Efficacy and cardiac safety of adjuvant trastuzumab-based chemotherapy regimens for HER2-positive early breast cancer

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Background: Trastuzumab-based adjuvant therapy has become the standard of care for human epidermal growth factor receptor-2 (HER2)-positive early breast cancer (EBC). Both anthracycline- and non-anthracycline-containing trastuzumab regimens are approved in the United States, but cardiotoxicity is increased with anthracycline-containing regimens.

Design: This paper reviews published and reported efficacy and cardiac safety data from the adjuvant trastuzumab trials [National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31/North Central Cancer Treatment Group (NCCTG) N9831, Breast Cancer International Research Group (BCIRG) 006, Herceptin Adjuvant (HERA), FinHer, and Programme Adjuvant Cancer Sein (PACS) 04].

Results: The addition of trastuzumab to adjuvant chemotherapy significantly improved disease-free survival (from 24% to 58%) in five of the six trials. Overall survival was significantly improved (23%–35%) in the large trials. In NSABP B-31/NCCTG N9831, 5.0%–6.6% of patients who received doxorubicin and cyclophosphamide (AC) were unable to receive trastuzumab. Cardiac event rate was highest in the anthracycline-containing trastuzumab arms (1.9%–3.8%) and lowest with the regimen of docetaxel, carboplatin, and trastuzumab (TCH) (0.4%).

Conclusions: Incorporation of trastuzumab into anthracycline and non-anthracycline adjuvant chemotherapy regimens has substantially improved outcomes in HER2-positive EBC. The TCH regimen has the lowest rates of cardiac dysfunction, but uncertainty exists regarding the relative efficacy of TCH compared with anthracycline-containing trastuzumab regimens. Cardiac risk factor assessment can aid in selection of trastuzumab-based adjuvant therapy regimens.

Key words: adjuvant, anthracyclines, breast cancer, cardiac dysfunction, HER2, trastuzumab

Introduction

Adjuvant chemotherapy for early-stage breast cancer significantly reduces the risk of disease recurrence and prolongs overall survival (OS) [1]. Trials conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), the members of the North American Breast Cancer Intergroup, and the Breast Cancer International Research Group (BCIRG) have established anthracyclines and taxanes as important components of adjuvant chemotherapy regimens [2–7]. Retrospective studies conducted on available tumor specimens from patients treated in these and other adjuvant trials have attempted to identify subsets of patients who benefited from the incorporation of anthracyclines and taxanes. The overexpression or gene amplification of human epidermal growth factor receptor-2 (HER2, HER2/neu, or ErbB-2) is associated with a more aggressive phenotype and poor prognosis [8, 9]. Analyses of pooled trial data have demonstrated that HER2 positivity predicts for benefit from anthracyclines as well as from paclitaxel [10, 11]. The humanized monoclonal antibody trastuzumab (Herceptin®; Genentech USA, Inc., San Francisco, CA) has high affinity for the extracellular domain of HER2 and is active as monotherapy for HER2-positive metastatic breast cancer (MBC) in both first-line and subsequent settings [12–14]. A pivotal phase III trial evaluating first-line chemotherapy treatment with or without trastuzumab in HER2-positive MBC demonstrated that the addition of trastuzumab significantly improved time to progression and OS. However, the concurrent administration of anthracyclines and trastuzumab resulted in an unacceptably high rate (27%) of cardiac dysfunction (CD) [15].

The efficacy and safety of anthracycline- and non-anthracycline-based chemotherapy regimens combined with trastuzumab were evaluated in four large and two small...
adjuvant trials. The addition of trastuzumab to adjuvant chemotherapy resulted in substantial improvements in outcomes and did not appreciably increase toxicity with the important exception of left ventricular (LV) dysfunction. This article reviews the critical issues of the relative efficacy and cardiac safety of the regimens evaluated in these trials. One of the authors (CEG) was an author on the cited manuscripts and abstracts reporting results of NSABP B-31.

**clinical trials of adjuvant trastuzumab**

**patient selection criteria and study designs**

Patients with HER2-positive invasive breast cancer were enrolled in four large trials: NSABP B-31 [16], North Central Cancer Treatment Group (NCCTG) trial N9831 [16], BCIRG 006 [17], and the Herceptin Adjuvant (HERA) trial [18]. In addition, the FinHer [19] and PACS-04 [20] trials of adjuvant chemotherapy included a secondary randomization to trastuzumab or no antibody in women with HER2-positive breast cancer.

