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Anthracycline Cardiotoxicity: From Bench to Bedside

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Abstract

Anthracyclines remain among the most widely prescribed and effective anticancer agents. Unfortunately, life-threatening cardiotoxicity continues to compromise their usefulness. Despite more than four decades of investigation, the pathogenic mechanisms responsible for anthracycline cardiotoxicity have not been completely elucidated. In addition, new drugs and combination therapies often exacerbate the toxicity. The First International Workshop on Anthracycline Cardiotoxicity, held in fall 2006, in Como, Italy, focused on the state-of-the-art knowledge and discussed the research needed to address the cardiotoxicity of these drugs. Here, we incorporate these discussions into the framework of a broader review of preclinical and clinical issues.

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INTRODUCTION

The First International Workshop on Anthracycline Cardiotoxicity was held in fall 2006, in Como, Italy, and was sponsored by the Menarini Foundation. Anthracyclines were discovered in Italy by Dr. Federico Arcamone, an attendee who first isolated doxorubicin from cultures of *Streptomyces peuceticus* var. *caesius* almost half a century earlier.[1]

Anthracycline treatment is compromised by an insidious cardiomyopathy and heart failure. There is insufficient understanding of anthracycline cardiotoxicity to prevent its occurrence. Anthracycline cardiotoxicity is exponentially dose-dependent, with an average incidence of 5.1% at 400 mg/m^2 that becomes higher above 500 mg/m^2, albeit with substantial individual variation.[2,3]

Dose-limitation strategies have reduced the incidence of anthracycline-related cardiac events. In modern adjuvant therapy for breast cancer (240 to 360 mg/m^2 of doxorubicin), the incidence of heart failure is approximately 1.6%, increasing to approximately 2.1% in patients who receive doxorubicin followed by paclitaxel.[4] However, clinicians are facing new problems, such as asymptomatic ventricular dysfunction, cardiovascular events in long-term survivors, and higher than expected occurrences of cardiotoxicity in patients receiving anthracyclines with new targeted drugs, such as the anti-ErbB2 (human epidermal growth factor receptor 2 [HER-2]) antibody trastuzumab.[4,5]

The pathogenic mechanisms responsible for anthracycline cardiotoxicity have not been fully elucidated. Difficulties in separating primary mechanisms of toxicity from secondary molecular events have limited the development of cardioprotective measures and of less cardiotoxic anthracycline analogs and have also delayed the development of guidelines for monitoring or treating patients.[6]

The Como meeting brought together a diverse group of experts, including basic scientists, oncologists, cardiologists, pharmacologists, and other health professionals, to address these issues. The two main goals of the meeting were to review molecular mechanisms and clinical correlates of anthracycline cardiotoxicity and to discuss means of ameliorating the impact of this cardiotoxicity on patients. The first goal was accomplished, and the proceedings of the scientific and clinical presentations were published.[7]

The second goal was addressed by panel discussions of controversial issues and existing hypotheses. This article is drawn largely from these discussions, and we acknowledge the intellectual input of the participants. The main points of these discussions are summarized and incorporated into a broader perspective.

DIMENSION OF THE PROBLEM

Formal estimates of the worldwide prevalence of anthracycline cardiotoxicity are lacking. Differences between pediatric, adult, and elderly patients and the lack of uniformity in detecting and reporting cardiac events make such estimates even more difficult to make.

Focusing on a defined anthracycline-sensitive adult malignancy illustrates the problem. Between 1996 and 2006, the incidence of breast cancer in the United States increased approximately 19%, from 180,000 to 215,000 cases per year, but improvements in early diagnosis and treatment decreased breast cancer–specific mortality by approximately 24% between 1990 and 2000.[4,8] This translates into more than 2 million women in the United States with a high probability of anthracycline exposure and a survival expectancy long enough to carry a lifetime risk for anthracycline-related cardiotoxicity. The risk for cardiovascular events is magnified by an overlap of anthracycline-specific subclinical

damage with comorbidities and unfavorable lifestyle choices, such as reduced physical activity.[4]

The potential for cardiovascular consequences in so many adults treated with anthracyclines will become apparent in the coming years.[4] Sixty-five percent of adults newly diagnosed with cancer will survive 5 or more years.[8,9] There are more than 10 million cancer survivors in the United States.[8,9] A population-based study of breast cancer survivors shows that women aged 66 to 70 years who received anthracyclines and had more than 10 years of follow-up experienced higher rates of heart failure than did women who received nonanthracycline or no chemotherapy.[10] These observations raise concerns that adult-onset cancer survivors might be plagued by increased cardiovascular morbidity similar to that of long-term survivors of childhood cancer (see Needed Basic Research, point 7).

