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REVIEW

New and emerging treatments for estrogen receptor-positive breast cancer: focus on everolimus

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Abstract: Management of patients with metastatic hormone receptor-positive breast cancer poses a challenge due to the inevitable development of endocrine resistance. Hormone resistance is associated with a complex interaction of the estrogen receptor with growth factors, transmembrane receptors, and intracellular growth cascades. The PI3K/Akt/mTOR pathway plays a major role in hormone resistance and proliferation of breast cancer. Preclinical and clinical data indicate that inhibitors of human epidermal growth factor receptor-2, epidermal growth factor receptor, insulin-like growth factor-1 receptor, and the mammalian target of rapamycin pathway may act synergistically with hormone therapy to circumvent endocrine resistance. Everolimus is currently approved for combination with exemestane in postmenopausal women with advanced hormone receptor-positive breast cancer. However, we still need to unfold the full potential of targeted agents in the hormone-refractory setting and to identify the subsets of patients who will benefit from combination hormonal therapy using targeted agents.

Keywords: everolimus, estrogen receptor-positive breast cancer, hormone resistance, mammalian target of rapamycin, inhibition

Background

Breast cancer is the most common malignancy among women in the US, accounting for nearly one in three cancers diagnosed.[1] It is estimated that 226,870 women will be diagnosed and 39,510 women will die of breast cancer in 2012.[2] Approximately two-thirds of breast cancers are estrogen and/or progesterone receptor-positive. Hormone receptor status is determined using immunohistochemistry on paraffin-embedded tissues. The presence of at least 1% staining nuclei is required to define hormone-positive disease and predict clinical response to hormone-directed therapy.[3]

The natural history of hormone receptor-positive breast cancer tends to be different from hormone receptor-negative disease. The presence of hormone sensitivity is usually associated with a favorable prognosis. Use of adjuvant endocrine therapy has dramatically decreased breast cancer mortality in patients with early-stage disease, and hormone therapy is the cornerstone treatment in advanced stages. However, a subset of hormone receptor-positive breast cancers do not benefit from endocrine therapy (intrinsic resistance), and all hormone receptor-positive metastatic breast cancers ultimately develop resistance to hormonal therapies (acquired resistance). Most patients who have experienced treatment failure after several hormonal agents in the metastatic setting are treated with chemotherapy, which is associated with increased toxicity.[4,5]

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This review focuses on new and emerging treatments for hormone receptor-positive breast cancer and particularly on the role of inhibition of mTOR (mammalian target of rapamycin) in reversing resistance to endocrine agents.

Endocrine therapy

Tamoxifen, a selective estrogen receptor modulator, had been the standard of care for all stages of hormone receptor-positive breast cancer since its initial approval by the US Food and Drug Administration in 1986.[6] Aromatase inhibitors, which act by blocking the peripheral conversion of androgens to estrogen and therefore decrease levels of circulating estrogens in postmenopausal women, were approved for the treatment of metastatic breast cancer, and subsequently for early-stage cancer. The currently approved third-generation aromatase inhibitors are divided into steroidal (exemestane) and nonsteroidal (anastrozole and letrozole) agents.[7]

A study comparing anastrozole and tamoxifen in more than 1000 patients with advanced breast cancer showed that anastrozole was superior to tamoxifen in terms of time to progression, although there was no difference in overall survival.[8,9] BIG 1-98 was a Phase III trial of letrozole versus tamoxifen in postmenopausal women with advanced breast cancer, which demonstrated that time to progression was increased from 6 to 9.4 months in the letrozole arm. The response rate and overall clinical benefit were also increased in the letrozole arm when compared with tamoxifen.[10–12] Exemestane was also shown to be superior to tamoxifen in terms of clinical benefit in postmenopausal patients with breast cancer.[13] The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial demonstrated that aromatase inhibitors were superior to tamoxifen in the adjuvant setting. Aromatase inhibitors have thus become the preferred regimen in postmenopausal women.[14,15]

Fulvestrant, an estrogen receptor downregulator with no known agonist activity, was initially found to be equivalent to anastrozole in patients previously treated with tamoxifen.[16] Fulvestrant was also compared with tamoxifen in the first-line setting in women with metastatic disease and was found to have similar efficacy in patients with hormone receptor-positive tumors.[17] Fulvestrant was initially approved at a dose of 250 mg as a monthly intramuscular injection. Subsequent studies have examined the efficacy of different doses and schedules. CONFIRM (COmparisoN of Faslodex In Recurrent or Metastatic breast cancer) was a Phase III trial examining the difference in progression-free survival between the doses of 250 mg and 500 mg, and demonstrated that the higher dose improved the median progression-free survival, reducing the risk of progression by 20%.[18]

