Anthracycline Use for Early Stage Breast Cancer in the Modern Era: a Review

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Opinion statement

Anthracycline-based regimens have been an important treatment component for patients with breast cancer. As demonstrated in the last Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, anthracycline-based regimens decrease breast cancer mortality by 20–30%. Anthracycline toxicities include the rare—but potential morbid—cardiotoxicity or leukemogenic effect, and the almost universal—but very distressing—alopecia. Due to potential toxicities, and large number of patients being exposed, several worldwide trials have re-examined the role of anthracycline-based regimens in the management of breast cancer. Current literature supports that anthracyclines are not required for all patients with breast cancer and should be avoided in those with high cardiac risk. Recent results from the ABC trials suggest that anthracyclines should not be spared for patients with triple negative breast cancer (regardless of axillary node involvement) or HER2–/ER+ with significant node involvement. Based on current literature, for HER2-negative patients with low-risk breast cancer, anthracyclines could be spared with regimens such as cyclophosphamide, methotrexate, and fluorouracil (CMF) or docetaxel and cyclophosphamide (TC). Patients with intermediate or high-risk breast cancer should be considered for anthracycline-based regimens based on other factors such as age, comorbidities, tumor grade, lymphovascular invasion, and genomic profiling. Patients with HER2-positive breast cancer with low risk could be treated with paclitaxel and trastuzumab. For the remaining patients with HER2 overexpression, while docetaxel, carboplatin, and trastuzumab (TCH) has demonstrated to improve disease-free survival (DFS), anthracycline-containing regimens should be discussed, especially for those with very high-risk breast cancer. Although several biomarkers, such as topoisomerase II

(TOP2A) and chromosome 17 centromeric duplication (Ch17CEP) have been proposed to predict benefit from anthracycline regimens, further research is required to delineate their proper utility in the clinical setting.

Introduction

Breast cancer (BC) is the most common malignancy and a leading cause of cancer-related death among women worldwide [1, 2]. Approximately 80% of patients present with local or locally advanced disease and undergo resection, followed by adjuvant therapies which may include chemotherapy, endocrine, biologic, or radiation therapy. Mortality from BC has been steadily decreasing since 1989. The 5-year overall survival (OS) rates for patients with stage I and stage II BC are around 99 and 93%, respectively [3]. This improvement in OS can be attributed to improved screening, as well as more effective adjuvant systemic therapeutic options [4]. Early in the 1970s, chemotherapy was explored in the management of BC, and with further studies, anthracyclines have been incorporated into the backbone of adjuvant regimens. Anthracycline-based regimens have led to significant improvement in clinical outcomes [5], but these regimens are also associated with adverse events [6, 7]. In the present article, we review the role of anthracyclines in the management of early stage BC.

Pharmacologic and toxicity profile of anthracyclines

Derived in the 1950s from rhodomycin B, anthracyclines were isolated from a species of actinomyces, *Streptomyces peucetius*, and demonstrated antibacterial activity in vitro. Anthracyclines exert their antitumor effects via three mechanisms [8]: (A) Through interaction with the DNA gyrase, topoisomerase II (TOP2A), anthracyclines can intercalate DNA to form a "drug-stabilized cleavable complex," causing double-stranded chromosomal DNA breaks which inhibits transcription and replication, leading to cell cycle arrest and apoptosis [9]. (B) Anthracyclines can modulate signal transduction pathways such as the Fas ligand pathway which has been implicated in growth inhibition [10][8]. (C) Anthracyclines can generate reactive oxygen species (ROS) which can induce DNA damage and lipid peroxidation, known to be the mechanism behind anthracycline-induced cardiotoxicity [11]. In fact, dexrazoxane, an agent used to prevent cardiotoxicity from anthracyclines, acts by chelating iron and reducing the formation of ROS [12]. The most worrisome toxicities associated with anthracyclines include cardiotoxicity and leukemogenic effects, whereas alopecia is almost universal with these regimens [6, 7, 13–15].

Anthracycline cardiotoxicity

Anthracyclines can accumulate in the mitochondria of myocardial cells, inhibiting oxidative phosphorylation and generating ROS, leading to endomyocardial interstitial fibrosis and vacuolation [16, 17]. Cardiac acute/subacute toxicity can start either at the time of infusion or within the first 2–3 days and includes arrhythmias, supraventricular tachycardia, and hemodynamic instability [18]. Chronic dilated cardiomyopathy occurs in a dose-

dependent manner and is observed at peak incidence 1 to 3 months post exposure, but cases have been reported several years after initial therapy [19].

