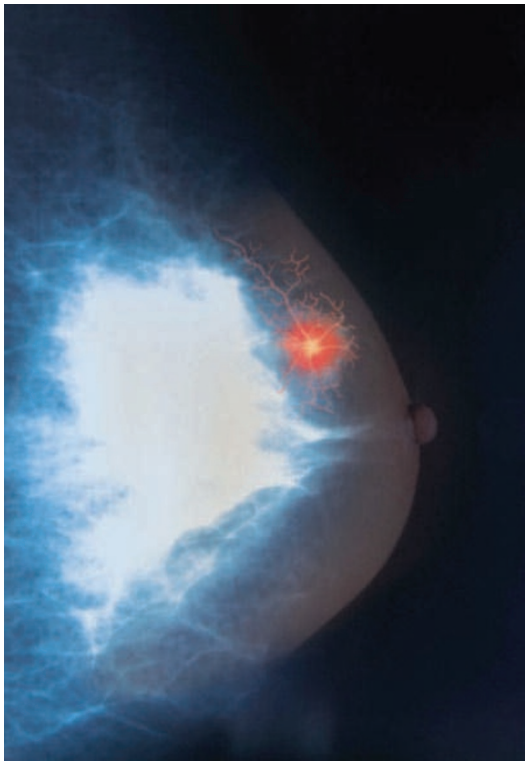
MEDICAL ONCOLOGY

New insight into lapatinib



Human epidermal growth factor receptor 2 (HER2) is overexpressed in 25–30% of human breast tumors and this overexpression is associated with a malignant phenotype and worse prognosis. The HER2 tyrosine kinase inhibitor, lapatinib, has shown clinical benefit in human breast cancers that overexpress HER2. Trastuzumab, a humanized monoclonal antibody directed at the extracellular domain of HER2, is also active in the same group of patients with breast cancer. Proposed mechanisms of action of trastuzumab include receptor downregulation, cell-cycle arrest, inhibition of angiogenesis and induction of antibody-dependent cell-mediated cytotoxicity. Despite the activity of lapatinib and trastuzumab, many HER2-positive tumors are resistant to these agents. Delivering these two agents in combination can decrease resistance, and a phase III trial has shown improved clinical outcome with a combination of lapatinib and trastuzumab compared with lapatinib alone. Scaltriti *et al.* explored the differences between the mechanism of action of lapatinib and trastuzumab to try to understand the reason for the increased activity of the combination.

Treatment with lapatinib resulted in increased levels of HER2 at the cell surface. The researchers evaluated the degree of receptor ubiquitination in cells with lapatinib-induced HER2 accumulation and found that in cells treated with laptinib alone or in combination with trastuzumab, the levels of ubiquinated receptor were barely detectable. The researchers used a time-course experiment to determine the turnover rate of HER2 in cells treated with either agent alone or in combination. Cells treated with lapatinib alone or in combination with trastuzumab demonstrated clear HER2 stability with high levels remaining for up to 48 h, compared with untreated cells or those treated only with trastuzumab. Treatment with trastuzumab, however, resulted in increased HER2 ubiquitination and degradation compared with untreated cells. Scaltriti *et al.* showed that laptinib has a higher affinity for HER2 monomers than for EGFR monomers, and a higher affinity than ATP for HER2 monomers. Lapatinib causes increased stability of the HER2 dimers. The researchers investigated the effects of lapatinib and trastuzumab on BT474 xenografts and showed that both agents caused tumor regression. All mice that received the combination achieved complete tumor regression after 10 days of treatment. HER2 expression was increased in tumors treated with lapatinib alone and decreased in tumors treated with trastuzumab. The accumulation of HER2 by lapatinib was also shown to significantly increase trastuzumab-dependent cell cytotoxicity—cells with high HER2 expression experienced higher trastuzumab-mediated cytolysis.

The results of this study suggest a new mechanism of action for the combination of trastuzumab and laptinib that should be further investigated in clinical trials. The authors added "Our results provide a new explanation for the enhanced effects of the combination of lapatinib and trastuzumab." The mechanism involves lapatinib reducing HER2 ubiquitination, preventing degradation, and inducing the formation of inactive HER2 dimers at the cell surface. This provides an increase in trastuzumab binding and a bigger trastuzumab-mediated immune response.

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Original article Scaltriti, M. *et al.* Lapatinib, a HER2 tyrosine kinase inhibitor, induces stabilization and accumulation of HER2 and potentiates trastuzumab-dependent cell cytotoxicty. *Oncogene* **28**, 803–814 (2009).