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Clinical strategies for rationale combinations of aromatase inhibitors with novel therapies for breast cancer☆

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Abstract

Improving endocrine responsiveness and preventing the development of resistance is the goal of many current strategies that are looking to combine aromatase inhibitors with novel drugs that target various pathways in estrogen receptor (ER) positive breast cancer. Pre-clinical models of acquired resistance to aromatase inhibitors have suggested an increase in several signaling pathways including peptide growth factor signaling (EGFR, HER2) and activation of the mTOR signaling pathway. These may result in associated 'cross-talk' activation of ER-dependent gene transcription, such that dual blockade of ER together with other signaling pathways has become a logical approach to improve endocrine responsivness. Clinical strategies with aromatase inhibitors are looking to prevent activation of these pathways either through combination with the selective ER downregulator fulvestrant, or with various signal transduction inhibitors (STIs) including monoclonal antibodies (trastuzumab), small molecule tyrosine kinase inhibitors (TKIs) against EGFR or HER2 (lapatinib, gefitinib) and mTOR antagonists (temsirolimus). Early clinical data have emerged this year for some of these approaches with mixed results. This article reviews the rationale for these strategies, and discusses the lessons that need to be learnt if we are to successfully integrate these new drugs with aromatase inhibitors in the clinic.

Keywords: Aromatase inhibitors; Endocrine resistance; Fulvestrant; Signal transduction inhibitors; Clinical trials; Endpoints

1. Introduction

While aromatase inhibitors have resulted in significant clinical progress in the endocrine treatment of postmenopausal women with oestrogen recptor (ER) positive breast cancer [1], initial (de novo) or subsequent (acquired) resistance still limits their benefit for many patients. Laboratory studies using various models to investigate these mechanisms of resistance have demonstrated that both peptide growth factor pathways and oncogenes involved in the signal transduction cascade become activated in breast cancer cells during either long-term estrogen deprivation (LTED) or tamoxifen therapy [2–4]. In resistance to aromatase inhibitors, estrogen receptor (ER) signaling may still play a crucial role in these resistant cells as they adapt and become hypersensitive to low levels of residual estrogen, utilising the various activated signaling pathways via cross-talk to activate and further enhance ER-dependent gene transcription [5–11]. As such, these various signaling pathways, including activated ER itself, represent attractive targets for pharmacologic intervention.

This article reviews the clinical strategies for combining either the ER downregulator fulvestrant or various different signal transduction inhibitors (STIs) with aromatase inhibitors in an attempt to enhance endocrine responsiveness and delay acquired resistance. Early results from some of these clinical trials are discussed, together with lessons that may need to be learnt regarding optimal clinical trial design for these strategies in the future.

2. Resistance to oestrogen deprivation

Pre-clinical data indicate that exposure to long-term oestrogen deprivation (LTED) similar to that caused by

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aromatase inhibitors may be accompanied by adaptive increases in ER gene expression and intercellular signaling, resulting in hypersensitivity to low estradiol levels [5–8]. ER may become activated and super-sensitised by a number of different intracellular kinases, including mitogen-activated protein kinases (MAPKs) [6,8,9], HER2/HER3 signaling [6] and the insulin-like growth factor (IGF)/AKT pathway [10,11]. A number of pharmacological approaches against EGFR or MEK have been used to block the pathways in the various models, and as such restore endocrine sensitivity. An equally effective approach may be use of fulvestrant to degrade the ER that remains an integral part of 'cross-talk' signaling in the hypersensitive LTED resistant cells.

3. Integrating fulvestrant with aromatase inhibitors

Fulvestrant (Faslodex^{TM}) is a novel type of ER antagonist that unlike tamoxifen, has no known agonist effects [12]. Fulvestrant binds to the ER, but due to its steroidal structure and long side-chain, induces a different conformational shape with the receptor that prevents ER dimerisation and leads to the rapid degradation of the fulvestrant–ER complex, producing the loss of cellular ER [13]. Due to this degradation of ER protein and more complete inhibition of endocrine-dependent signaling, fulvestrant can delay emergence of acquired resistance to tamoxifen in an MCF-7 hormone-sensitive xenograft model [14]. Our own recent pre-clinical studies have shown that fulvestrant is considerably more effective than tamoxifen in this regard [15].