Combination of hormonal agents

Fulvestrant has been evaluated in combination with anastrozole in two trials with differing results. Mehta et al recently reported the results of a study combining anastrozole and fulvestrant in the metastatic setting.[19] The authors hypothesized that the combination would be more effective than anastrozole alone in patients with hormone receptor-positive metastatic breast cancer. The trial randomized postmenopausal women with previously untreated metastatic disease to anastrozole alone or anastrozole plus fulvestrant. Fulvestrant was administered intramuscularly at a dose of 500 mg on day 1, 250 mg on days 14 and 28, and monthly thereafter. The median progression-free survival was 13.5 months in the anastrozole alone arm and 15.0 months in the combination arm (hazards ratio 0.80; $P = 0.007$). The combination therapy was generally more effective than anastrozole alone in all subgroups, with no significant interactions. Overall survival was also improved in the combination arm compared with anastrozole alone (median 47.7 versus 41.3 months, respectively). In this study, 41% of patients in the anastrozole arm crossed over to fulvestrant after progression. The study concluded that the combination of anastrozole and fulvestrant was more effective and better tolerated than anastrozole alone. It is notable that this study enrolled hormone-naïve patients who, judging from the outcomes seen in the anastrozole alone arm, included a large percentage of hormone-sensitive patients. The results of this study are in contrast with those of FACT (Fulvestrant and Anastrozole in Combination Trial), an open-label, randomized Phase III investigation of fulvestrant plus anastrozole versus anastrozole alone as first-line treatment for patients with receptor-positive postmenopausal breast cancer.[20] This trial reported no significant differences in time to progression or median overall survival between the two groups. The different results reported in these two studies may be attributed to the size and choice of patient population. Combination of hormonal therapies may warrant further investigation, but it does not address the issue of hormone resistance, which eventually develops in all patients.

Mechanisms of resistance to endocrine therapy

Estrogen receptor activation leads to phosphorylation, dimerization, and downstream signaling through estrogen response elements which promote cell survival, division, and growth of cancer.[21,22] Clinical and preclinical data indicate that hormone receptors interact with growth factor receptors, including human epidermal growth factor receptor

(HER2/neu), epidermal growth factor receptor (EGFR), and insulin-like growth factor-1 receptor (IGF1R), which likely play a role in hormone resistance.[23,24] Crosstalk between the estrogen receptor and membrane tyrosine kinase receptors (EGFR, HER2, and IGF1R) can lead to gene expression and cell growth independent of hormonal activation, mainly via activation of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways. The estrogen receptor can also be regulated by these membrane receptors, which act as coactivators and lead to estrogen receptor phosphorylation in the absence of estrogen (ligand-independent receptor activation, Figure 1). The interaction of the estrogen receptor with growth factor receptors is complex. It is believed that the estrogen receptor can activate membrane growth factors via expression of transforming growth factor-alpha and IGF1. However at the same time, it downregulates EGFR and HER2 while inducing IGF1R. In turn, activation of MAPK and PI3K pathways by growth factor receptors downregulates estrogen receptor signaling.[25]

In summary, it appears that membrane growth factor receptors can phosphorylate and activate the estrogen receptor independently of estrogen and they can activate downstream pathways and induce cell growth independently of estrogen receptor activation, but can also downregulate estrogen receptor expression, leading to hormone independence.

