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Lapatinib

A Viewpoint by Gottfried E. Konecny

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The convergence of preclinical science (identification of the biological role of human epidermal receptor [HER] 2), novel biotechnology (development of a humanised monoclonal antibody) and new translational research strategies (development of preclinical models and rational clinical study design) led to the development and availability of trastuzumab as the first monoclonal antibody that has been shown to prolong life in patients with a human epithelial malignancy (reviewed by Hudis[1]). However, more recent advances in biotechnology have led to the development of the oral dual tyrosine kinase inhibitor lapatinib, which has been shown to have significant activity in trastuzumab-refractory breast cancer.[2]

The small inhibitor molecule lapatinib may have the following therapeutic advantages over the recombinant humanised monoclonal antibody trastuzumab: (i) in preclinical experiments, unlike trastuzumab, lapatinib has demonstrated phosphatase and tensin homologue deleted on chromosome 10 (PTEN)-independent activity (this may be particularly important as preliminary data indicate that PTEN deficiency may play an important role in trastuzumab resistance);[3] (ii) lapatinib appears to be a stronger inducer of tumour cell apoptosis compared with trastuzumab in preclinical experiments;[4] (iii) lapatinib can inhibit the truncated form of the HER2 receptor (p95HER2); and (iv) its small molecular weight promises higher activity in CNS lesions. Furthermore, lapatinib has the additional capacity to inhibit the epidermal growth factor receptor (EGFR), which may form heterodimers with HER2. These findings may help to explain the lack of cross resistance with trastuzumab.

However, all of these effects have merely been demonstrated in preclinical experiments and have yet to be validated in clinical trials. Some of the most important questions that are currently being investigated are: Will lapatinib be more active than trastuzumab? Will it be more beneficial in combination with trastuzumab or following trastuzumab treatment? How long should patients receive lapatinib? Will it be less cardiotoxic than trastuzumab when given in combination with anthracyclines? Will lapatinib treatment achieve clinically meaningful responses in patients with CNS metastases?

A recent trial compared paclitaxel monotherapy with paclitaxel plus lapatinib as a first-line treatment for unselected patients with metastatic breast cancer.[5] Patients were not selected based on the expression of EGFR; however, a retrospective subset analysis revealed no clinical benefit in patients with HER2-negative tumours. Importantly, novel biomarkers may help to identify tumours where EGFR is biologically important and may thus help to select patients with HER2-negative tumours that may nevertheless respond to lapatinib.

Regardless of these unresolved issues in HER2-positive or HER2-negative patients, lapatinib has a mechanism of action distinct from that of trastuzumab and thus warrants further evaluation earlier in the treatment of HER2-positive breast cancer. The ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) trial, which will compare lapatinib, trastuzumab and lapatinib plus trastuzumab in combination with adjuvant chemotherapy in patients with HER2-positive primary breast cancer, should help to define the optimal use of lapatinib in breast cancers with HER2 overexpression. ▲

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