Editorial

Tamoxifen
Preventing Breast Cancer and Placing the Risk of Deep Vein Thrombosis in Perspective

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Breast cancer exposes hidden psychological fears and raises fundamental questions about mortality, self-image, and sexuality. It conjures fear of pain, disfigurement, and metastases to bone, liver, and brain. All of us have known young women stricken suddenly with aggressive breast cancer that leads to rapid deterioration, immobility, and death. More common is indolent breast cancer, perhaps controlled, perhaps spreading slowly, for which waiting 10 years or more will eventually help us declare whether an individual patient has achieved a cure.

Four trials have now reported on the use of tamoxifen as prophylaxis against breast cancer. All tamoxifen prevention trials compared tamoxifen 20 mg daily with placebo for at least 5 years. Overall, 14,192 patients were randomized to tamoxifen, and 14,214 patients received placebo. Of these, 289 breast cancers developed among women receiving tamoxifen as compared with 465 in the placebo group. The number of new breast cancers was 38% lower in tamoxifen-treated patients, with 95% confidence intervals (CI) of 28% to 46% (P<0.0001). All 4 studies trended in favor of tamoxifen, and the 2 largest studies were individually statistically significant (Table). These spectacular efficacy results are similar to the end point reductions observed in most trials that used statins to prevent coronary artery disease.

The most frequent side effect in patients treated with tamoxifen versus placebo was a doubling of the rate of deep vein thrombosis (DVT) and pulmonary embolism (PE): 118 versus 62 cases. A similar increase in superficial phlebitis (68 versus 30 cases) also occurred. Overall, the evidence clearly shows that tamoxifen, used as a chemopreventive agent, can reduce the risk of developing breast cancer.

Analogous to statins, tamoxifen was first shown to be effective as an adjuvant therapeutic agent before its role in breast cancer prevention was demonstrated. An overview was undertaken of 14,170 patients participating in 11 clinical trials of treatment of early breast cancer with tamoxifen 20 to 40 mg daily (versus placebo) as adjuvant therapy. This analysis yielded impressive results favoring tamoxifen. Five years of adjuvant tamoxifen resulted in a proportional reduction in breast cancer recurrence of 47%. Remarkably, a preventive benefit was also observed. With an average of 5 years of follow-up, there were 105 new breast cancers in the contralateral breast with tamoxifen versus 192 with placebo.

Thus, tamoxifen is highly beneficial as adjuvant therapy for breast cancer, and more recently, its effectiveness has been demonstrated for prevention of breast cancer in high-risk women. This makes tamoxifen a breakthrough drug. One model examining the potential survival benefit of tamoxifen administered for prevention predicts an 18% reduction in mortality and an absolute decrease of 3 deaths from breast cancer per 1000 women prophylaxed.

In this issue of Circulation, Decensi and colleagues analyze risk factors for venous thromboembolism and superficial phlebitis on the basis of their previously published Italian breast cancer prevention trial of tamoxifen (Table). They found, in a multivariate analysis, the following risk factors for venous thromboembolism in their population of women at risk for breast cancer: age >60 years, diastolic blood pressure >90 mm Hg,
and angina. Current smoking ($P=0.054$) and obesity ($P=0.10$) emerged as risk factors of borderline statistical significance.

They concluded that women with conventional risk factors for atherosclerosis have a higher risk of developing venous thromboembolism during therapy with tamoxifen. To minimize the risk of developing superficial thrombophlebitis, DVT, or PE, they recommended that women using tamoxifen be counseled with these data. They defined venous thromboembolism as encompassing DVT, PE, and superficial phlebitis. Most of the “venous thromboembolism” end points that they reported were cases of superficial phlebitis, whereas the conventional definition of venous thromboembolism excludes superficial phlebitis. Nevertheless, their findings remind us that modification of risk factors for coronary atherosclerosis might also reduce the frequency of venous thromboembolism. Their report reinforces the emerging concept that atherosclerosis and venous thromboembolism are closely intertwined.

Prandoni and colleagues described an association between carotid atherosclerosis and venous thromboembolism. At least 1 carotid plaque was detected in 72 of the 153 patients with spontaneous venous thromboembolism (47.1%; 95% CI 39.1 to 55.0) and 48 of the 150 control subjects (32.0%; 95% CI 24.5 to 39.5). The odds ratio for carotid plaques in patients with venous thromboembolism, as compared with controls, was 1.8 (95% CI 1.1 to 2.9).

The detection of classic atherosclerosis risk factors in patients who develop venous thromboembolism has been reported previously. In the Nurses’ Health Study, obesity, cigarette smoking, and systemic arterial hypertension were risk factors for PE. Women with a body mass index exceeding 29 kg/m² had a 3-fold increase in PE risk. The risk of PE increased with each quintile of body mass index. Women who smoked >35 cigarettes daily doubled their PE risk. PE risk was significantly increased over baseline among women who smoked at least 25 cigarettes per day.

As cardiovascular specialists, we are likely to provide care to women with risk factors for coronary atherosclerosis who are also taking tamoxifen. We can increase their participation in devising a strategy for their own well-being by discussing with them the link between coronary risk factors and venous thromboembolism. These women may become extremely motivated to quit smoking, maintain blood pressure in the normotensive range, and develop nutrition and exercise regimens that promote a normal body mass index.

