Medical Progress

Doxorubicin (Adriamycin) Cardiomyopathy

A Critical Review

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Despite its vast utility in clinical oncology, the use of doxorubicin hydrochloride (Adriamycin) is limited by a potentially fatal cardiomyopathy. The following critical review, which examines the natural course, histopathologic effects, risk factors and monitoring indicators of this toxicity, also analyzes recent research of proposed mechanisms, including free radical formation with depletion of detoxifying enzymes, inhibition of vital enzyme systems and alterations in relative calcium concentrations. Prevention of the adverse reaction has been attempted by using such agents as α-tocopherol, selenium sulfide, coenzyme Q_{10}, sulfhydryl donors, nucleosides and razoxane, and via liposomal carriage and alternative methods of administration.

The immense value of doxorubicin hydrochloride (Adriamycin) in treating a variety of solid and hematologic malignant conditions is unquestioned. Its usefulness is limited, however, by its cardiotoxicity, an adverse effect of the drug that can preclude its use in some patients and limit the duration of its use in many others. During the past seven years, a number of reviews have been published regarding this chronic and often dose-limiting toxicity of doxorubicin, which underscores its significance.[1-6] The deleterious effects of doxorubicin on the heart can be categorized into acute effects and a chronic cardiomyopathy; this review will focus on the latter toxic effect.

The well-known chronic cardiomyopathy of doxorubicin use greatly limits the usefulness of this broad-spectrum antineoplastic agent. With the increased utilization of chemotherapeutic agents as adjuvants to surgical treatment and irradiation, there will be a greater likelihood of more patients receiving cardiotoxic doses of doxorubicin or even dying of this drug-related toxic effect without evidence of malignant disease. With this in mind, the need to identify risk factors, to predict those persons capable of tolerating further doses of the drug and to possibly prevent cardiomyopathy becomes obvious.

Overview

Prevalence

The overall prevalence of doxorubicin cardiomyopathy is 1.7% to 6.8%[6-13] and is highly dependent on total dose.

Time Course

The outstanding clinical feature of this toxic reaction is its insidious onset, followed by a rapidly progressive biventricular failure and death. The time course varies but symptomatic cardiac failure most frequently appears within a week to 2½ months of the final dose of doxorubicin[1,4,6-8,10,12,14-24] and sometimes there is no latency period.[7,12,17,19,20,25] The median latency period has been reported to be between three and eight weeks[6,7,12,14,15] and has been as long as 2½ years.[26] A number of investigators have noted that the severity of congestive heart failure is greater when the latency period is shorter.[3,6,7,15,17,18]

Signs and Symptoms

The signs and symptoms of doxorubicin cardiomyopathy are typical of any biventricular failure; tachycardia, shortness of breath, neck vein distention, gallop rhythms, ankle edema, hepatomegaly, cardiomegaly

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and pleural effusions were the most frequently noted in a series of 88 cases.[12] Other case reports confirm these findings. Minow and co-workers[6] warn that the first symptom may be as nonspecific as a dry cough and they urge that any new symptom consistent with congestive heart failure should be investigated to rule out a cardiac origin because further doses of doxorubicin may lead to progressive ventricular failure.

Prognosis and Natural Course

In early trials of doxorubicin, the onset of congestive heart failure was abrupt and had an exceedingly poor prognosis; fatality was reported in 70% to 80%.[14,25] It is the hope, however, of many who work with the agent that now that doxorubicin cardiomyopathy is a well-known entity, it will be carefully looked for and that medical treatment at an earlier phase will be more successful. Reviewing cases from the literature, one can now find not only nonresponsive cardiomyopathies with rapid death,* but also many cases of doxorubicin cardiomyopathy that were diagnosed and treated early with good results, the patients still living six months to two years later.†

The natural course of doxorubicin cardiomyopathy begins well before congestive heart failure develops. By analyzing endomyocardial biopsy specimens, it has been well established that myocardial damage is an early phenomenon, occurring after as little as 180 mg per sq m of body surface.[32] It appears, however, that little to no functional deterioration occurs until a certain patient-specific critical dose or critical degree of damage is surpassed.[33] If doxorubicin therapy is discontinued after left ventricular deterioration has occurred, the degree of dysfunction remains but is stable.[34] This may persist for years without the development of congestive heart failure.[35]

In summary, subclinical myocardial lesions can be found early during doxorubicin therapy. After a critical point in therapy, function will begin to deteriorate. Following therapy, noninvasive studies of left ventricular function can show one subset of asymptomatic patients with low resting ejection fractions and another group whose ejection fractions are normal at rest but respond abnormally to stress.[35] This ventricular dysfunction appears to persist for at least a few years. Clinical congestive heart failure, if it is diagnosed early and treated aggressively, may respond to medical management. Patients in whom it develops shortly after their last dose of doxorubicin are less likely to respond to treatment and have a poorer prognosis than those who have a relatively longer latency period.

