TARGETED THERAPIES

Lapatinib is effective in patients with p95HER2-positive tumors

Overexpression of HER2 occurs in approximately 20% of human breast cancers and is associated with a poor prognosis. Although the anti-HER2 monoclonal antibody trastuzumab has improved survival outcomes, treatment resistance remains a challenge. Trastuzumab resistance is partly explained by the coexpression of p95HER2, a truncated receptor fragment of HER2 that retains kinase activity but lacks the extracellular binding domain. p95HER2 is expressed in 30% of HER2-positive breast cancers and is associated with a reduced disease-free survival.

> “...Lapatinib...may be a preferred therapeutic option for p95HER2 tumors”

Scaltriti and coauthors have previously shown that tumor xenografts expressing p95HER2 were not inhibited by trastuzumab, and that patients with p95HER2 tumors did not respond to the drug. Lapatinib targets the intracellular ATP binding site of HER1 and HER2. Cells that express p95HER2 are sensitive to lapatinib, so Scaltriti's team tested whether it might be active in patients with p95HER2-positive tumors. First they studied the antitumor activity of lapatinib in two animal models and then assessed the relationship between p95HER2 expression and lapatinib response in women with HER2-positive tumors who were treated with lapatinib monotherapy or lapatinib and capecitabine.

Lapatinib substantially reduced tumor growth in mice with mammary tumors refractory to trastuzumab. Moreover, phosphorylation and activation of p95HER2 was downregulated after lapatinib treatment. Progression-free survival and overall response rates were assessed in lapatinib-treated patients who were stratified according to p95HER2 status. There was no significant difference in outcomes between patients with p95HER2-positive or p95HER2-negative tumors, regardless of lapatinib monotherapy or combined treatment.

“Our results suggest that lapatinib, as well as other tyrosine kinase inhibitors, may be a preferred therapeutic option for [p95HER2] tumors. Hence the presence of p95HER2 could determine the choice of anti-HER2 therapy if the results are further validated” concludes Scaltriti. Jose Baselga, senior investigator comments “The correlation between p95HER2 and response to lapatinib will be prospectively analyzed in a clinical study restricted to patients with p95HER2 tumors where trastuzumab will be compared to lapatinib. Furthermore, p95HER2 is also being analyzed in the neadjuvant and adjuvant studies NeoALTTO and ALTTO.”

Lisa Hutchinson

Original article Scaltriti, M. *et al*. Clinical benefit of lapatinib-based therapy in patients with human epidermal growth factor receptor-2–positive breast tumors coexpressing the truncated p95HER2 receptor. *Clin. Cancer Res.* **16**, 2688–2695 (2010)