Review

Trastuzumab combined to neoadjuvant chemotherapy in patients with HER2-positive breast cancer: A systematic review and meta-analysis

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ABSTRACT

Purpose: To perform a meta-analysis in order to quantify the actual cumulative randomized evidence for the benefit and toxicity of trastuzumab combined with neoadjuvant chemotherapy in HER2-positive breast cancer.

Methods: Potentially eligible trials were located through PubMed and Cochrane Library searches and abstracts of major international conferences. The endpoints that we assessed were pathologic complete response (pCR) rate, breast-conserving surgery (BCS) rate and toxicity.

Results: Five trials were identified with 515 eligible patients. The probability to achieve pCR was higher for the trastuzumab plus chemotherapy arm (RR 1.85, 95\% CI: 1.39–2.46; \textit{p}-value < 0.001). No significant difference in terms of breast-conserving surgery between the two treatment arms was observed (OR: 0.98, 95\% CI: 0.80–1.19, \textit{p}-value = 0.82). Regarding toxicity, the addition of trastuzumab did not increase the incidence of neutropenia, neutropenic fever, and cardiac adverse events.

Conclusion: The addition of trastuzumab in HER2-positive breast cancer in the neoadjuvant setting improves the probability of achieving higher pCR with no additional toxicity. Based on the available evidence, the use of trastuzumab combined with neoadjuvant chemotherapy in patients with HER2-positive breast cancer seems to offer substantial benefit in terms of pCR.

Introduction

Neoadjuvant therapy is the standard of care in patients with locally advanced breast cancer.\textsuperscript{1} The survival benefit gained from chemotherapy in breast cancer patients has been found to be equal regardless whether chemotherapy is administered preoperatively or postoperatively.\textsuperscript{2} Neoadjuvant chemotherapy offers some attractive benefits since it can downstage the primary tumor in most women allowing higher breast-conserving surgery rates or improving resectability\textsuperscript{3} and it can also provide an in vivo assessment of tumor response to chemotherapy since pathologic complete response (pCR) to neoadjuvant treatment could be a reliable prognostic factor.\textsuperscript{4,5}

Overexpression or amplification of HER2 in breast cancer cells has been traditionally associated with more aggressive disease and poor prognosis.\textsuperscript{6} However the administration of trastuzumab, a humanized monoclonal antibody that blocks the activity of HER2, has improved survival of HER2-positive breast cancer both in the adjuvant\textsuperscript{7} and the metastatic settings.\textsuperscript{8} Recent data showed that women with HER2/neu-positive disease who received trastuzumab with systemic therapy may have either comparable or even better prognosis compared with women with HER2/neu-negative disease.\textsuperscript{9}

Considering the benefits from neoadjuvant chemotherapy and the well-documented effect of trastuzumab in HER2 positive breast cancer in the adjuvant and the metastatic settings, the addition of trastuzumab to neoadjuvant treatment appears to be appealing since it might also be associated with better overall responses and survival outcomes. Furthermore, preclinical data indicate that the use of trastuzumab prior to surgery might be of great benefit by limiting the proliferation and improving the control of residual tumor.\textsuperscript{10}
Since several randomized\textsuperscript{11–15} trials evaluating the role of trastuzumab in neoadjuvant setting are reported, we conducted a meta-analysis of randomized trials that evaluated the efficacy of incorporating trastuzumab into neoadjuvant chemotherapy for HER-2 positive breast cancer. We aimed to determine whether this approach improves pathologic complete response with acceptable toxicity.

**Methods**

**Search strategy**

We searched MEDLINE and the Cochrane Central Register of Controlled Trials, without year and language restriction, by using the following searching algorithm: (neoadjuvant OR preoperative OR induction OR primary systemic OR primary chemotherapy) AND (trastuzumab OR herceptin). The last search was updated in July 2010. Because recent trials with trastuzumab in neoadjuvant setting may still be unpublished, we also searched electronically the major international congresses’ proceedings (American Society of Clinical Oncology Annual Meeting, San Antonio Breast Cancer Symposium, European Cancer Conference). The reference lists of all studies fulfilling the eligibility criteria were also examined for other relevant articles missed by the electronic searches.

