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Monitoring Cardiac Function in Patients Receiving Doxorubicin

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Despite its well-known cardiotoxicity, doxorubicin continues to be an effective and widely used antineoplastic agent. Many efforts have focused on understanding the mechanism of doxorubicin-induced cardiotoxicity and on preventing it completely. Currently protective agents, eg, liposomal doxorubicin formulation, which results in less myocardial uptake, and the use of dexrazoxane, an intracellular iron chelator reducing the formation of radical complexes, have shown evidence of reducing incidences of cardiotoxicity at high dose of doxorubicin. However, they have not been able to completely eliminate cardiotoxicity. Therefore, it is crucial that careful monitoring to identify those patients who are at risk of developing unpredictable and sometimes-irreversible cardiac dysfunction is conducted while allowing other patients who respond to doxorubicin-containing therapy to receive their maximal therapeutic dose. Serial measurement of left ventricular ejection fraction by radionuclide angiocardiography remains a useful and widely adopted modality in monitoring patients that are receiving doxorubicin. Efforts are continuing on finding a more sensitive and reliable predictor of eventual clinical cardiac dysfunction.
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Doxorubicin is classified as an anthracycline antibiotic. Doxorubicin also is frequently referred to by its trade name, Adriamycin. Other major anthracycline antibiotics include daunorubicin (daunomycin) and epirubicin. Doxorubicin is an effective antineoplastic agent and is widely used as one of the components in multiple-drug chemotherapy in treating Hodgkin's lymphoma, aggressive non-Hodgkin's lymphomas, acute lymphoblastic leukemia, metastatic breast carcinoma, ovarian carcinoma, lung carcinoma, and sarcoma. The cardiotoxicity of doxorubicin is well known, and many efforts have made to monitor, reduce, and prevent the development of severe chronic cardiomyopathy, which often leads to congestive heart failure and death. Daunorubicin is severely toxic, and its use has been limited to patients with myeloid leukemia. Epirubicin also cause cardiotoxicity, although it may be administered at a higher dose than doxorubicin.

There are 3 major activities of doxorubicin in its antineoplastic role: blocking DNA and RNA synthesis by inserting itself between adjacent base pairs and interacting with topoisomerase II to break the DNA double helix; altering a variety of cellular functions by binding to cell membranes; and generating superoxide ion, hydrogen peroxide, and hydroxyl radicals after the reduction from doxorubicin to semiquinone and interaction with oxygen by means of Cu (II) and Fe (III) reduction (Fig. 1).[1] Usually, tissues with abundant antioxidant enzymes, eg, superoxide dismutase (SOD), are protected. The heart generally contains low levels of those enzymes, which makes it vulnerable to free radical damage or cardiotoxicity.[1] Recent studies have shown that cells treated with doxorubicin demonstrate characteristic morphologic changes associated with apoptosis or programmed cell death.[2-4] Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

Doxorubicin-associated myocardial damage is cumulative, dose-related, progressive, and may lead to congestive heart failure. The incidence of congestive heart failure varies as the result of differences in study populations, treatment regimens, and the duration of follow-up. Von Hoff and coworkers[5] reported 3%, 7%, and 18% of patients developed clinical congestive heart failure while receiving cumulative doses of 400, 550, and 700 mg/m^2 of doxorubicin, respectively (Fig. 2). Swain and coworkers[6] showed slightly higher rate of congestive heart failure of 5%, 26% and 48% in patients who received cumulative doses of 400, 550, and 700 mg/ m^2 of doxorubicin, respectively. A cumulative dose of 450 to 500 mg/m^2 generally is considered as a dangerous dose for inducing cardiotoxicity. However, considerable variation exists in an individual's susceptibility to developing chronic cardio-