The eligibility criteria and trial designs for these trials are depicted in Figure 1; details of each trial have been published or reported previously [16–20]. In summary, B-31 compared AC followed by paclitaxel (AC → T) with AC followed by paclitaxel initiated concurrently with trastuzumab (AC → PH → H) [16], N9831 compared AC → P with AC → PH → H or AC followed by paclitaxel followed by trastuzumab (AC → P → H) [16]. Because of the similarities of the control arms and the concurrent investigational arms in B-31 and N9831, both protocols were amended before the first interim analysis of each trial to conduct joint efficacy analyses comparing the combined control arms with the combined concurrent arms. BCIRG 006 evaluated AC followed by docetaxel (AC → T) versus AC followed by docetaxel plus trastuzumab (AC → TH → H) versus docetaxel plus carboplatin plus trastuzumab (TCH → H) [17], B-31, N9831, and BCIRG 006 administered trastuzumab for 1 year. HERA evaluated trastuzumab monotherapy (either 1 or 2 years of trastuzumab) versus observation following completion of adjuvant or neoadjuvant chemotherapy and radiation therapy if administered [18]. FinHer compared 9 weeks of trastuzumab with three cycles of docetaxel or vinorelbine followed by three cycles of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) versus chemotherapy alone in HER2-positive cancers [19], and PACS-04 randomized patients to receive FEC or epirubicin plus docetaxel with a secondary randomization in HER2-positive cancers to 1 year of trastuzumab or observation [20]. None of the trials administered trastuzumab concurrently with an anthracycline because of the high rate of CD of the combination identified in the pivotal MBC trial [15].

**efficacy results**

The most recently reported primary end point data [disease-free survival (DFS)] for the six trials are summarized in Table 1.

**joint analysis of B-31 and N9831.** At the first joint interim analysis of these trials (N = 3351; median follow-up 2.0 years), DFS was improved by 52% [hazard ratio (HR) = 0.48; 95% confidence interval (CI) 0.39–0.59; P < 0.0001], which widely crossed prespecified early reporting boundaries. OS was also improved with a HR for death of 0.67 (95% CI 0.48–0.93; P = 0.015) [16]. A subsequent analysis with a median follow-up of 2.9 years showed that the improvements persisted for both DFS (HR = 0.48; 95% CI 0.41–0.57; P < 0.0001) and OS (HR = 0.65; 95% CI 0.51–0.84; P = 0.0007); 4-year DFS improved from 73.1% to 85.9% (Table 1) [21].

**NCCTG N9831.** The joint analysis with NSABP B-31 comparing the concurrent regimens with the control arms did not alter the plans for comparing the sequential regimen with the control regimen or the comparison between the concurrent and the sequential regimens. The second interim analysis of sequential administration of trastuzumab following chemotherapy versus chemotherapy alone (AC → P → H versus AC → P) crossed reporting boundaries and was recently presented. With a median follow-up of 5.4 years, sequential administration of trastuzumab improved DFS with a HR of 0.67 (95% CI 0.55–0.82; P < 0.001). There was a nonsignificant trend for improvement in OS with a HR of 0.86 (95% CI 0.65–1.13; P = 0.281) [22].

The first interim analysis of the comparison of concurrent versus sequential administration of trastuzumab (AC → PH → H versus AC → P → H) was also recently conducted. The results did not cross early reporting boundaries but the Independent Data Monitoring Committee recommended reporting the results. The HR for the concurrent versus the sequential regimen was 0.77 (95% CI 0.61–0.96; P = 0.019). This was not considered statistically significant since it did not cross the early reporting boundary for statistical significance, which had been preset at 0.00116 [22].

