Playing the Old Piano: Another Tune for Endocrine Therapy?

Daniel F. Hayes

In 1896, George Thomas Beatson, a gentleman farmer and surgeon, reported his experience in treating three young women who had locally advanced breast cancer by removing their ovaries (1). All three of these women experienced a reduction in the size of their breast cancers; this result introduced the era of endocrine treatment for cancer. Beatson postulated that “there is some ovarian influence which works the change [growth of cancer]. It may be an altered secretion or it may be the migration of cells—it might even be a parasite in the ovarian cells, for it should be borne in mind in regard to the secretions of the reproductive glands ‘that unlike other secretions, their essential constituents are living cells’ (Stewart)” [author’s note: Beatson did not provide a more specific reference to Stewart in his treatise].

After Beatson’s observation, oophorectomy became the treatment of choice for premenopausal women with breast cancer. However, over the next 80 years, endocrine therapy for breast cancer generated a series of enigmatic but fascinating clinical conundrums. First, as opposed to oophorectomy, the most effective therapy for postmenopausal patients was found to be pharmacologic doses of estrogenic compounds, such as diethylstilbestrol (DES) (2). Second, after initiation of DES therapy, 15%–20% of women experienced short periods of apparent progression (tumor flare) that were often followed by response (3). Third, of women who responded to DES and then progressed, approximately 25% experienced a subsequent response to estrogen withdrawal, the so called “rebound response” (4,5). Fourth, as other methods of endocrine manipulation were studied, it became clear that these therapies could be applied serially, with a second modality often inducing responses after a previously successful therapy had failed (6). The introduction of tamoxifen generated even more contradictory clinical observations. This agent, which was supposedly an “antiestrogen,” produced flare reactions and rebound responses in a manner identical to those seen previously with estrogen (5,7–9).

How can these seemingly disparate effects occur with therapies that are, at first glance, apparently acting via the same mechanism—antagonism of the effect of estrogen on its receptor? It is important to understand the difference between hormone-independent cancers, for which the malignant phenotype is not dependent on the estrogen/estrogen receptor (ER) axis, and hormone-dependent malignancies, for which estrogen is required for growth and survival. From preclinical and clinical studies that relate response with hormone receptor status, it appears that growth of all ER-negative tumors and growth of a fraction (approximately 25%) of ER-positive tumors are intrinsically hormone-independent. In these patients, all endocrine therapies fail to work (10). The therapeutic story for breast cancers that are hormone-dependent is more complex. These tumors, which are all ER-positive, may be sensitive to certain endocrine therapies but resistant to others, and such resistance may be intrinsic or acquired. In this regard, several different endocrine treatment strategies have been developed, including modalities that decrease circulating estrogens, such as surgical or radiation-induced ablation of estrogen-producing organs, administration of luteinizing hormone–releasing hormone agonists/antagonists, and treatment with agents that specifically inhibit aromatase activity. A second strategy is aimed at direct blockade of the interaction between estrogen and the ER by the use of agents such as tamoxifen, toremifene, raloxifene, or fulvestrant. The mechanisms of other active hormonal agents, including the progestational agents (megestrol acetate and medroxyprogesterone) and the androgen halotestin have never been satisfactorily elucidated, although they appear to function by inducing hormonally driven feedback inhibition of estrogen production.

The mechanisms of resistance to individual endocrine treatment strategies in hormone-dependent cancers lie in an understanding of the biology of ER activity. As with all steroid hormones, estrogen exerts its agonistic effect by initially binding to its receptor. The ligand-bound, dimerized receptor interacts with estrogen response elements present in promoter regions of estrogen-dependent genes (11). Of interest, estrogen and other natural and synthetic ER ligands may induce different effects (agonistic or antagonistic) in different tissues. For example, tamoxifen has antiestrogenic activity in benign and malignant breast tissue but has estrogenic activity in the bone, liver, and uterus (12,13). We now have some understanding of the mechanism of this ligand-specific activity in several tissues, which appears to be due, in part, to a relative balance of nuclear coactivating and corepressing proteins within a specific tissue.
that interact with the ligand–ER–estrogen response element complex to stimulate or suppress the agonistic activity (14). Reflecting this complex diversity, tamoxifen and other ER-binding drugs have been designated selective estrogen receptor modulators (SERMs), rather than the misnomer antiestrogens (15).

