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Strategies to Overcome Resistance to Hormonal Therapy

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Hormone receptor-positive tumors account for 70% or more of breast cancers (BCs).[1,2] The introduction of tamoxifen in the early 1970s for the treatment of this subtype of BC marked the beginning of successful targeted therapy in oncology.[3] To date, endocrine therapy remains the most effective treatment for estrogen receptor (ER)-positive advanced BC. Endocrine agents act through direct targeting of ER and blockade of ER binding (eg, tamoxifen and fulvestrant) or through tumor deprivation from estrogen (eg, aromatase inhibitors [AIs] and gonadotropin-releasing hormone agonists).

Despite the great improvement achieved in ER-positive BC outcomes with endocrine treatment, approximately 50% of patients with advanced disease do not respond to first-line treatment with endocrine agents (ie, *de novo* resistance), and almost all patients who initially respond to treatment will eventually develop resistance (ie, acquired resistance). Subsequent lines of endocrine therapy may be followed by a shorter response interval. Thus, endocrine resistance is a frequent and limiting event in the treatment of ER-positive BC.[4] To understand resistance, the activity of ER must be understood.

The ER signaling pathway is involved in a complex bidirectional communication with a number of other intracellular pathways and molecules that regulate physiological functions, and tumor proliferation and survival. Mainly a nuclear protein, ER is activated by ligand binding. Estrogen binding recruits co-regulatory proteins that direct the transcriptional activity on specific estrogen response elements (EREs) on the DNA and promote ER nuclear (or genomic) activity. The recruitment of specific co-activator or co-repressor proteins can enhance or suppress the transcriptional activity of the controlled genes. Additionally, ER regulates the transcription of genes at non-ERE DNA sites through its interaction with other transcription factors. Signaling from various tyrosine kinase receptors (TKRs) also promotes ER genomic activity through the phosphorylation of components of the ER pathway or of ER itself.[5]

Estrogen exerts a rapid stimulatory effect on signaling pathways through a non-nuclear mechanism. This is initiated by a small portion of the ER protein tethered to the inner surface of the plasma membrane. Membrane-bound ER interacts with TKRs (eg, epidermal growth factor receptor [EGFR], insulin-like growth factor receptor, and human epidermal growth factor receptor [HER]), non-receptor tyrosine kinases (Src), and G proteins and triggers secondary downstream signaling through the Raf/Mek/MAPK and AKT/PI3K pathways.[5]

Mechanisms of resistance to endocrine therapy have been identified at various levels of cellular signaling. Understanding these mechanisms has allowed the development of treatment strategies aimed toward overcoming endocrine resistance in ER-positive BC.

The crosstalk between ER and other signaling pathways and molecules has been of particular interest. Targeting the downstream mammalian target of rapamycin protein with everolimus was the first successful strategy to overcome endocrine resistance. In the phase III BOLERO-2 trial,[6] progression-free survival (PFS) more than doubled with the addition of everolimus to exemestane compared with exemestane alone in a population of patients with advanced hormone receptor-positive BC that was previously resistant to a nonsteroidal AI.

A retrospective exploratory analysis of this trial did not identify genetic alterations that would predict benefit from the combination therapy. However, the analysis did show that the benefit was lower in patients with multiple genetic alterations than in patients with fewer alterations.[7] Also, a number of newer PI3K inhibitors, including selective inhibitors and pan inhibitors, are under investigation. Studies are combining both fulvestrant and AIs with the novel agents. Moreover, studies of adjuvant treatment with everolimus may reveal whether primary resistance can be overcome using this agent with endocrine therapy.

Overexpression of TKRs is a common compensatory mechanism during endocrine therapy that provides cancer cells with alternative growth pathways. The EGFR family of receptors, which plays an important role in this mechanism, has garnered great interest, with a number of studies using available agents to inhibit its activity. After showing the efficacy of the combination of gefitinib, an EGFR inhibitor, with tamoxifen in preclinical studies, Osborne and colleagues[8] reported on this combination in 2 cohorts. The group that was untreated or had previously received tamoxifen had minor improvement in PFS, but patients who had undergone previous treatment with an AI had no such improvements. Other similar studies have been reported; for example, AZD8931 is a reversible inhibitor of EGFR, HER-2, and HER-3 and was evaluated in the randomized phase II MINT trial. No benefit was seen when AZD8931 was added to anastrozole.[9] However, the population evaluated in this study might not have been appropriately selected as all patients were treatment naïve. The lack of exposure to endocrine agents might preclude the overexpression of EGFR as a compensatory mechanism to endocrine therapy. Despite a number of studies, the role of targeting the HER family remains an unanswered question.

