Trastuzumab in metastatic breast cancer

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Summary

Metastatic breast cancer is an incurable disease in a very high percentage of patients. Despite new progress in endocrine and other systemic therapies, this evidence remains challenging for patients and clinicians. HER2 protein is a member of the epidermal growth factor family of transmembrane receptors. HER2 is overexpressed in approximately 20% to 30% of breast cancers. Overexpression of HER2 has been shown to be associated with increased tumor proliferation and relative resistance to some types of chemotherapy and hormonal therapies. Trastuzumab, a humanized monoclonal antibody directed against HER2 protein, has been shown to be an efficacious and well tolerated treatment for HER2-overexpressing metastatic breast cancer, both as a single agent and when it is used in combination with chemotherapy.

Key words: Metastatic breast cancer; Trastuzumab; HER2.

Introduction

In the end of '80s it was found that proto-oncogene HER2 was involved in the development of breast cancer [1]. This gene product (HER2/erb B-2 protein) is a member of the tyrosine-kinase receptor family of EGF. In absence of growth factors the receptor is in a monomeric form and enzymatically inactive. When EGF binds to the extracellular domain it induces receptor dimerization and then the activation of a catalytic tyrosin-kinase site [2].

Autophosphorylation allows the receptor to bind and phosphorylate target proteins. Thus activated target proteins induce cellular growth and differentiation via a group of failing processes, one of which has a pleiotropic effect on cytoskeletric organization, cellular motility, cellular adhesivity and protease expression. Many mechanisms can induce proto-oncogene HER2 persistent transformation in an oncogene, which causes cancer [3]:

– Genomic remodelling resulting in fusion between the tyrosine-kinase domain and another protein that induces constitutive receptor activation;
– Small delections in the cytoplasmatic domain of receptor;
– Receptor overexpression and/or gene amplification;
– Loss of normal regulation systems of kinase activation.

HER2 amplification is associated with increasing neoangiogenesis, a process that probably contributes to metastatic ability enhancement. It seems that neoangiogenesis is mediated by vascular endothelium growth factor overexpression. The receptor, codified by gene HER2 (localized on cromosome 17), is overexpressed in 20-30% of breast cancers. HER2 overxpression has been shown to be associated with increased tumor proliferation and relative resistance to some types of chemotherapy and hormonal therapies [4, 5].

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HER2 detection

Several techniques have been used in the past and are still used today to detect gene HER2 amplification (Southern blotting, polymerase chain reaction [PCR], chromogenic in-situ hybridization [CISH], fluorescence in situ hybridization [FISH], Nothern blotting) or to detect modified receptor overexpression (Western blotting, enzyme-linked immunoabsorption assay [ELISA], immunohistochemistryl [IHC]). The most used tecniques are immunohistochemistry and FISH which respectivelly individuate protein HER2 overexpression and gene amplification. At the present time, FISH needs particular support not always present in hospitals; for this reason the method could be considered impratical for routine use and is generally limited to the research laboratory alone. Published studies have shown that there is usually a high grade of concordance between immunohistochemestry and FISH, except for results with a score of 2+ at immunohistochemistry [6-8]. Samples with a score of 0 or 1+ at immunohistochemistry must be considered negative for HER2, while those with a score of 3+ must be considered positive. In 10-15% of cases the score resulting from immunohistochemistry is of 2+ and then FISH is necessary to confirm positivity. It has been discussed whether HER-2 expression should be systematically valued on primitive tumors at the time of diagnosis or on primitive tumors at second look or on metastasis.

The ASCO (American Society of Clinical Oncology) recommends detection of HER2 expression in each patient with primitive breast cancer both at the moment of diagnosis and at the time of disease recurrence in order to identify patients with metastatic breast cancer that can be treated with trastuzumab [9].

Trastuzumab

Trastuzumab is a monoclonal chimeric anti-HER2 antibody (Mab), IgG1, produced by mammalian cellular lines (ovarian cells of Chinese hamsters).

This immunoglobulinic molecule binds the extracellular domain of the HER2 receptor and represents the founder of a series of drugs called "intelligent"; differently from classic chemotherapic agents these drugs act selectively on neoplastic cells interacting with molecular targets expressed exclusively or prevalently by tumoral cells.

Trastuzumab use was approved in the USA in 1998 and today this drug plays an important part in the treatment of metastatic breast cancers with HER2 overexpression. Further recent evidence suggests the use of this monoclonal antibody in the neoadjuvant and also adjuvant setting.

Trastuzumab is generally well tolerated. Hypersensibility reactions are always limited to the first administrations of the drug or to the period immediately following. These reactions can be severe and include: infusional reactions, like an allergic response, and pulmonary toxicities. Patients with resting dyspnea, due to complications of advanced disease and comorbility, could be exposed to an increased risk of infusional reactions with a fatal outcome. The most important infusional adverse reactions of Trastuzumab are dyspnea, hypotension, bronchospasm, tachycardia, reduction in O^2 saturation, anaphylaxis, urticaria and angioedema. The majority of these events occur two and a half hours after the first infusion. If an infusional reaction occurs, Trastuzumab infusion must be stopped and the patient should be monitored until symptoms resolve. In very rare cases these events have occurred six hours after infusion. Hematological toxicity is uncommon, while anemia and leucopenia can sometimes be present in patients treated with a combination trastuzumab-chemotherapy. Diarrhea has occurred in some patients, otherwise cardiotoxicity represents the most important collateral effect. It is possible to hypothesize several mechanisms which can cause cardiotoxicity [10]:

– Trastuzumab, binding HER2 protein (expressed on myocardial cells), could be able to induce this protein to agglomerate in homodimeric compounds, thus causing aberrant signal transduction;

– Trastuzumab, binding HER2 protein, may interfer with neuregulin receptor activity which regulates calcium ion flow and the activity of proteins deputed to ionic transport on endoplasmatic reticulum.

