Raising the Therapeutic Index for HER2-Targeted Therapy: Can We Safely Omit Anthracyclines in the Adjuvant Setting?

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Abstract

The majority of patients who develop breast cancer are diagnosed with early-stage disease amenable to surgical resection. On a population basis, adjuvant therapies for curative intent provide a modest improvement in overall survival over resection alone, but the majority of individual patients are likely to be cancer-free after surgery and thus at risk of toxicity without benefit. For patients with HER2-positive disease, development of cardiomyopathy secondary to the combined effects of anthracycline-based therapy and the HER2-targeted antibody trastuzumab is especially worrying in the curative setting. In the absence of reliable clinical predictive tools for cardiomyopathy, it is reasonable to prioritize HER2-targeted treatment with adjuvant trastuzumab over anthracylines by using a non–anthracycline-based regimen of similar efficacy.

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Introduction

Gene amplification of *HER2* occurs in approximately 15% to 25% of breast cancers, resulting in overexpression of HER2 on the cell surface. Before the advent of trastuzumab (Herceptin; H), *HER2* amplification was associated with a more aggressive disease course and poorer overall survival.[1,2] Prognosis for patients with HER2-positive disease, defined by strong overexpression (3+) of HER2 by immunohistochemistry, or by a *HER2* to chromosome 17 copy number ratio of >2 by fluorescence in situ hybridization, dramatically improved with the advent of HER2-targeted therapy.[3] Trastuzumab was approved by the FDA in 1998 in combination with chemotherapy for metastatic HER2-positive breast cancer based on an improvement in overall survival (OS) compared with chemotherapy alone, and approved in 2006 for use in the adjuvant setting after joint analysis of interim results of National Surgical Adjuvant Breast and Bowel Project (NSABP) B31 and North Central Cancer Treatment Group (NCCTG) 9831 demonstrated a 52% reduction in relative risk of recurrence, second primary, or death (hazard ratio, 0.48) at a median follow-up of 2 years.[1,3-9] While the earliest adjuvant chemotherapy-trastuzumab combination regimens utilized an anthracycline, several non–anthracycline-based regimens have since been evaluated in clinical trials (**Table 1**). This paper will review the long-term benefits of trastuzumab-based adjuvant therapy and will consider the relative safety and efficacy of each of these regimens.

Outcomes for patients with HER2-positive breast cancer treated with HER2-targeted therapy are now similar to or better than outcomes for patients with HER2-negative disease.

Strong evidence indicates that in the absence of HER2-targeted therapy, patients with HER2-positive breast cancer have a significantly shorter survival compared with those with HER2-negative disease.[1,3,10,11] While the majority of published studies assessing trastuzumab in patients with early-stage HER2-positive breast cancer have only compared outcomes based on whether or not patients received trastuzumab, a handful of trials also provided disease-free survival (DFS) and OS for those with HER2-negative breast cancer. Collectively, these trials give us insights into how trastuzumab has altered the natural history of HER2-positive disease (**Table 2**).

Two concurrently run trials led by the Breast Cancer International Research Group (BCIRG), 1 of which enrolled patients with centrally confirmed HER2-negative disease (BCIRG-005)[12] and 1 of which enrolled patients with centrally confirmed HER2-positive disease (BCIRG-006),[13] have reported 10-year follow-up. Though these were 2 separate studies, they were run in parallel over a similar time period and at many of the same sites with patients triaged based on HER2 status. Thus for the purpose of this review, data from these 2 studies are considered together. BCIRG-005 was a phase III trial comparing adjuvant chemotherapy with 4 cycles of doxorubicin (Adriamycin; A) plus cyclophosphamide (C) followed by 4 cycles of docetaxel (Taxotere; T) (AC➔T) versus 6 cycles of doxorubicin plus cyclophosphamide plus docetaxel (TAC) in node-positive breast cancer.[12] BCIRG-006 was a phase III study in patients with HER2-positive stage I-III breast cancer treated in the adjuvant setting with AC followed by docetaxel with or without trastuzumab (AC➔T or AC➔TH) versus 6 cycles of docetaxel plus carboplatin plus trastuzumab (TCH).[13] At a median 10 years of follow-up, 86% of patients with HER2-positive disease treated with trastuzumab (BCIRG-006) were alive compared with 80% of patients with HER2-negative disease (BCIRG-005) and 81% of HER2-positive patients who did not receive trastuzumab (BCIRG-006).[13] Patients with HER2-positive disease treated with

TABLE 1. Dosages of Chemotherapy Regimens.