The efficacy of fulvestrant in the setting of activated and hypersensitive ER in LTED resistant cells may be critically dependent on the competing levels of estradiol. Experiments in tamoxifen-stimulated breast cancer xenografts demonstrated paradoxical effects on tumour growth dependent on whether fulvestrant was administered in the presence or absence of estrogen [16]. Long-term tamoxifen-treated tumours which became resistant and growth stimulated by tamoxifen were inhibited by estradiol due to enhanced apoptosis and Fas ligand expression, associated with reduced ER and HER2 expression. The addition of fulvestrant to estradiol-treated tumours reversed these effects and stimulated growth of TAM-R tumours, but when fulvestrant was given in the absence of estradiol the resistant tumours failed to grow. Similar results have been reported in LTED-R cells where titration back of increasing amounts of estradiol resulted in re-growth of cells which fulvestrant was unable to effectively antagonize [15]. These results imply that in endocrine resistant cells fulvestrant may be more effective when combined with continued oestrogen deprivation.

On the basis of these pre-clinical findings with fulvestrant in the presence/absence of estradiol, several phase III clinical trials of fulvestrant are investigating additional roles for fulvestrant in breast cancer therapy, either following prior non-steroidal AI treatment or in combination with AIs as first-line therapy. Two randomised, controlled trials are comparing the efficacy and tolerability of fulvestrant versus exemestane in postmenopausal women progressing after long-term oestrogen deprivation resulting from prior AI therapy. The Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) has assessed the efficacy of fulvestrant versus exemestane in patients who have progressed on treatment with non-steroidal AIs. There have been previous phase II studies which have suggested modest efficacy for exemestane in this setting due to partial non-cross resistance with non-steroidal AIs—hence, exemestane is a valid control arm against which to test the efficacy of fulvestrant following progression on non-steroidal AIs [17]. The primary aim of the UK Study of Faslodex versus Exemestane with/without Arimidex trial (SoFEA) is to compare progression-free survival in patients who have progressed on a non-steroidal AI, and who are subsequently treated with either fulvestrant plus continued anastrozole, or with fulvestrant alone. The major difference, therefore, from EFECT is that randomisation in SoFEA to continued AIs or not with concurrent fulvestrant will test the hypothesis cited above regarding influence of background estradiol levels on the activity of fulvestrant. In addition, two trials (FACT and SWOG 226) are comparing the efficacy of a combination of fulvestrant plus anastrozole with anastrozole alone in the first-line setting. As AIs move forward into the adjuvant setting the results of these trials will help define optimal sequencing of endocrine therapies, and in particular whether fulvestrant should be used alone or in combination with aromatase inhibitors.

4. Integrating HER2 targeted therapies with aromatase inhibitors

Enhanced expression of HER2 and subsequent downstream MAPK activation has been found in breast cancer cells that become resistant over time to endocrine therapy with either tamoxifen or estrogen deprivation. As such treatment with drugs that target HER2 has been investigated in pre-clinical models in an attempt to treat this resistance by blocking these upregulated growth factor pathways. Data have been reported by other groups in tamoxifen-resistant HER2-transfected MCF-7 cells with AG1478, a HER2 tyrosine kinase inhibitor, and with trastuzumab [18,19]. Likewise, use of trastuzumab has been shown to reverse tamoxifen resistance in HER2 transfected breast cancer cells [20]. In the clinical neo-adjuvant setting, primary breast cancers that co-express both ER and HER2 are known to be relatively resistant to tamoxifen, and somewhat more sensitive to aromatase inhibitors [21,22]. Given the increasing evidence for cross-talk between ER and HER2 resulting in endocrine resistance, together with the clinical efficacy and tolerability of trastuzumab, it became logical to examine whether combined trastuzumab and aromatase inhibitors could be more effective than AIs alone in patients with tumours that co-expressed both receptors. A multicentre randomised phase II trial (TAnDEM) was conducted in 207 patients with known