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REVIEW

Comparative efficacy of adjuvant trastuzumab-containing chemotherapies for patients with early HER2-positive primary breast cancer: a network meta-analysis

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Abstract

Background Trastuzumab (H) with chemotherapy benefits patients with HER2+ breast cancer (BC); however, we lack head-to-head pairwise assessment of survival or cardiotoxicity for specific combinations. We sought to identify optimal combinations.

Methods We searched PubMed, updated October 2017, using keywords "Breast Neoplasms/drug therapy," "Trastuzumab," and "Clinical Trial" and searched Cochrane Library. Our search included randomized trials of adjuvant H plus chemotherapy for early-stage HER2+ BC, and excluding trials of neoadjuvant therapy or without data to obtain hazard ratios (HRs) for outcomes. Following PRISMA guidelines, one investigator did initial search; two others independently confirmed and extracted information; and consensus with another investigator resolved disagreements. Before gathering data, we set outcomes of overall survival (OS), event-free survival (EFS), and severe cardiac adverse events (SCAEs). Analyzing 6 trials and 13,621 patients, we made direct and indirect comparisons using network meta-analysis on HR for OS or EFS and on odds ratio (OR) for SCAE; ranked therapy was done based on outcomes using *p* scores.

Results Compared with anthracycline-cyclophosphamide with taxane (ACT), ACT with concurrent H (ACT+H) showed best OS (HR 0.63, 95% confidence interval [CI] 0.55, 0.72), followed by taxane and carboplatin (TC) with concurrent H (TC+H) (HR 0.77, 95% CI 0.59, 1) and ACT with sequential H (ACT-H) (HR 0.85, 95% CI 0.68, 1.05). Pairwise comparisons showed statistically significant OS benefit for ACT+H over others; similar results for EFS. TC+H showed statistically significant lower SCAE risk compared to ACT+H (OR 0.13, 95% CI 0.03, 0.61).

Conclusions Concurrent H with ACT or TC showed most clinical benefit for early-stage HER2+ BC; TC+H had lowest cardiotoxicity.

Keywords Anthracycline · Carboplatin · Cardiotoxicity · Cyclophosphamide · Overall survival · Taxane

Introduction

Despite early detection and treatment advances, breast cancer remains a major cause of cancer death in the United States [1]. The human epithelial growth factor receptor 2 (HER2)/*neu* is known to regulate cell growth, differentiation, and tumorigenicity in normal and malignant breast epithelial cells [2, 3]. HER2 is overexpressed in approximately 20–25% of all invasive breast cancer [4, 5], which is traditionally associated with poor prognosis [6–13]. An anti-HER2 agent, trastuzumab (H), used in combination with standard chemotherapy in adjuvant settings, has reduced the risk of disease recurrence and disease-specific death among patients with HER2-positive (HER2+) primary breast cancer [4, 5, 14, 15]. The standard chemotherapy regimens include

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anthracycline-cyclophosphamide (AC), anthracycline-cyclophosphamide with sequential or concurrent taxane (ACT), and docetaxel and carboplatin (TC) [16–23].

Despite the rapid dissemination of HER2-targeted agents into clinical practice, unanswered questions remain for the optimal use of these agents with standard chemotherapy in the adjuvant setting. Most controlled clinical trials (RCTs) have randomized patients with HER2+ breast cancer to a standard chemotherapy with or without H, while one RCT has assessed ACT with H concurrently versus ACT with H sequentially. Although RCTs have demonstrated the clinical benefit of adding H, it lacks head-to-head assessments of H-containing chemotherapies and these regimes are presumed by many to be equivalent. The optimal adjuvant H-containing chemotherapy for treating early-stage HER2+ breast cancer is still unclear. This is particularly important in discerning whether anthracyclines provide an independent benefit given the higher risk, although rare, of cardiomyopathy when combined with trastuzumab [24]. In HER2-negative breast cancer, anthracyclines do appear to provide a small benefit with respect to recurrence [25], but there is ongoing debate as to whether this is the case with trastuzumab in HER2+ disease.

Network meta-analysis facilitates direct and indirect comparisons using a network of existing clinical trials in comparative effectiveness research [26–29], thereby allowing us to combine data derived from direct comparisons of *X* to *Y* and *Y* to *Z* to obtain an indirect comparison of *X* to *Z*. Thus, we conducted a network meta-analysis to evaluate the relative efficacy of H-containing chemotherapies regarding patients' overall survival (OS) and event-free survival (EFS) and to compare the associated severe cardiac adverse events (SCAEs) using all relevant RCTs that target early-stage HER2+ breast cancer patients. The synthesized evidence will help physicians and patients make treatment decisions by balancing the tradeoff between efficacy and cardiotoxicity outcomes.

Methods

Search strategy and selection criteria

We conducted a systematic literature review to identify relevant RCTs according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis [30]. We employed a computerized search of PubMed up to October 2013 and updated our search in October 2017, using the following combined key words: "Breast Neoplasms/drug therapy," "Trastuzumab," and "Clinical Trial." The flowchart for the literature search appears in Supplementary Fig. S1 (available online).

We included the eight published reports of RCTs [19–22, 31–34] that evaluated H-containing chemotherapy regimens versus chemotherapy alone in the adjuvant setting for HER2+ breast cancer, assessing anthracycline-containing regimen alone (AC), AC followed by one year of sequential H (AC-H), or followed by 2 years of sequential H (AC-H2y), anthracycline with sequential or concurrent taxane (ACT), combined with concurrent H (ACT+H), and ACT followed by sequential H (ACT-H). We also assessed docetaxel and carboplatin (TC), combined with concurrent H (TC+H), and chemotherapy without H in the respective comparisons of AC and ACT.