Risk factors for anthracycline-induced cardiotoxicity include previous cardiac disease, gender, age, prior mediastinal irradiation, and concomitant exposure to other cardiotoxic agents such as trastuzumab [20, 21]. Moreover, cardiotoxicity risk correlates to cumulative doses of anthracyclines [22, 23]. In a retrospective review of three phase III trials (two breast cancer trials and one lung cancer trial), doxorubicin-related congestive heart failure (CHF) was defined as cardiomegaly on chest X-ray, basilar rales, S3 gallop, or either paroxysmal nocturnal dyspnea, orthopnea, or significant dyspnea on exertion. Doxorubicin-related CHF was identified in 5 or 26% of patients treated at a cumulative doxorubicin dose of 400 or 550 mg/m^2, respectively, and 66% of these patients had decline in left ventricular ejection fraction (LVEF) 0–30% from baseline while on study. Cardiac events were defined as a decline in absolute value ≥ 20% in LVEF from baseline, a decline in absolute value ≥ 10% in LVEF from baseline and to below 50%the institution's lower limit of normal (LLN), a postbaseline decline in absolute value ≥ 5% in LVEF below the institution's LLN, or the occurrence of CHF on study. Cardiac events were identified in 9 or 65% of patients at a cumulative doxorubicin dose of 250 or 550 mg/m^2, respectively [15]. In addition, a review of the Surveillance, Epidemiology, and End Results (SEER) Medicare database showed that among women aged 66–70 years with stage I–III breast cancer and no history of CHF, those who received anthracycline-based regimen had a higher incidence of CHF (identified through claims in Medicare inpatient, outpatient, and physician files containing ICD-09 of CHF) compared to those receiving other regimens (hazard ratio [HR] = 1.26, 95% confidence interval [CI] 1.12–1.42) [24]. Each anthracycline drug differs with respect to their pharmacokinetic profile and the cumulative dose at which chronic cardiotoxicity can develop (Table 1).

With the introduction of anti-HER2 agents, concomitant infusion of trastuzumab and anthracyclines became a challenge given significant increase in cardiac toxicity in trials evaluating concurrent use of these drugs. The herceptin adjuvant (HERA) trial showed a 1.73% 1-year incidence of symptomatic CHF in the group receiving trastuzumab (with 94% of these patients previously undergoing anthracycline-based chemotherapy) vs. 0.06% in the observation group, while the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial showed a 4.1% 3-year incidence of New York Heart Association (NYHA) Class III or IV heart failure in trastuzumab and anthracycline-treated patients vs. 0.8% in the control group [25, 26].

Current American Society of Clinical Oncology (ASCO) guidelines define a subset of patients that are at a higher risk of developing cardiac dysfunction following treatment with anthracyclines [27•]. These include patients who (1) receive high-dose anthracyclines (doxorubicin > 250 mg/m^2 or epirubicin > 600 mg/m^2), (2) receive low-dose anthracyclines (doxorubicin < 250 mg/m^2 or epirubicin < 600 mg/m^2) with concomitant lower dose radiation therapy (< 30 Gy) involving the heart in the treatment field, (3) receive low-dose anthracyclines and have multiple cardiovascular risk factors (smoking, hypertension, hyperlipidemia, diabetes or obesity), are older than 60 years of age or have baseline cardiac dysfunction (LVEF < 50%), or (4) receive low-dose anthracyclines followed by trastuzumab. For these patients, ASCO recommends obtaining echocardiogram, or if not available, either cardiac magnetic

Table 1. Anthracycline drugs used in early breast cancer

	Regimen for breast cancer	Pharmacokinetic profile	Toxicities	Drug interactions

Doxorubicin	1st generation:
	  AC ×4
	2nd generation:
	  FAC ×6 CAF ×6
	  AC ×4–paclitaxel ×4 (q3 weeks)
	3rd generation:
	  concurrent AC-docetaxel
	  Dose-dense AC ×4–paclitaxel ×4 (q3 weeks)
	  AC ×4–weekly paclitaxel ×12
	  AC ×4-docetaxel (q3 weeks)
		Poor oral bioavailability, given in an IV formulation (can also be given as a bladder or intraperitoneal instillation)
		Excreted via the biliary system with $t1/2$ of 20 h
		Substrate of CYP3A4 and CYP2D6
		Pregnancy category D
			-Dose-dependent cardiotoxicity (arrhythmias, myocarditis, pericarditis, dilated cardiomyopathy) at cumulative dose > 450 mg/m^2. Higher rates of subclinical cardiotoxicity with lower cumulative doses when compared to epirubicin.
			-Risk of cutaneous radiation recall, alopecia, hyperpigmentation, erythema
			-Myelosuppressive
			-Highly emetogenic
			-Potent vesicant
				1. Cyclophosphamide: increased risk of hemorrhagic cystitis and cardiotoxicity
				2. Mitomycin C and trastuzumab: Increased risk of cardiotoxicity
				3. Fluorouracil: incompatible, will form a precipitate
				4. 6-Mercaptopurine: increased risk of hepatotoxicity
				5. Palbociclib: increased concentration of CYP3A4 substrates such as doxorubicin