Despite these advances in the understanding of ER function and biology, the precise mechanisms of resistance to specific endocrine treatments remain elusive. One appealing hypothesis for resistance to endocrine therapies is that the ER itself might contain mutations that make it supersensitive to estrogen, agonistic after tamoxifen binding, or even functionally nonfunctional regardless of ligand. However, the clinical role of such mutations has been difficult to validate (16,17). Alternative theories, which also have inconsistent experimental support, include the possibility of aberrant estrogen metabolism in the local tumor environment and/or cross-talk between the epidermal growth factor receptor family and the ER (18–21). One of the more strongly supported hypotheses is that abnormal expression of proteins that modulate ER function might lead to resistance to SERMs by changing the biologic effect induced by specific ligand binding with ER, rendering these ligands estrogenic rather than antiestrogenic (14,22). In this issue of the Journal, Jordan and his colleagues (23,24) have extended an area of research that they and others have pursued over the last several years in which they have generated in vitro and in vivo breast cancer models that mimic such mechanisms of resistance to SERMs. The wild-type MCF7 cultured human breast cancer cell line is estrogen dependent and inhibited by tamoxifen (25). Jordan’s group and others (19,26) have previously described conversion of this cell line to one that is dependent on tamoxifen; in other words in this cell line, tamoxifen acts as an agonist rather than an antagonist. Thus, one mechanism of clinical resistance to tamoxifen might be the emergence of cell clones that have become dependent on tamoxifen as an agonist. This phenomenon has been put forth to explain the perplexing results of two clinical trials first reported more than 10 years ago that suggest that longer duration of treatment with adjuvant tamoxifen appears no better, and may even be worse, than stopping treatment at 5 years (27,28).

The Jordan group has now developed similar MCF7 derivatives that are resistant to a more recently studied SERM, raloxifene. Like tamoxifen, raloxifene reduces bone mineral loss and prevents emergence of new breast cancers (29,30). Their data suggest that raloxifene is unlikely to induce a response in tamoxifen-resistant cancers and might even stimulate growth of such tumors (23). Indeed, as expected, small, phase II clinical studies (31,32) demonstrate that, within the SERM class of agents, cross-resistance is high. However, the studies in this issue of the Journal by Jordan’s group (23,24) also raise a relatively unexpected, although not unprecedented, finding. The tamoxifen-resistant or raloxifene-dependent breast cancer cells are supersensitive to suppression by concentrations of estradiol that were previously required by the parenteral MCF7 cell line for proliferation (23,24). A second set of results adds even more confusion to the endocrine therapy story. The inhibitory effects of estradiol were reversed and, indeed, proliferation of these cells was stimulated by concurrent administration of estradiol and fulvestrant, an agent that is felt to work by irreversibly binding the ER and mediating its degradation (24,33). The mechanisms of these paradoxical effects are unclear, although the investigators have offered some insights by studying the effects of their manipulations on cellular nuclear factor kB and the Fas/Fas ligand system. Other investigators have reported similar changes in sensitivity of breast cancer cells (including MCF7 cells) to differing concentrations of estrogen. Santen et al. (34) attribute this effect to stimulation of mitogen-activated protein kinase activity in the presence of estrogen depletion.

Importantly, what do these results mean to the investigative and clinical community? Clearly, they need confirmation in other preclinical models. Although the MCF7 cell line is arguably one of the most valuable models used in breast cancer, it is not entirely clear whether these results can be generalized to the vastly heterogeneous world of human breast malignancies. Nonetheless, they are provocative and raise yet another question: should we dust off the old standard, estrogen? If so, the results from Jordan and his colleagues suggest that rather than using pharmacologic doses of estrogen as first-line therapy, as was done before tamoxifen’s introduction, low doses should be used after SERM treatment. This theory is certainly too conjectural to apply in routine clinical practice. In fact, it would seem to run counter to the hypotheses that have led to completed and ongoing prospective clinical trials in which 5 years of adjuvant tamoxifen is followed by randomization to aromatase inhibitors or placebo, as well as to other trials in which tamoxifen and aromatase inhibitors are alternated within the first 5 years after diagnosis (35). To their credit, Jordan and his colleagues have proposed a clinical trial to test their theories. Such a trial would be fascinating but difficult to execute. Proper controls for the tamoxifen withdrawal effect and careful attention to the dose of estrogen are required to be certain that any results reflect the effects proposed by Jordan’s group and do not just recapitulate findings from the past. Their results also suggest that the order in which serial endocrine therapies are administered might be critical, because the combination of fulvestrant and estrogen in their hands produced results in diametric opposition to those expected. Standard practice currently calls for fulvestrant therapy for patients after their disease has progressed on tamoxifen and aromatase inhibitor treatment. Given that physiologic levels of estrogen might reappear in such patients after discontinuation of aromatase inhibition, the data from Jordan and his colleagues would suggest that fulvestrant might be contraindicated in this setting!

Do these results mean that we should write a new arrangement for the old tune of estrogen therapy? Endocrine treatment is certainly a well-played piano, but perhaps even greater understanding of the biology of the estrogen–ER axis will permit us to write yet another song.

**REFERENCES**