HER2/EGFR

Breast cancers with high levels of HER2 expression are more likely to be resistant to hormonal therapy. Transfection of HER2 in estrogen receptor-positive breast cancer cells renders them resistant to tamoxifen.[26,27] Further, it has been shown that selective estrogen receptor modulator-resistant breast cancer cells have increased expression of HER2 compared with selective estrogen receptor modulator-sensitive

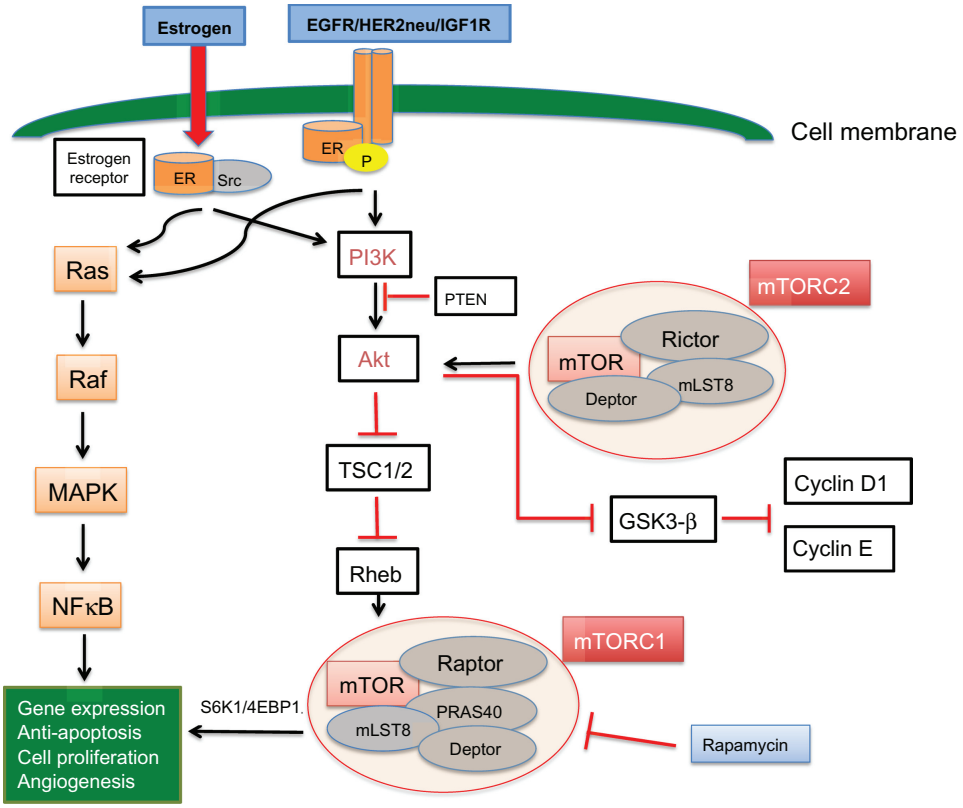

Figure 1 Crosstalk between the estrogen receptor and EGFR/HER2/IGF1R membrane tyrosine kinase receptors can lead to gene expression and cell growth independent of hormonal activation, mainly via activation of the MAPK and PI3K pathways.

Notes: The estrogen receptor can also be regulated by these membrane receptors, which act as coactivators and lead to phosphorylation of estrogen receptors in the absence of estrogen (ligand-independent receptor activation). The PI3K/Akt/mTOR pathway is a major downstream cellular circuit, which leads to cell proliferation via the mTORC1 complex. The mTORC2 complex activates Akt, which in turn inhibits the proteolysis of cyclin D1/E.

Abbreviations: EGFR, epidermal growth factor receptor; IGF1R, insulin-like growth factor-1 receptor; mTOR, mammalian target of rapamycin; HER2, human epidermal growth factor receptor-2; ER, estrogen receptor; TSC1/2, tuberous sclerosis complex proteins 1/2; PI3K, phosphatidylinositol 3-kinase; MAPK, mitogen-activated protein kinase; Src, steroid receptor coactivator.

breast cancer cells.[28,29] A meta-analysis by De Laurentiis et al reported that HER2-positive patients with metastatic receptor-positive breast cancer treated with tamoxifen had a shorter time to treatment failure when compared with patients having HER2-negative disease.[30] These findings suggest that HER2 plays a significant role both in intrinsic and acquired hormone resistance. Preclinical evidence supports that crosstalk between HER2 and the estrogen receptor leads to tamoxifen resistance, and disruption of this crosstalk can restore tamoxifen sensitivity.[31,32]

