

Inhibition of HER2/estrogen receptor cross-talk, probable relation to prolonged remission of stage IV breast cancer: a case report

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ABSTRACT

Metastatic breast cancer to the liver is considered incurable. Though many patients with liver metastases may enjoy response to chemo-, immuno- and hormonal therapy, those so inflicted rarely remain disease-free from the time of diagnosis for longer than 6-11 months. New laboratory and clinical research identified that cross-talk between activation of the epidermal growth factor family of tyrosine kinase transduction pathways (EGF/HER2) and estrogen receptor (ER) activation plays a role in resistance to hormonal therapy.

A 59-year-old woman with a 4.5-cm invasive ductal, ER-positive/PR-negative, grade III adenocarcinoma of the breast was treated with mastectomy. Staging revealed biopsy-proven liver metastases. Surgery was immediately followed with vinorelbine, trastuzumab, tamoxifen and exemestane. The patient underwent a bone scan and PET/CT documented complete remission. She has remained in complete remission for 7 years.

It is proposed that a possible mechanism for prolonged remission of stage IV breast cancer in this patient may be related to suppression of EGF/HER2 by trastuzumab, thus inhibiting cross-talk-associated tamoxifen/estrogen withdrawal resistance.

Introduction

This report presents a postmenopausal patient with biopsy-proven metastatic breast cancer to the liver who continues to enjoy a 7-year complete response to maintenance therapy with combination trastuzumab, tamoxifen and exemestane. A possible mechanism for prolonged remission duration based on cross-talk between HER2 and estrogen receptor (ER) is presented.

Case report

A 54-year-old Caucasian woman underwent a left mastectomy for a 4.5-cm, grade III infiltrating ductal adenocarcinoma. Immunohistochemistry revealed ER = 10% (positive), progesterone receptor (PR) <5% (reported as negative), HER2 = 3+ (overexpressed), %S phase = 30%, DNA index = 2.3 (hyperdiploid). There was marked lymphovascular invasion and left axillary node dissection revealed 2 of 15 positive nodes, one measuring 1.9 cm, the other 1.3 cm in diameter. PET/CT imaging was positive for 2 right hepatic lobe masses; the largest was 2.5 cm in greatest diameter. A needle biopsy of the larger hepatic mass led to a diagnosis of metastatic adenocarcinoma compatible with breast metastasis. The patient was started on weekly vinorelbine 25 mg/m² plus trastuzumab at an initial dose of 4 mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly. Trastuzumab administration was extended to 6 mg/kg every 3 weeks for 12 months. This was followed by 6 mg/kg every 6 weeks after the initial 2 years. Tamoxifen and exemestane were started after discontinuation of vinorelbine after only 6 weeks of therapy due to a vinorelbine-induced rash.

Key words: cross-talk, epidermal growth factor, HER2, estrogen receptor, breast cancer, liver metastasis, trastuzumab, tamoxifen, exemestane.

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Complete clinical response was confirmed after 2 months from the start of therapy. The patient has remained free of disease for 7 years and receives trastuzumab 6 mg/kg every 6 weeks, tamoxifen 20 mg daily, and exemestane 25 mg daily.

Discussion

Hormonal therapy for ER-positive metastatic breast cancer induces an initially high response rate; however, all patients eventually develop resistance. In the pres-

ence of estrogen, the ER is phosphorylated, changes shape and dimerizes, resulting in recruitment of coactivator molecules such as “augmented in breast cancer protein-1” (AIB-1). Tamoxifen binding to ER induces a distinct receptor conformation leading to ER association with corepressor complexes, such as nuclear corepressor 1 (NCoR1) and NCoR2 (SMRT)¹⁻³; this in turn will lead to suppression of DNA transcription (Figure 1).

Activation of receptor-associated tyrosine kinases through ligand-activated binding of various membrane-associated epidermal growth factor receptors (EGFR, HER2, HER3, HER4) leads to homodimers and