**Eligibility criteria**

Eligibility and exclusion criteria were prespecified. Studies were considered eligible for our systematic review if they were randomized phase II or III and evaluated the administration of trastuzumab plus chemotherapy versus chemotherapy alone in the neoadjuvant setting. All cytotoxic chemotherapy regimens were considered eligible for the meta-analysis, provided that the same drugs were given at the same dose in all study arms and that the arms differed systematically only regarding trastuzumab administration.

From the systematic review we excluded all the non-randomized studies.

If multiple publications of the same trial were retrieved or if there was a case mix between publications, only the most recent publication (and the most informative) was included.

**Data extraction**

Two authors (AV and D. Mauri) extracted data independently and reached consensus on all items. Disagreement on specific studies between the two reviewers was resolved through discussion.

From each eligible trial we recorded for both arms the following items: authors’ name, journal and year of publication, country of origin, years of patient enrollment, and number of centers involved; number of patients randomized and analyzed per arm, age, ER/PR status, node positivity, median follow up, technique used for HER2 identification, type/dose of chemotherapy and dose and duration of trastuzumab therapy. Primary and secondary outcome measures, as described below, were recorded. We also recorded, whenever possible, issues that reveal the quality of included studies: randomization model, allocation concealment, blindness, withdrawals description.

**Outcome definition**

The primary outcome of our study was the rate of pCR achieved. In case the primary study reported separate pCR rate in breast tissue and in breast tissue plus axilla, we included the pCR rate from the combination of breast tissue plus axilla. Secondary objectives were the rate of breast-conserving surgery and the rate of toxicities including grade III-IV neutropenia, febrile neutropenia, overall cardiac adverse events, congestive heart failure (CHF) and treatment-related deaths.

We could not evaluate complete clinical response since only two trials\textsuperscript{11,15} presented such data. In addition, outcomes such as overall survival and disease free survival were not analyzed because only 2 trials\textsuperscript{14,18} presented sufficient data and a meta-analysis of two studies with enormous difference between observed events (deaths and recurrences) has no validity.

**Statistics**

Two-by-two tables were constructed, using the intention-to-treat (ITT) assignment when applicable, and risk ratio (RR) was calculated for each primary study to estimate the relative risk of each outcome in patients with HER2-positive breast cancer receiving chemotherapy plus trastuzumab versus chemotherapy alone as neoadjuvant therapy. For each eligible study group, we estimated the relative risk for the outcome measures between the groups in comparison and the 95% confidence interval (CI).

We then synthesized the data across studies using fixed effects (Mantel–Haenszel) or random effects (Der Simonian and Laird) modeling when between-study heterogeneity was present. The significance of the heterogeneity test suggests a preference for the random-effect estimation for a more appropriate evaluation of the results. The RRs are to be interpreted as follows: an RR < 1.0 indicates fewer events in the trastuzumab arm.

To test for heterogeneity between trials, the Q statistic was used. The presence of statistical heterogeneity was assessed with Cochran's Q test (considered significant for \( p < 0.10 \)) and quantified using I^2 and respective 95% confidence intervals. For I^2 values, >50% indicate large heterogeneity and values >75% indicate very large (extreme) heterogeneity. The meta-analysis calculations were accomplished by RevMan v 5.0 (Centre TNC: Review Manager (RevMan). In Version 5 for Windows edn. Copenhagen: The Cochrane Collaboration; 2008). All p-values are two-tailed.

**Results**

**Study selection**

Electronic search yielded 650 hits from PubMed and 32 from Cochrane. Five eligible randomized trials were retrieved, four from peer-reviewed reports\textsuperscript{11,12,14,15} and one from congress abstracts.\textsuperscript{13} One eligible trial\textsuperscript{12} was also presented in the American Society of Clinical Oncology Annual Meeting on two occasions, 2006\textsuperscript{16} and 2008,\textsuperscript{17} but the data included in our meta-analysis was retrieved from a review article\textsuperscript{12} from the same author, in which updated and unpublished data of the study were included. Furthermore, one eligible trial\textsuperscript{11} has published updated results\textsuperscript{18} and data regarding toxicity were extracted from the most recent publication. A flow chart indicating the identification of randomized controlled trials for inclusion in the meta-analysis is reported in Fig. 1.

