Anthracycline Cardiotoxicity After Breast Cancer Treatment

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Anthracyclines are among the most effective and widely prescribed anticancer agents. They were first isolated from cultures of Streptomyces peucetius by Dr. Federico Arcamone in the early 1960s.[1] Anthracyclines have since become an essential component of breast cancer treatment, and their use in combination regimens as adjuvant therapy is the standard of care for most women with early-stage disease.[2] Two commonly used anthracyclines in breast cancer are doxorubicin and epirubicin, a semisynthetic derivative of doxorubicin.

ABSTRACT: Anthracyclines are among the most active agents for the treatment of breast cancer; their use in combination regimens improves both disease-free and overall survival in patients with breast cancer. Unfortunately, the clinical utility of anthracycline use is limited by a cumulative dose-dependent cardiac toxicity resulting in congestive heart failure. As methods for detecting and treating breast cancer improve, there has been a steady decline in breast cancer mortality over the past 15 years. With an increasing number of long-term breast cancer survivors, the number of patients experiencing anthracycline-induced cardiotoxicity may also continue to grow. Moreover, new agents used in the treatment of breast cancer can potentiate cardiac toxicity. Recently, studies of non-anthracycline-containing regimens have been found to be effective in preventing recurrence of breast cancer (as compared with anthracycline-containing regimens) in patients with early-stage breast cancer, with a reduced incidence of adverse cardiac outcomes. In this article, we summarize the incidence, presentation, and mechanism of anthracycline-associated cardiotoxicity. We also discuss risk factors for the development of anthracycline-induced cardiotoxicity and new therapies, such as trastuzumab, that may potentiate cardiac toxicity. Finally, we review monitoring and preventive practices that may reduce the long-term risk of anthracycline-related cardiotoxicity.

Anthracyclines are among the most effective and widely prescribed anticancer agents. They were first isolated from cultures of Streptomyces peucetius by Dr. Federico Arcamone in the early 1960s.[1] Anthracyclines have since become an essential component of breast cancer treatment, and their use in combination regimens as adjuvant therapy is the standard of care for most women with early-stage disease.[2] Two commonly used anthracyclines in breast cancer are doxorubicin and epirubicin, a semisynthetic derivative of doxorubicin.

The therapeutic activity of an anthracycline is mediated by its insertion into the DNA of replicating cells and its inhibition of topoisomerase II enzyme, thereby preventing DNA and RNA synthesis.[3] Unfortunately, the long-term use of anthracyclines is limited by the development of cardiomyopathy and congestive heart failure (CHF). While still rare, the cardiovascular complications of treatment may be seen acutely, or years following exposure. The toxic effect of anthracyclines in long-term survivors of cancers can lead to increased rates of cardiac morbidity and mortality, and may result in patients avoiding potentially lifesaving therapy.

Epidemiology/Clinical Presentation

Anthracycline-induced cardiac toxicity is potentiated when the cumulative dose of doxorubicin exceeds 300 mg/m². In a study of 534 breast cancer patients treated with a combination of fluorouracil (5-FU), doxorubicin, and cyclophosphamide, the incidence of CHF was 1% in patients treated with a cumulative doxorubicin dose of 300 mg/m², and 4% in patients who received 450 mg/m² of doxorubicin.[4] In a multicenter study of more than 3,000 breast cancer patients treated with a cumulative doxorubicin dose between 240 and 360 mg/m², symptomatic heart failure occurred in 1% to 2% of patients after a 5-year follow-up.[5]