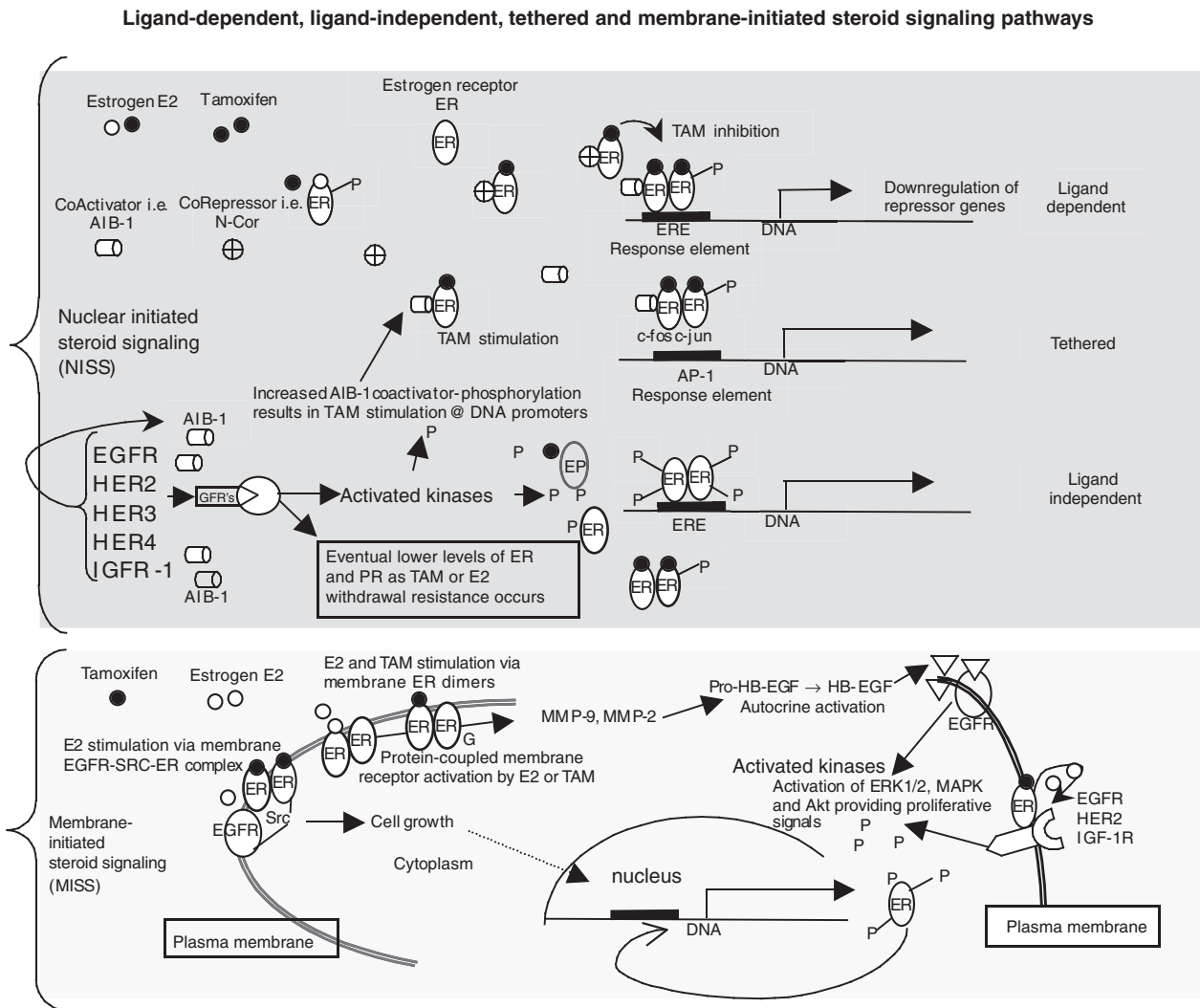


Figure 1 - Tamoxifen (TAM) when complexed with ER and corepressor (i.e., N-cor) induces, by transcription, cell death. However, in the presence of elevated levels of “augmented in breast cancer protein-1” coactivator (AIB-1), TAM-ER becomes stimulatory through transcription. TAM through membrane-associated ER stimulation is stimulatory in part by activation of EGFR. Membrane-associated ER dimers work in concert with G-protein-coupled receptors through matrix metalloproteins producing autocrine stimulation of EGFR by heparin binding-EGF. Membrane ER complex with EGFR and Src responds to E2, inducing cell growth. E2 stimulation of clusters of ER with EGFR, HER2, IGF-1R induces transactivation stimulate kinase activity activating ER by phosphorylation. Upregulation of HER1-4 and insulin-like growth factor-1 receptor (IGFR-1) results in increased tyrosine kinase activity, which leads to direct phosphorylation of ER and activation of transcription through the ligand-independent NISS pathway and to elevated levels of AIB-1.

heterodimers of EGFR/HER(2-4) and first to phosphorylation of receptor-associated kinases followed by sequential activation of downstream intracytoplasmic kinases. Kinase activation can lead to ER phosphorylation, which may change the ER metabolism, resulting in estrogen (E2)-independent activation of ER^{4,6}. Activation of downstream protein kinase pathways is one mechanism of resistance (cross-talk-induced resistance) to tamoxifen and aromatase-induced estrogen withdrawal and in some cases may be associated with tamoxifen stimulation of breast cancer^{7,8}.