Description of Myocardial Damage

As stated previously, doxorubicin cardiomyopathy is clinically indistinguishable from other biventricular cardiomyopathies. In dogs, long-term administration of doxorubicin leads to a diffuse cardiomyopathy that is most severe in the left ventricle and intraventricular septum, least severe in the right atrium and intermediate in the right ventricle and left atrium.[36] The disseminated nature of the pathologic effects in the myocardium is well established, and atrial lesions similar to those in the ventricles have been documented in mice and rabbits after long-term therapy.[37] Humans may have a greater incidence of left-sided disease, however.[38] The morphologic nature of doxorubicin cardiomyopathy has been reviewed.[39]

Human histopathologic effects have been studied at autopsy[8] and before death by endomyocardial biopsy.[40] Myocardial sections examined microscopically at autopsy define a rather distinctive vacuolar degeneration of cardiac cells with interstitial edema. Inflammatory changes are notably absent in contradistinction to those seen in viral cardiomyopathy. Ultrastructurally, the intracellular vacuoles are due to distention and swelling of the sarcoplasmic reticulum. The incidence and severity of these changes increase as the total dose of doxorubicin increases.[8]

With the advent of endomyocardial biopsy, it has been possible to observe the progression of myocyte damage at various stages of total dose. The lesions are indeed disseminated yet focal, as normal tissue can be found adjacent to damaged tissue. Two main types of myocyte damage are as follows:

- myofibrillar loss of "drop-out"; the mitochondria are small and remain intact;
- vacuolar degeneration; the earliest manifestation is distention of the sarcoplasmic reticulum, with subsequent swelling and coalescing.

Both lesions progress to death of the myocyte, at which point the mitochondria degenerate with swelling and cristolysis. These changes have been noted after the administration of as little as 180 mg per sq m of doxorubicin, and have been entirely absent after doses as high as 400 mg per sq m.[40] Many of the ultrastructural changes, including vacuolization and dilatation of sarcoplasmic reticulum, are nonspecific and occur with other forms of cardiomyopathy.[41]

In general, the same histopathologic changes that occur in humans develop in a number of animal models in studies of short- and long-term therapy. In fact, studies in animals have allowed us to realize that "clinically evident CHF [congestive heart failure] is . . . a late manifestation of steadily accumulating subclinical damage."[42] After early vacuolar degeneration of myocytes, myofibrillar lysis and cell death ensue. Ultrastructurally, sarcoplasmic vacuolization and mitochondrial degeneration can be seen before myofibrillar separation.[43] The most frequently used and best studied animal models are rabbits, rats and mice; monkeys have also been found to have good correlation with humans. Of these, the rabbit is the most fully understood model of chronic toxic reaction.[42] Although rabbits and rats were the first models to be used and

*References 17, 19, 20, 22, 24, 26-28.

†References 10, 11, 17, 20-23, 29-31.

understood, an excellent study in mice has shown that they too can be used as a model for chronic toxic reaction[44] and justifies the use of this model in the simultaneous assessment of toxicity and efficacy.

Risk Factors for Doxorubicin Cardiomyopathy

In an effort to predict which patients are at greater risk for doxorubicin cardiomyopathy, numerous prospective and retrospective studies and case reports have been published, attempting to alert clinicians.

Age

Those 70 years of age or more are thought to be at increased risk. In the retrospective analysis by Von Hoff and associates of 4,018 patients,[12] there was gradually increasing risk with increasing age, but this appeared to be insignificant at total doses below 500 mg per sq m. It is not clear if this risk is independent of underlying coronary artery disease.

Mediastinal Irradiation

Several investigators have found that prior or concurrent mediastinal irradiation is associated with poorer cardiac assessment scores[19,40] and an increased risk of doxorubicin cardiomyopathy.[7,25] In contradistinction, neither Von Hoff nor Minow and their colleagues[12,15] were able to establish in retrospective analyses mediastinal irradiation as an additional risk factor. Although conflicting information can be found on this controversial area, patients who have received or are receiving irradiation to the mediastinum should be observed more carefully for the development of this toxic condition.

Cyclophosphamide

In the study of Ulmer and co-workers,[19] in children receiving multidrug chemotherapy, which included cyclophosphamide as well as doxorubicin, longer preejection periods developed than in those receiving only doxorubicin. The hypothesis that cyclophosphamide may be a risk factor, though frequently mentioned in reviews, has not been confirmed in at least three large-scale studies.[7,12,15] Recently, however, Gottdiener and colleagues[45] found cardiomyopathy to be a frequent complication of high-dose cyclophosphamide therapy, occurring in 28% of patients within three weeks of treatment. Similar findings were recently reported in rats.[46] As higher doses of this alkylating agent are more frequently being incorporated into chemotherapeutic protocols, the risk of adding cyclophosphamide to a regimen containing doxorubicin will have to be reassessed.

