

Cardiac Involvement in Patients With Hematologic Malignancies

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Abstract: Authors have reviewed literature about the management of patients with cardiologic disease occurring secondary to hematologic pathology itself or its therapy, with a focus on infiltration of myocardium in acute and chronic leukemia, lymphoma, multiple myeloma, and hypereosinophilic syndrome. Moreover, they evaluated chemotherapy-associated toxicity, particularly for new drugs such as monoclonal antibody therapy, tyrosine kinase inhibitors, arsenic trioxide, bortezomib, and epigenetic therapy. In fact, cardiac toxicity may range from asymptomatic subclinical abnormalities, such as electrocardiographic changes and left ventricular ejection decline, to life-threatening events and lead to chemotherapy dose reduction and delay and, in some cases, for patients with severe side effects, discontinuation of treatment.

Finally, they discussed on the identification of early markers of cardiac injury and on cardiac stem cell therapy as a promising approach to facilitate myocardial regeneration.

Key Words: heart failure, chemotherapy, cardiac neoplasm, hematology (*J Investig Med* 2010;58: 859–874)

Cardiac failure constitutes a vital threat for a patient with cancer and often justifies an admission to intensive care. If the clinical picture can be considered similar in all respects to that of other patients, the hematologic neoplasia and its treatments often are responsible for etiological, diagnostic, prognostic, and therapeutic particularities that merit being known.

Several factors can influence cardiovascular changes in patients with hematologic malignancies, such as neoplastic cardiac infiltration, metastatic involvement of the coronary vessels, amyloidosis of myocardium, hyperviscosity syndrome, hemodynamic changes, and hypoxia. Moreover, cancer patients receiving chemotherapy have an increased risk of developing cardiovascular complications even if they have normal hearts, and the risk is greater if there is known history of heart disease. Various clinical cardiac complications that have been reported are arrhythmias, cardiomyopathy, vaso-occlusion or vasospasm resulting in angina, or myocardial infarction.

CARDIAC PARENCHYMA INFILTRATION

To assess the incidence of cardiac neoplasm at autopsy and to determine the sites of origins of metastatic cardiac neoplasm, Butany et al.¹ reviewed 11,432 consecutive autopsies. Autopsy cases involving cardiac neoplasm represented 2.33% of the total number of autopsies, and among them, 2 neoplasms were primaries, whereas 264 were metastatic in origin. Metastatic

cardiac neoplasms most frequently metastasized from the respiratory system, followed by the hematopoietic system.

Although a large number of hematologic neoplasms can infiltrate the heart, their clinical impact is usually minimal. However, different hematologic malignancies can affect the heart in a different manner. Although a neoplastic cardiac infiltration rarely can occur in patients with acute leukemia,^{2–5} it was found that 40% of patients with acute leukemia showed a hypokinetic type of circulation, with a cardiac index lower than 2.0 L/min/m². Prognostically, unfavorable factors were revealed, leukocytosis with high percentage of blasts in peripheral circulation and thrombocytopenia that are of significance in cardiovascular morbidity and mortality.^{6–9}

In patients with chronic myeloid leukemia, leukemic infiltration of the heart and pericardium is common, but clinical manifestations are unusual. In fact, myocardial infiltrates, even when marked, usually do not alter the basic architecture of the myocardium. Changes reported with heavy leukemic infiltration include lysis, as well as hydropic, fatty, or eosinophilic degeneration of myocardial fibers, with necrosis an unusual finding.^{10–14}

Leukemic infiltrates also were rarely found in the endocardial scar tissue, myocardium, and coronary arteries of patients with chronic lymphocytic leukemia, sometimes with a picture of endocardial fibroelastosis.^{15–18}

Cardiac involvement in malignant lymphoma is one of the least investigated subjects in oncology. Primary cardiac lymphomas are not frequent. Gross tumor formation in any of the cardiac chambers is rare, particularly at the time of presentation and diagnosis of lymphoma.

Primary cardiac lymphoma is typically of a non-Hodgkin type and involves only the heart and pericardium with no or minimal evidence of extracardiac involvement.^{19–21}

Symptoms are usually very subtle and nonspecific, particularly in the setting of coexisting comorbidities. Authors have described primary cardiac lymphomas presenting with pericardial effusion, arrhythmias, and heart failure.^{22,23}

Although echocardiography is known to be a sensitive method for the diagnosis of cardiac involvement in patients with lymphoma, cardiac lymphomas often mimic other cardiac neoplasms, including myxomas and angiosarcomas, and often require multimodality cardiac imaging, in combination with endomyocardial biopsy, excisional biopsy, or pericardial fluid cytology, to establish a definitive diagnosis.^{24,25}

Cardiac metastases are found in 20% to 25% of patients with lymphoma, whereas studies by Roberts et al.²⁶ and Cains et al.²⁷ reported that 9% of all cardiac tumors are related to lymphoma.

The pattern of cardiac involvement varies with different types of lymphoma, suggesting that different pathological types of lymphoma may have different mechanisms of metastasis to the heart. Diffused myocardial infiltration documented by echocardiography has rarely been described as a presenting feature of this condition, but it is commonly found postmortem.

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Lymphomas involve the pericardium mostly via lymphatic or hematogenous metastasis. This type of pericardial involvement generally results in pericardial effusion as a consequence of the obstruction of the venous and lymphatic flows of pericardial fluid. Although most cases are clinically silent, effusions can impair cardiac function. In severe cases, it can even lead to pericardial tamponade, which is a life-threatening condition.^{28–39}

Heart failure in patients with multiple myeloma has been attributed to metastatic involvement of the heart, amyloidosis of myocardium, hyperviscosity syndrome, or coexisting coronary artery disease.^{40–43}

Myelomatous involvement of the heart at autopsy varied from extensive myocardial and pericardial infiltration of plasma cells to isolated involvement of the epicardial fat,^{44,45} whereas extramedullary plasmacytoma of the heart is extremely rare. Keung et al.⁴⁶ reviewed the literature and found 9 cases involving the heart followed by a report of a case presenting as a cardiac emergency that required surgical intervention. Metastatic involvement of the coronary vessels is reported even less often. Champeaux et al.⁴⁷ report only a case of metastatic plasmacytoma to the myocardium and coronary vessels in a 57-year-old man with multiple myeloma.

Bessmel'tsev and Abdulkadyrov⁴⁸ and Bessmel'tsev⁴⁹ carried out an echocardiographic study on patients with multiple myeloma. Disorders of the contractile and pumping function of the left ventricle myocardium and changes of the central hemodynamic were revealed. It was shown that at stage I, the main functions of the heart are maintained because of myocardial hypertrophy. In progression of the disease, development of chronic renal failure, and concomitant pathology of the cardiovascular system, the contractile function of the myocardium is essentially reduced, and the left ventricle and left atrium are dilated.^{48–50}

However, another mechanism that received less attention is myeloma-induced high-output failure. This typically presents in patients with extensive bony involvement, and the diagnosis is supported by physical examination findings, echocardiography, and cardiac catheterization. In these patients, traditional heart failure therapies, such as beta blockers, angiotensin-converting enzyme inhibitors, and diuretics, are not useful and may be detrimental. As with other causes of high-output failure, the treatment is to correct the underlying cause of the high-output state.

The pathophysiology behind myeloma-induced high-output failure is not entirely understood, but hypotheses include increased splenic flow due to splenomegaly and a plasma cell produced cytokine-mediated process (interleukin [IL] 2, IL-6, and gamma interferon).^{51,52} There is literature that supports the high-output state being secondary to innumerable intramedullary arteriovenous fistulas.^{53,54}

Restrictive cardiomyopathy from amyloid deposition in the myocardium is a well-described complication of multiple myeloma.⁵⁵ However, cardiac amyloidosis should be considered in any patient presenting with congestive heart failure (CHF), preserved systolic function, and a discrepancy between a low QRS voltage on electrocardiography and an apparent left ventricular hypertrophy on sonogram.

Congestive heart failure in cardiac amyloidosis has been attributed to the development of diastolic dysfunction because severe CHF symptoms have been observed despite a normal or only mildly reduced left ventricular ejection fraction (LVEF). However, the pattern of left ventricular diastolic dysfunction changes during the course of amyloidosis, and the classically described restrictive physiology occurs only in advanced stages of the disease.⁵⁶ An early impairment of longitudinal systolic function has been described by means of tissue Doppler-derived myocardial deformation imaging ("strain rate imaging").^{57–59}

Clinical manifestations of heart involvement are variables, and they can range from CHF to arrhythmias and conduction disorders; myocardial infarction also has been reported.^{60–62}

Cardiac magnetic resonance imaging and measurement of B-type natriuretic peptide are particularly helpful in distinguishing restrictive cardiomyopathy from constrictive pericarditis.⁶³

Although standard treatment options for CHF may provide symptomatic relief in cardiac amyloidosis, prognosis remains dismal. Judicious diuretic use remains the mainstay of therapy, but achieving optimal fluid balance is difficult because patients are usually "preload dependent." Angiotensin-converting enzyme inhibitors in low doses often are helpful but may lead to orthostatic hypotension, particularly in patients who also have involvement of the autonomic nervous system. Beta blockers may be useful if given relatively early in the disease process but should be used with caution in patients with advanced disease because they may exacerbate symptoms. Therapy aimed at the underlying disease process in primary systemic amyloidosis is based on treatment regimens used in multiple myeloma, such as melphalan and prednisone. These offer limited benefit when cardiac involvement is significant, but newer treatments, including the 4'-iodo-4'-deoxydoxorubicin, potentially combined with autologous stem cell transplantation, offer some hope for the future.⁶⁴ If this is the case, pharmacotherapy with the ability to inhibit angiogenesis is an intriguing therapeutic option. Lenalidomide and thalidomide, both of which are acceptable therapies for multiple myeloma, have these pharmacological properties.⁶⁵

Hypereosinophilic syndrome (HES) is defined as prolonged, unexplained peripheral eosinophilia in a patient presenting with evidence of end-organ damage.

The prevalence of HES is unknown, although a rate of 1 case per 200,000 people has been postulated. The disease is more common in men and tends to occur between the ages of 20 and 50 years. Various organs may be involved, but those most commonly affected are the brain, skin, and lungs. The heart is frequently involved, resulting in eosinophilic endomyocardial disease (EED) and restrictive cardiomyopathy. The mortality rate is high because of progressive heart failure, ventricular arrhythmias, or thromboembolic events originating from intraventricular thrombus.⁶⁶

Myeloproliferative variants are associated with a high prevalence of cardiac involvement, which is very unusual in lymphocytic variants.

The mechanism of tissue damage has not been delineated, although the cytotoxic effects of protein produced by eosinophils are important. In patients with HES, circulating eosinophils have structural and functional abnormalities, and many of them are degranulated. Sequestration of eosinophils in the endocardium and in other organ tissues occurs by unknown mechanisms. Eosinophil-derived neurotoxin, eosinophil cationic protein, and major basic protein are enzymes released by eosinophils that can cause endothelial damage and promote thrombosis.

Disruption of the normal endothelial lining exposes von Willebrand factor, collagen, and tissue factor (TF); the stimulation of fibrin formation by TF may be important because eosinophils contain TF in their specific granules, and they can induce endothelium to express it. Secreted eosinophil proteins also may modify the anticoagulant properties of the endothelium membrane by binding to thrombomodulin, and they also can activate factor XII. Thrombus formed on denuded endocardium is replaced by fibrosis.⁶⁷

Moreover, a terminal deoxynucleotidyl transferase assay revealed apoptosis in several cardiomyocytes and vascular cells mainly in the myocardial areas with higher eosinophil density.⁶⁸

The most characteristic cardiovascular abnormalities in HES are endomyocardial fibrosis (Davies disease) and eosinophilic endocarditis (Loeffler "SQ" endocarditis).⁶⁹

Three different stages in EED have been described. The first stage is the necrotic stage, with microabscesses of the endocardium. The second stage, or thrombotic, is characterized by the formation of thrombi along the damage of the ventricles and atria. Thrombi also may form on the atrioventricular valve leaflets. The third stage is fibrotic, with fibrotic thickening of the endocardium.⁷⁰

Echocardiographic assessment, magnetic resonance imaging, and endomyocardial biopsy are used in diagnosing EED.⁷¹⁻⁷³

The differential diagnosis of cardiac disease with hyper-eosinophilia includes HES, Churg-Strauss syndrome, early giant myocarditis, hypersensitivity reactions, parasitic infection, Loeffler endomyocardial fibrosis, and malignancy.⁷⁴⁻⁷⁸

Various treatments have been proposed, with glucocorticoids generally accepted as being first-line therapy. Alternative therapies include vincristine, alkylating agents, etoposide, interferon alpha, anti-IL-5, and imatinib mesylate. After the fibrotic stage of EED occurred, surgical resection may offer palliation of symptoms.⁷⁵

However, all patients should be screened by fluorescence in situ hybridization or polymerase chain reaction for the FIP1L1-PDGFR mutation because imatinib is the treatment of choice for patients with this mutation.⁷⁹

Korczyk et al.⁸⁰ reported a case of a patient with endomyocardial fibrosis due to HES who underwent orthotopic heart transplantation.

