Effectiveness of trastuzumab as adjuvant therapy in patients with early stage breast cancer: A systematic review and meta-analysis

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Abstract

Background: Trastuzumab in combination with chemotherapy has long been established as a standard treatment for HER2-positive patients in early stage breast cancer (BC). The present study aimed at assessing the effectiveness of trastuzumab adjuvant therapy in early stage BC in overall survival (OS) and disease-free survival (DFS).

Methods: A systematic review and meta-analysis was performed to evaluate the effectiveness of trastuzumab adjuvant therapy. PubMed, Cochrane library, Scopus, Web of Science, and Embase databases were searched for relevant RCTs from the beginning to February 2017. Quality assessment of studies was conducted using the Cochrane Risk of Bias Tool. The desired outcomes were OS and DFS.

Results: A total of 1818 articles were identified first, however, only 11 studies were eligible to be included in this study. Our findings and meta-analysis results revealed that trastuzumab is effective in increasing OS (OS hazard ratio: -0.286 ± 0.049, 95%CI (-0.381, -0.191)) and improving DFS (DFS hazard ratio: -0.419± 0.077, 95% CI (-0.569, -0.269)). The most serious but negligible side effect of trastuzumab is congestive heart failure.

Conclusion: Adding trastuzumab as adjuvant therapy in early stages of BC in HER2 positive patients could increase OS and DFS of the patients effectively.

Keywords: Trastuzumab, Breast Cancer, Herceptin, Meta-analysis, Adjuvant Therapy

Introduction

Breast cancer (BC) is the most common type of cancer worldwide and is one of the leading causes of death in cancer patients. Although the rate of BC is decreasing in developed countries, it is rapidly increasing in developing countries (1, 2). Statistics show that every year more than one million new cases of cancer are diagnosed in the world and more than 400 000 people are lost to cancer (3). Early diagnosis and treatment of BC in its early stages could significantly increase the survival rate of BC patients (4). Trastuzumab in combination with chemotherapy has been confirmed as the standard treatment of BC for HER2-positive patients (5). Many studies have found that trastuzumab in combination with chemotherapy prolongs overall survival (OS) (6) and improves progression-free survival (PFS) (7). Women with HER2 positive breast cancer are at greater risk for progression of disease and death compared to women who are not HER2 positive (8, 9).

Thus, the purpose of treatment strategies of this type of cancer is blocking HER2 positive BC. Trastuzumab is a recombinant human monoclonal antibody that binds to the
Trastuzumab as adjuvant therapy in patients with early stage breast cancer

The present study aimed at evaluating the effectiveness of trastuzumab in the treatment of early stage BC.

**Methods**

**Literature search**

A systematic review and meta-analysis was conducted to evaluate the effectiveness of trastuzumab using updated data. PubMed, Cochrane library, Web of Science, Embase, and Google Scholar databases were searched from the beginning to February 2017. The reference list of the selected RCTs and reviews were also searched for additional citations.

**Structured questions**

Our focus was on studies that evaluated the results of treatment in women with early BC. Our interested intervention was trastuzumab as adjuvant therapy in comparison with basic treatment without trastuzumab. Overall survival (OS) and disease-free survival (DFS) were considered as desired outcomes. Randomized controlled trials (RCTs) were the preferred study design. Studies that reported the results of monotherapy of the trastuzumab in BC were excluded. Observational, experimental, and animal studies were also excluded.

All selected studies were saved in Endnote library. After removing duplications, titles and abstracts were screened independently by 2 authors. The disagreements between the 2 authors were resolved by discussion.

**Search strategy**

Our search strategy for PubMed is presented as follows:

![PRISMA diagram of study selection](http://mjiri.iums.ac.ir)

**Fig. 1.** PRISMA diagram of study selection

**Breast Neoplasms[Mesh]  
Breast [Title/Abstract] AND (cancer*[Title/Abstract] OR tumour*[Title/Abstract] OR tumor*[Title/Abstract] OR neoplas*[Title/Abstract])  
Trastuzumab or Herceptin [Title/Abstract]  
1 OR 2  
3 And 4 Filters: Clinical trial; Humans
Total number of 20,924 patients were included in the selected studies, most of them followed-up the patients for more than 6 months. The summary of the characteristics of the studies are presented in Table 1.