This cardiotoxicity risk and the need for surveillance or specific treatment increase health care costs and compromise quality of life.[11,12] The potential for cardiotoxicity may also restrict or exclude the beneficial aspects of anthracyclines from treatment plans, particularly in older women.[13] Such limitations should be considered after risk-benefit assessment. This assessment should consider medications to ameliorate the symptoms of anthracycline cardiotoxicity (see Needed Clinical Research, points 3 and 5).

NEEDED BASIC RESEARCH

1. The Need to Move Beyond the Oxidative Stress Hypothesis As a Primary Mechanism of Anthracycline Cardiotoxicity

Anthracyclines generate reactive oxygen species by various means, including redox cycling, iron complexation, chaotropic effects in mitochondria, and the consequent uncoupling of the electron transport chain.[14–16] Anthracyclines can also disturb antioxidant defense systems and repair pathways.[17,18] As a result, adding anthracyclines to cardiac preparations increases the formation of reactive oxygen species. These effects have been documented using various oxidative stress markers.[19]

The effect of oxidative stress in clinical cardiotoxicity is increasingly questioned. One reason for the uncertainty is the apparent lack of protection provided by antioxidants, such as vitamin E and *N*-acetylcysteine in long-term experimental and clinical trials.[20,21] Although the protective effects of carvedilol, an α1-β1,2-adrenoceptor blocker, were tentatively attributed to its antioxidant properties, confirmation awaits comparisons of carvedilol with other adrenolytic agents without antioxidant properties.[22]

The only compound consistently found to be cardioprotective in experimental[23] and clinical studies[24,25] is the iron chelator dexrazoxane. Dexrazoxane also alters the toxicity of several other substances (alloxan, acetaminophen, oxygen, and bleomycin) that act through iron-catalyzed formation of free radicals.[26] Dexrazoxane does not directly inactivate free radicals but, instead, attenuates their formation through intracellular iron chelation.[27] Interestingly, the protective effect of dexrazoxane may not always be associated with its ability to prevent iron-catalyzed hydroxyl radical formation, showing that the role of iron in anthracycline-induced cardiotoxicity might not be confined to forming free radicals.[19,28] Iron-independent actions of dexrazoxane have also been postulated.[29]

Although considerable data indicate that anthracyclines can promote reactive oxygen species formation in cardiac tissue, the evidence that oxidative stress is the sole or the main cause of chronic anthracycline cardiotoxicity in humans is inconclusive. Studies of alternatives are needed to clarify the pathogenic mechanism(s).

2. The Need for Long-Term Studies in Animal Models

The clinical importance of anthracyclines in chemotherapy has stimulated development of experimental models to study their cardiotoxicity. One reason the mechanisms of chronic and delayed anthracycline cardiotoxicity are not yet clear is related to the selection of an appropriate experimental model of toxicity.[30] Many studies looking for molecular or cellular pathogenic cardiotoxic mechanisms evaluate effects in vitro or in vivo, which appear within hours or days. These studies usually use relatively high drug concentrations. In contrast, the effects of chronic anthracycline cardiotoxicity in vivo require weeks to appear, are associated with lower drug concentrations, and may cause toxicity in only a few drug-treated animals. Adequate studies require large numbers of animals to be monitored for extended periods, increasing costs and could exceed the capacity of a single laboratory.

Nevertheless, to simulate clinical scenarios, long-term studies of anthracycline cardiotoxicity in animals must take precedence over short-term in vitro treatments of isolated cells.[31] In long-term animal studies, anthracyclines should be administered intravenously because subcutaneous, intramuscular, and intraperitoneal administrations are associated with localized tissue damage that could alter tissue distribution and bias conclusions.[30] In addition, long-term studies are necessary to more accurately evaluate the actions of potential cardioprotectants. As indicated earlier, antioxidants, such as vitamin E and *N*-acetylcysteine, were protective in models that used single, high anthracycline doses but were not protective when examined in models where cardiotoxicity was induced by long-term administration of low anthracycline doses.20 Thus, the protective effects of previously identified investigational agents (such as probucol32 or sildenafil33) or other emerging strategies need to be re-evaluated using long-term animal studies that use clinically relevant routes and doses of the drugs.