Erdheim-Chester disease is a rare non-Langerhans form of histiocytosis, characterized by the xanthomatous infiltration of tissue with foamy CD68+/CD1a histiocytes. Cardiac involvement in Erdheim-Chester disease is quite frequent. Haroche et al.⁸¹ analyzed 72 patients and found pericardial infiltration, myocardial infiltration, right atrial tumors, symptomatic valvular heart disease, heart failure, myocardial infarction, and periaortic fibrosis. Among the 58 patients with available follow-up, 35 died. Death was due to the cardiovascular involvement in 31% of the cases.

CHEMOTHERAPY-INDUCED CARDIAC TOXICITY

The myocardium is formed by cells with limited regenerative ability, and thus, if injured, it shows permanent dysfunction. Chemotherapy is used in several hematologic malignancies, but its use may be hampered by induced cardiac toxicity. This can lead to heart failure and worsening of the patient's quality of life or death. Cardiac toxicity may, in fact, range from asymptomatic subclinical abnormalities, such as electrocardiographic changes and left ventricular ejection decline, to life-threatening events.

Drug-induced cardiotoxicity leads to chemotherapy dose reduction, delay, and in some cases, discontinuation of treatment.

Chronic cardiotoxicity after chemotherapy usually manifests as congestive heart failure, cardiomyopathy, and pericarditis, but it can result in the alteration of cardiac rhythm, changes in blood pressure, and ischemia.⁸²

Several anticancer drugs can induce cardiac and cardiovascular toxicity.

Anthracycline-Induced Cardiotoxicity

The best studied drugs able to induce cardiotoxicity are probably the anthracyclines.

Anthracyclines are a group of antibiotics that are among the most active chemotherapeutic agents and are effective

against several malignancies including both hematologic and solid tumors, such as lymphoma, gastric cancer, sarcoma, and breast cancer.⁸³

Doxorubicin and daunorubicin can induce late-onset cardiomyopathy with a dilated, thin-walled left ventricle. In different studies, the frequency of anthracycline-related CHF ranged from 0% to 16%,⁸⁴ but the incidence of cardiomyopathy, which is dose dependent, may exceed 30% in patients who received more than 600 mg/m² of anthracycline. Moreover, Kremer et al.⁸⁵ evaluated the cumulative incidence of anthracycline-induced clinical heart failure in a cohort of 607 children who had been treated with anthracyclines (37 children received only daunorubicin, 352 children received only doxorubicin, 95 children received only epirubicin, and 118 children received a combination of doxorubicin, daunorubicin, and epirubicin). A cumulative anthracycline dose in excess of 300 mg/m² has been associated with a risk of clinical heart failure of 5% after 15 years.

The risk for cardiotoxicity in anthracycline-exposed patients can be increased by hypertension; cardiac abnormalities; exposure to other drugs, such as cyclophosphamide, dactinomycin, vincristine, bleomycin, methotrexate, mytomyacin C, and dacarbazine; mediastinal irradiation; electrolyte imbalance; sex; and age.⁸⁶⁻⁹³

Early morphological changes after anthracycline therapy include vacuolization and myofibrillar loss of myocytes caused by dilatation of the sarcoplasmic reticulum. The mechanism of doxorubicin-induced myocardial damage is not exactly known but is believed to involve production of free radicals that induce peroxidation of myocyte membranes and subsequent influx of intracellular calcium.⁹⁴ Oxidative stress is in fact generally held as the mediating mechanism leading to Adriamycin (ADR) cardiotoxicity, by tissue-specific mitochondrial DNA damage, redox-mediated superoxide radical production, and disturbance of calcium or iron homeostasis.⁹⁵⁻⁹⁹

Adriamycin, in fact, can generate a large amount of O₂ via a redox cycling reaction catalyzed by several endogenous reductases and endothelial isoform of nitric oxide synthase. One source of such oxygen reactive species generated in the myocardium and responsible for tissue damage is the formation of conventional doxorubicin-iron complexes in mitochondrial membranes that may lead to increased inner membrane permeability in heart mitochondria as a result of increasing the sensitivity of a Ca²⁺-dependent pore of the inner mitochondrial membrane to calcium, leading to dissipation of membrane potential and release of preaccumulated Ca²⁺. Mitochondrial dysfunction also may be caused by accumulation and persistence of 8-hydroxyguanosine adducts in cardiac mitochondrial DNA.

Finally, doxorubicin-induced cardiotoxicity is attributed to the degradation of doxorubicin to its toxic metabolite doxorubicinol.

The vulnerability of the heart to reactive oxygen species is further intensified by doxorubicin inhibition of reactive neutralizing enzymes.¹⁰⁰⁻¹⁰³

A subacute anthracycline cardiotoxicity also has been reported. Cardiotoxicity can be, in fact, subclinically present for years before its manifestation. The reported frequency of sub-clinical cardiotoxicity ranged from 0% to 57%. Seven years after doxorubicin therapy, echocardiographic abnormalities have been found in 23% of subjects who had received at least 228 mg/m², whereas depression of left ventricular contractility was present in 57% of patients.¹⁰⁴ Epirubicin also is associated with cardiotoxicity but, on a mg/mg basis, is less cardiotoxic than doxorubicin and can therefore be administered at higher cumulative doses (up to a total of ~900 mg/m² vs a total of 450 mg/m² for doxorubicin before cardiotoxicity limits further therapy).

However, to achieve the same clinical benefit as doxorubicin, epirubicin tends to be given at 25% to 50% higher doses, which potentially negates the advantages of any higher cumulative dose threshold.

Regimens of combination chemotherapy that includes newer agents, such as trastuzumab or cisplatin, augment the cardiotoxicity of anthracyclines.¹⁰⁵ However, Daosukho et al.¹⁰⁶ pointed out that phenylbutyrate, a histone deacetylase inhibitor, protects against ADR-induced cardiac injury, decreasing cardiac mitochondrial and total cellular damages by approximately 75% and 70%, respectively. Moreover, phenylbutyrate decreased the ADR-associated elevation of serum lactate dehydrogenase (LDH) and creatine kinase activities.¹⁰⁷

Doxorubicin-induced cardiotoxicity could be prevented by continuous infusion of the drugs,¹⁰⁸⁻¹¹⁰ although these data are not confirmed by other studies.¹¹¹ Although not all oncologists agree, the use of liposome-type anthracycline derivatives for patients with risk factors for cardiovascular morbidity (such as age, sex, obesity, and physical inactivity) or with risk factors for cardiotoxicity from antineoplastic drugs (such as preexisting cardiac dysfunction, long-standing hypertension, and intercurrent cardiotoxic therapies) has been recommended.¹¹²

Clinical trials of dexrazoxane (a drug that remove iron from anthracyclines) have investigated the action of this molecule as cardioprotectant.¹¹³ This agent, in fact, is an iron chelator that strips iron from the anthracycline-iron complex, thereby preventing free radical formation in cardiac tissue. Patients treated with doxorubicin alone had elevated troponin T levels than those who received dexrazoxane.¹¹⁴⁻¹¹⁷

Cisplatin-Induced Cardiotoxicity

Cisplatin is a potent chemotherapeutic agent with a broad-spectrum antineoplastic activity against various types of tumors. However, a major factor limiting the treatment with cisplatin is the acute and cumulative cardiotoxicity. This includes atrial fibrillation, supraventricular tachycardia, left bundle-branch block, and myocardial infarction.

The possible mechanisms of cisplatin-induced cardiotoxicity are mainly alteration in oxidant/antioxidant balance.¹¹⁸ Thus, antioxidative agents could provide possible approaches to reduce toxicity induced from the clinical use of cisplatin. Wang et al.¹¹⁹ showed that cisplatin led to cardiac function deterioration, myocardial injury, increased LDH, creatine kinase, malondialdehyde activities, and decreased activities of superoxide dismutase, glutathione, glutathione peroxidase, and catalase. Treatment with resveratrol, a polyphenolic phytoalexin that has been shown to have cardioprotective properties, partly because of its antioxidant, antiapoptotic, and antiarrhythmic effects, effectively hindered the adverse effects of cisplatin in a dose-dependent manner, such as myocardial injury and impaired heart function via the suppression of oxidative stress.

In an animal model, cisplatin-treated mice developed myocardial contractile dysfunction evidenced by reduction in left ventricular developed pressure and the first derivative of left ventricular developed pressure (\pm dP/dt). Cisplatin treatment significantly prolonged time-to-90% relengthening, depressed peak shortening, maximal velocity of shortening/relengthening, and augmented negative staircase in myocyte peak shortening frequency response. The cisplatin-induced cardiac dysfunction was associated with mitochondrial membrane depolarization. Transmission electron microscopy analysis revealed that cisplatin induces ultrastructural abnormalities of the mitochondria. Moreover, with cisplatin treatment, cardiomyocytes show activation of endoplasmic reticulum (ER) stress response and

increase caspase-3 activity and terminal deoxynucleotidyl transferase dUTP nick end labeling staining.¹²⁰

Tyrosine Kinase Inhibitors–Induced Cardiotoxicity

Although tyrosine kinase inhibitors (TKIs) overall seem to be a very tolerate drug class, possible long-term cardiac toxicity with CHF is under debate in patients receiving this kind of drugs.¹²¹

Imatinib mesylate is a drug approved in 2002 as first-line treatment in patients with chronic myelogenous leukemia (CML) and gastrointestinal stromal tumor. It is a competitive inhibitor that inhibits the BCR-ABL tyrosine kinase fusion protein.

Several studies have reported that imatinib use may be associated with CHF.

Kerkela et al.¹²² described 8 patients who presented with severe CHF while receiving imatinib therapy.^{123,124} They found that imatinib has deleterious effects on cardiomyocytes in culture. The triggering mechanism could be activation of the ER stress response, also known as the unfolded protein response, a response that protects cells by shutting down general protein translation while upregulating the expression of protein stress response genes. However, if ER is prolonged, prodeath pathways are activated, leading to profound alterations of mitochondrial function and to cardiomyocytes death. They performed myocardial biopsies on patients who developed significant left ventricular dysfunction during their course of therapy with imatinib. Transmission electron micrographs of biopsies showed prominent membrane whorls in the myocytes, whereas other abnormalities included pleomorphic mitochondria with effaced cristae and scattered cytosolic lipid droplets and vacuoles. Moreover, glycogen accumulation in cardiomyocytes was noted. Imatinib did not cause apoptosis in cardiomyocytes in vitro. However, although in vivo administration of imatinib did not cause overt cardiac failure, it did result in inhibition of the protein kinases Akt and Erk 1/2, both of which have been shown to play a cardioprotective role in the setting of vascular stress.^{125,126}

Although specific recent reports indicated a low incidence of New York Heart Association (NYHA) class III-IV heart failure due to imatinib, varying from 0.2% to 1.8%,^{127,128} lower NYHA class, as well as subclinical cardiotoxicity, may be more frequently observed in patients treated with imatinib.¹²⁹ Atallah et al.¹³⁰ reviewed more than 1200 CML patients treated with imatinib and reported the presence of CHF in 1.7% of patients.

Perik et al.,¹³¹ however, pointed out that, in patients with gastrointestinal stromal tumor, imatinib treatment was not associated with an increase in plasma N-terminal pro B-type natriuretic peptide and cardiac troponin, indicating that the risk of subclinical cardiac toxicity is limited with the use of this agent.

As regard other TKI, recent concern over cardiac toxicity has arisen. Orphanos et al.¹³² found that cardiac toxicity can be caused by the TKI dasatinib, nilotinib, sunitinib, sorafenib, and lapatinib, whereas gefitinib and erlotinib have not been related to toxic effect on the heart.

Sofarenib, a multitargeted TKI inhibiting KIT, VEGF, PDGFR, and RAF kinase family has been associated with cardiac ischemic/infarct events in as many as 2.9% of patients.¹³³

It has been suggested that inhibition of the intended target RAF1 could interfere with cardiac survival and apoptotic pathways through interaction with MEK and possible interactions with ASK1 and MST2, leading to BAX-mediated mitochondrial cytochrome c release and cell death.

