“Braking” the Cycle of Resistance in Endocrine Therapy for Breast Cancer

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Disclosure of Potential Conflicts of Interest

A. DeMichele is a consultant/advisory board member for Pfizer. L.A. Chodosh reports acting as an expert witness on behalf of Pfizer in matters relating to hormone replacement therapy. No other potential conflicts of interest were disclosed.
Summary

Endocrine resistance leads to recurrence and death from breast cancer. Animal models of endocrine resistance enable preclinical identification of efficacious therapeutic combinations and further our understanding of resistance. This strategy provides new insights into optimally targeting interactions between estrogen receptor (ESR-1) activity and the cell cycle by CDK4/6 inhibitors.
In this issue of Clinical Cancer Research, Wardell and colleagues utilized mouse models of endocrine therapy-resistant breast cancer to probe the relative efficacy of the cyclin-dependent kinase (CDK) 4/6 inhibitor, palbociclib, emerging endocrine agents, and their combination (1). Estrogen receptor (ER)-expressing breast cancer is the most common form of the disease, comprising nearly 80% of the more than 200,000 new cases diagnosed annually. While highly treatable by therapies that block ER signaling or prevent the production of its ligand, estrogen, resistance to endocrine therapy is universal in the metastatic setting and is also thought to be a common mechanism of recurrence in early-stage disease. The frequent occurrence of therapeutic resistance, coupled with the unparalleled high prevalence of this malignancy, mandates new approaches to overcoming endocrine resistance if continued improvements in survival are to be achieved.

Current therapies targeting ER function include depletion of endogenous estrogens through aromatase-inhibition (AIs), as well as blockade of estrogen binding to ER by selective estrogen receptor modulators (SERMS) and/or degraders (SERDS). While these approaches are highly effective for some cancers, alterations resulting in estrogen-independent nuclear signaling or activation of escape pathways engender resistance. For example, activating mutations in ESR1 can render ER signaling ligand-independent (2). Similarly, changes in ER coactivators and corepressors can enable growth of ER+ cells despite low levels of estrogen.

Alternative resistance mechanisms involve ER-driven activation of oncogenic signaling pathways, including the PI3K/Akt/mTOR pathway (3), and interactions with the
core program that controls proliferation and cell cycle progression. These include inhibition or inactivation of negative regulators of the cell cycle, including RB family members, as well as amplification and up-regulation of cell cycle promoting oncogenes, such as cyclin D1 (CCND1) and c-myc (4). CCND1 drives RB inactivation and cell cycle progression by complexing with the cyclin-dependent kinases, CDK4 and CDK6. Given that ER activation, among other stimuli, can induce c-myc and CCND1 expression (5), CDK4 and CDK6 represent a nexus of signaling between the ER pathway and growth promoting pathways in the cell. More recent data suggest that CDK4 and CDK6 can also regulate levels of steroid-metabolizing enzymes, including the AKR1C-family, influencing the estrogenic state of breast tumors (6).

Enter the new class of oral, highly selective CDK 4/6 inhibitors, including palbociclib (Pfizer), ribociclib (Novartis) and abeneciclib (Lilly). Early work with the first-in-class compound, palbociclib, demonstrated greatest inhibition of proliferation in luminal ER+ and HER2-amplified breast cancer cell lines (7), synergy with Tamoxifen in ER+ cell lines and with trastuzumab in HER2-amplified cell lines, and enhanced inhibition of tumor growth in an ER+ patient-derived xenograft model with palbociclib plus the AI letrozole vs. either agent alone. Notably, these preclinical models accurately predicted clinical activity as shown in the PALOMA-1 trial (8), where addition of palbociclib to letrozole resulted in significantly longer progression-free survival (PFS) compared to letrozole alone (10 vs. 20 months; p=0.0004) in the first-line metastatic setting, leading to FDA approval of this agent in February, 2015. Notably, CCND1 amplification or p16 loss did not enhance the effect as was hypothesized. The effect of palbociclib was even
more striking in combination with the SERD Fulvestrant in patients with demonstrated endocrine resistance in the advanced setting, prolonging PFS from 3 to 9 months in the PALOMA-3 trial (p<0.001) (9).

Despite these early successes, many questions remain regarding the biological underpinnings of combination therapy, optimal endocrine therapy partner(s) for CDK4/6 inhibitors, selection of patients most likely to respond, and why resistance to these combinations eventually develops. Can mouse models of endocrine-resistant breast cancer provide biological insights capable of answering these critical questions?

Wardell and colleagues focused on activity of the SERD Fulvestrant (ICI) and two third-generation SERD/SERM hybrids (SSHs), bazedoxifene (BZA) and pipendoxifene (PIP; ERA-923), which function as agonists in bone while inhibiting ESR1 action in the reproductive system (1). Both BZA and PIP are under active investigation as therapies for breast cancer, and the former has already been approved for the treatment of osteoporosis. The effects of these agents, and their combination with the CDK 4/6 inhibitor palbociclib, were examined in tamoxifen-sensitive (wild-type) or tamoxifen-resistant (TamR) MCF7 cell lines, MCF7 cells with acquired resistance to long-term estrogen-deprivation (LTED) as a model of AI-resistance, and tamoxifen-resistant xenograft and PDX models.