3. The Need to Identify Predictive Markers of Cardiac Damage

Noninvasive or systemic markers that can predict or track anthracycline cardiotoxicity are needed, both for clinical monitoring and as surrogate end points in research. Cardiac troponins and brain natriuretic peptides have been suggested as potentially useful biomarkers for detecting anthracycline cardiotoxicity. Small increases in the serum concentration of cardiac troponin T in children after the first dose of doxorubicin predicted subsequent risk for left ventricular dilation and wall thinning.[34] Increases in serum cardiac troponin T levels were detected in rats administered doxorubicin (2 to 12 mg/kg) chronically that correlated with the degree of myocardial damage in these animals.[35] Feasibility studies of new cardiac surveillance modalities would be valuable to clinicians treating patients with anthracyclines or other potentially cardiotoxic chemotherapeutic agents.36,37

Long-term animal studies using the clinically relevant route of drug administration should also explore how to use the increased degradation of sarcomeric proteins or damage to mitochondrial DNA as early markers of cardiac damage. The molecular mechanisms that disrupt sarcomere stability and suppress sarcomeric gene expression may indicate even earlier damage to the myocardium.[38]

4. The Need to Determine the Relative Impact of Different Mechanisms of Myocardial Damage

Anthracycline effects on cardiac myocytes may vary and include the following: damage to nuclear DNA,[39] disruption of the sarcomeric protein titin,[40] changes in calcium handling and cellular contractility,[41] suppression of transcription factors that regulate cell survival, and sarcomeric protein synthesis.[42] The timing of anthracycline-induced cellular effects may also vary considerably. Alterations in phospholipid content and turnover occur early,[43] whereas mitochondrial DNA mutations tend to accumulate and continue after completion of

anthracycline treatment.[44] More information is needed to incorporate the relative importance of individual mechanisms into a comprehensive picture of anthracycline cardiotoxicity. Specifically, to what extent and when do these changes take place, and how do they interact during the development of cardiomyopathy?

Other potential causes of anthracycline-associated cardiotoxicity should be investigated. Some investigators have suggested that there are final common pathways in the development of clinical cardiovascular phenotypes.45,[46] For systolic dysfunction disorders (eg, dilated cardiomyopathy), the at-risk portion of the cardiomyocyte can be the link between the sarcolemma and sarcomere, whereas diastolic dysfunction disorders (eg, hypertrophic or restrictive cardiomyopathy) might occur as a result of disruption of sarcomere function. Hence, protein studies of these regions of interest may be worthwhile. Because mitochondria function to generate adenosine triphosphate and the beta-myosin heavy-chain head is an adenosine triphosphate–requiring portion of the sarcomere required for normal function, this secondary abnormality of sarcomere function (caused by anthracycline toxicity) could be relevant to study in combination with the contractile apparatus function.

Dystrophin, a cytoskeletal protein critical for myocyte-myocyte and myocyte-matrix force coupling, is susceptible to genetic or acquired disruptions. Dystrophin, which has been implicated in a final common pathway in the development of inherited, viral, and ischemic cardiomyopathies, is an at-risk protein in dilated cardiomyopathy[45,46] and should be considered in anthracycline cardiotoxicity. For example, dystrophin-deficient mice have increased susceptibility to doxorubicin-induced cardiac injury, suggesting that alterations to dystrophin might represent a final common pathway for the development of anthracycline-induced cardiomyopathy.[47] From a broader point of view, these results also suggest that dystrophin variants might determine the individual sensitivity to anthracycline-induced cardiotoxicity.[47]

The time and effort needed to address these points in long-term animal studies (as discussed in Needed Basic Research, point 2) requires coordinated efforts by several laboratories, each specializing in one or more mechanism and studying the same cohort of animals.

