Lapatinib, trastuzumab or the combination added to preoperative chemotherapy for breast cancer: a meta-analysis of randomized evidence

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CRD summary
The authors concluded that a clear improvement in pathological complete response was shown by addition of both trastuzumab and lapatinib to neoadjuvant chemotherapy in human epidermal receptor 2-positive breast cancer; trastuzumab demonstrated a better toxicity profile and superiority to lapatinib in this setting. These conclusions reflect available evidence for tumour response and toxicity, and are likely reliable.

Authors' objectives
To compare the efficacy and safety of the addition of lapatinib, trastuzumab, or their combination to neoadjuvant chemotherapy with human epidermal growth factor receptor 2 (HER2) positive breast cancer.

Searching
MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to May 2012, with no language or date restrictions. Search terms were reported. The reference lists of all eligible studies and the proceedings of two international cancer congresses (named in paper) were searched.

Study selection
Eligible studies were randomised phase II or III trials that evaluated lapatinib plus chemotherapy, versus trastuzumab plus chemotherapy or their combination plus chemotherapy in a neoadjuvant setting. Any cytotoxic chemotherapy regimen was considered eligible, as long as identical drugs of identical doses were administered in all trial arms with only differences related to anti-HER2 treatment. The primary eligible outcome was the rate of pathological complete response achieved in breast tissue and in breast tissue plus axilla (where reported). Secondary eligible outcomes included discontinuation of treatment and rates for breast-conserving surgery and grade III or IV toxicities.

Over half of included trials were three-armed and compared all of the three eligible interventions with one another; the remainder were two-armed, with comparison of trastuzumab plus chemotherapy versus lapatinib plus chemotherapy. Most trials based treatment on a sequential anthracycline-taxane combination. Half of the trials only administered anti-HER2 therapy with taxanes; the other half administered anti-HER2 therapy concurrently with the chemotherapy, regardless of the chemotherapeutic agent. All therapy regimens varied across the trials. Duration of anti-HER2 therapy ranged from 12 to 26 weeks.

The authors did not state how many reviewers selected the studies for inclusion.

Assessment of study quality
Two reviewers independently used the Cochrane risk of bias tool to assess adequacy of study descriptions for randomisation, allocation concealment, blinding, selective outcome reporting, and other sources of bias. Trials were classified as being low quality if two or more of the quality domains were assessed as being at high or unclear risk of bias.

Data extraction
Data were extracted to calculate risk ratios and 95% confidence intervals for the outcomes. Where applicable, data were extracted on an intention-to-treat basis. Two reviewers independently extracted the data, with any disagreements resolved by discussion.

Methods of synthesis
Effect estimates and 95% confidence intervals were pooled using the fixed-effect Mantel-Haenszel method, or the random-effects DerSimonian and Laird method when statistical heterogeneity was shown. Statistical heterogeneity was assessed using the Cochrann's Q and I² (where I² values of more than 50% indicated large heterogeneity and I² values of more than 75% indicated very large, extreme heterogeneity). Publication bias was assessed using funnel plots.
Results of the review
Six randomised controlled trials (RCTs) were included in the review (1,917 patients, from 100 to 615 per trial): three phase II trials (323 patients) and three phase III trials (1,596 patients). Only the three trials with full text reports were quality assessed; limited reporting stated that they all had adequate randomisation and allocation concealment. Two had blinded outcome assessment.

The probability of achieving a pathological complete response was statistically significantly higher for trastuzumab compared with lapatinib (RR 1.24, 95% CI 1.08 to 1.44; six trials; I²=19%). A greater statistically significant probability of pathological complete response was observed for the combination of trastuzumab and lapatinib versus trastuzumab alone (RR 1.39, 95% CI 1.20 to 1.63; four trials; I²=20%).

Significantly greater rates of diarrhoea, dermatologic toxicities, and treatment discontinuations were observed for lapatinib arms compared to trastuzumab arms, and greater rates of diarrhoea were observed for combination arms compared to trastuzumab alone. No other statistically significant differences were found between the treatment options.

Authors’ conclusions
Evidence showed clear improvement in pathological complete response by adding a dual-HER2 blockade (trastuzumab and lapatinib) to neoadjuvant chemotherapy in HER2-positive breast cancer. Trastuzumab was superior to lapatinib in this setting and had a better toxicity profile.

CRD commentary
The review question was clear and inclusion criteria were well defined. Relevant data sources were accessed and no language or date restrictions were made which reduced the risk of relevant studies being missed. Steps were taken to reduce any error or bias during data extraction and quality assessment, although this was unclear for the study selection stage. Suitable quality assessment criteria were employed but only half of the included trials could be assessed due to unavailable full texts. Study details were presented and showed some clinical heterogeneity across trials, but statistical heterogeneity between trials was low.

Despite the unknown quality of three trials, the authors’ conclusions reflect the relatively homogenous evidence available for the outcomes of tumour response and toxicity, and are likely reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for clinical practice.
Research: The authors did not state any implications for research but stated that the question of survival benefit would be answered when long term data from the NeoALTTO and NSABP B-41 trials became available.

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