Editorial

Combined anti-EGF receptor and anti-HER2 receptor therapy in breast cancer: a promising strategy ready for clinical testing

Human breast carcinomas frequently co-express the epidermal growth factor (EGF) receptor and the other three members of the EGF receptor family (HER2, -3 and -4). These receptors are composed of an extracellular binding domain, a transmembrane lipophilic segment, and an intracellular protein tyrosine kinase domain with a regulatory carboxyl terminal segment. Upon ligand binding, these receptors form homo/heterodimers and activate downstream signaling pathways involved in cell proliferation and survival such as the Ras/Raf/ MAPK and the PI3-K/Akt pathways, (for review see Yarden and Sliwkowski 2001 [1]). There is strong evidence that at least two of these receptors, the EGF receptor and HER2, play a role in breast cancer as they are frequently overexpressed and their overexpression confers a more aggressive clinical behavior [2–4]. Furthermore, emerging anti-HER2 and anti-EGF receptor therapies are showing promising activity in the clinical setting. Trastuzumab (Herceptin®), a humanized monoclonal antibody directed at the HER2 has shown activity in HER2 overexpressing metastatic breast carcinomas [5–7], and enhances survival when given in combination with chemotherapy [8]. Similarly, early studies with anti-EGF receptor monoclonal antibodies (MAbs) and small molecule inhibitors of the EGF receptor tyrosine kinase (EGF receptor TKIs) have shown clinical activity in a variety of EGF receptor expressing epithelial tumors [9].

Since the early days of oncology one of the prevailing principles of cancer therapy has been the combined use of active chemotherapeutic agents (combination polychemotherapy). As these new anti-EGF receptor-family agents are being brought into the clinic, great effort will be aimed at increasing their antitumor activity by using them in combination with other agents. In this regard, the antitumor activity of conventional chemotherapy and radiation therapy has been enhanced markedly by the addition of anti-HER2 MAbs, anti-EGF receptor MAbs and EGF receptor TKIs [8, 10–12]. The elegant article by Normanno et al. in this issue of Annals of Oncology goes one step further by analyzing whether a combination of an anti-HER2 MAb and an EGF receptor TKI does result in enhanced antitumor activity [13].

The rationale for targeting simultaneously the two receptors stems from their frequent co-expression in breast cancer and from their capacity to form heterodimers that activate signal transduction pathways [1]. In the laboratory, the combinatorial use of anti-EGF receptor and anti-HER2 MAbs results in additive anti-proliferative effects, which are accompanied by enhanced G1 cell distribution, a greater increase in the level of p27Kip1 and a greater decrease in the activities of CDK kinases [14]. In the current study by Normanno et al. a combinatorial approach was undertaken with trastuzumab and ZD1839 (Iressa), an orally bioavailable highly specific and potent inhibitor of the EGF receptor TKIs which requires a dose almost 200-fold higher to inhibit HER2 [9]. The combined therapy was studied in two breast carcinoma cell lines, SKBR3 and BT-474, which express high levels of HER2 and have a lower number of EGF receptors. Their findings were that the combined treatment was synergistic in vitro and apoptosis was markedly enhanced when trastuzumab and ZD1839 were given together when compared with trastuzumab alone (no apoptosis) or with ZD1839 alone. Interestingly, these two agents had different effects on the inhibition of p42/p44 MAPK and Akt phosphorylation, while ZD1839, but not trastuzumab, inhibited EGF receptor and HER2 receptor phosphorylation. It is also of interest that ZD1839 treatment did not result in receptor downregulation, while trastuzumab is known to be a potent inducer of HER2 receptor downregulation [15]. Therefore, it is likely that these two agents, in addition to targeting different receptors, may also exert their activity by different and non-overlapping mechanisms.

The findings of Normanno et al. are complemented by recent findings of at least two additional groups, including ours [16, 17]. Moulder et al. analyzed whether the HER2 constitutive activation that occurs in breast cancer could be the result of transactivation by the EGF receptor. This is a distinct possibility since HER2 is a ligand-less receptor and, as mentioned, both the EGF receptor and HER2 are frequently co-expressed in breast cancer. To test this possibility, they examined the effects of ZD1839 against a panel of HER2-overexpressing human breast tumor lines. They observed that treatment of these breast carcinoma cell lines with ZD1839 resulted in inhibition of HER2 phosphorylation and growth, and that these effects were probably mediated by inhibition of the EGF receptor. The combined therapy with the anti-HER2 receptor monoclonal trastuzumab and ZD1839 also resulted in a marked apoptotic effect and enhanced antitumor activity both in vitro and in BT474 human breast carcinoma xenografts in nude mice. In the study by Anido et al. [17], it was demonstrated that ZD1839 was capable of preventing Heregulin (a ligand that only binds to HER3 and HER4) -mediated activation of HER2, and a profound apoptotic effect was also observed for the combination of ZD1839 and trastuzumab.
Taken together, these data suggest that inhibition of the EGF receptor TKIs prevents HER2 activation in vivo in breast cancer.

In summary, the findings of Normanno et al. provide a strong rationale for studying the combination of ZD1839 and trastuzumab in the clinic, and clinical trials are already ongoing in patients with advanced breast cancer. As with trastuzumab, several issues will only be addressed in carefully planned and executed clinical trials. In addition to choosing clinically meaningful endpoints to assess efficacy and to monitor safety, the most burning question would appear to be how to select the patients that may benefit from the combined therapy? Ideally, the levels of EGF receptor and HER2 receptor expression would have to be prospectively analyzed in order to be able to establish correlations between receptor expression profiles and benefit from therapy. Furthermore, taking into consideration the richly interactive network of downstream signaling triggered by these two receptors, a major effort will have to be directed at identifying additional molecular markers that are predictive of a response to the combination. Other important questions that will need addressing will be the optimal dosages of each of these compounds when given in combination and whether this combination will be active in other tumor types in addition to breast cancer. While we eagerly await the results of these clinical trials, it would seem logical to continue to explore in pre-clinical models the antitumor activity of combination therapy with targeted agents against growth factor receptor and downstream signaling molecules.

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References