5. The Need to Study the Relationship Between Growth Factors and Anthracyclines

The unexpected synergy between the cardiotoxicities of anthracyclines and the anti-ErbB2 (HER-2) antibody trastuzumab was the first clue to the importance of paracrine growth and survival factors in anthracycline-induced cardiac dysfunction.[48] Since that observation, the impairment of tyrosine kinase–mediated signaling pathways has been studied, both in vitro and in vivo. The clinical relevance of paracrine factors translates into varying levels of cardiotoxicity induced by tyrosine kinase inhibitors (imatinib, dasatinib, and lapatinib), angiogenesis inhibitors (the anti–vascular endothelial growth factor antibody bevacizumab), or vascular endothelial growth factor receptor kinase/multikinase inhibitors (sunitinib and sorafenib).49

Interaction between the HER-2 signaling pathway and the regulation of sarcomere stability is emerging as an alternative to the oxidative stress hypothesis of anthracycline cardiotoxicity.[38] Several questions need to be addressed in light of these new findings. Do survival and growth factors determine an individual’s susceptibility to anthracycline cardiotoxicity? Do anthracyclines impair survival pathways and cause heart failure? Can ErbB signaling be modulated to alleviate anthracycline cardiotoxicity?[50]

6. The Need to Understand Drug Interactions in New Combination Therapies

Clinical trials show that new combination therapies are highly effective in treating cancer. Therefore, experimental studies to determine how the new and old drugs interact and the pathways through which they affect ventricular function are now critical. Potential pitfalls caused by the differences in anthracycline metabolism between animals and humans necessitate wider use of translational models with human myocardial samples.[30,51–53]

7. The Need to Assess the Effects of Anthracyclines on Cardiac Development

Anthracyclines have been and are widely used in children; more than 50% of childhood cancer survivors in the United States have likely been treated with anthracyclines.[54] The 5-year survival rate for childhood cancer is 79%.[8,9,55] There are currently more than 300,000 long-term survivors of childhood cancer in the United States, and this number is increasing.[8,9,55] The therapeutic success in children is marred by delayed cardiotoxicity that may manifest years or decades later.[56] The standardized mortality rate for cardiac death in 20-year long-term survivors of childhood cancer was 8.2 times higher than expected, and the cumulative probability of cardiac death increased from 15 to 25 years after diagnosis.[57] Sudden, presumed cardiovascular death was more than four-fold higher than expected.[58] Cardiotoxic associations with anthracyclines have been demonstrated.[59,60] Thirty-year survivors had a 15-fold higher rate of heart failure, a 10-fold higher rate of other cardiovascular diseases, and a nine-fold higher rate of stroke than expected.[55] Studies of late-onset anthracycline cardiotoxicity in childhood cancer survivors indicate that doses of doxorubicin as low as 100 mg/m^2 increase the risk of reduced fractional shortening and higher afterload, whereas a cumulative dose of 270 mg/m^2 increases the risk of such abnormalities 4.5-fold.[61,62] The large increase in the number of long-term survivors of childhood cancer and appreciation of the fact that there is no safe dose of anthracyclines in this population[56,63] impose an additional challenge of keeping the hearts of these patients healthy.

The mechanisms, predictors, and preventive strategies for late-onset anthracycline cardiotoxicity in children remain under-explored, as do the mechanisms by which this dilated cardiomyopathy often progresses to a restrictive cardiomyopathy (diastolic dysfunction with elevated left ventricular filling pressure).[56,]63 Comprehensive, long-term animal and clinical studies examining the effects of anthracyclines on cardiac development are needed to resolve these questions.

8. The Need to Assess the Effects of Anthracyclines on Nonmyocyte Cardiac Cells

Myocytes comprise approximately 80% of the cardiac mass but constitute less than 20% of the total cell count. Other cell types, including fibroblasts, endothelial cells, smooth muscle cells, and adipocytes, provide structural and trophic support to the myocytes. The effect of anthracyclines on noncardiomyocytes needs to be evaluated. Cardiac endothelial cells and fibroblasts may be more sensitive to the toxic effects of doxorubicin than are cardiomyocytes, suggesting that cardiomyocyte deterioration may be preceded by alterations in matrix composition, in paracrine signals, and in doxorubicin distribution across extracellular fluids and cardiomyocytes.[64] Studies of endothelial cells support this concept,[65,66] but more studies are needed to obtain a comprehensive picture.