**BCIRG 006.** The first interim analysis of this trial (N = 3222; median follow-up 1.9 years) with 322 DFS events demonstrated an improvement in DFS with both trastuzumab arms relative to AC → T, with a HR of 0.49 (95% CI 0.37–0.65; P < 0.0001) for the AC → TH → H arm and 0.61 (95% CI 0.47–0.79; P = 0.0002) for the TCH → H arm. Both results crossed early reporting boundaries. In a recent updated analysis with 656 DFS events, DFS was improved by 36% with AC → TH → H (HR = 0.64; 95% CI 0.53–0.78; P = 0.001) and by 25% with TCH → H (HR = 0.75; 95% CI 0.63–0.90; P = 0.04) relative to the AC → T arm (Table 1). The risk of death was reduced by 37% with AC → TH → H (HR = 0.63; 95% CI 0.48–0.81; P < 0.001) and 23% with TCH → H (HR = 0.77; 95% CI 0.60–0.99; P = 0.038) relative to the AC → T arm [23]. The BCIRG 006 trial was not powered to compare the two trastuzumab-containing arms, and both regimens demonstrate important activity relative to the control regimen. However, while there is not a statistically significant difference between the trastuzumab regimens (P = 0.21) [23], the persistent difference between the HRs with additional follow-up continues to provide uncertainty regarding the activity of TCH → H relative to AC → TH → H.

**HERA trial.** Patients in this trial (N = 3387) were initially treated with chemotherapy chosen at the investigator’s discretion. Most patients (94%) received anthracycline-based regimens, but only 26% received a taxane [18]. The initial interim analysis with a median follow-up of 1 year demonstrated a 46% improvement in DFS with trastuzumab.
monotherapy versus observation (HR = 0.54; 95% CI 0.43–0.67; P < 0.0001) [18]. OS differences were not statistically significant [19]. With 2 years of median follow-up, improvement in DFS with trastuzumab persisted with a HR of 0.64 (95% CI 0.54–0.76; P < 0.0001) (Table 1). A significant improvement in DFS was also observed (HR = 0.66; 95% CI 0.47–0.91; P = 0.0115) [24]. A recent update with 4 years of median follow-up demonstrated continued improvement in DFS (HR = 0.76; 95% CI 0.66–0.87; P < 0.0001), though the difference in OS (HR = 0.85; 95% CI 0.70–1.04; P = 0.109) was no longer statistically significant. This latter analysis was biased by eventual administration of trastuzumab to 65% of women on the control arm of HERA [25].

_FinHer trial._ This trial randomized 1010 patients to primarily address a chemotherapy question [19]. A subset of 232 women...
with HER2-positive breast cancer were secondarily randomly assigned to receive trastuzumab with three cycles of non-anthracycline chemotherapy followed by FEC without trastuzumab or to receive the chemotherapy regimens alone (Figure 1). With a median follow-up of 3 years, recurrence-free survival was significantly better among those who received trastuzumab (HR = 0.42; 95% CI 0.21–0.83; P = 0.01) with a trend toward improved OS (HR = 0.41; 95% CI 0.16–1.08; P = 0.07) [19]. An update with a median follow-up of 5.2 years reported on an amended primary end point of distant disease-free survival (DDFS) for the final analysis. Trastuzumab improved DDFS from 73% to 83% (HR = 0.65; 95% CI 0.38–1.12; P = 0.12). Patients receiving trastuzumab had a higher rate of axillary nodal involvement (90% versus 78%; P = 0.02).

An analysis on the basis of adjustment for the greater number of women with axillary nodal metastases in the trastuzumab groups demonstrated a HR of 0.57 (95% CI 0.38–0.99; P = 0.047). The trend for improved OS persisted (unadjusted HR = 0.55; 95% CI 0.27–1.11; P = 0.094) [26].

PACS-04 trial. This trial enrolled 3010 patients with axillary node-positive disease to also primarily address a chemotherapy question. A cohort of 528 women with HER2-positive disease were randomly assigned to receive 1 year of trastuzumab or observation following completion of chemotherapy and radiation (Figure 1). With a median follow-up of 3.9 years, the HR for DFS was 0.86 (95% CI 0.61–1.22; P = 0.41) for trastuzumab relative to observation. The 3-year DFS rates were 78% and 81%, respectively. Of note, 25% of patients in the intent-to-treat analysis received trastuzumab treatment for <30 weeks [20].

