**Point/Counterpoint**

**Tamoxifen or Raloxifene in Postmenopausal Women for Prevention of Breast Cancer: A Tale of Two Choices—Counterpoint**

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Postmenopausal women 50 years or older with an estimated 5-year Gail model breast cancer risk of >1.66% or prior history of lobular carcinoma *in situ* now have two choices of prevention drug therapy: approved by the Food and Drug Administration for breast cancer risk reduction tamoxifen and raloxifene.

It has been estimated that ~2 million women living in the United States would realize a health benefit from 5 years of tamoxifen given as primary breast cancer prevention therapy (1, 2); yet, only 5% to 30% of risk-eligible women choose to take tamoxifen because of potential side effects and incomplete efficacy (3-5). Serious side effects that can occur with tamoxifen, such as deep venous thrombosis, pulmonary embolism, and uterine cancer, occur primarily in women over 50 years. Treatment of elderly, average-risk women with raloxifene in the Multiple Outcomes of Raloxifene Trial was associated with fewer breast cancers without the increase in uterine cancer observed with tamoxifen. However, raloxifene was associated with a 3-fold increase in thromboembolic phenomenon, similar to what would be expected with tamoxifen (6).

Subsequently, the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) trial was launched in high-risk postmenopausal women with the hope that raloxifene would have similar efficacy but fewer serious side effects than tamoxifen. The initial assessment of the primary end point of the STAR Trial would seemingly indicate that this hope was realized. Compared with tamoxifen, women randomized to 5 years of raloxifene in the STAR trial had a similar incidence of invasive breast cancer and similar quality of life but a lower incidence of serious side effects (7, 8). Women randomized to raloxifene had 30% fewer thromboembolic events, 25% fewer uterine cancers, and 21% fewer cataracts compared with those randomized to tamoxifen. These differences were significant for cataracts and the combination of deep venous thrombosis and pulmonary emboli (7).

Marring this otherwise perfect story is the disquieting observation that in the STAR trial the incidence of noninvasive breast cancer was 40% lower for women randomized to tamoxifen than those randomized to raloxifene, and ductal carcinoma *in situ* comprised 54% of these *in situ* cancers (7). The clinical relevance is obvious in that >20% of newly diagnosed breast cancers projected for 2007 will be ductal carcinoma *in situ* (9). Management of ductal carcinoma *in situ*, which often incorporates 5 years of antihormone therapy following surgery ± radiation makes this a life-altering event.

Although not quite statistically significant at the time of the analysis (*P* = 0.052), the reduced incidence of *in situ* cancers in women randomized to tamoxifen versus raloxifene in STAR is consistent with results in prior placebo-controlled trials. In trials in high-risk women, tamoxifen has been observed to reduce ductal carcinoma *in situ* by 37% to 49% compared with placebo (10, 17). Raloxifene has not been compared with a placebo in high-risk women, but in average to low-risk postmenopausal women, raloxifene was not associated with either a significant or numerical reduction in ductal carcinoma *in situ* compared with placebo (see Fig. 1; refs. 12, 13). The observation that raloxifene is similar to tamoxifen in preventing invasive but less efficacious in preventing *in situ* cancer seems to counter the existing paradigm but that most invasive cancers are derived from associated *in situ* lesions.

What then might be the explanation for the differences between raloxifene and tamoxifen with regard to emergence of *in situ* cancer? This seeming paradox could be explained if changes in gene expression giving rise to *in situ* cancer are different than those associated with progression from *in situ* to invasive cancer, and tamoxifen modulated those genes key to development of breast precancer differently than raloxifene. Although there does not seem to be any gene universally up-regulated or down-regulated in *in situ* or invasive cancer, several investigators have noted differences in patterns of change in gene expression between normal and *in situ* cancer and between *in situ* and invasive cancer (14-16). Further, Frasor et al. (11) have reported that there is a set of at least 60 genes up-regulated or down-regulated by tamoxifen but not by raloxifene. If, as generally thought, hormone receptor–positive invasive cancer emerges from *in situ* cancer, the implications are that tamoxifen might be more efficacious than raloxifene in the long run for preventing invasive disease.