In the United States, four cycles of AC (doxorubicin at 60 mg/m² plus cyclophosphamide at 600 mg/m²) is frequently used as a component of adjuvant therapy for patients with early-stage breast
cancer. Although symptomatic heart failure with a cumulative dose of 240 mg/m^2 is rare, asymptomatic cardiac toxicity is often observed. In the North Central Cancer Treatment Group (NCCCTG) N9831 trial, after four cycles of anthracycline-containing chemotherapy, 8.5% of 2,992 breast cancer patients had an asymptomatic left-ventricular ejection fraction (LVEF) decline ≥ 10% but < 15% compared with baseline, and 5.0% had an asymptomatic decline > 15% or ≤ 15% to below the lower limit of normal.[6] Adjunct trials incorporating trastuzumab (Herceptin) concurrent with AC and paclitaxel have consistently observed that approximately 5% to 7% of patients who have completed four cycles of AC experience cardiotoxicity precluding the subsequent administration of trastuzumab.[7]

Anthracycline-induced cardiotoxicity can be categorized into three distinct types: acute, early and late, depending on its temporal relationship to treatment. Acute cardiotoxicity occurs during anthracycline infusion or within a week of therapy. Sinus tachycardia is the most common presenting symptom, but arrhythmias, including ventricular tachycardia, have been reported. The estimated incidence of acute symptomatic toxicity is less than 1%, and it usually resolves when therapy is discontinued.[8,9] The relationship between acute toxicity and the subsequent development of delayed cardiotoxicity is unclear.

Early-onset cardiotoxicity occurs within 1 year after anthracycline treatment. Patients may develop electrophysiologic changes, left-ventricular dysfunction, and symptoms of clinical heart failure. The peak time for the appearance of symptoms of heart failure is 3 months after the last anthracycline dose, and mortality in these patients is quite high.[10,11] Late-onset cardiotoxicity occurs more than 1 year after completion of anthracycline treatment. The late toxicity is a major concern in clinical scenarios where anthracyclines are used as part of a curative or adjuvant regimen—for example, in patients with breast cancer. Patients can be asymptomatic initially, and ventricular dysfunction, heart failure, and arrhythmias may occur later, even decades after the discontinuation of anthracycline therapy.

**Mechanism of Cardiotoxicity**

The etiology of anthracycline-induced cardiotoxicity is not completely understood. Myocardial changes following anthracycline treatment include myocardial cell loss by necrosis or apoptosis, myofibrillar loss, distention of the sarcoplasmic reticulum, and mitochondrial swelling.[12] The leading mechanistic hypothesis for doxorubicin-induced cardiotoxicity is that doxorubicin differentially increases reactive oxygen species (ROS) within cardiac myocyte mitochondria, as compared to other tissues. Anthracyclines can induce the generation of oxygen-derived free radicals through two main pathways: a nonenzymatic pathway that utilizes iron, and an enzymatic mechanism using the mitochondrial respiratory chain.[13,14] Free radicals are highly toxic, and can cause direct damage to proteins, lipids, and DNA. Adult myocytes are more susceptible, because myocytes are terminally differentiated and cannot sufficiently replace cells damaged during treatment.[14,15] Administering doxorubicin in humans results in an elevation of plasma, tissue ROS, and products of lipid peroxidation, and a decrease in plasma and tissue antioxidant levels. The level of doxorubicin-induced oxidative stress is up to 10 times greater in the heart than in the liver, kidney, and spleen.

The experience from concurrent anthracycline and trastuzumab therapy in metastatic breast cancer has triggered further research into the molecular mechanism of anthracycline-induced cardiotoxicity. Gene targeting studies in mice show that HER2, a proto-oncogene and a member of the erbB family of transmembrane tyrosine kinases, is essential for cardiac development.[16] and conditional deletion of HER2 leads to the development of a dilated cardiomyopathy.[17] In mice that are deficient in HER2 protein or its associated ligand, neuregulin (NRG), a paracrine peptide messenger that activates HER2, the induction of cardiac stress pathways by an anthracycline promotes the onset of left-ventricular dysfunction.[17]

These results have provided an explanation for the increased cardiotoxicity observed with concurrent administration of an anthracycline and trastuzumab, an anti-HER2 monoclonal antibody. In response to acute stress such as exposure to anthracycline, the cardiomyocytes-survival pathway is activated by neuregulins binding to the HER2:HER4 heterodimer, preventing death of cardiomyocytes.[18] Trastuzumab, by inhibiting the HER2 receptor, interferes with this survival signaling pathway and thus promotes the cardiotoxic effects of anthracycline.

