review

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Anthracycline–trastuzumab regimens for HER2/neu-overexpressing breast cancer: current experience and future strategies

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Anthracycline–trastuzumab-containing regimens demonstrate significant clinical activity in human epidermal growth factor receptor 2 (HER2)-positive breast cancer; however, the utility of this strategy is limited by unacceptably high rates of significant cardiotoxicity, particularly with concurrent administration. Anthracycline-induced cardiotoxicity is thought to be mediated primarily through increased myocardial oxidative stress, modified partly by the activity of neuregulins. Trastuzumab-induced cardiotoxicity is thought to be mediated by the ErbB/neuregulin system, with exposure to trastuzumab partly blocking the protective effect of neuregulins on the myocardium. As a result, trastuzumab increases the risk of anthracycline-induced cardiotoxicity. Several strategies have been adopted in attempts to minimize cardiotoxicity, including patient selection on the basis of preexisting cardiac risk, monitoring of cardiac function during treatment, and early management of cardiac dysfunction. The use of less cardiotoxic anthracyclines may be one strategy to lessen the risk of cardiotoxicity. Liposomal doxorubicin products offer similar efficacy compared with conventional doxorubicin, with significantly less cardiotoxicity, and have been successfully used in combination with trastuzumab in the metastatic and neo-adjuvant setting. Clinical trials are currently underway to assess the safety of pegylated liposomal doxorubicin during concurrent administration with trastuzumab compared with standard sequential treatment using conventional doxorubicin in the adjuvant setting.

Key words: adjuvant therapy, anthracyclines, breast cancer, cardiotoxicity, HER2+, pegylated liposomal doxorubicin, trastuzumab

introduction

HER2 is a proto-oncogene and member of the ErbB family of transmembrane tyrosine kinases. Approximately 15%–25% of patients with breast cancer have tumors that overexpress the HER2 protein or amplify the HER2/*neu* gene. These HER2-positive tumors are associated with a more aggressive clinical course compared with HER2-negative tumors [1, 2].

Current adjuvant treatment for HER2-positive tumors is centered on use of the anti-HER2 mAb trastuzumab, either concurrent with or sequential to systemic chemotherapy. The addition of trastuzumab to standard adjuvant chemotherapy yields significant improvements in both disease-free survival (DFS) and overall survival (OS) compared with chemotherapy alone [3–6].

Most of the published data support the preferential use of an anthracycline-containing adjuvant regimen for individuals with HER2-positive tumors [7–9]. Concurrent anthracyclines and trastuzumab, however, are contraindicated due to the observation of unacceptably high rates of cardiotoxicity in a large randomized trial in the metastatic setting [10]. Due to this, and despite the observed clinical efficacy of concurrent anthracycline–trastuzumab therapy, all large adjuvant trials have evaluated only the sequential strategy of administering anthracyclines and trastuzumab.

Cardiotoxicity remains an important clinical issue even with sequential therapy, and strategies to minimize this toxicity have been proposed [11]. An adjuvant anthracycline–trastuzumab regimen with less cardiotoxicity, potentially allowing for concurrent administration, is an area of clinical relevance and potential value for patients with HER2-positive breast cancer.

This review article will present the rationale for concurrent anthracycline–trastuzumab therapy, review available clinical efficacy and cardiac safety data, outline the mechanisms of cardiotoxicity related to both agents, and review potential strategies for minimizing cardiac risk with concurrent anthracycline and trastuzumab treatment regimens.

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rationale for adjuvant anthracycline–trastuzumab regimens for HER2-positive disease

Before the introduction of HER2-targeted therapy, HER2-positive breast cancer was treated with protocols similar to those employed for HER2-negative tumors. The development of the anti-HER2 mAb trastuzumab led to clinical trials of trastuzumab in combination with systemic chemotherapy for the treatment of HER2-positive metastatic breast cancer (MBC).

The selection of systemic chemotherapy for use in combination with trastuzumab was on the basis of preclinical data demonstrating enhanced antitumor activity when trastuzumab was combined with doxorubicin or with the taxane, paclitaxel [12–14]. These preclinical data were confirmed in the pivotal phase III trastuzumab study involving women with HER2-positive MBC randomized to treatment with standard chemotherapy alone or standard chemotherapy plus concurrent trastuzumab [10]. Anthracycline-naive women received doxorubicin plus cyclophosphamide (AC) with or without trastuzumab (H). Women with prior exposure to anthracyclines received paclitaxel (T) with or without trastuzumab. The addition of trastuzumab to either the anthracycline- or taxane-based regimen led to a significant improvement in overall response rate (50% versus 32%; $P < 0.001$) and OS (25 versus 20 months; $P = 0.046$) compared with the same chemotherapy alone. Although difficult to compare directly due to more favorable baseline characteristics, results in the anthracycline group were numerically superior to those observed in the taxane group, with an objective response rate of 42% for AC alone and 56% for AC–H, versus 17% for T alone and 41% for TH. Despite demonstrable disease activity, however, the utility of concurrent trastuzumab–anthracycline combinations was obviated by unacceptably high rates of New York Heart Association (NYHA) class III/IV cardiotoxicity (16%). The taxane–trastuzumab combination was also associated with an increased incidence of class III/IV cardiotoxicity, but at a lower rate (2%) [10, 15].