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particularly after treatment has been stopped (carryover effect). In fact, a beneficial carryover effect is beginning to emerge in the initial primary prevention trials of tamoxifen versus placebo such that reduction in risk for breast cancer seems to continue after treatment with tamoxifen is completed, but risk for most side effects is reduced (2, 17, 18). This means the long-term benefit to risk ratio with tamoxifen may be higher than originally anticipated. No comparable data on the carryover effect exist for raloxifene.

What about other differences between raloxifene and tamoxifen that might affect the choice of one drug over another? In the STAR trial, both drugs were associated with similar effects on quality of life but raloxifene was associated with a higher incidence of dyspareunia, musculoskeletal complaints, and weight gain, whereas tamoxifen was associated with a higher incidence of hot flashes, vaginal discharge, bladder control problems, and leg cramps but better overall sexual function (8). Women already troubled by loss of libido and dyspareunia might then choose tamoxifen over raloxifene.

Pharmacokinetics of these drugs are different. Due to better bioavailability and longer terminal half-life of tamoxifen, systemic drug levels are not as likely to be affected as much by missed doses of tamoxifen as by missed doses of raloxifene, a consideration for women with average or worse compliance with chronic medication intake (19-22). On the other hand, raloxifene is likely to be the better choice for the 5% to 10% of individuals homozygous for low-activity CYP2D6 alleles or those on potent CYP2D6 inhibitors. CYP2D6 mediated generation of the potent tamoxifen metabolites 4-OH-tamoxifen and endoxifen is thought to be responsible for much of the antitumor activity of tamoxifen (23).

Cost differential for the two drugs may be important for women with no or limited prescription benefits. In our Medical Center Retail Pharmacy, the cost of 30 days of generic tamoxifen is $16.60 compared with $95.70 for 30 days of raloxifene. Retail prices for the two drugs at a national pharmacy chain outlet in town were $61.59 for tamoxifen and $96.99 for raloxifene. If, however, all women considering tamoxifen were to have CYD2D6 alleles tested before initiating drug, cost differential in favor of tamoxifen might disappear. Currently, testing for CYP2D6 activity before tamoxifen use is uncommon.

In the end, the high-risk postmenopausal patient and her physician are likely to make the choice between tamoxifen and raloxifene based on the relative importance of efficacy versus safety and factors in her personal health history (see Table 1). The decision-making process is likely to be complex. The risk-eligible woman who already has cataracts, evidence of benign uterine conditions, or low CYP2D6 activity might be better served with raloxifene. Conversely, the risk-eligible postmenopausal woman who has no uterus, is already bothered by dyspareunia, and/or whose greatest concern is efficacy might opt for tamoxifen, which is associated with reduced risk for both noninvasive and invasive cancer. A quantitative method for weighing the relative risks and benefits of tamoxifen versus raloxifene based on personal health history and preferences would be helpful in this decision-making process. Although expanding the number of alternatives increases the complexity of decision making, it may also increase the proportion of women willing to consider prevention therapy. Two choices are better than one.

References

Table 1. Factors considered when making the choice between tamoxifen and raloxifene for primary prevention in postmenopausal women

<table>
<thead>
<tr>
<th>Factor</th>
<th>Drug favored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy concern greatest</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Safety concern greatest</td>
<td>Raloxifene</td>
</tr>
<tr>
<td>Dyspareunia/reduced libido</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Benign uterine conditions</td>
<td>Raloxifene</td>
</tr>
<tr>
<td>Cataracts</td>
<td>Raloxifene</td>
</tr>
<tr>
<td>Low-activity CYP2D6 alleles</td>
<td>Raloxifene</td>
</tr>
<tr>
<td>Increased risk for thromboembolism</td>
<td>Neither</td>
</tr>
</tbody>
</table>

Annual rate of in situ breast cancers in randomized trials of tamoxifen and raloxifene.

**Figure 1.** Annual rate of in situ breast cancers in randomized trials of tamoxifen and raloxifene in low/average [Continuing Outcomes Relevant to Evista (CORE) and Raloxifene Use For The Heart (RUTH)] or high-risk (P1 and STAR) women (7, 10, 12, 13).
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