**Risk Factors**
TABLE 1

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<th>Risk Factors for Anthracycline-Induced Cardiotoxicity</th>
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<td>A number of risk factors for the development of anthracycline-induced cardiotoxicity have been identified (Table 1). The strongest risk factor is cumulative dose. Other potential risk factors include age, preexisting cardiac risk factors, radiation therapy, and other chemotherapy agents. However, while some of these are known risk factors for the development of CHF in the general population, it is unclear from most studies whether they potentiate the effects of anthracyclines or whether their effects are simply additive.</td>
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**Cumulative Dose**

A high cumulative anthracycline dose is the most recognized risk factor for cardiac damage and remains the best predictor of subsequent cardiac dysfunction. This association was first observed by Von Hoff et al in a retrospective analysis showing that anthracycline toxicity and heart failure were dose-related, with the incidence of complications rising sharply as cumulative doses of doxorubicin increase.[10] The estimated percentage of patients who developed CHF at a dose of 400 mg/m² was 3%, increasing to 7% at 550 mg/m² and to 18% at 700 mg/m².[10] This led to a recommended limit on lifetime cumulative doxorubicin dose of 450 to 550 mg/m².

Subsequent studies have confirmed this observation, but most did not control for competing causes of mortality or take into account the effect of time on the risk of cardiotoxicity.[19] This was addressed by Ryberg et al in a recent retrospective study of 1,097 patients with metastatic breast cancer treated with epirubicin over a 20-year period.[20] They first identified independent predictive factors for the development of cardiotoxicity and other causes of mortality, respectively. Using competing risk analysis, they were able to determine the maximum dose resulting in no more than a 5% rate of CHF for patients with different sets of risk factors. For a patient aged 40 years with no other risk factors for CHF, the recommended dose yielding a 5% risk of CHF at 2.5 years of treatment would be 806 mg/m². If the same woman were 70 years old, the maximum cumulative dose drops to 609 mg/m².[20] This analysis showed that maximum cumulative dosage of anthracycline would differ among patients depending on preexisting cardiac risk factors and other competing factors for mortality.

**Age**

An early study by Von Hoff has suggested that anthracycline-induced cardiotoxicity may be more pronounced with advancing age.[10] In a retrospective analysis of three clinical trials involving 630 patients who were treated with doxorubicin, Swain et al showed that patients more than 65 years old are 2.25 times more likely to experience anthracycline-induced CHF compared with patients less than 65 years old, but the effect is only pronounced after a cumulative dose of 400 mg/m².[19] In addition, the number of CHF events that occurred in the subgroup analysis was small, and a non–anthracycline-treated comparison group was not included. Therefore, the interpretation of the findings is difficult.

Several studies have used the Surveillance, Epidemiology and End Results (SEER)-Medicare database to evaluate the risk of CHF following anthracycline administration in women with early-stage breast cancer,[21] finding over a twofold increase in the risk of cardiomyopathy and a 40% increase in CHF. These studies found that CHF was associated with advanced age, black race, increased number of comorbid conditions, and a prior history of cardiac conditions and cardiac risk factors.[21] The risk of CHF after anthracycline treatment in these studies appeared to be higher than the rate of CHF observed by other adjuvant breast cancer trials, where patients were generally younger.[7] While these studies were strengthened by large numbers of subjects and up to 10 years of follow-up, they were limited by a lack of anthracycline dose information in the database, and the outcomes of CHF being determined only through billing claims.