Other Drugs

A number of other drugs, including mitomycin,[16,27] vinblastine sulfate,[16] vincristine sulfate,[7,30] dacarbazine (DTIC),[30,47] bleomycin sulfate,[7] etoposide (VP-16),[20] amsacrine (AMSA)[48] and megestrol acetate[26] have been reported to increase the risk of doxorubicin cardiomyopathy. With the exception of that for mitomycin,[27] none of these reports is well documented.

Preexisting Cardiac Disease

Several investigators have noted an association between pretreatment cardiac disease and hypertension and a greater incidence in the development of doxorubicin cardiomyopathy.[7,8,12] Any patient who falls into this category should be considered at risk.

Dosing Regimen

Apparently a weekly regimen is associated with less cardiotoxic reaction than a regimen calling for a dose every three weeks.[12,49,50] This is conceivably due to the higher doses used with the latter, more common regimen. More frequent administration using smaller doses would produce lower plasma concentrations, and a relationship between cardiotoxic reaction and plasma concentrations has recently been suggested.[51] If doxorubicin cardiomyopathy occurs via free radical or superoxide formation, a single large dose would more likely lead to total depletion of glutathione protection and subsequent myofibrillar damage than would several smaller doses. This area certainly deserves further investigation.

Miscellaneous

It has been suggested that liver dysfunction predisposes to doxorubicin cardiomyopathy [30] Because doxorubicin is eliminated by the liver, this suggestion appears likely. The report is poorly documented, however.

Total Dose

By far the greatest and most well-known risk factor for doxorubicin cardiomyopathy is unrestrained use of the drug. Praga and associates[7] noted an elevation in the incidence curve at 450 to 550 mg per sq m. Lefrak and co-workers[9] found the incidence to be 0.3% at total doses below 550 mg per sq m and 30% at above this dose. Von Hoff and colleagues[12] found a sharp increase in the incidence curve at 550 mg per sq m. At this dose the incidence was 7%, whereas at 700 mg per sq m, the incidence was 18%. The most striking example of the dose dependency of doxorubicin cardiomyopathy is a report by Cortes and associates[10] in which in seven of ten patients receiving more than 600 mg per sq m, congestive heart failure developed, whereas in none of the 88 patients receiving less than 600 mg per sq m did it occur.

The risk factors, as well as the natural course of daunorubicin-induced heart failure, are very similar to those of doxorubicin, but have been far less studied. This subject has recently been reviewed.[14] Of note is that children appear to be at greater risk than adults at any given dose.

Because congestive heart failure develops in a few patients at total doses less than 550 mg per sq m and does not develop in many patients receiving doses above this figure, a total dose guideline appears inade-

quate and the need for monitoring for early and subclinical development of cardiomyopathy is obvious.

Monitoring for Doxorubicin Cardiomyopathy

Several noninvasive and invasive techniques to assess cardiac function have been developed, and most of these techniques have been used to study patients receiving doxorubicin. The ideal test would be free of morbidity and would be able to assess cardiac function accurately at subclinical levels, to predict all patients at risk of congestive heart failure developing with further doses of doxorubicin and to identify those patients who could tolerate further doses of doxorubicin without sequelae. Such a test is not yet available. Many tests have claimed good reliability and specificity for predicting doxorubicin cardiomyopathy; none is foolproof, however.

The use of noninvasive techniques to assess cardiac function has been reviewed.[52] These include electrocardiography, systolic time intervals, echocardiography and radionuclide angiography. A detailed description of the mechanisms of these tests is beyond the scope of this paper; however, their possible usefulness for predicting doxorubicin cardiomyopathy is discussed.

Electrocardiography

Minow and co-workers[13] were the first to suggest that electrocardiography (EKG) would be a good monitoring tool in predicting doxorubicin cardiomyopathy. Since then, however, several investigators have noted that the EKG changes—specifically a reduction of QRS amplitude in the anterior leads—occur late in therapy, frequently do not precede clinical onset of congestive heart failure and thus should not be used as predictive tools.[11,17,53]

Systolic Time Intervals

By using the simultaneous recordings of a phonocardiogram, an EKG and a carotid pulse tracer, one can determine the preejection period, the left ventricular ejection time and the ratio of preejection period to left ventricular ejection time, frequently referred to as the systolic time interval. Although examples of pronounced or sustained elevations in systolic time interval preceding the development of congestive heart failure exist,[21,24,31] there appears to be a high incidence of false-positive elevations in this test,[21,24,25,29,31,54] thus limiting its usefulness. In addition, the incidence of false-negative results has been noted to be as high as 33%.[25] Thus, systolic time intervals do not appear to be a valid predictor of doxorubicin cardiomyopathy.