Targeting cell cycle regulatory proteins has been the objective of other recent studies. Amplification of cyclin D1 is known to occur in 15% to 20% of BCs and is associated with resistance mechanisms. Inhibition of cyclin D1-dependant kinases 4 and 6 with palbociclib (PD 0332991) in combination with letrozole has shown promising results in a phase II trial with a median PFS of 7.5 months for letrozole alone versus 26.2 months for the combination arm (hazard ratio [HR] = 0.32; 95% confidence interval [CI], 0.19-0.56).[10] The confirmatory phase III trial is ongoing, and studies of tissue may determine which patients benefit.

Epigenetic mechanisms are also being investigated as a possible target for overcoming endocrine resistance. Post-translational modifications to histones by methylation and acetylation are involved in carcinogenesis, and the histone deacetylase (HDAC) inhibitor entinostat is under investigation. A phase II trial evaluated entinostat in combination with exemestane in patients with advanced ER-positive BC who were previously exposed to a non-steroidal AI. The combination treatment improved the median PFS to 4.3 months versus 2.3 months with exemestane alone (HR = 0.73; 95% CI, 0.50-1.07) and the median overall survival to 28.1 months versus 19.8 months (HR = 0.59; 95% CI, 0.36-0.97).[11] A phase III study is being initiated to establish the role of HDAC inhibitors in treating endocrine-resistant BC.

Loss of ER-α expression is an important event leading to resistance to endocrine treatment.[12,13] Expression of a truncated ER-α variant, ER-α36, although uncommon (<1%), has also been associated with tamoxifen resistance and poorer outcomes.[14] Recent studies described a novel mechanism of endocrine resistance that is associated with mutations at residues 537 and 538 of the ER-α. These mutations confer constitutive activity to the receptor, which becomes resistant to currently available endocrine agents.[15,16] Surprisingly, these mutations have not been evident in The Cancer Genome Atlas database, which included only treatment-naïve BC samples.[17] Exposure to previous endocrine treatment appears to be necessary for the occurrence of these specific activating mutations. When pretreatment tumor samples were paired with endocrine-resistant tissue from the same patient at a later stage of the disease, tumor analysis revealed the emergence of activating mutations in about 20% of the post treatment samples.[15,16]

These new findings highlight the selective pressure of drugs, including endocrine agents, on tumor cells. Clonal evolution appears to be a major determinant in the development of resistance, and efforts to elucidate and overcome endocrine resistance mechanisms have been limited by the availability of serial tissue sampling in the clinical setting. Tumors are evolving ecosystems of malignant cells, and the molecular characteristics present at the time of disease recurrence/progression are most likely not the same as those present at the time of initial diagnosis.

To further our understanding of endocrine resistance and begin to test strategies in a rational manner, we must understand the evolution of cells over time and in response to treatment. Studies that involve both circulating tumor DNA and liquid biopsies in the near future, as well as the acquisition of tumor tissue at different times in the course of the disease, are important to enable research today that will guide treatment decisions in the future and to determine whether we can monitor the cancer without serial biopsies. Cancer cells are clever and employ an incredible machinery to maintain proliferation and survival. If we want to outsmart cancer, we need to understand it better and combine appropriate targeted therapies and better define the populations who will benefit from specific therapies.

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Breast Cancer or a Lack of Communication: Which is the Greater Killer?

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Breast cancer is the second leading cause of cancer deaths among women in the United States. The breast cancer death rate is decreasing faster in white women than in women of other races and ethnicities. Black women have the highest death rate of all racial and ethnic groups and are 40% more likely to die of breast cancer than white women.[1-3]

THE QUESTION IS: WHY?

I will address what concerns the African American woman. Even when one accounts for the possibility that African American women have more aggressive cancers and fewer social and economic resources, it does not answer this question. You ultimately have to look at treatment.