Trastuzumab (Herceptin) in the treatment of breast cancer with HER2 overexpression

Joel M. Salazar Cavazos, Juan Francisco González Guerrero, William O. Brito Villanueva, Joan Albanell Mestres and José M. Baselga Torres

HER2 is a 185 kDa transmembrane receptor with tyrosine kinase activity encoded by the HER2/neu gene. HER2 is overexpressed in 25%-30% of breast cancer and confers an aggressive clinical course. Trastuzumab (Herceptin) is a monoclonal antibody directed against HER2 receptor that has a favorable toxicity profile and produces responses as a single agent in women with metastatic breast cancer with HER2 overexpression. A multicenter phase III trial in HER2 positive metastatic breast cancer, compared first line chemotherapy with adriamycin/cyclophosphamide or paclitaxel alone or the same chemotherapy plus trastuzumab. Response rate, duration of response and time to progression, were better with the combination. Remarkably, overall survival was significantly improved in patients with trastuzumab and chemotherapy. These studies led to the approval of trastuzumab for HER2 positive metastatic breast cancer. Ongoing trials are analyzing new combinations of trastuzumab and chemotherapy or hormonal therapy. The role of trastuzumab in adjuvant and neoadjuvant therapy is also under investigation.

Key words: Breast cancer, trastuzumab, herceptin, HER2.
gands, a transmembrane lypophilic segment, and an intracellular domain with intrinsic tyrosine kinase activity that has a terminal carboxyl (Fig. 1). HER3, however, is different from the other members of the family since it has a faulty tyrosine kinase segment.

The receptors of this family are activated by dimerization that can be between identical receptors (homodimerization) or between different members of the same family (heterodimerization) (Fig. 1). The mechanisms that cause the dimerization are the binding by ligands (growth factors), the overexpression of the receptor and the transactivation by another receptor. The most important receptor within the family is the HER2. This is the only member for which there is no known specific ligand; however, it is the preferred co-receptor to form dimers with EGFR, HER3 or HER4. The heterodimers between HER2 and the other receptors show a greater capacity for translating mitogenic signals than the homodimers and they are synergetic for cellular transformation. HER2 is considered the main coordinator of the signaling network activated by the ErbB family receptors. When the receptors dimerize, their tyrosine kinase activity is triggered and specific tyrosine residuals of the intracellular domain autophosphorylate. These events cause the activation of a series of biochemical and physiological responses involved in the transduction of cellular mitogenic signals.

HER2 is overexpressed at low levels in many normal tissues, in the mammary gland; it regulates growth, differentiation and cell survival. HER2 is overexpressed at high levels (overexpression) in 25%-30% of human breast cancers. A series of observations support the concept that the overexpression of HER2 plays a direct role in the pathogenesis and clinical aggressiveness of tumors: a) the introduction of HER2 in healthy cells cause malignant transformation; b) transgenic mice that express HER2 develop breast tumors; c) the human breast tumors that over-express HER2 have a more aggressive clinical course, and d) the monoclonal antibodies (MoAb) directed against HER2, inhibit the growth of tumors that express high levels of this receptor. These observations make us consider that HER2 is a potential target for the treatment of those breast cancers that over-express it.

TRASTUZUMAB AS A SINGLE AGENT

Preclinical studies of trastuzumab as a single agent

Based on the hypothesis mentioned before, the Genetech company produced a series of murine monoclonal antibodies (MoAb) directed against HER2, some of these antibodies inhibit the proliferation of breast and ovary tumoral cell cultures that over-express HER2. The first studies showed a correlation between a higher level of HER2 receptor expression and a greater sensitivity to the antiproliferative effects of these antibodies. The MoAb did not inhibit the cell lines from breast carcinoma with a low expression of HER2. The SK-BR-3 and BT-474 lines that are those that express the highest levels of HER2, were the most sensitive to the antiproliferative effects (70% inhibition). The MoAb were also capable of inhibiting the growth of cellular lines of ovary, stomach and lung cancer that over-express HER2. One of the most potent MoAb denominated 4D5, was selected to be used in the treatment of patients. Since the murine Ab are limited clinically because they are immunogenic and this can hinder their repeated administration, the 4D5 antibody was humanized by genetic engineering. The resultant recombinant MoAb antiHER2 is called trastuzumab (Herceptin). Trastuzumab has a greater affinity for HER2 (Kd = 0.1 nM) than the murine MoAb 4D5 and it inhibits the growth of breast cancer cells that over-express HER2. Also, trastuzumab is more efficient in inducing cellular cytotoxicity dependent of antibody against human tumoral cellular lines in the