META-ANALYSIS

Deescalating Adjuvant Trastuzumab in HER2-Positive Early-Stage Breast Cancer: A Systemic Review and Meta-Analysis

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Abstract

Background: One year of adjuvant trastuzumab in combination with chemotherapy is the standard of care in early-stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer. Existing data on shortening trastuzumab treatment show conflicting results.

Methods: A search of PubMed and abstracts from key conferences identified randomized trials that compared abbreviated trastuzumab therapy to 1 year of treatment in early-stage HER2-positive breast cancer. Hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted for disease-free survival (DFS) and overall survival (OS). Subgroup analyses evaluated the effect of nodal involvement, estrogen receptor expression, and the duration of abbreviated trastuzumab (9–12 weeks vs 6 months). Odds ratios (ORs) and 95% confidence intervals were computed for prespecified cardiotoxicity events including cardiac dysfunction and congestive heart failure. P values were two-sided.

Results: Analysis included six trials comprising 11,603 patients. Shorter trastuzumab treatment was associated with worse DFS (HR = 1.14, 95% CI = 1.05 to 1.25, P = .002) and OS (HR = 1.15, 95% CI = 1.02 to 1.29, P = .02). The effect on DFS was not influenced by estrogen receptor status (P for the subgroup difference = .23), nodal involvement (P = .44), or the different duration of trastuzumab in the experimental arm (P = .09). Shorter trastuzumab treatment was associated with lower odds of cardiac dysfunction (OR = 0.67, 95% CI = 0.55 to 0.81, P < .001) and congestive heart failure (OR = 0.66, 95% CI = 0.50 to 0.86, P = .003).

Conclusions: Compared with 1 year, shorter duration of adjuvant trastuzumab is associated with statistically significantly worse DFS and OS despite favorable cardiotoxicity profile. One year of targeted HER2 treatment should remain the standard adjuvant treatment in early-stage HER2-positive disease with appropriate cardiac monitoring.

Overexpression of human epidermal growth factor receptor 2 (HER2) occurs in 15%–20% of early-stage breast cancers (1). Randomized control trials (RCTs) exploring the addition of trastuzumab to standard adjuvant chemotherapy have shown a statistically significant improvement in outcome (2–4). The majority of studies explored 1 year of trastuzumab therapy, which subsequently became the standard of care in early-stage HER2-positive breast cancer (5).

There is uncertainty regarding the optimal duration of adjuvant trastuzumab. The decision to treat for 1 year was somewhat arbitrary, because there were no clinical or preclinical data to guide the optimal duration of treatment (6). Although most women tolerate treatment with trastuzumab well, this drug can cause cardiac dysfunction, and longer duration of treatment is associated with higher odds for cardiotoxicity (4,7–9). Additionally, trastuzumab requires periodic heart
function monitoring and regular 3-weekly treatment administra-
tion and has financial implications (10).

The FinHER study showed that the addition of 9 weeks of
traztuzumab to standard chemotherapy improved disease-free
survival (DFS) and overall survival (OS) (11,12) compared with
placibo, with a magnitude of effect similar to this seen in RCTs
evaluating 1 year of traztuzumab (2–4). Consequently, several
RCTs compared a shorter duration of adjuvant traztuzumab
with the standard 1-year treatment with conflicting results (13–
18). Although the PERSEPHONE trial, the largest study evaluat-
ing abbreviated duration of adjuvant traztuzumab, did meet its
objective of observing noninferiority (17), other large-scale stud-
ies, including the SOLD study and the recently updated PHARE
study, failed to show noninferiority (16,18).

The magnitude of benefit from adjuvant traztuzumab varies
and depends typically on stage and hormone receptor expres-
sion, with lower absolute benefit in patients with less-advanced
stage and hormone receptor-positive disease (19–21). The in-
fuence of these classical prognostic factors on the difference in
benefit between 1 year of traztuzumab and abbreviated therapy
is unknown.

Here, we report on a meta-analysis evaluating the efficacy
and toxicity of shorter duration of adjuvant traztuzumab com-
pared with 1 year of treatment in women with HER2-positive
eyard stage breast cancer. We also aimed to identify whether
specific subgroups, defined by nodal status and estrogen recep-
tor (ER) expression, have a differential relative effect from
shorter traztuzumab treatment. We hypothesized that a shorter
duration of traztuzumab would be associated with worse out-
come despite favorable cardiac toxicity.

