the magnitude of this reduction between the different doses. At the same time, a statistically significant dose response was observed when blood biomarkers of breast cancer (insulin-like growth factor-I and sex hormone-binding globulin) and cardiovascular disease (low-density lipoprotein [LDL] cholesterol, ultrasensitive C-reactive protein [CRP], fibrinogen, and antithrombin-III) were compared. In each of these cases, standard-dose tamoxifen was more effective at modulating the blood biomarkers than was low-dose tamoxifen. On the basis of these results, the authors concluded that low-dose tamoxifen retains its ability to suppress breast cell proliferation but has diminished activity in modulating serum biomarkers. The authors also conclude that the risk-to-benefit ratio associated with tamoxifen may be improved by using lower doses of the drug and recommend further clinical studies to define the utility of low-dose tamoxifen for the treatment and prevention of breast cancer.

The modulation of biomarkers observed in the study by Decensi et al. *(11)* is similar to results of other studies using tamoxifen. Decensi et al. published previous studies demonstrating that doses as low as 10 mg/day or every other day are comparable with the 20-mg/day dose in modulating blood bio-markers *(12,13)*. In the current study *(11)*, the response to lower tamoxifen doses was investigated. In addition, breast tissue proliferation was also measured, allowing the investigators to associate the changes seen in the breast tissue with changes in blood biomarkers.

Other investigators have shown that a reduction in Ki-67 expression in breast cancer cells similar to that seen in the current study is associated with a clinically relevant response *(14–16)*. Makris et al. *(14)* observed a median decrease in Ki-67 expression of 4.8% in patients who had a clinically significant response to tamoxifen. In addition, failure to decrease Ki-67 expression substantially has been associated with a lack of response to tamoxifen *(14)* and increased risk of relapse *(16)*. Thus, the reductions of Ki-67 expression observed with the lower doses of tamoxifen used by Decensi et al. *(11)* are in a range that would be expected to predict a response to treatment.

To investigate the efficacy of low-dose tamoxifen for the prevention of breast cancer, it will be necessary to demonstrate an effect on normal or premalignant breast tissue. Studies of 10 mg/day of tamoxifen compared with 20 mg/day or placebo demonstrated that both doses of tamoxifen were equally effective at reducing normal breast cell proliferation *(17)*. However, the results of a more recent study by de Lima et al. *(18)* demonstrate that lower doses of tamoxifen (5 mg/day and 10 mg/day) are less effective than the 20 mg/day dose at reducing normal breast cell proliferation, as measured by mitotic index. These data argue against using lower doses of tamoxifen for breast cancer prevention.

Although all doses of tamoxifen reduced Ki-67 expression in the study by Decensi et al. *(11)*, the other biomarkers examined varied with tamoxifen dose. One possible explanation for this difference may be the differential response of the breast tissue versus other tissues to tamoxifen. Tamoxifen is well known to have differential effects on the breast tissue relative to effects on the endometrium. It is also possible that low-dose tamoxifen is able to block the growth-promoting effects of estrogen in the breast, without affecting estrogen-regulated genes in the liver (LDL cholesterol, CRP, or antithrombin-III). Alternatively, this differential effect on breast cell proliferation relative to other estrogen-regulated biomarkers may result from differences in specific gene-regulatory elements or proteins that mediate the

response to tamoxifen. It is possible that low-dose tamoxifen acts as an antagonist to suppress expression of genes regulating proliferation but is neutral or acts as an agonist on the other biomarker genes. Future studies will be needed to elucidate the molecular mechanism of the differential effect of low-dose tamoxifen.

Which endocrine agent is optimal for the treatment and prevention of breast cancer remains one of the most important questions in breast cancer research. At this time, tamoxifen remains the standard therapy for premenopausal women with ER-positive breast cancer and an acceptable option for many postmenopausal women. In addition, tamoxifen is the only drug approved for cancer risk reduction in healthy women at increased risk of breast cancer. Given the concern about the toxicities of this drug, efforts to circumvent these toxicities are very appropriate. Thus, continued studies of tamoxifen for the treatment and prevention of breast cancer certainly are warranted. However, continued efforts to develop other endocrine therapies for breast cancer, such as other SERMs, pure antiestrogens, and aromatase inhibitors, may make it difficult to complete long-term studies of multiple doses of tamoxifen using cancer incidence, response, or progression as endpoints.

The results of several ongoing clinical trials comparing tamoxifen and raloxifene (the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene [STAR] trial for the prevention of breast cancer), tamoxifen and the aromatase inhibitor anastrozole (the Arimidex, Tamoxifen, Alone or in Combination [ATAC] trial comparing anastrozole versus tamoxifen versus anastrozole plus tamoxifen for the treatment of breast cancer), and comparing tamoxifen and anastrozole for the treatment of ER-positive ductal carcinoma *in situ* (the National Surgical Adjuvant Breast and Bowel Project B-35 Trial) should help clarify which of these agents are to be used in the future. However, regardless of which agent is most effective, defining the optimal dose will remain an issue. The concept of the "minimally effective dose" has been applied to the development of chemopreventive agents. Studies such as the one reported by Decensi et al. *(11)* demonstrate that it is equally applicable to the study of effective therapeutic drugs that have clinically significant side effects.

A final question is whether the current study by Decensi et al. *(11)* is sufficiently compelling to change the standard practice of using 20 mg/day of tamoxifen for breast cancer treatment or risk reduction. Although the results reported by Decensi et al. *(11)* are provocative, in our opinion these studies should not alter current practice. Although Makris et al. *(14)* and Chang et al. *(16)* have demonstrated that a reduction in proliferation in the breast tissue correlates with clinical response, it is not yet clear whether the growth suppression induced by low-dose tamoxifen would produce the approximately 50% reduction in risk of recurrence or risk of primary breast cancer seen with tamoxifen at the standard dose. We agree with Decensi et al. *(11)* that the results provide strong rationale for future randomized trials of low-dose tamoxifen; however, their results should not overshadow the results of large-scale randomized clinical trials showing clinically significant benefit of tamoxifen at the 20-mg/day dose. So, is low-dose tamoxifen useful for the treatment and prevention of breast cancer? Possibly, but for now, clinicians should continue to use tamoxifen at the current standard dose of 20 mg/day.

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