On the basis of the results from B-31/N9831, the HERA trial, and BCIRG 006, the Food and Drug Administration approved trastuzumab for the adjuvant treatment of HER2-positive, node-positive or node-negative breast cancer (estrogen receptor/progesterone receptor negative or with one high-risk feature) combined with either anthracycline- or non-anthracycline-containing chemotherapy regimens, or following chemotherapy [27].

### Cardiac safety in the adjuvant trials of trastuzumab

Important differences in the cardiac end points employed in the trials are summarized in Table 2 along with the reported rates and severity of LV dysfunction.

**Table 1. Large adjuvant trastuzumab trials: primary efficacy and safety data**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Efficacy Events</th>
<th>DFS (%)</th>
<th>DFS hazard ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-31/NCCTG N9831 [21]</td>
<td>AC/P versus AC/P/H</td>
<td>619 (2.9)</td>
<td>78 (3 years)</td>
<td>88 (3 years)</td>
<td>0.48 (0.41–0.57)</td>
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<tr>
<td>NCCTG N9831 [22]</td>
<td>AC/P versus AC/P/H</td>
<td>386 (5.5)</td>
<td>72 (5 years)</td>
<td>80 (5 years)</td>
<td>0.65 (0.55–0.86)</td>
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<tr>
<td>NCCTG N9831 [22]</td>
<td>AC/P/H versus AC/P/H</td>
<td>312 (5.3)</td>
<td>75 (5 years)</td>
<td>80 (5 years)</td>
<td>0.77 (0.61–0.96)</td>
</tr>
<tr>
<td>BCIRG 006 [23]</td>
<td>AC/T versus AC/TH</td>
<td>442 (6.4)</td>
<td>75</td>
<td>81</td>
<td>0.64 (0.53–0.79)</td>
</tr>
<tr>
<td>HERA [24]</td>
<td>1 year H versus observation</td>
<td>59 (6.4)</td>
<td>74</td>
<td>81</td>
<td>0.65 (0.54–0.76)</td>
</tr>
</tbody>
</table>

**Note:** For significance of first interim analysis was preset at 0.0016. DFS, disease-free survival; NSABP, National Surgical Adjuvant Breast and Bowel Project; NCCTG, North Central Cancer Treatment Group; AC, doxorubicin and cyclophosphamide; P, paclitaxel; H, trastuzumab; BCIRG, Breast Cancer International Research Group; T, docetaxel; TCH, docetaxel, carboplatin, and trastuzumab; HERA, Herceptin Adjuvant trial.

**Table 2. Large adjuvant trastuzumab trials: primary efficacy and safety data**

<table>
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<tr>
<th>Trial</th>
<th>Design</th>
<th>Events (median follow-up, years)</th>
<th>DFS (%)</th>
<th>DFS hazard ratio (95% CI)</th>
<th>P value</th>
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Table 2. Reported rates and severity of left ventricular dysfunction by regimen on large adjuvant trastuzumab trials

<table>
<thead>
<tr>
<th>Trials regimens</th>
<th>Severe CHF NYHA Class III/IV (%)</th>
<th>Mild CHF NYHA Class II (%)</th>
<th>Asymptomatic confirmed LVEF drop (%)</th>
<th>Total LVEF systolic toxicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-31, AC → q3wkP</td>
<td>0.9</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>NSABP B-31, AC → q3wkPH → H</td>
<td>3.8</td>
<td>11.7</td>
<td>15.5</td>
<td></td>
</tr>
<tr>
<td>NCCTG N9831, AC → q1wkP</td>
<td>0.3</td>
<td>0.5</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>NCCTG N9831, AC → q1wkPH → H</td>
<td>3.3</td>
<td>6.6</td>
<td>9.9</td>
<td></td>
</tr>
<tr>
<td>NCCTG N9831, AC → q1wkP → H</td>
<td>2.8</td>
<td>5.0</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>BCIRG 006, AC → T</td>
<td>0.7</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>BCIRG 006, AC → TH → H</td>
<td>2.0</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>BCIRG 006, TCH → H</td>
<td>0.4</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>HERA, chemotherapy</td>
<td>0.0</td>
<td>0.1</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>HERA, chemotherapy → H</td>
<td>0.6</td>
<td>1.6</td>
<td>1.4</td>
<td>3.6</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; NSABP, National Surgical Adjuvant Breast and Bowel Project; AC, doxorubicin and cyclophosphamide; q3wk, every 3 weeks; P, paclitaxel; H, trastuzumab; NR, not reported; NCCTG, North Central Cancer Treatment Group; q1wk, every week; BCIRG, Breast Cancer International Research Group; T, docetaxel; TCH, docetaxel, carboplatin, and trastuzumab; HERA, Herceptin Adjuvant trial.