Will et al.¹³⁴ examined the effects of the TKI drugs dasatinib, sunitinib, and sorafenib on adenosine triphosphate (ATP) content in H9c2 cells. According to their results, of the

4 kinase inhibitors examined, only sorafenib directly impaired mitochondrial function at clinically relevant concentrations, potentially contributing to the cytotoxic effect of the drug.¹³⁵

Effects on cardiac function have also been associated with sunitinib, a multitargeted tyrosine kinase inhibitor inhibiting KIT, fms-like tyrosine kinase, VEGFR, PDGFR, CSF, and glial cell-derived neurotrophic factor, which has been associated with increases in patients with LVEFs below the lower limit of normal leading to CHF in some cases. Sunitinib inhibition of AMPK is thought to lead to ATP depletion, whereas RSK inhibition could lead to activation of bcl-2-associated death promoter-induced mitochondrial cytochrome c release. In addition, it is possible that a direct interaction of sunitinib with the mitochondria may lead to cell death.^{136–138}

Tyrosine kinase cardiac toxicity could be further increased during conditioning therapy received before a myeloablative allo-hemopoietic stem cell transplantation,¹³⁹ although Burke et al.¹⁴⁰ pointed out that imatinib use in either pre- or post-allogeneic hematopoietic cell transplantation does not increase cardiac toxicity in patients with CML.

It is not known if regimens of combination chemotherapy that include newer agents can augment the cardiotoxicity of TKi; however, in 2 CML murine models, low-dose imatinib in combination with bortezomib did not cause cardiotoxicity.¹⁴¹

Finally, Fernandez¹⁴² presented an approach using structure-based rational drug design and medicinal chemistry to reengineer imatinib to retain its anticancer activity but without the risks of cardiotoxicity. This compound, named WBZ_4, was designed to retain binding to KIT ATP-binding pockets, not to bind ABL, and to bind and inhibit c-Jun N-terminal kinase for the purpose of increased cardioprotection.

Arsenic Trioxide-Induced Cardiotoxicity

Arsenic trioxide is highly effective in the treatment of acute promyelocytic leukemia. Unfortunately, the clinical usefulness of arsenic trioxide (ATO) has been limited by its toxicity. Cardiac toxicity includes QT prolongation, torsades de pointes, and sudden cardiac death.¹⁴³

In a mouse model, analysis of myocardial function revealed that arsenic causes a significant decrease in the maximum rate of rise in intraventricular pressure during ventricular contraction and significant increases in the end diastolic pressure and ventricle minimum diastolic pressure. The functional alterations were accompanied by cardiomyopathy.¹⁴⁴

Cardiac tissue of rats treated with arsenic showed significant increases in serum creatine kinase isoenzyme, glutathione peroxidase, LDH, and aspartate aminotransferase activity levels. Moreover, cardiac tissue of rats treated with arsenic showed significant increases in levels of reduced glutathione content, GPx activity, malondialdehyde, and total nitrate/nitrite.¹⁴⁵

The possible mechanisms of arsenic trioxide-induced cardiotoxicity are, in fact, mainly alteration in DNA repair and methylation, generation of reactive oxygen species, changes in cardiac ion channels, and apoptosis. Arsenic trioxide-induced cardiotoxicity is mediated at least in part, by activation of caspase-3 pathway, which may be triggered by reactive oxygen species formation and intracellular Ca(2+) overload.¹⁴⁶

Westerveldt et al.¹⁴⁷ reported cardiac side effects occurring during treatment, especially in young African Americans, despite weekly monitoring of the QTc interval. Patel et al.¹⁴⁸ reported arrhythmias in 5% of patients. The precise mechanism leading to African Americans' increased susceptibility to ATO-induced cardiac arrhythmias is unknown; however, numerous highly polymorphic candidate genes involved in arsenic metabolism are known, and methylenetetrahydrofolate reductase,

human purine nucleoside phosphorylase, and human glutathione-S-transferase omega 1-1 (hGSTO1-1) have a specific set of polymorphisms in African Americans versus other populations.

Several studies suggest that ATO has a direct effect on cardiac repolarization. Patients who are receiving ATO should avoid concomitant administration of other QT-prolonging agents or conditions in favor of delaying cardiac repolarization.¹⁴⁹

The prolonged QTc and spatial heterogeneity are responsible for the As(2)O(3)-induced ventricular tachyarrhythmias. In addition to prolongation of the action potential duration, cellular Ca(2+) overload and lipid peroxidation might contribute to the electrophysiological abnormalities caused by ATO.¹⁵⁰

Moreover, ATO exposure caused alteration in mitochondrial integrity, generation of reactive oxygen species, and apoptosis in cardiac cells in dose- and duration-dependent manner. There was no DNA fragmentation. Results show that ATO causes apoptosis in cardiomyocytes by generation of reactive oxygen species and the induction of calcium overload.¹⁵¹

In any case, it seems that electrolyte imbalance (hypomagnesemia and hypokalemia) can cause amplification of ATO toxicity.¹⁵²

Finally, Zhao et al.¹⁵³ reported that resveratrol reduced arsenic-induced QT interval prolongation and cardiomyocyte injury (apoptosis, myofibrillar loss, and vacuolization).

Bortezomib-Induced Cardiotoxicity

Bortezomib is a cytotoxic agent that inhibits the 26S proteasome, a complex involved in intracellular protein breakdown in mammals. It is able to impair the activation of nuclear factor (NF)-κB, blocking the degradation of inhibitory κB, which is required for NF-κB translocation into the nucleus and activation of target genes. Bortezomib is mainly used for the treatment of multiple myeloma. Animal studies indicated a possible risk of cardiotoxicity, and cases of cardiac arrhythmias and conduction disorders were observed in clinical trials.¹⁵⁴

In multiple myeloma patients treated with bortezomib, Orciuolo et al.¹⁵⁵ noticed an unexpected increase of cardiac complications, ranging from heart failure to arrhythmias.

The presence of a reduced proteasome activity is associated with an increased rate of apoptosis in smooth muscle cells, determining atherosclerotic plaque instability. Bortezomib may cause atherosclerotic plaque progression and tendency to rupture and facilitate ischemic heart complications by reducing myocardial preconditioning.

Marfella et al.¹⁵⁶ evaluated the role of ubiquitin-proteasome system, NF-κB, and tumor necrosis factor α in the cardiac tissue injury of acute ischemia/reperfusion in streptozotocin-hyperglycemic rats and elucidated whether an intervention on UPS with bortezomib, an inhibitor of UPS, may counteract the extensive myocardial infarction and increased inflammatory reaction into the hyperglycemic myocardium. They found that lesions from hyperglycemic rats treated with bortezomib showed low levels of ubiquitin-proteasome activity, inflammation, and myocardial damage.

Monoclonal Antibody Therapy-Induced Cardiotoxicity

Cervera Grau et al.¹⁵⁷ reported a complete atrioventricular block secondary to treatment with rituximab, a monoclonal antibody that targets the CD20 antigen. However, although both cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP) and R-CHOP cause diastolic dysfunction in the early period after their administration, the addition of rituximab to CHOP chemotherapy does not significantly increase the risk of doxorubicin-induced cardiotoxicity during this period.¹⁵⁸

Alemtuzumab is a humanized monoclonal antibody that targets the CD52 antigen, which is present on the cell membrane of most T and B lymphocytes. The drug has been approved for treatment of fludarabine-refractory chronic lymphocytic leukemia and has been used in the treatment of T lymphoproliferative malignancies, as Sezary syndrome.¹⁵⁹ Although rarely, cardiac events may occur in patients treated with alemtuzumab and may necessitate discontinuation of the therapy.^{160,161}

The association between cardiac events, alemtuzumab, and hematologic malignancies (especially T-cell diseases) may be explained by a cytokine-release syndrome, defined as an increased level of serum tumor necrosis factor α , interferon γ , and IL-6 after alemtuzumab infusion.^{162,163} The drug may activate or kill T cells that secrete these cytokines, leading to coronary vasospasm and potentially cytomegalovirus-related myocarditis.

However, alemtuzumab could target the heart directly. Although there is no evidence that CD52 is expressed on cardiac myocytes, alemtuzumab could kill T cells that infiltrate the heart, causing electrical disturbance or myocyte dysfunction.¹⁶⁴

Cardiac Toxicity Due to Conditioning Regimen

Administration of preparative regimen and hemopoietic stem cell transplantation in most acute leukemia patients is associated with acute neurohumoral activation. Persistent N-terminal pro-B-type natriuretic peptide (BNP) elevations, in 63.2% of patients, indicate subclinical cardiotoxicity and risk for development of heart failure. More pronounced N-terminal proBNP elevations in patients with preparative regimen containing combination of high-dose (HD) cyclophosphamide (CY) and total body irradiation confirm that these therapeutic procedures seem to be more cardiotoxic and not very appropriate for patients with cumulation of risk factors for cardiac toxicity from antineoplastic drugs.¹⁶⁵

The use of HD CY in the conditioning regimens has been considered to be the main cause of cardiac toxicity of HD therapy protocols. This toxicity may present clinically as myocarditis, CHF, and even sudden death.^{166,167} These complications most often occur within a few weeks after HD CY, but they may be detectable already a few days after the treatment.^{168,169}

Kuittinen et al.¹⁷⁰ showed that HD CY resulted in very acute cardiac toxicity characterized by enlargement of the heart chambers in a patient with non-Hodgkin lymphoma previously treated with anthracyclines. This toxicity can be detected with increased concentrations of circulating natriuretic peptides but not with LVEF measurement.

The pathophysiology of HD CY-associated cardiac toxicity is due to toxic endothelial damage followed by extravasation of toxic metabolites with resultant myocyte damage and interstitial hemorrhage and edema. HD CY-associated cardiotoxicity occurs during or soon after (within 3 weeks) administration. It is manifested as acute or subacute onset of CHF with pulmonary congestion, weight gain, and oliguria. Pericardial effusion, in some cases with cardiac tamponade, may be the only manifestation of cardiac toxicity.¹⁷¹

Although previous papers reported an incidence up to 43%, in recent years, the percentage of patients receiving single-agent HD CY up to 7g/m² or 200mg/kg experiencing cardiotoxicity has diminished to nearly zero with the adoption of multifractionated schedule of administration.

Administration of HD cytarabine has been associated with both cardiac arrhythmias and pericarditis.¹⁷² The highest incidence and severity of cardiac toxicity was reported when CY and cytarabine were coadministered.^{173,174}

Mitoxantrone, an anthracenedion derivative, has been synthesized in an attempt to develop an agent that has a reliable

anticancer activity without the compromising cardiotoxic effects.¹⁷⁵

Human and animal studies demonstrated that the cardiotoxic effects of mitoxantrone are significantly less severe at clinically equivalent anticancer doses compared with those observed with other drugs such as anthracyclines.¹⁷⁶ In a study, the effects of mitoxantrone on the functions of the sarcoplasmic reticulum were examined in isolated muscle preparations obtained from the guinea pig heart. In electrically stimulated left atrial muscle preparations, incubation in vitro for 4 hours with 30 or 100 μ M mitoxantrone significantly prolonged the time to the peak of twitch tension, markedly increased the developed tension observed at lower stimulation frequencies, thereby attenuating the slope of positive force-frequency relationships, and increased the postrest contraction observed after a 60-second quiescent period. In myocytes isolated from ventricular muscles, 30 μ M mitoxantrone increased the peak and the size of intracellular Ca²⁺ concentrations ([Ca²⁺]_i) and prolonged the time to peak [Ca²⁺]_i. In skinned muscle fiber preparations obtained from the left ventricular muscle, 30 μ M mitoxantrone significantly increased the caffeine-induced contraction without affecting the Ca²⁺ sensitivity of contractile proteins. These results suggest that mitoxantrone enhances Ca²⁺ release from the sarcoplasmic reticulum in isolated atrial muscle preparations obtained from the guinea pig heart. Apparent enhancement of the sarcoplasmic reticulum functions, in contrast to anthracyclines that has been shown to suppress these functions, seems to explain the relative lack of marked cardiotoxicity of mitoxantrone.¹⁷⁷

In fact in vivo treatment of rats with doxorubicin results in a prolongation of the time to the peak of twitch tension, a reduction of the developed tension observed at lower stimulation frequencies and an attenuation of the postrest contraction (contraction that is evoked by the first stimulus after a brief quiescent period) observed in electrically stimulated heart muscle preparations obtained from the drug-treated animals.¹⁷⁸⁻¹⁸⁰

However, in nonhematologic patients, significant cardiotoxicity also has been reported for the association of HD CY and HD mitoxantrone. In one report, 4 of 6 patients with no preexisting cardiac disease experienced severe cardiotoxicity with 2 treatment-related deaths.^{181,182}

The alkylating agent melphalan has been used in myeloablative conditioning regimens before stem cell transplantation for diseases, such as Hodgkin disease, non-Hodgkin lymphoma, and multiple myeloma. Single-agent melphalan has not been shown to affect cardiac contractility in prospective studies, with the exception of atrial fibrillation.¹⁸³⁻¹⁸⁹

Regimens combining melphalan and fludarabine have been associated with veno-occlusive disease, but development of cardiotoxicity had not been specifically reported.^{190,191} On the other hand, fludarabine has only been rarely associated with cardiac dysfunction, with a single report of nonfatal CHF in 2 of 27 patients treated for chronic lymphocytic leukemia.¹⁹²

However, Giralt et al.¹⁹³ reported that reduced-intensity conditioning with melphalan and purine analogues was associated with the development of Beraman grade 3 to 4 cardiotoxicity in 4 of 86 patients, whereas Richtie et al.¹⁹⁴ observed the development of severe left ventricular failure in 3 of 21 patients treated with melphalan and fludarabine.

