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Review

What clinicians need to know about antioestrogen resistance in breast cancer therapy

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ABSTRACT

Tamoxifen is the drug most used for early breast cancer treatment in oestrogen receptor (ER) positive patients. Unfortunately, despite high ER tumour levels in a tumour, resistance to endocrine therapy, either *de novo* or acquired after prolonged treatment, can occur. In this review, we will try to summarise the postulated mechanisms of hormonal-resistance, namely, the role of co-regulators and the crosstalk between the HER-2, IGF-IR, Cox-2 and ER pathways. Other predictive markers of tamoxifen-resistance/response, such as cyclin E and UPA/PAI-1, are also discussed.

1. Introduction

Tamoxifen has been the drug most widely used for breast cancer treatment. Administered after loco-regional and adjuvant chemotherapy treatment of early breast cancer, it significantly reduces the risk of relapse and death in women with hormone-receptor positive disease. Specifically, 5 years of tamoxifen reduces the annual risk of recurrence and death by 47% and 26%, respectively.[1] In addition, tamoxifen has been shown to reduce the risk of contralateral breast cancer by almost 50%.[2] Tamoxifen is beneficial irrespective of age, nodal and menopausal status. The magnitude of the effect of adjuvant tamoxifen is directly correlated to duration of treatment and to oestrogen receptor (ER) status in the primary tumour, with no effect on ER-negative cancers.[1] Unfortunately, many patients experience resistance to endocrine therapy either *de novo* (at the beginning of the treatment) or acquired (after prolonged use), despite detectable levels of ER in their tumours. Several mechanisms could contribute to the development of this resistant phenotype. These include the following: loss of ER in the tumour; selection of ER mutations; alteration in the intracellular pharmacology and/or

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binding of antioestrogens to breast cancer cells; perturbation of the interactions between ER-coregulatory proteins;[3,4] and crosstalk between the ER and the growth factor receptor pathways [c-erbB2/neu (HER-2) and EGFR and/or their downstream effectors].[5–8] or other pathways, such as IGF-IR[9] and Cox-2.[10] In addition to these already identified mechanisms, the development of tamoxifen resistance is the subject of intense ongoing research, which includes the interaction with other (ER-independent) signalling pathways, such as those driven by protein kinase C (PKC) and oxidative stress.[11,12] The role of the non-genomic effects of tamoxifen, mediated by membrane ER, is also being evaluated. Very recently another pool of ER has been identified in the mitochondria of several cell types including MCF-7 breast cancer cells, and it is thought that oestradiol can act on this ER pool, preventing the activation of the intrinsic mitochondrial death pathway, and thus providing an additional mechanism for cancer cell survival and possibly treatment resistance.[13]

In the last St. Gallen consensus panel, the experts agreed that, rather than focusing on patient's risk of relapse, treatment decisions should first take into account the tumour's 'endocrine responsiveness'. Three categories were defined (endocrine responsive, endocrine response uncertain and endocrine unresponsive) in which any detectable steroid hormone receptor indicates some degree of endocrine responsiveness.[14] This 2005 St. Gallen breast cancer conference also emphasised the importance of the rapid progress made in understanding the biology of the ER function, including the characterisation of a large number of proteins that participate in oestrogen signalling. It is hoped that this knowledge will lead to improved tailoring of effective endocrine therapy, according to ER status and other biological predictive markers. Notwithstanding this progress, nowadays the only predictive markers for endocrine therapy that yield sufficient level of evidence to be recommended for routine clinical practice are the presence and the level of ER and PgR, and to a lesser extent HER-2 status.

