

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Chemoprevention in Breast Cancer

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H&O What is the rationale behind chemoprevention in breast cancer?

VV Chemoprevention is different from chemotherapy. The idea behind chemoprevention is not to provide a preventive intervention for everyone, but rather to identify individuals who are at increased risk. There are 2 reasons to identify such individuals. First, the absolute benefit will be greater. For example, among a population of 100 women in which half would develop breast cancer, diminishing the risk by 50% means preventing cancer in 25 people. By contrast, in a population of 100 women in which only 10% will develop breast cancer, a 50% decreased risk prevents 5 cases. Thus, the absolute benefit is greatest among women with the highest risk of developing breast cancer. Accordingly, the aim in breast cancer prevention research for the past 30 years has been to identify those women at increased risk.

Also, because there is not a prevention drug that could be considered perfect, with no side effects, the risk:benefit ratio is best in patients at highest risk. In other words, if side effects occur with a chemopreventive agent, the net benefit (the benefit of preventing breast cancer and any other benefits provided by these drugs vs side effects, such as blood clots or uterine cancer) is best among those at highest risk. For these reasons, all of the strategies to prevent breast cancer over the past several decades have been targeted at women with increased risk.

H&O Technically, how does chemoprevention work?

VV Breast cancer cannot be thought of as a single event; rather, it develops as a process. Published estimates note that there are approximately 2 million white women in North America who are at increased risk for breast cancer. For many of these women, it is possible to detect a pre-malignant condition. A routine screening mammogram may reveal an abnormality that, although nonmalignant, may indicate a process called hyperplasia—too many breast cells—in which the cells are normal, but exist in increased numbers. Occasionally biopsies reveal atypical hyperplasia, in which some but not all of the excess cells appear to have some features of malignant cells; the tissue is not cancerous, but is heading in that direction. Atypical hyperplasia is associated with a 5-fold greater risk for developing breast cancer compared with women without this condition, and when it is combined with having a first-degree relative with breast cancer, the risk increases to 10-fold. Another abnormality often found serendipitously upon postmammogram biopsy is lobular carcinoma in situ, associated with a breast cancer risk of 1–2% per year, equal to that for women with mutated genes, responsible for familial breast cancer.

Assessing risk is an essential part of chemoprevention, and an extensive list of risk factors has been described over the years that are known to reliably predict risk. Aside from sex (women are 100 times more likely to develop breast cancer than men), the most important risk factor is age. The risk of breast cancer for an 80-year-old woman is 6–8 times higher than that for a 20-year-old woman. Having first-degree relatives with breast cancer is also a major risk factor. Age of menarche is important; women who began menstruating before the age of 12 have a 20–30% higher lifetime risk of developing breast cancer. Likewise, women who never have children or who are over age 30 when they have their first child double their lifetime risk of breast cancer. Breast biopsies are also associated with an increased risk, not as a direct cause, but as a marker. If an individual has abnormalities in the breast and the only way to determine whether they are benign or malignant is by biopsy, then there is likely a process in the breast that is associated with breast cancer risk.

H&O Are investigators seeking to understand what causes abnormalities such as atypical hyperplasia and lobular carcinoma in situ?

VV Yes, and it is not known what characteristic of atypia triggers breast cancer development or why 3 of 4 women with atypia never develop breast cancer and 1 in 4 does. Uncovering the mechanism behind this occurrence will likely represent a significant breakthrough in breast cancer prevention. There are several hypotheses regarding acquired and accumulated genetic changes, but none have yet been proven. However, multiple environmental factors have been studied and none has been shown to positively correlate with breast cancer, other than exposure to atomic radiation. Drinking alcohol is the only lifestyle factor that has been associated with increased risk, but only when the alcohol intake is excessive (2–3 drinks per day for years).

H&O Could you discuss the Breast Cancer Prevention Trial (BCPT)?

VV BCPT is the largest breast cancer prevention trial completed thus far. This double-blind randomized trial was started by the National Surgical Adjuvant Breast and Bowel Project in 1992 and was reported in 1998. Both pre- and postmenopausal women (approximately one third and two thirds of the study population, respectively) were enrolled, with a median age of 52. The women were administered either tamoxifen (n=6,700) or placebo (n=6,700). At the time the study was stopped, the breast cancer risk reduction in the tamoxifen group was 49%. Among the women with atypical hyperplasia, the risk reduction was 86%, and women with lobular carcinoma in situ experienced a 554% reduction in risk.

Premenopausal women taking tamoxifen did not have an increased risk of uterine cancer or thrombosis. However, postmenopausal women did experience an age-dependent increased risk of clotting, pulmonary embolism, deep vein thrombosis, and strokes, and the major risk factor for clotting among those women in the tamoxifen group was obesity. There was also a 1% risk of uterine malignancy among postmenopausal women who had received tamoxifen for 5 years (a 2-per-1,000 risk per year). These uterine malignancies appeared not to be life threatening, and were managed with hysterectomies. This risk of uterine cancer may explain why 50% of the women who volunteered for the BCPT reported having hysterectomies for benign conditions prior to enrollment in the trial.

Other benefits seen with tamoxifen included a reduction in the risk of fractures by approximately 30% among postmenopausal women compared with the placebo group; there was some bone loss among premenopausal women but no increase in fractures. In addition, there was a 50% reduction in the risk of ductal carcinoma in situ.