(5 of 814; 95% CI 0.3–1.9) in the control arm and 4.1% (31 of 850; 95% CI 2.9–5.8) in the trastuzumab arm, for an absolute difference of 3.3% [28]. Trastuzumab was discontinued before the completion of 52 weeks in 28% of patients. Additionally, 6.6% of patients randomly assigned to the trastuzumab arm never received trastuzumab because of declines in left ventricular ejection fraction (LVEF) while receiving AC.

Potential predictors for increased risk of CD were evaluated. Age >50 years (P = 0.03), need for hypertension medication at entry (P = 0.07), and baseline LVEF <55% (P = 0.0001) were predictors for a CE. Women <50 years had a risk of 2%, women aged 50–59 had a risk of 5.4%, and women ≥60 years had a risk of 5.3%. The need for hypertension medication elevated risk to 5.2%. The major increase in risk occurred in women with baseline LVEF within the normal range but with a value <55%. Their 3-year cumulative risk was 14.5%. Several other potential risk factors such as left-sided radiation therapy, smoking history, family history, diabetes, and hyperlipidemia were not predictive [28].

A five-year update of the cardiac safety data from B-31 demonstrated that the cumulative incidence of CEs with trastuzumab remained essentially the same at 3.8% (Table 2) [29]. Patients followed for information on recovery of LVEF after cardiac toxicity were divided into three cohorts: (i) symptomatic patients meeting criteria for a CE, (ii) symptomatic patients not meeting criteria for a CE, and (iii) confirmed asymptomatic declines requiring early discontinuation of trastuzumab (Figure 2). While substantial improvement in LVEF was present in all three groups, not all patients return to the normal range and some who sustained a CE remain <40%. Additionally, 5 of the 33 patients who sustained a CE and were followed for at least 6 months remained symptomatic for CHF and 20 of the 33 remained on medication [29].

NCCTG N9831. This study employed the same definitions for a CE and the same LVEF monitoring and guidelines for discontinuing trastuzumab as B-31. The 3-year cumulative incidence of CEs among the 1944 patients who began post-AC therapy was 0.3% in the control arm, 2.8% in the sequential trastuzumab arm, and 3.3% in the concurrent trastuzumab arm (Table 2). Among the 2992 patients who completed AC, 5.0% had LVEF decreases that did not allow treatment with trastuzumab. The incidence of asymptomatic LVEF decreases requiring holding trastuzumab was 8%–10%; confirmation of the decline in LVEF requiring discontinuation of trastuzumab occurred in half of those patients [30].

The analysis of risk factors for a CE from N9831 supported the findings of B-31. Women ≥60 years had a risk of 6.6%, women aged 50–59 years had a 2.8% risk, and women <50 years had a 2.1% risk (P = 0.003). Previous or current use of antihypertensive agents increased the risk to 6.0% (P = 0.005). Baseline LVEF above the lower limit of normal but <55% increased the risk to 5.6% (P = 0.033) [30].