The postnatal human heart contains pluripotent cardiovascular progenitor cells that can differentiate in vitro into a functional cardiomyocyte phenotype.[67,68] It is unknown whether these types of progenitor cells can transform in vivo and repopulate anthracycline-induced foci of myocyte damage. It is also unknown whether early progenitor cell damage affects progressive anthracycline cardiotoxicity.[69] Given recent observations linking growth factors and cardiac toxicity and the possible use of myocyte regeneration against the progression of

anthracycline-induced cardiomyopathy,[70] the role of cardiac progenitor cells should be explored. This is particularly true for pediatric long-term survivors in whom anthracycline-associated cardiomyocyte loss leads to inadequate compensatory left ventricular hypertrophy.[56] This results in chronic afterload excess that progressively impairs ventricular function.[56]

9. The Need to Assess Risk-Benefit Factors in Groups With Compounding Risk Factors for Cardiomyopathy

The risks and benefits of anthracycline-based treatments in cancer patients with hypertension, coronary or valvular disease, diabetes mellitus, tobacco use, hypothyroidism, physical inactivity, and overweight or obesity are not established. Animal studies have confirmed that hypertension increases sensitivity to doxorubicin's cardiotoxic effects.[71] The effect of extremes of age also needs to be addressed. Similar concerns extend to other risk factors, such as previous exposure to radiation or anthracycline therapy and pre-existing heart disease. Long-term animal and clinical studies are needed to advance understanding of how these potential risk factors might influence the lifetime incidence of anthracycline cardiotoxicity.[72,73]

10. The Need to Determine Genetic Predispositions to Anthracycline Cardiotoxicity

Identifying genetic polymorphisms was useful in avoiding severe hematologic toxicity in patients treated with thiopurines[74] or irinotecan. [75] Recognition of genetic and proteomic markers of individual patient susceptibility to the cardiotoxic effects of doxorubicin could improve the safety of anthracycline treatment. This topic has not been extensively studied. The potential value of this information must be tempered by the fact that it may take a decade or more until the value of cardiotoxicity-associated polymorphisms will be sufficiently assessed.[76] The search for genetic predisposing factors for anthracycline-induced cardiotoxicity should be broad and not focused solely on genes known to regulate cellular stress responses or drug transport. Furthermore, cardioprotective measures tailored to carriers of predisposing polymorphisms must not markedly interfere with anthracycline's antitumor activity.

NEEDED CLINICAL RESEARCH

1. The Need to Reduce Anthracycline Cardiotoxicity in Clinical Practice

Anthracyclines are key components in many treatment strategies, but cardiotoxicity remains an important dose- and treatment-related clinical problem.77 Solutions are needed for the following several reasons: (1) cumulative anthracycline dose restrictions currently limit the short-term lifesaving potential of these drugs to treat cancer but may not completely eliminate the risk of immediate or delayed cardiotoxicity4; (2) the additional acute cardiac morbidity from new combination therapies needs to be understood and prevented, particularly in patients with comorbidities where there are heightened concerns about reversibility or long-term progression of cardiotoxicity78; and (3) anthracycline-induced cardiac dysfunction might also occur in large numbers of long-term cancer survivors, and in this population, definitive comparative efficacy and cost-effectiveness studies of therapies for controlling cardiac symptoms are lacking.6

In the case of long-term survivors of childhood cancer, it is necessary to understand that every anthracycline exposure may lead to cardiac damage and that the development of untreatable diastolic cardiac failure is possible, even when cardiac systolic function is unchanged.[79,80]

2. The Need to Identify Early Signs of Cardiac Damage

A decrease in left ventricular ejection fraction does not always predict symptomatic events, including heart failure, in either adults or children. No biomarker measured during anthracycline chemotherapy has yet been validated as a surrogate end point for clinically important cardiovascular disease. Therefore, for example, the preclinical evidence for a higher diagnostic value of myocardial strain and strain rate as detected with Doppler echocardiography needs to be validated as a surrogate end point before such determinations become routine for monitoring anthracycline cardiotoxicity.[81–83]

The need for the means to detect early signs of cardiac deterioration that relate to subsequent clinically significant cardiovascular events is urgent. In particular, markers of cardiomyocyte degeneration (such as serum levels of cardiac troponins) or elevated ventricular end-diastolic pressure or volume (such as serum levels of natriuretic peptides) should be further evaluated in adults and children treated with standard- and high-dose chemotherapies.[84,85]

Other issues of concern are the need to adopt common definitions of cardiotoxicity and to establish a cardiotoxicity database. Some questions to be addressed include the following: Are the Common Toxicity Criteria valid? Should NewYork Heart Association criteria or similar criteria of functional status be considered? Are there instances where a mixed or alternative set of definitions is more appropriate?