In the Danish study of metastatic breast cancer patients treated with epirubicin (described...
previously), Ryberg et al showed that age at the start of epirubicin treatment had a statistically significant association with risk of cardiotoxicity: The cardiotoxicity rate increased by 28.7% for every 10 years of age.[20] Using competing risk analysis, they were able to generate predictive models accounting for a number of known risk factors associated with risk, including age, prior cardiac disease, known cardiac risk factors, thoracic radiation, prior hormonal therapy, and prior cyclophosphamide-based chemotherapy. As one would expect, some of these known risk factors for CHF in the general population are also associated with risk in patients treated with epirubicin. It is unclear from this analysis, however, if any of these factors potentiate the effects of epirubicin, or if their effects are purely additive.

Radiation Therapy

Given the role of radiation in reducing local recurrence and improving survival, a considerable number of women are treated with both local radiation and systemic anthracycline. Meta-analysis of randomized controlled trials by the Early Breast Cancer Trialists’ Group (EBCTG) confirmed that patients who received radiation had a higher risk of vascular mortality than those who did not, and that this association was strongest among older patients. As a result, concern over the synergistic effects of radiation and anthracyclines have been raised, with some small studies suggesting that left-sided radiotherapy with higher cumulative doses of an anthracycline may exacerbate the drug’s cardiac toxicity.[22,23]

In a study using the SEER-Medicare database, evaluating more than 45,000 breast cancer patients with up to 13 years of follow-up, Doyle et al did not find an increased risk of cardiac morbidity or CHF associated with radiation therapy or left-sided radiation therapy in patients treated after 1992.[24] In addition, radiation did not increase the risk of CHF in patients treated with anthracycline.[25] Recent studies have not observed increased CHF in breast cancer patients who received radiation therapy in combination with a standard dose of doxorubicin (60 mg/m$^2$) given for four cycles.[26,27]

Preexisting Cardiac Risk Factors

People with preexisting cardiac risk factors are at increased risk for developing CHF in the absence of anthracycline therapy, and therefore, it is important to evaluate cardiotoxicity in the context of these cardiac risk factors and to understand how they interact with anthracycline treatment. In the study by Ryberg et al, cardiotoxicity was approximately threefold higher in patients with a condition predisposing to heart disease (such as hypertension, diabetes, obesity, thyrotoxicosis, and chronic obstructive lung disease), independent of the cumulative dose of epirubicin.[20]

Several other studies have suggested that patients with previous cardiac disease (coronary, valvular, or myocardial) and hypertension may have an increased risk of developing CHF when treated with an anthracycline.[6,12,28] However, none of these studies had specifically evaluated the interaction of preexisting cardiac conditions with treatment. Using SEER-Medicare data, one study evaluating 9,438 patients with non-Hodgkin’s lymphoma who had been treated with anthracycline-based therapy, showed that hypertension was the only preexisting cardiac risk factor that potentiated the effect of the anthracycline on the heart (hazard ratio = 1.8, $P = .01$).[29]

Taxanes

cetaxel (Taxotere) are active agents in the treatment of breast cancer. They are microtubule inhibitors that are thought to induce apoptosis and inhibit tumor angiogenesis. In multiple phase II trials, the combination of an anthracycline plus taxanes demonstrated high response rates in advanced breast cancer.[30] However, the incidence of cardiac adverse effects increased when cumulative doxorubicin doses exceeded 360 mg/m$^2$.[30] The increase in cardiac toxicity is thought to be the result of taxanes stimulating the conversion of doxorubicin to the more potent cardiotoxic metabolite doxorubicinol inside human myocardium, and potentiating anthracycline-induced cardiotoxicity, especially at high, cumulative anthracycline doses. Slow infusion of paclitaxel and doxorubicin[31] or increased time between doxorubicin and paclitaxel treatment decreased cardiotoxicity.[32] When combined with paclitaxel, the cumulative doxorubicin dose should not exceed 360 mg/m$^2$.