Regimen	Dosing
AC➔T	**Doxorubicin** 60 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days for 4 cycles *Followed by:* **docetaxel** 100 mg/m² every 21 days for 4 cycles
AC➔P	**Doxorubicin** 60 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days for 4 cycles *Followed by:* **paclitaxel** 80 mg/m² weekly for 12 cycles or **paclitaxel** 175 mg/m² every 3 weeks for 4 cycles
AC➔PH	**Doxorubicin** 60 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days for 4 cycles *Followed by:* **paclitaxel** 80 mg/m² weekly for 12 cycles or **paclitaxel** 175 mg/m² every 3 weeks for 4 cycles + **trastuzumab** (4 mg/kg loading dose x1, then 2 mg/kg) weekly for 52 weeks
AC➔P➔H	**Doxorubicin** 60 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days for 4 cycles *Followed by:* **paclitaxel** 80 mg/m² weekly for 12 cycles *Followed by:* **trastuzumab** (4 mg/kg loading dose x1, then 2 mg/kg) weekly for 52 weeks
TAC	**Doxorubicin** 60 mg/m² + **cyclophosphamide** 500 mg/m² + **docetaxel** 75 mg/m² every 21 days for 6 cycles
TCH	**Docetaxel** 75 mg/m² + **carboplatin** AUC 6 mg/mL/min every 21 days for 6 cycles + **trastuzumab** (4 mg/kg loading dose x1, then 2 mg/kg weekly) for 17 weeks *Followed by:* **trastuzumab** 6 mg/kg IV every 21 days to complete 1 year of treatment
EC➔T	**Epirubicin** 90 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days for 4 cycles *Followed by:* **docetaxel** 100 mg/m² every 21 days for 4 cycles
EC➔TX	**Epirubicin** 90 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days for 4 cycles *Followed by:* **docetaxel** 75 mg/m² every 21 days for 4 cycles + **capecitabine** 900 mg/m² twice daily on days 1 to 14 of a 21-day cycle
EC➔T➔X	**Epirubicin** 90 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days for 4 cycles *Followed by:* **docetaxel** 75 mg/m² every 21 days for 4 cycles *Followed by:* **capecitabine** 900 mg/m² twice daily on days 1 to 14 of a 21-day cycle for 4 cycles
AP➔P➔CMF	**Doxorubicin** 60 mg/m² + **paclitaxel** 150 mg/m² every 21 days for 3 cycles *Followed by:* **paclitaxel** 175 mg/m² every 21 days for 4 cycles *Followed by:* **cyclophosphamide** 600 mg/m² + **methotrexate** 40 mg/m² + **5-fluorouracil** 600 mg/m² on days 1 and 8 of a 28-day cycle for 3 cycles
FEC	**5-Fluorouracil** 600 mg/m² + **epirubicin** 60 mg/m² + **cyclophosphamide** 600 mg/m² every 21 days (as described in FinHer study)
APT	**Paclitaxel** 80 mg/m² weekly × 12 weeks + **trastuzumab** (4 mg/kg loading dose x1, then 2 mg/kg weekly x11) *Followed by:* **trastuzumab** 6 mg/kg IV every 21 days to complete 1 year of treatment
TCHP	**Docetaxel** 75 mg/m² + **carboplatin** AUC 6 mg/mL/min + **trastuzumab** (8 mg/kg loading dose x1, then 6 mg/kg) + **pertuzumab** (840 mg loading dose x1, then 420 mg) every 21 days for 6 cycles *Followed by:* **trastuzumab** 6 mg/kg IV every 21 days to complete 1 year of treatment