To ensure a reasonably homogeneous cohort of patients with early-stage HER2+ breast cancer, we excluded RCTs for patients with stage IV HER2+ breast cancers, trials in neoadjuvant settings, and trials that evaluated H combined with hormonal therapies. For trials represented in multiple publications, we used the publication with the most updated results. To facilitate indirect comparisons and link two separate networks with adjuvant H-containing chemotherapies, we included three RCTs of adjuvant treatments without H for early-stage breast cancer that compared AC versus ACT [35–37] (Fig. 1). More details on the regimen dose and schedule for each treatment arm can be found in Table 1. Thus, we included a total of 9 RCTs [19–22, 31–37] to assess the following seven treatment regimens: AC, ACT, ACT+H, ACT-H, AC-H, AC-H2y, and TC+H.

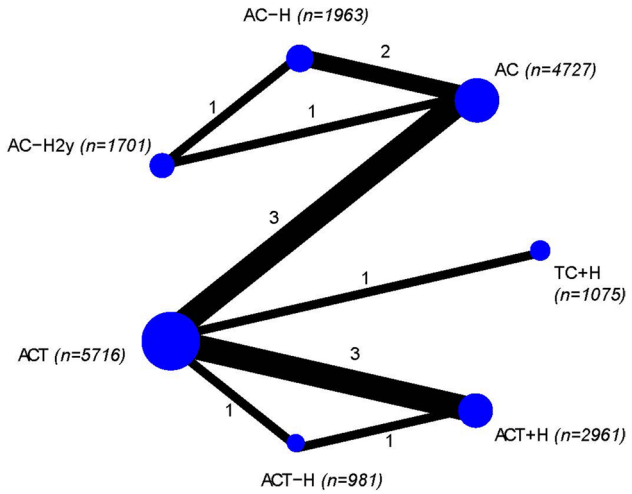

Fig. 1 Network of meta-analysis comparisons. *AC* anthracycline-containing regimen without taxane, *ACT* anthracycline with sequential or concurrent taxane, *ACT+H* ACT with concurrent trastuzumab, *ACT-H* ACT followed by sequential trastuzumab, *AC-H* AC followed by sequential trastuzumab, *AC-H2y* AC with sequential trastuzumab of 2 years, *TC+H* docetaxel, and carboplatin with concurrent trastuzumab

Table 1 Characteristics of studies analyzed for comparing trastuzumab in the setting of adjuvant chemotherapy

Study	Journal/year published	Median follow-up (months)	Age[a] (years)	# per arm (# analyzed)	Adjuvant treatment	Dose of trastuzumab (H)	Duration of H (weeks)
NSABP B-31 [19–21]	JCO/2005 JCO/2012 JCO/2014	101[b]	22–80	1024 (814)	ACT	None	NA
				1019 (850)	ACT+H	4 mg/kg loading 2 mg/kg q. wk	52
FinHer [31]	JCO/2009	62	NA	58	ACT	None	NA
				54	ACT+H	4 mg/kg loading 2 mg/kg q. wk	9
PACS-04 [32]	JCO/2009	47	48	268	AC	None	NA
				260	AC-H	8 mg/kg loading 6 mg/kg q. 3 wk	52
BCIRG 006 [33]	NEJM/2011	65	49	1073	ACT	None	NA
				1074	ACT+H	Not reported	52
				1075	TC+H	Not reported	52
N9831 [20, 22]	JCO/2011	72	22–80	819	ACT	None	NA
				981	ACT-H	4 mg/kg loading 2 mg/kg q. wk	52
				814	ACT+H	4 mg/kg loading 2 mg/kg q. wk	52
HERA [34, 35]	Lancet/2013 Lancet/2017	132	49	1698 (1697)	AC	None	NA
				1703 (1702)	AC-H	8 mg/kg loading 6 mg/kg q. 3 wk	52
				1701 (1700)	AC-H2y	8 mg/kg loading 6 mg/kg q. 3 wk	104
NABCITE 2197 [36]	JCO/2008	79.4	51	1476 (1441)	ACT	NA	NA
				1476 (1441)	AC	NA	NA
ADNPBC [37]	NEJM/2005	55	49	745 (744)	ACT	NA	NA
				746 (736)	AC	NA	NA
ADHRNNBC [38]	NEJM/2010	77	23–74	521	ACT	NA	NA
				539	AC	NA	NA