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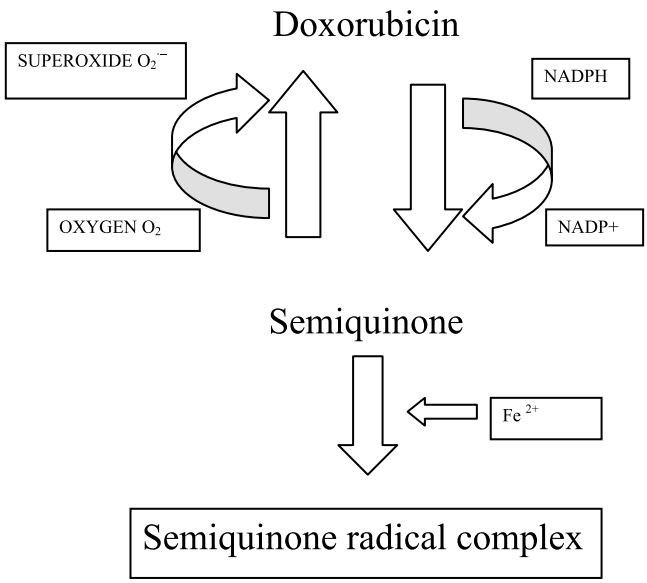

Figure 1 Schematic representation of reduction of doxorubicin and generation of free radical complex.

myopathy and congestive heart failure, and discontinuation of doxorubicin therapy prematurely using simply empiric maximal dose limits may defer those patients who may actually benefit from this powerful antineoplastic agent at higher dose. Other risk factors associated with increased doxorubicin-induced congestive heart failure also have been noted, including older age (>65 years), younger age (<4 years), exposure to radiation therapy to the chest wall, previous exposure to anthracyclines, concomitant administration of other cardiotoxic agents, for example, paclitaxel or monoclonal antibody trastuzumab, and preexisting cardiac disease or risk factors.

The congestive heart failure induced by doxorubicin usually is subclinical and may present as acute or early-onset (during therapy), chronic (within the first year), or late-onset (one year or more after completion of treatment).[7] Acute or subacute cardiotoxicity immediately after infusion is rare and usually is transient (eg, electrocardiographic abnormalities and pericarditis–myocarditis syndrome). Left ventricular dysfunction may occur but usually is reversible. The chronic cardiomyopathy induced from anthracycline can be progressive and irreversible in some patients despite maximal medical therapy, whereas other patients may present with permanent reduction in left ventricular ejection fraction (LVEF) and persistent symptoms of congestive heart failure, or others, sometimes experience gradual improvement in symptoms and LVEF after congestive heart failure therapy. Late-onset cardiotoxicity is observed most often in children and may occur up to 20 years after the completion of anthracycline therapy.[8,9] However, 27.6% of patients developed >25% decreased fractional shortening by echocardiography at a median doxorubicin dose of 300 mg/m^2 after 5 years,[10] and 59% of patients developed 25% reduction of LVEF after 3 years when administered 850 to 1000 mg/m^2 of epirubicin.[11]

Serial Measurements of Left Ventricular Systolic Function

The measurement of LVEF by echocardiography and radionuclide angiocardiography or radionuclide ventriculography has been used extensively to monitor cardiac function in patients receiving anthracyclines. Radionuclide angiocardiography is used more commonly in monitoring patients receiving doxorubicin chemotherapy, either in standard treatment regimens or in investigational regimens, because of its better reproducibility in measuring LVEF[12,13] and its proven value in reducing the incidence of congestive heart failure.[14-17] Echocardiography has been used frequently in the younger pediatric population to reduce radiation exposures and to measure structural changes and hemodynamic status.