Echocardiography

The use of echocardiography in assessing left ventricular function has recently been reviewed.[55] M-mode measurements are taken along a single axis and are used to approximate the minor hemiaxis of an ellipse in estimating left ventricular dimensions. Hence, one of the limitations of this test is that it assumes uniform wall motion throughout the ventricle. Henderson and Frei[56] state that because doxorubicin cardiomyopathy is diffuse, this would not pose a problem. But if regional wall motion abnormalities exist or develop independently of doxorubicin, interpretation could be difficult. Two-dimensional echocardiograms provide imaging of the left ventricle from base to apex, thus lessening the need to rely on the assumption of uniform motion. Unfortunately, most studies to date have used the M-mode echocardiogram. The major limitation of either test is in obtaining technically adequate studies for interpretation.[55]

The three assessments of left ventricular function most frequently obtained from echocardiograms are the left ventricular fractional shortening (%SF) or change in internal diameter (%SID), the mean velocity of circumferential fiber shortening (V_{cf}), and the ejection fraction (EF). Because many feel that M-mode determinations of ejection fraction may be inaccurate,[55] the fractional shortening is the most frequently reported value. On the other hand, ejection fractions derived from two-dimensional echocardiograms do compare favorably with more advanced tests.[55] Although some investigators question the usefulness of echocardiography in predicting the onset of congestive heart failure associated with doxorubicin cardiomyopathy,[56] several studies have shown serial decrements in fractional shortening or ejection fraction with increasing doses of doxorubicin, preceding the onset of congestive heart failure.[22,28,34]

Normal value of ventricular fractional shortening ranges from 28% to 40% or even 50%,[22,55] and at least two groups of investigators[22,28] recommend serial measurements with discontinuation of therapy when fractional shortening falls to below 20%. It appears that echocardiography, especially with the advent of two-dimensional imaging, has a role in the noninvasive monitoring of patients receiving doxorubicin.

Radionuclide Angiography

The use of radioactive tracers in assessing heart disease in general[57] and of ventricular function specifically[58] has been reviewed. Two approaches are available: The "first pass" technique—which is rapid—and equilibrium blood pool imaging—which allows multiple images and the ability to "gate" or synchronize the images to a simultaneous EKG tracing and establish composite data. The major measurement obtainable from these studies is the ejection fraction. There is no significant difference between the two methods to reproducibly determine ejection fraction.[59] A normal value has been established at greater than 0.50,[31] with an abnormal value arbitrarily chosen to be from less than 0.45[35] to less than 0.50[54]; Alexander and co-workers[31] set a value of less than 0.45 with a drop of at least 0.15 from baseline to describe "moderate cardiomyopathy," whereas an ejection fraction of less than 0.30 was chosen as a marker of "severe cardiomyopathy." Using the above criteria, they administered an additional doxorubicin dose to five patients who had angiographically defined doxorubicin-induced moder-

ate cardiomyopathy[31]; in all five congestive heart failure developed. Thereafter, six other patients with moderate cardiotoxic manifestation based on radionuclide ejection fraction had their doxorubicin therapy discontinued; in none did congestive heart failure develop, nor did they have worsening of their ejection fraction. In addition, 13 patients were given more than 550 mg per sq m, as their ejection fractions were maintained above the requisites of discontinuation; congestive heart failure did not develop in any of these patients. Other examples of the predictive ability of radionuclide angiography have been published as well.[60] From another study,[60] it should be noted that a low baseline ejection fraction (less than 0.45), without signs or a history of cardiovascular disease, does not place a patient at greater risk of doxorubicin cardiomyopathy developing. In these patients, a drop in ejection fraction of greater than or equal to 0.15 should be used as the marker for moderate cardiomyopathy. Tests should always be done before administration of doxorubicin, as abrupt, transient reductions of ejection fraction have been noted 24 to 96 hours after a dose.[61]

Recently, two sets of investigators were able to identify a greater number of patients with abnormal ejection fractions after doxorubicin by stress-testing these patients either by exercise[35] or by administration of methoxamine hydrochloride.[54] With exercise an ejection fraction should rise by at least 0.05. We feel that stress testing has great usefulness in the assessment of doxorubicin cardiomyopathy, especially in borderline cases.

Transvenous Endomyocardial Biopsy

The use of biopsies has also been recommended as a more invasive but more accurate assessment of myocardial damage due to doxorubicin. The history, technique and use of the transvenous procedure were recently reviewed.[62] The usefulness of this test is based on the frequent finding that the histopathologic grade of the biopsy taken from the right ventricle, on a 0 to 3+ scale, correlates favorably with the total dose of doxorubicin.[32,40,63,64] In addition, biopsy grade has also been shown to correlate with evidence for myocardial dysfunction by cardiac catheterization. However, the predictive capabilities obtained from these biopsy results are as yet uncertain. Many patients with grade 3+ biopsy results have catheterization evidence of dysfunction, and in several congestive heart failure will develop.[64] Very few patients with 1+ biopsy results appear to be at risk of congestive heart failure developing. The problem of predictability centers around the patients with 2+ results. In addition, although morbidity has not been a major problem (0.5% to 4.9%),[51,62,63] few centers are capable of doing a transvenous endomyocardial biopsy. It is generally recommended that patients in whom a 2+ biopsy grade develops, even without other evidence of cardiomyopathy, should not receive further doses of doxorubicin.[51,64] This technique may prove very useful in the further understanding of the relationship between structural abnormality and myocardial function. In medical centers in which myocardial biopsies are routinely done, this procedure appears to be the most accurate determinant of cardiomyopathy at subclinical levels.