NABCITE North American Breast Cancer Intergroup Trial E 2197, *ADNPBC* adjuvant docetaxel for node-positive breast cancer, *ADHRNNBC* adjuvant docetaxel for high-risk, node-negative breast cancer, *NSABP B-31* doxorubicin plus cyclophosphamide (60 mg/m^2 and 600 mg/m^2, respectively, every 21 days for 4 cycles) followed by paclitaxel (175 mg/m^2 every 21 days for 4 cycles), *FinHer* docetaxel (100 mg/m^2 every 3 weeks for 3 cycles) followed by fluorouracil plus epirubicin plus cyclophosphamide (600 mg/m^2, 60 mg/m^2, and 600 mg/m^2, respectively, every 3 weeks for 3 cycles), *PACS-04* fluorouracil plus epirubicin plus cyclophosphamide (FE100C: F and C 500 mg/m^2, E 100 mg/m^2) every 3 weeks for 6 cycles, or epirubicin plus docetaxel (both 75 mg/m^2) every 3 weeks for 6 cycles, *BCIRG 006* doxorubicin plus cyclophosphamide (60 mg/m^2 and 600 mg/m^2, respectively, every 3 weeks for 4 cycles) followed by docetaxel (100 mg/m^2 every 3 weeks for 4 cycles), docetaxel plus carboplatin (both 75 mg/m^2 every 3 weeks for 6 cycles), *N9831* doxorubicin plus cyclophosphamide (60 mg/m^2 and 600 mg/m^2, respectively, every 21 days for 4 cycles) followed by paclitaxel (80 mg/m^2 weekly for 12 doses), *HERA* anthracyclines alone (68% of patients in each group), anthracyclines plus taxanes (26% of patients in each group) or a regimen without anthracyclines, including cyclophosphamide, methotrexate, and fluorouracil (6% of patients in each group), *AC* Anthracycline-containing regimen without taxane, *ACT*: anthracycline with sequential or concurrent taxane, *ACT+H* ACT with concurrent trastuzumab, *ACT-H* ACT followed by sequential trastuzumab, *AC-H* AC followed by sequential trastuzumab, *AC-H2y* AC with sequential trastuzumab for 2 years, *TC+H* docetaxel and carboplatin (TC) with concurrent trastuzumab

[a]Age: median, mean, or range in years

[b]The joint analysis of B31 and N9831 based on results reported in JCO2014 [20]

Data extraction

One investigator (N.F.) performed the initial literature search given the above selection criteria. Two other investigators (L.X., T.F.) independently reviewed and confirmed the extracted information. Any disagreements were discussed with another investigator (Y.S.) and consensus was achieved.

Table 1 lists characteristics of the studies. We extracted aggregate data on OS, EFS, and SCAEs. The primary outcome was OS, and EFS and cardiotoxicity were secondary outcomes. We define OS as the time from the date of randomization to the date of death or last follow-up; EFS as the time from the date of randomization to the date of first cancer recurrence, including locoregional, contralateral breast

cancer, distant recurrence, or death; and SCAEs using the original definition given in each RCT. SCAEs included New York Heart Association class III/ IV heart failure, possible/ probable cardiac death, and discontinuation of treatment due to cardiac toxicities, for which some studies defined cardiac toxicities using significant left ventricular ejection fraction (LVEF) decrease ≥ 10% from baseline and absolute LVEF < 50% or symptomatic heart failure.

The overall quality of the trials in this analysis was assessed using the Cochrane risk-of-bias tool [38] regarding sequence generation, allocation concealment, blinding outcome, incomplete outcome data, selective reporting, and other sources of bias. The items were ranked as low, high, or unknown risk of bias for each RCT.

Two RCTs (FinHer and PACS-04 trials) [31, 32] included treatment arms for patients with HER2-negative breast cancer, which is irrelevant to this study, so we excluded them from the analysis. For the FinHer trial [31], we additionally excluded two arms that used vinorelbine because those arms could not be linked directly or indirectly to any other treatments in the network.

Statistical analysis

We conducted network meta-analysis to integrate direct and indirect comparisons of adjuvant chemotherapy combinations for early-stage HER2+ breast cancer. We extracted HRs and the corresponding 95% confidence intervals (CIs) from the published studies. If HRs were not reported, we used the reported median survival times and the log-rank test p value to estimate the corresponding HRs, assuming an exponential distribution for survival times in each arm. Given the aggregate data, we used the methods by Parmar [39, 40] to compute the natural logarithm of the HR and its standard error, and then used the random effect models to perform network meta-analysis to account for within-trial correlation of multi-arm RCTs and heterogeneity between studies [41].

To compare the SCAE risk, we assumed that one SCAE corresponded to one patient for the calculation of the odds ratios (ORs). We calculated the natural logarithm of the ORs and the corresponding standard errors as inputs for the network meta-analysis.

We used p scores to rank the H-containing chemotherapy combinations based on OS, EFS, and SCAE, respectively, and jointly presented the ranks for OS and SCAE [42]. The p scores use network estimators to measure the mean extent of certainty that a treatment is better than the competing treatments while accounting for the precision of the estimator. A larger p score indicates a better treatment.

We used Cochran's Q statistics and the I^2 index to examine heterogeneity and inconsistency beyond what would be expected from the sampling error within each trial. In general, an I^2 index less than 25% implies low heterogeneity, 25–50% implies moderate heterogeneity, and greater than 50% indicates high heterogeneity [43–45]. We used a descriptive, net heat plot to assess any inconsistency, which is defined as disagreement between the direct and indirect treatment effects beyond the difference among the same treatment arms by the studies [44]. We used R software v3.0.2 and netmeta package version 0.8-0 for data analysis. Probabilities with p value < 0.05 were considered statistically significant. All statistical tests were two-sided.

Results

The initial search in PubMed yielded 321 records. No additional RCTs were identified upon our updated search in October 2017. We thoroughly reviewed 27 full-text versions of articles that satisfied the selection criteria with the most updated results. Among them, six unique RCTs for treating early-stage HER2+ breast cancer met the eligibility criteria and were included in our network meta-analysis (Supplementary Fig. S1).