In total, 515 patients were included in the meta-analysis; of those 259 patients had been randomized to trastuzumab plus chemotherapy arm, and 256 to chemotherapy alone arm.

**Study characteristics**

Table 1 presents the characteristics of the 5 trials that met the eligibility criteria for this study. Regarding study design, two studies\textsuperscript{12,15} were phase II and three phase III.\textsuperscript{11,13,14} Two studies\textsuperscript{11,12} were single-institutional while 3\textsuperscript{13–15} were multicentre. We were
able to evaluate quality of included studies only in those published in full text (4 studies). Two studies\textsuperscript{11,14} describe adequately the randomization model and only one\textsuperscript{14} the allocation concealment. One study\textsuperscript{11} was terminated early because the primary objective of the study had been reached in interim analysis.

In all trials, except one,\textsuperscript{12} the treatment was based on a combination of anthracycline and taxanes concomitantly or sequentially. In two trials\textsuperscript{12,15} all HER2-positive patients received trastuzumab in the adjuvant setting, while in one study\textsuperscript{14} adjuvant trastuzumab was administered only in patients randomized to receive trastuzumab preoperatively and only 16% of the HER2-positive patients in the chemotherapy alone arm received adjuvant trastuzumab.

Table 2 presents the characteristics of the analyzed patients in each eligible trial and an overview of the outcomes in each study.

**Overall effect of trastuzumab on pathologic complete response**

The pCR rates for each eligible trial were available. The pCR was defined as no evidence of residual invasive cancer, both in breast and axilla in two studies\textsuperscript{11,15} while in two studies\textsuperscript{12,13} the definition of pCR was unclear. In one study\textsuperscript{14} a separate pCR rate in breast tissue and in breast tissue plus axilla was reported and, based on our study protocol, we used in meta-analysis the pCR rate from the combination of breast tissue plus axilla (Figs. 2 and 3).

### Table 1

**Characteristics of the included studies.**

<table>
<thead>
<tr>
<th>Study [ref]</th>
<th>No of pts analyzed</th>
<th>Clinical stage</th>
<th>HER2 status</th>
<th>Follow up, months</th>
<th>Arms</th>
<th>Neoadjuvant chemotherapy</th>
<th>Neoadjuvant Trastuzumab schedule</th>
<th>Adjuvant chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buzdar au, 2005\textsuperscript{11,18}</td>
<td>42</td>
<td>II-III, non-inflammatory</td>
<td>IHC + 3 or FISH</td>
<td>36.1</td>
<td>23</td>
<td>P(4 c) → FEC(4 c)</td>
<td>4 mg/kg → 2 mg/kg weekly for 24 wks</td>
<td>None</td>
</tr>
<tr>
<td>H2269s, 2010\textsuperscript{12}</td>
<td>29</td>
<td>T2-4, any N, M0</td>
<td>FISH</td>
<td>NR</td>
<td>19</td>
<td>P(4 c) → FEC(4 c)</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>ABCG-24, 2009\textsuperscript{13}</td>
<td>89</td>
<td>T1-4, any N, M0</td>
<td>NR</td>
<td>NR</td>
<td>14</td>
<td>Doc + Carbo 4 c</td>
<td>No</td>
<td>Doc + Carbo 4 c + trastuzumab for 52 weeks</td>
</tr>
<tr>
<td>NOAH, 2010\textsuperscript{14}</td>
<td>235</td>
<td>T3N1 or T4 or any T N2-3</td>
<td>IHC + 3 or FISH</td>
<td>38.4</td>
<td>47</td>
<td>ED + Cap (5 c)</td>
<td>8 mg/kg → 6 mg/kg every 3 wks during chemotherapy</td>
<td>Trastuzumab (overall 1 year)</td>
</tr>
<tr>
<td>Pierga JY, 2010\textsuperscript{15}</td>
<td>120</td>
<td>II-III</td>
<td>IHC + 3 or FISH</td>
<td>NR</td>
<td>62</td>
<td>Doco + P(3 c) → P(4 c) → CMF(3 c)</td>
<td>No</td>
<td>Trastuzumab 1 year (only 17% of pts)</td>
</tr>
</tbody>
</table>