Data indicating that patients with HER2-positive tumors may derive preferential benefit from anthracyclines in the adjuvant setting come from multiple clinical trials. One of the earliest reports examining this issue, the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-11, involved patients with lymph node-positive, hormone receptor-negative breast cancer randomized to treatment with melphalan plus fluorouracil with or without doxorubicin. In a retrospective analysis, patients with HER2-positive tumors had improved DFS (relative risk (RR) = 0.60; $P = 0.001$), OS (RR = 0.66; $P = 0.01$), relapse-free survival (RFS; RR = 0.58; $P = 0.002$), and distant DFS (RR = 0.61; $P = 0.003$) when treated with the doxorubicin-containing regimen. There was no benefit to the addition of doxorubicin in the HER2-negative subset [7].

The relationship between HER2 status and responsiveness to adjuvant anthracycline-containing therapy was evaluated in premenopausal women with node-positive breast cancer enrolled in the MA-5 trial led by the National Cancer Institute of Canada. In this study, patients were randomly assigned to treatment with cyclophosphamide, epirubicin, and fluorouracil (CEF) or classic cyclophosphamide, methotrexate, 5-fluorouracil (CMF). At median follow-up times of 5 and 10 years, outcomes were superior for those receiving CEF [16, 17]. In a recent report, tumor specimens from these trials were analyzed for HER2 status. For those with HER2-positive tumors, CEF was superior to CMF, with hazard ratios (HRs) of 0.52 ($P = 0.003$) and 0.65 ($P = 0.06$) for RFS and OS, respectively. There was no observed difference between CEF and CMF in patients with HER2-negative disease [9]. In a separate analysis, topoisomerase II alpha protein overexpression also predicted for improved DFS and OS in patients treated with CEF versus CMF [18].

A pooled analysis of the interaction between HER2 status and benefit of adjuvant chemotherapy as a function of whether or not an anthracycline was administered as part of an adjuvant regimen included eight large randomized controlled clinical trials that examined this issue, two of which were summarized above. The HR for DFS was 0.71 [95% confidence interval (CI) 0.61–0.83; $P = 0.001$) and for OS was 0.73 (95% CI 0.62–0.85; $P < 0.001$) favoring the inclusion of anthracyclines for HER2-positive disease. No significant benefit was observed for anthracycline inclusion for HER2-negative disease with a HR for DFS of 1.0 (95% CI 0.9–1.11; P = NS) and for OS of 1.03 (95% CI 0.92–1.16; P = NS). The test for interaction between HER2 status and receipt of anthracyclines was significant for both DFS ($\chi^2 = 13.7$; $P < 0.001$) and OS ($\chi^2 = 12.6$; $P < 0.001$) [19].

adjuvant doxorubicin/trastuzumab—clinical data

Data from randomized controlled trials in HER2-positive disease provide clear evidence of a DFS and OS benefit when trastuzumab is added to standard chemotherapy in the adjuvant setting (Table 1) [3–5, 20]. Cardiac safety was an important aspect of all the trials. Criteria for the definition of a cardiac event differed among trials but concurrent trastuzumab–chemotherapy strategies consistently led to higher event rates compared with strategies where trastuzumab was administered after completion of chemotherapy (e.g., as in the HERA trial) [3–5, 20–22]. Due to unacceptably high rates of cardiotoxicity observed in the metastatic setting as discussed previously [15], all concurrent strategies avoid administration of trastuzumab during the anthracycline treatment period.

More recently, data from two adjuvant trials have led to controversy regarding the superiority of anthracyclines in HER2-positive disease. In a phase III study, adjuvant docetaxel plus cyclophosphamide (TC) was associated with an improved DFS and OS compared with AC. HER2 status was only assessed in a minority of patients and interaction with treatment was not significant [23, 24].

Breast Cancer International Research Group (BCIRG) study 006 compared AC–docetaxel (T), AC–TH, and T plus carboplatin plus H (TCH) in women with HER2-positive breast cancer (Table 1). At the second interim analysis, there were no statistically significant differences in DFS and OS rates between the two trastuzumab-containing regimens (AC–TH

Table 1. Phase III trials of adjuvant trastuzumab plus anthracyclines

Trial (last follow-up)	Regimen[a]	N	Efficacy					Cardiac events			Trastuzumab discontinuation
			DFS			OS		Severe CHF	Systolic dysfunction		
			%	HR versus control (*P* value)		%	HR versus control (*P* value)				
HERA (24 months) [3, 20, 21]	Any Ctx[b]	1693	74	–		90	–	0	0.5%[c]		
	Any Ctx[b] → H	1694	81	0.64 (0.0001)		92	0.66 (0.0115)	0.6%	3.0%[c]		4.3%
NCCTG N9831 and NSABP B-31	AC → T	1679	67	–		91	–	0.8%[d]	17%[e]		–
(24 months) [4, 22]	AC → TH	1672	85	0.48 (<0.0001)		87	0.67 (0.015)	4.1%[d]	34%[e]		19%
BCIRG-006 (second interim	AC → T	1073	77	–		86	–	0.4%	10%[f]		–
analysis at 36 months) [5]	AC → TH	1074	83	0.61 (<0.0001)		92	0.59 (0.004)	1.9%	18.1%[f]		Not yet published
	TCH	1075	82	0.67 (0.0003)		91	0.66 (0.017)	0.4%	8.6%[f]		Not yet published
FinHER (36 months) [6]	T or V → FEC[g]	116	78	–		90	–	4%	3%[e]		–
	T or V + H → FEC +H[g]	115	89	0.42 (0.01)		96	0.41 (0.07)	0	0		Not reported

