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REVIEW

Adjuvant endocrine therapy in HER2-positive breast cancer patients: systematic review and meta-analysis

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Background: Approximately 50% of human epidermal growth factor receptor 2 (HER2)-positive breast cancer lesions express hormone receptors. These tumors present a unique therapeutic challenge, and the optimal endocrine therapeutic approach remains controversial. We aimed to study the optimal adjuvant endocrine therapy in this setting, to better establish the basis for clinical recommendations in HER2-positive disease.

Methods: We conducted a literature search up to May 2020, in which we identified randomized controlled trials (RCTs) that investigated the efficacy of various adjuvant hormonal therapies among premenopausal and postmenopausal patients with hormone receptor (HR)-positive, HER2-positive early breast cancer. Disease-free survival (DFS) was calculated with the random effect model and hazard ratios (HRs) with 95% confidence intervals (CI).

Results: Six RCTs ($N = 5390$ patients) were included in the final analysis. There was no significant difference in DFS between adjuvant treatment with aromatase inhibitors and tamoxifen (HR 0.99, 95% CI 0.68-1.44, $P = 0.96$). Furthermore, after omitting the ALTTO trial, as it did not randomize patients to hormonal therapy, no significant difference was observed between the two protocols (HR 1.06, 95% CI 0.65-1.73, $P = 0.81$).

Conclusion: Our study demonstrates similar DFS with tamoxifen and aromatase inhibitors as adjuvant endocrine treatment in HER2-positive HR-positive early-stage breast cancer patients. Future larger prospective studies focusing on the various contemporary endocrine regimens are warranted to validate our findings.

Key words: breast cancer, endocrine therapy, HER2-positive, adjuvant treatment

INTRODUCTION

Approximately 20% of breast cancers[1] present with overexpression of human epidermal growth factor 2 (HER2), and 70% present with expression of hormone receptors (HR-estrogen receptor and/or progesterone receptor).[2,3] HR-positive (luminal B, HER2-positive) and HR-negative (HER2-positive, non-luminal) represent two different biologic subgroups within the HER2-positive group.[4] The concurrent expression of HER2 and hormone receptors may affect the natural history, response to therapy and oncologic outcomes of patients with HER2-positive early-stage breast cancer.[5] Clinical outcomes differ between the two subgroups. Patients with HR-negative/HER2-positive tumors have a high risk of early relapse, while those with HR-positive/HER2-positive disease have better overall survival (OS) outcomes, and show a relatively constant annual risk of recurrence over time.[6,7] Moreover, HER2-positive tumors have distinct patterns of relapse according to HR expression.[8] Specifically, patients with HR-positive tumors are more likely to experience first recurrence in the bone and less likely in the brain or visceral organs compared with those with HR-negative disease.[9-11] Additionally, patients with HR-positive/HER2-positive tumors have a slightly lower response to adjuvant trastuzumab compared with HR-negative/HER2-positive tumors.[7]

Endocrine therapy is administered for a duration of 5-10 years to patients with HR-positive early breast cancer.[12-14] The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis demonstrated that aromatase inhibitors are superior to tamoxifen in reducing the risk of recurrence during years 0-4 of treatment, but not significantly thereafter.[15] A 2.1% absolute improvement in 10-year breast cancer mortality was observed with the administration of aromatase inhibitors over tamoxifen.[15] Recent data among premenopausal, early-stage breast cancer patients showed that aromatase inhibitors with the addition of ovarian function suppression improve disease-free survival (DFS) by approximately 4% at 8 years [hazard ratio (HR) 0.77]. There was an absolute 1% OS benefit

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among high-risk, early-stage breast cancer patients who received chemotherapy and ovarian suppression in addition to endocrine therapy with either tamoxifen or aromatase inhibitors (92.1% versus 93.3%, respectively).[16]

The optimal endocrine therapy approach remains controversial in patients with HR-positive/HER2-positive disease. An analysis that included data from the ATAC, BIG 1-98 and TEAM trials in postmenopausal patients indicated that postmenopausal women with HR-positive/HER2-positive disease derive a lower benefit from the use of aromatase inhibitors over tamoxifen (HR 1.13, 95% CI 0.75-1.71) compared with those with HER2-negative tumors (HR 0.70, 95% CI 0.56-0.87). However, the small number of patients with HR-positive/HER2-positive breast cancer included in that analysis ($n = 1092$ across three trials) and the small number of events ($n = 111$) precluded strong conclusions. Additionally, trastuzumab was not available at the time for the majority of patients included in those trials.[17]