Methods

Literature Review and Study Identification

A literature search using MEDLINE (Host: PubMed) identified
RCTs published between January 2008 and December 31, 2018
that compared 1 year of adjuvant traztuzumab with a shorter
duration of therapy in early-stage HER2-positive breast cancer.
The terms “adjuvant,” “breast cancer,” and “traztuzumab” and
similar terms were cross-searched by using the following search
algorithm: (adjuvant OR neoadjuvant) AND (breast neoplasm
MeSH OR [(breast OR mammary) AND (carcinoma OR malignan-
OR neoplasm OR tumor)]) AND (Herceptin OR traztuzumab OR
anti HER2 OR HER2 monoclonal antibody). To improve the sen-
tivity, we also searched databases from the Annual Meetings of
the American Society of Clinical Oncology (2015–2018) and
the San Antonio Breast Cancer Symposium (2015–2018) and
reviewed citation lists. The search was restricted to the English
language only.

Data Extraction

Data were collected independently by two reviewers (H.
Goldvaser and Y. Korzets). Discrepancies were resolved by a
third reviewer (E. Amir). Collected data included year of publica-
tion, number of patients, median age, proportion of premeno-
pausal patients, and median duration of follow-up. We also
collected trial-level tumor characteristics including median tu-
mor size and the proportion of patients with nodal involve-
ment, high-grade tumors, and hormone receptor-positive
disease. For the efficacy analyses, data on the hazard ratio (HR)
and 95% confidence intervals (CIs) for DFS and OS were
collected. Data on the number of DFS and distant relapse events
were also collected as were the number of patients at risk in
each group. When available, data on DFS for subgroups based
on ER status (positive and negative) and nodal status (positive
and negative) were extracted. We then collected data on cardiac
toxicity including the number of congestive heart failure (CHF)
and cardiac dysfunction events as defined by the Cardiac
Review and Evaluation Committee (22) or definitions closely
related to these criteria (referred to as cardiac dysfunction
henceforth).

Data Synthesis and Statistical Analysis

The primary analysis compared DFS and OS between patients
who were randomly assigned to short traztuzumab treatment
with those randomly assigned to 1 year of treatment. HR and
95% CI for DFS and OS were pooled in a meta-analysis using
RevMan 5.3 (The Cochrane Collaboration, Copenhagen,
Denmark) using generic inverse variance. Subgroup analyses
were performed to explore the effect of abbreviated traztuzu-
mb treatment based on ER expression and nodal status.
Additionally, the difference between the shorter-duration treat-
ments of the included studies (9–12 weeks vs 6 months) was
also analyzed in a subgroup analysis. Differences between
the subgroups were assessed using methods describes by Deeks et
al. (23). For the number of DFS, distant relapse and cardiotoxic-
ity events, pooled estimates of odds ratio (OR) were computed
using the Mantel-Haenszel odds ratio method (24) unless the
absolute event rates in the experimental and control groups
were less than 1% in at least one study, in which case the Peto
one-step odds ratio (25) was used. Absolute difference in out-
comes and the number needed to treat (NNT) with shorter tras-
tuzumab therapy to avoid one event were computed. Statistical
heterogeneity was reported using Cochran Q and I² statistics.
Statistically significant heterogeneity was defined as Cochran Q
P less than .10 or I² greater than 50%. Fixed-effects modeling was
used in the absence of statistically significant heterogeneity;
otherwise, the random-effects model was used. To address the
potential influence of clinical heterogeneity between studies, a
sensitivity analysis using random-effects modeling was con-
ducted for analyses performed initially using fixed effects.
Additional sensitivity analyses included the exclusion of studies
in which traztuzumab was not always given concurrently with
chemotherapy, the exclusion of studies in which there was con-
tamination reported in more than 10% of the study population,
and the exclusion of studies in which anthracycline dosage of
the experimental and the control arm was not identical. Meta-
regression analyses explored the influence of duration of follow-
up, median age, and the proportion of premenopausal women and
those with larger (>2 cm) tumor size and high-
grade tumors. The analysis was performed first for DFS and
then repeated for OS. Meta-regression was performed using
SPSS version 25 (IBM Corp, Armonk, NY) using the weighted
least squares (mixed-effects) function (26). Statistical signifi-
cance was defined as P less than .05. No corrections were made
for multiple testing.

