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Tumour Review

Prognostic relevance of receptor tyrosine kinase expression in breast cancer: A meta-analysis

Arnoud J. Templeton [a,1], Laura Diez-Gonzalez [b,1], Olga Ace [a], Francisco Vera-Badillo [a], Boštjan Šeruga [c], Joaquín Jordán [b], Eitan Amir [a], Atanasio Pandiella [d], Alberto Ocaña [b,*]

[a] Divisions of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Department of Medicine, University of Toronto, Toronto, Canada
[b] Translational Oncology Unit, Albacete University Hospital, Albacete, Spain
[c] Department of Medical Oncology, Institute of Oncology Ljubljana, Slovenia
[d] IBMCC-CSIC, Universidad de Salamanca, Spain

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ABSTRACT

Background: Receptor tyrosine kinases (RTKs) may facilitate tumor progression if activated aberrantly. The prognostic impact of human epidermal growth factor receptor 2 (HER2) overexpression and effectiveness of its therapeutic targeting is well established, but the effects on prognosis of overexpression of other RTKs is unknown. Here we evaluate the association of RTK expression and survival in breast cancer.

Methods: PubMed was searched to identify studies evaluating the association between expression of RTKs other than HER2 and survival of women with breast cancer. Published data were extracted and computed into odds ratios (OR) for death at 5 years with 95% confidence intervals (CI). Data were pooled in a meta-analysis using the Mantel–Haenszel random-effect model. For studies reporting data for more than one RTK the lowest and highest OR were used for separate analyses.

Results: Sixteen studies comprising 11,056 patients were included in the analysis. There was an association between overexpression of RTKs and decreased 5-year OS and this was highly significant when using highest ORs from studies reporting more than one RTK (OR = 2.42; 95% CI = 1.92–3.06, $P < 0.001$). Similar results were observed for 5-year BCSS. Worse OS was seen with overexpression of fibroblast growth factor receptor 2/3 (FGFR) (OR = 3.81; 95% CI = 1.79–8.11) and epidermal growth factor receptor (EGFR)/HER1 (OR = 2.45; 95% CI = 1.90–3.15).

Conclusion: Overexpression of various RTKs is associated with poor outcomes. This data suggests the clinical evaluation of combination of agents against RTKs or relevant oncogenic nodes.

Background

Receptor tyrosine kinases (RTKs) are trans-membrane proteins with a C-terminal cytoplasmic catalytic domain and an N-terminal extracellular domain that binds activating ligands [1]. Phosphorylation of the cytoplasmic domain is usually required for initiation of signal transduction [2].

Deregulation of several RTKs has been linked to the pathophysiology of human tumors including breast, lung or colon cancer [1]. Mechanisms associated with their pathologic activation include: structural change (e.g. point mutations or protein truncations), amplification of the gene leading to protein overexpression, or activation by ligands [1,3–5]. Lack of regulatory mechanisms due to loss of phosphatases can also be involved in their activation [5–7].

Because of their potential role in the genesis/progression of several tumors, RTKs represent potential therapeutic targets and different strategies have been developed to inhibit their function. These include small kinase inhibitors that compete at their kinase domain and antibodies that bind to the extracellular region of the kinase receptor. In addition, targeting of ligands with antibodies or traps is another therapeutic option under evaluation [8,9] (Fig. 1).

In breast cancer, overexpression of the human epidermal growth factor receptor 2 (HER2) due to gene amplification is associated with poor prognosis [10–13] and the effectiveness of its therapeutic targeting with trastuzumab and other agents is well established [14,15]. Other RTKs are also potential therapeutic

* Corresponding author. Address: Medical Oncology Department and Translational Research Unit, Albacete University Hospital, Edificio de Investigación, Calle Francisco Javier de Moya, 02006 Albacete, Spain. Tel.: +34 967 59 71 00x37087; fax: +34 967 59 71 73.
E-mail address: albertoo@sescam.jccm.es (A. Ocaña).
[1] Equal credit.