Aromatase inhibitors demonstrated superiority to tamoxifen in women with HR-positive/HER2-negative disease (5.4% absolute benefit in DFS at 8 years, HR 0.70) among the population of premenopausal patients who were treated with ovarian function suppression in the SOFT/TEXT trials. However, tamoxifen resulted in a superior DFS over aromatase inhibitors (3.2% absolute benefit in DFS at 8 years, HR 1.18) among the patients with HR-positive/HER2-positive disease. Notably, a comparatively small number of patients with HR-positive/HER2-positive breast cancer ($n = 695$) were included in the combined two trials. Similar to the trials with postmenopausal patients, only approximately one-half of HER2-positive women included in the SOFT/TEXT trials received anti-HER2 targeted therapy.[16] In a recent exploratory analysis of the ALTTO trial, the use of aromatase inhibitors was associated with reduced risk of DFS events.[18]

Taken together, the evidence on the optimal regimen among the various available endocrine therapies in premenopausal and postmenopausal patients with HR-positive/HER2-positive breast cancer remains limited to validate a single optimal approach.

The objective of this systematic literature search was to consolidate and compare evidence of adjuvant endocrine therapies in this setting, to better characterize the clinical recommendations most effective for patients with HR-positive/HER2-positive disease.

METHODS

Search strategy and study identification

A systematic literature search of the Medline database and key conferences up to May 2020 was carried out independently by two authors (SPH and AS). The following keywords were used: 'breast cancer', 'HER2', 'endocrine treatment', 'hormonal treatment', 'tamoxifen', 'aromatase inhibitors', 'letrozole', 'anastrazole', and 'exemestane'. Any discrepancies were resolved by discussion with a third author (IW). This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19]

Selection criteria and data extraction

Criteria for inclusion in the meta-analysis involved eligible studies satisfying all of the following measures: (i) phase III randomized controlled trials (RCTs); (ii) RCTs including HER2 patients who received adjuvant hormonal therapy in the experimental arm; (iii) studies with available information on DFS rates in the experimental and control arms to estimate the odds ratio (OR) and 95% confidence interval (CI). Exclusion criteria were: (i) non-RCTs conducted to evaluate the role of hormonal adjuvant treatment in HER2-positive breast cancer patients; (ii) RCTs investigating hormonal treatment in patients with breast cancer subtypes other than HER2.

Study objectives

The primary objective of this meta-analysis was to determine the efficacy of the different available adjuvant endocrine treatment options as measured by DFS in patients with HR-positive/HER2-positive early-stage breast cancer. Two main analyses were conducted: (i) all RCTs irrespective of menopausal status or primary endpoint of the RCT trials; (ii) RCTs without inclusion of the ALTTO trial, in which the primary objective was to optimize different anti-HER2 treatments and did not randomize patients to hormonal therapy.

Statistical analysis

HRs and 95% CIs were calculated for the effect of different hormonal treatments in terms of DFS. Heterogeneity was observed with the I^2 index. Since the trials were found to be heterogenetic, a random effects model was applied, and the inverse variance-weighted method was used to calculate the CI. A funnel plot was drawn to assess publication bias. R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for the statistical analysis.

RESULTS

The literature search identified 113 publications (Figure 1). Nine additional studies were identified through other sources. After the exclusion of 111 non-relevant articles, nine potentially eligible RCTs were considered,[16,17,20-24] including two updates of studies that had been published earlier, leading to a final number of six RCTs for inclusion in the current meta-analysis (Figure 1).

The main characteristics of the included RCTs are listed in Table 1. All six trials were phase III RCTs, and they included a total of 35 680 patients. Overall, 5390 (15%) patients had HER2-positive disease, ranging from 6.3% ($n = 389$) in the BIG 1-98 trial, 10.6% ($n = 178$) in the ATAC trial, 11.9% ($n = 366$) in the SOFT trial, 12.3% ($n = 525$) in the TEAM trial, 12.3% ($n = 329$) in the TEXT trial and 100% in the ALTTO trial.