A indicates doxorubicin (Adriamycin); AUC, area under the curve; C, cyclophosphamide or carboplatin as above; E, epirubicin; F, fluorouracil; H, trastuzumab (Herceptin); IV, intravenous; M, methotrexate; min, minute; P, paclitaxel or pertuzamab; T, docetaxel (Taxotere); X, capecitabine (Xeloda).

trastuzumab also fared better than those with HER2-negative disease in terms of OS in the retrospective Italian Registry study of patients diagnosed with stage I-III breast cancers in Parma, Italy, between 2004 and 2007.[14] The OS of patients with HER2-positive breast cancer treated with trastuzumab-based therapy was 98% compared with 87% for those with HER2-positive non–trastuzumab-treated disease and 93% for patients with HER2-negative disease.

The phase III NOAH[15] and GeparQuattro[16] trials investigated outcomes in patients treated with neoadjuvant chemotherapy with or without the addition of 1 year of perioperative trastuzumab. In NOAH, patients with locally advanced or inflammatory breast cancer were given neoadjuvant paclitaxel (P) plus doxorubicin every 3 weeks for 3 cycles followed by paclitaxel every 3 weeks for an additional 4 cycles followed by cyclophosphamide plus methotrexate (M) plus 5-fluorouracil (F) on days 1 and 8 of a 28-day cycle for 3 cycles (AP➔P➔CMF).[15] At 5.4 years of median follow-up in these high-risk patients, OS was 74% in the HER2-positive/trastuzumab arm and 76% in the HER2-negative arm. OS in the HER2-positive cohort randomized to neoadjuvant chemotherapy without trastuzumab was 63%, which is likely an overestimate of survival due to crossover. During the study, the NOAH protocol was amended to allow all patients with HER2-positive cancer to receive trastuzumab based on positive data from HERA17 and NSABP B-31,[8] discussed below. GeparQuattro explored the addition of capecitabine (Xeloda; X) to an anthracycline-taxane backbone of epirubicin (E) plus cyclophosphamide (EC) for 4 cycles followed by docetaxel (T) for 4 cycles (EC➔T) with or without 4 cycles of capecitabine given concurrently with docetaxel or following docetaxel (EC➔TX, EC➔T➔X).[16] Trastuzumab was given to all patients with HER2-positive breast cancer starting with cycle 1 for a year. At a median follow-up time of 5.4 years, OS was 88% in the HER2-positive/trastuzumab arm and 85% in the HER2-negative arm.

The FinHer trial was a phase III adjuvant study of node-negative tumors less than or equal to 5 cm but greater than 2 cm (T2) or node-positive breast cancers without distant metastases treated with adjuvant vinorelbine 25 mg/m² weekly for 9 weeks or docetaxel 100 mg/m² every 3 weeks for 3 cycles followed by fluorouracil, epirubicin, and cyclophosphamide (FEC).[18] Women with HER2-positive cancer were randomly assigned to receive or not receive trastuzumab for 9 weeks during vinorelbine or docetaxel therapy. At 5 years, 90% of women with HER2-positive disease treated with 9 weeks of adjuvant trastuzumab were alive compared with 92% of patients with HER2-negative disease who received the

TABLE 2. Overall Survival (OS) of Patients With HER2-Positive Breast Cancer.
The OS of those treated with adjuvant trastuzumab is similar to or better than the OS of those with HER2-negative disease.

Clinical study	Arms	Median follow-up (years)	HER2-positive disease				HER2-negative	
			Chemotherapy + trastuzumab		Chemotherapy, no trastuzumab		Chemotherapy	No trastuzumab
BCIRG 005/006[12,13†]	AC➔T AC➔TH➔H TAC TC_{AUC6}H➔H	10.3	1841/2149	% of Patients 86%	870/1073	% of Patients 81%	2647/3298	% of Patients 80%
NOAH[15*‡]	AP➔P➔CMF APH➔PH➔CMFH➔H	5.4	87/117	74%	74/118	63%	75/99	76%
Italian Registry[14†]	Regimens not described.	4.1	52/53	98%	140/161	87%	1108/1186	93%
GeparQuattro[16‡]	EC➔T EC➔TX EC➔T➔X ECH➔TH➔H ECH➔TXH➔H ECH➔TH➔XH➔H	5.4	392/446	88%	N/A	N/A	889/1049	85%
FinHer[18†]	T➔FEC V➔FEC TH➔FEC VH➔FEC	5	103/115	90%	95/116	82%	717/778	92%