Recommendations

At institutions where endomyocardial biopsies are not readily available, we presently recommend a baseline (before giving doxorubicin) radionuclide angiographically obtained ejection fraction on every patient scheduled to receive doxorubicin. Thereafter, we stratify patients into those with risk factors and those without risk factors, as per previous discussion. We measure ejection fractions preceding each doxorubicin dose after a cumulative doxorubicin dose of 350 to 400 mg per sq m in the former group, and after 550 mg per sq m in the latter group. Additionally, we recommend stress testing for any questionable or borderline result, and to discontinue therapy if there is not a rise greater than or equal to 0.05 in the ejection fraction with exercise. Other recommendations for discontinuation of therapy follow those of Alexander and coworkers—that is, an ejection fraction of less than 0.45 with a drop of at least 0.15 from baseline.

At institutions where radionuclide angiography is not available, echocardiograms should be substituted, using the above criteria for discontinuation. An M-mode echocardiographic fractional shortening of less than 25% should necessitate discontinuation.

At institutions where endomyocardial biopsies are done, we would use the recommendations of Bristow and Legha and colleagues,[51,65] as follows: The first biopsy should be done after 300 mg per sq m has been given in patients with risk factors, after 420 mg to 480 mg per sq m has been given in patients without risk factors or after noninvasive test results indicate left ventricular dysfunction. Thereafter, biopsy specimens should be obtained every 120 to 240 mg per sq m, and therapy discontinued at a biopsy result of 2+ or 3+.

Postulated Mechanisms of Doxorubicin Cardiomyopathy

As should be clear from the foregoing discussion, a foolproof noninvasive method for predicting which patient's heart is at risk for irreversible insult from additional doses of doxorubicin does not currently exist. Thus, much research effort has been expended in trying to elucidate the specific mechanism or mechanisms by which doxorubicin produces its toxic effect on the heart. Elucidation of a mechanism for cardiotoxicity would make possible (1) analogue synthesis that would theoretically circumvent the toxic effects or (2) development of blocking agents for the toxic manifestations, which would improve the therapeutic index.

Although one mechanism of antitumor activity is felt to be related to DNA intercalation in which subsequent strands break, a second mechanism involving free radical formation has also been described.[66] Whether one or both of these mechanisms is causally related to the cardiotoxicity is as yet unclear. The fol-

lowing discussion will focus on what is known about the mechanisms of doxorubicin cardiomyopathy and some of the research that attempts to abrogate the dose-limiting cardiotoxicity of this agent.

In vitro and in vivo, anthracyclines have been shown to stimulate superoxide production[42,67,68] via a process dependent on the reduced form of nicotinamide-adenine dinucleotide phosphate (NADPH).[68] This reaction is thought to be preceded by reduction of the anthracycline to a semiquinone radical, with a subsequent redox reaction with water that produces the superoxide.[42] This electron-flow process, which involves a free radical intermediate, follows Michaelis-Menten kinetics, indicating a saturable protective mechanism.[69] Superoxide radicals are toxic to tissues in and of themselves; in addition, their dismutation to peroxide initiates a radical chain reaction resulting in conversion of unsaturated fatty acids to lipid peroxides, which in turn rapidly decompose to yield, among other products, malondialdehyde.[68] Although unable to detect malondialdehyde in untreated cardiac tissues, Myers and colleagues[68] detected this end-product two to six days after doxorubicin was administered to rats. This rise in malondialdehyde content was also noted by Stuart and associates[70] in human platelet-rich plasma.

Enzymatic protection of cells against oxygen radicals such as superoxides and peroxides consists of glutathione peroxidase, [71] which is dependent on both glutathione and selenium stores,[72] superoxide dismutase[73] and catalase.[67,71] In animal models, cardiac concentrations of these protective enzymes are far lower than those in other organs.[67,73] Doxorubicin produces an acute depression of cardiac glutathione peroxidase,[67] the enzyme that catalyzes the degradation of lipid peroxides and hydrogen peroxide to nontoxic compounds. Thus, by inhibiting the enzymatic degradation of the toxic oxygen radicals for which it is responsible, doxorubicin potentiates its own toxicity. In addition, due to the relatively lower concentrations of detoxifying enzymes in cardiac tissue, the heart would appear to be at greater risk of damage than other organs.

