

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Venous Thromboembolic Disease and Stroke in Women Taking Tamoxifen for Breast Cancer Chemoprevention

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H&O What was the rationale for using tamoxifen as a chemopreventive agent for breast cancer?

CI Tamoxifen has been used for many years as adjuvant therapy for women with hormone receptor–positive breast cancer. One of the observations from the trials examining the role of tamoxifen in the adjuvant setting was that tamoxifen not only reduced the risk of distant metastases, but also reduced the risk of contralateral breast cancer by approximately 40–50%.

H&O How has this chemoprevention strategy been studied in clinical trials?

CI A clinical trial of tamoxifen for breast cancer chemoprevention was initiated in 1992 by the National Surgical Adjuvant Breast and Bowel Project (the P-1 study) based on these observations. It was hypothesized that since tamoxifen reduced the risk of contralateral breast cancer, it might also be effective in reducing the risk of developing breast cancer in the first place in healthy women with an increased risk of this disease for a variety of reasons. In this study, over 13,000 women with at least a 1.66% 5-year risk of developing breast cancer were randomized to receive 5 years of tamoxifen or placebo. The results, published initially in 1998, demonstrated that tamoxifen was effective and reduced the incidence of invasive and noninvasive breast cancer by approximately 40–50%.

It is important to note that once tamoxifen was found to be an effective chemopreventive agent, the study

was unblinded, and women enrolled in the study were told whether they were taking tamoxifen or placebo. Those receiving placebo were offered the opportunity to take tamoxifen or to participate in a subsequent chemoprevention study comparing tamoxifen with raloxifene (Study of Tamoxifen and Raloxifene trial). Thus, in the follow-up years, the control arm included many women who received placebo followed by chemoprevention with tamoxifen or raloxifene.

H&O Were hematologic side effects a concern from the start of the initial chemoprevention trial?

CI Yes. It has long been known that selective estrogen receptor modulators, such as tamoxifen, are associated with an increased risk of thrombosis, and thus this side effect was carefully monitored in the study.

H&O What was the incidence of thrombosis?

CI Before looking at the incidence of hematologic side effects, it is important to consider the difference between evaluating adverse events in a chemoprevention study versus a treatment study. Chemoprevention involves administering a drug to a healthy individual who is at an increased risk of developing a disease, so it is essential to have a very clear understanding of the side effects and the risk:benefit ratio. Therefore, the participants in the tamoxifen chemoprevention study were monitored very carefully for side effects.

Given the known effects of estrogen on thrombosis, there was concern about the potential occurrence of various thromboembolic effects, such as stroke, pulmonary embolism, and deep vein thrombosis. The P-1 study findings, reported by Fisher et al, showed about a 40% increase in the risk of stroke associated with the tamoxifen arm versus the placebo arm (relative risk of 1.42). This difference did not achieve statistical significance, although there was a trend in that direction. The risk was higher among women over the age of 50 compared with women under age 50. No difference in the risk of transient ischemic attacks was noted. There was an approximately 2-fold higher risk of pulmonary embolism associated with the tamoxifen arm versus the placebo arm, which was statistically significant. Additionally, there was a trend toward

higher overall risk of deep vein thrombosis associated with the tamoxifen arm (relative risk 1.44), but again this rate did not reach statistical significance.

H&O Have any markers been identified that indicate a subpopulation of women who may be more likely to develop thrombosis?

CI A case-control study conducted by the Cancer and Leukemia Group B evaluated women who received adjuvant therapy with tamoxifen for breast cancer and who experienced a documented thromboembolic event during therapy in order to see if there was a correlation with the presence of factor V Leiden. The control arm was composed of women who underwent tamoxifen therapy but did not experience a thromboembolic event. Among the women who developed thrombosis during tamoxifen therapy, 15.6% had factor V Leiden mutations, versus 5% among controls. The odds ratio was 3.9. This study evaluated women with breast cancer who were treated with tamoxifen, not women undergoing tamoxifen chemoprevention. Nonetheless, it suggests that the presence of a factor V Leiden mutation predisposes women to develop thromboembolic events while on tamoxifen.

A substudy of the P-1 trial examined changes in antithrombin protein C, protein S, and activated protein C ratio in women enrolled in the study. After 6 months of treatment, no changes in levels were observed in the placebo group, but reductions in antithrombin and protein S, but not protein C or activated protein C ratio, were found in those on tamoxifen, suggesting that these changes may be related to the increased risk of thromboembolic disease in women receiving tamoxifen.

H&O How does one decide whether tamoxifen chemoprevention is appropriate for someone?

CI The risk:benefit ratio must be calculated on an individual basis, based on age and various factors that might put a person at risk for breast cancer and/or complications associated with chemoprevention, such as hematologic events as well as endometrial cancer. There is an approximately 1% risk of endometrial cancer when women receive 5 years of tamoxifen. In a 2005 updated publication of the P-1 study in the *Journal of the National Cancer Institute*, it was determined that for women under the age of 50 who had at least a 2.5% 5-year risk of developing breast cancer, the benefits of tamoxifen chemoprevention outweighed the risks.

Women over the age of 50 are generally required to have a higher baseline risk of breast cancer in order to exceed the side effects profile, because these women have a higher risk of developing the associated side effects. The

data from the P-1 study indicated that Caucasian women aged 60–69 needed to have at least a 4.5% 5-year risk of developing breast cancer in order for the benefits of tamoxifen to exceed its potential for risks.

In general, for African American women, who have a higher risk of developing thrombosis and endometrial cancer, there must be a higher baseline risk of breast cancer in order for the benefit of chemoprevention to exceed its risk.

The decision about whether to take a medication as a chemopreventive agent is a very personal one. Individual women may have very different views on whether a particular risk:benefit ratio is worth it to them. However, if the Gail or other model shows that a woman has an increased risk of developing breast cancer, one should discuss the potential risks and benefits of such treatment with her.

H&O Is it possible to determine who might be likelier to develop thrombosis during tamoxifen chemoprevention?

CI Whenever one is considering tamoxifen, either as a chemoprevention agent or as therapy for breast cancer, it is necessary to obtain a careful history to determine if there is an increased likelihood of thrombosis, such as a personal or family history of thromboembolic events, or a history of repeated miscarriages. Through this initial evaluation, it is then possible to determine whether a hypercoagulable work-up should be considered. If an increased risk of thromboembolic disease exists, then one should be very cautious about recommending chemoprevention with tamoxifen as the risks would likely exceed the potential for benefit.

Suggested Reading

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