Summary of direct comparisons

Figure 1 presents the network diagram with 7 direct comparisons from six RCTs for early-stage HER2+ breast cancer, and three RCTs for early-stage breast cancer to compare ACT against AC to facilitate connection of the networks. We evaluated a total of 7 adjuvant chemotherapy regimens (each circle in Fig. 1 represents one treatment regimen), although the focus was to compare 5 adjuvant H-containing chemotherapy regimens. The size of each circle in Fig. 1 is proportional to the number of patients treated under a regimen, and the thickness of the connecting line is proportional to the number of RCTs. In total, 2961 patients were treated with ACT+H versus ACT in a direct comparison within 3 RCTs. Two RCTs were conducted to investigate AC-H versus AC. The rest of the "head-to-head" comparisons were done in a single trial, and three RCTs were conducted to compare AC against ACT. Blinding was not used in most of the RCTs. Our evaluation of the primary outcome, OS, was rated as having low risk of bias, since OS was unlikely to be biased by the lack of blinding (Supplementary Table S1).

Table 1 summarizes the characteristics of the six RCTs for 13,621 HER2+ primary breast cancer patients treated with adjuvant chemotherapy regimens with or without H [21, 23, 24, 31–34, 46] and 3 RCTs that compared ACT to AC [35–37] for 5422 patients with early-stage breast cancer. The median follow-up time ranged from 47 to 132 months. The number of patients with HER2+ primary breast cancer randomized per trial ranged from 112 to 5102.

The estimated HRs and corresponding 95% CIs to compare OS and EFS between treatments for each study are,

respectively, summarized in Supplementary Fig. S2a, b. The addition of H indicated an OS benefit compared with chemotherapy alone in all direct comparisons, even though some of the benefits were not statistically significant within the individual trials. For direct comparison of ACT versus ACT+H, two of the three RCTs showed that the addition of concurrent H to ACT had statistically significant benefits. Similar to the OS outcome, compared to chemotherapy alone, the addition of H significantly reduced the risk of disease recurrence or progression, except in the comparison of ACT-H versus ACT in one trial, in which the reduction in events related to EFS was not statistically significant.

Network meta-analysis

OS outcome

Figure 2 presents comparisons of study regimens against ACT in the network meta-analysis. ACT+H (HR 0.63, 95% CI 0.55, 0.72) showed the most OS benefit, followed by TC+H (HR 0.77, 95% CI 0.59, 1) and ACT-H (HR 0.85, 95% CI 0.68, 1.05). Supplementary Table S2 lists the HRs and corresponding 95% CIs for all the possible pairwise comparisons from the seven treatments evaluated. Among the pairwise comparisons between H-containing adjuvant chemotherapies, ACT+H showed greater statistically significant OS benefit than the other combinations, except for a non-significant advantage against TC+H (HR 0.82, 95% CI 0.61, 1.1). The net heat plot (Supplementary Fig. S3a) shows no strong inconsistency among the RCTs for the OS analysis, where less intense colors in the plot indicate consistent treatment comparisons relative to the network.

EFS outcome

Results for EFS were similar to those for OS (Fig. 2 and Supplementary Table S3). Compared to ACT, ACT+H (HR 0.59, 95% CI 0.51, 0.69) most effectively decreased the risk of disease progression or recurrence among the comparisons. It was followed by ACT-H (HR 0.73, 95% CI 0.59, 0.90) and TC+H (HR 0.75, 95% CI 0.58, 0.97). In the pairwise comparisons of H-containing regimens, ACT+H showed statistically significant EFS advantages over AC-H and AC-H2y, and a non-significant benefit over ACT-H (HR