Epirubicin	1st generation:
	  FEC50 ×6
	2nd generation:
	  FEC100 ×6
	  CEF ×6
	  E ×4–CMF ×4
	3rd generation:
	  FEC ×4-T ×3
	  FEC ×4–weekly paclitaxel ×8
		Poor oral bioavailability, given in IV formulation
		
		Can concentrate in RBCs
		No CNS penetration
		Hepatic metabolization by the microsomal P-450 system
		Excreted via the biliary system with some renal elimination
		Pregnancy Category D
			-Dose-dependent cardiotoxicity (arrhythmias, myocarditis, pericarditis, dilated cardiomyopathy). Increased risk at cumulative dose > 900 mg/m^2
			-Myelosuppressive with leukopenia being common
			-Secondary leukemias, particularly in combination with cytotoxic drugs
			-Moderate to highly emetogenic
			-Potent vesicant
				Cimetidine: increases epirubicin's area under the curve by 50%, thus increasing exposure to the drug

CMF cyclophosphamide, methotrexate, fluorouracil, *AC* doxorubicin, cyclophosphamide, *TC* docetaxel, cyclophosphamide, *FAC* fluorouracil, doxorubicin, cyclophosphamide, *AC-T* doxorubicin, cyclophosphamide, docetaxel, *FEC* fluorouracil, epirubicin, cyclophosphamide, *FEC-T* fluorouracil, epirubicin, cyclophosphamide, docetaxel, *T* docetaxel

resonance imaging (MRI) or multigated acquisition (MUGA) scan, with serum cardiac biomarkers if there is evidence of cardiac dysfunction on physical exam [27•]. Although dexrazoxane is approved for use to prevent anthracycline-

related toxicity, there is concern that it might lead to decreased antitumor efficacy [28]. Not only does it inhibit formation of ROS, but it is also a TOP2A inhibitor, directly interfering with anthracycline activity [29]. ASCO recommends against routine use of prophylactic dexrazoxane in the adjuvant setting, limiting their use to patients who have received cumulative doses of anthracyclines up to 300 mg/m^2, but may still benefit from continued use [30].

Anthracycline-associated leukemogenic effect

There is also evidence that anthracyclines are potentially leukemogenic, particularly when combined with platinums or alkylators [31, 32]. Both acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) have been observed, with a relatively short time to onset of 2–3 years [33]. Translocations in chromosome 11q23, 21q22, and 3q23 have been implicated in the pathogenesis of anthracycline-induced leukemia [33]. Similar to cardiotoxicity, a cumulative dose effect has also been observed in anthracycline-induced leukemia. In an analysis of 19 randomized trials, there were 7110 patients treated with epirubicin (92% of whom received cyclophosphamide) and the 8-year risk of developing treatment-related AML/MDS was 0.55% (95% CI, 0.33–0.78) with the risk being higher as the epirubicin dose per cycle and cumulative doses of epirubicin with cyclophosphamide increased. In particular, for patients who received a total dose of epirubicin and cyclophosphamide less than the standard dose (< 720 and < 6300 mg/m^2, respectively), the 8-year cumulative probability of AML/MDS was 0.37% (95% CI, 0.13–0.61) compared to 4.97% (95% CI, 2.06–7.87) for those who received higher than standard cumulative doses of the same drugs [13].

Among 20,063 patients in the National Comprehensive Cancer Network (NCCN) with stage I to III breast cancer treated between 1998 and 2007, 50 patients developed treatment-associated marrow neoplasm(MN) (not limited to AML/MDS); of these, 14 had received no chemotherapy, while 30 and 6 patients had received 4 and 6 cycles of chemotherapy (anthracycline and/or cyclophosphamide), respectively. The probability of OS after MN diagnosis was 50% at 1 year and 30% at 2 years. The MN risk was similar for those treated with surgery plus radiation compared with surgery alone (HR = 2.6, 95% CI 0.57–11.9, P = 0.21). However, there was a significant increase in MN risk among patients treated with both surgery plus chemotherapy (HR = 6.8, 95% CI 1.3–36.1, P = 0.03) and those treated with all three modalities (HR = 7.6, 95% CI 1.6–35.8, P = 0.01). The cumulative incidence of MN doubled between years 5 (0.27%) and 10 (0.49%) for those receiving chemotherapy. In addition, the incidence of MN was greater than that observed in general SEER population after controlling for age and race (50 vs. 14.1 cases, observed/expected ratio = 3.6, 95% CI 2.6–4.6, P < 0.01) [34••].