The proposed mechanism for the cardiotoxicity of nucleoside analogues is uncertain. Nucleoside analogues can undergo phosphorylation by the mitochondrial deoxyguanosine kinase resulting in impaired cellular energy metabolism.¹⁹⁵

As far the management of HD chemotherapy-associated cardiac toxicity, therapy with diuretics should be started in the

first instance. The addition of an angiotensin-converting enzyme inhibitor in case of electrocardiographic and/or 2-dimensional echo evidence of impaired left ventricular contraction should be considered according to established guidelines. Oral digoxin therapy also may be considered if heart failure persists. Sustained or recurrent cardiac arrhythmias should be treated with appropriate antiarrhythmic agents and correction of precipitating factors such as electrolyte disturbances. In the case of pericardial effusion, therapeutic aspiration is indicated if there is evidence of cardiac tamponade. Chemotherapy is of limited practical value.

Other agents with cardiac effects include vinca alkaloids, fluorouracil, amsacrine, and asparaginase, trastuzumab, etoposide, and teniposide. The heart is relatively vulnerable to oxidative injuries from oxygen radicals generated by chemotherapy. The cardiac effects of these drugs include asymptomatic electrocardiographic abnormalities, blood pressure changes, arrhythmias, myocarditis, pericarditis, cardiac tamponade, acute myocardial infarction, cardiac failure, shock, and long-term cardiomyopathy. These effects may occur during or immediately after treatment or may not be apparent until months or years after treatment.

Epigenetic Therapy–Induced Cardiotoxicity

A growing number of evidence has supported the hypothesis that—at least in part—the neoplastic phenotype and the differential biological behavior of tumor cells could be explained in terms of inheritable changes in the patterns of gene expression that occur without a change in the primary nucleotide sequence; this regulation of transcriptional activity is the result of an enzyme-mediated reorganization of chromatin 3-dimensional structure that modulates its accessibility for transcription factors and other proteins involved in the process of gene expression.^{196,197}

DNA methyltransferase inhibitors and histone deacetylase inhibitors are the 2 most advanced classes of epigenetic drugs in terms of experimental development and clinical applicability because a couple of molecules of these 2 classes already have been approved for several indications in hematologic malignancies, ranging from cutaneous T-cell lymphoma to all subtypes of myelodysplastic syndromes.^{198–200}

Depsipeptide is a novel agent that inhibits the histone deacetylase enzymes that has been shown to be a potent inducer of growth inhibition, apoptosis, and differentiation of multiple cancer cell lines in vitro and in vivo.^{201–203} However, the National Cancer Institute sponsored phase II clinical trial in a patient with metastatic neuroendocrine tumors treated with depsipeptide was terminated prematurely because of a concern that there was an unexpected high number of potentially serious cardiac adverse effects. A sudden death attributed to possible fatal ventricular arrhythmia occurred within 24 hours after the fifth dose of depsipeptide. Furthermore, asymptomatic grade 2 ventricular tachycardia and prolonged QTc probably related to depsipeptide were observed.²⁰⁴

Heat-Shock Protein 90 Inhibitors–Induced Cardiotoxicity

Heat-shock protein inhibitors have been identified as promising cancer treatments as, although they only inhibit a single biological function, the chaperone-protein association, their effect is widespread because it results in the destruction of numerous client proteins, either intracellular or cell surface ones, whose number is still expanding, which are functionally involved in multiple crucial regulatory pathways, such as the process of cell cycle control and protection from apoptosis.²⁰⁵

Pharmacological inhibition of heat-shock protein 90 (Hsp90) is currently being evaluated in a wide array of hema-

tologic malignancies, including acute leukemia, chronic myeloid leukemia, and multiple myeloma.^{206–209}

Antineoplastic Hsp90 inhibitors, such as geldanamycin, are able to reduce hERG/I(Kr) currents not by direct block but by inhibition of hERG/I(Kr) trafficking to the cell surface. The cardiac potassium channel *hERG* (human ether-a-go-go-related gene) encodes the alpha subunit of the rapid delayed rectifier current I(Kr) in the heart, which contributes to terminal repolarization in human cardiomyocytes. This can produce acquired long QT syndrome characterized by drug-induced QT prolongation and torsades de pointes arrhythmias.^{210,211}

Radiation Therapy–Induced Cardiotoxicity

In patients with nonhematologic malignancies, a meta-analysis by Cuzick²¹² showed a 62% increase in cardiac death in women receiving radiation therapy, although Pisteveu-Gompaki et al.²¹³ showed that radiation therapy for left breast cancer was not associated with significant alteration in heart morbidity or mortality within 5 years of treatment.

Pericardial effusion, constrictive pericarditis, or pancarditis can be associated with irradiation. The risk is associated with radiation dose and volume, although pericarditis has been seen after doses as low as 15 Gy.^{214,215}

Symptomatic pericarditis usually develops 10 to 30 years after therapy, with a frequency of 2% to 10%, but myocardial damage and valvular abnormalities are more common.²¹⁶ Coronary artery disease also has been reported after radiation to the mediastinum.²¹⁷

Of any interest is the datum that previous therapy with total body irradiation can increase the risk for development of cardiac dysfunction after hematopoietic cell transplantation.^{218,219}

Mild myocardocyte injury from chemotherapy or radiation therapy may be of more concern in children than in adults because of the need for subsequent cardiac growth to match somatic growth and because survival is longer in children. In this kind of patients, primary prevention is therefore important. Patients should be educated about the cardiotoxic risks of treatment and the need for long-term cardiac monitoring before chemotherapy is begun. Cardiotoxicity may be prevented by screening for predisposing risk factors for cardiovascular disorders, monitoring for signs and symptoms during chemotherapy, and continuing follow-up that may include electrocardiographic and echocardiographic studies, angiography, and measurements of biochemical markers of myocardial injury. Secondary prevention should aim to minimize progression of left ventricular dysfunction to overt heart failure. Approaches include altering the dose, schedule, or approach to drug delivery; using analogues or new formulations with fewer or milder cardiotoxic effects; using cardioprotectants and agents that reduce oxidative stress during chemotherapy; correcting for metabolic derangements caused by chemotherapy that can potentiate the cardiotoxic effects of the drug; and cardiac monitoring during and after cancer therapy. Avoiding additional cardiotoxic regimens also is important in managing these patients. Treating the adverse cardiac effects of chemotherapy will usually be dependent on symptoms or will depend on the anticipated cardiovascular effects of each regimen. Treatments include diuresis, afterload reduction, beta-adrenoceptor antagonists, and improving myocardial contractility.²²⁰

Markers of Cardiac Damage

The identification of early markers of cardiac injury is fundamental for the clinical management of chemotherapy-related cardiotoxic effects.

Heart failure biomarkers can be categorized as markers of myocyte injury and remodeling, neurohormonal mediators, and

indicators of systemic inflammation. Moreover, a role for cellular adhesion molecules emerged as a screening tool for cardiovascular thrombotic complications such as stroke.²²¹

Diastolic indexes; brain natriuretic peptides; markers of myocyte injury, such as troponins heart-type fatty acid binding protein, myosin light chain-1, and endothelin-1 could be biomarkers useful for identification of disease precursors and onset or progression of overt disease.²²²

Troponins are actin-associated regulatory proteins, not normally present in serum. Cardiac troponins are released within 4 to 12 hours after an episode of myocardial necrosis. They have been applied to the early detection of chemotherapy-induced cardiac toxicity.²²³

According to some studies, in cardiotoxicity associated with the use of anthracycline chemotherapeutic agents, serum troponin-I value has been shown to be related to the histopathological change of the myocardium, and particularly, its elevation persistent for longer than 1 month is associated with not only cardiac dysfunction that would be developed in the future but also more serious cardiac complications. Patients with cardiac troponin I levels of less than 0.4 ng/mL had a small median drop in LVEF at 3 months of follow-up examination, which subsequently normalized, whereas those with cardiac troponin I levels of more than 0.4 ng/mL had a greater decrease in LVEF (16%), which was still evident at later follow-up.^{224,225}

B-type natriuretic peptide is a type of cardiac neurohormone secreted by ventricles because of increase of ventricular volume and pressure. Elevation of serum concentration of BNP has been known to be significantly correlated to the left ventricular end diastolic pressure and pulmonary capillary wedge pressure in patients with heart failure. It reflects the remodeling process and could have use in both the diagnosis and management of heart failure.

Lee et al.²²⁶ demonstrated that the clinical correlation between BNP and cardiotoxicity was significant in patients with systemic anthracycline chemotherapy.²²⁷⁻²³¹

However, although BNP is a prognostic indicator in all stages of heart failure, current available BNP assay has limitations relating to clinical variability and assay specificity.²³²

Elbl et al.²³³ pointed out the relationship between plasmatic levels of BNP and echocardiographic indicators of left ventricle function in patients who were in a long-term remission after the therapy of hematologic malignancy and examined to diagnose the late cardiotoxicity of doxorubicin. They found that cutoff BNP of 11.4 pM has sufficient negative predictive value to exclude subclinical damage to the myocardium.

To detect cardiac damage, the estimation of LVEF by echocardiography is the preferred diagnostic approach, but it has a low sensitivity for an early detection of the cardiomyopathy.

Elbl et al.²³⁴ conducted a study to compare the presence of cardiotoxicity after the treatment of Hodgkin disease with the standard Adriamycin, Bleomycin, Vinblastine, and Dacarbazine or Cyclophosphamide, Adriamycin, Etoposide, Vincristine, Bleomycin, Procarbazine, and Prednisone protocol. Using rest echocardiography, they assessed the left ventricular function before and after the therapy. One year after the completion of therapy, a control examination was performed with a battery of tests; the rest and dynamic stress echocardiography and cardiopulmonary tests were carried out to assess cardiopulmonary performance. A similar significant deterioration of ejection fraction and diastolic function was apparent after the treatment in both subgroups with a further progression at the 1-year control. They found a significant relationship of the parameters of the left ventricular function compared with age, the cumulative dose of doxorubicin, and the cumulative dose of radiotherapy. Multi-

variate analysis demonstrated that diastolic dysfunction correlated with advanced age and the cumulative dose of doxorubicin, and decreased cardiopulmonary performance with advanced age, radiotherapy, and female sex.

Two-dimensional echo evaluation of both systolic and diastolic indexes potentially suffers from interobservatory variability. To diminish the confounding effect of varying hemodynamic conditions, ultrasounds technique, such as Doppler tissue imaging and color M-mode mitral flow propagation study can be used to study intrinsic diastolic myofiber properties (relaxation and elastic recoil).²³⁵

QT dispersion analysis (ie, the difference between the maximum and minimum QT intervals on standard 12-lead electrocardiogram) is a measure of cardiac electrical heterogeneity for identification of patients at increased risk for serious ventricular arrhythmias and sudden cardiac death and has showed promising results. QT dispersion and corrected QT interval (QTc) have been reported to predict acute heart failure after HD chemotherapy.²³⁶

Other methods have been performed to discover cardiac damage.

Billingham et al.²³⁷ developed a histological scoring system based on endomyocardial biopsy that displays higher sensitivity for early cardiac damage. However, it is an invasive test with its attendant morbidity, thus making it impractical for day-to-day monitoring.

A study performed using radionuclide ventriculography suggests that serial radionuclide ventriculography is an appropriate approach for the prediction of impending heart failure.²³⁸

Radio labeled antimyosin antibody scintigraphy is a sensitive test for the monitor of cardiotoxicity. The myocardial uptake of antimyosin antibody is highly correlated with the severity of myocardial injury.²³⁹

Elevated levels of activity and of circulating metalloproteinases 2 and 9 protein levels suggest the presence of persistent extracellular remodeling in patients with heart failure.²⁴⁰

Finally, chronic congestive heart failure is associated with an increase in cytokine and inflammatory marker, particularly in elderly patients. Bolignano et al.²⁴¹ showed that increased plasma neutrophil gelatinase-associated lipocalin levels predict mortality in elderly patients with chronic heart failure. Neutrophil gelatinase-associated lipocalin values increased in parallel with the clinical severity of CHF, the highest levels being reached in NYHA class IV patients.