[a]The first regimen shown for each study is the control regimen.
[b]Approximately 94% of patients received anthracycline-containing chemotherapy.
[c]Absolute decline of >10% from baseline and to <50%, conformation after 3 weeks.
[d]Cumulative incidence.
[e]Absolute decline of >10% from baseline and to <50%.
[f]Relative decline of LVEF >10%.
[g]Second randomized group to trastuzumab or no trastuzumab only included the HER2-positive patients.
A, anthracycline; C, cyclophosphamide; Ctx, chemotherapy; CHF, congestive heart failure; H, trastuzumab; HR, hazard ratio; T, taxane; V, vinorelbine.

and TCH; DFS 83% versus 82%; OS 92 versus 91%, respectively). Both trastuzumab-containing regimens led to improved DFS and OS rates compared with the nontrastuzumab-containing regimen. Grade III/IV congestive heart failure (CHF) was significantly more common with AC–TH compared with TCH ($P = 0.0015$) [5], thus emphasizing the importance of maximizing cardiac safety for anthracycline–trastuzumab regimens in the adjuvant setting.

The BCIRG 006 trial joins the MA.5 trial and others in which an association between topoisomerase II–HER2/neu coamplification and anthracycline benefit has been demonstrated [25–28]. A systematic review of data from published, randomized, controlled trials conducted in the adjuvant setting and reporting HER2 status showed an incremental efficacy benefit for anthracycline-based therapies only when HER2 and topoisomerase II are coamplified [29]. In BCIRG 006, 35% of patients had topoisomerase II–HER2 coamplification. Results from the second interim analysis of this trial demonstrated that, in the coamplified population, DFS was not statistically significantly different among the three arms (AC–T, AC–TH, and TCH). Conversely, in the non-coamplified population, DFS was significantly poorer in the AC–T arm compared with AC–TH ($P < 0.001$) and TCH ($P < 0.001$) [5]. These results indicate that the anthracycline benefit was lost in patients with non-coamplified tumors and has created an as yet unresolved controversy about the role of anthracyclines and the potential utility of the TCH regimen in the treatment of breast cancer.

cardiac safety of doxorubicin

cardiotoxicity rates with conventional doxorubicin

Comparisons of anthracycline-induced cardiotoxicity rates between studies are problematic due to inconsistencies in patient populations, treatment regimens, definitions of cardiac toxic effects, and cardiac assessment tools. However, available data clearly demonstrate an important risk of cardiotoxicity in patients treated in either the adjuvant or metastatic setting with conventional anthracyclines alone or in combination with standard chemotherapy or trastuzumab.

doxorubicin monotherapy. In a retrospective analysis of 630 patients with MBC or advanced small-cell lung cancer treated with single-agent doxorubicin, the estimated cumulative percentage with symptomatic CHF was 5% at a cumulative dose of 400 mg/m^2, 16% at 500 mg/m^2, and 26% at 550 mg/m^2. When all cardiac events were considered [defined as (i) ≥20 point left ventricular ejection fraction (LVEF) decline from baseline; (ii) 10-point LVEF decline from baseline to below the institution's lower limit of normal (LLN); (iii) LVEF decline ≥5 points to below the institution's LLN; or (iv) symptomatic CHF on study], the estimated cumulative incidence was 7% at a lifetime doxorubicin dose of 150 mg/m^2, 9% at 250 mg/m^2, 18% at 350 mg/m^2, 38% at 450 mg/m^2, and 65% at 550 mg/m^2 [30].

AC therapy. Adjuvant AC is also associated with decreases in LVEF. After a cumulative doxorubicin dose of 240 mg/m^2 administered within the AC regimen in NCCTG N9831, 17% of

1536 patients had an asymptomatic LVEF decline ≥10% but <20% compared with baseline and 7% had an asymptomatic decline ≥20% to below the LLN [31]. Adjuvant trials incorporating trastuzumab concurrent with paclitaxel and following AC have consistently observed that ~7% of patients who complete four cycles of AC experience cardiotoxicity precluding the subsequent administration of trastuzumab [4, 22]. In addition, several trials have shown that a lower LVEF before initiation of trastuzumab, as well as increasing age, increases the risk of treatment-associated contractile dysfunction [21, 22].

cardiac safety of doxorubicin–trastuzumab combination therapy

Trastuzumab monotherapy carries a risk of cardiotoxicity when administered to patients with metastatic disease, with an incidence of cardiac dysfunction (symptomatic CHF, cardiomyopathy, or >10 point decrease in LVEF) ranging from 2% to 9% [15, 32, 33]. The risk of trastuzumab-associated contractile dysfunction appears to be lower in anthracycline-naive patients [22].

In the anthracycline–trastuzumab arm of the pivotal trial in HER2-positive MBC, patients were treated for a planned duration of six cycles (cumulative anthracycline dose 360 mg/m^2), with further cycles administered at investigator discretion. With this, the incidence of cardiac dysfunction and NYHA classes III–IV cardiotoxicity (i.e., symptomatic CHF) was 27% and 16%, respectively [10, 15, 34]. Cardiotoxicity rates were lower in subsequent trials conducted in patients with MBC after the risk of cardiotoxicity was recognized and concurrent administration with anthracyclines was avoided. In an analysis of pooled data from six MBC trials, 11.6% of patients treated with trastuzumab after prior anthracyclines experienced a fall in LVEF of ≥15 points to a level <50% [34].