A indicates doxorubicin (Adriamycin); AUC, area under the curve; C, cyclophosphamide; $CAUC_6$, carboplatin AUC_6; E, epirubicin; F, fluorouracil; H, trastuzumab (Herceptin); M, methotrexate; P, paclitaxel; T, docetaxel (Taxotere); V, vinorelbine; X, capecitabine (Xeloda).

* Crossover in HER2-positive arms allowed.
‡ Neoadjuvant chemotherapy + adjuvant trastuzumab to complete 1 year of therapy.
† Adjuvant therapy.

same cytotoxic regimen and 82% of HER2-positive patients who did not receive trastuzumab.

These studies, each utilizing different chemotherapy regimens, consistently demonstrated that the poor outcome associated with the HER2 alteration is improved by the use of trastuzumab. Based on survival benefits imparted by trastuzumab, current National Comprehensive Cancer Network guidelines recommend consideration of trastuzumab-based therapy for all HER2-positive tumors and as a standard-of-care therapy for HER2-positive tumors over the size of 1 cm.[19] The question is thus no longer "Should we use trastuzumab?" but is instead "Which chemotherapy regimen yields the best therapeutic index in combination with adjuvant trastuzumab?"

Why is therapeutic index so important when choosing an adjuvant regimen?

More than 60% of patients diagnosed with breast cancer in 2016 had disease localized to the breast.[20] While the DFS and OS clearly support the use of adjuvant trastuzumab, the risk of cardiotoxicity must be carefully considered in those with early-stage breast cancers, many of whom are potentially cured by local therapies alone and thus derive no benefit from adjuvant systemic therapy.[21] The 6-year cumulative incidence of congestive heart failure (CHF) or cardiac death in the NCCTG N9831 trial comparing AC followed by paclitaxel without trastuzumab (AC➔P), trastuzumab given with paclitaxel (AC➔PH), or AC➔P followed by trastuzumab (AC➔P➔H) was 0.6% in patients receiving AC➔P, 3.4% for AC➔PH, and 2.8% for AC➔P➔H.[22] Results were similar in the NSABP B-31, with a 7-year cumulative incidence of CHF or cardiac death of 1.3% in the AC➔P arm and 4.0% in the AC➔PH arm.[23]

The combination of anthracyclines and trastuzumab augments the risk of cardiomyopathy.

Anthracyclines are well known to be associated with cardiotoxicity in a cumulative, dose-related manner, necessitating lifetime dosage caps to minimize toxicity. In fact, myocardial depression can occur at any dosage of anthracycline, and patients must be carefully monitored for evidence of heart failure throughout their treatment courses, typically by assessment of left ventricular ejection fraction (LVEF) by echocardiogram or multigated acquisition.[24]

During the early trastuzumab monotherapy trials,[4,5] cardiac dysfunction similar to that related to anthracyclines was noted, leading to the establishment of an independent Cardiac Review

and Evaluation Committee to characterize the severity, treatment, and clinical outcomes of clinical trial patients treated with trastuzumab.[25] The risk of New York Heart Association functional classification III or IV CHF (NYHA III/IV CHF) with trastuzumab monotherapy is estimated to be 2% to 4%.[4,5,26]

In the pivotal trial of trastuzumab in combination with chemotherapy in patients with HER2-positive metastatic breast cancer, the incidence of NYHA III/IV CHF was 16% in those who received concomitant therapy with an anthracycline (doxorubicin or epirubicin), cyclophosphamide, and trastuzumab, compared with 3% for those who received the same regimen without trastuzumab.[5] This was surprisingly higher than the risk of doxorubicin-associated NYHA III/IV CHF, which was estimated to be about 7%,[27] and firmly established cardiotoxicity evaluation as an essential component of trastuzumab clinical trials. Moreover, based on these data, concurrent use of anthracyclines and trastuzumab was avoided in the majority of subsequent studies.