Results

The search identified 1674 studies. After exclusions, nine pub-
cations (13–18,27–29) reporting on outcomes from six studies
were included in the analysis (cardiotoxicity outcomes from
two studies were reported separately from efficacy data [27,28]).
Details of the study selection schema are shown in Figure 1. Included studies comprised 11,603 patients. Individual study characteristics are shown in Table 1. In one study, reassessment of HER2 status found that 17.6% of the patients were HER2 negative (29). This study was therefore subjected to a sensitivity analysis. The duration of adjuvant trastuzumab in the control group was 1 year in all studies, and the duration of trastuzumab in the experimental group was either 9–12 weeks (15,16,29) or 6 months (13,14,17,18). In four studies, the adjuvant chemotherapy composed of an anthracycline and taxane regimen and treatment with trastuzumab was started concurrently with chemotherapy (13,15,16,29). Of note, in one study, compared with the control arm, the dose of anthracycline given in the abbreviated arm was lower (15); therefore, this study was also subject to sensitivity analysis. In two studies, different combinations were allowed, but most patients were treated with a combination of anthracyclines and taxanes, and only a minority of the patients (approximately 10%) were treated with taxanes only (14,18) or taxane-based chemotherapy (17). In these two studies, trastuzumab was given both in sequence and concurrently with chemotherapy (14,17,18).

Efficacy

All six studies reported on DFS and OS (13–18,29) and three studies reported on distant relapse (13,14,16,18). Compared with 1 year of treatment, shorter trastuzumab treatment was associated with worse DFS (HR = 1.14, 95% CI = 1.05 to 1.24, P = .003) and OS (HR = 1.15, 95% CI = 1.02 to 1.29, P = .02) (see Figure 2, A and B). Studies using trastuzumab for 9–12 weeks showed worse DFS than trastuzumab treatment for 6 months (HR = 1.28, 95% CI = 1.09 to 1.50 vs HR = 1.09, 95% CI = 0.98 to 1.20), but this did not reach statistical significance (Psubgroup difference = .09). For OS no difference was seen between the two abbreviated trastuzumab durations (P = .44). After an estimated median follow-up of 71 months, shorter treatment with trastuzumab was associated with an absolute increase in DFS events of 2.3% (NNT 43). Similarly, after an estimated median follow-up of 76.8 months, there was a 1.5% higher absolute risk of distant relapse with abbreviated trastuzumab therapy (NNT 67).

Four studies reported DFS by nodal status (13–16,18) and five studies reported data by ER status (13–18). The inferior outcomes with abbreviated trastuzumab treatment were of greater magnitude for node-positive compared with node-negative disease and for ER-negative compared with ER-positive disease, although neither of these differences met statistical significance (P = .44 and P = .23, respectively; Figure 2, C and D). Multiple sensitivity analyses for all efficacy endpoints did not show a statistically significant effect on the results (see Supplementary Appendix A, available online). Results of the meta-regression are shown in Table 2. None of
| Trial, median follow-up | Chemotherapy* | Duration of short trastuzumab | Sample size | Age (median or mean), y | Premenopausal No., % | Tumor size | Nodal status† | Homone-receptor–positive, % | Grade 3, % |
|------------------------|---------------|-----------------------------|-------------|------------------------|---------------------|------------|--------------|--------------------------|------------|
| Pivot 2013, 2018 PHARE (14,18) 90 months | Investigators' choice of chemotherapy (at least 4 cycles)‡ followed by trastuzumab | 6 months | 3380 | 55 | NR | T≤2 cm: 43.7% T 2–5 cm: 45% T>5 cm: 11.3% | N0: 55% N1: 30.1% N2-3: 14.9% | 58.3 | 55.8 |
| Schneider 2015, E2198 (29) 77 months | P(175) + H q 21*4 — AC (60,600) q21*4 | 12 weeks | 227 | 49 | NR | NR | N0: 0% N1: 53.7% N2: 29.5% N3: 16.8% | 61.7 | NR |
| Mavroudis 2015, HORG (13) 47–51 months | FEC (700,75,700) q14*4 — D (75) + H q14*4 | 6 months | 481 | 54–56 | 38.1 | NR | N0: 21% N1: 42.4% N2: 22.3% N3: 14.3% N: 4.9% | 66.7 | 52.4 |
| Joensuu 2018, SOLD study (16) 62.4 months | D (80/100) + H q 21*3 — FEC (600,75,600) q21*3 | 9 weeks | 2174 | 56 | 33 | T≤2 cm: 56% T 2–5 cm: 41% T>5 cm: 3% | N0: 60% N1: 29% N2: 3: 11% N2–3: 15.8% | 66 | 66.5 |
| Conte 2017, Short-HER (15) 62.4 months | Experimental: D (100) q21*3 — weekly H 9 — FEC (60) q21*3 Control: AC (60,600) / EC (90/600) q21*4 — D (100) + H q21*4§ | 9 weeks | 1253 | 55 | 36 | Stage|| I: 39.1% II: 48.8% III: 15.9% | N0: 53.5% N1: 30.7% N2: 15.8% | 68.2 | NR |
| Earl 2018, PERSEPHONE (17) 64.8 months | Different regimen $§$ | 6 months | 4088 | 56 | 39 | T≤2 cm: 48% T 2–5 cm: 47% T>5 cm: 5% | N0: 59% N1: 28% N2–3: 13% | 69 | 67 |

