Defining the Role of Raloxifene for the Prevention of Breast Cancer

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Over the last 5 years, the results of several breast cancer prevention trials have demonstrated the usefulness of anti-estrogen selective estrogen receptor modulators (SERMs) for the prevention of breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 breast cancer prevention trial was the first trial to show a major benefit of a SERM: The anti-estrogen SERM tamoxifen reduced the risk of breast cancer in women who were at high risk of the disease by 49% (1). The results of several other breast cancer prevention trials confirmed the cancer-preventive benefit of tamoxifen [reviewed in Cuzick et al. (2)], although the magnitudes of benefit reported in these other trials were lower than that reported by the P-1 trial. Together, these results provide strong support for the use of tamoxifen to reduce the risk of breast cancer in women at high risk of this disease. However, since 1998, tamoxifen has not been widely used for this purpose largely because of concerns over its side effects, which include the induction of hot flashes as well as increased risks of thromboembolic events and uterine cancer. These potentially serious side effects have caused physicians to carefully weigh the risks and benefits of tamoxifen before prescribing it for women at high risk of breast cancer.

Other agents currently being tested for breast cancer prevention include other SERMs (e.g., raloxifene and arzoxifene) as well as aromatase inhibitors (e.g., anastrazole). Raloxifene is an anti-estrogen SERM that blocks the effects of estrogen in the breast and stimulates calcium uptake in the bone (3,4). Both tamoxifen and raloxifene increase the risk of thromboembolic events (1,3,4). However, unlike tamoxifen, raloxifene does not appear to increase the risk of uterine cancer (3,4). Thus, raloxifene may be safer than tamoxifen.

In this issue of the Journal, Martino et al. (5) present results from the Continuing Outcomes Relevant to Evista (CORE) trial, a breast cancer prevention trial designed to determine whether treatment with raloxifene reduced the incidence of breast cancer among women who were previously enrolled in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, a multicenter, double-blind trial designed to examine the reduction in risk of vertebral fractures among approximately 7700 postmenopausal women with osteoporosis who were randomly assigned to receive either placebo or raloxifene at 60 mg/day or 120 mg/day (3,4). This trial demonstrated that raloxifene reduced vertebral bone fractures in women with osteoporosis by 35% (60-mg dose) to 47% (120-mg dose) (3). Analysis of a secondary endpoint of the MORE study demonstrated a 72% reduction in invasive breast cancer incidence after 4 years of raloxifene (4). The results from the CORE study indicate that continued treatment with raloxifene reduces breast cancer incidence in postmenopausal women with osteoporosis. However, the results from this study do not answer several other important questions concerning preventive therapy, including: 1) what is the most effective drug to use for breast cancer prevention? 2) which agent is safest? 3) who should be treated with preventive therapy? 4) how are the risks and benefits of preventive therapy best assessed? and 5) what is the optimal duration of preventive therapy?

Because breast cancer incidence was a secondary endpoint in the MORE trial, investigators developed the CORE trial as an extension of the MORE trial to evaluate the effect of 4 additional years of raloxifene treatment on the incidence of invasive breast cancer in postmenopausal women with osteoporosis. Women who agreed to participate in the CORE study were assigned to continue raloxifene at 60 mg/day or placebo for 4 more years according to their initial randomization assignment in the MORE trial. The primary endpoint was the incidence of invasive breast cancer. A secondary endpoint was the incidence of invasive estrogen receptor (ER)–positive breast cancer.

Martino et al. (5) report that, among patients treated with up to 4 additional years of raloxifene, the annual incidence of invasive breast cancer was reduced by 59% and the annual incidence of ER-positive breast cancer was reduced by 66%.
There was no reduction in the incidence of ER-negative breast cancer. However, these results are not entirely straightforward because of the complex study design of the CORE trial.