### Table 1. Study characteristics

<table>
<thead>
<tr>
<th>No.</th>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Jadad scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B31(10)</td>
<td>394</td>
<td>&gt;6 months</td>
<td>Trastuzumab</td>
<td>Without Trastuzumab</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>BCIRG006(11)</td>
<td>1703</td>
<td>&gt;6 months</td>
<td>Trastuzumab</td>
<td>Without Trastuzumab</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Buzdar(12)</td>
<td>42</td>
<td>6 months</td>
<td>Trastuzumab</td>
<td>Without Trastuzumab</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Finher(13)</td>
<td>1010</td>
<td>&lt;6 months</td>
<td>Trastuzumab</td>
<td>Without Trastuzumab</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Hera(14)</td>
<td>5081</td>
<td>&gt;6 months</td>
<td>Trastuzumab</td>
<td>Without Trastuzumab</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Noah(15)</td>
<td>235</td>
<td>&gt;6 months</td>
<td>Trastuzumab</td>
<td>Without Trastuzumab</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>Pacs-04(16)</td>
<td>528</td>
<td>&gt;6 months</td>
<td>Trastuzumab</td>
<td>Without Trastuzumab</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Goldhirsch(17)</td>
<td>5102</td>
<td>&gt;6 months</td>
<td>Trastuzumab</td>
<td>Without Trastuzumab</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>Joensuu(18)</td>
<td>1500</td>
<td>&lt;6 months and &gt;6 months</td>
<td>Trastuzumab</td>
<td>Chemothe rapy without Trastuzumab</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>Schneider(19)</td>
<td>227</td>
<td>&lt;6 months and &gt;6 months</td>
<td>Trastuzumab</td>
<td>1 year or 12 weeks Trastuzumab</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>Gianni(20)</td>
<td>5102</td>
<td>&gt;6 months</td>
<td>Trastuzumab</td>
<td>Without trasuzumab</td>
<td>3</td>
</tr>
</tbody>
</table>

### The OS results

The results of the Cochran’s Q test revealed that the homogeneity between selected studies was appropriate (Cochran’s Q = 12.3437, I² = 0.35%), presented in the Galbraith plot. This plot shows that all studies are placed within the confidence interval of the regression line of Galbraith plot, and thus confirm that the homogeneity of the studies is sufficient. When the homogeneity criterion of the studies was met, the fixed model was used to combine the results of OS (Fig. 2).

The results of the relative weight of the studies showed that all studies had reported statistically similar effects with nonzero results. The significance level of chi square test was less than 0.05. Moreover, the logarithm of the hazard ratio for "moderate the impact of" was less than zero, indicating that the hazard ratio was between 0 and 1. Therefore, it is concluded that trastuzumab is effective in increasing patient survival (Fig. 3).

### The DFS Results

The results of the Cochran’s Q test indicated that homogeneity was not met among the selected studies (Cochran’s Q = 32.9034, I² = 0.69%). Therefore, the random model was applied to aggregate the results of DFS. Figure 4 demonstrates the heterogeneity of DFS within the selected studies with Galbraith plot.