Data on the risk of cardiotoxicity in the adjuvant setting continue to evolve. Recognition of cardiotoxic risk with anthracycline–trastuzumab combinations has led to rigorous cardiac eligibility criteria for adjuvant trastuzumab trials; most trials now require a normal postanthracycline LVEF before initiating treatment with trastuzumab. Cardiac safety data from the individual trials of adjuvant sequential anthracycline–trastuzumab are shown in Table 1. The cumulative long-term risk of symptomatic or asymptomatic cardiac dysfunction in patients treated in these trials is unknown as are the implications of less severe cardiac toxic effects not meeting the trial definition of an event [35]. These issues are especially germane to patients treated in the adjuvant setting as long-term increases in cardiotoxic risk may counterbalance a portion of the benefit of successful breast cancer treatment.

The differences in rates of cardiac events and trastuzumab discontinuations between concurrent and sequential strategies merits discussion. In an analysis of cardiac dysfunction in the NSABP B-31 trial carried out at a median follow-up of 27 months, the cumulative incidence of class III/IV CHF 3 years after initiating treatment with the TH portion of the AC–TH regimen was 4.1%. In this trial, 19% of women discontinued trastuzumab treatment for cardiac reasons. Both post-AC LVEF and older age were found to be important predictors of cardiotoxicity in this analysis [22, 36]. In the N9831 trial comparing AC–T chemotherapy alone to the same chemotherapy plus trastuzumab, either concurrent (with T) or subsequent to chemotherapy, the incidence of grade III/IV cardiotoxicity was 2.8% and 3.3% for the trastuzumab-containing arms (trastuzumab sequential to, versus concurrent with, paclitaxel) versus 0.3% for the nontrastuzumab arm. Factors associated with increased risk of cardiac events included older age, lower baseline LVEF, and prior/current use of antihypertensive medications [36]. In an analysis of cardiac dysfunction in the HERA trial carried out at a median follow-up of 12 months, the rate of severe (class III/IV) CHF in the trastuzumab arm was 0.6%. Trastuzumab was discontinued for cardiac reasons in 4.3% of women [21]. A direct comparison of these trials is complicated by the use of different methodologies; however, certain differences are of interest. First, the cardiac eligibility criteria for beginning trastuzumab were more stringent in HERA where patients were required to have a LVEF ≥55% [3]. In contrast, the LVEF threshold was effectively ≥50% in NSABP B-31 as patients were allowed to receive trastuzumab if their LVEF was above the institution's LLN as long as they did not experience a drop in LVEF from the prechemotherapy value of >15 percentage points [22]. Second, the amount of time elapsed between the completion of anthracyclines (received by all patients in NSABP B-31/N9831 and 94% of patients in HERA) and trastuzumab initiation was longer in the HERA trial. The median time between last dose of anthracycline and trastuzumab was 89 days in the HERA trial compared with 21 days in NSABP B-31/N9831 [4, 21, 36]. Thus, it is possible that the longer elapsed time between administration of the anthracycline and trastuzumab may result in less oxidative stress to the myocardium, supporting a potential role for anthracycline-associated oxidative stress as a risk factor for trastuzumab-related cardiac dysfunction. As well, a longer elapsed interval may avoid the blockade of erbB2-driven mechanisms involved in tissue rescue of acutely injured myocardium as a result of anthracycline exposure, potentially mitigating observed cardiotoxicity.

Two neo-adjuvant studies incorporating anthracyclines and trastuzumab have documented significant pathologic complete response (pCRs) rates in this patient population. Buzdar et al. [37] have updated their initial cohort, treated preoperatively with paclitaxel followed by an anthracycline-based regimen (FEC75; 5-fluorouracil, epirubicin, cyclophosphamide), to include a final patient sample of 64, of whom 45 received concurrent chemotherapy plus trastuzumab for HER2-overexpressing disease. The pCR in this group was 60% (95% CI 44.3% to 74.3%) versus a pCR rate of 26.3% (95% CI 9% to 51%) in the nontrastuzumab arm. Median LVEF values in the trastuzumab-receiving cohort declined from 65% at baseline to 60%, with the LVEF median and range decreasing over time and a 95% CI of the probability of cardiac failure between 0% and 7.87%. The NOAH trial, published in abstract form to date [38], randomized a subset of patients with HER2-positive disease to sequential neo-adjuvant chemotherapy (AT; doxorubicin–paclitaxel × 3, T; paclitaxel × 3 and CMF; cyclophosphamide, methotrexate, 5-fluorouracil × 3) either with or without concurrent trastuzumab. Early results indicate a significant improvement in pCR rates for the

trastuzumab-containing arm (pCR 43% versus 23%; $P = 0.002$) with cardiotoxicity rates (LVEF decline by 10% or greater, congestive heart failure) of 15.7% for the trastuzumab regimen versus 11.5% for the nontrastuzumab arm.