Abbreviations: ref, reference; No, number; pCR, pathologic Complete Remission; IHC, immunohistochemistry; FISH, Fluorescent In Situ Hybridization; P, paclitaxel; FEC, Fluorouracil–Epirubicin–Cyclophosphamide; c, cycles; mg, milligram; kg, kilogram; wks, weeks; Doc, Docetaxel; Carbo, Carboplatin; ED, Epirubicin, Docetaxel; Cap, Capecitabine; NR, Not-Reported; Doco, Doxorubicin; CMF, Cyclophosphamide–Methotrexate–Fluorouracil; pts, patients; EC, Epirubicin–Cyclophosphamide.
In the overall population (515 patients; 5 RCTs), the absolute pCR rate was 38% (99 out of 259 patients) in trastuzumab arm in comparison with 21% (53 out of 256 patients). As a result, the probability to achieve pCR was higher for the trastuzumab plus chemotherapy arm (RR 1.85, 95% CI: 1.39–2.46; p-value < 0.001). No recurrence and survival analysis was performed due to the short term follow up and lack of such data.

Overall effect of trastuzumab on breast-conserving surgery and toxicity profile

The number of patients who underwent BCS were available in four trials (280 patients). We found no difference in terms of breast-conserving surgery between the two treatment arms (OR: 0.98, 95% CI: 0.80–1.19, p-value = 0.82).

Regarding toxicity, pooled relative ratios with 95% CI for the use of trastuzumab versus no trastuzumab in neoadjuvant setting are reported in Table 3. Overall, the incidence of neutropenia, neutropenic fever, and cardiac adverse events were similar between the two arms. Two out of 217 (0.9%) patients in the trastuzumab arms presented CHF compared with none in the chemotherapy alone arms. None of the patients either in trastuzumab or the chemotherapy only arm died due to treatment-related toxicities.

Discussion

This study, with the inclusion of all available randomized data regarding trastuzumab as neoadjuvant therapy, provides evidence that the addition of trastuzumab in the neoadjuvant setting in HER2-positive breast cancer patients offers a significant benefit is pCR with no additional toxicity. Nevertheless this benefit could not change the rate of breast-conserving surgery in favor of trastuzumab. Moreover we were unable to analyze recurrences and survival for the neoadjuvant use of trastuzumab vs non use, due to the lack of data and short follow up of original studies.

Several non-randomized phase II trials have examined the potential benefit of neoadjuvant trastuzumab combined with chemotherapeutic agents in patients with HER2-positive tumors and have reported pCR rates ranging from 7% to 78%[12,19] with the largest trial, Geparquattro trial, revealing a pCR rate of 31.7%[20]. Recently, an exploratory pooled analysis of eight German, both randomized and non-randomized, neoadjuvant studies was presented[21] and showed a 3.2-fold improvement in pCR in Her2-positive patients receiving trastuzumab when compared with Her2-positive patients who did not received trastuzumab. In addition, a Chinese meta-analysis of three studies[22] was published and showed that neoadjuvant regimens combined with trastuzumab can significantly improve the pCR without increasing the toxicity. However, this meta-analysis had several drawbacks, since one included study was a cohort study and only two small randomized trials were included in the analyses. Therefore, no firm conclusions could be driven from the Liao’s analysis.