On a related topic, Olson and associates[74] found an acute reduction in the cardiac concentration of reduced glutathione (GSH) after treatment with doxorubicin. Furthermore, pre-doxorubicin depletion of reduced glutathione potentiated the lethality of the anthracycline, indicating that reduced glutathione has a protective role against the effects of doxorubicin on the heart. The exact role of reduced glutathione in the myocardium is not known, but Kosower[75] found a significant role for it in muscle contraction, lending greater credence to a role for its depletion in the development of heart failure due to doxorubicin.

A second postulated mechanism is inhibition of coenzyme Q_{10} (CoQ_{10} or ubiquinone), a coenzyme of mitochondrial succinoxidase and NADH (the reduced form of nicotinamide-adenine dinucleotide) oxidase, which is involved in the electron-transfer process of respiration and coupled phosphorylation.[76] Doxorubicin has been shown to inhibit the functioning of these enzyme systems.[77] The well-known high concentrations of mitochondria in myocardial tissue coupled with the histopathologic findings of alteration of cardiac mitochondria after exposure to doxorubicin lend some credence to this mechanism. A study in rats[78] indicated that doxorubicin's inhibitory effect is due to its binding to the apoenzyme, thus disallowing the binding of the true coenzyme, CoQ_{10}, which it resembles structurally.

A third hypothesis for the mechanism of doxorubicin-induced cardiotoxic reaction is through an increase in intracellular calcium concentrations and calcium transport perturbation. Although high intracellular calcium concentrations have been associated with doxorubicin cardiomyopathy in animal studies,[8] a more recent study showed that disturbed calcium transport is a function of acute but not chronic doxorubicin cardiomyopathy.[79] Thus, it seems unlikely that calcium transport has a key role in the chronic cardiomyopathy seen with anthracyclines. Its role in acute toxic reaction remains to be established. The long-term effect of calcium channel blockers in patients receiving doxorubicin is an area worthy of study.

Other less supported theories on the mechanism of doxorubicin cardiomyopathy include inhibition of sodium-potassium-adenosine triphosphatase,[80] diminution of adenylate charge,[81] inhibition of guanylate cyclase,[82] DNA degradation[83] and inflammation.[84]

Prevention of Doxorubicin Cardiomyopathy

Based to a great extent on the supported theories of the mechanism of doxorubicin's deleterious effects on the heart, numerous investigators have attempted to minimize the degree of injury by using pharmacologic or endogenous substances or other novel approaches.

One of the most intensively studied agents is α-tocopherol, or vitamin E. Among its many pharmacologic and physiologic properties, this vitamin is a scavenger of free radicals, and its deficiency in rabbits or mice produces a myopathy whose histopathologic effects are very similar to those seen in cardiac lesions produced by doxorubicin.[68]

In vitro, vitamin E has been shown to reduce doxorubicin-induced formation of free radicals and malondialdehyde.[70] In animal studies, vitamin E pretreatment has been shown to prevent doxorubicin-induced diminution of reduced glutathione[85] and to reduce the incidence of typical cardiac lesions[86] and of cardiomyopathy.[85] More recently, Van Vleet and Ferrans[87] noted that vitamin E supplementation prolonged survival in doxorubicin-treated rabbits, but only very large doses of the vitamin provided protection from cardiomyopathy. In another study, Van Vleet and co-workers[36] found no benefit of the vitamin in dogs, but the sample size was small. Finally, in a long-term dosing study involving rabbits, Breed and associates[88] found that even very high doses of vitamin E did not have a protective effect on doxorubicin cardiomyopathy. Thus, animal studies have produced mixed results using a large range of doses of vitamin E. The encouraging results, however, of some of the studies, the lack of obvious

toxicity and the observation that the tumoricidal activity of doxorubicin does not appear to be altered have spurred enough interest to initiate studies in humans.

Legha and colleagues[89] administered α-tocopherol in a dose of 2 grams per sq m given orally each day, starting five to seven days before chemotherapy. Doxorubicin in a dose of 50 mg per sq m was administered to 21 patients with breast cancer. The authors noted that plasma levels of α-tocopherol were four to five times greater than baseline, levels that protected rabbits from doxorubicin cardiomyopathy based on Billingham's biopsy criteria. The authors concluded, based on endomyocardial biopsy results, that this dose and schedule of vitamin E did not offer significant protection against cardiotoxic manifestations in humans, but no control group was used. In addition, many of the studies in animals that showed positive results used doses of vitamin E that, when extrapolated to 70 kg of body weight, far exceeded the doses used here. Finally, the duration of vitamin E administration was not stated in the abstract, and may have been inadequate.

Thus many questions exist about the prophylactic use of vitamin E. Although encouraging results have been found in animal studies, the doses and regimens used have varied considerably and indeed may be different from those required in humans. This is an area that will receive much attention in the coming years.