Cardiac Stem Cell Therapy

Cardiovascular disease remains the leading cause of death. Cardiomyocytes that die in response to disease processes or anticancer therapy are replaced by scar tissue instead of new muscle cells. Although heart transplantation is a viable option, this life-saving intervention suffers from shortage of cardiac organ donors and compliances. Cardiac stem cell therapy is a promising approach to facilitate myocardial regeneration after acute myocardial infarction or in CHF.²⁴²

The use of stem cells to generate cells for damaged heart muscle, valves, vessels, and conduction cells holds, in fact, great potential.²⁴³⁻²⁴⁵

Several types of cells grafted in heart can integrate into the cardiac muscle and establish gap junctions, which allow electrical conductance between the host and the donor cells, such as fetal cardiomyocytes, skeletal muscle cells, and bone marrow-derived mesenchymal stem cells, embryonic stem cells, or adipose-derived stem cells.²⁴⁶⁻²⁵⁵ Several phase I/II/III clinical trials have been performed.²⁵⁶⁻²⁵⁸

Although some trials suggest a benefit from cell transplant, other studies do not find any benefit. The discrepancy has been attributed to the type of patients or to the heterogeneity of the type of cells used.²⁵⁹ However, intracoronary administration of progenitor cells derived from bone marrow is associated with recovery of left ventricular contractile function in patients with acute myocardial infarction. At 4 months, the absolute improvement in the global LVEF was greater in the progenitor cells derived from bone marrow group than in placebo group.²⁶⁰

The positive action of cell transplant could result from transdifferentiation of the administered cells; however, exogenous cells could stimulate proliferation of endogenous cardiac precursors through neovascularization of paracrine signaling actions facilitating the ability of the heart to heal itself, or they could act via fusion of donor cells with host cardiomyocytes. Finally, exogenous cells could alter the mechanic properties of the scar.^{261–263}

The secretion of factors with paracrine effects by the transplanted cells is a recognized phenomenon. Identification of these factors by secretome analyses and bioinformatic approaches could advance protein-based therapies to promote healing and inhibit pathological remodeling of the heart after cardiac damage. Moreover, these agents could stimulate resident population of cell with cardiomyogenic potential.²⁶⁴ The adult heart, in fact, contains a resident population of progenitor cells with cardiomyogenic potential that possess the ability to self-renew and differentiate into myocytes, smooth muscle cells, and endothelial cells.^{265–272}

Future research will face many hurdles. The ability not only to guide and expand stem cells into the cardiac lineage but also to repress alternative fates will be crucial to avoid differentiation into cell types that may be harmful to cardiac homeostasis. Methods for safe delivery, migration, and proper integration of stem cells will need to be perfected to avoid complications and abnormal electrical coupling that could lead to arrhythmias. Moreover, it will be essential to solve the immunologic issue surrounding rejection. Technologies to develop individual-specific stem-cell lines through somatic-cell nuclear transfer or cell fusion may allow engineered stem cell containing the individual's own genetic material to be used for treatment.²⁷³

CONCLUSIONS

Patients with hematologic malignancies are at increased risk of drug-induced cardiotoxicity because of the high prevalence of predisposing risk factor for cardiac toxicity from anti-neoplastic drugs such as electrolytic abnormalities, concomitant medications, and starvation.

Novel approaches, such as functional genomics, proteomics, and metabonomics, will significantly improve our understanding of cardiotoxicity induced by drugs in patients with hematologic malignancies.

REFERENCES

- Butany J, Leong SW, Carmichael K, et al. A 30-year analysis of cardiac neoplasms at autopsy. *Can J Cardiol*. 2005;21:675–680.
- Jankovic M, Bonacina E, Masera G, et al. Cardiac relapses in myeloid leukemia: case report and review of the literature. *Pediatr Hematol Oncol*. 1987;4:237–245.
- Makaryus AN, Tung F, Liu W, et al. Extensive neoplastic cardiac infiltration in a patient with acute myelogenous leukemia: role of echocardiography. *Echocardiography*. 2003;20:539–544.
- Jost E, Lorenzen J, Haage P, et al. Heart and muscle involvement by extra-medullary myeloid leukemia: a case report and review of the literature. *Leuk Lymphoma*. 2005;46:1819–1824.
- Wright TL, Bardy PG, Disney P, et al. Isolated cardiac recurrence of acute lymphoblastic leukemia characterized by t(11;19) two years after unrelated allogeneic bone marrow transplantation. *Cancer Genet Cytogenet*. 2002;137:146–149.
- Bessmel'tsev SS, Abdulkadyrov KM. Changes in the functional status of the myocardium in acute leukemia patients. *Vrach Delo*. 1991;52–57.
- McCormick J 3rd, Henderson SO. Leukemic hyperleukocytosis-induced unstable angina and congestive heart failure. *Am J Emerg Med*. 1999;17:217–219.
- Nie YL, Jan SL, Fu LS, et al. Congestive heart failure as presentation of acute lymphoblastic leukaemia with eosinophilia. *Br J Haematol*. 2010. [Epub ahead of print].
- Hon KL, Leung A, Chik KW, et al. Critical airway obstruction, superior vena cava syndrome, and spontaneous cardiac arrest in a child with acute leukemia. *Pediatr Emerg Care*. 2005;21:844–846.
- Summers JE, Johnson WW, Ainger LE. Childhood leukemic heart disease, a study of 16 hearts of children dying of leukemia. *Circulation*. 1969;40:575–581.
- Roberts WC, Bodey GP, Wertlake PT. The heart in acute leukemia—a study of 420 autopsy cases. *Am J Cardiol*. 1968;21:388–412.
- Bisel H, Wroblewski F. Incidence and clinical manifestations of cardiac metastases. *JAMA*. 1953;153:712–715.
- Dameshek W, Gunz F. *Leukemia*. (ed 2). New York, Grune & Stratton, 1964, pp 187–188.
- Gary A, Bergeron GA, Datnow B. Acute myocardial infarction due to chronic myelogenous leukemia. *Chest*. 1974;65:452–455.
- Appelfeld MM, Milner SD, Vigorito RD, et al. Congestive heart failure and endocardial fibroelastosis caused by chronic lymphocytic leukemia. *Cancer*. 1980;46:1479–1484.
- Gonçalves Pide A, Almeida MA, Andrade MJ, et al. Cardiac mass in a patient with chronic lymphocytic leukemia. *Rev Port Cardiol*. 2002;21:1371–1373.
- Trofimov VS, Tumanova MV, Seregin NV, et al. A rare form of myocardial involvement in chronic lympholeukemia. *Ter Arkh*. 1995; 67:64–65.
- Rogachikova TA, Sambulov VI. Lymphocytic lymphoma of the nasal septum and myocardium. *Vestn Otorinolaringol*. 1990;62–63.
- Patel J, Melly L, Sheppard MN. Primary cardiac lymphoma: B- and T-cell cases at a specialist UK centre. *Ann Oncol*. 2009; [Epub ahead of print].
- Nascimento AF, Winters GL, Pinkus GS. Primary cardiac lymphoma: clinical, histologic, immunophenotypic, and genotypic features of 5 cases of a rare disorder. *Am J Surg Pathol*. 2007;31:1344–1350.
- Kilicaslan F, Erikci AA, Kirilmaz A, et al. Rapid normalization of a highly thickened pericardium by chemotherapy in a patient with T-cell acute lymphoblastic lymphoma. *Clin Cardiol*. 2009; 32:E52–E54.
- Tanaka T, Sato T, Akifuji Y, et al. Aggressive non-Hodgkin's lymphoma with massive involvement of the right ventricle. *Intern Med*. 1996;10:826–830.
- Zaharia L, Gill PS. Primary cardiac lymphoma. *Am J Clin Oncol*. 1991;14:142–145.
- Johri A, Baetz T, Isotalo PA, et al. Primary cardiac diffuse large B cell lymphoma presenting with superior vena cava syndrome. *Case Rep*. 2009;25:e210–e212.
- Qingyi M, Hong L, Lima J, et al. Echocardiographic and pathological characteristics of cardiac metastasis in patients with lymphoma. *Oncol Rep*. 2002;9:85–88.

26. Roberts WC, Glancy DL, DeVita DT. Heart in malignant lymphoma: a study of 196 cases. *Am J Cardiol.* 1968;22:85–107.
27. Cains P, Butany J, Fulop J, et al. Cardiac presentation of non-Hodgkin's lymphoma. *Arch Pathol Lab Med.* 1987;111:80–83.
28. Zuppiroli A, Cecchi F, Ciaccheri M, et al. Two-dimensional echocardiographic findings in a case of massive cardiac involvement by malignant lymphoma. *Acta Cardiol.* 1985;5:485–492.
29. Cabin HS, Costello RM, Vasudevan G, et al. Cardiac lymphoma mimicking hypertrophic cardiomyopathy. *Am Heart J.* 1981;102:466–468.
30. Roberts WC. Primary and secondary neoplasms of the heart. *Am J Cardiol.* 1997;80:671–682.
31. Chandler S. Tumors of the heart. *Arch Pathol Lab Med.* 1986;110:371–374.
32. Klatt EC, Heitz DR. Cardiac metastasis. *Cancer.* 1990;65:1456–1459.
33. Bashir H, Hudson MM, Kaste SC, et al. Pericardial involvement at diagnosis in pediatric Hodgkin lymphoma patients. *Pediatr Blood Cancer.* 2006;49:666–671.
34. Amirmoghaddam Z, Khoddami M, Nayeri D, et al. Hodgkin's lymphoma presenting with heart failure: a case report. *J Med Case Rep.* 2010;4:14.
35. O'Mahony D, Peikar RL, Bandettini WP, et al. Cardiac involvement with lymphoma: a review of the literature. *Clin Lymphoma Myeloma.* 2008;8:249–252.
36. Kaderli AA, Baran I, Aydin O, et al. Diffuse involvement of the heart and great vessels in primary cardiac lymphoma. *Eur J Echocardiogr.* 2010;11:74–76.
37. Mioulet D, Braem L, Heno P, et al. Cardiac extension of a non-Hodgkin lymphoma revealed by an atrial flutter. *Ann Cardiol Angeiol (Paris).* 2009;58:117–121.
38. Tanoue K, Sanada J, Kayano T, et al. Malignant lymphoma with various cardiac manifestations: a case report. *J Cardiol.* 2002;40:117–123.
39. Ban-Hoefen M, Zeglin AM, Bisognano JD. Diffuse large B cell lymphoma presenting as a cardiac mass and odynophagia. *Cardiol J.* 2008;5:471–474.
40. Goncalvesová E, Uhlířiková E, Vahancik A, et al. Hypercirculatory heart failure in a patient with plasmacytic leukemia. *Vnitř Lek.* 1995;41:773–776.
41. Iglesias FJ, Wong A, Carrasco F, et al. Cardiac amyloidosis secondary to multiple myeloma detected by echocardiography. *Rev Med Panama.* 1994;19:147–153.
42. Rusznák M, Jakó J, Francz M, et al. Obstructive cardiomyopathy, caused by amyloidosis, associated with bone marrow myeloma. *Orv Hetil.* 1993;134:1033–1036.
43. Windhagen A, Bufler J, Neudecker S. Gross muscle pseudohypertrophy in myeloma-associated light chain amyloidosis. *Neurology.* 2005;65:1670.
44. Brahmabhatt T, Hari P, Cinquegrani M, et al. Case report: delayed enhancement on cardiac MRI in a patient with multiple myeloma without amyloidosis. *Br J Radiol.* 2008;81:e272–e275.
45. Mitchell MA, Homeffer MD, Standiford TJ. Multiple myeloma complicated by restrictive cardiomyopathy and cardiac tamponade. *Chest.* 1993;103:946–947.
46. Keung YK, Lau S, Gill P. Extramedullary plasmacytoma of the heart presenting as a cardiac emergency: review of literature. *Am J Clin Oncol.* 1994;17:427–429.
47. Champeaux AL, Blaser JL, Myers JB, et al. Multiple myeloma involving the myocardium and coronary vessels. *Arch Pathol Lab Med.* 2000;6:910–912.
48. Bessmel'tsev SS, Abdulkadyrov KM. Heart involvement in patients with multiple myeloma based on echocardiographic data. *Vrach Delo.* 1991;49–53.
49. Bessmel'tsev SS. Myocardial function and rheologic properties of blood in multiple myeloma. *Gematol Transfuziol.* 1992;37:22–25.
50. Schattner A, Epstein M, Berrebi A, et al. Case report: multiple myeloma presenting as a diastolic heart failure with no evidence of amyloidosis. *Am J Med Sci.* 1995;310:256–257.
51. Kosinski DJ, Roush K, Fraker TD. High cardiac output state in multiple myeloma. *Clin Cardiol.* 1994;17:678–680.
52. Kohrt H, Logan A, Temmins C, et al. Reversible high-output cardiac failure, an unusual marker of disease status in multiple myeloma. *Leuk Lymphoma.* 2008;49:581–585.
53. McBride W, Jackman JD, Gammon RS, et al. High output cardiac failure in patients with multiple myeloma. *N Engl J Med.* 1988;319:1651–1653.
54. İnanir S, Haznedar R, Atavci S, et al. Arteriovenous shunting in patients with multiple myeloma and high-output failure. *J Nucl Med.* 1998;39:1–3.
55. Madhavan S, Sasidharan PK, Udayabhaskaran K, et al. Restrictive cardiomyopathy due to primary plasma cell leukemia. *J Assoc Physicians India.* 2004;52:826–827.
56. Sedaghat D, Zakir RM, Choe J, et al. Cardiac amyloidosis in a patient with multiple myeloma: a case report and review of literature. *J Clin Ultrasound.* 2009;37:179–184.
57. Niedeggen A, Breithardt OA, Franke A. Detection of early systolic dysfunction with strain rate imaging in a patient with light chain cardiomyopathy. *Z Kardiol.* 2005;94:133–136.
58. Kizaki M, Ieda M, Satoh T, et al. IgD myeloma with systemic amyloidosis with chest discomfort as an initial symptom. *Keio J Med.* 2004;53:178–190.
59. Morbach C, Breunig M, Weidemann F, et al. 52 year-old patient with severe heart failure due to multiple myeloma. *Internist (Berl).* 2009;50:225–229.
60. Fabbian F, Stabellini N, Sartori S, et al. Light chain deposition disease presenting as paroxysmal atrial fibrillation: a case report. *J Med Case Rep.* 2007;1:187.
61. Garton MJ, Walton S, Ewen SW. Systemic lambda light-chain deposition presenting with predominant cardiac involvement. *Postgrad Med J.* 1993;69:588–591.
62. Staros E, Katz MS. Myocardial necrosis in light chain deposition. *Am Heart J.* 1985;110:1295–1296.
63. Foley PW, Hamilton MS, Leyva F. Myocardial scarring following chemotherapy for multiple myeloma detected using late gadolinium hyperenhancement cardiovascular magnetic resonance. *J Cardiovasc Med (Hagerstown).* 2010;11:386–388.
64. Parikh S, de Lemos JA. Current therapeutic strategies in cardiac amyloidosis. *Curr Treat Options Cardiovasc Med.* 2005;7:443–448.
65. Robin J, Fintel B, Pikovskaya O, et al. Multiple myeloma presenting with high-output heart failure and improving with anti-angiogenesis therapy: two case reports and a review of the literature. *J Med Case Rep.* 2008;2:229.
66. Lin CH, Chang WN, Chua S, et al. Idiopathic hypereosinophilia syndrome with Loeffler endocarditis, embolic cerebral infarction, and left hydranencephaly: a case report. *Acta Neurol Taiwan.* 2009;18:207–212.
67. Olsen EG, Spry CJ. Relation between eosinophilia and endomyocardial disease. *Prog Cardiovasc Dis.* 1985;27:241–254.
68. Corradi D, Vaglio A, Maestri R, et al. Eosinophilic myocarditis in a patient with idiopathic hypereosinophilic syndrome: insight into mechanisms of myocardial cell death. *Hum pathol.* 2004;35:1160–1163.