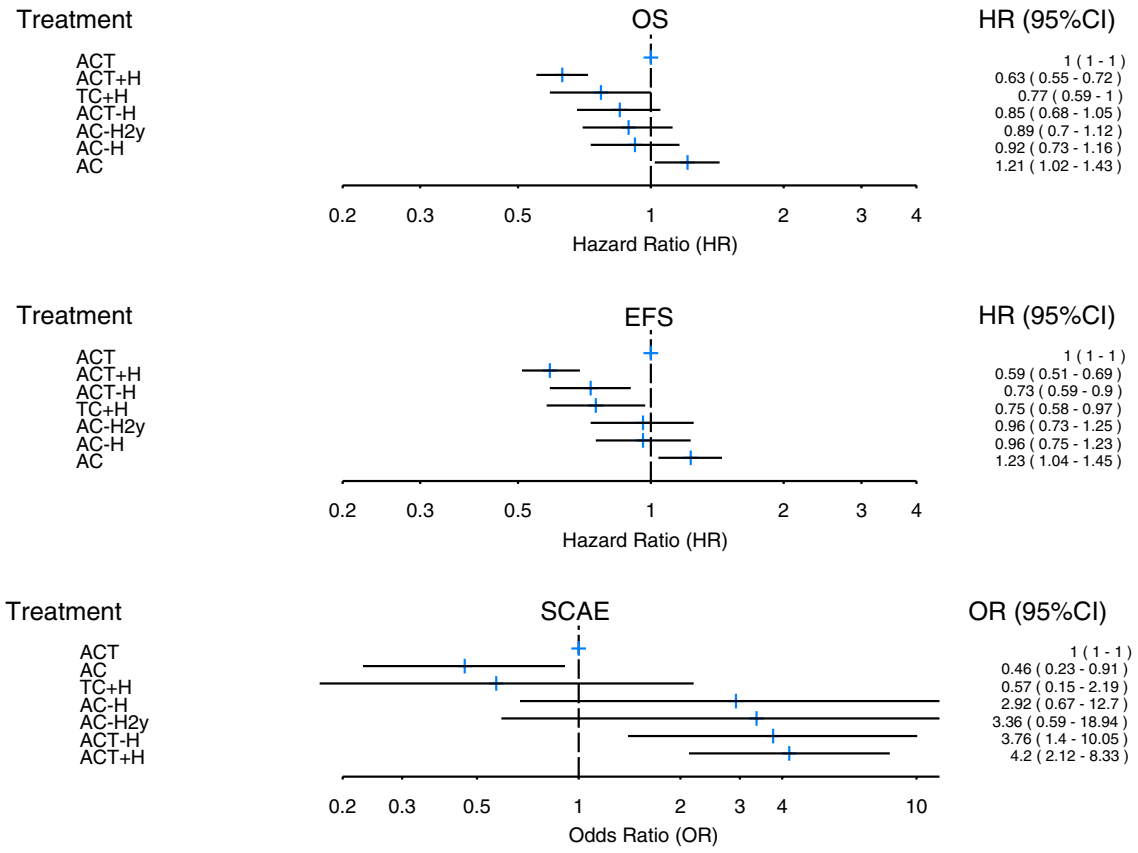

Fig. 2 Network meta-analysis estimated hazard ratios (HRs) for comparison of overall survival (OS) or event-free survival (EFS) between each adjuvant therapy and ACT and odds ratios (ORs) for comparison of incidence of severe cardiac adverse events (SCAEs) between each adjuvant therapy and ACT

0.82, 95% CI 0.66, 1.01) and TC+H (HR 0.79, 95% CI 0.59, 1.06). The net heat plot (Supplementary Fig. S3b) shows no strong inconsistency among the RCTs for the EFS analysis.

SCAEs

ACT+H was associated with the highest SCAE risk compared to ACT alone (OR 4.2, 95% CI 2.12, 8.33), and ACT-H had the second highest OR (OR 3.76, 95%CI 1.4, 10.5) (Fig. 2). TC+H had the lowest SCAE risk compared with ACT alone (OR 0.57, 95% CI 0.15, 2.19). Among the H-containing chemotherapies in the pairwise comparisons, TC+H had a statistically significant lower SCAE risk than ACT+H (OR 0.13, 95% CI 0.03, 0.61) and ACT-H (OR 0.15, 95 CI 0.03, 0.8), and had non-significant lower risks than the other two H-containing adjuvant therapies (Supplementary Table S4).

Ranking adjuvant chemotherapy regimens by efficacy and toxicity outcomes

ACT+H and TC+H had the highest *p* scores (0.981 and 0.732, respectively) for OS and were ranked as the most and second most effective adjuvant chemotherapy with H, followed by ACT-H (0.586). For EFS, ACT+H and ACT-H had the highest *p* scores (0.985 and 0.75, respectively), followed by TC+H (0.715) (Supplementary Table S5). For SCAE, TC+H had the lowest cardiotoxicity among the H-containing chemotherapies. Figure 3 shows the rankings of the competing treatment strategies in terms of OS and SCAE. Treatments shown at the upper right corner have better efficacy and lower cardiotoxicity. ACT+H and TC+H were, respectively, ranked as the best and second best for OS benefit, whereas TC+H exhibited the lowest ranking for cardiotoxicity compared to other H-containing chemotherapy regimens.

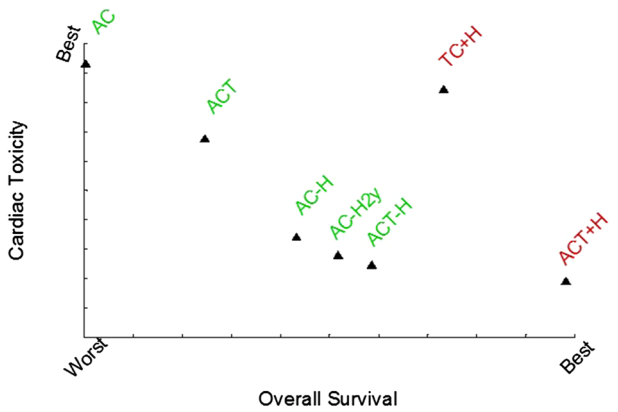

Fig. 3 Ranking of treatments in terms of overall survival and cardiotoxicity

Discussion

By combining hierarchies of evidence from published RCTs for H-containing chemotherapy regimens in the adjuvant treatment of early-stage HER2+ breast cancer, our network meta-analysis derived head-to-head comparisons and ranked the treatments in terms of clinical outcomes. ACT+H showed the highest OS benefit, followed by TC+H. For EFS, ACT+H was the most effective combination, followed by ACT-H and TC+H, which performed similarly. It is important to note that while the BCIRG 006 trial included H-containing arms with and without anthracycline that showed similar clinical outcomes, the statistical design did not plan for a formal comparison between these arms. The risk of H-induced cardiotoxicity was similar for all the combination therapies, except that TC+H had a significantly lower risk of SCAE compared to ACT+H or ACT-H. Balancing the tradeoff between clinical benefits and cardiotoxicity, ACT+H may be a viable choice for treating younger patients with HER2+ primary breast cancer who have lower risk of cardiovascular disease, whereas TC+H might be best recommended as a reasonable option for patients at increased risk of cardiotoxicities [47].