While the use of adjuvant trastuzumab has undoubtedly improved survival for early-stage disease, its use in conjunction with anthracycline-based chemotherapy leads to increased rates of cardiomyopathy. A meta-analysis of 8 adjuvant trastuzumab studies (N = 11,991) showed that the addition of trastuzumab to primarily anthracycline-based chemotherapy regimens increased the risk of CHF by more than 5 times and almost doubled the risk of decline in LVEF.[28] Analysis of the 4 largest of these studies suggests that while the rates of grade 3/4 heart failure are relatively low (<4%) with the use of adjuvant trastuzumab, a patient's ability to start or complete the full year of adjuvant HER2-targeted therapy and the rates of clinically occult cardiomyopathy may be affected by choice of chemotherapy backbone.[3,29,21,22] Data relating to these issues will be discussed below.

The problem with anthracyclines: Cardiomyopathy results in truncation of trastuzumab therapy.

The risk of cardiomyopathy has been partially ameliorated by temporally separating anthracycline administration from trastuzumab, hence the move to treatment regimens such as doxorubicin plus cyclophosphamide sequentially followed by taxane plus trastuzumab (AC➔TH or AC➔PH). Even with this amended treatment regimen, however, cardiomyopathy remains a challenging clinical problem. Patients with HER2-positive disease diagnosed with cardiomyopathy during their therapy typically receive a truncated course of trastuzumab. In 2 large studies of AC followed by paclitaxel with or without trastuzumab, 7% of patients in NSABP B-31 and 5% of patients in NCCTG N9831 were ineligible to receive trastuzumab due to decreased cardiac function after AC.[21,22,30] An additional 15.5% (n = 147) of patients in NSABP B-31 receiving AC➔PH stopped trastuzumab before completion of 1 year of therapy because of cardiac-related issues.[23] In the BCIRG-006 study, discussed in more detail below, 2.1% of patients randomized to adjuvant AC➔TH did not receive planned trastuzumab therapy due to cardiac dysfunction during or after AC. Fortunately, with discontinuation of cardiotoxic therapy and the addition of heart failure therapy (eg, beta blockers, angiotensin converting enzyme inhibitors, diuretics) for left ventricle (LV) dysfunction, recovery of pretherapy cardiac function is possible, typically over the course of years.[29]

Clinically occult cardiomyopathy: Are we appreciating the magnitude of toxicity?

The development of clinically silent cardiac dysfunction has been fairly well documented in the NSABP B-31 and N9831 trials with the use of serial cardiac function monitoring for 18 to 21 months. In B-31, 12% of patients came off trastuzumab due to asymptomatic declines in LVEF. In the N9831 trial, 26% of patients receiving AC➔P, 40% of those on AC➔PH, and 35% of those on AC➔P➔H experienced an LVEF decrease of ≥10 points with 12%, 24%, and 17% dropping below normal LVEF, respectively.[21] Unfortunately, these studies did not follow asymptomatic patients in the long term. Therefore, it is unknown if patients treated with an anthracycline-trastuzumab–based regimen have a higher long-term risk of asymptomatic or symptomatic cardiomyopathy 10 years after treatment.

It should be noted that rates of cardiotoxicity in the HERA trial were fairly low (4.1%) in patients receiving 1 year of trastuzumab after standard chemotherapy (94% of whom received an anthracycline-based regimen).[29] The rate of NYHA III/IV CHF was only approximately 1%, which is much lower than has been seen in other studies. These lower rates in comparison with those of other large trials may relate to the fact that patients with an LVEF below 55% after anthracycline-based therapy were excluded.

Non–anthracycline-based chemotherapy provides similar efficacy outcomes with less risk of cardiotoxicity.