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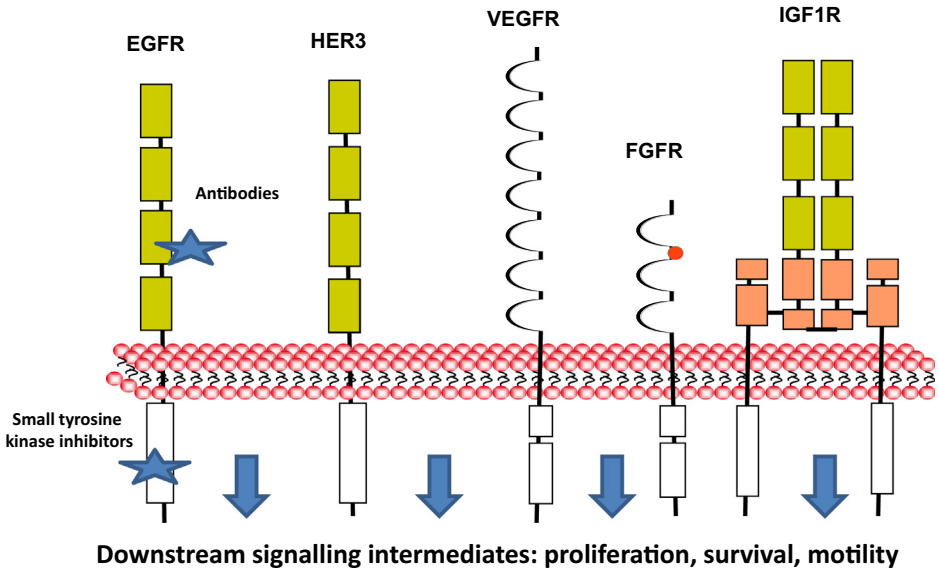

Fig. 1. Representation of tyrosine kinase receptors.

targets. For example, expression of the epidermal growth factor receptor (EGFR, also known as HER1) and fibroblast growth factor receptor (FGFR) has been described in breast tumors and is associated with a more aggressive phenotype and with relative resistance to treatment [16,17]. Strategies aiming to neutralize the function of RTKs have therefore been explored.

Compared to activation of a single protein, concomitant activation of multiple protein kinases has been linked with a more aggressive phenotype in laboratory models, suggesting that inhibition of several RTKs will produce a higher antitumor effect than single inhibition [18,19]. Consequently, drugs like nintedanib which targets vascular endothelial growth factor receptor (VEGFR) and FGFR [20,21] or vandetanib which targets both VEGFR and EGFR [22] are in clinical development. In addition targeting of other receptors like c-Met are currently under evaluation [1].

Here we aim to evaluate the association of RTK expression and outcome in breast cancer. We hypothesized that expression of several RTK is linked to worse outcome with the implication that combined targeted strategies should be pursued for clinical development.

Methods

This analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [23].

Data sources and searches

Medline (Host: PubMed) was searched for studies published between June 2000 and June 2013, which evaluated the expression of RTKs in breast cancer. We used the MeSH terms "breast cancer" and the most frequent RTKs described in breast cancer including Vascular Endothelial Growth Factor Receptor 1, 2 and 3 (VEGF R1, VEGF R2, VEGF R3), C-ret, Macrophage Colony-stimulating factor (M-CSF R), Fit-3, c-KIT, Platelet Derived Growth Factor Receptor (PDGF R), c-Met, MSP R, Insulin-like Growth Factor I Receptor (IGF-IR), Insulin R, Fibroblast Growth Factor Receptor 1, 2, 3 and 4 (FGF R1, FGF R2, FGF R3, FGF R4), Human Epidermal Growth Factor Receptor 1, 2, 3 and 4 (HER1, HER 3, HER4), and Epidermal Growth Factor Receptor (EGFR); and adding the limitation of human studies and publications in English. In these searches we also included kinase signaling intermediates like Stat 1, Stat 3, Src, Erk 1/2, Akt S473, Akt T308, to identify additional studies evaluating RTK activities that could be included in the analyses. Studies evaluating only HER2 were not included as the association of this protein with poor outcome is well established. Additional studies were identified through citation lists.

Study selection and data extraction

Two reviewers (LDG, AO) evaluated independently all the titles identified by the search strategy. The results were then pooled and all potentially relevant publications retrieved in full and assessed for eligibility. Disagreement was resolved by consensus.

Inclusion criteria for studies were: (i) reporting of differential expression of RTKs in breast cancer by immunohistochemistry (IHC) (studies using other assays were excluded to maintain homogeneity) and (ii) availability of Kaplan Meier (KM) survival curves with at least 60 months on the time axis. Studies reporting outcome of patients who had received a targeted agent directed against these RTKs were excluded as were studies reporting only disease free survival. KM curves for overall survival (OS) were preferred but if not available, KM curves for breast cancer specific survival (BCSS) was captured and analyzed separately.

The following information was captured using data abstraction forms: First author, year of publication, RTKs studied, number of patients, age of patients, proportion of patients with estrogen receptor (ER) expression, progesterone receptor (PR) expression, HER2/neu overexpression, histological grade tumors, metastatic disease, as well as the duration of follow-up, methods used for the evaluation of RTK, and cut-off used for defining overexpression. Survival data were estimated from Kaplan–Meier curves independently by two authors (AT, LDG) and disagreement was resolved by consensus.

Data synthesis and statistical analyses

The primary outcome was the probability of survival at five years. Proportion of patients surviving 5 years was estimated from the Kaplan–Meier curves for both patients without (control group) and with RTK overexpression in their primary tumors (experimental group). The relative frequency of survival at 5 years between