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Abstract

Breast cancer is the most frequently diagnosed non-skin cancer in women, and one in eight women will develop breast cancer within their lifetimes. Unfortunately, the strongest risk factors for breast cancer (i.e. age, family history, hormonal factors) are not easily modified. There is some evidence that chemopreventive drugs may be able to prevent breast cancer in high-risk patients. Tamoxifen and raloxifene have been shown to reduce the risk of breast cancer in high-risk women but may be associated with several serious adverse events. Clinical trials are currently in progress to determine if aromatase inhibitors are a viable alternative for breast cancer prevention, as they may be considered effective in the early treatment of breast cancer. For patients with *BRCA1* and *BRCA2* mutations, a bilateral prophylactic mastectomy may be an option. This article discusses the risks and benefits of available treatment options for breast cancer prevention in high-risk patients.

Introduction

Breast cancer is the most frequently diagnosed non-skin cancer in women and the second most common cause of cancer death in women.[1] One in eight women will develop breast cancer within their lifetimes.[2] Some breast cancers are estrogen-dependent for growth and are known as estrogen receptor positive (ER-positive) breast cancers; other breast cancers are considered estrogen receptor negative (ER-negative) and composed of cells without estrogen receptors.[3] The presence of these receptors is an important part of identifying useful treatment options.[4]

Unfortunately, the strongest risk factors for breast cancer (i.e. age, family history, hormonal factors) are not easily modified. In high-risk patients, mutations in *BRCA1*/*BRCA2* greatly increase lifetime risk of cancer.[5] Prophylactic mastectomies for *BRCA1* and *BRCA2* mutation carriers are a growing trend in breast cancer prevention. However, since not all women with these mutations will develop breast cancer, those considering this alternative should receive counseling on all available options before making a final decision.[1] Thus, other preventive strategies must be considered. There is some evidence that chemopreventive drugs may be able to prevent breast cancer. Currently, chemoprevention may be considered for patients at a high risk for developing breast cancer based upon family history, as the benefits do not outweigh the risks for routine use in all patients.[6]

Tamoxifen

Tamoxifen, a selective estrogen receptor modulator (SERM), was approved by the Food and Drug Administration (FDA) in the late 1990s for breast cancer chemoprevention. By competitively binding estrogen receptors in breast tissue, decreasing DNA synthesis and inhibiting estrogen effects, tamoxifen is shown to reduce the risk of breast cancer by 30-50 percent in high-risk women.[7,9] In contrast, estrogen receptors in the uterus are stimulated rather than inhibited by tamoxifen. Estrogenic effects in the uterus increase the risk of endometrial cancer. Patients taking tamoxifen are also at increased risk of thromboembolic events. These risks require tamoxifen to carry black box warnings for uterine malignancies, stroke and pulmonary embolism, which limit the use of this drug for prophylactic measures.[7,10] Despite the possible side effects, the use of tamoxifen as a prophylactic measure is supported by two long-term studies, which concluded these side effects do not persist, while the benefits do.[9,11]

The Royal Marsden Trial included 2,471 women between 30 and 70 years of age with a family history of breast cancer who were randomized to take either tamoxifen or placebo for eight years. Results did not show an overall reduction in breast cancer events between the tamoxifen and placebo groups (p=0.2). However, following the eight-year active phase, the women participated in six-month follow-ups, and a blinded follow-up study was performed 20 years later (median follow-up 13 years) to determine whether tamoxifen provided long-term benefits to overall breast cancer and, specifically, with ER-positive breast cancers. Overall, 209 breast cancer cases, including 186 invasive cases, were documented with no differences noted between tamoxifen and placebo groups (p=0.2). Of the invasive breast cancer cases, the estrogen receptor status was available for 180. Of these, 139 were ER-positive, with 53 occurring in the tamoxifen group and 86 occurring in the placebo group. Results showed that the tamoxifen group had a 39 percent lower incidence of invasive ER-positive breast cancers versus the placebo group (p=0.005). The adverse event profiles for both arms occurred predominantly during the treatment period, with gynecologic toxicity being the most clinically important. There was no evicence of any increase in the incidence of non-breast and non-endometrial cancers. This study suggests tamoxifen provides long-term risk reduction for ER-positive breast cancer.[9]

The International Breast Cancer Intervention Study (IBIS-I) was a five-year, double blind, randomized trial comparing tamoxifen to placebo in women with an increased risk for breast cancer.[11] The results of this study, which included a total of 7,154 women, found a statistically significant decrease in the incidence of ER-positive breast cancer in the tamoxifen group (p=0.013). Regarding side effects, a significant increase in endometrial cancer was found in the tamoxifen group during the active period (p=0.02), but following the active period, the difference was not significant (p=0.2). The tamoxifen group also had a significant increase in thromboembolic events (p=0.001) as well as deaths (p=0.028), but no specific cause of death was significant. The 96-month follow-up of this study also demonstrated the efficacy of tamoxifen for the prevention of breast cancer, reporting the development of 337 total breast cancer cases with a 27 percent lower incidence rate with tamoxifen than placebo (p=0.004). Overall, a 32 percent reduction in breast cancer was seen in years zero to four, and 44 percent thereafter; no reduction was seen in ER-negative breast cancer. The risk reduction was found to be greater for premenopausal women, who also had a lower number of endometrial cancer cases and thromboembolic events. Therefore, these results support the use of tamoxifen as chemoprevention in premenopausal women. This follow-up study supports long-term benefits of tamoxifen for ER-positive breast cancer risk reduction while showing the adverse effects are unlikely to persist past the treatment phase.