Anthracycline-induced alopecia

Alopecia is almost universal for patients receiving adjuvant anthracyclines for breast cancer and is rated by patients as one of the most distressing adverse toxicities [35, 36]. Scalp cooling can cause cutaneous vasoconstriction in the scalp which reduces blood—and chemotherapy—uptake in the hair follicles, and reduces biochemical activity, which make hair follicle less susceptible to chemotherapy-induced damage [37]. In the multicenter, randomized, non-

blinded scalp cooling to prevent chemo-related hair loss (SCALP) trial, women with early breast cancer undergoing adjuvant chemotherapy were randomized to scalp cooling or not, and the outcome hair preservation was defined as grade 0 (no hair loss) or grade 1 (< 50% hair loss not requiring a wig) alopecia. For those who received anthracycline-based regimen, none of the patient in the non-cooling arm achieved hair preservation, whereas the cooling arm achieved a hair preservation rate of 16% (95% CI, 4–46) [38].

The role of adjuvant chemotherapy in breast cancer

Adjuvant chemotherapy, targeted to treat micrometastatic disease, has improved breast cancer mortality and recurrence [39••, 40••]. After initial trials with adjuvant melphalan monotherapy showing improvement in disease-free survival (DFS) in early BC [41], Bonadonna et al. proposed a move towards combination chemotherapy [42] comparing cyclophosphamide, methotrexate, and fluorouracil (CMF) (N = 207) for 12 cycles vs. placebo (N = 179) in premenopausal and postmenopausal patients who had undergone radical mastectomy and had one or more histologically proven positive axillary lymph nodes. Treatment failure, defined as local, regional, or distant recurrence, occurred in 24% of placebo patients and 5.3% of patients in the combination chemotherapy arm (P < 0.01) at 27-month follow-up [42]. These results demonstrated that there was a benefit to treating operable disease with adjuvant chemotherapy. A meta-analysis performed by Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that adjuvant chemotherapy with regimens such as CMF improves 10-year breast cancer recurrence (relative risk (RR)= 0.70, $2P$ < 0.001) and mortality (RR = 0.76, $2P$ < 0.001) compared to placebo[40••].

Pivotal trials of anthracyclines in the management of early breast cancer

The concept that anthracyclines could be effectively incorporated into adjuvant chemotherapeutic regimens was first proposed by the NSABP B-11 study which found a significant improvement in DFS with the addition of doxorubicin to melphalan (L-PAM) and fluorouracil (PAF); doxorubicin treatment was not associated with increase in hematologic and cardiac toxicity [43]. Patients were defined as "tamoxifen-nonresponders," i.e., less than 49 years of age, or 50–59 years with progesterone receptor (PR) levels less than 10 fmol/mg of cytosolic protein. Estrogen receptor (ER) status was not taken into consideration [44]. Although these early studies were suggestive of a benefit to the addition of anthracyclines, it was not until the NSABP B-15 study that anthracyclines were adopted as standard of care. In the NSABP B-15 trial, 6 cycles of CMF were compared to 4 cycles of doxorubicin plus cyclophosphamide (AC) and 4 cycles of AC followed by 3 cycles of CMF among 2194 women with at least one histologically axillary lymph node-positive, tamoxifen non-responsive, operable BC [5]. There was no significant statistical difference in 3-year DFS (P = 0.5) or OS (P = 0.8) among the three groups. However, the AC regimen could be given over a shorter course of time (63 vs. 154 days). In addition, AC was

associated with milder short-term toxicities such as nausea, vomiting, or infusion site reactions.

Epirubicin was investigated in BC management given decreased cardiotoxicity and potentially equivalent antitumor effect compared to doxorubicin. In a combined analysis of the French Adjuvant Study Group (FASG) 02 and 07 trials to determine the role of epirubicin in chemo-hormonal therapy, 457 patients with ER+, axillary node-positive BC received tamoxifen with or without fluorouracil, epirubicin (50 mg/m^2), and cyclophosphamide for six 21-day cycles (FEC50). Addition of FEC50 to tamoxifen improved 9-year DFS (84 vs. 72%, $P = 0.008$), with similar OS (86 vs. 78%, $P = 0.11$) [45]. The EBCTCG meta-analysis demonstrated that anthracycline-based regimes improve 10-year breast cancer mortality (RR = 0.79, $2P < 0.001$) and recurrence (RR = 0.73, $2P < 0.001$) compared to no chemotherapy. Moreover, AC for 4 cycles vs. CMF were equivalent for recurrence (RR = 0.99, 95% CI 0.90–1.08, $2P = 0.76$) and breast cancer-related mortality (RR = 0.98, 95% CI 0.89–1.08, $2P = 0.67$) [40••].

