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Endocrine therapy and strategies to overcome therapeutic resistance in breast cancer

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ABSTRACT

Despite the remarkable success of endocrine therapy in the treatment of patients with estrogen receptor (ER)- positive breast cancer, not all patients derive benefit from such therapy, or may benefit only temporarily before disease progression or relapse occurs. The value of endocrine therapy, which blocks ER signaling by a variety of strategies, lies in its simplicity, lower toxicity, and better alignment with preserved quality of life, particularly when compared to chemotherapy, which is more toxic and has only modest benefits for many patients with ER-positive breast cancer. It is therefore critical that we discover ways to extend endocrine therapy benefit in patients and prevent therapeutic resistance whenever possible.

The tremendous evolution in our understanding of endocrine resistance mechanisms, coupled with the increasing availability of novel agents that target resistance pathways, has led to enhanced treatment approaches for patients with ER-positive breast cancer, primarily through combinations of endocrine agents with a variety of pathway inhibitors. Despite these treatment advances and our changing view of ER-positive breast cancer, there is much work that needs to be done. It remains a problem that we cannot reliably predict which subsets of patients will experience disease relapse or progression on endocrine

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therapy, and as such, combination strategies with targeted agents have largely been used in unselected patients with ER-positive breast cancer, including those who continue to have endocrine-sensitive disease. Patient selection is a significant issue since most of the targeted therapeutics that we use with endocrine therapy are expensive and can be toxic, and we may be inadvertently overtreating patients whose disease can still be controlled with endocrine therapy alone. In this article, we will review current and future strategies in the treatment of ER-positive breast cancer, as well as the evolving role of targeted therapy in the management of endocrine-resistance.

Introduction

Breast cancer is a major health problem worldwide with more than 1 million new cases diagnosed each year and approximately 400,000 deaths annually.[1] Approximately 70%-80% of all breast cancers express the estrogen receptors (ER) and progesterone receptors (PgR),[2] at times referred to collectively as hormone receptor-positive breast cancer. The presence of hormone receptors is associated with certain predictable tumor characteristics and a biologic behavior that is more indolent when compared with hormone receptor-negative tumors. Importantly, ER and its ligand estrogen play a key role in the development and progression of breast cancer, and disruption of the ER signaling pathway using a variety of endocrine strategies has been a mainstay in the treatment of this disease (Fig).

More than 120 years ago, and long before we knew about the existence of ER in breast cancer, Beatson[3] described the benefit of estrogen deprivation by oophorectomy in treatment of premenopausal women with advanced breast cancer. Although this estrogen deprivation strategy was the original endocrine therapy described, and the first targeted therapy approach, endocrine strategies evolved to include agents that target ER itself, with the selective estrogen receptor modulator tamoxifen as the prototype endocrine therapy modality for decades.[4-7] Although effective, tamoxifen was limited by the problem of therapeutic resistance[2] and additional treatment modalities were needed. With time, therapeutic options for treatment of ER-positive breast cancer evolved further with the addition of several new and more powerful anti-ER strategies, including third-generation aromatase inhibitors (AIs), which cause estrogen deprivation in postmenopausal women,[8] and fulvestrant, which leads to the degradation of ER.[9]

Despite the addition of these expanded endocrine therapy options with more effective inhibition of ER signaling,[10] therapeutic resistance remained a major problem limiting the benefit of *all* forms of endocrine therapy, but also created more opportunity to study mechanisms of resistance and to target new resistance pathways to improve endocrine therapy action and modulate resistance. This has become possible with significant advances in our understanding of ER biology and the unraveling of an intricate interplay between ER and other survival and growth factor signaling pathways in a breast cancer cell (Fig).[2,11] Consequently, we have witnessed a progressive shift away from viewing ER as an isolated and static pathway in breast cancer, and increasingly view it as an interactive partner with other signaling pathways, as well as a dynamic target in response to the effect of treatment.

In this article, we highlight 2 key strategies that can be used to modulate endocrine response and resistance in patients. The first strategy involves inhibition of the PI3K/AKT/mTOR pathway, which is a key driver of endocrine resistance in patients with progressive disease on endocrine therapy. The second strategy involves cell cycle inhibition using agents that target cyclin dependent kinases (CDK) 4 and 6, and this strategy is increasingly taking center stage as a