Another nutritional agent, selenium, has received some attention. Selenium is a cofactor for most, if not all, of cardiac glutathione peroxidase[69] and thus plays a role in the detoxification of free radicals. Selenium-containing diets have been associated with a beneficial effect on survival in animals.[69,87] When used in combination with vitamin E, a reduction in doxorubicin cardiomyopathy has been noted,[90] but when used alone no such benefit was found.[87] Although selenium deficiency in other countries has been associated with heart failure, a deficiency of this mineral in this country is rare, and it appears unlikely that selenium will prove beneficial in the prophylaxis of doxorubicin cardiomyopathy.

Based on the hypothesis that doxorubicin inhibits coenzyme Q_{10} and thus interferes with oxidative metabolism in the heart, the administration of this coenzyme in a prophylactic effort has been studied. In vitro, the addition of coenzyme Q_{10} reduces the inhibitory effect of doxorubicin on both succinoxidase and oxidase of the reduced form of nicotinamide-adenine dinucleotide (NADH).[77] Coenzyme Q_{10} given to rabbits[91] or mice[78] has been shown to prevent inhibition of succinoxidase by doxorubicin and has prevented cardiotoxic reactions in these animal systems. Cortes and co-workers[29] gave coenzyme Q_{10} in a dose of 50 mg a day at the start of a doxorubicin-containing protocol to humans in a small noncontrolled study. Of the eight patients observed, only two showed evidence of progressive cardiac dysfunction, as assessed by increasing systolic time intervals. In a previously studied group not receiving coenzyme Q_{10}, eight of ten patients had steadily increasing systolic time intervals with successive doxorubicin doses. Although the use of systolic time intervals in assessing cardiac dysfunction and predicting congestive heart failure in doxorubicin recipients has been criticized, these encouraging results deserve further study.

The findings of doxorubicin-induced depletion of reduced glutathione and the role of the latter in muscle contraction have spurred interest in the use of *N*-acetylcysteine and cysteamine as sulfhydryl substitutes for reduced glutathione in protecting against doxorubicin cardiomyopathy. In the mouse model, use of these agents has prevented a fall in cardiac sulfhydryl concentrations[74] and has been associated with reduced mortality and cardiac lesions,[74,92] without a change in the efficacy of doxorubicin against P-388 ascites tumor. The efficacy of *N*-acetylcysteine was related to dose as well as scheduling (administering before treatment was more effective than concurrent administration or after treatment).[92]

Due to the noted decrease in adenylate charge with doxorubicin, adenosine used in vitro[81] and in mice[93] has been studied. Positive results on cardiac tissue activity and survival have been noted with short-term studies. Intermediate- and long-term studies with assessment of influence on myocardial lesions are lacking but appear worthy of study, based on these encouraging results.

Razoxane (ICRF 159) is an ethylenediaminetetraacetic acid (EDTA) derivative with antineoplastic properties, which may enhance the antitumor activity of doxorubicin.[94] ICRF 187 is the *d*-isomer of razoxane.[95] Animal studies have shown a decrease in mortality when razoxane[96] or its isomer[95] is given before daunorubicin. Protection from cardiac lesions was also noted.[95] The effects against doxorubicin-induced damage, however, appear to be dose-dependent, as low doses are protective but high doses may increase mortality.[96] The reason for the discrepancy in dose requirement of the ICRF cogeners in their protective effects of the two anthracyclines, as well as their mechanism of action, has not been worked out. Due to their tumoricidal activity, however, work in this area is quite interesting, as well as promising.

Two novel approaches in an attempt to decrease the incidence of doxorubicin cardiomyopathy consist of administering the drug by continuous intravenous infusion or encapsulating it within liposomes. Legha and associates[51] administered doxorubicin by continuous infusion into a central vein over 48 to 96 hours to patients with various malignant diseases, and compared their results with matched control patients who received the drug by standard intravenous injection. Although the mean total dose received by the infusion group was significantly greater than by the control group, substantially fewer infusion patients had their doxorubicin therapy discontinued due to severe pathologic changes seen on endomyocardial biopsy. Antitumor effect was not diminished. Peak plasma levels of doxorubicin were substantially lower in the infusion group, possibly indicating lower myocardial concen-

trations. This supposition parallels the finding that smaller doses given weekly are less deleterious than standard doses given every three weeks.[12,49,50] Doxorubicin cardiomyopathy appears to be related to the length of the infusion as a 96-hour infusion was less cardiotoxic than a 24- to 48-hour infusion.[97] With the broadened utilization of ambulatory central catheters (for example, Broviac or Hickman), this mode of administration may have practical implications in the near future.

Rahman and colleagues[98] found that positively charged liposomes retarded the uptake of doxorubicin entrapped in cardiac tissue in mice. In addition, myocytic and myofibrillar structures were well preserved, as compared with controls, and antitumor activity was not altered. These same investigators have more recently extended their findings to a long-term study in mice.[99] Benefit, as measured by posttreatment pathologic grade, was substantial and supports enthusiasm for this idea.