Role of anthracyclines in modern era

Anthracycline-free regimens

Taxanes were found to have clinical activity in breast cancer [46••], and trials have investigated taxane-based regimens that exclude anthracyclines due to their potential long-term toxicities [47]. The US Oncology Research trial group 9735 enrolled 1016 women with both node positive and negative operable BC, and randomized them to 4 cycles of docetaxel plus cyclophosphamide (TC) or AC [48]. At 7-year follow-up, DFS was improved with TC (81 vs. 75%, HR = 0.74, 95% CI 0.56–0.98, $P = 0.033$), and OS also favored the TC arm (87 vs. 82%, HR = 0.69, 95% CI 0.50–0.97, $P = 0.032$). Grade 3–4 anemia occurred more frequently in older women receiving AC compared to TC (5 vs. < 1%), whereas the incidence of febrile neutropenia was higher among older women in the TC arm compared to AC arm (8 vs. 4%). There were three treatment-related deaths without relapse, all in the AC group, one due to cardiomyopathy and CHF, and two older patients dying secondary to complications related to MDS and myelofibrosis.

A significant limitation of earlier adjuvant trials in BC was the unintentional inclusion of patients with HER2-positive disease. Given that HER2 expressing tumors have increased sensitivity to anthracyclines, it has been argued that the inclusion of such patients may have led to an overestimation of the benefit derived from anthracyclines. The ABC trials are a joint analysis of three sequential trials, USOR 06-090 ($N = 1286$), NSABP B-46 ($N = 1051$), and NSABP B-49 ($N = 1819$), which randomized women with node-positive or high-risk node-negative early stage, HER2-negative BC to either TC for 6 cycles (TC6) or one of the several available taxane and anthracycline-based regimens (TaxAC) which most often included docetaxel as the taxane of choice [49••]. These anthracycline-based regimens included (1) docetaxel, doxorubicin, and cyclophosphamide (TAC) every 21 days for 6 cycles; (2) AC every 3 weeks for 4 cycles followed by weekly paclitaxel for 12 cycles; (3) dose-dense AC every 2 weeks for 4 cycles followed by paclitaxel for 12 weeks; and (4) dose-dense AC followed by paclitaxel every 2 weeks for 4 cycles. These trials were designed to determine whether TC6 was non-inferior to the standard TaxAC regimen with the primary

endpoint being invasive DFS (IDFS). Follow-up in the studies ranged from 2.2 to 6.3 years, and included 2094 women in the TC6 group and 2062 women in the TaxAC group, with 40% being node negative. The 4-year IDFS rate was 88.2% in the TC6 group vs. 90.7% in the TaxAC group (HR = 1.23, 95% CI 1.01–1.50, P = 0.04). Planned exploratory interaction tests by protocol, hormone receptor status, and nodal status were negative, with a suggested benefit favoring TaxAC in the hormone-negative group (HR 1.42, 95% CI 1.04–1.94) but not for hormone-positive patients (HR 1.12, 95% CI 0.86–1.45). However, unplanned interaction tests by combined hormone receptor and nodal status revealed a statistically significant interaction for hormone-positive and nodal status (P = 0.026) with suggested benefit of TaxAC for node-positive patients (0 nodes: HR 0.69, 95% CI 0.39–1.19; 1–3 nodes: HR 1.14, 95% CI 0.77–1.69; ≥ 4 nodes: HR 1.46, 95% CI 0.95–2.26), but interaction test was not statistically significant for hormone-negative patients (P = 0.71). Five out of 2062 patients (0.24%) in the TaxAC cohort developed leukemia, whereas no cases were seen in the TC6 cohort. These results revealed that TC6 is statistically inferior to TaxAC in terms of IDFS, suggesting that anthracyclines should not be spared in patients with high risk of breast cancer recurrence such as those with triple negative disease or HER2–/hormone positive with significant axillary node involvement [49••].

