Commentary

Breast cancer chemoprevention: beyond tamoxifen

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Abstract

A large number of new potential chemoprevention agents are available that target molecular abnormalities found in estrogen receptor (ER)-negative and/or ER-positive precancerous breast tissue and have side effect profiles that differ from tamoxifen. Classes of agents currently undergoing evaluation in clinical prevention trials or those for which testing is planned in the near future include new selective ER modulators, aromatase inactivators/inhibitors, gonadotrophin-releasing hormone agonists, monoterpenes, isoflavones, retinoids, rexinoids, vitamin D derivatives, and inhibitors of tyrosine kinase, cyclooxygenase-2, and polyamine synthesis. New clinical testing models will use morphological and molecular biomarkers to select candidates at highest short-term risk, to predict the response to a particular class of agent, and to assess the response in phase II prevention trials. If validated, morphological and molecular markers could eventually replace cancer incidence as an indicator of efficacy in future phase III trials.

Keywords: breast cancer chemoprevention, clinical models, new agents

Introduction

The demonstration by the National Surgical Adjuvant Breast and Bowel Project that tamoxifen reduces breast cancer risk by approximately 50% for at least some groups of high-risk women was a milestone in the chemoprevention of breast cancer [1]. However, other than women with a prior diagnosis of atypical hyperplasia, *in situ* or invasive cancer, it is not clear what groups of women receive enough benefit to offset the potential side effects. These side effects include increased risk of menstrual abnormalities and bone loss in young premenopausal women, and increased risk of hot flashes, sexual dysfunction, cataracts, uterine cancer, and thromboembolic phenomena in perimenopausal and postmenopausal women [1–3]. Concerns about the risk : benefit ratio, particularly in women over 50, have led to the recommendation that this group not receive tamoxifen unless their short-term risk approaches 1% per year for women with a uterus and 0.5% per year for women without a uterus [4]. In the USA, many women are not given the option of simultaneous tamoxifen and hormone replacement for fear of increasing thromboembolic risk [1,5]. Furthermore, it is clear that the incidence of estrogen receptor (ER)-negative cancers is not reduced with preventive tamoxifen therapy and that some ER-positive precancerous lesions might be resistant to tamoxifen [1].

Drug development

Important priorities for breast cancer prevention are to develop a variety of new prevention agents that have fewer side effects or a different side effect profile from that of tamoxifen, that are compatible with hormone replacement

AP-1 = activator protein-1; COX = cyclooxygenase; DCIS = ductal carcinoma *in situ*; ER = estrogen receptor; FNA = fine needle aspirate; HRT = hormone replacement therapy; IEN = intraepithelial neoplasia; NSABP = National Surgical Adjuvant Breast and Bowel Project; RAR = retinoic acid receptor; SERM = selective estrogen receptor modulator.

therapy (HRT), and that are effective in ER-negative as well as in tamoxifen-resistant ER-positive precancerous tissue.

To develop new drugs in a short period and at reasonable cost, more efficient clinical testing models are being developed for phase I and II prevention trials. These models use potentially reversible morphological and molecular biomarkers that will enhance short-term risk prediction, that will improve the probability of response by matching the biomarker profile in precancerous tissue to agents in the appropriate drug class, and that will be used to assess response in a preliminary fashion before a cancer incidence trial [6].

Biomarkers

Several potentially reversible biomarkers have been associated with increased cancer risk, including mammographic breast density, insulin growth factor-1 and its binding protein, serum estrogen and testosterone levels, and intraepithelial neoplasia (IEN) [7–13]. IEN is probably the risk biomarker most closely related to the underlying neoplastic process [11]. IEN can be functionally defined as a condition with morphological, molecular and genetic abnormalities as well as an increased risk for breast cancer. Using this definition, breast IEN can be viewed as beginning with simple hyperplasia and extending through atypical hyperplasia and *in situ* carcinoma.

Molecular alterations noted in at least a subset of IEN that clamor for targeted intervention include the following: (1) aberrant methylation and histone deacetylation of the promoter region of many tumor suppressor genes [14–16]; (2) increased growth factor and growth factor receptor expression/activation, resulting in increased mitogen-activated kinase activity; (3) increased cyclooxygenase-2 (COX-2) expression, tissue polyamines, angiogenesis and protease activity [17–21]; (4) overexpressed ER and hypersensitive ER variants [22,23]; and (5) increased aromatase and sulfatase activities, which result in increased breast estrogen levels [24,25].

Potential agents

Histone deacetylase inhibitors combined with demethylating agents are promising as a means of rehabilitating silenced tumor suppressor genes in ER-negative or ER-positive precancerous tissue [26,27]. Inhibitors of activated tyrosine kinase, COX-2, metalloproteases, and polyamine synthesis should also have activity in ER-negative as well as ER-positive tamoxifen-resistant precancerous tissue. These types of agents might be used in premenopausal women or postmenopausal women taking HRT without altering the menstrual cycle or inducing hot flashes [17,28]. The same can be said of monoterpenes [29] and sulindac sulfone [30], which may act primarily to induce apoptosis [31]. Several compounds such as difluoromethylornithine (an inhibitor of polyamine synthesis) and perillyl alcohol (a monoterpene) are already in phase I–II prevention testing, and trials for others such as celecoxib, a COX-2 inhibitor, and ZD1839, a tyrosine kinase inhibitor, are in the active planning stage [32–35].