Conventional meta-analyses based on the RCTs comparing various chemotherapy regimens combined with H in the adjuvant setting to the chemotherapy regimen alone confirmed the efficacy of the targeted chemotherapies for HER2+ breast cancer [17, 18, 48, 49]. However, these investigations focused on the effect of adding adjuvant H by pooling all adjuvant chemotherapies in the analyses without differentiating the types of chemotherapy agents or schedule of H (i.e., concurrent, sequential or duration). Therefore, the analyses did not provide information to identify the optimal H-containing chemotherapy regimen among the targeted adjuvant therapies. Nagayama et al. [50] conducted a network meta-analysis to compare different anti-HER2 agents for the outcome pathologic response rate in the neoadjuvant setting for HER2+ breast cancer. To the best of our knowledge, our report is the first network meta-analysis to compare the effect of currently approved adjuvant H-containing chemotherapies on OS, EFS, and cardiotoxicity among patients with early-stage HER2+ primary breast cancer. Such comparisons will help physicians and patients select the most appropriate adjuvant H-containing chemotherapy combination based on the tradeoff between clinical benefits and drug toxicities, including SCAE concerns.

Since 2000, several pivotal RCTs have been initiated to assess the combination of H with conventional first-line chemotherapies among patients with early-stage HER2+ breast cancer, which led to its approval in the

adjuvant setting in 2006 [23]. The combination of anthracycline-containing agents plus taxane was evaluated with or without H in the HER2-targeted adjuvant setting in four trials (FinHer [31], BCIRG 006 [33], NSABP B-31 [19–21, 23], and N9831 [20–23]). The analysis combining B-31 and N9831 showed an increased incidence of severe cardiotoxicity under the ACT+H regimen compared to ACT alone, with overall SCAE rates of 1.3% and 0.9% in the ACT arms and 3.8% and 2.3% in the ACT+H arms of B-31 and N9831, respectively [21]. An analysis of women at least 66 years of age with stages I–III breast cancer who received chemotherapy found higher rates of H-related congestive heart failure in Medicare–SEER and Texas Cancer Registry–Medicare databases than the rates reported in clinical trials [51]. The cardiotoxicity concern of ACT-based therapy has led to a trial using a non-anthracycline H-based regimen (i.e., TC+H), which was tested in the BCIRG 006 trial. TC+H had a similar efficacy profile as ACT+H, but was associated with fewer acute toxic events (0.4%) and lower risk of cardiotoxicity than ACT+H. The findings from this large RCT suggest that the risk–benefit ratio favored the TC+H regimen over the ACT+H regimen [33]. In 2008, the FDA approved TC+H for adjuvant treatment of early-stage HER2+ breast cancer.

Limitations

Our study has several limitations. Most of the RCTs we analyzed were open-label studies. However, the clinical outcomes of OS, EFS, and SCAE can be measured objectively, so the impact of not using blinding should be minimal. For data organization, we grouped the chemotherapies into three categories, whether including anthracycline-based (AC), taxane-based (TC), or both (ACT). If a treatment arm contained two or more chemotherapy groups, adjuvant chemotherapy was defined as the combination used to treat the highest proportion of patients in that trial. While ACT was the most commonly used adjuvant chemotherapy in these RCTs, the trials might have used different ACT agents or sequence. AC agents could be doxorubicin plus cyclophosphamide, fluorouracil plus epirubicin plus cyclophosphamide or epirubicin only, and taxanes were either paclitaxel or docetaxel. Second, the administered sequence for AC and taxanes can be either concurrent or sequential. However, these different AC agents with either sequential or concurrent administration have shown similar OS outcomes in the literature [52–54].

In the HERA trial, where trastuzumab was always given sequentially after chemotherapy [34, 46], we classified the chemotherapy regimens as AC according to the rule of majority; however, several agents were used: about 68%, 26%, and 6% of patients, respectively, received AC, ACT, and anthracyclines or taxanes. In the PACS 04 trial [32], more than half of the patients received AC, while the others received ACT; we similarly classified the regimen as AC. Since the sample size of the PACS 04 trial is small compared to those of the other RCTs, the impact of this approximation is minor. Our sensitivity analyses classifying the chemotherapy regimen as ACT in the PACS 04 trial yielded the same ranking of the adjuvant therapies for all outcomes (OS, EFS, and SCAE) as the results from the analyses that classified the regimen as AC in the PACS 04 trial.

While all reported RCTs in this study had at least 5 years of median follow-up, one trial PACS-04 had a median follow-up time less than 5 years (47 months). The sensitivity analyses excluding the PACS-04 trial lead to the same as those from the primary analyses (see Supplementary Tables S10, S11). Considering the efficacy outcomes may be different between patients with hormonal (HR) positive HER2+ from those with HR negative HER2+, or by lymph node status, we provided the results of subset/sensitivity analyses (see Supplementary Tables S6–S9). Due to smaller trial sizes for the subset analyses, some of the comparisons are not statistically significant (e.g., HR negative subgroup), but the ranks of the treatment regimens for OS and EFS remained similar to those in the primary analyses.

The SCAEs in the literature were not counted per patient. Because there was no individual-level data available for these trials, we used the aggregate data by counting one event per patient. Since a single patient can experience multiple cardiac events, the number of patients that experienced cardiotoxicity may be overestimated. In addition, data on SCAEs were collected from the published RCTs, for which the clinicians might have defined SCAEs differently across trials. For example, thresholds for significant LVEF decline included > 10% from baseline to an absolute LVEF < 50% in the HERA trial [34, 46], but > 20% decline from baseline in the FinHer trial [31]. Since the overall number of SCAEs is small, a slight change in the definition of severe heart failure or LVEF threshold might have a large impact on the OR estimates in the comparisons of SCAE risk between treatment regimens. This level of uncertainty indicates that we should cautiously interpret the SCAE results. The secondary leukemia due to anthracycline can be a concern. Only the BCIRG-006 trial reported that 0.6% of patients in the ACT arm and 0.1% of patients in the TC+H arm and ACT+H arm, respectively, experienced secondary leukemia [33].

