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Review

Mechanisms of resistance to selective estrogen receptor down-regulator in metastatic breast cancer

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ABSTRACT

Based on the prominent role estrogen receptor (ER) plays in breast cancer, endocrine therapy has been developed to block the ER pathway and has shown great effectiveness. Fulvestrant, the first selective ER down-regulator (SERD), was demonstrated to completely suppress ERα and notably efficient. However, resistance to fulvestrant occurs, either intrinsic or acquired during the treatment. Several potential mechanisms inducing fulvestrant resistance have been proposed, composed of activated ERα-independent compensatory growth factor signaling, stimulated downstream kinases, altered cell cycle mediators, etcetera. Experimentally, combinations of fulvestrant with targeted treatments were reported to eliminate the resistance and improve the effect of fulvestrant. Meanwhile, some clinical trials associated with the targeted combination therapies are in progress. This review focuses on the underlying mechanisms that contribute to fulvestrant resistance in ER-positive breast cancer and provides an overview of combined fulvestrant with targeted agents to shed light on optimal therapies for patients with ER-positive breast cancer.

1. Introduction

Accounting for about 75% of breast cancer, estrogen receptor (ER) drives the development, progression and metastasis of all the hormone receptor (HR)-positive cases [1,2]. Endocrine therapy, specifically targeting the ER pathway, is commonly used as a highly effective treatment for HR-positive breast cancer [3]. ER modulators (e.g., Tamoxifen) interfering with estrogen signaling, aromatase inhibitors (e.g., Letrozole) blocking estrogen biosynthesis and selective ER down-regulators (e.g., Fulvestrant) degrading ER consist of endocrine therapy [4–7]. Despite the recognized efficacy of this approach, it is evident that nearly half of ER-positive breast cancer does not respond to endocrine therapy (de novo resistance) or eventually develops unresponsiveness and acquired resistance to it, resulting in poor outcome [8–11].

Estrogens, especially 17β-estradiol, participate in a variety of physiological processes and regulate the development and progression of HR-positive breast cancer. Estradiol binds to ER to form estradiol/ER complex and functions via genomic (nuclear ER) and non-genomic (non-nuclear ER) pathways [12]. In the genomic pathway, the complex induces receptor dimerization and nuclear translocation to mediate gene transcription [13]; in the non-genomic pathway, the complex, through crosstalk with growth factors and G-protein-coupled signaling pathways, activates downstream mitogen-activated-protein-kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/AKT [14].

Multifactorial pathways have been shown to develop tamoxifen resistance in both preclinical and clinical studies, including over-expressed human epidermal growth factor-2 (HER2) [15,16], and the crosstalk between ER and growth factor pathways [14,17–19]. As such, several cell-autonomous and non-cell autonomous mechanisms in ER-positive breast cancer and the tumor microenvironment lead to

Abbreviations: AI, aromatase inhibitor; AR, androgen receptor; CAF, cancer-associated fibroblast; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; ctDNA, circulating tumor DNA; DNMT3B, DNA methyltransferase 3B; ER, estrogen receptor; *ESR1*, ER gene; HDAC1, histone deacetylase 1; HER2, human epidermal growth factor receptor-2; HIF-1α, hypoxia-inducible factor 1α; HR, hormone receptor; hSWI/SNF, human SWItch/Sucrose NonFermentable; IGF-1R, insulin-like growth factor 1 receptor; INPP4B, inositol polyphosphate-4-phosphatase type II B; InsR, insulin receptor; MAPK, mitogen-activated-protein-kinase; mPFS, median progression-free survival; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin-containing complex 1; mTORC2, mammalian target of rapamycin-containing complex 2; NF-κB, Nuclear Factor-κB; OS, overall survival; PDK1, phosphoinositide-dependent kinase 1; PFS, progression-free survival; PH, pleckstrin homology; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PR, progesterone receptor; *PTEN*, phosphatase and tensin homolog deleted from chromosome ten; Rb, retinoblastoma; RTK, receptor tyrosine kinase; SERD, selective estrogen receptor down-regulator; TIGAR, TP53-induced glycolysis and apoptosis regulator; TKI, tyrosine kinase inhibitor; TTP, time to progression; VEGF, vascular endothelial growth factor

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aromatase inhibitors (AIs) resistance [20]. Notably, ER gene (*ESR1*) alterations, such as point mutation, translocation and amplification, are all potential drivers that generate the most acquired resistance to AI treatment [21].

