Risk Reduction Strategies: Medical Oncology

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Virginia Kaklamani

Introduction

In the United States it is estimated that in 2012 more than 40,000 women will die of breast cancer and 229,060 women will be diagnosed with the disease [1]. Although early detection strategies, such as mammograms, have been successfully implemented, 10 (of women will be diagnosed with four or more lymph nodes involved [2]. It has long been thought that the steps leading to cancer development in the breast take place during a long period of time. Support of this notion comes from data in women exposed to radiation. Among patients who received chest radiation for Hodgkin's disease, a cancer of the lymph nodes, as well as the survivors of the atomic bombing, it has been found that the greatest risk of developing breast cancer is when the radiation exposure took place during the early teen years [3]. However breast cancer in those individuals occurred at least 10–15 years later. Additional data come from infants undergoing radiation to the thymic gland, a gland located in the chest, [4] and girls in puberty who received radiation during a procedure for the diagnosis of tuberculosis [5].

V. Kaklamani, M.D., D.Sc. (✉)
Division Hematology/Oncology,
Northwestern University, 676 North St. Clair Street,
Suite 850, Chicago, IL 60611, USA
e-mail: v-kaklamani@northwestern.edu

Owing to the long natural history of cancer initiation, and the high incidence and severity of the disease, breast cancer is a unique model for successful prevention [6]. Lifestyle modification has been suggested but so far such strategies have been implemented in clinical trials for too short a period to prove successful in preventing breast cancer. Most of the focus has been on developing medications for prevention (chemoprevention). To date three medications have been extensively studied and approved as chemopreventive agents for breast cancer: tamoxifen, raloxifene, and exemestane. However several other agents are currently undergoing clinical testing.

Selective Estrogen Receptor Modulators

These agents change the effect of estrogen in tissues. The word selective is used because in some tissues they promote the effect of estrogens and in other tissues they inhibit its effect. Therefore these agents can have estrogenic effects in some tissues but antiestrogenic effects in others.

Tamoxifen

Tamoxifen was initially developed in the 1960s to be used as a contraceptive pill. It was found however to have strong antiestrogenic properties

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and to prevent the growth of breast tumors in rats [7, 8]. Tamoxifen, like other selective estrogen receptor modulators (SERMs), is unique and acts as an estrogen in some tissues and as an antiestrogen in others [9]. It has long been the hormone drug of choice for all stages of hormone responsive breast cancer and has been shown to decrease the risk of recurrence as well as mortality in early stage breast cancer [10].

Tamoxifen was considered for breast cancer chemoprevention for three reasons. Primarily tamoxifen has an excellent safety profile [6]. This is important since any agent used for chemoprevention would have to be used for a long period of time, in healthy individuals. Secondly, tamoxifen has been found to prevent breast cancer in mice and rats [7, 8]. Finally, studies showed that when giving tamoxifen to treat breast cancer, there was a decreased risk of developing breast cancer in the other breast [10].

NSABP P-1

The NSABP P-1 trial was the first large preventive trial in breast cancer and enrolled 13,388 patients between June 1992 and September 1997 [11]. Women were eligible to participate in the trial if they were over the age of 60 or between 35 and 59 years of age with a high risk for breast cancer. Women with lobular carcinoma in situ (LCIS), a high-risk factor for breast cancer, were also eligible for the study. After a median follow-up of 7 years tamoxifen was found to reduce the incidence of breast cancer by 43(and that of precancerous lesions by 37 (, in all age groups [12]. The benefit was found to be only in hormone receptor-positive breast cancers where the overall risk was reduced by 69(. The rate of hormone receptor-negative tumors did not significantly differ from the placebo group. Tamoxifen led to a 32(reduction in bone fractures due to osteoporosis and increased the risk of uterine cancer, stroke, blood clots, and cataracts whereas there was no difference in the risk of heart attacks and death in the two arms [12].