69. Princess O, Douglas RR, McDonald KH. Cardiovascular manifestation of hypereosinophilic syndromes. *Immun Allergy Clin North Am*. 2007;27:457–475.
70. Sen T, Ponde CK, Udawadia ZF. Hypereosinophilic syndrome with isolated Loeffler's endocarditis: Complete resolution with corticosteroids. *J Postgr Med*. 2008;54:135–137.
71. Blauwet LA, Breen JF, Edwards WD, et al. Atypical presentation of eosinophilic endomyocardial disease. *Mayo Clin Proc*. 2005;80:1078–1084.
72. Salanitri GC. Endomyocardial fibrosis and intracardiac thrombus occurring in idiopathic hypereosinophilic syndrome. *Am J Roentgenol*. 2005;184:1432–1433.
73. Sato Y, Fukunaga T, Hayashi T, et al. Hypereosinophilic syndrome associated with occlusive coronary thrombosis and right ventricular thrombus. *Pathol Int*. 2008;58:138–141.
74. Ginsberg F, Parrillo JE. Eosinophilic myocarditis. *Heart Fail Clin*. 2005;1:419–429.
75. Harzy T, Allali F, Amine B, et al. Cardiac manifestations of idiopathic hypereosinophilic syndrome. *Rev Med Intern*. 2005;26:386–392.
76. Gleich GJ, Leiferman KM, Pardananani A, et al. Treatment of hypereosinophilic syndrome with imatinib. *Lancet*. 2002;359:1577–1578.
77. Garcia-Alvarez A, Sitges M, Garcia-Albeniz X, et al. Atypical cardiac manifestation of hypereosinophilic syndrome and reversible cardiotoxicity to imatinib. *Int J Cardiol*. 2010;139:e29–e31.
78. Garrett JK, Jameson JSC, Thomson B, et al. Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol*. 2004;113:115–119.
79. Klion AD, Bochner BS, Gleish GJ, et al. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. *J Allergy Clin Immunol*. 2006;117:1292–1302.
80. Korczyk D, Taylor G, McAlister H, et al. Heart transplantation in a patient with endomyocardial fibrosis due to hypereosinophilic syndrome. *Transplantation*. 2007;83:514–516.
81. Haroche J, Cluzel P, Toledano D, et al. Cardiac involvement in Erdheim-Chester disease. *Circulation*. 2009;119:587–588.
82. Jones RL, Ewer MS. Cardiac and cardiovascular toxicity of nonanthracycline anticancer drugs. *Expert Rev Anticancer Ther*. 2006;6:1249–1269.
83. Floyd JD, Nguyen DT, Lobins RL, et al. Cardiotoxicity of cancer therapy. *J Clin Oncol*. 2005;23:7685–7696.
84. Kremer LC, van Dalen EC, Offringa M, et al. Frequency and risk factors of anthracycline-induced clinical heart failure in children: A systematic review. *Ann Oncol*. 2002;13:503–512.
85. Kremer LC, van Dalen EC, Offringa M, et al. Anthracycline-induced clinical heart failure in a cohort of 607 children: long-term follow-up study. *J Clin Oncol*. 2001;19:191–196.
86. Minow RA, Benjamin RS, Lee ET, et al. Adriamycin cardiomyopathy—risk factors. *Cancer*. 1977;39:1397–1402.
87. Kushner JR, Hansen VL, Hammarm SP. Cardiomyopathy after widely separated courses of Adriamycin exacerbated by actinomycin D and mithramycin. *Cancer*. 1975;36:1577–1584.
88. Smith PJ, Eckert H, Waters KD, et al. High incidence of cardiomyopathy in children treated with Adriamycin and DTIC in combination chemotherapy. *Cancer Treat Rep*. 1977;61:1736.
89. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. *Drug Saf*. 2000;22:263–302.
90. Lipshultz SE, Lipsitz SR, Mone SM, et al. Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl JMed*. 1995;332:1738–1743.
91. Krischer JP, Epstein S, Cuthbertson DD, et al. Clinical cardiotoxicity following anthracyclines treatment of childhood cancer. The Pediatric Oncology Group Experience. *J Clin Oncol*. 1997;15:1544–1552.
92. Pratt CB, Ransom JL, Evans WE. Age-related Adriamycin cardiotoxicity in children. *Cancer Treat Rep*. 1978;62:1381–1385.
93. Ryberg M, Nielsen D, Cortese G, et al. New insight into epirubicin cardiac toxicity: competing risk analysis of 1097 breast cancer patients. *JNCI*. 2008;100:1058–1067.
94. Andrieu-Abadie N, Jaffrezou JP, Hatem S, et al. L-carnitine prevents doxorubicin-induced apoptosis of cardiac myocytes: role of inhibition of ceramide generation. *Faseb J*. 1999;13:1501–1510.
95. Lebrecht D, Kokkori A, Ketelsen UP, et al. Tissue-specific mtDNA lesions and radical-associated mitochondrial dysfunction in human heart exposed to doxorubicin. *J Pathol*. 2005;207:435–444.
96. Solem LE, Henry TR, Wallace KB. Disruption of mitochondrial calcium homeostasis following chronic doxorubicin administration. *Toxicol Applied Pharmacol*. 1994;129:214–222.
97. Minotti G, Cairo G, Monti E. Role of iron in anthracycline cardiotoxicity: new tunes for an old song? *Faseb J*. 1999;13:199–212.
98. Kotamraju S, Chitambar CR, Kalivendi SV, et al. Transferrin receptor-dependent iron uptake is responsible for doxorubicin-mediated apoptosis in endothelial cells—role of oxidant-induced iron signaling in apoptosis. *J Biol Chem*. 2002;277:17179–17187.
99. Chen Y, Daosukho C, Opii WO, et al. Redox proteomic identification of oxidized cardiac proteins in Adriamycin-treated mice. *Free Radic Biol Med*. 2006;41:1470–1477.
100. Rahman AM, Yusuf SW, Ewer MS. Anthracycline-induced cardiotoxicity and the cardiac-sparing effect of liposomal formulation. *Int J Nanomed*. 2007;2:567–583.
101. Mohamed HE, El-Sweify SE, Hagar HH. The protective effect of glutathione administration on Adriamycin-induced acute cardiac toxicity in rats. *Pharmacol Res*. 2000;42:115–121.
102. Minotti G, Ronchi R, Salvatorelli E, et al. Doxorubicin irreversibly inactivates iron regulatory proteins 1 and 2 in cardiomyocytes: evidence for distinct metabolic pathways and implications for iron-mediated cardiotoxicity of antitumor therapy. *Cancer Res*. 2001;61:8422–8448.
103. Li T, Danelisen I, Bello-Klein A, et al. Effects of probucol on changes of antioxidant enzymes in Adriamycin-induced cardiomyopathy in rats. *Cardiovasc Res*. 2000;46:523–530.
104. Lipshultz SE, Colan SD, Gelber RD, et al. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med*. 1991;324:843–845.
105. Minotti G, Salvatorelli E, Menna P. Pharmacological foundations of cardio-oncology. *J Pharmacol Exp Ther*. 2010;334:2–8.
106. Daosukho C, Chen Y, Noel T, et al. Phenylbutyrate, a histone deacetylase inhibitor, protects against Adriamycin-induced cardiac injury. *Free Radic Biol Med*. 2007;42:1818–1825.
107. Rephaeli A, Waks-Yona S, Nudelman A, et al. Anticancer prodrugs of butyric acid and formaldehyde protect against doxorubicin-induced cardiotoxicity. *Br J Cancer*. 2007;96:1667–1674.
108. Legha SS, Benjamin RS, Mackay B, et al. Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. *Ann Intern Med*. 1982;96:133–139.
109. Weiss AJ, Metter GE, Fletcher WS, et al. Studies on Adriamycin using a weekly regimen demonstrating its clinical effectiveness and lack of cardiac toxicity. *Cancer Treat Rep*. 1976;60:813–822.
110. Chlebowski RT, Paroly WS, Pugh RP, et al. Adriamycin given as a weekly schedule without a loading course: Clinically effective with reduced incidence of cardiotoxicity. *Cancer Treat Rep*. 1980;64:47.