Fulvestrant, different from tamoxifen, is a pure ER antagonist and has no partial agonist effect on ER. After binding to ER, fulvestrant impairs dimerization and nuclear translocation of ER as well as induces ER cytoplasmic aggregation, eventually resulting in unresponsiveness of ER to estradiol and suppression of ER signaling pathway [9,22]. In spite of the potency of fulvestrant, resistance occurs and leads to disease progression. Therefore, herein we briefly discuss the potential mechanisms that associate with acquired resistance to fulvestrant and promising approaches to enhance the efficacy of fulvestrant.

2. Clinical relevance to fulvestrant

For postmenopausal women with metastatic breast cancer who experience progression following antiestrogen therapy, fulvestrant is recommended as a valid treatment [23,24]. Initially, the dosage of fulvestrant was approved 250 mg every 28 days [25,26]. It was demonstrated that in treating postmenopausal women with disease progression on prior endocrine therapy, fulvestrant (250 mg/28 days, i.m. injection) was at least as effective as anastrozole (non-steroidal AI; 1 mg/day, orally) in terms of time to progression (TTP) while being well tolerated [25–27]. Another phase III trial further confirmed the activity of fulvestrant (500 mg i.m. injection on day 0, 250 mg on days 14 and 28, and 250 mg every 28 days thereafter) versus exemestane (steroidal AI; 25 mg/day, orally) in patients that experienced progression or relapse after non-steroidal AI [28]. In a first-line clinical trial of fulvestrant (250 mg/28 days, i.m. injection) versus tamoxifen (20 mg/day, orally), noninferiority was not met by fulvestrant in the overall population. However, the analysis in the subgroup that was confirmed to be HR-positive breast cancer showed that fulvestrant had a similar efficacy to tamoxifen [29].

Based on an observation that explored the effects of fulvestrant at three doses (50 mg, 125 mg and 150 mg) and showed a dose-dependent reduction in ER, PR and Ki67, more studies were conducted and suggested that 250 mg might not enough to maximize the efficacy of fulvestrant [30,31]. Indeed, the phase III comparison of fulvestrant in recurrent metastatic breast cancer (CONFIRM) trial proved that fulvestrant 500 mg, compared with fulvestrant 250 mg, significantly increased the progression-free survival (PFS) without increasing toxicity [32,33]. Therefore, the Food and Drug Administration (FDA) approved fulvestrant 500 mg every 28 days after an initial month of biweekly loading dose in metastatic breast cancer with the progression on previous endocrine treatment. The final analysis of overall survival (OS) was subsequently carried out and further demonstrated the superiority of fulvestrant 500 mg, which was associated with a 19% reduction in risk of death and a 4.1-month difference in median OS, in comparison with fulvestrant 250 mg [34]. A phase II study comparing OS for fulvestrant 500 mg versus anastrozole as a first-line endocrine therapy for advanced breast cancer suggested that fulvestrant 500 mg could extend OS [35–37]. This result was confirmed by the larger phase III fulvestrant versus anastrozole compared in hormone therapy-naive ER-positive breast cancer (FALCON) study that fulvestrant was superior to third-generation AIs and considered as a first-line treatment for those with HR-positive locally advanced or metastatic breast cancer [24]. Because ER downregulation by fulvestrant was proved to be dose-related, a phase II clinical trial was set up to evaluate the effect of fulvestrant at a higher dose and found out fulvestrant 750 mg, with good tolerance, was effective in reducing ER and Ki67. Although no studies have further demonstrated that patients would benefit more from fulvestrant 750 mg than 500 mg, this result suggested that there might be scope to optimize the activity of fulvestrant via improving its dosage [38].

