Endocrinology of Breast Cancer

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12 Role of Angiogenesis in the Transition to Hormone Independence and Acquisition of the Metastatic Phenotype

Francis G. Kern, PhD

INTRODUCTION

Breast cancer becomes a life-threatening illness when the malignant tumor cells have acquired the capability of invading through the basement membrane and into the circulation, where they are then disseminated to distant sites in the body. Therefore it may seem intuitive that tumors that have acquired a capability of stimulating the growth of new blood vessels would possess a greater threat to the patient, and indeed a good amount of correlative clinical data now link tumors that have a higher number of microvessels with poor prognosis *(1–5)*. However, while neoangiogenesis is likely to be important in the dissemination of tumor cells, it is becoming more apparent that additional factors are required to allow proliferation of disseminated tumor cells at the distant sites.

When breast cancer presents as an invasive disease, it has been useful to use estrogen receptor (ER) content as a basis for choice of therapy. This relates to the fact that estrogen itself can stimulate the growth of breast cancer cells that contain ER through still unknown mechanism that involves binding of estrogen to nuclear ER and subsequent stimulation of its transcriptional activation functions. Consequently, a highly useful treatment for most patients with ER-positive tumors is hormonal therapy with antiestrogens, the most common being tamoxifen *(6–8)*. Although other ER-independent mechanisms may also contribute to the therapeutic effect of this agent *(9–11)*, it is commonly assumed that the benefit of this drug derives from its ability to bind to ER without stimulating the same type of transcriptional activity as an estrogen-bound receptor.

An invariable and unfortunate outcome of treatment of patients with tumors that initially respond to tamoxifen is the outgrowth of populations of cells that no longer respond to this treatment. In addition, some ER-positive tumors fail to show any initial response to this relatively benign form of treatment. What may not seem so intuitive is how expression of angiogenic growth factors might also be involved in either acquired or *de novo* antiestrogen resistance, yet recent studies with transfected breast cancer cell lines (discussed in greater detail below) raise this as a possibility. If this turns out to be

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substantiated by clinical studies, then in the appropriate context, treatment with agents that inhibit angiogenesis may afford a means of restoring antiestrogen sensitivity to patients with acquired resistance or a means of conferring sensitivity to patients with *de novo* resistance.

CLINICAL DILEMMAS ASSOCIATED WITH TAMOXIFEN TREATMENT

A major dilemma for the clinician currently confronted with a patient with an ER-positive breast tumor is trying to make the best guess as to whether a patient will respond to this type of antiestrogen therapy in either an adjuvant or advanced breast cancer treatment setting. Since approximately 60% of patients with invasive ductal carcinoma present with ER-positive tumors, this particular question is relevant for a significant portion of women with breast cancer. It is also known that around 65–70% of patients with ER-positive tumors with advanced stage disease will show at least some response to tamoxifen *(12,13)*. Among those that eventually fail on this therapy, 50–70% of these patients still have tumors that contain ER when these sites are biopsied *(12–15)*. Therefore loss of ER is not the primary mechanism involved in the acquisition of antiestrogen resistance.

Two different types of second-line antihormonal therapies are currently in the final stages of clinical trials for use in patients who have failed on tamoxifen. One approach involves the use of inhibitors of the enzyme aromatase, which is involved in the biosynthesis of estradiol produced at extraovarian sites *(16–23)*. A second form of second-line therapy is the use of what have been called *pure antiestrogens (24)*. These are compounds that bind to the ER, result in no transcriptional activation, and may increase the degradation of the receptor *(25)*. They also do not possess any of the partial agonist properties of tamoxifen.

Various recent studies have shown that 20–40% of patients who have failed on tamoxifen therapy show some response to these second-line therapies and that an additional 30% show no immediate disease progression when switched to these forms of therapy *(19–23,26–28)*. Therefore these second-line approaches are likely to be of some value, but they also raise another dilemma for the oncologist. In addition to needing help from molecular oncologists and epidemiologists in determining who is most likely to respond initially to tamoxifen, the clinician will soon also need assistance in determining which patients who do not respond are likely to benefit from these alternative hormonal therapies.

MECHANISMS OF TAMOXIFEN RESISTANCE

A number of different mechanisms have been proposed for tamoxifen resistance. Based on what is known about some of these mechanisms, some educated guesses can be made as to whether the patient with a tamoxifen-resistant tumor that is due to one of these mechanisms is likely to respond to a second-line therapy. However, for many of these mechanisms for which a molecular basis for tamoxifen resistance has been demonstrated with cell lines or with in vitro assays, subsequent examination of patient samples has revealed that these types of alterations are unlikely to be responsible for most tamoxifen-resistant tumors. This includes point mutations in the hormone binding domain of the estrogen receptor, alterations in splicing of the ER mRNA that can result in con-

There is now recent evidence that the balance in the amounts of recently discovered steroid receptor coactivators and corepressors can influence whether tamoxifen will act as an antagonist or agonist of the estrogen receptor. At this point, work with in vitro systems suggests that the pure antiestrogens will still act as antagonists when tamoxifen is changed to an agonist as a result of alterations in the ratio of coactivators to corepressors *(36)*. Therefore other mechanisms are also probably responsible for those ER-positive tamoxifen-resistant breast tumors that fail to respond to second-line therapies.

Two potential mechanisms involve the downstream signaling events associated with activation of growth factor receptors. Work from a number of laboratories has demonstrated what has been termed cross talk between steroid receptors and either growth factor tyrosine kinase receptors or G-protein-coupled receptors *(37–44)*. In examples relevant to the question of tamoxifen resistance, phosphorylation of the estrogen receptor by MAP kinases, which are downstream effectors of a number of different signaling pathways including those mediated by growth factor receptors, or activation of G-protein-coupled receptors can result in tamoxifen acquiring agonistic properties *(37,38,43)*. However, the same studies show that the ER is not activated by these mechanisms when pure antiestrogens are present *(37–43)*.

Therefore at least one additional mechanism probably remains underlying the *de novo* or acquired tamoxifen resistance of ER-positive tumors that do not subsequently respond to a second-line treatment with the pure antiestrogens. Recent data suggest that one such mechanism may also involve growth factor signaling, which provides the breast tumor cell with an alternative pathway to the growth stimulation mediated by ER *(45)*. This would bypass the requirement for activation of the ER by an agonist for growth promotion to occur and would account for the failure of second-line antihormonal therapies.

ROLE OF GROWTH FACTORS IN THE ACQUISITION OF TAMOXIFEN RESISTANCE

It can now be seen that growth factor signaling can affect the resistance of a breast tumor cell to tamoxifen in a number of different ways, with two of these mechanisms potentially leading to tamoxifen acting as an agonist. In one scenario, growth factor signaling can affect the level of coactivators or corepressors. Although no experimental data currently exist indicating that this type of regulation is indeed occurring in breast cancer cells, the field is very new, the number of coactivators and corepressors being identified is continually expanding, and the experiments remain to be performed *(46)*. In a second scenario, growth factor signaling could result in activation of ER via phosphorylation, leading to increased agonistic activity for tamoxifen. In the third scenario, growth factor signaling could bypass the requirement for ER activation for growth. These three scenarios are not mutually exclusive, and all three mechanisms may be operating simultaneously within a cell to provide additive or perhaps synergistic growth-stimulatory effects. As such, these mechanisms may account for the clinical response observed in some patients when tamoxifen is withdrawn *(47,48)*. However the available evidence to date suggests that a better understanding is required of what particular growth factor signaling pathways can bypass the need for ER since these pathways may also be responsible for resistance to second-line therapies.

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