HER2 receptors seem to have a critical role in regulation of the structure/function of myocardic cells, because small mutations in HER2 signalling are not tolerated.

Cardiotoxicity development depends on the capability of anti-HER2 antibodies of binding or activating HER2 receptors. Considering that cardiotoxicity does not occur in all patients treated with trastuzumab, it probably has a multifactorial genesis:

– A specific mutation in the germinal cells of ErbB2 receptor or its partner ErbB4, or of another protein involved in neuregulin synthesis could induce HER2 myocardial receptors to bind to trastuzumab and become active;

– ErbB2 expression is probably dynamically modulated in cardiovascular disease. Lee *et al.* [11] have shown ErbB2 expression increases in ventricular hypertrophy;

– Previous treatment with anthracyclines (myocardial damage produced by anthracyclines for oxidative stress and energetic metabolism alterations) can cause HER2 over-regulation in myocardial cells. This fact could explain the synergic effect of trastuzumab and anthracyclines.

Cobleigh *et al.* used trastuzumab [12] in monotherapy in second-third line treatment of 222 women affected by metastatic breast cancer, HER2+ and heavily pretreated with chemotherapy. This phase II study showed a total percentage of response of 15% with eight complete clinical responses and 26 partial responses. The same authors [13], using trastuzumab in monochemotherapy as first-line treatment, obtained an increase in objective responses (RR = 26% vs 15%) and survival rates and increased survival in comparison with the same regimes used as second- and third-line treatment. Therefore this study showed that monotherapy with trastuzumab represents a valid and innovative treatment for first-line chemotherapy in metastatic breast cancer with HER-2 overexpression.

Trastuzumab combined with different schedules of chemotherapy is a new alternative and attractive approach in the medical treatment of metastatic breast cancer. When trastuzumab is associated with chemotherapeutic agents, the efficacy is incremented in case of HER2 overexpression [14]. In consideration of the results obtained with a trastuzumab-paclitaxel regimen, new combinations of trastuzumab and chemotherapic agents are today under investigation. The spectrum of possible combinations is wide since there are several active drugs in metastatic breast cancer: vinorelbine, docetaxel, liposomal anthracyclines and 5-fluorouracil derivates such as capecitabine [14].

A combination of trastuzumab and vinorelbin has shown significant and synergic activity [15]. Vinorelbin seems to be the best candidate for a trastuzumab association considering that it is a manageable drug and generally not cardiotoxic.

Burstein *et al.* conducted a phase II study [16] on 40 treated patients with a trastuzumab-vinorelbin combination (25 mg/mq weekly); of these patients 82% had been pretreated with chemotherapy. A global response of 75% was observed. The response rate (RR) reached 84% in patients treated with this pharmacological combination as first-line treatment for metastatic breast cancer. The RR was also significant in those patients who received first-line treatment with anthracyclines (RR = 88%), with taxane (RR = 50%), or with a combination of two drugs (RR = 73%). Neutropenia G3-4 was observed in 43% of patients and only one case of severe febrile neutropenia was detected.

Jahanzed *et al.* have recently confirmed the results obtained by Burstain *et al.* On 40 non-pretreated patients with metastatic breast cancer, a RR of 78% was obtained, with 11% complete responses and 68% partial responses. Cardiotoxicity was not significant, while neutropenia G3-4 was observed in 9% of patients.

Some studies have shown that a trastuzumab-taxane combination is very active in HER2+ metastatic breast cancer and well tolerated.

Seidman *et al.* [17], in a study conducted on a subset of pretreated patients with MBC that did or did not express HER2, analyzed the efficacy of a weekly administration of trastuzumab-paclitaxel association. Treatment was well tolerated. No cardiotoxicity G4 was present. RR was 83% in patients with HER2 overexpression and 45% in HER2 absence.

In a phase II study conducted by Uber *et al.* [18, 19] patients with HER2-overexpressing metastatic breast cancer received weekly administration, as first-and second-line treatment, of a trastuzumab-docetaxel association (35 mg/mq); a RR of 63% was observed. In another study, Burris [19] analyzed the efficacy of this association (75 mg/mq of docetaxel each 21days + trastuzumab weekly). RR was 45% with one complete response and six partial responses in a total of 16 patients.

In vivo studies showed that capecitabine and trastuzumab have an additional effect. Two small studies [21, 22] have analyzed the efficacy of this pharmacological association. In one of these reports the schedule with capecitabine (1125 mg/mq) showed a percentage of response of 62% (9/13 patients). In the second study a dose of 1000 mg/mq of capecitabine was administered obtaining a percentage of response of 53%.

Because of the growing availability of new active drugs in the combined treatment of metastatic breast cancer, it appears mandatory to investigate these novel agents in combination with this monoclonal antibody. Moreover trastuzumab has to be used more extensively in association with other molecular targeted agents (gefitinib, bevacizumab) in order to kill neoplastic cells by using drugs with different antineoplastic sites of action.

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