In an effort to circumvent cardiac toxicity without compromising efficacy, alternative chemotherapy regimens have been actively sought. After preclinical data suggested synergy with the combination of trastuzumab and docetaxel or a platinum agent in vitro, 2 independent phase II adjuvant trials were performed demonstrating the efficacy of 6 cycles of docetaxel combined with carboplatin given concurrently with trastuzumab followed by trastuzumab to complete 1 year of therapy (TCH).[31,32]

BCIRG-006 was the first prospective randomized adjuvant trial that evaluated not only standard AC➔TH, but also a non–anthracycline-based regimen of TCH. These 2 regimens were compared with standard AC➔T.[3] In the final analysis after 10 years of follow-up, both trastuzumab-containing regimens yielded a significantly improved DFS (AC➔TH, 74.6%; TCH, 73.0%; AC➔T, 67.9%) and OS (AC➔TH, 85.9%; TCH, 83.3%; AC➔T, 78.7%). While the trial was not powered to test for noninferiority of TCH to AC➔TH, the DFS and OS were similar for the 2 arms in the overall population and in high-risk patients with lymph node–positive disease. Importantly, the rates of leukemia and cardiotoxicity were signifi-

cantly higher in the AC➔TH arm.[13] Heart failure (NYHA III/IV) developed in 2% in the AC➔TH arm versus 0.4% in the TCH arm, and 19.2% of patients had a sustained LVEF loss of more than 10 points on AC➔TH compared with 9.4% on TCH. Additionally, 7 patients on AC➔TH developed leukemia with anthracycline treatment versus 0 with TCH.[13] To date, more than 4700 patients have been treated with TCH-based therapy on neoadjuvant or adjuvant trials.[33-37] These studies have demonstrated consistently low rates of cardiac toxicity as well as high rates of DFS, OS, and pathological complete response (pCR) rates.

Additional anthracycline-free treatment regimens have also been reported. In a single-arm phase II adjuvant study of 12 weekly doses of paclitaxel combined with 1 year of trastuzumab for lymph node–negative, HER2-positive breast cancer (n = 406), Tolaney et al reported a 98.7% rate of survival free from invasive disease at 3 years of follow-up with a 0.5% rate of symptomatic congestive heart failure.[38] A single-arm phase II study of adjuvant docetaxel plus cyclophosphamide and trastuzumab for stage I or II patients with up to 3 positive lymph nodes (n = 493) reported a DFS of 94% in lymph node–positive disease and an OS of 98% at 3 years.[39]

The addition of a second HER2-targeted therapy, pertuzumab (P), to anthracycline-free trastuzumab-based regimens has also been evaluated in the neoadjuvant setting. Six cycles of combination therapy with docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) yielded a 64% total pCR in TRYPHAENA (n = 75)[36] and TCHP x4 cycles resulted in a 41% pCR in patients with breast cancer co-expressing HER2 and hormone receptors in NSABP B52.[34] Positive results from the phase III adjuvant APHINITY trial (NCT01358877) investigating pertuzumab plus trastuzumab and chemotherapy with full results just published showing a small, but statistically significant, improvement in DFS with the addition of adjuvant pertuzumab to standard chemotherapy plus trastuzumab.[40]

Conclusion

HER2-directed therapy has resulted in dramatic improvements in outcomes for patients with HER2-positive breast cancers, becoming standard-of-care in the metastatic, neoadjuvant, and adjuvant settings, but the optimal concurrent cytotoxic chemotherapy regimen is still a matter of debate. In the adjuvant setting, there is no reliable way to separate those who will benefit from systemic therapy from those who will be cured with local therapy alone. Overtreatment is unavoidable, and there are those who incur the risks of treatment without benefit. Therefore, it is critical to weigh the risks of a regimen against the potential benefits. In the adjuvant setting, when trastuzumab is used with a non–anthracycline-based regimen, the risk of clinically evident cardiomyopathy is on the order of 0.5%, according to data from the BCIRG-006 and APT studies. In contrast, when trastuzumab is used in sequence with an anthracycline-based regimen, the rate of moderate to severe cardiac toxicity increases fivefold. Moreover, 2% to 7% of patients who start with an anthracycline are ineligible to ever receive trastuzumab due to a decline in cardiac function related to doxorubicin. Importantly, available data show numerically similar DFS and OS when comparing anthracycline and non–anthracycline-based regimens.

To conclude, treatment strategies to maximize efficacy and minimize long-term complications are particularly important in the curative setting, and replacement of anthracycline-based regimens is desirable and feasible.

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