The results in Table 3 clarify that the significance level of chi square test was less than 0.05, and thus it is concluded...
Trastuzumab as adjuvant therapy in patients with early stage breast cancer

**Table 3. The results of meta-analysis of DFS outcome**

<table>
<thead>
<tr>
<th>Study</th>
<th>Ln(HR)</th>
<th>SE Ln(HR)</th>
<th>Confidence interval</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>B31</td>
<td>-0.73</td>
<td>0.11</td>
<td>(-0.946,-0.514)</td>
<td>12.49</td>
</tr>
<tr>
<td>BCIRG006</td>
<td>-0.45</td>
<td>0.1</td>
<td>(-0.646,-0.254)</td>
<td>13.07</td>
</tr>
<tr>
<td>Buzdar</td>
<td>-2.27</td>
<td>1.11</td>
<td>(-4.44,-0.094)</td>
<td>0.462</td>
</tr>
<tr>
<td>Finher</td>
<td>-0.87</td>
<td>0.35</td>
<td>(-1.56,-0.184)</td>
<td>3.72</td>
</tr>
<tr>
<td>Hera</td>
<td>-0.46</td>
<td>0.09</td>
<td>(-0.636,-0.284)</td>
<td>13.65</td>
</tr>
<tr>
<td>Noah</td>
<td>-0.53</td>
<td>0.22</td>
<td>(-0.961,-0.099)</td>
<td>7.04</td>
</tr>
<tr>
<td>Pacs-04</td>
<td>-0.15</td>
<td>0.18</td>
<td>(-0.503,0.203)</td>
<td>8.72</td>
</tr>
<tr>
<td>Goldhirsch</td>
<td>-0.274</td>
<td>0.07</td>
<td>(-0.412,-0.137)</td>
<td>14.75</td>
</tr>
<tr>
<td>Joensuu</td>
<td>-0.892</td>
<td>0.271</td>
<td>(-1.423,-0.514)</td>
<td>5.51</td>
</tr>
<tr>
<td>Schneider</td>
<td>0.262</td>
<td>0.253</td>
<td>(-0.234,0.758)</td>
<td>5.93</td>
</tr>
<tr>
<td>Gianni</td>
<td>-0.274</td>
<td>0.07</td>
<td>(-0.412,-0.137)</td>
<td>14.75</td>
</tr>
<tr>
<td>Overall</td>
<td>-0.419</td>
<td>0.077</td>
<td>(-0.569,-0.269)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 4. The summary of risk of BIAS results**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>B31</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
</tr>
<tr>
<td>BCIRG006</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
</tr>
<tr>
<td>Buzdar</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Finher</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>HERA</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>NOAH</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>PACS-04</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>Gianni</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Goldhirsch</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Joensuu</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Schneider</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

that trastuzumab as adjuvant therapy is effective in improving DFS (Fig. 5).

Risk of bias results is presented in Table 4.

**Discussion**

The present study aimed at evaluating the effectiveness of trastuzumab on OS and DFS as adjuvant therapy in the treatment of early stage BC. The primary results of RCTs revealed that the hazard ratio (HR) of OS in trastuzumab protocol was significantly lower than ordinary chemotherapy. However, Buzdar study reported a HR equal to 1, with no difference between the 2 treatment groups. Maximum HR was reported in Schneider B.P study (HR= 1.4), and minimum HR was related to FinHer study (HR= 0.55).

The primary results of RCTs revealed a significant in-
crease in DFS for trastuzumab adjuvant therapy. Schenei
der study, with HR = 1.3, has reported the highest effective-
ness rate; and Buzdar study, with HR = 0.103, showed the
lowest effectiveness rate for trastuzumab adjuvant therapy.
The number of patients in RCTs varied from 42 to 5102.

This meta-analysis was conducted to determine the rela-
tive weights of various studies. We combined the HRs and
the number of patients in the studies to obtain more accu-
rate and reliable results. We meta-analyzed the OS with 9
RCTs and DFS with 11 RCTs.

Considering the results of the relative weight of the se-
lected studies and HR, Goldhirsch study reported the max-
imum influence on the OS of the patients, with numerical
value of 28.85. The second best results belonged to Luca
Gianni study, with the numerical value of 19.37. FinHer
study, with the value of 0.999, had the lowest effectiveness
in this regard. Buzdar study, with the value of 1.000.8, showed
that the rate of OS with and without trastuzumab is the same in BC
patients.