In addition to the analyses just discussed, there has been a meta-analysis of cardiac effects in >11 000 women enrolled in adjuvant trials of chemotherapy plus trastuzumab including the five trials shown in Table 1. When considering only the arms in which trastuzumab was administered for 1 year, a significantly increased risk of NYHA class III or IV CHF (RR, 7.05, 95% CI 3.88–12.83; $P < 0.0001$) was observed with an absolute difference of 1.61% compared with the nontrastuzumab-containing treatment arms. The risk of asymptomatic contractile dysfunction was also significantly increased (RR, 2.18, 95% CI 1.45–3.27; $P = 0.00016$). The absolute OS benefit observed in the trastuzumab-treated cohort was 1.96% on the basis of relatively short-term follow-up [11]. Both cardiac event rates and absolute OS benefits may change over time and will need to be more fully elucidated before a more complete understanding of both the benefits and risks of anthracycline–trastuzumab-containing adjuvant breast cancer regimens can be achieved.

mechanisms of cardiotoxicity

Anthracycline-induced cardiotoxicity is a progressive disease that evolves in a stepwise fashion, with changes in cardiac ultrastructure occurring in advance of clinical manifestations of cardiac dysfunction [39]. Depending on dose, pharmacokinetics, and type of anthracycline used, myocardial cell loss or functional damage can occur. Initially, only a relatively modest decline in contractile function may occur because physiologic mechanisms can compensate for myocardial cell loss and declines in pump function. Additional cardiac insult and secondary damage may subsequently, over time, lead to left ventricular remodeling and symptomatic heart failure. Compensatory mechanisms include activation of the neurohumoral pathways (such as the renin-angiotensin and adrenergic system), myocardial hypertrophy, and possibly survival factors such as the neuregulin/ErbB system [40–42]. The exact changes that occur during the transition to symptomatic disease are not yet entirely elucidated [40, 41].

Morphologic myocardial change following anthracycline treatment includes myocardial cell loss by necrosis or apoptosis, myofibrillar loss as well as sarcoplasmic reticulum, and mitochondrial swelling [43]. The major mechanism underlying these structural changes is anthracycline-induced oxidative stress with interventions attenuating oxidative stress being generally cardioprotective [44].

In addition to their expression in certain tumors, ErbB receptors are expressed in the myocardium where they serve as receptors for neuregulins. Neuregulins are pivotal for myocyte survival in the stressed myocardium [45] and it is likely that trastuzumab-induced cardiotoxicity results from interference with the action of neuregulin [46]. Thus, the inhibition of ErbB2 signaling by trastuzumab in patients receiving doxorubicin may interfere with the protective effects of neuregulin on the anthracycline-damaged myocardium. This may account for the increased clinical cardiotoxicity observed with concurrent and sequential anthracycline–trastuzumab administration [3–5, 47].

Furthermore, studies conducted in rat cardiocytes demonstrate that the neuregulin/ErbB system, the target for trastuzumab, can attenuate anthracycline-induced myocardial damage [46] by reducing anthracycline-associated oxidative stress [44]. When myofibrillar structure was assessed in cultured adult rat ventricular myocytes, doxorubicin induced a concentration-dependent increase in myofilament disarray and cell death [46]. This suggests that cardiotoxicity is increased as myocardial doxorubicin concentration increases, likely due to higher levels of oxidative stress.

alternative anthracycline-based strategies

epirubicin

Equipotent epirubicin is considered to be less cardiotoxic than conventional doxorubicin, with comparative cardiotoxicity reported to be 1 : 1.8 in favor of epirubicin [48]. The concurrent administration of epirubicin plus trastuzumab is being assessed in a multicenter phases I–II trial. The phase I portion of the study evaluated the cardiac safety of up to six cycles of epirubicin (E, 60 or 90 mg/m^2) and C (600 mg/m^2) with or without H in anthracycline-naive women with MBC. Those with HER2-positive disease received E60CH ($n = 26$) or E90CH ($n = 25$), with HER2-negative patients receiving E90C and serving as controls ($n = 23$). Protocol-defined cardiac toxicity (>10 point decrease in LVEF to <50%) occurred in three patients receiving trastuzumab (6%) and in no patients in the control group. Two patients treated with E90CH experienced symptomatic CHF and one patient treated with E60CH experienced an asymptomatic decrease in LVEF to <50%. Asymptomatic decreases in LVEF >10% but with an LVEF ≥50% were reported in 48% of patients treated with E60CH and in 56% treated with E90CH compared with 24% in the control group [49]. Data from this phase I trial seem to indicate similar issues regarding additive cardiotoxicity with concurrent epirubicin–trastuzumab as has been observed with doxorubicin.

A large retrospective analysis suggests that epirubicin-associated cardiotoxicity may be more common than previously thought. Of 1097 anthracycline-naive patients with MBC treated with epirubicin, 11.4% developed ≥grade II cardiotoxicity. For every 100 mg/m^2 of epirubicin administered, the risk of cardiotoxicity increased 37%. Risk of cardiotoxicity developed at a progressively lower cumulative dose as a function of age (806 mg/m^2 at age 40 versus 609 mg/m^2 at age 70) [50].

liposomal anthracyclines

Liposomal anthracyclines have been developed in an attempt to improve the overall safety profile, and in particular the cardiac safety profile, of conventional anthracyclines. Two liposomal doxorubicin formulations are available: pegylated liposomal doxorubicin (PLD; Caelyx®, Schering Plough, Kenilworth, NJ; Doxil®, Ortho Biotech, Raritan, NJ) and nonpegylated liposomal doxorubicin (LD; Myocet™; Zeneus Pharma

Limited, Oxford, UK and Sopherion Therapeutics, Princeton, NJ). Liposomal daunorubicin (DaunoXome®, Diatos, Paris, France) is available in Europe and Brazil.