Several points about the study design should be considered when interpreting the results of the CORE study. First, women in the MORE trial who participated in the CORE trial remained blinded to their original treatment assignment in MORE. They were asked if they wished to participate in the CORE trial and continue study medication (either raloxifene or placebo), which could select for participants who did not experience side effects from their previous treatment. Approximately half of the women from each treatment group (placebo versus raloxifene) of the MORE trial enrolled in the CORE study. Those women previously on 120 mg/day of raloxifene were continued at 60 mg/day of raloxifene in the CORE study. Thus, the study tested the ability of continued raloxifene (at a dose of 60 mg/day) versus continued placebo to reduce breast cancer incidence. Second, the participants were not rerandomized in the CORE study; they continued in the CORE trial under the same randomization assignment from which they started in the MORE study. This lack of rerandomization clouds the issue of additional benefit from longer treatment because the raloxifene group had previously been treated with raloxifene. Thus, the effect of treatment in CORE is confounded with possible protective carryover effects from MORE. Third, 1217 women without breast cancer, who were still completing the MORE trial and who did not enroll in the CORE trial, were added in the CORE primary breast cancer analysis. Although this addition of women without breast cancer likely improved the power of the analysis of breast cancer incidence, it would also decrease overall breast cancer incidence and complicate the issue of whether additional raloxifene reduced breast cancer incidence in the raloxifene group. Fourth, there was a relatively long interval from the end of MORE trial participation to the start of CORE trial enrollment, which ranged from 2.6 to 62 months (median time = 10.6 months). Women who would later enroll in CORE may have been off study drug for as long as 5 years before enrolling in CORE, and 18% of these women reported being on either hormone replacement therapy or another SERM during this time. It is not clear from this report whether the length of this time gap was balanced between the arms of the CORE trial. In addition, the women who developed breast cancer or experienced a serious adverse event during the long gap were excluded from CORE enrollment. This exclusion would lower the breast cancer incidence and the incidence of thromboembolic events in this cohort. Taken together, these study design issues tend to weaken the possible conclusions from the CORE trial.

Another important aspect of the CORE trial is the level of breast cancer risk of the participants. Formal breast cancer risk assessment was not performed at the time of MORE trial registration but was done at the time of CORE trial enrollment. There was no difference in the 5-year predicted risk of breast cancer, as predicted by the Gail model, between women in the raloxifene and placebo groups in the CORE trial. However, only 52.9% of those in the placebo group and 54.4% of those in the raloxifene group had an elevated 5-year predicted risk of breast cancer, leaving approximately 50% of those in each group who were not at high risk of developing breast cancer. An exploratory subgroup analysis of the high-risk patients would be useful. Such an analysis would allow physicians to begin to decide whom to give raloxifene to for breast cancer prevention.

Despite the above study design issues, the results from the CORE trial and the previous MORE study support the conclusion that raloxifene treatment reduces the risk of breast cancer. However, the CORE trial does not address a pressing clinical question: Which hormonal agent should be used for breast cancer prevention in women at high risk of breast cancer?

This question will be partially answered once the results of the NSABP Study of Tamoxifen and Raloxifene (STAR) trial are available. The NSABP STAR trial is an ongoing breast cancer prevention study that compares the ability of tamoxifen and raloxifene to reduce the incidence of breast cancer in postmenopausal women at high risk of breast cancer (6). The STAR trial provides a direct comparison of these agents regarding breast cancer prevention efficacy as well as safety, and the results from this trial should help clinicians decide whether to use tamoxifen or raloxifene for the prevention of breast cancer. In addition, the results of a European study, the International Breast Cancer Intervention Study 2 (IBIS-II) trial, should determine whether the aromatase inhibitor anastrazole is effective in preventing breast cancer in high-risk postmenopausal women (7). However, even after these results are known, clinicians will still be left not knowing whether a SERM (raloxifene or tamoxifen) or an aromatase inhibitor (anastrozole or another aromatase inhibitor) is the preferred choice for breast cancer prevention. It is hoped that future clinical trials will be designed to answer this question.

In summary, the CORE trial provides additional results that indicate that raloxifene reduces breast cancer incidence in postmenopausal women with osteoporosis. The data suggest that this benefit continues with additional treatment (up to 8 years) with raloxifene and that the safety profile of long-term raloxifene use is similar to that seen in the MORE trial. Thus, for postmenopausal women with osteoporosis, raloxifene is a reasonable choice to treat osteoporosis and also to reduce the risk of breast cancer. Should postmenopausal women who do not have osteoporosis but are at increased risk of breast cancer receive raloxifene to prevent breast cancer? At this time, the results of the CORE trial do not help to answer this question because all of the women enrolled in the CORE trial had osteoporosis. For women without osteoporosis who are at high risk of breast cancer, tamoxifen, in our opinion, remains the “gold standard” chemoprevention agent to reduce the risk of breast cancer in high-risk pre- and postmenopausal women. We anticipate that the results of several large-scale chemoprevention trials will help clarify the role of raloxifene, as well as other hormonal agents, for breast cancer prevention.

REFERENCES


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