Several other methods of decreasing the cardiotoxic potential of doxorubicin have been studied but have produced less promising results. Included are attempted prophylaxis with digoxin,[23] verapamil,[8,79] antiinflammatory agents,[84] and carnitine, a vitamin essential for the normal oxidation of fatty acids,[100] and the complexation of doxorubicin with a specific antibody,[80] DNA[101] or dextran.[102]

In summary, a variety of methods directed at reducing the cardiotoxicity of doxorubicin have been investigated. The more promising techniques include prophylaxis with vitamin E with or without selenium, coenzyme Q_{10}, *N*-acetylcysteine or cysteamine, adenosine or razoxane and its isomer and administration of doxorubicin by continuous infusion through a central vein or entrapped within liposomes. As several of these techniques are currently undergoing human trials, there is hope that encouraging preclinical data will translate into new clinical methods, allowing greater usage of this important class of antineoplastic drugs.

At a more basic level, the chemical synthesis of doxorubicin analogues that have a greater therapeutic-to-toxic ratio is an avenue continually being pursued. Such a compound—that is, with similar antitumor activity and spectrum as doxorubicin, but lacking or possessing significantly less cardiotoxicity than the parent compound—would be of great use. Although it is not the intent of this paper to review analogue synthesis, a brief discussion of this area follows.

As has previously been mentioned, several good animal models exist for the assessment of anthracycline-induced cardiotoxic reaction, including rabbits, rats and mice. Several investigators have quantified the cardiotoxic potential of various anthracyclines relative to that of doxorubicin using these model systems. Only the mouse model, however, has been shown to be a valid indicator of the therapeutic potential for the anthracyclines. Thus, for a study to fully assess the relative benefit of a novel anthracycline agent as compared with doxorubicin, the dose requirement for a specific tumor cell kill and for specific histopathologic changes in the myocardium due to the agent in question and to doxorubicin must be compared in mice. Unfortunately, very few studies to date have achieved this. This may be due primarily to historical reasons as the rat and rabbit models of cardiotoxic effects were the first to be widely used. As has been discussed, however, mice provide a similarly good model and allow for simultaneous quantification of tumoricidal activity. As an example of the inappropriate use of animal models, mitoxantrone hydrochloride (dihydroxyanthracenedione), which was found devoid of cardiotoxic potential in dogs and monkeys in preclinical trials, was recently shown to be associated with congestive heart failure in 4 of 31 patients treated for breast cancer.[103]

Summary

The usefulness of doxorubicin in the treatment of a variety of malignant disorders is limited by a chronic cardiomyopathy, a frequently fatal toxic reaction that affects 2% to 7% of those given the drug. The cardiomyopathy, which assumes the clinical appearance of a biventricular congestive heart failure, most frequently occurs one to six weeks after the last dose of the drug is administered. Prognosis has been exceptionally poor in the past, with death rates of up to 79% reported, but as the entity is more fully appreciated early treatment can lead to patient recovery. The pathologic change begins well before clinical symptoms. Following discontinuation of therapy, a degree of left ventricular dysfunction apparently persists for years. The pathologic changes of the cardiac lesions are of two major types—myofibrillar drop-out and vacuolar degeneration, with subsequent mitochondrial degeneration. A number of risk factors for doxorubicin cardiomyopathy have been suggested. The most significant is total dose, with the incidence of cardiomyopathy increasing dramatically above 500 mg per sq m. Preexisting cardiac disease and age over 70 years are major risk factors. Other potential risks include mediastinal irradiation, prior cyclophosphamide therapy and, less likely, other drugs, especially mitomycin. Many noninvasive tests are available to monitor for subclinical toxic reaction. Although it is a controversial area, the most promising measurement appears to be the ejection fraction, obtained by two-dimensional echocardiography or radionuclide angiography. Invasively, endomyocardial biopsies may be done and appear to be the best predictor. Among the postulated mechanisms of doxorubicin cardiomyopathy, the most promising include radical formation with lipid peroxidation, depletion of cardiac reduced glutathione, inhibition of cardiac coenzyme Q_{10} and a decrease in cardiac adenylate charge. Finally, a number of measures to protect against cardiomyopathy have been investigated. Of these, the most encouraging are concurrent administration of vitamin E, coenzyme Q_{10}, *N*-acetylcysteine, cysteamine, razoxane (ICRF 159) and its isomer, ICRF 187, and administration of doxorubicin by continuous intravenous infusion or within liposomal carriers. As a

greater understanding of the mechanism of doxorubicin cardiomyopathy unfolds and clinicians utilize noninvasive monitoring, hope exists for reducing the incidence of the crippling toxic effects and for increasing the use of this potentially life-saving chemotherapeutic agent in those patients who need it.

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