Overall the NSABP P-1 trial was able to demonstrate a 43(reduction of the incidence of breast cancer among healthy but high risk for breast cancer women who took tamoxifen for 5 years. So far it hasn't been shown that women who will take tamoxifen for 5 years will live longer although they will have a significantly lower risk of being diagnosed with breast cancer. It has been suggested, however, that a longer follow-up is needed to demonstrate that women at high risk for developing breast cancer will live longer if they take tamoxifen for 5 years.

IBIS-I

A total of 7,145 women aged 35–70 and at high risk for breast cancer were randomly assigned to take either tamoxifen or a sugar pill (placebo) for a 5 years [13]. After a median follow-up of 96 months women in the tamoxifen arm had a 27% reduced risk for breast cancer compared with placebo. This reduction in risk was again seen only in hormone receptor positive tumors whereas there was no difference in the risk for hormone receptor negative tumors. Side effects associated with tamoxifen therapy were similar to those observed in the NSABP P-1 trial.

Royal Marsden and Italian Trial

Two other trials failed to show an advantage to the use of tamoxifen as a chemopreventive agent. The Royal Marsden trial [14] enrolled 2,494 healthy women aged 30–70 years with a family history of breast cancer. The trial accrued patients between October of 1986 and April of 1996. Unlike the NSABP trial, 40(of women in this trial were on hormone replacement therapy (HRT). After a median follow-up of 70 months, the overall incidence of breast cancer was similar between the two arms. It has been suggested that the reason for not finding a benefit for tamoxifen in this trial is because of the relatively small number of patients as well as the unknown effect of HRT in combination with tamoxifen.

An Italian trial randomized 5,408 women, unselected for breast cancer risk, who had undergone hysterectomy followed by tamoxifen versus placebo [15]. However, only 149 of those participating in the trial completed 5 years of

tamoxifen. Furthermore 47(of the participants had had their ovaries removed at that time of their hysterectomy which decreased their risk of subsequent breast cancer. The study did not show any difference between the two groups as far as breast cancer development. This study has been criticized for the small number of participants completing 5 years of therapy, as well as the fact that the high rate of ovarian removal would place these women in a low-risk group for developing breast cancer. Despite these drawbacks the Italian study showed a trend toward a significant benefit of tamoxifen among the patients who took it for 1 year.

Based on the NSABP P-1 trial tamoxifen at a dose of 20 mg/day was approved by the FDA for use as a chemopreventive agent in high-risk individuals for developing breast cancer. It is unclear, however, if tamoxifen is preventing breast cancer or treating early stage breast cancer present at the initiation of therapy.

Raloxifene

Raloxifene is an SERM that like tamoxifen acts as an antiestrogen in the breast tissue and prevents breast cancer in mice and rats [16, 17]. Furthermore it has an estrogenic-like effect on the bones and therefore prevents and treats osteoporosis and appears to be less estrogenic than tamoxifen in the human uterus and therefore does not seem to increase the risk of uterine cancer [16, 18]. It is approved for the prevention of osteoporosis in postmenopausal women at a dose of 60 mg/day. Early data on raloxifene suggested that like tamoxifen it may be a useful chemopreventive agent for breast cancer. Furthermore the potential advantage of raloxifene is the fact that it is less estrogenic on the uterus and may therefore not cause an increased incidence of uterine cancer [18]. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial in which 7,704 postmenopausal women were randomized to receive two different doses of raloxifene or placebo [19] found that there was a 70(reduction in breast cancer incidence in the raloxifene treated arms.

STAR Trial

Based on these findings, the Study of Tamoxifen and Raloxifene (STAR) trial was initiated in postmenopausal women at high risk for breast cancer [20]. The STAR trial randomized 19,747 eligible postmenopausal women to tamoxifen 20 mg/day or raloxifene 60 mg/day for 5 years. With a median follow-up of 81 months tamoxifen was found to be a better chemopreventive agent compared with raloxifene, indicating that the rate in the raloxifene group was about 24(higher than the rate in the tamoxifen group. There was no difference in the two treatment groups in precancerous lesions. The incidence of uterine cancer was significantly lower in the raloxifene group as was the incidence of blood clots and cataracts [20]. Overall this study demonstrated that both tamoxifen and raloxifene are effective chemopreventive medications with tamoxifen potentially being the better chemopreventive agent and raloxifene being the less toxic agent. However since raloxifene has only been studied in postmenopausal women, tamoxifen is still the only medication used for breast cancer prevention in premenopausal women. Both agents have only been found to prevent hormone receptor positive breast cancer [20].