EFS also might have been defined differently across trials (e.g., disease-free or local/distant recurrence). That could be why modest but not statistically significant heterogeneity was observed among the RCTs for EFS (p value for Q statistics = 0.13; I^2 index = 39%). However, Cochran's Q statistics for OS did not detect statistically significant heterogeneity among the RCTs, and the estimated I^2 index of 6.8% confirmed low heterogeneity ($p = 0.38$). No significant

heterogeneity was observed among the studies for SCAE (p value for Q statistics = 0.30; I^2 index = 16.5%).

We did not include more recently developed agents that target HER2+ breast cancer, such as pertuzumab in combination with H and docetaxel, because these newer agents were approved by the FDA to treat HER2+ metastatic breast cancer [55]; and pertuzumab was only approved recently for early-stage breast cancer, whereas this meta-analysis focuses only on early-stage HER2+ breast cancer with mature survival data. Moreover, the two recent RCTs, ALTTO and APHINITY, were designed to test whether the addition of pertuzumab or lapatinib to adjuvant trastuzumab would improve the outcome of patients with HER2+ tumor status [56, 57]. A future meta-analysis will be warranted to investigate this broader group of targeted chemotherapies for HER2+ patients compared to the adjuvant therapies with trastuzumab alone evaluated in the current study.

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Compliance with ethical standards

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

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics (2016) CA Cancer J Clin 2016; 66(1):7–30
2. Hynes N, Stern DF (1994) The biology of ErbB-2/neu/HER-2 and its role in cancer. Biochim Biophys Acta 1198(2–3):165–184
3. Yarden Y, Sliwkowsk MX (2001) Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2(2):127–137
4. Slamon DJ, Clark GM, Wong SG et al (1987) Human breast cancer: correlation of relapse and survival with amplification of HER-2/neu oncogene. Science 235(4785):177–182
5. Slamon DJ, Goldophin W, Jones LA et al (1989) Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 244(4905):707–712
6. Arboleda MJ, Lyons JF, Kabbinavar FF et al (2003) Overexpression of AKT2/protein kinase Bbeta leads to up-regulation of beta1 integrins, increased invasion, and metastasis of human breast and ovarian cancer cells. Cancer Res 63(1):196–206
7. Benz CC, Scott GK, Sarup JC et al (1992) Estrogen-dependent, tamoxifen-resistant tumorigenic growth of MCF-7 cells transfected with HER2/neu. Breast Cancer Res Treat 24(2):85–95
8. De Luca A, Carotenuto A, Rachiglio A et al (2008) The role of the EGFR signaling in tumor microenvironment. J Cell Physiol 214(3):559–567
9. Feigin ME, Muthuswamy SK (2009) ErbB receptors and cell polarity: new pathways and paradigms for understanding cell migration and invasion. Exp Cell Res 315(4):707–716
10. Izumi Y, Xu L, di Tomaso E et al (2002) Tumour biology: herceptin acts as an antiangiogenic cocktail. Nature 416(6878):279–280
11. Marcotte R, Muller WJ (2008) Signal transduction in transgenic mouse models of human breast cancer—implications for human breast cancer. J Mammary Gland Biol Neoplasia 13(3):323–335
12. Pietras RJ, Arboleda J, Reese DM et al (1995) HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells. Oncogene 10(12):2435–2446
13. She QB, Chandarlapaty S, Ye Q et al (2008) Breast tumor cells with PI3K mutation or HER2 amplification are selectively addicted to Akt signaling. PLoS ONE 3(8):e3065
14. Baselga J, Carbonell X, Castañeda-Soto NJ et al (2005) Phase II study of efficacy, safety, and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule. J Clin Oncol 23(10):162–171
15. Slamon DJ, Leyland-Jones B, Shak S et al (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344(11):783–792
16. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (2015) https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed 5 Aug 2015
17. De Laurentiis M, Cancello G, D'Agostino D et al (2008) Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. J Clin Oncol 26(1):44–53
18. Gandhi S, Fletcher GG, Eisen A et al (2015) Adjuvant chemotherapy for early female breast cancer: a systematic review of the evidence for the 2014 Cancer Care Ontario systemic therapy guideline. Curr Oncol 22(Suppl 1):S82–S94
19. Tan-Chiu E, Yothers G, Romond E et al (2005) Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 23(31):7811–7819
20. Perez EA, Romond EH, Suman VJ et al (2014) Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol 32(33):3744–3752
21. Romond EH, Jeong JH, Rastogi P et al (2012) Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 30(31):3792–3799
22. Perez EA, Suman VJ, Davidson NE et al (2011) Sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer. J Clin Oncol 29(34):4491–4497
23. Genentech. Herceptin (trastuzumab) development timeline. Genentech product information. https://www.gene.com/media/product-information/herceptin-development-timeline. Accessed 20 Oct 2017