111. Lipshultz SE, Giantris AL, Lipsitz SR, et al. Doxorubicin administration by continuous infusion is not cardioprotective: the Dana-Farber 91-01 Acute Lymphoblastic Leukemia Protocol. *J Clin Oncol*. 2002;20:1677–1682.
112. Speyer JL, Green MD, Kramer E, et al. Protective effect of the bispiperazinedione ICRF-187 against doxorubicin-induced cardiac toxicity in women with advanced breast cancer. *N Eng J Med*. 1988;319:745–752.
113. Wexler L. Ameliorating anthracycline cardiotoxicity in children with cancer: clinical trials with dexrazoxane. *Semin Oncol*. 1998;25:86.
114. Lipshultz SE, Rifai N, Dalton VM, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. *N Engl J Med*. 2004;351:145.
115. van Dalen EC, Caron HN, Kremer LC. Prevention of anthracycline-induced cardiotoxicity in children: the evidence. *Eur J Cancer*. 2007;43:1134–1140.
116. Bryant J, Picot J, Baxter L, et al. Clinical and cost-effectiveness of cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review. *Br J Cancer*. 2007;96:226–230.
117. Ozben B, Kurt R, Oflaz H, et al. Acute anterior myocardial infarction after chemotherapy for testicular seminoma in a young patient. *Clin Appl Thromb Hemast*. 2007;13:439–442.
118. Fadilliglu E, Erodan H, Sogut S, et al. Protective effects of erdoesteine against doxorubicin-induced cardiomyopathy in rats. *J Appl Toxicol*. 2003;23:71–74.
119. Wang J, He D, Zhang Q, et al. Resveratrol protects against cisplatin-induced cardiotoxicity by alleviating oxidative damage. *Cancer Biother Radiopharm*. 2009;24:675–680.
120. Ma H, Jones KR, Guo R, et al. Cisplatin compromises myocardial contractile function and mitochondrial ultrastructure: role of endoplasmic reticulum stress. *Clin Exp Pharmacol Physiol*. 2010;37:460–465.
121. Hartmann JT, Haap M, Kopp HG, et al. Tyrosine kinase inhibitors—a review on pharmacology, metabolism and side effects. *Curr Drug Metab*. 2009;10:470–481.
122. Kerkela R, Grazette L, Yacobi R, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med*. 2006;12:908–916.
123. Sawyers CL, Hochhaus A, Feldman E, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. *Blood*. 2002;99:3530–3539.
124. Fisher T, Reifemrath H, Hess GR, et al. Safety and efficacy of STI-571 (imatinib mesylate) in patients with bcr/abl-positive chronic myelogenous leukemia (CML) after autologous peripheral blood stem cell transplantation (PB SCT). *Leukemia*. 2002;16:1220–1228.
125. Dorn GWII, Force T. Protein kinase cascades in the regulation of cardiac hypertrophy. *J Clin Invest*. 2005;115:527–537.
126. Trent JC, Patel SS, Zhang J, et al. Rare incidence of congestive heart failure in gastrointestinal stromal tumor and other sarcoma patients receiving imatinib mesylate. *Cancer*. 2010;116:184–192.
127. Rosti G, Martinelli G, Baccarani M. In reply to “cardiotoxicity of the cancer therapeutic agent imatinib mesylate”. *Nat Med*. 2007;13:15–16.
128. Verweij J, Casali PG, Kotasek D, et al. Imatinib does not induce cardiac left ventricular failure in gastrointestinal stromal tumours patients: analysis of EORTC-ISG-AGITG study 62005. *Eur J Cancer*. 2007;43:974–978.
129. Force T. In reply to “cardiotoxicity of the cancer therapeutic agent imatinib mesylate”. *Nat Med*. 2007;13:15–16.
130. Atallah E, Durand JB, Kantarjian H, et al. Congestive heart failure is a rare event in patients receiving imatinib therapy. *Blood*. 2007;110:1233–1237.
131. Perik PJ, Rikhof B, de Jong FA, et al. Results of plasma N-terminal pro B-type natriuretic peptide and cardiac troponin monitoring in GIST patients do not support the existence of imatinib-induced cardiotoxicity. *Ann Oncol*. 2008;19:359–361.
132. Orphanos GS, Ioannidis GN, Ardavanis AG. Cardiotoxicity induced by tyrosine kinase inhibitors. *Acta Oncol*. 2009;48:964–970.
133. Nexavar USPI (2007) November revision. Available at: www.nexavar.com/hcp_REACH. Accessed July 29, 2008.
134. Will Y, Dykens JA, Nadanaciva S, et al. Effect of the multitargeted tyrosine kinase inhibitors imatinib, dasatinib, sunitinib, and sorafenib on mitochondrial function in isolated rat heart mitochondria and H9c2 cells. *Toxicol Sci*. 2008;106:153–161.
135. Galinski I, Buchanan S. Practical management of dasatinib for maximum patient benefit. *Clin J Oncol Nurs*. 2009;13:329–335.
136. Fabian MA, Bigg WH 3rd, Treiber DK, et al. A small molecule-kinase interaction map for clinical kinase inhibitors. *Nat Biotechnol*. 2005;23:329–336.
137. Force T, Krause DS, Van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. *Nat Rev Cancer*. 2007;7:332–344.
138. Will Y, Dykens JA, Nadanaciva S, et al. Effect of the multi-targeted tyrosine kinase inhibitors Imatinib, Dasatinib, Sunitinib and Sorafenib on mitochondrial function in isolated rat heart mitochondria and H9c2 cells. *ToxSci Advance*. Accessed July 29, 2008.
139. Sohn SK, Kim JG, Kim DH, et al. Cardiac morbidity in advanced chronic myelogenous leukaemia patients treated by successive allogeneic stem cell transplantation with busulphan/cyclophosphamide conditioning after imatinib mesylate administration. *Br J Haematol*. 2003;121:469–477.
140. Burke MJ, Trotz B, Luo X, et al. Imatinib use either pre- or post-allogeneic hematopoietic cell transplantation (allo-HCT) does not increase cardiac toxicity in chronic myelogenous leukemia patients. *Bone Marrow Transplant*. 2009;44:169–174.
141. Hu Z, Pan X, Wu F, et al. Synergy between proteasome inhibitors and imatinib mesylate in chronic myeloid leukemia. *PLoS One*. 2009;4:6257.
142. Fernandez A. An anticancer C-kit kinase inhibitor is reengineered to make it more active and less cardiotoxic. *J Clin Invest*. 2007;117:40–44.
143. Li Y, Sun X, Zhou Z, et al. Myocardial toxicity of arsenic trioxide in a mouse model. *Cardiovasc Toxicol*. 2002;2:63–73.
144. Saad SY, Alkharfy KM, Arafah MM. Cardiotoxic effects of arsenic trioxide/imatinib mesilate combination in rats. *J Pharm Pharmacol*. 2006;58:567–573.
145. Zhao X, Feng T, Chen H, et al. Arsenic-trioxide-induced apoptosis in H9c2 cardiomyocytes: implications in cardiotoxicity. *Basic Clin Pharmacol Toxicol*. 2008;102:419–425.
146. Sun HL, Chu WE, Dong DL, et al. Choline-modulated arsenic trioxide-induced prolongation of cardiac repolarization in Guinea pig. *Basic Clin Pharmacol Toxicol*. 2006;98:381–388.
147. Westervelt P, Brown RA, Adkins DR, et al. Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide. *Blood*. 2001;98:266–271.
148. Patel SP, Garcia-Manero G, Ferrajoli A, et al. Cardiotoxicity in African-Americans patients treated with arsenic trioxide for acute promyelocytic leukemia. *Leukemia Res*. 2006;30:362–364.
149. Chiang CE, Luk HN, Wang T-M, et al. Prolongation of cardiac repolarization by arsenic trioxide. *Blood*. 2002;100:2249–2252.

150. Yamazaki K, Terada H, Satoh H, et al. Arrhythmogenic effects of arsenic trioxide in patients with acute promyelocytic leukemia and an electrophysiological study in isolated guinea pig papillary muscles. *Circ J*. 2006;70:1407–1414.
151. Raghu KG, Cherian OL. Characterization of cytotoxicity induced by arsenic trioxide (a potent anti-APL drug) in rat cardiac myocytes. *J Trace Elem Med Biol*. 2009;23:61–68.
152. Raghu KG, Yadav GK, Singh R, et al. Evaluation of adverse cardiac effects induced by arsenic trioxide, a potent anti-APL drug. *J Environ Pathol Toxicol Oncol*. 2009;28:241–252.
153. Zhao X-Y, Li G-Y, Chai L-M, et al. Resveratrol protects against arsenic trioxide-induced cardiotoxicity in vitro and in vivo. *Br J Pharmacol*. 2008;154:105–113.
154. Editorial. Bortezomib: new indication. Second line treatment of myeloma: limited efficacy, major risks. *Prescure Int*. 2006;15: 98–100.
155. Orciuolo E, Buda G, Cecconi S, et al. Unexpected cardiotoxicity in haematological bortezomib treated patients. *Br J Haematol*. 2007;138:396–403.
156. Marfella R, Di Filippo C, Portoghese M, et al. The ubiquitin-proteasome system contributes to the inflammatory injury in ischemic diabetic myocardium: the role of glycemic control. *Cardiovasc Pathol*. 2009;18:332–345.
157. Cervera Grau JM, Esquerdo Galiana G, Belso Candela A, et al. Complete atrioventricular block induced by rituximab in monotherapy in an aged patient with non-Hodgkin's diffuse large B-cell lymphoma. *Clin Transl Oncol*. 2008;10:298–299.
158. Kilickap S, Yavuz B, Aksoy S, et al. Addition of rituximab to CHOP does not increase the risk of cardiotoxicity in patients with non Hodgkin's lymphoma. *Med Oncol*. 2008;25:437–442.
159. Ferrajoli A, O'Brien SM, Cortes JE, et al. Phase II study of alemtuzumab in chronic lymphoproliferative disorders. *Cancer*. 2003;98:773–778.
160. Keating MJ, Finn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath 1-H) in patients who failed fludarabine: results of a large international study. *Blood*. 2002;99:3554–3561.
161. Uppenkamp M, Engert A, Diehl V, et al. Monoclonal antibody therapy with CAMPATH 1H in patients with relapsed high and low-grade non-Hodgkin's lymphomas: a multicenter phase I/II study. *Ann Hematol*. 2002;81:26–32.
162. Lenihan DJ, Alencar AJ, Yang D, et al. Cardiac toxicity of alemtuzumab in patients with mycosis fungoides/Sézary syndrome. *Blood*. 2004;104:655–658.
163. Wing MG, Moreau T, Greenwood J, et al. Mechanism of first dose cytokine-release syndrome by CAMPATH-1H: involvement of CD16 (Fcγ3R1) and CD11a/CD18 (LFA-1) on NK cells. *J Clin Invest*. 1996;98:2819–2826.
164. Damaj G, Rubio MT, Audard V, et al. Severe cardiac toxicity after monoclonal antibody therapy. *Eur J Hematol*. 2002;68:324.
165. Horacek JM, Pudil R, Tichy M, et al. Biochemical markers and assessment of cardiotoxicity during preparative regimen and hematopoietic cell transplantation in acute leukemia. *Exp Oncol*. 2007;29:243–247.
166. Kupari M, Volin L, Suokas T, et al. Cardiac involvement in bone marrow transplantation: electrocardiographic changes, arrhythmias, heart failure and autopsy findings. *Bone Marrow Transplant*. 1990;5: 91–98.
167. Bearman SI, Appelbaum FR, Buckner CD, et al. Regimen-related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol*. 1998;6:1562–1568.
168. Murdych T, Weisdorf DJ. Serious cardiac complications during bone marrow transplantation at the University of Minnesota 1977–1997. *Bone Marrow Transplant*. 2001;28:283–287.
169. Morandi P, Ruffini PA, Benvenuto GM, et al. Serum cardiac troponin I levels and ECG/Echo monitoring I breast cancer patients undergoing high-dose (7g/m²) cyclophosphamide. *Bone Marrow Transplant*. 2001;28:277–282.
170. Kuittinen T, Husso-Saastamoinen M, Sipola P, et al. Very acute cardiac toxicity during BEAC chemotherapy in non-Hodgkin's lymphoma patients undergoing autologous stem cell transplantation. *Bone Marrow Transplant*. 2005;36:1077–1082.
171. Morandi P, Ruffini PA, Benvenuto GM, et al. Cardiac toxicity of high-dose chemotherapy. *Bone Marrow Transplant*. 2005;35: 323–334.
172. Stamatopoulos K, Kanellopoulou G, Vaiopoulos G, et al. Evidence for sinoatrial blockade associated with high dose cytarabine therapy. *Leukemia Res*. 1998;22:759–761.
173. Nakamae H, Tsumura K, Hino M, et al. QT dispersion as a predictor of acute heart failure after high-dose cyclophosphamide. *Lancet*. 2000;355:805–806.
174. Kanda Y, Matsumura T, Maki K, et al. Fatal cardiac toxicity in two patients receiving same-day administration of cyclophosphamide and cytarabine as conditioning for hematopoietic stem cell transplantation. *Haematologica*. 2001;86:1002–1003.
175. Faulds D, Balfour JA, Chrisp P, et al. Mitoxantrone, a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the chemotherapy of cancer. *Drugs*. 1991;3:400–449.
176. Henderson IC, Allegra JC, Woodcock T, et al. Randomized clinical trial comparing mitoxantrone with doxorubicin in previously treated patients with metastatic breast cancer. *J Clin Oncol*. 1989;7: 560–571.
177. Chugun A, Uchide T, Tsurimaki C, et al. Mechanisms responsible for reduced cardiotoxicity of mitoxantrone compared to doxorubicin examined in isolated guinea-pig heart preparations. *J Vet Med Sci*. 2008;70:255–264.
178. Chugun A, Temma K, Oyamada T, et al. Doxorubicin-induced late cardiotoxicity: delayed impairment of Ca²⁺-handling mechanisms in the sarcoplasmic reticulum in the rat. *Can J Physiol Pharmacol*. 2000;78:329–338.
179. Bers DM. Na/Ca exchange and the sarcolemmal Capump. In: *Excitation-Contraction Coupling and Cardiac Contractile Force*. 2nd ed. Dordrecht, The Netherlands: Kluwer Academic Publishers; 2001:133–160.
180. Stuyvers BD, McCulloch AD, Guo J, et al. Effects of stimulation rate, sarcomere length and Ca²⁺ on force generation by mouse cardiac muscle. *J Physiol (Lond)*. 2002;544:817–830.
181. Dazzi C, Cariello A, Rosti G, et al. Neoadjuvant high dose chemotherapy plus peripheral blood progenitor cells in inflammatory breast cancer: a multicenter phase II pilot study. *Haematologica*. 2001;86:523–529.
182. Gralow JR, Livingston RB. University of Washington high dose cyclophosphamide, mitoxantrone, and etoposide experience in metastatic breast cancer: unexpected cardiac toxicity. *J Clin Oncol*. 2001;19:3903–3904.
183. Escoto H, Ringewald J, Kalpatthi R. Etoposide-related cardiotoxicity in a child with haemophagocytic lymphohistiocytosis. *Cardiol Young*. 2010;20:105–107. [Epub ahead of print].
184. Kandyliis K, Vassilomanolakis M, Tsoussis S, et al. Ifosfamide cardiotoxicity in humans. *Cancer Chemother Pharmacol*. 1989;24: 395–396.
185. Quezado ZM, Wilson WH, Cunnion RE, et al. High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. *Ann Intern Med*. 1993;118:31–36.
186. Ghielmini M, Zappa F, Menafoglio A, et al. The high-dose sequential (Milan) chemotherapy/ PBSC transplantation regimen

