Prevention of breast cancer: the case for studying inhibition of IGF-1 actions

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Measures to prevent breast cancer are receiving particular attention by women at high risk from either clinico-pathologic findings or genetic susceptibility. Life-style and nutritional interventions have been difficult to quantify, but merit further study. Chemoprevention with tamoxifen and subsequently with the related raloxifene demonstrates some efficacy, but may be not be applicable to premenopausal women (with regard to raloxifene), or have low acceptance (with regard to tamoxifen). Based on the importance of the insulin-like growth factor-1 pathway in mammary gland development, and the availability of a potent inhibitor, pilot studies are ongoing to evaluate such an inhibitor in women with demonstrable high risk to develop breast cancer. Short-term interventions with the inhibitor have been completed, and subsequent interventions are planned.

Breast cancer prevention trials have been developed during the past two decades after risk factors for the development of breast cancer were identified through epidemiologic studies. A ‘Gail score’ was developed and utilized as an entry criterion for clinical studies of interventions in populations at higher risk [1]. Workshops were held to help catalyze concepts of chemoprevention of breast cancer [2]. The stage was set for studying tamoxifen, a selective estrogen receptor modulator (SERM) in the prevention setting, following its extensive experience as the preferred endocrine intervention in the treatment of ER-positive breast cancer, initially in the metastatic setting, and subsequently in a series of adjuvant studies. Recently, additional lines of investigation have been addressing dietary interventions, nutritional supplements and exercise. Factors relating to life style are difficult to study without a better understanding of how these affect the hormonal environment of all women and women at risk in particular.

In the initial chemoprevention trials, tamoxifen resulted in a 50% decrease in estrogen receptor (ER)-positive breast cancer. In the largest randomized study that was conducted it was compared with placebo in a population of women at risk for development of the disease carried out by the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (P1) [3]. Subsequently, the study of tamoxifen and raloxifene (STAR; P2) confirmed the reduction of invasive breast cancers by both these agents to the same extent, but this P2 trial was confined to postmenopausal women because raloxifene had never been tested in premenopausal women [4]. The toxicity spectrum was considered to favor raloxifene. Therefore, at present, preventive measures are generally introduced after the menopause and are often not applied to younger women, even in instances of high familial risk.

In addition to not meeting the challenge of reducing the threat of breast cancer in younger women, problems remain with these approaches to prevention. The risk of breast cancer remains substantial and many women refuse or discontinue chemopreventive treatment because of its unacceptable side-effects. In premenopausal women, symptoms related to estrogen withdrawal predominate; in older women there are increased thromboembolic risks, an excess of strokes (relative to placebo) and for tamoxifen, a doubling in the incidence of endometrial cancer [3]. In the prevention setting, a considerable emotional bias exists that many women find difficult to accept as a risk-reducing measure. While raloxifene has fewer side-effects, the absence of data in premenopausal women is a major limitation.

Options for prevention that are both more effective and more acceptable to women need to be developed. Our work has focused on the development of a novel prevention strategy through inhibition of insulin-like growth factor-1 (IGF-1), which would not require a woman to endure systemic estrogen deficiency, thus not causing menopausal symptoms; also one would not expect to enhance the risk of blood clots and stroke, while having the advantage of indirectly preventing estrogen action on the breast.

The IGF-1 pathway is critical for mammary gland evolution and is required for estrogen to cause ductal development [5]. It is also necessary for progesterone action and for IGF-1 activities unrelated to sex steroid action. Deregulation of the IGF-1 pathway is also strongly correlated with risk of breast cancer, and is implicated in breast cancer progression. Several recent studies referenced below have shown that IGF activity is increased in both in vitro and in vivo animal models, and women with BRCA mutations.
Strategies to inhibit IGF-1 action are currently in clinical trial, and preclinical results indicate that this will be a therapeutic option for both ER-positive and possibly ER-negative breast cancer. These include blockade of IGF-1 signaling, which should block estrogen and progesterone effects at the tissue level [6, 7], and IGF-1 receptor antibodies or small molecule blockers. A number of lines of experimental evidence support the concept that inhibition of IGF-1 in the mammary gland would achieve our goal of breast cancer prevention. These include: (i) both estradiol and progesterone require IGF-1 in order to act in the mammary gland; (ii) restoration of IGF-1 in IGF-I(–/–) animals allows both steroids to act by enhancing the actions of IGF-1 on increasing cell proliferation and phosphorylation of Insulin-response signaling-1 (IRS-1) and inhibiting apoptosis [6].