Eligibility criteria for the BCPT included age 35 years or older and a risk score, using the Gail Model, which takes into account the risk factors discussed above, of at least 1.6% in 5 years, which is the risk of the average 60–65-year-old woman. Women with lobular carcinoma in situ could also enter the trial if that was their only risk factor, as could women 60 years or older with no other obvious risk factors. Approximately one third of the women in the trial were over 60 years of age.

H&O Could you discuss the International Breast Cancer Intervention study (IBIS)?

VV This study followed the BCPT, and was conducted in the United Kingdom. The design was the same: tamoxifen versus placebo in a double-blind randomization. The study enrolled approximately 7,000 women with approximately 20,000 person-years of observation (compared with approximately 54,000 person-years in the BCPT). The results were very similar. The women enrolled were at high risk of developing breast cancer, although there were fewer women with either atypia or lobular carcinoma in situ than in the BCPT. In the IBIS trial, tamoxifen was shown to reduce the risk of breast cancer by 32%. It is likely that the reason why the reduction seen in this trial was lower than that seen in the previous study (49%) was because atypia and lobular carcinoma in situ were not as prevalent among the IBIS-I participants. With BCPT, when patients with atypical hyperplasia are excluded the risk reduction is 34%. The same side effects of uterine malignancy and thrombosis were observed in IBIS-I.

H&O What is the status of the Study of Tamoxifen and Raloxifene (STAR) trial?

VV The STAR trial has finished enrollment, with 19,747 women enrolled, making it the largest prevention trial ever conducted. All women in the study are postmenopausal, and the average age is 62 years. In this double-blind study, women were randomized into 2 groups of approximately 9,800 each and received either tamoxifen or raloxifene (Evista, Eli Lilly). Raloxifene is approved by the US Food and Drug Administration for treating and preventing osteoporosis. In clinical trials of raloxifene, women taking this agent to treat or prevent osteoporosis experienced a 70% reduction in the risk of breast cancer. This reduction was achieved with no uterine malignancies, indicating that this agent may be a more effective and safer chemopreventive agent than tamoxifen. The eligibility criteria were the same as in the BCPT, save that premenopausal women could not enroll. The trial was initiated in 1999 and many women have completed their planned 5 years of study medication. Enrollment was completed in October 2004, and final results are expected in mid-2006.

H&O Were the women who enrolled referred to the trial by their primary care physicians?

VV We don't think so. It appears that primary care physicians are not yet consistently aware of the notion of breast cancer risk reduction. After the BCPT, there was virtually no increase in the sales of tamoxifen, indicating that this agent was not being recommended by primary care physicians for chemoprevention. It is more likely the case that the women who enroll in these trials are highly motivated and self-educated, and took the initiative to find the trial. The STAR trial was promoted in the media, at medical meetings, and among breast cancer advocacy groups, and this strategy seems to have been more responsible for enrollment than physician referrals. In other words, they found us, we did not find them.

H&O Are any breast cancer chemoprevention trials still enrolling patients?

VV There is an ongoing trial, called ExCel or MAP-3. This study was initiated by Dr. Paul Goss, now at Harvard Medical School, and is evaluating the aromatase inhibitor exemestane (Aromasin, Pfizer) in the prevention of breast cancer. Aromatase inhibitors reduce the concentration of circulating estrogen in postmenopausal women and are effective breast cancer treatment drugs, having replaced tamoxifen in the treatment of hormone-responsive early and late breast cancer in postmenopausal women (these agents are not effective in premenopausal women because they do not inhibit ovarian estrogen synthesis).

This trial is comparing exemestane and placebo in the prevention of breast cancer among high-risk postmenopausal women, with a similar design to the other trials discussed above. I am absolutely certain that the women in the exemestane group will have a decreased risk of breast cancer compared to those in the placebo group.

Aromatase inhibitors are not associated with an increased incidence of clotting or uterine cancer. However, they do cause some bone loss; approximately 2% more women who are administered aromatase inhibitors develop fractures compared with women taking placebo over a 5-year period. Therefore, it will be important to monitor bones and for patients in the exemestane group to take calcium supplements or bisphosphonates to protect their bones. Aside from this side effect, aromatase inhibitors will most likely prove to be superior to both tamoxifen and raloxifene in the prevention of breast cancer.

Once the findings of the STAR trial are known, another trial will likely be initiated to compare whichever agent proves superior (most likely raloxifene) to an aromatase inhibitor.

H&O Is it likely that chemoprevention will become a standard recommendation for a subpopulation of women?

VV Yes, for high-risk women who are outside of child-bearing age or who do not plan on having children. Most likely we will come to view chemoprevention of breast cancer in much the same way as we do hypertension treatments and cholesterol-lowering treatments. Breast cancer prevention should ultimately be considered in the same way as any general medicine risk-reduction strategy. However, just as in the treatment of hypertension or high cholesterol, medications are not given universally, but rather to a high-risk subpopulation.

H&O Is cost an issue?

VV Yes, because as a society preventive strategies are not generally embraced. The predominant approach in medicine is crisis treatment. Physicians need to be educated that preventive medicine is cost-effective because, simply, it prevents illness. Pediatricians are aware of this approach—children are immunized and screened for disease. Much of the general medicine community also understands the need for prevention. However, too much of medical practice in the United States is crisis-oriented; there needs to be a greater focus on preventive medicine.

H&O How will this focus increase?

VV This focus will only increase when the payers agree to pay for preventive services. There is reluctance to cover preventive care. Preventive services that have been established with prospective clinical trials need to be added to the list of items that payers are willing to cover. There is some willingness to cover some preventive services, but that list needs to be increased. When this increased awareness and coverage are accomplished, then doctors will start focusing more on preventive care.

Suggested Reading

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