Liposome encapsulation alters the safety profile of anthracyclines by modifying their pharmacokinetics and biodistribution. Following administration of a liposomal formulation, most of the doxorubicin in plasma is encapsulated. Once in the tissue, encapsulated doxorubicin is released from the liposome. Due to their size (100–180 nm in diameter), liposomes cannot escape the circulation through the tight capillary junctions found in normal tissue such as the heart, but can escape through the weakened vasculature that feeds tumor cells [51]. Thus, with a liposomal product, the drug is preferentially directed away from sites of toxicity to the site of action.

Adverse effects such as acute nausea and vomiting and cardiotoxicity are thought to be related to peak plasma and tissue concentrations of free doxorubicin. The rationale for the observed reduction in nausea, vomiting, and cardiotoxicity with liposomal formulations compared with conventional doxorubicin is on the basis of lower plasma and tissue (particularly myocardial)-free doxorubicin concentrations [52, 53]. Minimization of myocardial exposure to free doxorubicin induces less myocardial oxidative stress compared with conventional doxorubicin. This reduction in oxidative stress should attenuate doxorubicin-induced cardiotoxicity [54, 55].

Conventional liposomal formulations are cleared rapidly from plasma [52]. Pegylation of the liposome protects the product from detection by phagocytes, thus increasing the plasma half-life and allowing for enhanced accumulation in tumor [56]. Thus, while LD has a half-life of 2–3 h, PLD has a half-life in excess of 55 h [51].

monotherapy. Clinical data confirm that monotherapy with liposomal products is associated with similar efficacy and reduced cardiotoxicity compared with conventional doxorubicin in women with MBC (Table 2) [57, 58]. In these monotherapy studies, percentage LVEF decrease from baseline was correlated with cumulative dose of both conventional anthracycline and the liposomal product, but the HR for cardiotoxicity consistently favored the liposomal products [57, 58]. In patients treated with PLD 50 mg/m^2 every 4 weeks, there was a mean decrease from baseline LVEF of 2%–3% and a median decrease from baseline LVEF of 2.5% (lifetime dose <450 mg/m^2) to 5% (lifetime dose ≥450 mg/m^2) (Figure 1). At cumulative anthracycline doses of 450 mg/m^2 or more, there was a seven-fold greater mean percentage decrease in LVEF with conventional doxorubicin compared with PLD. There were no cases of CHF in 254 patients treated with PLD [57]. In patients treated with LD 75 mg/m^2 every 3 weeks, the median LVEF decrease from baseline ranged from 0 (at a lifetime dose of 0–99 mg/m^2) to 10% (at a lifetime dose ≥700 mg/m^2). There were two cases of CHF in 108 patients treated with LD [58].

concurrent trastuzumab. Both liposomal doxorubicin products have been evaluated in combination with trastuzumab in phase II studies for patients with HER2-positive MBC (Table 3). A phase I/II study evaluated LD (60 mg/m^2 every 3 weeks) plus trastuzumab in patients with advanced breast cancer, some with prior exposure to anthracyclines (38%) and trastuzumab (30%). Among 37 assessable patients, there was one case each of symptomatic CHF and asymptomatic cardiotoxicity, both in patients with prior anthracycline exposure. The overall tumor response rate was 58% (95% CI 41% to 75%) [59].

Table 2. Phase III studies of single-agent nonpeglyated LD or PLD versus conventional doxorubicin as first-line therapy for metastatic breast cancer

Study	Treatment	*N*	Efficacy			Safety	
			PFS	Response rate	Median survival	Cardiotoxicity[a]	Other toxic effects (liposomal versus conventional)
O'Brien et al. [57]	PLD 50 mg/m^2 every 4 weeks	254	6.9 months, HR = 1.00	NR	NR	4% (no cases of CHF) HR = 3.16 ($P < 0.001$)	Alopecia: 20% versus 66%; nausea: 37% versus 53%; vomiting: 19% versus 31%; stomatitis: 22% versus 15%; mucositis: 23% versus 13%; neutropenia: 4% versus 10%; PPE: 48% versus 2%
	Doxorubicin 60 mg/m^2 every 3 weeks	255	7.8 months	NR	NR	19%	
Harris et al. [58]	LD 75 mg/m^2 every 3 weeks	108	NR	26%	16 months	13% (two cases of CHF) HR = 3.56 ($P = 0.0001$)	Alopecia: 81% versus 88%[b]; nausea/vomiting: 13% versus 24%[c]; stomatitis/mucositis: 9% versus 14%[c]; neutropenia: 50% versus 58%[d]; PPE: one case with LD
	Doxorubicin 75 mg/m^2 every 3 weeks	116	NR	26%	20 months ($P = 0.09$)	29%	

[a]At least a 20-point decrease in LVEF from baseline to a value of 50% or greater (i.e., within normal range) or at least a 10-point decrease from baseline to a value <50% or clinical CHF.

[b]Grade 2.

[c]Grade ≥ 3.

[d]Absolute neutrophil count <500 cells/μl.

LD, liposomal doxorubicin; NR, not reported; PLD, pegylated liposomal doxorubicin; PPE, palmar-plantar erythrodysesthesia.