A randomized Phase III, double-blind, multicenter study by Johnston et al enrolled 1286 postmenopausal patients with advanced or metastatic estrogen receptor-positive and/or progesterone receptor-positive breast cancer. No prior treatment was allowed, except for neoadjuvant/adjuvant hormonal or anti-HER2 therapy. Patients were randomly assigned to receive letrozole and lapatinib or letrozole and placebo. Median progression-free survival was significantly improved in patients with HER2-positive disease who received lapatinib plus letrozole, compared with letrozole alone (3 months in the placebo arm and 8.2 months in the combination arm, hazards ratio 0.71, $P = 0.019$). Among the HER2-negative patients, there was no significant improvement in progression-free survival or clinical benefit. However, a subset of patients with HER2-negative disease and estrogen receptor expression in the lowest quartile appeared to benefit from adding lapatinib to letrozole (progression-free survival 13.6 versus 6.6 months, hazards ratio 0.65, $P < 0.005$).[33,34]

Similarly, expression of EGFR in vivo and in vitro has been shown to be associated with endocrine resistance, and in preclinical models EGFR inhibition can restore sensitivity to hormone treatment.[35–38] A Phase II, randomized, double-blind, placebo-controlled study by Cristofanilli et al evaluated the combination of anastrozole and gefitinib (a selective EGFR tyrosine kinase inhibitor) versus anastrozole and placebo in postmenopausal patients with hormone receptor-positive metastatic breast cancer. The study population consisted of patients who had not received prior endocrine therapy for this stage or had developed metastatic disease during/after adjuvant tamoxifen. Although the study was closed early due to slow accrual, the combination arm showed improvement in progression-free survival versus placebo (median progression-free survival 14.7 versus 8.4 months, respectively). The treatment was tolerated very well.[39] Osborne et al reported a randomized Phase II trial of tamoxifen with or without gefitinib in patients with metastatic disease who had experienced treatment failure while on tamoxifen or aromatase inhibitors. The combination arm showed improved progression-free survival in patients who had relapsed after adjuvant tamoxifen. However, no clinical benefit was seen in patients who had been previously treated with aromatase inhibitors.[40]

IGF1R

The IGF1R pathway plays a significant role in tumor growth and inhibition of apoptosis. IGF1R can activate the estrogen receptor pathway in the absence of estrogen and thus lead to tumor growth. It appears that there is crosstalk between IGF1R and the estrogen receptor, which possibly contributes to hormone resistance. In vivo and in vitro models show that IGF1R inhibition can act synergistically with hormone therapy.[41–44] However, a clinical study of AMG 479 (a human anti-IGF1R monoclonal antibody) in combination with exemestane or fulvestrant in postmenopausal women failed to show a clinical benefit or difference in progression-free survival with IGF1R inhibition.[45]

Steroid receptor coactivator

The steroid receptor coactivator (Src) is a nonreceptor tyrosine kinase, which plays an essential role in the life cycle of the cell.[46] Breast cancer tissue has higher expression of Src than normal breast tissue. In hormone receptor-positive breast cancer cells, Src binds and phosphorylates the estrogen receptor and activates downstream signaling pathways (Figure 1). Src is thought to play a pivotal yet complex role in endocrine resistance. Elevated levels of cytoplasmic Src have been linked with an attenuated response to hormone therapy in vitro, and high expression of Src has been associated with increased metastatic potential and poor survival in the clinical setting.[47,48] Preclinical studies indicate that treatment of resistant cells with Src inhibitors restores sensitivity to tamoxifen.[49] However, a Phase II study of dasatinib (an oral multi-BCR/ABL and Src family tyrosine kinase inhibitor) as a single agent showed very limited activity in women with advanced HER2-positive or estrogen receptor-positive metastatic breast cancer, probably due to the complexity of the cellular circuits which ultimately lead to hormone resistance.[50]

PI3K, Akt, and mTOR

The PI3K/Akt/mTOR pathway is a major intracellular cascade, which can be regulated by nutrient availability and growth factor receptors, including EGFR, HER2, IGF1R, and the estrogen receptor. When activated, this pathway induces tumor growth, proliferation, and resistance to targeted agents and chemotherapy.[51,52] The PI3K/Akt pathway can activate

both estrogen-dependent and estrogen-independent estrogen receptor alpha.[53]

In this pathway, a central role is played by PI3K heterodimer, which consists of a p85 regulatory and p110 catalytic subunit. Activation of PI3K will phosphorylate Akt. Akt is a serine/threonine kinase, which activates major downstream intracellular effectors. Akt can directly activate the estrogen receptor by phosphorylation in the absence of estrogen, thus promoting estrogen-independent growth and resistance to hormone therapy.[54–58] The PI3K/Akt pathway is often aberrantly regulated in cancer, and the PIK3CA mutation is the most common point mutation seen in breast cancer.[59] Akt can be also activated by loss of PTEN, a mechanism that has been associated with a poor prognosis and increased risk of relapse after treatment with tamoxifen.[60]