Adjuvant regimens including taxanes, however, do not seem to increase anthracycline cardiotoxicity. In the European Cooperative Trial in Operable breast cancer (ECTO), comparing doxorubicin (75 mg/m$^2$) followed by CMF (cyclophosphamide, methotrexate, and 5-FU) with the combination of paclitaxel and doxorubicin (60 mg/m$^2$) followed by CMF, the incidence of symptomatic cardiac events were similar between arms with and without paclitaxel.[33] In clinical trials, docetaxel has not been associated with increased cardiotoxicity when combined with doxorubicin or epirubicin.

Trastuzumab
Human epidermal growth factor receptor 2 (HER2) is a proto-oncogene and a member of the erbB family of transmembrane tyrosine kinases. Approximately 20% to 25% of patients with breast cancer have tumors that overexpress the HER2 protein or amplify the HER2/neu gene; such alterations are associated with a more aggressive clinical course.[34] Trastuzumab, an anti-HER2 monoclonal antibody, represents the most significant improvement for treating this poor-risk group of patients.[35]

During the pivotal metastatic breast cancer trials of trastuzumab, cardiac dysfunction was observed in women treated with trastuzumab-containing chemotherapy regimens.[35,36] The incidence and severity of cardiac dysfunction was greatest among patients who received trastuzumab in combination with an anthracycline. Symptomatic or asymptomatic cardiac dysfunction was observed in 27% of patients who received concomitant anthracycline and trastuzumab therapy. The rate of cardiac events was much lower in patients given trastuzumab alone (4.7%), or with paclitaxel (13%).[36] Thus, trastuzumab appears to increase the susceptibility of the heart to anthracycline. Due to the high rate of cardiotoxicity, later trials have avoided administration of trastuzumab during anthracycline treatment.

Trials of adjuvant trastuzumab have incorporated careful monitoring of LVEF, and most now require a normal postanthracycline LVEF before initiating treatment with trastuzumab. In a combined analysis of the NCCTG N9831 and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trials, 6.7% of patients who had completed anthracycline treatment had a lower LVEF or developed cardiac symptoms preventing the initiation of trastuzumab.[37] A lower LVEF before initiation of trastuzumab ($P = .033$), age ≥ 60 ($P = .003$), and use of antihypertensive medications ($P = .005$) increased the risk of trastuzumab-associated cardiac dysfunction following AC therapy.[7]

### Monitoring

Both echocardiogram and multigated acquisition (MUGA) scan are methods used to monitor anthracycline-induced cardiotoxicity. Guidelines for monitoring the use of both modalities are available from the American Heart Association and American College of Cardiology. Because the two techniques cannot be compared directly, patients should always be assessed with the same technique when monitoring cardiac changes during treatment over time. MUGA is highly reproducible and able to detect a decline in LVEF in patients treated with anthracycline, but cumulative radiation exposure limits the applicability of this technique for frequent monitoring. Echocardiography is used regularly to monitor LVEF and is more widely available than MUGA. Unlike MUGA, it does not expose the patient to ionizing radiation. However, it is considered more prone to operator-dependent variability. Both modalities may overlook early changes that could identify patients at risk for anthracycline-related cardiotoxicity.

Newer imaging techniques have been evaluated to enhance earlier detection of subclinical myocardial changes in the course of anthracycline treatment. One modality is cardiac magnetic resonance imaging (MRI), which can measure morphologic and functional tissue changes, and has little between-test variability. The technique can visualize the site and extent of myocardial infarction by imaging of the associated edema as well as the necrotic area. Increased myocardial signal enhancement might be an early marker for myocardial changes independent of cardiac function.[38] Cardiac MRI thus has the potential to investigate cardiac function even before tissue changes that generally precede the functional alterations.