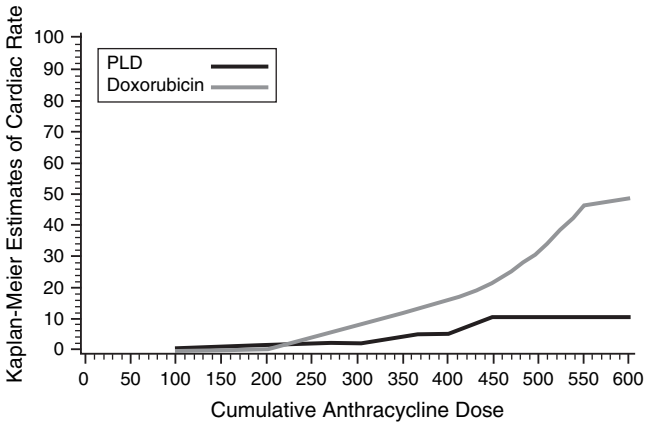

Figure 1. Cardiac event rate in patients treated with pegylated liposomal doxorubicin (PLD) versus conventional doxorubicin. At the same cumulative anthracycline dose, PLD is associated with a lower rate of cardiac events (based on multiple-gated acquisition scan) during treatment than conventional doxorubicin (hazard ratio = 3.16; 95% confidence interval 1.58–6.31; $P < 0.001$ for comparison of cumulative anthracycline dose at the time of first protocol-defined cardiac event). Data from a phase III study in 509 women receiving first-line treatment. With permission from O'Brien et al. [57].

A phase III study (M77035) is currently evaluating the effect of first-line treatment with paclitaxel, LD, and trastuzumab in patients with metastatic or locally advanced HER2-positive breast cancer.

Four studies have evaluated the cardiac effects of PLD administered concurrently with trastuzumab. A multicenter phase II study was conducted in 30 patients with HER2-overexpressing MBC; 13 had prior treatment with conventional anthracyclines at a mean cumulative dose of 251 mg/m^2 of doxorubicin (range 180–288 mg/m^2) and 530 mg/m^2 epirubicin (range 309–703 mg/m^2). Cardiotoxicity was defined as (i) clinical signs and symptoms of CHF with ≥10 point decline from baseline in LVEF to a value below the LLN, (ii) ≥15 point decline from baseline in LVEF in an asymptomatic patient, or (iii) <10 point decline from baseline in LVEF in an asymptomatic patient with an absolute value <45% on multiple-gated acquisition scan. After a mean of 5.5 cycles of PLD (50 mg/m^2 every 4 weeks), cardiotoxicity was detected in three patients (10%), none of whom developed symptomatic CHF and all of whom had received prior treatment with anthracyclines. The disease response rate was 52% with an additional 38% experiencing stable disease (failure to acheive a response or failure to demonstrate progressive disease following 2 cycles of PLD and trastuzumab) for >6 months for an overall clinical benefit rate of 90%. With median follow-up of 13.9 months, the median PFS was 12.0 months and median OS had not been reached [60].

In a second study, concurrent PLD 30 mg/m^2 and docetaxel 60 mg/m^2 every 3 weeks plus trastuzumab 4 mg/kg the first week followed by 2 mg/kg weekly thereafter were administered as first-line therapy to 48 anthracycline- and trastuzumab-naive patients with HER2-positive MBC. Forty-one patients with HER2-negative MBC were treated with PLD plus docetaxel at the same dosage to serve as internal controls for cardiotoxic end points. There were no significant differences in mean LVEF reductions between treatment arms. After four and eight cycles of therapy, LVEF fell a mean of 2.4% and 5.3%, respectively, in the PLD plus docetaxel arm and 2.0% and 5.3%, respectively, in the PLD, docetaxel and trastuzumab arm. No patient in either group developed symptomatic CHF, but 9% of patients in the control group and 11% in the group receiving PLD plus docetaxel plus trastuzumab experienced a LVEF decline ≥20% or a LVEF below the LLN after eight cycles of therapy. A response rate of 46%, median duration of response of 16.3 months, and median survival of 28 months were observed in the HER2-positive arm [61]. Two smaller studies have also been conducted as detailed in Table 3 [62, 63].

investigation of PLD plus trastuzumab in adjuvant therapy

On the basis of the previous discussion, if anthracycline-induced oxidative stress can be minimized by the use of a liposomal doxorubicin product, the impact of the loss of the myocardial protective effects of neuregulin that occurs with concurrent administration of trastuzumab may be reduced and cardiotoxicity minimized.

Collectively, data from adjuvant and metastatic trials indicate that substitution of a liposomal product for conventional anthracyclines in standard chemotherapy regimens may allow for the safe, concurrent administration of anthracyclines and trastuzumab in the adjuvant setting. This concept is being investigated in a randomized phase II multinational trial. The Breast cancer Adjuvant Caelyx Herceptin (BACH) study will evaluate the cardiotoxicity of a doxorubicin-based and a PLD-based adjuvant chemotherapy regimen in 180 women with operable, node-positive or high-risk node-negative HER2-positive breast cancer.

Following surgical removal of the tumor, patients will be randomly assigned in a 1 : 2 ratio to treatment with four cycles of standard AC followed by weekly paclitaxel and trastuzumab or four cycles of PLD (35 mg/m^2) [64] and cyclophosphamide (CC), with concurrent weekly trastuzumab followed by weekly paclitaxel and ongoing trastuzumab. After eight cycles of chemotherapy, further treatment will continue as per the standard of care of the institution and at the discretion of the investigator. Thus, trastuzumab will be expected to continue for a total of 1 year on the basis of current knowledge gleaned from prior large adjuvant trastuzumab trials.