The reported findings provide important insights into the biological activity of newer SERM/SSHs and palbociclib in the setting of endocrine therapy resistance, both in the presence and absence of activating ESR1 mutations. Notably, ICI, BZA and PIP each inhibited proliferation and down-regulated ESR1 activity in LTED and TamR cell lines to
an extent similar to that in sensitive (wild-type) cells, albeit with lower potency. When treated with palbociclib alone, these cell lines demonstrated decreased RB phosphorylation without changes in either ESR1 expression or 17β-estradiol-stimulated ER transcriptional activity, suggesting that palbociclib does not exert its effects through ERα. All cell lines, whether sensitive or resistant, exhibited similar sensitivity to palbociclib-induced inhibition of proliferation, which was further unaffected by the presence or absence of ICI, BZA or PIP. As such, each of the SSHs/SERDs efficiently inhibited ESR1 transcriptional activity regardless of palbociclib treatment, and palbociclib treatment decreased RB phosphorylation without affecting ESR1 expression or activity. These findings led Wardell and colleagues to the important conclusion that while the anti-proliferative activities of palbociclib and SSHs/SERDs may converge on common pro-growth stimulatory pathways, their effects occur by distinct mechanisms.

In tamoxifen-resistant xenograft models, palbociclib increased the efficacy with which SSHs inhibited tumor growth/proliferation. Each of the SSHs/SERDs efficiently down-regulated ESR1, inhibited ESR1 transcriptional activity, and inhibited tumor growth. Surprisingly, palbociclib alone in these models induced regression followed by rapid resistance, without loss of RB. While palbociclib had no effect on ESR1 expression or activity, the combination of BZA and palbociclib – but not the combination of palbociclib with ICI or PIP – significantly extended the duration or response compared to either treatment alone. In the PDX model, BZA and palbociclib had similar inhibitory effects on growth, both in the presence and absence of the ESR1-Y537S mutant, and in
combination demonstrated better and more complete suppression of Ki-67 and longer duration of response.

How can these results help us in the clinic? Importantly, the recently reported results of the PALOMA-3 study demonstrating superiority of fulvestrant plus palbociclib over fulvestrant alone, in patients with clinically endocrine-resistant disease, validate the findings in these models of additive effects of ICI and palbociclib. This adds to the weight of evidence that mouse models can accurately predict benefits of combination treatments and provide insights into the underlying mechanisms of response. As such, observations in mice supporting the combination of BZA and palbociclib argue for the analogous human experiment: a randomized trial of BZA with or without palbociclib in endocrine resistant disease. This could provide yet another option for patients with ER+ breast cancer that is likely to be as easily tolerated as other endocrine therapy combinations, while having the added benefit of effectiveness in the 10-20% of patients whose tumors harbor an activating mutation in \textit{ESR1}.

As exciting as these new insights are, much more is needed to fully understand the interactions between ESR1 function and CDK 4/6 inhibition, as well as their intersection with other signaling pathways in the cells. For example, are the growth-inhibiting effects of combined ESR1 and CDK 4/6 inhibition truly as independent and additive as they appear from these experiments? If so, why does single-agent palbociclib therapy have such modest activity (10)? To what extent are the effects of CDK4/6 inhibition specific to luminal tumors with active ESR1 and/or HER2 signaling? What is the mechanism by which concurrent inhibition of ESR1 prevents rapid resistance to
palbociclib therapy? And what are the effects of combined ESR1/palbociclib inhibition on the G1/S checkpoint, specifically with regard to expression of CDKs 4 and 6? Are these a source of resistance to palbociclib? Are they reversible?

More broadly, with respect to mechanisms of endocrine resistance, it is clear that multiple pathways beyond ESR1 are important and capable of driving growth in the absence of ER signaling, as amply demonstrated by the comprehensive genomic analysis of human breast cancers along with decades of molecular and cellular analyses demonstrating a formidable array of recurrently mutated oncogenic driver pathways. Furthermore, resistance emerging from therapy-induced selection pressures acting upon an ocean of genetically heterogeneous tumor cells will have to be grappled with.

For these reasons and others, it is highly likely that overcoming endocrine resistance will require understanding the complex cellular dynamics of tumor evolution and the ability to target multiple alternate escape pathways simultaneously or sequentially. Ultimately, it is unclear whether approaches to preventing the emergence of endocrine resistance in the setting of metastatic disease will be applicable to escape from endocrine therapy in the setting of micrometastatic minimal residual disease, particularly to the extent that this may involve a dormant state of cellular quiescence. Animal models hold great promise both to further our understanding of the biology of endocrine resistance and to speed the discovery of improved therapeutic approaches. Further development of these models and genomic assessment of the cellular effects of therapy are of paramount importance to informing translational human trials.

References


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