3. The Need to Educate Clinicians: Anthracycline-Induced Cardiotoxicity Can Initially Respond to Cardiac Medications

The understanding of anthracycline cardiotoxicity has evolved greatly since its first appearance in the 1970s. Data from the widespread use of anthracyclines in potentially curable patients support the conclusion that anthracycline-induced cardiomyopathy can initially respond to cardiac medications and does not necessarily lead to early cardiac death.[79,80,86] This information needs more emphasis because many physicians treat anthracycline cardiotoxicity less aggressively than recommended.[87] However, early beneficial responses to cardiac medications for anthracycline cardiotoxicity may not be associated with sustained cardiac recovery because early cardiotoxicity is a strong predictor of late cardiotoxicity in anthracycline-treated long-term survivors of cancer.[88] The most effective recovery regimens need to be validated and widely promoted through specific guidelines and recommendations. For example, one study suggested that recovery regimens should be initiated soon after anthracycline therapy, particularly in patients with elevated troponin levels during chemotherapy.[85]

Comprehensive, evidence-based prevention, detection, and treatment strategies for anthracycline-associated cardiotoxicity are needed. For many anthracycline-treated patients, the balance between cardiovascular toxicity and oncologic efficacy is dynamic over their lifetime. This affects not only the risk or benefit of a particular regimen, but also the optimal interventions for maximizing oncologic efficacy while reducing toxicity and late effects. Therefore, an optimal strategy to prevent or treat cardiotoxicity based on reducing 1-year combined risk after anthracycline therapy may not remain the optimal means of dealing with cardiac issues in either pediatric or adult 10-year survivor patient populations.

4. The Need to Determine the Cardiotoxicity of Targeted and Combination Therapies

Trastuzumab aggravates anthracycline cardiotoxicity; however, with careful treatment and surveillance strategies, the benefits of combining trastuzumab with anthracyclines outweigh the risk of fatal cardiac events during the follow-up periods studied to date.[89] Trastuzumab is no longer a singular example of how targeted drugs may be less than specific in their

mode of action. Over the last few years, published reports and US Food and Drug Administration alerts have raised concerns about cardiotoxicity from tyrosine kinase inhibitors, antibodies such as bevacizumab, and combinations of targeted therapies. [49,81,90] Some of these drugs might be combined with anthracyclines, creating new clinical conditions that need to be incorporated into the current classification of chemotherapy-related cardiac dysfunction (type 1 for anthracyclines *v* type 2 for trastuzumab).[91] This situation should be dealt with by an expert panel that will establish a database, define classification criteria, and develop evidence-based guidelines for identifying and treating the cardiotoxicity of approved or investigational multiagent regimens.

5. The Need to Balance the Risk of Cardiotoxicity With Clinical Benefit

Establishing stricter or more universal guidelines for safe cumulative anthracycline doses is not prudent without clinical risk-benefit data for specific subpopulations of patients. A downside of defining a safe cumulative dose is that it may lead physicians to arbitrarily restrict lifesaving chemotherapy, thus compromising rather than saving a patient.[92] Randomized trials of patients treated with or without anthracyclines for Hodgkin's disease or operable breast cancer and with 5 to 20 years of follow-up found that the lifesaving impact of anthracyclines outweighed the risk of cardiac-related deaths. These findings illustrate the importance of never looking at cardiotoxicity in isolation but always in the context of defined therapeutic windows.[93–95]