A number of alternative endocrine treatments have been developed. These include several selective oestrogen receptor modulators (SERMS) and selective oestrogen receptor down regulators,[15] which compete with oestrogens for binding to ER. Fulvestrant (ICI 182,780) is a specific antioestrogen that binds, blocks and accelerates the degradation of ER protein, leading to complete inhibition of oestrogen signalling through ER. Fulvestrant has no agonist effects,[16,17] contrary to tamoxifen, which has a mixed oestrogen antagonist/agonist effect (Fig. 1). Preclinical studies have demonstrated that a fraction of ER positive, tamoxifen resistant breast tumours are still sensitive to fulvestrant.[18,19] This has been confirmed also in clinical studies.[20,21] Recently, a possible mechanism for this difference has been suggested: resistance to tamoxifen in these breast tumours was mediated by a modification of ER by protein kinase A (PKA), which converted the antagonist tamoxifen into an agonist; consequently tamoxifen's effect on tumour cell growth was reversed, whereas the tumour's sensitivity to fulvestrant remained unaltered.[22] Moreover, recent studies identified differences in the effects of different classes of antioestrogens on cell-cycle arrest. In fact, tamoxifen arrests

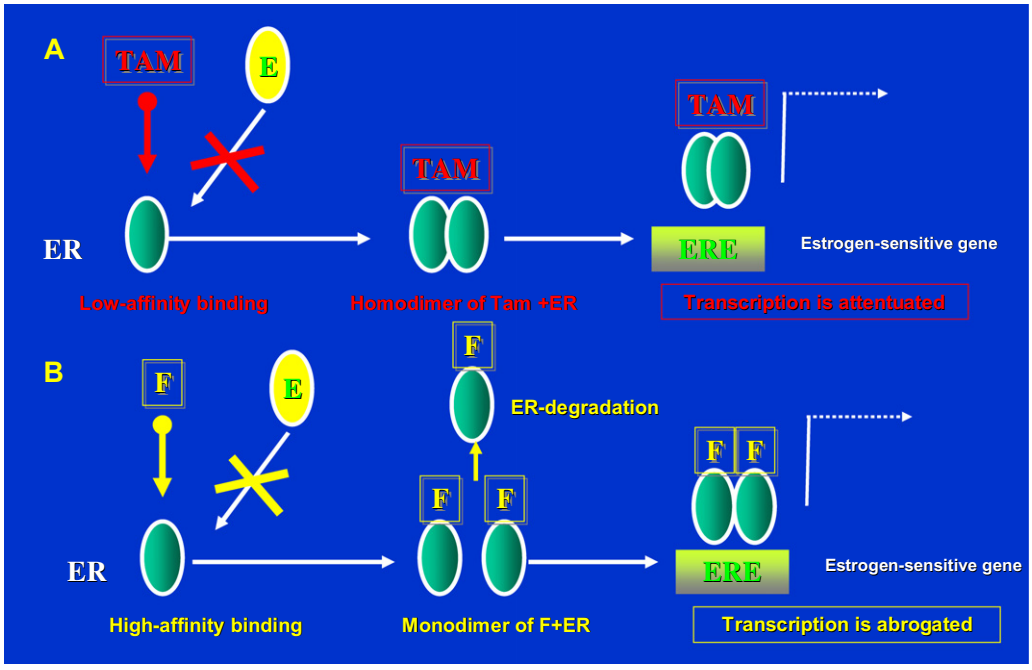

Fig. 1 – This figure shows the difference between tamoxifen and fulvestrant. (A) tamoxifen competes with oestrogen for binding to ER and inhibits the transcription of oestrogen-sensitive genes to a greater or lesser degree depending on the target tissue. Tamoxifen exhibits both oestrogen agonist and antagonist effects; in the breast, it acts primarily as an oestrogen-antagonist, whereas in bone, liver, and in the uterus, it acts predominantly as an oestrogen-agonist. (B) fulvestrant competitively inhibits the binding of oestrogen to ER, prevents dimerisation, promotes ER degradation and prevents transcription of oestrogen-sensitive genes. Fulvestrant is a pure antioestrogen. *ER = oestrogen receptor; E = oestrogen; TAM = tamoxifen; F = fulvestrant; ERE = oestrogen response elements.*