*In parentheses the dose of chemotherapy is in mg/m², respectively. A = adriamycin; C = cyclophosphamide; D = docetaxel; DFS = disease-free survival; E = epirubicin; F = fluorouracil; H = trastuzumab (Herceptin); NR = not reported; P = paclitaxel; T = tumor size.
†Nodal status: N0: no lymph node metastases, N1: 1–3 lymph nodes, N2: 4–9 lymph nodes, N3: 10 or more.
‡Chemotherapy regimens used in the PHARE study: anthracycline based: 15.7%, anthracycline and taxanes: 73.3%, taxanes: 10.9%, other: 0.1%. Trastuzumab was given concurrently with chemotherapy in 56.4% of the patients.
Chemotherapy used in the PERSEPHONE study: anthracycline based: 42%, anthracycline and taxanes: 48%, taxanes-based: 10%, other: less than 1%. Trastuzumab was given concurrently with chemotherapy in 47% of the patients.
§Patients age 65 years and older received 80 mg/m² docetaxel. In the control group 11% received 175 mg/m² paclitaxel.
¶Data for tumor size were not available; detailed data on stage.
Figure 2. Forest plots for efficacy, hazard ratio for A) disease-free survival (DFS), B) overall survival, C) DFS by nodal involvement (negative or positive), and D) DFS by estrogen receptor status (positive or negative). Hazard ratios for each trial are represented by squares, the size of the square represents the weight of the trial in the meta-analysis, and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated pooled effect. All P values are two-sided.
the evaluated variables had a statistically significant impact on DFS and OS.

Cardiotoxicity

Definitions for cardiac events and frequency of cardiac monitoring in individual studies are reported in Supplementary Appendix B (available online). Data on cardiac dysfunction and CHF were available in five studies (13,16,26–28) with an estimated median follow-up of 60.7 months. Shorter duration of trastuzumab was associated with statistically significantly lower odds for cardiac dysfunction (OR = 0.67, 95% CI = 0.55 to 0.81, P < .001) and CHF (OR = 0.66, 95% CI = 0.50 to 0.86, P = .003) (see Figure 3, A and B). These differences were comparable in studies using trastuzumab for six months and those using shorter periods of trastuzumab (P subgroup difference = .27 and P = .65 for cardiac dysfunction and CHF, respectively). The weighted absolute difference for cardiac dysfunction was 1.1% with an NNT of 89, and the weighted absolute difference for CHF was 1.0% with an NNT of 101. An additional study reported on all grade two or higher cardiac adverse events and found statistically significantly lower events with shorter trastuzumab treatment (15), but these data could not be included in the meta-analysis for cardiac dysfunction or CHF because of differences in the definition of cardiac toxicity.

Discussion

The discovery of trastuzumab has changed the natural history of HER2-positive breast cancer, and its addition to chemotherapy in early-stage disease is a gold standard (5). One year of adjuvant treatment has been the standard duration based on several large-scale adjuvant studies comparing 1 year of trastuzumab with placebo (2–4). Because trastuzumab is associated with cardiotoxicity and substantial direct and indirect costs,
investigating the impact of a shorter treatment duration is of interest.

In this meta-analysis, we found that a shorter duration of treatment resulted in statistically significantly worse DFS compared with 1 year of adjuvant trastuzumab. Over the course of almost 6 years of follow-up, this translated to a 2.3% absolute increase in DFS events, the majority of which were distant relapses. Unsurprisingly, therefore, shorter trastuzumab treatment was associated with worse OS. The statistically significant reduction in cardiotoxicity with shorter treatment did not translate into a statistically significant impact on OS, and the overall benefit of longer trastuzumab treatment on breast cancer outcome outweighed the increased risk of cardiac disease.

The studies included in this analysis were all designed as noninferiority trials. However, because of difficulties in combining noninferiority studies into a meta-analysis (30), we used data to infer inferiority of abbreviated trastuzumab therapy.