Dose-dense anthracycline regimens

The C9741 trial evaluated the effect of dose density (2 vs. 3 weeks) and treatment sequence (concurrent vs. sequential) in patients with operable breast cancer by randomizing 2005 patients (with 1973 included in final analysis) to four different treatment arms using a 2 × 2 factorial design: (1) concurrent AC-paclitaxel vs. sequential AC-paclitaxel and (2) every 3 weeks vs. a dose-dense regimen every 2 weeks [50]. Multivariate Cox analysis showed prolonged DFS for dose-dense regimens (RR = 0.74, 95% CI 0.59–0.93, P = 0.01) but no difference in concurrent vs. sequential therapy (RR = 0.93, 95% CI 0.75–1.18, P = 0.58). Similar findings were also observed for OS favoring dose-dense regimens (RR = 0.69, 95% CI 0.50–0.93, P = 0.013) with no significant difference for concurrent vs. sequential therapy (RR = 0.89, 95% CI 0.66–1.20, P = 0.48) [50]. In a meta-analysis, three trials, enrolling 3337 patients, evaluated the effect of dose-dense chemotherapy. Dose-dense chemotherapy improved OS (HR = 0.84; P = 0.03) and DFS (HR = 0.83; P = 0.005) compared to conventional schedule, although no benefit was observed in patients with hormone receptor-positive tumors [51].

Role of anthracyclines in HER2-positive breast cancer

The initial trials for adjuvant BC predate the utilization of anti-HER2 therapy [52]. Earlier studies of HER2 expressing cancers showed relative resistance to chemotherapy, throwing into uncertainty the efficacy of combination therapy [53, 54]. However, a significant limitation of those studies was the use of CMF instead of the standard AC regimen. In the CALGB-8541 trial, patients with HER2 overexpression who received higher doses of anthracycline-based chemotherapy [doxorubicin, cyclophosphamide, and fluorouracil (FAC)] had longer DFS and OS, compared to those who received the low-dose regimen [55, 56].

Trastuzumab, a humanized monoclonal antibody directed against the extracellular subdomain IV of the HER2 receptor, was approved by the Food and Drug Administration for the management of metastatic BC in 1998 [57]. In a joint analysis of the NSABP B-31 and NCCTG N9831 trials involving 3351 women with early BC, addition of 52-week trastuzumab to doxorubicin, cyclophosphamide, and paclitaxel improved the primary endpoint DFS (HR = 0.48, 95% CI 0.39–0.59, $P < 0.001$) and OS (HR = 0.67, 95% CI 0.48–0.93, $P = 0.015$) [26, 58●].

Although the exact mechanism of trastuzumab-induced cardiomyopathy remains unclear, in vivo studies have shown that in mice pretreated with anthracyclines, trastuzumab can cause myofibrillar disarray, potentiating the cardiotoxicity already caused by anthracyclines [59]. The BCIRG-006 trial ($N = 3222$) was conducted to compare a chemotherapy regimen of AC followed by docetaxel (AC-T) vs. chemotherapy plus 52-week trastuzumab (AC plus docetaxel/trastuzumab [ACTH] or docetaxel, carboplatin, and trastuzumab [TCH]) [60●●]. After 10-year follow-up, when compared to the control arm AC-T, DFS was improved by ACTH (74.6 vs. 67.9%, $P < 0.0001$) and TCH (73 vs. 67.9%, $P = 0.0011$). However, in the ACTH arm, there were 21 cases of grade 3/4 CHF, 7 cases of leukemia, and 200 cases of ≥ 10% decrease in LVEF. On the other hand, in the TCH group, there were 4 cases of grade 3/4 CHF, no cases of leukemia, and 97 cases of decreased LVEF [61]. This study was not adequately powered to prove non-inferiority between the two trastuzumab-containing regimens. There was a numerical benefit to receiving ACTH over TCH with respect to preventing BC recurrences (124 vs. 144 events), leading to the question of whether a better powered trial would demonstrate a bigger difference between the two regimens [62]. Although there was certainly a significant increase in the risk of cardiomyopathy, there were no deaths reported in the trial from CHF, leading to the question of whether the benefit of ACTH was offset by cardiac toxicity. In addition, critics argue that the study employed every 3-week dosing of anthracyclines which has previously been shown to be inferior to dose-dense regimens of every 2-week schedule, thus limiting the optimal use of anthracyclines.

An overview of important anthracycline-based trials for all breast cancer subtypes is provided in Table 2. In addition, Fig. 1 provides an illustration of the timeline of introduction of anthracyclines into adjuvant regimens and its evolution over the last few decades.

Biomarkers to predict anthracycline efficacy

Retrospective analysis of randomized trials suggested that anthracycline-based regimens had increased efficacy in patients with HER2 overexpression [64], and other studies suggested that the reason for this increased efficacy was amplification—and possible deletion—of the TOP2A gene [65, 66] which has been found to be amplified in 35% of HER2-positive BC [67]. Interestingly, the TOP2A and HER2 genes are both located on chromosome 17q21–22.