24. Peto R, Davies C, Godwin J et al (2012) Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 379(9814):432–444
25. Blum JL, Flynn PJ, Yothers G et al (2017) Anthracyclines in early breast cancer: the ABC Trials—USOR 06–090, NSABP B-46-I/USOR 07132, NSABP B-49 (NRG Oncology). J Clin Oncol 35:2647–2655
26. Bafeta A, Trinquart L, Seror R, Ravaud P (2014) Reporting of results from network meta-analyses: methodological systematic review. BMJ 348:g1741
27. Neupane B, Richer D, Bonner AJ et al (2014) Network meta-analysis using R: a review of currently available automated packages. PLoS ONE 9(12):e115065
28. Zhang J, Carlin BP, Neaton JD et al (2014) Network meta-analysis of randomized clinical trials: reporting the proper summaries. Clin Trials 11(2):246–262
29. Tonin FS, Rotta I, Mendes AM, Pontarolo R (2017) Network meta-analysis: a technique to gather evidence from direct and indirect comparisons. Pharm Pract (Granada) 15(1):943
30. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 62(10):31–34
31. Joensuu H, Bono P, Kataja V et al (2009) Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. J Clin Oncol 27(34):5685–5692
32. Spielmann M, Roché H, Delozier T et al (2009) Trastuzumab for patients with axillary-node-positive breast cancer: results of the FNCLCC-PACS 04 trial. J Clin Oncol 27(36):6129–6134
33. Slamon D, Eiermann W, Robert N et al (2011) Adjuvant trastuzumab in Her2-positive breast cancer. N Engl J Med 365(14):1273–1283
34. Cameron D, Piccart-Gebhart MJ, Gelber RD et al (2017) 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet 389(10075):1195–1205
35. Goldstein LJ, O'Neill A, Sparano JA et al (2008) Concurrent doxorubicin plus docetaxel is not more effective than concurrent doxorubicin plus cyclophosphamide in operable breast cancer with 0 to 3 positive axillary nodes: North American Breast Cancer Intergroup Trial E 2197. J Clin Oncol 26(25):4092–4099
36. Martin M, Pienkowski T, Mackey J et al (2005) Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 352(22):2302–2313
37. Martín M, Seguí MA, Antón A et al (2010) Adjuvant docetaxel for high-risk, node-negative breast cancer. N Engl J Med 363(23):2200–2210
38. Higgins J, Green S. (2011) Cochrane handbook for systematic reviews of interventions version 5.1.0. the cochrane collaboration. https://www.cochrane-handbook.org.
39. Parmar MK, Torri V, Stewart L (1998) Extracting summary statistics to perform meta-analysis of the published literature for survival endpoints. Stat Med 17(24):2815–2834. Erratum in Stat Med 2004; 23(11): 1817
40. Tierney JF, Stewart LA, Ghersi D et al (2007) Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 8:16
41. Rücker G (2012) Network meta-analysis, electrical networks and graph theory. Res Synth Methods 3(4):312–324
42. Rücker G, Schwarzer G (2015) Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol 15:58
43. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560
44. Krahn U, Binder H, König J (2013) A graphical tool for locating inconsistency in network meta-analyses. BMC Med Res Methodol 13:35
45. Jackson D, White IR, Riley RD (2012) Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. Stat Med 31(29):3805–3820
46. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ et al (2013) 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet 382(9897):1021–1028
47. Clinical Trials.gov. Trial Identifier: NCT00021255. Cancer International Research Group. https://clinicaltrials.gov/ct2/show/NCT00021255. Accessed 30 Nov 2017
48. Dahabreh IJ, Linardou H, Siannis F et al (2008) Trastuzumab in the adjuvant treatment of early stage breast cancer: a systematic review and meta-analysis of randomized controlled trials. Oncologist 13(6):620–630
49. Viani GA, Afonso SL, Stefano EJ et al (2007) Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials. BMC Cancer 7:153
50. Nagayama A, Hayashida T, Jinno H et al (2014) Comparative effectiveness of neoadjuvant therapy for HER2–positive breast cancer: a network meta-analysis. J Natl Cancer Inst 106(9):pii:dju203
51. Chavez-MacGregor M, Zhang N, Buchholz TA et al (2013) Trastuzumab-related cardiotoxicity among older patients with breast cancer. J Clin Oncol 31(33):4222–4228
52. Eiermann W, Pienkowski T, Crown J et al (2011) Phase III study of doxorubicin/cyclophosphamide with concomitant versus sequential docetaxel as adjuvant treatment in patients with human epidermal growth factor receptor 2-normal, node-positive breast cancer: BCIRG-005 trial. J Clin Oncol 29(29):3877–3884
53. Gradishar WG, Anderson BO, Blair SL et al (2014) Breast cancer version 3.2014. J Natl Compr Cancer Netw 12(4):542–590
54. Ganz PA, Land SR, Geyer CE et al (2009) NSABP B-30: definitive analysis of quality of life (QOL) and menstrual history (MH) outcomes from a randomized trial evaluating different schedules and combinations of adjuvant therapy containing doxorubicin, docetaxel and cyclophosphamide in women with operable, node-positive breast cancer. Cancer Res 69(2 Suppl):Abst 76
55. Baselga J, Cortés J, Kim SB et al (2012) Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 366(2):109–119
56. Minckwitz G, Procter MJ et al (2017) Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med 377:122–131
57. Moreno-Aspitia A, Holmes EM et al (2017) Updated results from the phase III ALTTO trial (BIG 2–06; NCCTG (Alliance) N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L) or their combination (L + T) in the adjuvant treatment of HER2-positive early breast cancer. J Clin Oncol 35:15_suppl, 502–502