Myosint cardiac scans using indium antimyosin antibody is another modality that may be useful in diagnosing early cardiac dysfunction and predicting toxicity. When cardiac myocytes are damaged, myosin is exposed and can be detected by antimyosin antibodies. Myosint cardiac scan compares the heart to lung ratio uptake of indium-radiolabeled antimyosin antibodies. When LVEF measured by MUGA was compared with myosint cardiac scan in patients who had been treated with high cumulative epirubicin doses, an increase in the heart-to-lung ratio preceded a decline in the LVEF.[39] More studies are needed to assess the utility of cardiac MRIs and myosint scans in clinical practice, but these imaging modalities may be useful outcome measures in cardiac safety studies. Researchers have also looked into serum markers such as troponin T and B-type natriuretic peptide (BNP) for earlier detection of cardiotoxicity, but due to small sample sizes and short follow-up, their ability to predict either early or long-term toxicity have not been established.

### Prevention and Management
Strategies for Preventing Anthracycline-Induced Cardiotoxicity

Besides limiting the lifetime dose of doxorubicin to less than 450 to 500 mg/m$^2$, several strategies have been developed to prevent and manage anthracycline-induced cardiotoxicity such as administration schedule, cardioprotectants, and new formulations (Table 2).

Administration Schedule

Several studies have indicated that high peak serum levels of anthracycline may increase the risk of cardiac injury, and administration schedules that result in lower serum drug levels may be cardioprotective.[40,41] For adults, continuous infusions of doxorubicin have been reported to be less cardiotoxic than bolus administration, as suggested by a meta-analysis comparing bolus infusion (up to 1 hour) with a longer infusion duration (varying from 6 to 96 hours).[42] Despite the possible benefit of prolonged doxorubicin infusion schedules, most doxorubicin is still given via bolus therapy, as the frequent need for hospitalization and placement of a central venous catheter make this approach less attractive to patients.

Liposomal Anthracyclines

Liposomal anthracyclines have been developed in an attempt to improve the cardiac safety profile of conventional anthracyclines. Due to their size, liposomes cannot escape the circulation through the tight capillary junctions found in normal tissue such as the heart, but can escape selectively through the weakened vasculature that feeds tumor cells.[43]

In several studies of women with metastatic breast cancer, monotherapy with liposomal products showed similar efficacy and reduced cardiotoxicity compared with conventional doxorubicin.[44,45] Liposomal products have also been evaluated in combination with trastuzumab in multiple phase II studies for patients with HER2-positive metastatic breast cancer, showing promising results with good efficacy and decreased risk of development of CHF. An ongoing randomized phase II multinational trial will evaluate the cardiotoxicity of doxorubicin-based and a liposomal doxorubicin (Doxil)-based adjuvant chemotherapy regimen in 180 women with early-stage breast cancer.[45]

Dexrazoxane

Dexrazoxane is the only US Food and Drug Administration (FDA)-approved cardioprotectant designed to decrease the effects of anthracyclines on the heart. It is an iron-chelating agent that reduces free-radical generation by anthracyclines, thereby preventing damage to cardiomyocytes. Dexrazoxane was approved for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer.[46] Current American Society of Clinical Oncology guidelines recommend its use for this indication only, and caution against its use in malignancies where doxorubicin has been shown to increase survival, because such agents are thought to reduce the efficacy of therapy.[47]

ACE Inhibitors/ARBs

The renin-angiotensin system plays an important role in the pathophysiology of hypertensive and ischemic heart disease in humans. Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) can reduce left-ventricular afterload and slow the progression of left-ventricular dysfunction. Interestingly, studies in rats showed that concurrent use of ACE inhibitors with doxorubicin prevents the decline in cardiac function related to doxorubicin.[48] In a randomized trial of 40 patients receiving doxorubicin-based therapy for lymphoma, Nakamae et al found that concurrent daily administration of valsartan ( Diovan ), an ARB, could inhibit doxorubicin-induced acute cardiotoxicity seen on echocardiogram and electrocardiogram several days after chemotherapy. However, it is unclear whether this strategy can also prevent late-onset cardiotoxicity.[49] Furthermore, in a prospective study of women who were monitored for evidence of left-ventricular dysfunction while receiving epirubicin for metastatic breast cancer, the value of
ACE inhibition was evident when seven of eight women treated had a sustained increase in cardiac function.[50] Although data are limited, they do suggest that ACE inhibitors should be used as first-line therapy for both asymptomatic left-ventricular dysfunction and overt heart failure due to systolic dysfunction secondary to anthracycline.