One of the first studies to show increased efficacy of anthracyclines in TOP2A-amplified BC was a retrospective analysis of the Danish Breast Cancer Cooperative Group (DBCCG) 89D trial, which examined the efficacy of

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Table 2. Selected anthracycline-based trials in early breast cancer

Trial	HER2 status	Treatment	No of pts	DFS rate	HR for DFS	HR for OS
NSABP B-15: CMF vs AC in tamoxifen non-responsive, node-positive breast cancers[5]	Unknown	CMF × 6 cycles	732	77%	3-year DFS, P = 0.5^a	3-year OS, P = 0.8^a
		AC × 4 cycles	734	77%		
		AC × 4 cycles → CMF × 3 cycles	728	79%		
INT C9741: dose-dense and concurrent vs. sequential therapy[50]	Unknown	Sequential AC-T every 3 weeks	484	81%	3-year DFS, concurrent vs. sequential, HR 0.93, 95% CI 0.75–1.18, P = 0.58	3-year OS, concurrent vs. sequential, HR 0.89, 95% CI 0.66–1.20, P = 0.48
		Sequential AC-T every 2 weeks	493	86%		
		Concurrent AC-T every 3 weeks	501	83%	3-year DFS, every 2 weeks vs. every 3 weeks, HR 0.74, 95% CI 0.59–0.93, P = 0.010	3-year OS, every 2 weeks vs. every 3 weeks, HR 0.69, 95% CI 0.50–0.93, P = 0.013
		Concurrent AC-T every 2 weeks	495	86%		
USOR-9735: taxane vs. anthracycline regimens [48]	Positive or negative	AC × 4 cycles	510	75%	7-year DFS, TC vs. AC, HR 0.74, 95% CI 0.56–0.98, P = 0.033	7-year OS, TC vs. AC, HR 0.69, 95% CI 0.50–0.97, P = 0.032
		TC × 4 cycles	506	81%		
ABC trials (NSABP B-46, B-49 and USOR 06-090): taxane vs. anthracycline regimens in HER2-negative patients [49••]	Negative	TC6	2094	88%	4-year IDFS, TC6 vs. TaxAC, HR 1.23, 95% CI 1.01–1.50, P = 0.04	Not reported
		TaxAC	2062	91%		Not reported

Table 2. (Continued)

Trial	HER2 status	Treatment	No of pts	DFS rate	HR for DFS	HR for OS
FASG 02/07 trial: chemohormonal therapy in breast cancer [45]	Unknown	Tamoxifen FEC and tamoxifen	233 224	72% 84%	9-year DFS, FEC + tamoxifen vs. tamoxifen, P = 0.008[a]	9-year OS, FEC + tamoxifen vs. tamoxifen, 86% vs. 78%, P = 0.11[a]
NSABP B-31, NCCTG N9831: addition of trastuzumab to anthracycline-based regimens [26•, 58•, 60••]	Positive	AC-paclitaxel AC-paclitaxel and trastuzumab	2017 2028	62% 74%	10-year DFS, AC-paclitaxel/trastuzumab vs. AC-paclitaxel, HR 0.60, 95% CI 0.53–0.68, P < 0.001	10-year OS, AC-paclitaxel/trastuzumab vs. AC-paclitaxel, HR 0.63, 95% CI 0.54–0.73, P < 0.001
BCIRG-006: taxanes vs. anthracyclines in addition to trastuzumab for HER2-positive cancer [60••, 63]	Positive	AC-T ACTH TCH	1073 1074 1075	68% 75% 73%	10-year DFS; ACTH vs. AC-T (HR 0.70, 95% CI 0.60–0.83, P < 0.001) 10-year DFS TCH vs. AC-T (HR 0.76, 95% CI 0.65–0.90, P < 0.001)	10-year OS ACTH vs. AC-T (HR 0.64, 95% CI 0.52–0.79, P < 0.001); TCH vs. AC-T (HR 0.76, 95% CI 0.62–0.93, P = 0.0081)