Other SERMs

Due to the toxicity profile of tamoxifen several other SERMs are currently being developed with the potential of being more potent chemopreventive agents with less toxicity. In a recent trial of 8,556 postmenopausal women lasofoxifene at a dose of 0.5 mg per day was found to significantly decrease hormone receptor positive breast cancer risk, coronary heart disease, stroke, and spinal fractures, whereas it increased blood clots and had no effect on uterine cancer [21]. In 9,354 postmenopausal women, arzoxifene at 20 mg/day was compared to placebo and found at 48 months to significantly reduce the risk of invasive breast cancer and spinal fractures. It was also found to significantly increase uterine polyps, blood clots, and muscle cramps but not heart attacks [22].

Aromatase Inhibitors

Aromatase inhibitors are a newer class of breast cancer drugs which block the production of estrogens. These agents work on an enzyme, called aromatase, which is responsible for the production of estrogens in postmenopausal women. They are currently used to treat breast cancer and have been shown to be more efficacious than tamoxifen in breast cancer treatment. However unlike tamoxifen they can only be used in postmenopausal women.

Exemestane

Exemestane is one of the three aromatase inhibitors which is currently being used for the treatment of breast cancer. Given data in invasive breast cancer where aromatase inhibitors (AIs) have been shown to decrease the incidence of a second breast cancer more so than tamoxifen, exemestane was studied in women at high risk for developing breast cancer. The NCIC CTG MAP3 [23] randomized 4,560 women at high risk for breast cancer to exemestane or placebo. Women received the medications for 5 years. At a median follow-up of 35 months women who received exemestane had a 65(decreased incidence of breast cancer. There were no significant differences in side effects between the two groups although women on placebo felt better than the women on exemestane. Furthermore, exemestane has been shown to increase the risk of bone fractures and the follow-up period in this trial may not have been enough to show this. The results of this trial lead to the approval of exemestane in the prevention of breast cancer in postmenopausal women.

Ongoing Trials with AIs

The IBIS-II trial [24] planned to randomize 6,000 women at high risk for breast cancer to anastrozole or placebo. As of January 2012, 6,844 women had already been randomized and the study was not accruing any more volunteers. Results should be expected in the next few years.

Future Strategies for Chemoprevention

Other Agents

Recent data has suggested that bisphosphonates, medications that are widely being used for the treatment and prevention of osteoporosis, can help prevent breast cancer. In women who participated in the Women's Health Initiative (WHI) oral bisphosphonate use was associated with a 30(decreased risk of hormone receptor positive breast cancer and a nonsignificant 44(decrease in the risk of hormone receptor negative breast cancer [25].

Other agents such as COX-2 inhibitors [26], statins [27], PARP inhibitors [28], metformin [29], and retinoids [30] are also being considered as chemopreventive agents although data are still preliminary.

Conclusions

Currently three agents have been approved for breast cancer chemoprevention, tamoxifen in pre- and postmenopausal women and raloxifene and exemestane only in postmenopausal women. Emerging agents such as bisphosphonates and COX-2 inhibitors show promise although their side effect profile may limit their use. However most of the agents to date show activity in preventing mostly hormone receptor positive breast cancers and the lack of any survival benefit in the prevention trials suggests that these agents may prevent breast cancers that would have been cured with our current treatments without having any effect in preventing aggressive, life-threatening breast cancers. It is our hope that future research will build on our current chemopreventive strategies finding novel agents to prevent all subtypes of breast cancers.

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