The guidelines for using radionuclide angiocardiography in monitoring patients receiving doxorubicin originally were proposed by Schwartz and coworkers[16] and have been adopted widely. These guidelines indicate a baseline radionuclide angiocardiography and LVEF before beginning chemotherapy or before 100 mg/m^2 doxorubicin administration. Further serial follow-up studies are based on the patient cardiac function, risk factors, and doxorubicin dose. If the baseline calculated LVEF is ≤30%, doxorubicin should not be chosen as an agent for therapy; if LVEF is from >30% to <50%, follow-up RNA should be obtained before each dose and doxorubicin therapy discontinued when LVEF declines to ≥10% and/or LVEF is ≤30%; if LVEF is ≥50%, radionuclide angiocardiography should be obtained at dose of 250-300 mg/m^2, 400-450 mg/m^2 (at 400 mg/m^2 in patient with risk factors), and before each higher doses after. Doxorubicin should be discontinued if the LVEF decreases to ≥10% to a level of ≤50%. Reduction of LVEF from >15% to a final value of <45% also is a criteria predictor of congestive heart failure.[14] LVEF depression presenting as early as at a cumulative dose of 200 mg/m^2 of doxorubicin has been reported.[18] This guideline emphasizes serial measurement of LVEF by radionuclide angiocardiography to monitor cardiotoxicity during doxorubicin therapy and does not mention follow-up

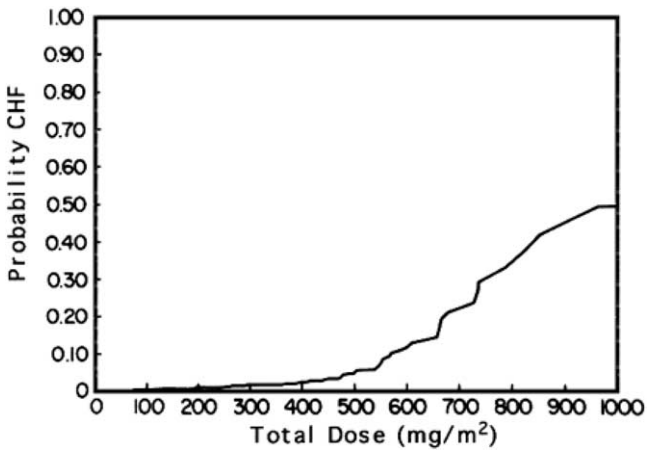

Figure 2 Cumulative probability of developing doxorubicin-induced congestive heart failure (CHF) versus total cumulative dose of doxorubicin. (Adapted from Von Hoff et al.[5])

studies in monitoring subclinical late-onset ventricular dysfunction, which have become evident now.[10,11] Guidelines for cardiac monitoring in children receiving anthracycline therapy were published in 1992 cover studies during therapy and long-term follow-up.[19] These guideline state that either echocardiography or radionuclide angiocardiography should be chosen as a consistent imaging modality for cardiac function monitoring. Baseline echocardiography and/or radionuclide angiocardiography should be obtained. Echocardiography is obtained before every other course when anthracycline is administered at <300 mg/m^2 and before every course when anthracycline is administered ≥ 300 mg/m^2 and when the patient is receiving mediastinal irradiation <1000 cGy. Radionuclide angiocardiography is added before every course when the cumulative dose of anthracycline is ≥ 300 mg/m^2 and when mediastinal irradiation >1000 cGy and before each additional course of cumulative dose ≥ 400 mg/m^2. Significant deterioration of cardiac function defined by radionuclide angiocardiography is indicated as follows: $\geq 10\%$ reduction of LVEF compared with the previous result; LVEF $<55\%$; or decreased LVEF at stress. It also suggests follow-up electrocardiography and echocardiography at 3 to 6 months and 12 months and follow-up radionuclide angiocardiography at 6 moths to 1 year. Thereafter, electrocardiography and echocardiography are obtained every 2 years, and radionuclide angiocardiography and 24 hour ECG are obtained every 5 years after completion of therapy.[19] More frequent tests are performed in patients with abnormal function at the end of therapy.