Tumor size and nodal involvement affect the absolute benefit from adjuvant treatment in early-stage HER2-positive breast cancer. Patients with small tumors and without nodal involvement have relatively low risk of recurrence. A singlarm study has shown that in patients with small tumors without nodal involvement, deescalating chemotherapy to only 12 weeks of weekly paclitaxel in combination with 1 year of trastuzumab results in excellent outcome (31). Exploratory analysis from two of the included studies in this meta-analysis did recognize a lower-risk population with comparable DFS between both arms (20,32). These data support the importance of finding a population with a lower risk that will not be harmed by deescalating adjuvant treatment. In the current analysis, many patients had high risk of recurrence with frequent nodal involvement or large tumors. Additionally, the vast majority were treated with polychemotherapy in addition to trastuzumab. Although compared with patients with node-positive disease, patients with node-negative disease had a lower degree of inferiority from abbreviated treatment; this difference was not statistically significant. Therefore, current data do not support shortening trastuzumab treatment when using the deescalated chemotherapy regimen of 12 weeks of single-agent paclitaxel even in low-risk patients.

Deescalating trastuzumab treatment could have several advantages. It is associated with reduced risk of cardiotoxicity (7,8,10,21) and lower cost compared with 1 year of treatment. Therefore, further research in selected low-risk populations is warranted to better tailor treatment in early-stage HER2-positive disease.

Although prior meta-analyses have reported similar results (9,33), neither of these studies included data from the E2198 study (29). Additionally, the current analysis was able to include updated results from the PHARE study, with much longer follow-up, in contrast to prior meta-analyses (18). Finally, in the current analysis, we performed meta-regression to evaluate the impact of several important characteristics, including tumor size, menopausal status, age, and grade on results. To our knowledge, these variables have not been tested in meta-regression analyses in prior analyses. The combination of more-inclusive eligibility criteria, data based on longer follow-up, and more extensive meta-regression likely result in the current analysis being a more robust evaluation of deescalated trastuzumab in early breast cancer than those reported previously.

This study has limitations. First, because this is a literature-based rather than an individual patient meta-analysis, data on comorbidities and concurrent medications were not available and could not be adjusted for. Second, there was limited information about reversibility of cardiac toxicity, and because of differences between studies in the duration of follow-up, we were unable to report actuarial rates of cardiotoxicity. Additionally, to better assess the potential benefit of reduced cardiotoxicity on mortality, a longer duration of follow-up is required. Third, there was some variability in the definitions of cardiac events among the included studies. Furthermore, we were unable to exclude ascertainment bias for cardiac toxicity because these studies were open label rather than placebo controlled. Additionally, in two studies there was a lack of consistency in the frequency of cardiac monitoring, with more assessments performed in the control group (13,29). This may have led to increased diagnosis of cardiac dysfunction in the control group. Fourth, although most included patients were treated with a combination of anthracyclines and taxanes, there was variability between included studies in the chemotherapy regimens administered, and in one study the dosage of anthracyclines was reduced in the abbreviated arm (15), which might also reduce the treatment efficacy in the experimental arm. Additionally, the duration of shorter trastuzumab treatment was not consistent among the included studies, and in two studies administration of trastuzumab in sequence with chemotherapy was allowed (14,17,18). This heterogeneity could have influenced our results.

In conclusion, compared with 1 year of treatment, abbreviated durations of trastuzumab in early-stage HER2-positive disease are associated with worse DFS and OS, but with reduced cardiotoxicity. One year of anti–HER2-targeted treatment along with cardiac monitoring should remain the standard of care in this population. Patients with low-risk disease, mainly small, ER-positive, node-negative disease, may be an appropriate group for further prospective study to evaluate shorter trastuzumab treatment together with deescalated chemotherapy regimens such as 12 weeks of paclitaxel.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Notes**

Affiliations of authors: Division of Medical Oncology, University of Toronto and Princess Margaret Cancer Centre, Toronto, Canada (HG, DS, DR, EA); Davidoff Cancer Center, Beilinson Hospital, Rabin Medical Center, Petach Tikva, Israel (HG, YK, DS, RS, MS); Sackler Faculty of Medicine, Tel Aviv University, Israel (HG, YK, RS, MS); Department of Radiation Oncology, University of Toronto and Princess Margaret Cancer Centre, Toronto, Canada (YK); Ted Rogers Program in Cardiotoxicity Prevention, Toronto General Hospital, Peter Munk Cardiac Center, University of Toronto, Toronto, Canada (PT).

Dr Goldvaser declared an honorarium payment from Roche as an invited speaker. Dr Yerushalmi declared a contracted grant and personal fees from Roche for expert consulting. Dr Sarfatty declared an honorarium payment from Roche and Novartis as an invited speaker. Dr Amir declared personal fees from Genentech/Roche for expert testimony. The other authors have no conflicts of interest to declare.