In the presence of tamoxifen resistance there is generally augmentation of EGFR/HER2 expression and overexpression of EGFR/HER2 receptors and tyrosine kinase activity⁷. Associated with this are decreased ER and PR levels⁹ with increased levels of coactivator AIB-1¹⁰. Elevated levels of AIB-1 bind to TAM-ER complexes, thus inducing DNA transcription products which support rather than suppress tumor growth¹⁰ (Figure 1).

Activation of cellular kinases may be responsible for phosphorylation of ER itself, thus driving direct, ligand-independent binding of ER to DNA, which will lead to subsequent transcription and tumor cell activation/stimulation. In addition, "tethered" binding of ligand-bound ER to DNA through c-Fos and c-Jun binding via AP-1 response elements may be a product of stimulated tyrosine kinase activity, leading to increased phosphorylation of kinases producing a more aggressive cellular phenotype¹¹.

G-protein-coupled membrane receptors cluster with ER^{12,13}, thus mediating estrogen activation of matrix metalloproteins MMP-2 and MMP-9 via the protooncogene Src, which codes for Src tyrosine kinase. This leads to the generation of pro-HB-EGF (pro form of heparin-binding EGF) and finally HB-EGF, thus inducing transactivation of EGFR. This estrogen-induced autocrine receptor tyrosine kinase signaling leads to intracytoplasmic stimulation of multiple kinase cascades.

The HER2 monoclonal antibody, trastuzumab (Herceptin), is associated with an objective response rate of 25-35% in patients with HER2 overexpressing tumors by immunohistochemistry (3+ positive)¹⁴. The response rate to hormonal therapy in HER2 overexpressing tumors is generally less than for HER2-negative tumors¹⁵. The median duration of response to trastuzumab when combined with vinorelbine is reported to be 10-17.5 months in advanced disease¹⁶.

In light of the cross-talk between EGFR/HER2 and ER there have been several laboratory and clinical studies to thwart or reverse resistance to tamoxifen inhibition and/or estrogen withdrawal by aromatase inhibitors (AIs). Studies employing trastuzumab inhibition of EGR2/HER2 receptor kinase activity and others utilizing various combinations of intracellular tyrosine kinase inhibitors (gefitinib, erlotinib, lapatinib, temsirolimus) revealed evidence of interference of cross-talk-induced resistance. In one clinical study of 10 HER2 overexpressing

and ER/PR-negative breast cancer patients, 3 were found to convert to an ER-positive status after 9, 12, and 37 months of therapy¹⁷. One of these 3 gained PR expression. A study by Mackey *et al.* revealed that trastuzumab prolonged progression-free survival in hormone-dependent and HER2-overexpressing metastatic breast cancer patients¹⁸. Preliminary mouse studies by Arpino *et al.* with multiagent HER2-targeted therapy aimed at receptor-associated tyrosine kinase and intracellular kinase activity was associated with complete disappearance of many transplanted breast tumors. They concluded that a combination of gefitinib, trastuzumab, and pertuzumab blocking all HER2 homo- and heterodimers inhibited growth of HER2-overexpressing xenografts better than single agents and dual combinations¹⁹.

The ATAC study reported less than optimal activity for the combination of tamoxifen and anastrozole when compared to the AI alone²⁰. It was decided, however, to continue this patient on the combination of tamoxifen plus AI because of the early success of therapy. It is possible that the addition of trastuzumab for this patient may have modulated any possible detrimental effect of the addition of tamoxifen to the AI. It is of interest that this patient was considered to be ER positive (only 10% positive cells) while declared by the laboratory to be PR negative (<5% positive cells). Under usual circumstances in the absence of trastuzumab therapy this ER+/PR- patient would be projected to demonstrate poor survival and poor response to hormonal therapy²¹. In spite of this, the patient has done remarkably well and enjoys prolonged complete remission.

It is conjectured that this patient's prolonged complete remission of 7+ years may represent the result of inhibition of EGFR/HER2-ER cross-talk, thus prolonging benefit from hormonal therapy. However, it is also possible – though less likely – that the independent effects of trastuzumab, tamoxifen and exemestane inhibition of tumor growth is responsible as well. It should be noted that the median duration of response to trastuzumab-vinorelbine combination therapy in metastatic disease is 10-17.5 months¹⁶.

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