Fulvestrant is a long-acting formulation that requires intramuscular injection, giving rise to sustained plasma concentration and being less influenced by gastrointestinal side effects. Nevertheless, its efficacy is limited because of the poor pharmacokinetic characteristic taking 3–6 months to achieve a steady-state plasma concentration with the 250 mg monthly dose. Compared to prior regimen, a loading dose schedule (500 mg day 0, 250 mg days 14 and 28 of month 1, and 250 mg every 28 days thereafter) shortens the time to steady state to 28 days. As a result of the earlier attainment of steady state, patients who are at risk of early relapse may benefit from it [39,40].

Despite the potency, fulvestrant is hampered by intramuscular administration and undesirable pharmacokinetics. Therefore, orally active SERDs have been developed. TAS-108 is a novel orally steroid whose good tolerance and anti-tumor activity have been verified, and a phase II clinical study revealed that 40 mg dose of TAS-108 was worth further evaluating [41,42]. Compound GW-5638, metabolically 4-hydroxylated to active form GW-7604 in the same way tamoxifen functions but no cross-resistant to tamoxifen breast cancer cell lines, is a newly discovered nonsteroidal ER antagonist [43]. However, due to unknown reasons, the phase I clinical trial of GW-5638 was discontinued. Another orally bioavailable SERD that encouragingly displayed potent activity when experimented on tamoxifen-resistant breast cancer xenografts, GDC-0810 (ARN-810), is currently being tested clinically in treating locally advanced or metastatic ER-positive breast cancer [44,45]. Orally administrated AZD-9496 was effective in MCF-7 xenograft model sensitive to antiestrogen therapy and showed anti-tumor activity in a long-term estrogen-deprived model of resistance, and it is also being evaluated in a phase I clinical trial at present [46,47]. RAD-1901, another oral SERD, prolonged survival of the intracranial MCF-7 tumor model versus fulvestrant and suggested a role in treating brain metastases from ER-positive breast cancer [48]. With robust activity, new orally available SERDs are prospectively to optimize the treatment of patients with ER-positive breast cancer.

3. Potential mechanisms for fulvestrant resistance

3.1. Activation of PI3K pathway

Currently, both preclinical and clinical studies have revealed that the growth factor receptor signaling pathways converge on PI3K and MAPK/ERK, mediating the resistance to the antiestrogen therapy (Fig. 1). Upon growth factor stimulation and subsequent activation of receptor tyrosine kinases (RTKs), PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to produce phosphatidylinositol 3,4,5-trisphosphate (PIP3) [49] which recruits pleckstrin homology (PH) domain-containing proteins, such as phosphoinositide-dependent kinase 1 (PDK1) and AKT, to the cell membrane [50,51]. Negative regulation of PI3K pathway is performed by phosphatase and tensin homolog deleted from chromosome ten (PTEN) and inositol polyphosphate-4-phosphatase type II B (INPP4B), preventing PDK1 and AKT from activation via dephosphorylation of PIP2 and PIP3 [52,53]. The activated AKT then elicits protein synthesis through the activation of the mammalian target of rapamycin (mTOR)-containing complex 1 (mTORC1) [54]. Overexpressed AKT in breast tumors has been implicated in the poor response to the antiestrogen therapy [55–58], and downregulated phosphorylated AKT by wortmannin (a PI3K inhibitor) suppressed fulvestrant resistant cell proliferation in laboratory studies [59]. Additionally, highly active AKT was verified to confer fulvestrant resistance which could be experimentally reversed by mTOR inhibitor RAD001 (everolimus) [60]. Further, the dual mTORC1/2 mTOR kinase inhibitors, such as AZD8055, plus fulvestrant were shown to provide superior control of resistant growth versus either agent alone [61].

PI3K pathway, as the most frequently altered pathway in breast cancer [62–64], is activated via diversified ways, in which loss of tumor suppressors and/or gain-of-function oncogenes may play a significant role. A gene expression signature of *PTEN* loss not only results in