I am often asked to evaluate women who are about to initiate tamoxifen to prevent the development of breast cancer. The question posed to me is whether they can tolerate tamoxifen safely, especially if they have risk factors for DVT or PE. On the basis of the spectacular data favoring tamoxifen, I believe the prevention of breast cancer should take priority over the risk of venous thromboembolism. Often, reassurance of the patient suffices. After all, one third of the venous thrombosis episodes reported in the 4 tamoxifen prevention trials were superficial phlebitis, not DVT or PE. In the International Breast Intervention Study (IBIS)-1, the largest breast cancer prevention trial that collected data on the frequency of superficial phlebitis, DVT, and PE, there were twice as many women with DVT as with PE. In that trial, there were 4 deaths from PE: 2 in the tamoxifen group and 2 in the placebo group. If the risk of developing DVT is high, then I recommend concomitant systemic anticoagulation for the 5-year planned treatment period with tamoxifen. If the risk of developing venous thromboembolism is moderate, then I recommend concomitant low-intensity anticoagulation, usually with low-molecular-weight heparin administered in prophylaxis doses.

The report by Decensi and colleagues also serves to remind us of the well-established association between cancer and venous thromboembolism. In the Swedish Cancer Registry, the risk of diagnosed cancer was highest during the first year after a first episode of venous thromboembolism. The standardized incidence ratio for newly diagnosed cancer was 3.4 during the first year after venous thromboembolism and remained between 1.3 and 2.2 for the following 5 years.

When we provide care to hospitalized patients with cardiovascular disease and cancer, we should be certain that we recommend prophylaxis to avoid the development of DVT or PE. Cancer patients treated with chemotherapy are at increased risk of developing venous thromboembolism. Preventive efforts should focus on these populations. Fortunately, large-scale clinical trials have shown the efficacy and safety of various pharmacological prevention regimens in hospitalized patients at risk, including enoxaparin 40 mg daily, dalteparin 5000 U daily, and fondaparinux 2.5 mg daily.

There is also speculation that anticoagulation with warfarin, unfractionated heparin, or the low-molecular-weight heparin dalteparin can prolong survival in certain subsets of patients with cancer. In a trial of 385 individuals with advanced cancer, patients were randomized to dalteparin 5000 U once daily versus placebo and were treated for 1 year. A trend toward survival in the dalteparin group was noted, but the differences were not significant. In a post hoc analysis of patients with a better prognosis, a significant survival advantage was found with dalteparin: 43 months in dalteparin-treated patients versus 24 months among those receiving placebo.

For cancer patients with newly diagnosed DVT or PE, a treatment strategy of low-molecular-weight heparin as monotherapy (using dalteparin) appears to be superior to the more traditional approach of low-molecular-weight heparin as a “bridge” to warfarin anticoagulation. With dalteparin mono-

<table>
<thead>
<tr>
<th>Tamoxifen Breast Cancer Prevention Trials</th>
<th>Royal Marsden</th>
<th>NSABP-P1</th>
<th>Italian</th>
<th>IBIS-1</th>
<th>All Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancers</td>
<td>1238 vs 1233</td>
<td>6681 vs 6707</td>
<td>2700 vs 2708</td>
<td>3573 vs 3566</td>
<td>14,192 vs 14,214</td>
</tr>
<tr>
<td>DVT and PE</td>
<td>62 vs 75</td>
<td>124 vs 244</td>
<td>34 vs 45</td>
<td>69 vs 101</td>
<td>289 vs 465</td>
</tr>
<tr>
<td>Superficial thrombophlebitis</td>
<td>12 vs 8</td>
<td>53 vs 28</td>
<td>10 vs 9</td>
<td>43 vs 17</td>
<td>118 vs 62</td>
</tr>
<tr>
<td></td>
<td>8 vs 5</td>
<td>NA</td>
<td>33 vs 16</td>
<td>27 vs 9</td>
<td>68 vs 30</td>
</tr>
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</table>

NSABP-P1 indicates National Surgical Adjuvant Breast and Bowel Project P-1.
therapy, the recurrence rate of venous thromboembolism was halved as compared with long-term oral anticoagulation.

In conclusion, treatment of venous thromboembolism can be accomplished effectively and at low risk. A superficial phlebitis or DVT is a small price to pay for prevention of breast cancer. Patients susceptible to venous thrombosis can be identified and risk-stratified. This process requires collaboration between the oncologist and the cardiovascular consultant. Often, modifying certain risk factors for coronary heart disease such as obesity, cigarette smoking, and hypertension can lower the risk of venous thromboembolism. Effective pharmacological agents to prevent DVT include low-molecular-weight heparins, fondaparinux, and warfarin. For patients in whom prophylaxis was initially omitted or has failed, more intensive dosing of anticoagulants will almost always suffice.

Cardiologists, oncologists, and patients should celebrate the overwhelming safety and efficacy of tamoxifen. Tamoxifen has been proven to save lives in women receiving adjuvant hormonal therapy for breast cancer and can markedly reduce the development of breast cancer among women at high risk. Tamoxifen is breast cancer’s equivalent of statins for coronary artery disease. Cardiologists should encourage breast cancer patients and those at high risk for developing breast cancer to follow the advice of oncologists who have prescribed tamoxifen. When oncologists ask their cardiologists colleagues whether the benefits of tamoxifen outweigh the risks of venous thromboembolism, the response should almost always be to proceed with tamoxifen therapy. Our role is to explain to patients and oncologists the minor nature of superficial phlebitis and the excellent lifestyle modification and pharmacological strategies that are available to prevent and treat DVT and PE.

In the future, worrying about DVT risk may become less problematic in breast cancer patients. Third-generation oral aromatase inhibitors, such as the irreversible steroidal inactivator exemestane, ten Cate H, Soeeman H, Ingels M, Richel DJ, Prins MH. Symptomatic venous thromboembolism in cancer patients treated with chemotherapy: an underestimated phenomenon. Arch Intern Med. 2004;164:190–194.


References


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