Raloxifene

Raloxifene is a selective estrogen receptor modulator (SERM) that competitively antagonizes estrogen-induced DNA transcription of estrogen on receptors in breast and uterine tissues.[12] It also acts as an estrogen agonist in bone, therefore increasing bone density. Labeled indications for raloxifene include prevention and treatment of osteoporosis in post-menopausal women as well as the prevention of breast cancer in high-risk patients.[13]

The clinical effectiveness of raloxifene is evident in two prominent trials. The Multiple Outcomes of Raloxifene Evaluation (MORE) is a multicenter, double-blind, randomized trial comprised of 7,705 women who were followed from 1994 to 1998.[12] The primary outcome of the trial was osteoporosis prevention, with breast cancer prevention as a secondary end point. Raloxifene reduced the risk of invasive ER-positive breast cancer by 90 percent but did not have a statistically significant effect on invasive ER-negative breast cancer. The overall risk of invasive breast cancer was reduced by 76 percent. It is also important to note that raloxifene did not increase the risk of endometrial cancer in the study patients. The Continuing Outcomes Relevant to Evista (CORE) trial is a continuation of the MORE trial, where patients' raloxifene treatment was continued for four additional years in order to study long-term effects of therapy.[14] Women who agreed to continue in the study (n= 4,011 patients) were either continued on placebo therapy or assigned to raloxifene if they received active treatment in the previous trial. The women who received raloxifene had a 59 percent reduced incidence of invasive breast cancer compared to the placebo group. This included a 76 percent reduction in ER-positive invasive breast cancer and no statistically significant reduction in ER-negative invasive breast cancer. It could not be determined whether the reduction was a result of the initial four-year therapy or the continuation of treatment in the CORE trial.

The adverse events from raloxifene treatment were similar for both the MORE and CORE trials.[12,14] Reported events included hot flashes, deep vein thrombosis, retinal vein thrombosis, leg cramps, myocardial infarction, stroke, cataracts, ovarian cancer and breast pain. However, none of the events were statistically significant in the treatment group versus the placebo group. A higher incidence of pulmonary embolism occurred in the raloxifene group compared to placebo for the eight-year period of treatment. Although the increased risk of thromboembolic disease was not overall statistically significant in the treatment group versus placebo, the researchers did note that raloxifene should be used with caution in patients who are already at an increased risk of thromboembolic events.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Tamoxifen and Raloxifene (STAR) trial was conducted as a follow-up to the Breast Cancer Prevention Trial (BCPT), which studied the effectiveness of tamoxifen for preventing breast cancer.[15] To obtain FDA approval of raloxifene as a preventative therapy for patients at high-risk for breast cancer, researchers compared tamoxifen to raloxifene. The STAR trial was a prospective, double-blind, randomized, phase-III trial conducted from July 1, 1999, to Dec. 31, 2005. Within that time period, therapy was given for five years with a one-year follow-up. Eligible participants included women who were required to have a five-year predicted breast cancer risk of at least 1.66 percent based on the Gail Model, postmenopausal, and not currently receiving tamoxifen or raloxifene therapy. At baseline, 19,747 women were enrolled into treatment with a mean age of 58.5 years and a mean five-year predicted breast cancer risk of 4.03 percent. Patients were randomized to receive tamoxifen or raloxifene and were stratified by age and race. Outcome comparison between treatment groups was based on determined rates of incidence per 1,000.

At the conclusion of the STAR trial, there was no statistically significant difference between tamoxifen (4.3 per 1,000) and raloxifene (4.41 per 1,000) in preventing invasive breast cancer.[15] The result was not statistically significant, although a difference was noted in prevention of non-invasive breast cancer; specifically, fewer patients in the tamoxifen group (1.51 per 1,000) developed non-invasive breast cancer than the raloxifene group (2.11 per 1,000). There are multiple secondary endpoints to be considered in the STAR trial. Within the raloxifene group, there was a trend towards a decreased incidence of uterine cancer, although the result was not statistically significant. Raloxifene did show a statistically significant reduction in uterine hyperplasia and hysterectomy events when compared to tamoxifen. Overall, raloxifene has a decreased effect on adverse events associated with uterine tissue. Raloxifene patients had significantly fewer cases of deep vein thrombosis and pulmonary embolism. This result is significant for those patients who have an already increased risk of thromboembolic event prior to SERM treatment.