Four trials included postmenopausal patients, while the TEXT and SOFT trials[16] included only premenopausal patients. In the present meta-analysis, we included only

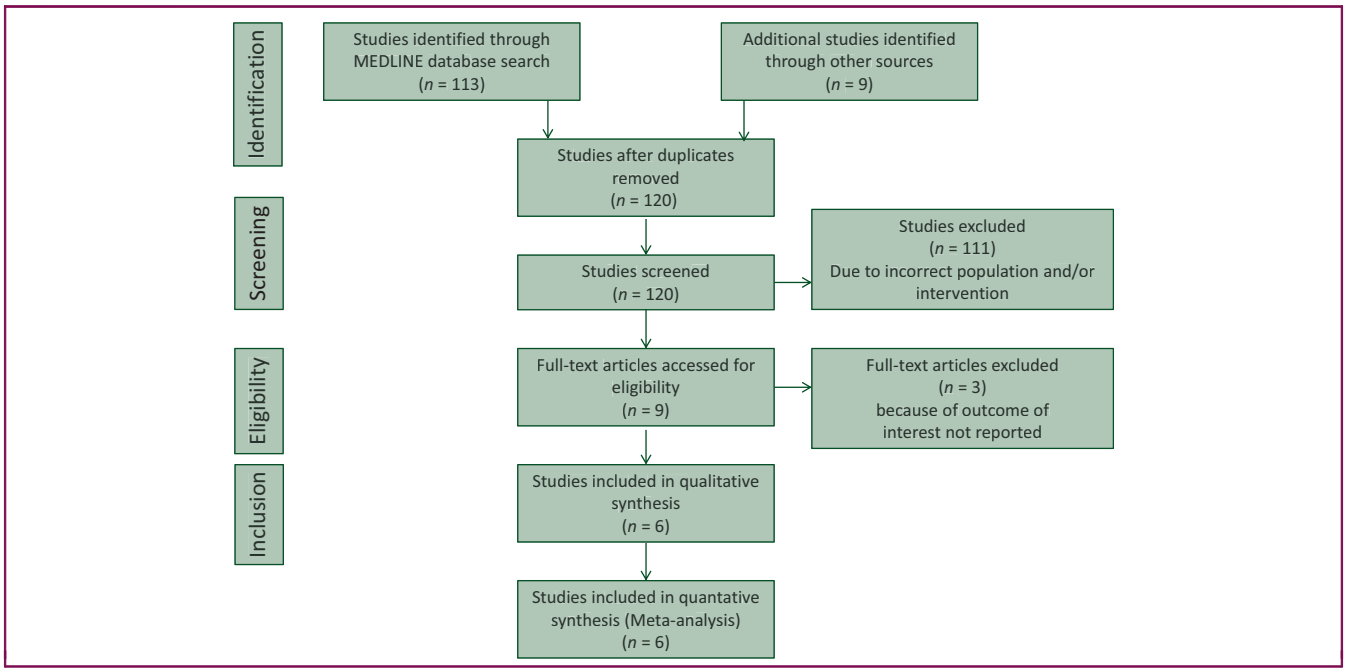

Figure 1. **The PRISMA flow chart summarizing the process for the identification of eligible randomized controlled trials.**

Table 1. **Main characteristics of the randomized controlled trials included in the present meta-analysis**

Study	Study design	Primary endpoint	Menopausal status	Treatment arms	HER2-positive patients, *n*	Total patients, *N*
TEAM	RCT phase III	DFS	Postmenopausal patients	Patients randomized in a 1 : 1 ratio to receive 5 years of oral exemestane monotherapy or a sequential scheme of oral tamoxifen followed by exemestane for a total duration of 5 years[a]	525 (12.3%)	9779
ATAC	RCT phase III	DFS	Postmenopausal patients	Patients randomized in a 1 : 1 : 1 ratio to receive anastrozole, tamoxifen or anastrozole plus tamoxifen	178 (10.6%)	5880
BIG 1-98	RCT phase III	DFS	Postmenopausal patients	Patients randomized in a 1 : 1 : 1 : 1 ratio to receive monotherapy with tamoxifen or letrozole for five years or sequential therapy comprising letrozole followed by tamoxifen or vice versa[b]	389 (6.3%)	8010
SOFT	RCT phase III	DFS	Premenopausal patients	Patients in a 1 : 1 : 1 ratio to receive tamoxifen, tamoxifen plus ovarian suppression or exemestane plus ovarian suppression for 5 years	366 (11.9%)	3066
TEXT	RCT phase III	DFS	Premenopausal patients	Patients were randomized in a 1 : 1 ratio to receive tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression for 5 years[c]	329 (12.3%)	2672
ALTTO	RCT phase III	DFS	Premenopausal patients (n = 1715, 47.6%) and postmenopausal (n = 1888, 52.4%)[e]	Patients were randomized in a 1 : 1 : 1 : 1 ratio to one of the following 1-year duration adjuvant anti-HER2 treatment arms: trastuzumab alone, lapatinib alone or trastuzumab followed by lapatinib and trastuzumab plus lapatinib[d]	6273 (100%) of them 57.4%, n = 3603, hr positive[f]	6273