Our meta-analysis, by including only randomized data, confirms and underscores the possible benefits for the use of trastuzumab in the neoadjuvant setting when compared with no use. Therefore the actual available cumulative randomized evidence supports the current guidelines of the National Comprehensive Cancer Network (NCCN) for the inclusion of trastuzumab as a standard drug in

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**Table 3**

Characteristics of analyzed patients and outcomes in eligible studies.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Arms</th>
<th>Characteristic</th>
<th>pCR (%)</th>
<th>cCR (%)</th>
<th>OS</th>
<th>DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buzdar AU, 2009</td>
<td>Trastuzumab</td>
<td>52 (29–71)</td>
<td>13 (57)</td>
<td>0</td>
<td>15 (65)</td>
<td>20 (87)</td>
</tr>
<tr>
<td></td>
<td>No trastuzumab</td>
<td>48 (25–75)</td>
<td>11 (58)</td>
<td>0</td>
<td>5 (26)</td>
<td>9 (47)</td>
</tr>
<tr>
<td>H2269s, 2010</td>
<td>Trastuzumab</td>
<td>NR</td>
<td>11</td>
<td>NR</td>
<td>60 (9)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>No trastuzumab</td>
<td>NR</td>
<td>10</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>ABCSG-24, 2009</td>
<td>Trastuzumab</td>
<td>51 (26–70)</td>
<td>17 (40)</td>
<td>0</td>
<td>17 (40)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>No trastuzumab</td>
<td>48 (29–68)</td>
<td>18 (38)</td>
<td>0</td>
<td>13 (28)</td>
<td></td>
</tr>
<tr>
<td>NOAH, 2010</td>
<td>Trastuzumab</td>
<td>NR</td>
<td>42 (36)</td>
<td>32 (27)</td>
<td>45 (38)</td>
<td>102 (87)</td>
</tr>
<tr>
<td></td>
<td>No trastuzumab</td>
<td>NR</td>
<td>42 (36)</td>
<td>31 (26)</td>
<td>23 (19)</td>
<td>87 (74)</td>
</tr>
<tr>
<td>Pierga JY, 2010</td>
<td>Trastuzumab</td>
<td>47</td>
<td>34 (55)</td>
<td>NR</td>
<td>16 (26)</td>
<td>21 (34)</td>
</tr>
<tr>
<td></td>
<td>No trastuzumab</td>
<td>46.5</td>
<td>34 (59)</td>
<td>NR</td>
<td>13 (19)</td>
<td>13 (22)</td>
</tr>
</tbody>
</table>

Abbreviations: ref, reference; ER, estrogen receptor; PR, progesterone receptor; pCR, pathologic complete response; cCR, clinical complete response; OS, overall survival; DFS, disease-free survival; NC, not calculated; NR, not reported.

- One death in no trastuzumab arm and 0 in trastuzumab arm.
- Disease free survival at 3-years (P-value = 0.041).
- In both arms.
- At 3 years. No significant difference.
- Overall response: clinical complete and partial response.
- At 3 years (P-value = 0.013).

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![Fig. 2. Meta-analysis evaluating the pathologic complete response (pCR) rate.](image-url)
neoadjuvant regimens for the treatment of Her2-positive breast cancer.23

Interestingly, despite the benefit in pCR rate, trastuzumab in patients with Her2-positive breast cancer does not result in a higher rate of breast-conserving surgery, which is one of the theoretical advantages of neoadjuvant treatment. This could partially be explained by the fact that data from only 280 patients was available for analysis.

It has been suggested that the use of trastuzumab prior to surgery might be of great benefit by limiting the proliferation and by improving the control of eventually sub-clinical not-detectable residual tumor. Residual HER2-positive breast carcinomas show a significant increase in proliferation within 48 days after surgery.10 Indeed, wound drainage fluid and postsurgical serum samples from patients after breast cancer surgery stimulate the in-vitro growth of HER2-overexpressing breast carcinoma cells. It seems, therefore, that surgery promotes the production of factors which can potentially stimulate the growth of HER2-positive breast cancer cells. The in-vitro proliferative activity is inhibited by the treatment of HER2 positive tumor cells with trastuzumab before adding drainage fluid.10 Unfortunately, early available clinical data from our review are not enough to confirm whether the observed preclinical benefits for the use of trastuzumab in neoadjuvant setting might be translated into better long-term tumor control by reducing the proportion of local and distant recurrences and prolonging overall survival. Larger trials and longer follow up are needed to confirm the promising data that have emerged from the lab with breast cancer cell lines.