CMF cyclophosphamide, methotrexate, fluorouracil, *AC* doxorubicin, cyclophosphamide, *TC* docetaxel, cyclophosphamide, *FAC* fluorouracil, doxorubicin, cyclophosphamide, *AC-T* doxorubicin, cyclophosphamide, docetaxel, *FEC* fluorouracil, epirubicin, cyclophosphamide, *FEC-T* fluorouracil, epirubicin, cyclophosphamide, docetaxel, *TaxAC* taxanes (docetaxel/paclitaxel) with AC, *ACTH* AC plus docetaxel and trastuzumab, *TCH* docetaxel, carboplatin, and trastuzumab, *DFS* disease-free survival, *IDFS* invasive disease-free survival, *OS* overall survival, *HR* hazard ratio, *pts.* patients
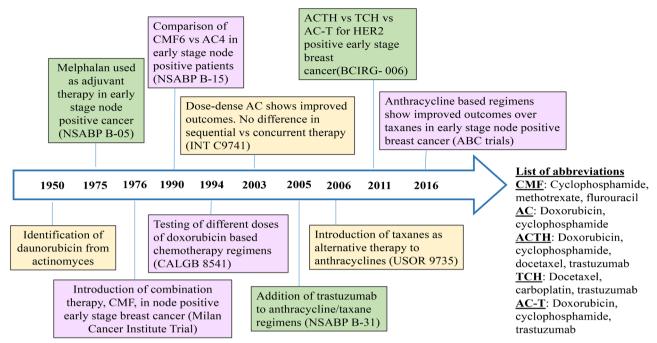[a]Hazard ratio not reported

Fig. 1. Timeline of pivotal clinical trials using anthracycline-based regimens in the management of breast cancer.

substituting methotrexate for epirubicin (CMF vs. CEF) in 980 premenopausal and postmenopausal women with early stage operable BC [68]. In this retrospective analysis, TOP2A amplification and deletion was seen in 12 and 11.3% of patients, respectively. Patients with TOP2A amplifications had an improved recurrence-free survival [RFS] (HR = 0.43, 95% CI 0.24–0.78) and OS (HR = 0.57, 95% CI 0.29–1.13) when treated with CEF compared to CMF; of note, similar results were found for TOP2A deletion. On the other hand, in patients with a normal TOP2A genotype, similar outcomes were observed between the two treatment arms [66]. In a meta-analysis of five randomized adjuvant trials, the benefit of treatment with anthracyclines over treatment with CMF was greater for individuals with HER2 gene amplification than it was for individuals without HER2 gene amplification when analyzing event-free survival (EFS) (P for interaction = 0.0485), but not when analyzing OS (P for interaction = 0.071); moreover, there was no significant difference in the benefit of treatment with anthracyclines over treatment with CMF when assessing the three separate TOP2A cohorts (normal, deleted, or amplified) in terms of either EFS (P for interaction = 0.0513) or OS (P for interaction = 0.1608) [69]. These results suggest that the benefit of anthracyclines is not limited to patients with HER2 amplification or TOP2A amplification/deletion.

Chromosome 17 centromeric duplication (Ch17CEP) has also been evaluated as a potential predictive biomarker for anthracycline sensitivity [70]. In a pooled analysis of five trials that compared anthracycline-based chemotherapy with CMF, both CEP17and *TOP2A* treatment-by-marker interactions remained significant in adjusted analyses for RFS and OS,

whereas HER2 did not. A combined CEP17 and TOP2A-adjusted model predicted anthracycline benefit across all five trials for both RFS (HR = 0.64; P = 0.001) and OS (HR = 0.66; P = 0.005) [71]. These data suggest that HER2 might not be a predictor of benefit from anthracyclines, and CEP17 and TOP2A alterations seem like potential biomarkers of anthracycline benefit regardless of HER2 status. However, it is unknown whether these results are maintained for regimens that include either concurrent or sequential taxanes.

Genomic profiling is being used to tailor management of ER+ breast cancer (Oncotype DX Recurrence score, MammaPrint, PAM50) [72, 73]. However, these agents have not been designed to decide specific chemotherapy regimens to be used. Gene signatures based in DNA damage repair pathways have been reported as potential biomarkers of anthracyclines in ER+ and ER– BC. However, these signatures require prospective validation before being considered as routine tools in the management of breast cancer. Currently, there is no indication for routine testing of these biomarkers to select specific chemotherapy regimens during clinical care of patients with breast cancer.

Conclusions

Anthracycline-based regimens are an important component in the management of patients with breast cancer, especially for patients with high risk of recurrence such as those with triple negative disease (regardless of axillary node involvement) or HER2–/ER+ with axillary node involvement. While cardiotoxicity and secondary hematological malignancies associated with anthracyclines have low incidence, the morbidity associated with these treatment-related complications could be significant; therefore, clinicians must carefully assess the risk/benefit of anthracycline use in patients who are at risk of these complications. Further research is required to identify biomarkers predictive of anthracycline response in breast cancer.

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Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance.

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