The high prevalence of heart failure in a population-based study of older breast cancer survivors might caution against the aforesaid concepts.[10] However, the inherent limitations and weaknesses of population-based studies may have biased the results of that study.[72] Different limitations pertain to studies of long-term cardiac fitness in adult patients exposed to anthracyclines and who are available to be recalled for a cardiac work-up.[93,94] The reassuring finding of no increased incidence of detected heart problems[93,94] should not dispel the concern that hearts exposed to anthracyclines are more liable to injury with subsequent stresses from viruses, pregnancy, arrhythmias, anemia, or other chemotherapy that may precipitate heart failure.[79,96] In addition, there is a lack of fine diagnostic tools to identify high-risk patients.[79,96] The long-term cardiovascular liability of anthracyclines and the progression of ventricular dysfunction to fatal events need to be evaluated in prospective studies that minimize the weaknesses of retrospective assessment.

6. The Need to Define Risks and Benefits for Subgroups of Patients

Little information is available on dose and follow-up adjustments needed for patients with hypertension, diabetes, concurrent radiation therapy, extremes of age, or obesity, as well as for patients with a history of anthracycline exposure or heart disease.[97,98] Although important insights can be gained from animal studies (see Needed Basic Research, point 9), clinical studies are necessary to establish absolute risk-benefit guidelines for these patient subgroups.

7. The Need to Manage Cardiac Dysfunction in Cancer Survivors Treated With Anthracyclines

Clinical practice guidelines for treating patients with asymptomatic left ventricular dysfunction or heart failure include a combination of β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, nitrates, and hydralazine. Large or multiple comprehensive studies have not been conducted on how these treatments could prevent the progression of cardiomyopathy in patients with adult-onset cancer who received anthracyclines and showed asymptomatic or mildly symptomatic contractile dysfunction. The transient value of angiotensin-converting enzyme inhibitor treatment has been noted in childhood cancer survivors with anthracycline cardiotoxicity, but there is no evidence for its

long-term therapeutic benefits.[88,99–101] In light of the growing number of cancer survivors, there is a great need for identifying effective interventions after anthracycline treatment that would result in evidence-based recommendations.

8. The Need for Specific Dietary and Exercise Recommendations for Anthracycline-Treated Patients

Although experimental evidence suggests that moderate dietary restrictions help prevent anthracycline cardiotoxicity,[86,102] no specific dietary recommendations have been proposed for patients receiving anthracyclines.[103] The effects of exercise on altering the risk-benefit ratio of anthracycline-based chemotherapy also need to be further examined.[4,104,105]

9. The Need to Understand the Progression of Anthracycline Cardiomyopathy: Systolic Versus Diastolic Heart Dysfunction

Both systolic (diminished contractility and impaired ejection fraction) and diastolic (impaired relaxation) dysfunction can occur in patients treated with anthracyclines. Because there is no absolutely safe dose of anthracyclines, more aggressive follow-up of even asymptomatic patients is required to understand the spectrum of abnormalities and the time pattern of systolic versus diastolic dysfunction.[82,106]

10. The Need to Expand the Use of Dexrazoxane and Liposomal Anthracyclines

Oncologists should become more aware of the benefit of using dexrazoxane as a cardioprotectant in anthracycline-containing regimens. Earlier reports of a possible interference of dexrazoxane with anthracycline activity seem to be overestimated; the evidence now shows that dexrazoxane protects the heart without diminishing oncologic efficacy.[107] Results from several clinical trials indicate that pegylated or uncoated liposomal anthracycline formulations induced less cardiotoxicity than standard anthracycline preparations, which calls for their wider therapeutic use.[108]

CONCLUSIONS

The Como meeting emphasized the following points.

- Continuous communication and exchange of ideas among basic scientists, oncologists, cardiologists, pharmacologists, and other health professionals must be encouraged. Agreement is growing that an oncologist and cardiologist should assess the risks and benefits to individual patients jointly because, for some patients, therapeutic decisions involve trading one potentially fatal disease for another. Therefore, the conceptual framework for a new discipline, cardio-oncology, seems justified.
- Pharmaceutical companies and grant-funding organizations should support development of both validated biomarkers that are surrogate end points for clinically important cardiovascular disease and treatments that prevent or control anthracycline cardiotoxicity. The simulation of clinically relevant scenarios in long-term animal models should be a priority for basic science studies.
- A cross-disciplinary approach has the best chance to define the pathogenic mechanisms responsible for anthracycline cardiotoxicity.

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