When analyzing DFS, we found that Luca Gianni and
Goldhirsch studies, with the value of 11.21, reported the maximum effectiveness on DFS. The lowest effectiveness
was shown in Buzdar study, with the value of 0.047. Thus,
it is concluded that trastuzumab is significantly effective in
improving DFS.

The most serious side effect of trastuzumab was improve-
ment of congestive heart failure (CHF) (24), but some studies
stated that the risk of CHF for BC patients could be con-
sidered zero (26). Furthermore, the results of studies showed that if cardiac performance is monitored during the
treatment time, the damage would not be life-threatening and
is allowed to continue (24). Also, it is recommended that
trastuzumab be added only to anthracycline-free chemother-
apy regimens (25).

The FinHer study (9 weeks treatment with trastuzumab)
demonstrated acceptable and appropriate effectiveness in
increasing OS and DFS (26), however, when considering the
low relative weight of the study, it is clear that the re-

results would not be confident enough and could not be con-
sidered proportional to the total BC population.

In summary, the main findings of this meta-analysis sup-
port and update the results of previous studies and confirm
that trastuzumab is effective in improving OS and DFS in
BC patients. These findings could help healthcare providers
to prescribe effective medication for their patients. Like-
wise, policy makers could use these results as a primary data
to provide better coverage for BC patients. Moreover, comp-
dimentary data would be the results of cost-effective-
ness analysis.

Conclusion
The addition of trastuzumab as adjuvant therapy in early
stages of BC in HER2 positive patients could increase OS
and DFS of the patients effectively. The result of FinHer
study encourage conducting further studies on this treat-
ment protocol to manage BC.

Recommendations for the future
Considering the shorter treatment period of FinHer study
comparing to other studies and because of lower costs and
lower side effects, it is strongly recommended that larger trials be conducted in this field.

Conflict of Interests
The authors declare that they have no competing interests.

References
2. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T,
et al. Lapatinib plus capecitabine for HER2-positive advanced breast
Mortality and prevalence in the European Union 1998. IARC Cancer
4. Corle DK, Shabbaugh C, Mateaki DJ, Coyne T, Paskett ED, Cahill J.
Self related quality of life measures: Effect of change to a low fat, high-
fiber, fruit and vegetable enriched diet. Ann Behav Med. August
2001;23(3):104-16.
5. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson
NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2
6. Perez EA, Romond EH, Suman VJ, Jeong JH, Davidson NE, Geyer CE
Jr, et al. Four-year follow up trastuzumab plus adjuvant chemotherapy
for operable epidermal growth factor receptor-2+ positive breast cancer:
2011 Sep 1;29(25):3366-73.
7. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E,
Proctor M, Suter M, et al. 2 years versus 1 year of adjuvant trastuzumab
for HER2-positive breast cancer (HERA): a randomised controlled study.
8. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A,
Tjulandin S, et al. Neoadjuvant chemotheraphy with trastuzumab fol-
lowed by adjuvant trastuzumab versus adjuvant chemotherapy alone,
in patients with HER2-positive locally advanced breast cancer (the
NOAH trial): a randomized controlled superiority trial with a par-
Human breast cancer: correlation of relapse and survival with amplifi-
10. Bartsch R, Wenzel C, Steger GG. Trastuzumab in the management of
early and advanced stage breast cancer. Biologics. 2007 Mar;1(1):
19-31.
11. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson
12. Smith I, Procter M, Gelber RD, Guillaume S, Feyerelroiva S, Dowsett M, et al. 2-year follow-up of trastuzumab after adjuvant chem-
otherapy in HER2-positive breast cancer: a randomised controlled trial.
RL, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluoroura-
cil, epirubicin, and cyclophosphamide chemotherapy and concurrent
trastuzumab in human epidermal growth factor receptor-2 positive oper-
able breast cancer: an update of the initial randomized study popul-
ation and data of additional patients treated with the same regimen.
14. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V,
Asola R et al. Adjuvant docetaxel or vinorelbin with or without
20.
15. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A,
Tjulandin S, et al. Neoadjuvant chemotherapy with trastuzumab fol-
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