The primary objectives are to determine the incidence of cardiotoxicity (based on ECG and LVEF measurements) and the percentage of patients unable to receive trastuzumab over the planned cycles of chemotherapy or for the full duration of 1 year, due to cardiac dysfunction.

discussion

Trastuzumab–chemotherapy regimens have dramatically altered the natural history of HER2-positive breast cancer. However, the long-term prognosis for patients with breast cancer depends not only on the efficacy of anticancer treatment but also on the impact of treatment-induced toxic effects.

Table 3. Phase II studies of liposomal doxorubicin formulations plus trastuzumab in MBC

Study	Treatment	*N*	Efficacy results	Safety results
Nonpegylated LD				
Theodoulou et al. [59]	LD 60 mg/m^2 i.v. every 3 weeks H 4 mg/kg i.v. week 1, then 2 mg/kg i.v. weekly	37	OR: 58%; SD: 16%	CHF: one patient; asymptomatic cardiotoxicity: 1 patient; grade 4 neutropenic fever: 2/203 cycles; grades 3–4 nausea 2/37 patients (5.4%)
PLD				
Chia et al. [60]	PLD 50 mg/m^2 i.v. every 4 weeks; H 4 mg/kg i.v. week 1, then 2 mg/kg i.v. weekly	30	OR: 52%; SD: 38%; PFS: 12.0 months	CHF: none; asymptomatic cardiotoxicity: 3 patients; grade 3 mucositis: 1/30 patients (3%); grade 3 PPE: 9/30 patients (30%); grades 3–4 neutropenia: 8/30 patients (27%)
Wolff et al. [61]	HER2-negative patients; PLD 30 mg/m^2 i.v. every 3 weeks; T 60 mg/m^2 i.v. every 3 weeks	41	OR: 40%; TTP: 10.5 months	CHF: none; grades 1–2 cardiotoxicity—cycle 8: 9/22 patients (41%); ≥30 days post-treatment: 1/9 patients (11%)
	HER2-positive patients; PLD 30 mg/m^2 i.v. every 3 weeks; T 60 mg/m^2 i.v. every 3 weeks; H 4 mg/kg i.v. week 1, then 2 mg/kg i.v. weekly	48	OR: 46%; TTP: 13.1 months	CHF: none; grades 1–2 cardiotoxicity—cycle 8: 10/18 patients (56%); ≥30 days post-treatment: 12/18 patients (67%); increased incidence grades 2–3 PPE in this arm
Stickeler et al. [62]	PLD 40 mg/m^2 i.v. every 4 weeks; H 4 mg/kg i.v. week 1, then 2 mg/kg i.v. weekly	15	CB: 42.9%; OS: 16.2 months	CHF: none; asymptomatic cardiotoxicity: 3/15 patients (20%)
Andreopoulou et al. [63]	PLD 30 mg/m^2 i.v. every 3 weeks; H 4 mg/kg i.v. week 1, then 2 mg/kg i.v. weekly	12	CB: 67%	CHF: one patient (grade 3); asymptomatic cardiotoxicity (grade 2): 3 patients (25%); grade 3 neutropenia: 2/12 patients (17%); grade 3 hypersensitivity: 2/12 patients (17%); grade 3 mucositis: 1/12 patients (8%); grade 3 rash: 1/12 patients (8%); grade 3 esophagitis: 1/12 patients (8%)

CB, clinical benefit (i.e., complete response + partial response + SD); CHF, congestive heart failure; H, trastuzumab; LD, liposomal doxorubicin; OR, objective or overall response; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; SD, stable disease; T, taxane (docetaxel); TTP, time to treatment failure.

Cardiotoxicity is a particularly important issue given the large number of women with breast cancer receiving anthracyclines in the adjuvant setting. While HER2-directed therapy provides significant clinical benefit for patients with HER2 positive disease, it presents new concerns regarding cardiotoxicity, particularly when used in conjunction with, or immediately following anthracycline-based chemotherapy.

Several strategies to reduce anthracycline–trastuzumab-induced cardiotoxicity have been proposed with key elements including establishing stringent LVEF criteria for patient selection, monitoring cardiac function during therapy, and discontinuing potentially cardiotoxic therapy when cardiotoxicity arises. Other strategies to impact cardiotoxic risk may include using a less cardiotoxic anthracycline and initiating aggressive management of cardiac dysfunction.

At present, the inclusion of anthracyclines in adjuvant chemotherapy regimens for patients with HER2-positive breast cancer is controversial, primarily due to the cardiotoxicity associated with these regimens and the potential efficacy of alternative, nonanthracycline-containing regimens such as TCH. Concurrent anthracycline–trastuzumab administration has not been attempted in the adjuvant setting and it is therefore unknown whether concurrent strategies might be more effective than regimens in which trastuzumab is administered sequentially following completion of the anthracycline. Strong evidence indicates that anthracycline-induced increases in myocardial oxidative stress are a major factor underlying anthracycline-associated cardiotoxicity and trastuzumab-associated contractile dysfunction. Future trials incorporating lapatinib, an oral dual tyrosine kinase inhibitor of EGFR/ErbB1 and HER2/ErbB2, with early reports of a favorable cardiac safety profile, may expand the range of strategies for concurrent HER2 blockade with anthracycline administration [65]. Liposomal anthracyclines may also allow for greater cardiac safety and results from the adjuvant BACH study evaluating concurrent PLD, cyclophosphamide, and trastuzumab may serve to further develop this strategy and provide insight into the potential benefits of concurrent anthracycline–trastuzumab use in the adjuvant treatment of HER2-positive breast cancer.

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