In conjunction with the STAR trial, the Patient-Reported Symptoms and Quality of Life During Treatment With Tamoxifen or Raloxifene for Breast Cancer Prevention trial captured the effects of SERM treatment on patients included in the trial.[16] The report concluded no significant difference between treatment groups for overall physical and mental health. Raloxifene patients did experience a significant decrease in sexual interest ($p= 0.009$) and experienced fewer musculoskeletal problems, such as leg cramps ($p= 0.002$). Tamoxifen patients experienced significantly more vasomotor symptoms ($p<0.001$). Both treatment groups experienced adverse events related to bladder problems ($p<0.001$), gynecological problems ($p<0.001$) and leg cramps ($p<0.001$). This report is a useful tool to evaluate quality-of-life outcomes for two treatment methods with similar pharmacological outcomes.[16]

At the conclusion of the STAR trial, the researchers noted some shortcomings of the study.[16] Although attempts were made to represent racial and ethnic groups within the population of North America, the trial did not meet the goal of proportional representation of the population. This is significant in evaluating the treatment of patient populations who may not have been adequately represented within the trial. The STAR trial was also unable to evaluate the adequate length of SERM treatment needed to prevent invasive breast cancer.[15] The trial did provide necessary data to show that eight years of treatment reduced the incidence of invasive breast cancer, but decreased adverse effects could be achieved with a shorter treatment. The researchers noted that lack of information on treatment duration should not deter treatment, as long-term studies have shown that tamoxifen is safe and effective 25 years after the drug was first approved for prevention. Whether or not one SERM was preferred over another was not concluded within the STAR trial; however, raloxifene was FDA-approved for preventative treatment of breast cancer.[15,17] Researchers believed that physicians may be more likely to convert to raloxifene treatment for breast cancer prevention since raloxifene therapy exhibited decreased adverse events in the STAR trial. Currently, neither SERM is recommended over another in prevention of invasive breast cancer guidelines.

Aromatase inhibitors

While tamoxifen and raloxifene are the medications conventionally used for breast cancer prevention, aromatase inhibitors are an emerging option.[18] Aromatase converts androgens to estrogen in the adrenal glands and other tissues; however, this is a minor estrogen synthesis pathway in premenopausal women, who synthesize estrogen mainly in the ovaries. For this reason, aromatase inhibitors have little effect on estrogen synthesis in premenopausal women. Conversely, aromatase is the main estrogen pathway in postmenopausal women, so aromatase inhibitors are reserved for use in this population.[19] Three aromatase inhibitors are currently available: anastrozole, letrozole and exemestane.[13] All three are indicated for the treatment of early to advanced ER-positive breast cancer, and all three drugs suppress almost all estrogen production in postmenopausal women.[13,18]

Within the MORE trial, it was hypothesized that inhibition of aromatase is at least equally effective to raloxifene in breast cancer prevention, which initiated the further research of all three aromatase inhibitors for FDA approval as preventative treatment of breast cancer.[12,20] Currently, letrozole and exemestane are in phase-III trials and include postmenopausal women with

no prior history of breast cancer. Letrozole and exemestane trials are set to be completed within the next five years.[21,22] However, anastrozole research is still in the recruiting phase with no estimated conclusion date.[23]

The role of aromatase inhibitors in preventing breast cancer has yet to be shown. Because aromatase inhibitors are known to be successful for early breast cancer treatment, it is possible that aromatase inhibitors are useful in preventing breast cancer. If efficacy is shown, aromatase inhibitors should be compared to the current standards of prevention, raloxifene and tamoxifen.

Bilateral prophylactic mastectomy

For patients who want a higher risk reduction than chemoprevention can provide, a bilateral prophylactic mastectomy (BPM) may be an option. This radical, irreversible procedure is mainly reserved for high-risk women classified by a mutation of the *BRCA 1 and BRCA2* or a genetic predisposition for breast cancer. Several studies on this topic have determined at least a 90 percent risk reduction.[7,24-26] Several different types of mastectomies exist, with each type removing varying amounts of breast tissue. However, the risk cannot be completely eliminated because 100 percent of the breast tissue is not removed in the surgeries. Mastectomies removing greater percentages of breast tissue are found to be more effective.[11] While studies show a significant risk reduction in incidence of breast cancer, mastectomies can also have psychosocial effects on the patient regarding appearance, sexuality, body image and emotional upset.[26] When discussing possible prophylactic measures with patients, it is important to weigh the risks versus benefits as well as to ensure that the patient clearly understands all aspects of this procedure.

Conclusion

In the past few decades, chemoprevention with tamoxifen and raloxifene has been used as the therapy of choice in preventing the development of breast cancer in high-risk patients. The studies have demonstrated similar efficacy in the prevention of breast cancer with either SERM treatment but, at the same time, noted different adverse event profiles. Additional therapies, such as aromatase inhibitors, are currently being studied for use in high-risk patients with possible significance in treatment for the future. Recently, mastectomies have gained attention as another option for breast cancer prevention, although they are reserved for the highest-risk patients due to the irreversible nature of this treatment option and its risks. Whether or not radical treatment or chemotherapeutic options are better for preventing breast cancer in high-risk patients has yet to be seen in a single study. Considering individual patients and their risk for breast cancer is important in deciding which type of preventative treatment patients should receive. As women continue to become more proactive in breast cancer prevention, it is anticipated that an expansion of preventative therapy will continue.

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