PI3K/Akt mutations, loss of PTEN, and constitutive activation of the PI3K/Akt pathway have been associated with hormone resistance. Activation of the PI3K pathway has been associated with intrinsic and acquired hormone resistance, and preclinical data indicate that PI3K inhibitors are active when combined with endocrine therapy.[56,61] Multiple clinical studies are currently evaluating PI3K inhibitors in hormone receptor-positive tumors.

Downstream of PI3K and Akt, mTOR is a serine/threonine protein kinase, which is activated by inhibition of the tuberous sclerosis complex proteins 1/2.[62] mTOR exerts its effects via two very different protein complexes. The mTORC1 complex includes the regulatory-associated protein of mTOR (Raptor), mLST8, and proline-rich Akt substrate 40.[63] It is irreversibly inhibited by rapamycin and exerts its action by activating S6K1 (40S ribosomal protein S6 kinase 1) and eukaryotic initiation factor 4E-binding protein, thus leading to protein production, cell activation, division, and tumor growth.[64,65] mTORC2 has been traditionally thought to be insensitive to rapamycin, but there is evidence that prolonged exposure to rapamycin can induce sufficient inhibition of mTORC2.[66] Although its role in the cell cycle remains largely unknown, mTORC2 is believed to modulate cell lipid metabolism and cell growth via Akt, by inhibition of glycogen synthase kinase-3β and cyclin D1/E proteolysis.[63] Studies suggest that targeted inhibition of TORC2 inhibits breast cancer cells in vitro and in vivo.[67]

Several preclinical studies provide evidence that mTOR inhibition can restore hormone sensitivity and induce apoptosis in breast cancer cells. The mTOR inhibitor, rapamycin, can reverse resistance to endocrine therapy when combined with tamoxifen or fulvestrant.[68,69] Interestingly, restoration of sensitivity to endocrine therapy can be associated with increased estrogen receptor-α protein expression levels and alteration of the phospho-ser167 estrogen receptor-α to total estrogen receptor-α ratio.[69] Treatment of letrozole-resistant or fulvestrant-resistant breast cancer cells with low concentrations of the mTOR inhibitor, everolimus, reverses Akt-mediated resistance and restores responsiveness to antiestrogen treatment.[70] When combined with letrozole, everolimus acts synergistically to promote cell cycle arrest and induce apoptosis.[71] In summary, these preclinical data strongly support that mTOR inhibition could play a significant role in the treatment of hormone receptor-positive breast cancer, especially in resistant tumors.

Clinical studies with mTOR inhibitors

Rapamycin (sirolimus) was the first identified mTOR inhibitor, and was initially used as an immunosuppressant to prevent organ transplant rejection. The novel inhibitors, everolimus, temsirolimus, and ridaforolimus, are rapamycin analogs with improved pharmacological properties.

Temsirolimus

In a randomized, Phase II three-arm study of temsirolimus in combination with letrozole in postmenopausal women with hormone receptor-positive metastatic breast cancer, combination treatment with an intermittent schedule of temsirolimus was tolerable and showed clinical activity, with preliminary results indicating improvement in progression-free survival.[72,73] A subsequent Phase III study by Chow et al who enrolled patients with metastatic breast cancer randomly assigned patients to letrozole or combination of letrozole with temsirolimus.[74] The study had to be closed prematurely because there was no clinical benefit from the combination. An unplanned subset analysis suggested that patients who had been previously treated with chemotherapy might benefit from addition of the mTOR inhibitor to hormonal therapy.[75] It is possible that this study failed to reach its endpoint due to suboptimal dosing and inappropriate selection of the study population.

Everolimus

BOLERO-2 (Breast Cancer Trials of Oral Everolimus) is a randomized Phase III investigation by Baselga et al which evaluated a combination of everolimus with the steroidal aromatase inhibitor, exemestane, in postmenopausal patients with advanced estrogen receptor-positive breast cancer who had recurrence or progression while receiving a nonsteroidal aromatase inhibitor.[76] In total, 724 patients were randomized to receive exemestane 25 mg daily plus everolimus 10 mg

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