Concerning toxicity, the addition of trastuzumab to neoadjuvant therapy does not appear to compromise the safety profile of neoadjuvant therapy. The use of trastuzumab, especially in conjunction with anthracyclines has raised concerns about increased cardiotoxicity. In this meta-analysis, less than 1% of the patients with neoadjuvant trastuzumab presented with CHF despite the fact that in most of the eligible studies a combination of trastuzumab and anthracyclines was used. This finding is in accordance with the results of 2 recently published24,42 studies which evaluated the cardiotoxicity of trastuzumab in adjuvant setting with a longer follow up. Both studies concluded that the incidence of symptomatic cardiac failure is less than 2% and in the majority of cases reversible.

Our meta-analysis has certain limitations which should be discussed. First, the number of studies and the number of patients included are relatively small and affects the power of the meta-analysis to reveal statistically significant results. Nonetheless, we have systematically identified all the available randomized studies, either published in peer-reviewed journals or presented in major international cancer congresses, so as to include in our analysis all the available randomized evidence on this topic. Second, the definitions of pCR used by each study are not the same and the pathological methods and criteria of assessment are not standardized. In order to minimize the risk for heterogeneity regarding pCR definition, in studies which reported separate pCR in breast tissue and in breast tissue plus axilla, we included the pCR rate from the combination of breast tissue plus axilla because this definition is more appropriate and is proposed by current recommendations.26 Furthermore, due to the limited number of the patients included in the analyses and the fact that primary studies did not present adequate data regarding patient (age, menopausal status) or tumor (ER status, node involvement) characteristics, we did not proceed to subgroup analysis in order to investigate the role of trastuzumab in different subgroups. Finally, the follow up of the included studies is relatively short with a median follow up no more than 3.5 years. The limited follow up does not allow a reliable evaluation of the potential benefit of neoadjuvant trastuzumab on overall survival or disease-free survival. The only studies with survival data available were NOAH trial14 and Buzdar et al.18 The NOAH trial14 revealed significantly better event-free survival in favor of trastuzumab and non-significant differences on overall survival. However, according to study protocol, the non-trastuzumab arm received no trastuzumab as adjuvant therapy despite the fact that patients were Her2-positive. As a result, since adjuvant trastuzumab is of recognized beneficial effects in HER positive breast cancer, the NOAH study is unable to evaluate the additional effects of neoadjuvant trastuzumab use on survival outcomes Buzdar et al. presented survival data in an update of previous publication but the number of events was limited (1 death and 3 recurrences) and the follow up short so the interpretation of the results is questionable.

Despite survival outcomes are the most important endpoints when assessing the benefit of any therapy, the tumor response assessment in neoadjuvant therapy is considered also crucial.
Indeed, patients achieving a pCR may have a highly favorable long-term outcome.27,28 Despite the above mentioned limitations, this meta-analysis summarizes all available randomized evidence for the use of trastuzumab in the neoadjuvant setting versus no use. Our results underscore the beneficial effects of trastuzumab treatment in neoadjuvant regimens among Her2-positive breast cancer patients in terms of pCR. Of interest no additional cardiotoxicity was documented in the trastuzumab arms. However, the data are still limited, therefore, based on the present evidence the combination of trastuzumab to neoadjuvant chemotherapy improves pCR in HER positive breast cancer but if this translates to survival benefit remains unknown.

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**Authorship statement**

AV, NPP and D. Mauri conceived the study. AV performed the analyses. AV, D. Mauri performed the literature searches and data extraction. AV and D. Mauri wrote the manuscript. D. Mavroudis and VG contributed to the initial revision of the manuscript. D. Mavroudis, VG and GC contributed to the critical revision of the manuscript before publication.

**Conflict of interest**

None.

**References**