DFS, disease-free survival; hr, hormone receptor; RCT randomized control trial.
[a] The protocol was amended after the publication of the IES trial (13 December 2004). Patients assigned to tamoxifen were switched after 2.5-3.0 years to exemestane therapy for a total duration of 5.0 years of treatment.
[b] From 1998 to 2000, women were initially randomly assigned to receive monotherapy with letrozole (2.5 mg orally daily) or tamoxifen (20 mg orally daily) for 5 years, and later, from 1999 to 2003, they were randomly assigned to one of four arms.
[c] Bilateral oophorectomy or ovarian irradiation was allowed at least 6 months of receipt of triptorelin.
[d] As per physician's choice, anti-HER2 treatment could be administered at the completion of chemotherapy.(design 1), after anthracycline-based chemotherapy and concomitantly with a taxane (design 2), or concurrently with an anthracycline-free regimen [six cycles of docetaxel and carboplatin (i.e. Taxotere Carboplatin Herceptin)].
[e] Among hr-positive patients.
[f] Only 3603 out of 6273 included in the analysis (57.4%) were hr-positive.

patients from the SOFT and TEXT trials who were treated with ovarian suppression. The ALTTO trial included both premenopausal patients (n = 1715, 47.6%) and postmenopausal patients (n = 1888, 52.4%) with HR-positive disease; however, there were no data on ovarian suppression treatment.

DFS and OS

All six RCTs reported the DFS outcomes. The median follow-up was 2-3 years in the ATAC, BIG1-98 and TEAM trials,[17] 8 years in the SOFT and TEXT trials[16] and 6.9 years in the ALTTO trial.[24] Analysis of all six trials included in our meta-analysis ($n = 5390$) revealed no significant difference between adjuvant treatment with aromatase inhibitors versus adjuvant treatment with tamoxifen (HR 0.99, 95% CI 0.68-1.44, $P = 0.96$; $I^2 = 72.9\%$, $P = 0.005$) (Figure 2A). A funnel plot with pseudo 95% confidence limits (Figure 2B) demonstrated the effect of hormonal therapy estimated from individual studies (horizontal axis) against the study size (vertical axis), and it revealed that the symmetric inverted funnel shape suggested that a publication bias was unlikely. After the omission of the ALTTO trial with its different study design, analysis of the five remaining trials yielded no significant difference between adjuvant treatment with aromatase inhibitors and that with tamoxifen (HR 1.06, 95% CI 0.65-1.73, $P = 0.81$; $I^2 = 71.6\%$, $P = 0.01$) (Figure 3).

DISCUSSION

Our meta-analysis included a total of 5390 women with HR-positive/HER2-positive early-stage breast cancer. The results demonstrated no difference in DFS between adjuvant endocrine treatment with aromatase inhibitors and tamoxifen.

HR-positive/HER2-positive tumors represent a unique subgroup that exhibits distinct clinical and biological behavior. Preclinical models of HR-positive/HER2-positive tumors revealed that concurrent anti-HER2 and endocrine therapy is needed to inhibit tumor growth.[25,26] Clinical data demonstrated late relapses with more frequent bone involvement in HR-positive/HER2-positive tumors than in patients with HR-negative/HER2-positive disease[27,28] suggestive of a distinctive clinical course.[29,30] In the neoadjuvant setting, lower rates of pathological complete response (pCR) were reported for HR-positive/HER2-positive tumors, with a lower association between a pCR and a favorable outcome.[31,32] In the NSABP B-52 trial,[33] the overall pCR rates were modestly higher with the addition of endocrine therapy to chemotherapy and anti-HER2 treatment. In the metastatic setting, the PERTAIN and ALTERNATIVE trials revealed that the use of dual HER2-targeted therapy together with an aromatase inhibitor was an effective treatment strategy for HR-positive/HER2-positive metastatic breast cancer.[34,35] Taken together, the preclinical and clinical data suggests the advantage of simultaneous inhibition of the HER2 and estrogen receptor signaling pathways. However, the optimal adjuvant treatment strategy for HR-positive/HER2-positive breast cancer has not yet been determined.