BCIRG 006. The definition of a CE in 006 differed from that in B-31 and N9831. Symptomatic grade 3 or 4 LV dysfunction (included NYHA Class II), grade 3 or 4 cardiac ischemia/infarction, grade 3 or 4 cardiac arrhythmias, and cardiac-related deaths were included in the end point [17]. In the initial report, the overall CE rate was 1.0% (95% CI 0.46–1.74) in the AC → T arm, compared with 2.3% (95% CI 1.52–3.44) in the AC → TH → H arm (P = 0.016), and 1.3% (95% CI 0.73–2.21) in the TCH → H arm (P = 0.54) [17]. In the updated safety analysis, rates of grade 3 or 4 LV dysfunction (similar to B-31 and N9831 but included NYHA Class II) were reported [23]. The percentage of patients with symptomatic LV dysfunction was 0.7% (7 of 1050) in the AC → T arm, 2.0% (21 of 1068) in the AC → TH → H arm, and 0.4% (4 of 1056) in the TCH → H arm (Table 2). The difference in CE rates between the AC → TH → H and TCH → H arms was statistically significant (P < 0.001). The percentages of patients with a ≥10% relative LVEF decline from baseline in the AC → T, AC → TH → H, and TCH → H arms were 11%, 19%, and 9%, respectively [23].
HERA trial. There were important design differences between HERA and the other large trials. Patients had to complete chemotherapy and radiotherapy before random assignment and have a postchemotherapy LVEF of \( \geq 55\% \). Severe CHF was defined as NYHA Class III/IV symptoms with a decrease in LVEF of \( >10\% \) to \( <50\% \) and did not include cardiac deaths, which were reported separately [31]. Since cardiac deaths were infrequent in all the trials, this category approximated the CE end point of B-31 and N9831.

Symptomatic CHF included severe CHF and was defined as any degree of CHF considered symptomatic by a cardiologist with a decrease in LVEF of \( >10\% \) points from baseline to \( <50\% \) [30]. This approximated the end point reported in the recent update of the initial findings of 006 [17]. A confirmed significant LVEF drop was an asymptomatic or mildly symptomatic decrease in LVEF of \( >10\% \) to \( <50\% \), which was confirmed with a second study [31]. This category approximated the group of patients on B-31 who discontinued trastuzumab due to asymptomatic declines in LVEF [28, 29].

At a median follow-up of 1 year, the cumulative risk of severe CHF was 0.6% in the trastuzumab arm and 0.0% in the observation arm. The rate of symptomatic CHF decreased to \( <50\% \) and did not include cardiac deaths, which were reported separately [31]. Since cardiac deaths were infrequent in all the trials, this category approximated the CE end point of B-31 and N9831.

FinHer trial. The incidence of symptomatic heart failure among the HER2-positive patients was 0.9% (one patient) with trastuzumab and 1.7% (two patients) without trastuzumab. The incidence of absolute declines in LVEF \( >20\% \) points from baseline was 6.8% with trastuzumab and 10.5% without the antibody [26].

PACS-04 trial. No cardiac deaths were reported in this trial. CHF was reported in 4 of 260 (1.5%) patients in the trastuzumab arm and in 1 of 268 (0.4%) patients in the observation arm. LVEF decreases to \( <45\% \) without symptoms were reported in 10 of 260 (3.8%) patients in the trastuzumab arm and in 4 of 268 (1.5%) patients in the observation arm [20].

clinical applications

The efficacy data from these trials have established the importance of trastuzumab as a component of adjuvant systemic therapy in patients with operable HER2-positive breast cancer. All the comparisons in the large trials between chemotherapy alone and chemotherapy with or followed by trastuzumab widely crossed early reporting boundaries. Follow-up data have demonstrated that the improvements in DFS have persisted.

Cardiac toxicity is more frequent with the regimens employing sequential AC and taxanes, though the majority of patients who received the therapy displayed neither acute nor delayed cardiac toxicity. None the less, data from B-31 indicate that women who develop more severe cardiac toxicity do not always fully recover [28]. Additionally, B-31 and N9831 demonstrated that 5.0%–6.6% of women who received AC were unable to receive trastuzumab [28, 29]. While liberalization of the strict criteria employed in the trials would allow some of these women to receive trastuzumab in routine clinical practice, a patient who develops cardiac toxicity on AC may lose the opportunity to potentially benefit from trastuzumab.

Three approaches to reduce the risk of cardiac toxicity have been demonstrated in these adjuvant trials. The first is the sequential approach employed in HERA, which resulted in very low rates of cardiac toxic effects, even though 94% of patients were treated with an anthracycline regimen. However, in the sequential arm of N9831, in which patients received paclitaxel before proceeding to trastuzumab, the rate of CEs was 2.8% compared with a rate of severe CHF in HERA (0.6%) in which...
only 26% received a taxane (Table 2) [29, 30]. These results suggest that the use of an anthracycline and a taxane before initiating sequential trastuzumab may be associated with a higher rate of cardiac toxicity than if anthracyclines are used without a taxane before beginning trastuzumab. Additionally the direct comparison of concurrent versus sequential administration of trastuzumab in N9831 suggests that while the sequential approach is effective, concurrent administration provides greater benefit with only minimally increased risk for cardiac toxicity.