It has long been a concern that LVEF as a measurement of global systolic function of the left ventricle may not be sensitive in detecting early manifestations of myocardial damage induced by doxorubicin. Exercise radionuclide angiocardiography has been suggested to detect early subclinical ventricular dysfunction in patients at high risk.[20] However, stress exercise LVEF does not appear to significantly add to resting LVEF in assessing when to discontinue doxorubicin therapy.[21] Most patients with malignant diseases who are undergoing chemotherapy are less likely tolerate the exercise test. Diastolic function, eg, peak filling rate and time to peak filling measured by radionuclide angiocardiography, also has been proposed as an index to detect early cardiac dysfunction,[22,23] but other results published have not proven its value.[24-26] Again, left ventricular diastolic function does not appear to offer a more sensitive index than resting LVEF in monitoring doxorubicin therapy. Resting LVEF remains the most widely used method in monitoring early anthracycline-induced cardiotoxicity.

In Vivo Detection of Myocyte Damage

In-111-antimyosin binds to exposed intracellular heavy chains of myosin after myocardial cell damage and is capable of detecting early cell damage and death. It has been demonstrated to localize in damaged cells induced by doxorubicin in rats.[27] Most patients receiving doxorubicin therapy show increased cardiac uptake of In-111-antimyosin when compared with the uptake before the administration of doxorubicin, and intensive In-111-antimyosin uptake is able to identify patients at risk of developing congestive heart failure before any evidence of significantly decreased LVEF.[26,28-31] In-111-antimyosin may be a sensitive imaging technique but it appears to have lower specificity.[31] This technique is currently limited because it is time-consuming and is not generally available.

The use of radioiodine-labeled metaiodobenzylguanidine (MIBG) can demonstrate the loss of myocardial adrenergic function in patients receiving doxorubicin defined by decreased MIBG uptake and rapid wash-out compared with normal controls and is associated with fibrotic myocardium.[32-36] The role of radioiodine-labeled MIBI in monitoring doxorubicin-induced cardiotoxicity is not clear at present.

Some experimental studies have observed apoptosis in doxorubicin-treated rats (Fig. 3).[2-4] Apoptosis is a form of cell death designed to eliminate unwanted host cells through the activation of a programmed series of events. In contrast to cell death from necrosis, apoptosis does not elicit inflammation. Apoptosis happens after multiple stimuli, including radiation and cytotoxic antineoplastic agents at low doses. Morphologically, apoptotic cells are small with condensed cytoplasm and nuclei that are intensely eosinophilic on hematoxylin and eosin stains. Cytoplasmic blebs and apoptotic bodies are seen on electron microscopy. Apoptotic cells are phagocytosed by macrophages or other parenchymal cells through their expression of phosphatidylserine in the outer layers of their plasma membranes that normally localized in the inner layers. Annexin V is a protein binding to phosphatidylserine "flipped" out from inner membranes during apoptosis. Tc-99m-labeled recombinant annexin has demonstrated in vivo imaging of apoptosis in detecting early tumor response to therapy, hypoxic ischemic injury, transplant rejection, and autoimmune diseases.[37] Tc-99 m-annexin also has been used to image early apoptosis of acute doxorubicin-induced cardiotoxicity in rats.[38] Although it is in the experimental stage, using Tc-99m-annexin to detect early myocardial damage induced by doxorubicin offers a new imaging technique to overcome the limitation of radionuclide angiocardiography.

Biochemical Markers

Measurement of serial troponin has become standard clinical practice in the diagnosis of acute myocardial infarct. It is a very sensitive biomarker in detecting myocardial damage. Several studies have suggested that elevated serum levels of troponin T or I may be useful in the early detection of myocardial damage induced by doxorubicin, even before any evidence is available of LVEF changes.[39-43] More consistent results are observed in experimental studies and in children, although some reports also show no significant correlations between serum troponin levels, cumulative doses, and systolic or diastolic function defined by echocardiography in children receiving doxorubicin.[44,45] Further studies are needed to define the role of serum troponin T, especially in