Based on the above, inhibition of IGF-1 action should, theoretically, be as or more effective than inhibition of estrogen (E2) alone, and possibly be additionally effective because IGF-1 is also required for progesterone action [6]. We recently noted that a somatostatin analog, pasireotide, inhibited IGF-1 action in the mammary gland via two pathways: direct inhibition of growth hormone secretion in the pituitary gland, and a direct inhibitory effect on IGF-1 action at the level of the mammary gland. While the exact mechanism of the latter is not fully worked out, preliminary data indicate that it works by stimulating IGF binding protein 5, which blocks the action of IGF-1 by preferentially binding to the protein. Other compounds, such as IGF binding protein 1, have also been shown to inhibit IGF-1 action in cancer and in the normal mammary gland [8].

We have hypothesized that inhibition of IGF-1 action might be an alternative to blocking estrogen action in prevention of breast cancer. As mentioned above, side-effects and toxic effects of tamoxifen, the standard SERM used for breast cancer prevention, have been well described. Pasireotide also has side-effects including temporary gastrointestinal distress and moderate elevation of blood sugar. Lengthening of QT interval has been described as well [9]. We are in the process of carrying out a clinical trial to determine whether pasireotide can affect biomarkers relying on histological changes indicative of reduced cell proliferation and/or increased apoptosis. In addition, although the antiestrogens, or SERMs such as tamoxifen, are effective prevention for women with high-risk lesions of the breast such as atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS), surgical excision of the initial lesion is often required. Based on our preclinical data, we further suggest that inhibition of IGF-1 action in the breast will be more effective than antiestrogens; raising the possibility it might be effective enough to stand alone as a treatment. As described, pasireotide is a somatostatin analog that prevents mammary development by inhibiting IGF-1 actions directly in the mammary gland and also indirectly, without causing menopausal symptoms and signs. Since both E2 and progesterone require IGF-1 in order to act, part of the inhibitory effect of pasireotide is in prevention of estrogen action on the mammary epithelium. Previous data indicate that IGF-1 also has independent effects on mammary development in the absence of estrogen [5, 7]. There is evidence that IGF-1 inhibition can affect estrogen-dependent and estrogen-independent pathways, opening up the possibility of affecting ER-negative breast tumors as well [10], and this needs to be more fully explored in future studies. If pasireotide does, in fact, inhibit both E2-related and E2-unrelated effects of IGF-1, it could prove to be more effective than antiestrogens. Under US Department of Defense (DOD) support, we initiated a pilot study to determine whether pasireotide had activity in women at high risk for breast cancer, recapitulating the effects observed in the rat model.

Our initial proposal is a proof of principle trial to assess whether short-term administration of pasireotide will inhibit IGF-1 action in human breast as it does in rats, i.e. increase cell death and decrease cell division, the first steps in preventing cancer and defining a potentially effective antineoplastic therapy. Assuming this process begins with a blockade of the effect of IGF-1, the process that leads to increased apoptosis and decreased cell proliferation should be inactivated as well.

In the design of the trial we selected women at high risk as determined by core biopsy of breast tissue demonstrating ADH, ALH or LCIS. Volunteers then received 9.5 days of 600 μg of pasireotide twice a day with an excisional biopsy on the 10th day. Tissue is analyzed for cell proliferation markers (Ki67) and markers of apoptosis (TUNEL) before and after taking the SOM230 (pasireotide).

Our next series of studies under DOD support will examine whether this work can be expanded to the treatment of ER-positive ductal carcinoma in situ (DCIS) by pasireotide. Currently, no effective medical therapy for DCIS exists. Tamoxifen, again, is the standard of care for diminishing the frequency of recurrence and/or progression to invasive breast cancer following diagnosis of DCIS and surgical and radiation therapy. However, tamoxifen is not sufficiently effective to be used as primary treatment of the disease. In the future we also plan to directly compare the effects in humans of pasireotide with tamoxifen; however, a larger patient population for study will be needed.

Studies on the effects and consequences of the BRCA mutation, as well as other specific genotypic conformations and the effects on other measures of metastatic potential, such as angiogenesis, on IGF-1 function and inhibition are planned for the future as well. Finally, the tolerability and side-effect profile, dosing and duration of treatment schedule and long-term sustainability of histological changes will need to be evaluated.

disclosures

The authors declare no conflict of interest.

references

4. Vogel VG, Costantino JP, Wickerham DL et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the
NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA 2006; 295: 2727–2741.