New selective estrogen receptor modulators (SERMs) that retain breast antagonist and bone agonist activity but lack uterine agonist activity might have a more attractive side effect profile than older SERMs such as tamoxifen [36]. Two new agents, EM 652 and LY 353381 (Arzoxifene), are particularly attractive in that they might be at least as efficacious as tamoxifen [37,38]. At present, it is unknown whether either compound will be effective in ER+ tissue which exhibits tamoxifen resistance due to ER activation and gene transcription at AP-1 sites or ligand-independent ER activation as a result of increased MAP kinase activity. [36]. Alternatively, short course treatment with pure anti-estrogens or SERMs plus tyrosine kinase inhibitors may circumvent those tamoxifen types of resistance [36,39,40].

Aromatase inhibitors/inactivators act by lowering peripheral and breast tissue estrogen levels. They do not promote uterine cancer, and are associated with fewer thromboembolic phenomena than tamoxifen [41]. Drawbacks include hot flashes, lack of bone agonist effects and unknown efficacy under conditions of moderate to high circulating endogenous or exogenous estrogen levels (premenopausal women or postmenopausal women receiving HRT). However, in view of recent reports of their equal or superior efficacy in direct comparison with tamoxifen in first-line metastatic and neoadjuvant studies [41–43], prevention studies with anastrazole, letrazole and exemestane are in the active planning stage in combination with bone-preserving agents such as oral biphosphonates or calcitonin nasal spray [44].

Hormonally targeted strategies not likely to result in menstrual irregularities or hot flashes and thus likely to be more attractive to young, premenopausal women include the following: (1) soy/isoflavones, which might result in less potent levels of estrogen or estrogen metabolites [45]; (2) gonadotrophin-releasing hormone agonist regimens combined with low-dose hormone replacement [46]; and (3) short-course hormonal combinations that mimic pregnancy for nulliparous women in their late teens and early twenties [47].

Retinoids, rexinoids and vitamin D analogues are also undergoing active investigation in premenopausal and postmenopausal women. These compounds might be more active in ER-positive than in ER-negative precancerous tissue [48]. Retinoids and vitamin D derivatives have complex mechanisms of action, which include the promotion of apoptosis through the upregulation of retinoic acid receptor (RAR) and retinoid X receptor and a decrease in

insulin growth factor levels [49–52]. In an Italian study [53], fenretinide administration resulted in a decreased incidence of contralateral breast cancer in premenopausal women with stage I breast cancer undergoing adjuvant treatment, and a phase II trial comparing fenretinide with placebo in postmenopausal women receiving HRT is nearing completion [54].

As RARβ2 expression may be decreased in IEN through hypermethylation, retinoids have been proposed as attractive partners for demethylating agents [27,55,56]. Because retinoids have demonstrated efficacy in tamoxifen-resistant cell lines, retinoids, rexinoids and deltanoids might be paired with SERMs in the future [57,58]. Other attractive combinations of chemoprevention agents include SERMs and tyrosine kinase inhibitors or aromatase inhibitors/inactivators and COX-2 inhibitors.

Dose selection

The first hurdle to overcome in the course of the clinical evaluation of some agents is often the selection of the proper dose for prevention trials, which might be quite different than for treatment trials. In general, the dose selected for prevention trials is that associated with minimal side effects but one that nevertheless consistently modulates biomarkers consistent with its mechanism of action [59]. A popular mechanism for dose finding is the presurgical model in which a diagnostic core biopsy for ductal carcinoma *in situ* (DCIS) or a small invasive tumor serves as the tissue sample for baseline biomarkers. Subjects are randomized to one of several doses of drug administered in the 2 weeks between core biopsy and re-excision [6]. Because an early decrease in proliferation in neoadjuvant studies seems to correlate with clinical response to SERMs and aromatase inhibitors, the dose selected is generally that associated with a consistent decrease in proliferation [38,42,60].

Response evaluation

Once a dose has been selected, how can we efficiently evaluate agents in a timely manner and at a reasonable cost? The current National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) trial with an endpoint of cancer incidence is estimated to require the enrollment of 22,000 subjects, will take 5–7 years to complete and will cost at least $200 million. Could we use potentially reversible morphological and molecular risk biomarkers to complete prevention trials in a more expedient and less costly manner? We have demonstrated in a prospective study that hyperplasia with atypia observed in random periareolar fine needle aspirates (FNAs) from high-risk women is associated with a short-term risk of detection of DCIS or invasive cancer of 3% per year [61]. An increase in breast cancer risk has also been noted for hyperplastic cells obtained from nipple aspirate cytology [62].

Response to a prevention agent might be evaluated in a preliminary fashion by sampling tissue before and after the drug intervention and evaluating the reversal of atypical cytological changes or the prevention of progression to hyperplasia with atypia in the treated group in comparison with a randomized control group. At the same time as breast tissue is sampled at baseline for evidence of IEN, molecular markers might be assayed to best match a subject's precancerous tissue to a particular agent (such as SERMs or aromatase inhibitors for ER-positive precancerous lesions). These strategies allow efficacy to be determined in a preliminary fashion with a fraction of the subjects, cost, and time of a cancer incidence trial. A phase II clinical trial, in which high-risk women with FNA hyperplasia with or without atypia were randomized to a polyamine synthesis inhibitor, difluoromethylornithine, or placebo for 6 months and then reaspirated, performed extremely well with consistent provision of material for analysis, excellent subject acceptance, and rapid accrual [32]. A phase II FNA study evaluating the SERM arzoxifene is ongoing.

Drugs that show promising morphological and molecular modulation in phase II trials might be moved into phase III cancer incidence trials, where they would be compared with standard prevention therapies. If the modulation of surrogate response biomarkers such as IEN can be validated as being correlated with a reduced cancer incidence in phase III trials, then prevention trials of the future might use IEN instead of cancer incidence as their main study endpoint. The concept of treatment and prevention of advanced IEN is a paradigm shift that would markedly speed prevention drug development across several disease sites; it is currently under active scrutiny by a special American Association of Cancer Research Task Force.

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