Risk of cardiac dysfunction with trastuzumab in breast cancer patients: a meta-analysis

CRD summary
The review found that trastuzumab plus anthracycline-based chemotherapy for treating breast cancer significantly increased rates of cardiac dysfunction; more research was required on non-anthracycline-based chemotherapy. These findings require cautious interpretation due to limitations in the review, including the suboptimal search, the unclear quality of included trials, and high levels of variation between trials for some outcomes.

Authors' objectives
To assess the risk of cardiac dysfunction associated with use of trastuzumab for treating breast cancer.

Searching
PubMed and Web of Science (1966 to July 2009) were searched. Search terms were reported. Conference proceedings from the American Society of Clinical Oncology (2000 to July 2009) were also searched. Food and Drug Administration submission documents, drug package inserts, review articles and reference lists of retrieved articles were also checked. An randomised clinical trial (RCT) filter appears to have been used.

Study selection
Phase II and III RCTs of trastuzumab versus placebo or best supportive care in addition to concurrent chemotherapy and/or biological agent for treatment of breast cancer were eligible for inclusion. Trials were required to report cardiac toxicity. Events of interest were symptomatic congestive heart failure (primary outcome), left ventricular ejection fraction decrease and definite or probable cardiac death.

 Patients in the included trials had early or advanced human epidermal growth factor receptor type 2 positive breast cancer. Patients were required to have satisfactory hepatic, renal and haematological function. From 0.5 to 100% of patients in each trial were node-positive, and 41 to 68% were hormone-receptor positive (where reported). Most studies excluded individuals with pre-existing cardiac disease. Chemotherapy regimens varied, but most studies used anthracyclines with or without sequential or concurrent trastuzumab. Trastuzumab was usually given as a loading dose, then at 2mg/kg weekly for 51-52 weeks or until disease progression. Most trials reported left ventricular ejection fraction decrease, usually assessed by echocardiography or MUGA (Multi Gated Acquisition Scan) scanning (the definition of decrease varied across trials). New York Heart Association criteria were used to classify congestive heart failure (defined in all cases as Class II or III).

The authors did not state how many reviewers performed the selection.

Assessment of study quality
Some components of study quality were assessed: allocation concealment, completeness of follow-up, and objectivity of outcome measures.

The authors did not state how the assessment was performed.

Data extraction
The incidence of cardiac dysfunction in the trastuzumab group was calculated for each study, with a 95% confidence interval (CI). Risk ratios (RRs) comparing events in the two groups of each study were also extracted or calculated, with 95% CIs. Two reviewers independently extracted the data, with disagreements resolved by consensus. Primary study authors and drug manufacturers were contacted for more information if required.

Methods of synthesis
The studies were combined to calculate pooled incidence rates, RRs and 95% confidence intervals. Heterogeneity was assessed using the Cochran Q and I² statistics. Fixed effect models were used unless there was significant heterogeneity.
Subgroup analyses were conducted to examine the effects of differences between the studies, including use versus non use of anthracyclines, sequential versus concurrent chemotherapy, and early versus metastatic disease. The Begg and Egger tests were used to assess publication bias for the primary endpoint.

**Results of the review**

Ten RCTs were included in the review (n=11,882 patients, range 42 to 5,102), including eight phase III and two phase II trials. Duration of follow-up ranged from 21 months to four years (where reported).

In breast cancer patients who received trastuzumab, the incidence of congestive heart failure was 1.9% (95% CI 1.0 to 3.8; 10 RCTs) and of left ventricular ejection fraction decrease was 7.5% (95% CI 4.2 to 13.1; eight RCTs).

Compared with controls, trastuzumab significantly increased the overall risk of congestive heart failure (RR 4.19, 95% CI 2.73 to 6.42; 10 RCTs; I²=16%) and left ventricular ejection fraction decrease (RR 2.13, 95% CI 1.31 to 3.49; eight RCTs; I²=78%). There was no significant difference between the groups for cardiac death rates (four RCTs).

In patients receiving anthracyclines, trastuzumab significantly increased the risk of congestive heart failure (RR 4.27, 95% CI 2.75 to 6.61; eight RCTs; I²=29%) or left ventricular ejection fraction decrease (RR 2.13, 95% CI 1.23 to 3.69; six RCTs; I²=82%). Trastuzumab did not significantly increase the risk of congestive heart failure or left ventricular ejection fraction decrease in non-users of anthracyclines (two RCTs).

There was high heterogeneity for analyses of left ventricular ejection fraction decrease.

No evidence of publication bias was found.

The review also reported the results of subgroup analyses for sequential versus concurrent chemotherapy, and early versus metastatic disease.

**Authors’ conclusions**

Use of trastuzumab in addition to anthracycline-based chemotherapy for treating breast cancer significantly increased rates of cardiac dysfunction. More research was required on non-anthracycline-based chemotherapy.

**CRD commentary**

The objectives and inclusion criteria of the review were clear. The search for studies was limited to two relevant databases and the proceedings of one professional body, so it was possible that some studies were missed. It was unclear whether the search was restricted by language. Publication bias was appropriately assessed. Steps were taken to minimise the risk of reviewer bias and error with more than one reviewer independently extracting the data, but it was unclear whether this was applied to study selection and quality assessment.

The results of trial quality assessment were not reported, which made it difficult to assess the reliability of the reported findings. Appropriate methods were used to combine the trials, assess heterogeneity and explore differences between the trials. There was substantial unexplained heterogeneity for analyses of left ventricular ejection fraction decrease, which the authors speculated could be due to variation in the outcomes definition. As they noted, the review was potentially biased by heterogeneity and by lack of long-term or patient-level data.

The authors’ conclusions may require caution in interpretation due to limitations in the review, including the suboptimal search, failure to report included trial quality and high statistical heterogeneity for some outcomes.

**Implications of the review for practice and research**

**Practice**: The authors stated that clinicians and patients should assess the risk/benefit ratio of trastuzumab for breast cancer, in view of the increased risk of cardiac toxicity. Cardiologists and oncologists should collaborate to monitor the risk in breast cancer patients, regardless of disease stage. Concomitant trastuzumab and anthracyclines should be avoided.
Research: The authors stated that further long-term studies were needed to evaluate the risk (including the long-term risk) of cardiac toxicity associated with non-anthracycline therapy. Studies should examine the effects of age and prior therapy (especially with anthracyclines) and explore ways to reduce the risk.

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