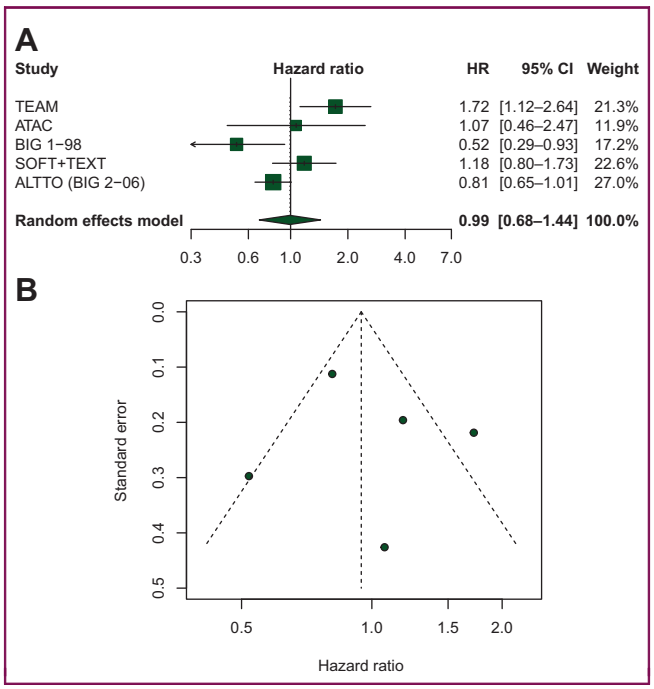

Figure 2. (A) Odds ratio for disease-free survival of tamoxifen versus aromatase inhibitors in all included randomized controlled trials (the size of the squares is proportional to the weight of each study). (B) Funnel plot with pseudo 95% confidence limits for the effect of (horizontal axis) against the study size (vertical axis): publication bias is unlikely as suggested by the symmetric inverted funnel shape.

AI, aromatase inhibitors; CI, confidence intervals; HR, hazard ratio; OR, odds ratio.

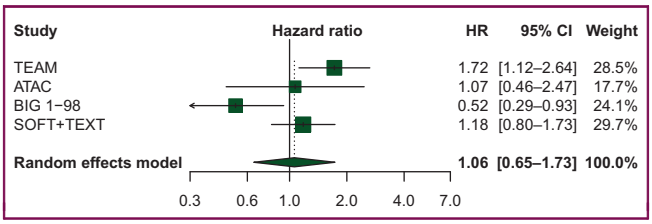

Figure 3. Odds ratio for disease-free survival of tamoxifen versus aromatase inhibitors in all included randomized controlled trials excluding ALTTO trial (the size of the squares is proportional to the weight of each study).

AI, aromatase inhibitors; CI, confidence intervals; HR, hazard ratio; OR, odds ratio.

In the adjuvant setting, the EBCTCG meta-analysis[15] demonstrated a significant reduction in recurrence of 30% during years 0-1 in HER2-positive cancers. Our analysis, that involved a longer duration of follow-up, contained premenopausal patients and included treatment with more contemporary HER2 regimens and combination therapies; we concluded that there was no difference between the regimens.

The adverse effects associated with various treatments differed between endocrine regimens. In the SOFT and TEXT trials, adverse events of grade 3 or higher were reported in more than 30% of the arms that included ovarian suppression. Thrombosis or embolism were more frequent among the tamoxifen-treated group compared with the exemestane-treated group (2.3% versus 1.2%), while musculoskeletal symptoms (11.4 versus 5.7), osteoporosis (14.8 versus 7.2%), and vaginal dryness were more frequent in the combined exemestane group. Efficacy, however, was uniform across treatment regimens, as reflected in the results of our meta-analysis of aromatase inhibitor versus tamoxifen. This finding is of major importance, freely assessing the side-effect profile to guide treatment.

We recognize that our study involves several limitations. One is the small number of HER2-positive cases across six

trials. In addition, trastuzumab treatment was not available for the majority of cases at the time of three of the trials (TEAM, ATAC and BIG 1-98). Furthermore, the TEAM, ATAC and BIG 1-98 results apply only to treatment and events occurring during the first years of treatment. Nevertheless, our study demonstrates a similar DFS among patients treated with tamoxifen versus aromatase inhibitors as adjuvant treatment in HER2-positive HR-positive early-stage breast cancer. Future larger prospective studies focusing on various endocrine regimens in this setting are warranted to validate our results.

FUNDING

None declared.

DISCLOSURE

The authors report no conflict of interest.

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