Studies help clarify the role of lapatinib and trastuzumab in treating HER2 positive breast cancer

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In patients with HER2-positive breast cancer, Tykerb (lapatinib) has been used both in combination with herceptin (trastuzumab) and as an alternative single-agent therapy for pre-surgery (neo-adjuvant) chemotherapy treatment. Two new studies are published today on these drugs. One published by *The Lancet Oncology*, showing lapatinib to be less beneficial than trastuzumab for single-agent therapy, and one by *The Lancet* showing that combining both drugs appears almost twice as effective as single-agent therapy (although lapatinib causes more side-effects).

The human epidermal growth factor receptor 2 (HER2) is a potent mediator of cellular growth and proliferation. Amplification of the HER2 gene, and the corresponding overexpression of the HER2 receptor , occurs in roughly 15% of breast tumours and is associated with a poor outcome.

In The *Lancet Oncology* study, Professor Gunter von Minckwitz (German Breast Group, Neu-Isenburg, Germany), Prof. Michael Untch (AGO-Breast Study Group, Berlin, Germany), and colleagues did a randomised trial of lapatinib versus trastuzumab in 620 patients in Germany. All patients received a standard chemotherapy regimen plus either trastuzumab (309) or lapatinib (311). The primary outcome of the study was the proportion of patients achieving pathological complete response (pCR—the absence of any residual invasive cancer in the breast

and absence of any metastatic cells in the regional lymph nodes). The researchers found that 30% of the trastuzumab group achieved a pathological complete response compared with 23% in the lapatinib group.

Side-effects were common in both groups. Chemotherapy with trastuzumab was associated with more swelling of legs (39% vs 29%) and shortness of breath (30% vs 21%), and lapatinib with more diarrhoea (75% vs 47%) and skin rash (55% vs 32%). Many more patients discontinued therapy due to toxic effects in the lapatinib group (33%) than in the trastuzumab group (14%). 70 serious adverse events were reported in the trastuzumab group and 87 in the lapatinib group.

The authors conclude: "This direct comparison of trastuzumab and lapatinib showed that pathological complete response rate with chemotherapy and lapatinib was significantly lower than that with chemotherapy and trastuzumab. Unless long-term outcome data show different results, lapatinib should not be used outside of clinical trials as single anti-HER2 treatment in combination with neoadjuvant chemotherapy."

In a Comment linked to *The* Lancet Oncology paper, Dr Stephen K Chia, Division of Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, Canada, says: "Moving forward into the future, no adjuvant (post-surgery) trials should be done without an adequate signal from preoperative trials showing safety, efficacy, target modulation, and, ideally, the identification of predictive biomarkers such that we no longer pick a loser to study in larger and more resource-intensive adjuvant trials."

In *The Lancet* study, Dr José Baselga (Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA) and colleagues from the SOLTI group and Breast International Group did a

randomised trial involving more than 400 women from 23 countries with HER2-postive breast cancer and tumours greater than 2 cm in diameter. 154 women received lapatinib, 149 trastuzumab, and 152 a combination of both treatments, all pre-surgery, with standard paclitaxel therapy added to each of these anti-HER2 regimens after 6 weeks. Following a further 12 weeks of treatment, patients underwent surgery and then received the same anti-HER2 therapy for 1 year. The new aspect in this study is that patients received the same anti-HER2 therapy post-surgery as in the pre-surgery component, so eventually data will be available to study the correlation between pCR, the primary study endpoint, and disease free survival and overall survival.

The authors say: "Dual targeting of HER2-positive tumours with trastuzumab and lapatinib is undertaken because of primary and acquired resistance to both agents, their partly non-overlapping mechanisms of action, and the well characterised synergistic interaction between them in HER2 breast-cancer models."

The research team found that the pCR rate was significantly higher in the group given combination treatment (51%) than in the group given trastuzumab alone (30%), a difference of 21%. No statistically significant difference in pCR between the lapatinib (25%) and the trastuzumab (30%) groups was recorded. No major cardiac dysfunctions occurred across the treatment groups (anti-HER2 therapy can cause cardiac toxicity). Frequency of grade 3 diarrhoea was far higher with lapatinib (23%) and lapatinib plus trastuzumab (21%) than with trastuzumab (2%). Similarly, grade 3 liver-enzyme alterations were more frequent with lapatinib (18%) and lapatinib plus trastuzumab (10%) than with trastuzumab (7%).

The authors conclude: "Overall, dual HER2 blockade could be an improved approach to treatment of patients with HER2-positive tumours. Our study shows that dual inhibition of HER2 by lapatinib and

trastuzumab in combination with paclitaxel is better than single-agent targeting of HER2 in the neoadjuvant (pre-surgical) setting. Dual HER2 blockade might be a valid approach in patients with early HER2-positive disease."

They add: "Our study also supports investigation of novel targeted agents for breast cancer in the neoadjuvant (pre-surgical)setting, when tumours have not yet acquired resistance to therapy and when chances of clinical benefit are highest."

In a Comment linked to *The Lancet* Article, Professor Michael Gnant and Dr Guenther G. Steger, Medical University of Vienna, Austria, say trials such as this are convincing enough to consider different routes of evaluating drugs from a both a scientific and regulatory perspective. They say: "Trials in the neoadjuvant setting based on research-based hypotheses (after establishment of drug safety) could lead to a saving of enormous sums in drug development costs, and promising new drugs for treatment of early breast cancer could become available much more quickly than at present."

More information:

-- www.thelancet.com/journals/lan … (11)70397-7/abstract
-- www.thelancet.com/journals/lan … (11)61847-3/abstract

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