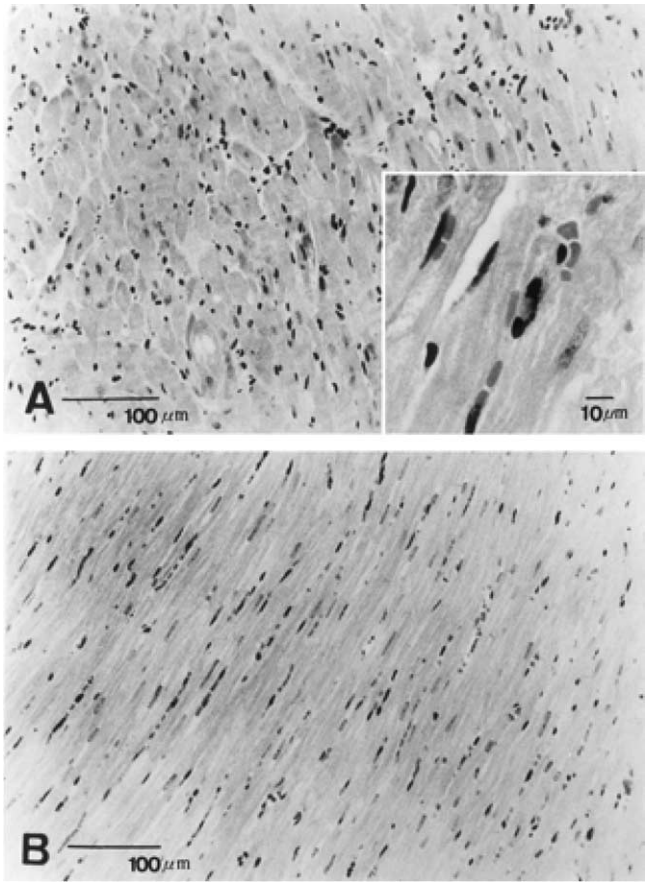

Figure 3 Hematoxylin and eosin-stained microscopic specicmen shows vacuolization and hypertrophy of the myocardium with pyknotic and fragmented nucleus (inset) in rats treated by doxorubicin (adriamycin) at week 10 (A), in contrast to the myocardium of rats treated with saline (B). (Modified and adapted from Nakamura et al.[3])

adult population, as a sensitive marker for monitoring cardiotoxicity induced by antineoplastic agents.

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are hormones that are secreted by myocytes and usually are elevated in patients with left ventricular dysfunction. BNP is an independent predictor of mortality in those patients.[46] Recent studies have shown increased BNP in patients received anthracycline therapy.[47-49] However, the elevation of BNP did not precede decreased LVEF, and no significant correlation was observed between elevated BNP and decreased LVEF.[48,49] The role of BNP in monitoring cardiotoxicity induced by antineoplastic agents is uncertain at this time.

Efforts have been made to reduce and prevent cardiotoxicity of anthracyclines by means of different delivery methods and formulation or by adding chelating agents. Liposomal anthracyclines, especially pegylated liposomal doxorubicin, and dexrazoxane seem promising,[50,51] although more consistent results of reduction in cardiotoxicity are observed in patients receiving dexrazoxane. Pegylated liposomal doxorubicin is formed by a polyethylene glycol layer surrounding the liposome-encapsulated doxorubicin and is associated with limited free doxorubicin distribution to the myocardium and less cardiotoxicity.[50] Dexrazoxane is an iron-chelating agent that prevents free radical formation by anthracyclines when given before the administration of anthracyclines. Significantly fewer incidents of cardiotoxicity and higher administered dose of doxorubicin have been observed in groups of patients received dexrazoxane when compared with control groups[51]

The evolution of more sensitive modalities in monitoring cardiotoxicity-induced by anthracyclines will no doubt continue to identify those patients who will benefit most from receiving higher dose of anthracyclines for cancer treatment, and yet will suffer the least in cardiotoxicity.

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