A second approach was employed in FinHer, in which the duration of trastuzumab was limited and was administered with a non-anthracycline chemotherapeutic agent before the anthracycline-based portion of the regimen. While the limited sample size results in uncertainty about the magnitude of the benefits of this approach, the results currently provide useful information for clinicians considering adjuvant trastuzumab-based therapy for women who do not meet the strict cardiac eligibility criteria employed in the large adjuvant trials. The 9-week infusion duration is being compared directly with the 1-year duration in several ongoing European trials. If the negligible cardiac toxicity reported in the FinHer trial can be confirmed and noninferiority for efficacy is demonstrated, this approach would become an important regimen for administering adjuvant trastuzumab.

The third approach was employed in the non-anthracycline TCH → H arm of BCIRG 006. The rate of symptomatic CHF was only 0.4% with TCH → H compared with a rate of 2.0% with AC → TH → H and 2.2% for a similar end point in HERA (Table 2) [22, 30]. TCH → H also avoids the risk of initial AC-related cardiac toxicity, which might preclude a patient from receiving trastuzumab, though reversal of the sequence as was employed in FinHer avoids this problem. To date, the small but important risk of acute leukemia associated with anthracyclines [32] has not been reported among the patients in the TCH → H arm [23]. Thus, TCH → H would be widely accepted as the preferred regimen if the uncertainty regarding the relative efficacy of TCH → H to AC → TH → H did not exist. With a median follow-up of 5.4 years, the point estimates for reduction in risks for DFS events were 0.64 with AC → TH → H relative to AC → T and 0.75 with TCH → H relative to the same control group. The 5-year DFS rates were 84% and 81%, respectively [22]. These more mature results suggest that the clear advantage of TCH → H relative to AC → TH → H in terms of reduced risk for cardiac toxicity may be offset by a small reduction in relative efficacy. Unfortunately, it is unlikely that an adequately powered study with a sufficient sample size could be conducted, so uncertainty with respect to this important question will persist.

Importantly, the risk for cardiotoxicity with the AC → taxane plus trastuzumab regimens can be reduced by identifying women who are at increased risk for CD and avoiding these regimens in these women. While younger women without hypertension and LVEF values ≥55% have a low risk for CEs, women with one or more of the identified risk factors have a degree of CE risk that was not considered acceptable when the adjuvant trials were designed. Given the documented activity and safety of TCH → H in BCIRG 006 and the sequential approach in the HERA trial, it is difficult to justify the use of AC followed by concurrent taxane with trastuzumab regimens in women with these risk factors.

**conclusions**

The results of these trials have provided physicians and their patients with operable HER2-positive breast cancer a number of effective adjuvant therapy regimens. Trastuzumab is approved for adjuvant therapy when initiated concurrently with paclitaxel or docetaxel following AC, concurrently with carboplatin and docetaxel, and as monotherapy following chemotherapy. In patients with a relatively low risk of recurrence following trastuzumab-based therapy such as women with node-negative cancer, a regimen with the lowest risk of cardiac toxicity such as TCH → H or the sequential approach from HERA would be preferable. Women with risk factors for a higher rate of cardiac toxicity would also be better served with TCH → H.

However, women without risk factors for increased rates of cardiotoxicity, who have a higher risk for recurrence, should be informed of the efficacy and cardiac safety data of both the anthracycline-based regimens (AC → PH → H, AC → TH → H, AC → P → H and HERA) as well as the TCH → H regimen. The data regarding the favorable cardiac toxicity profile of the TCH → H regimen are evident, but the uncertainty regarding the relative efficacy must be discussed as well. While the risk of severe cardiac toxicity with anthracycline-based regimens is low and is reversible in a majority of patients, full recovery does not occur in all. For some women, the safety advantages offered by TCH → H may outweigh the uncertainty regarding the efficacy of TCH → H relative to the anthracycline-containing regimens. For others, the uncertainty regarding relative efficacy will outweigh the differences in rates of cardiac toxicity.

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**references**


