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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