**Coenzyme Q**

Many natural supplements are being evaluated for use in reducing side effects from cancer therapy. Coenzyme Q10 (CoQ10) is a fat soluble vitamin-like substance that occurs naturally in organs such as the heart, liver, and kidney. It plays a role in cellular energy release, and also serves as an antioxidant by reducing free radicals, thereby preventing damage to structural lipids and proteins.

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Small in vitro studies have shown that administering CoQ10 either before or during doxorubicin administration can prevent doxorubicin-induced changes including cardiac beat inhibition[51,52] and reduced cardiac contractile tension.[53] Animal studies suggest that the impact of doxorubicin on mitochondria is cardioselective, that CoQ10 can prevent doxorubicin-induced mitochondrial damage, and that CoQ10 can prevent the progression of cardiomyopathy induced by doxorubicin.[54] In a pilot study by Iarussi et al, CoQ10 was given to a group of 20 young patients treated with anthracycline for acute lymphoblastic leukemia. The subjects receiving CoQ10 supplementation appeared to have some protection from the morphologic changes of heart disease such as septal wall thickening; however, no long-term data are available.[54] Larger studies are underway to further evaluate the possible cardioprotective effect of CoQ10.

**Conclusions**

Anthracyclines are a key component of breast cancer treatment. While their use is associated with a small increased risk of cardiotoxicity, this side effect has not prevented their use in the adjuvant setting because clinical benefits largely exceed the risk. However, efforts to prevent cardiotoxicity by monitoring cardiac function before and during therapy, limiting lifetime anthracycline dose, using cardioprotectants such as dexrazoxane, and developing lipid formulations, may reassure patients and physicians when the benefits are small.

Recently, investigators have also looked into the use of non-anthracycline-containing regimens in the treatment of women with early-stage breast cancer. Jones et al showed that four cycles of TC (docetaxel plus cyclophosphamide) achieved superior disease-free survival compared to four cycles of AC in 1,016 patients with early-stage breast cancer.[55] In the Breast Cancer International Research Group trial (BCIRG) 006 comparing three different combination chemotherapy regimens—AC plus docetaxel (AC-T), AC plus docetaxel and trastuzumab (AC-TH), and docetaxel, carboplatin and trastuzumab (TCH)—the second interim analysis at a medium follow-up of 36 months showed that TCH appeared to perform comparably to AC-TH (4-year overall survival of 91% vs 92%, respectively). The risk of grade 3 or 4 CHF, however, was lower among patients receiving TCH (0.4%) than among those receiving AC-TH (1.8%).[56]

Other researchers have also looked into identifying molecular predictors of response to anthracyclines. Preclinical data suggest that sensitivity to anthracyclines seems to be regulated by topoisomerase II alpha gene aberrations. A retrospective analysis of BCIRG 006 found that anthracycline-based chemotherapy was associated with increased disease-free survival among patients with HER2-positive tumors that overexpressed topoisomerase II and HER2 but not among patients with tumors that overexpressed HER2 only.[57] Prospective studies are needed to see if these markers can be used in the clinical setting for the selection of patients who are most suitable for anthracycline-based therapy, thus avoiding the potential anthracycline-associated cardiotoxicity for some subgroups.

Despite decades of use and research, anthracycline-induced cardiotoxicity remains a persistent problem in cancer survivors. Further research is needed to identify patients at increased risk of cardiotoxicity and to develop novel methods of monitoring, preventing, and treating this adverse effect.

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