- for patients with lymphoma is not cardiotoxic. *Ann Oncol.* 1999;10:533–537.
187. Phillips GL, Meisenberg B, Reece DE, et al. Amifostine and autologous hematopoietic stem cell support of escalating-dose melphalan. A phase I study. *Biol Blood Marrow Transplant.* 2004;10:473–483.
 188. Oliveri A, Corvatta L, Monatanari M, et al. Paroxysmal atrial fibrillation after high-dose melphalan in five patients autotransplanted with blood progenitor cells. *Bone Marrow Transplant.* 1998;21:1049–1053.
 189. Jost LM. Overdose with melphalan (Alkeran): symptoms and treatment. A review. *Onkologie.* 1990;13:96–101.
 190. Kottaridis PD, Milligan DW, Chopra R, et al. In vivo Campath-1h prevents graft-versus-host disease following non-myeloablative stem cell transplantation. *Blood.* 2000;96:2419–2425.
 191. Giralt S, Estey E, Albitar M, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. *Blood.* 1997;89:4531–4536.
 192. Spriano M, Clavio M, Carrara L, et al. Fludrabine in untreated and previously treated B-CLL: a report on efficacy and toxicity. *Haematologica.* 1994;79:2118–2124.
 193. Giralt S, Thall PF, Khouri I, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. *Blood.* 2001;97:631–637.
 194. Ritchie DS, Seymour JF, Roberts AW, et al. Acute left ventricular failure following melphalan and fludarabine conditioning. *Bone Marrow Transplant.* 2001;28:101–103.
 195. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet.* 1999;354:1084–1089.
 196. Jones PA, Baylin SB, et al. The role of events in cancer. *Nat Rev Genet.* 2002;3:415–428.
 197. Jenuwein T, Allis CD. Translating the histone code. *Science.* 2001;293:1074–1080.
 198. Mann BS, Johnson JR, Cohen MH, et al. FDA approval summary: vorinostat for treatment of advanced primary cutaneous T-cell lymphoma. *Oncologist.* 2007;12:1247–1252.
 199. Kaminskas E, Farrell AT, Wang YC, et al. FDA drug approval summary: azacitidine (5-azacytidine, Vidaza) for injectable suspension. *Oncologist.* 2005;10:176–182.
 200. Musolino C, Sant'antonio E, Penna G, et al. Epigenetic therapy in myelodysplastic syndromes. *Eur J Haematol.* 2010;84:463–473.
 201. Ueda H, Manda T, Matsumoto S, et al. FR901228, a novel antitumor bicyclic depsipeptide produced by *Chromobacterium violaceus* no. 968. III. Antitumor activities on experimental tumors in mice. *J Antibiot (Tokyo).* 1994;47:315–323.
 202. Byrd JC, Marcucci G, Parthun MR, et al. A phase I and pharmacodynamic study of depsipeptide (FK228) in chronic lymphocytic leukemia and acute myeloid leukemia. *Blood.* 2005;105:959–967.
 203. Piekarczyk RL, Robey R, Sandor V, et al. Inhibitor of histone deacetylation, depsipeptide (FR 1228), in the treatment of peripheral and cutaneous T-cell lymphoma: a case report. *Blood.* 2001;98:2865–2868.
 204. Shah MH, Binkley P, Chan K, et al. Cardiotoxicity of histone deacetylase inhibitor depsipeptide in patients with metastatic neuroendocrine tumors. *Clin Cancer Res.* 2006;12:3997–4003.
 205. Isaacs JS, Xu, W, Neckers L. Heat shock protein 90 as a molecular target for cancer therapeutics. *Cancer Cell.* 2003;3:213–217.
 206. Guo F, Sigua C, Bali P, et al. Mechanistic role of heat shock protein 70 in Bcr-Abl-mediated resistance to apoptosis in human acute leukemia cells. *Blood.* 2005;105:1246–1255.
 207. Nguyen TK, Rahmani M, Gao N, et al. Synergistic interactions between DMAG and mitogen-activated protein kinase kinase 1/2 inhibitors in Bcr/abl+ leukemia cells sensitive and resistant to imatinib mesylate. *Clin Cancer Res.* 2006;12:2239–2247.
 208. Andrulis M, Chatterjee M, Jain S, et al. Heat shock protein 90 alpha and beta are overexpressed in multiple myeloma cells and critically contribute to survival. *Verhandlungen der Deutschen Gesellschaft für Pathologie.* 2009;91:330–337.
 209. Mitsiades CS, Mitsiades NS, McMullan CJ, et al. Antimyeloma activity of heat shock protein-90 inhibition. *Blood.* 2006;107:1092–1100.
 210. Dennis A, Wang L, Wan X, et al. hERG channel trafficking: novel targets in drug-induced long QT syndrome. *Biochem Soc Trans.* 2007;35:1060–1063.
 211. Bagnes C, Panchuk PN, Recondo G. Antineoplastic chemotherapy induced QTc prolongation. *Curr Drug Saf.* 2010;5:93–96.
 212. Cuzick J. Radiotherapy for breast cancer. *J Natl Cancer Inst.* 2005;97:406–407.
 213. Pistevou-Gompaki K, Hatzitolios A, Eleftheriadis N, et al. Evaluation of cardiotoxicity five years after 2D planned, non-simulated, radiation therapy for left breast cancer. *Ther Clin Risk Manag.* 2008;4:1359–1362.
 214. Martin RG, Rukdeschel JC, Chang P, et al. Radiation-related pericarditis. *Am J Cardiol.* 1975;35:216–220.
 215. Srebot V, Sbrana F, Maffei A, et al. Cardiotoxicity induced by chemo- and radiotherapy. *Recent Prog Med.* 2009;100:493–498.
 216. Perrault DJ, Levy M, Herman JD, et al. Echocardiographic abnormalities following cardiac radiation. *J Clin Oncol.* 1985;3:546–551.
 217. Hancock SL, Donaldson SS, Hoppe RT. Cardiac disease following treatment of Hodgkin's disease in children and adolescents. *J Clin Oncol.* 1993;11:1208–1215.
 218. Leahey AM, Teunissen H, Friedman DL, et al. Late effects of chemotherapy compared to bone marrow transplantation in the treatment of pediatric acute myeloid leukemia and myelodysplasia. *Med Pediatr Oncol.* 1999;32:163–169.
 219. Eames GM, Crosson J, Steinberger J, et al. Cardiovascular function in children following bone marrow transplant: A cross-sectional study. *Bone Marrow Transplant.* 1997;19:61–66.
 220. Simbre VC, Duffy SA, Dadlani GH, et al. Cardiotoxicity of cancer chemotherapy: implications for children. *Paediatr Drugs.* 2005;7:187–202.
 221. Lee DS, Vasan RS. Novel markers for heart failure diagnosis and prognosis. *Curr Opin Cardiol.* 2005;20:201–210.
 222. Benvenuto GM, Ometto R, Fontanelli A, et al. Chemotherapy-related cardiotoxicity: new diagnostic and preventive strategies. *Ital Heart J.* 2003;4:655–467.
 223. Kremer LC, van Dalen EC, Offringa M, et al. Anthracycline-induced clinical heart failure in a cohort of 607 children: long term follow-up study. *J Clin Oncol.* 2001;19:191–196.
 224. Cardinale D, Sandri MT, Martinoni A, et al. Left ventricular dysfunction predicted by early troponin I release after high dose chemotherapy. *J Am Coll Cardiol.* 2000;36:517–522.
 225. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation.* 2004;109:2749–2754.
 226. Lee HS, Son CB, Shin SH, et al. Clinical correlation between brain

- natriuretic peptide and anthracyclin-induced cardiac toxicity. *Cancer Res Treat.* 2008;40:121–126.
227. Uusimaa P, Tokola H, Ylitalo A, et al. Plasma B-type natriuretic peptide reflects left ventricular hypertrophy and diastolic function in hypertension. *Int J Cardiol.* 2004;97:251–256.
228. Gardner DG. Natriuretic peptides: marker or modulators of cardiac hypertrophy? *Trends Endocrinol Metab.* 2003;14:411–416.
229. Law YM, Eteddgui J, Beerman L, et al. Comparison of plasma B-type natriuretic peptide levels in single ventricle patients with systemic ventricular heart failure versus isolated cavopulmonary failure. *Am J Cardiol.* 2006;98:520–524.
230. Latour-Perez J, Coves-Orts FJ, Abad-Terrado C, et al. Accuracy of B-type natriuretic peptide levels in the diagnosis of left ventricular dysfunction and heart failure: a systematic review. *Eur J Heart Fail.* 2006;8:390–399.
231. Doust JA, Glasziou PP, Pietrzak E, et al. A systematic review of the diagnostic accuracy of natriuretic peptides for heart failure. *Arch Intern Med.* 2004;164:1978–1984.
232. Isaac DL. Biomarkers in heart failure management. *Curr Opin Cardiol.* 2008;23:127–133.
233. Elbl L, Vasova I, Navratil M, et al. Comparison of plasmatic levels of B-natriuretic peptide with echocardiographic indicators of left ventricle function after doxorubicin therapy. *Vnitř Lek.* 2006;52:563–570.
234. Elbl L, Vasova I, Kral Z, et al. Evaluation of acute and early cardiotoxicity in survivors of Hodgkin's disease treated with ABVD or BEACOPP regimens. *J Chemother.* 2006;18(2):199–208.
235. Benvenuto GM, Ometto R, Fontanelli A, et al. Chemotherapy related cardiotoxicity: new diagnostic and preventive strategies. *Ital Heart J.* 2003;4:655–677.
236. Nakamae T, Hino M, Akahori M, et al. Predictive value of QT dispersion for acute heart failure after autologous and allogeneic hematopoietic stem cell transplantation. *Am J Hematol.* 2004;76:1–7.
237. Billingham ME, Mason JW, Bristow MR, et al. Anthracycline cardiomyopathy monitored by morphologic changes. *Cancer Treat Rep.* 1978;62:865–872.
238. Schwartz RG, McKenzie WB, Alexander J, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven years experience using serial radionuclide angiocardiology. *Am J Med.* 1987;82:1109–1118.
239. Valdes Olmos RA, Carrio I, Hoefnagel CA, et al. High sensitivity of radiolabelled antimyosin scintigraphy in assessing anthracycline related early myocyte damage preceding cardiac dysfunction. *Nucl Med Commun.* 2002;23:871–877.
240. Altieri P, Brunelli C, Garibaldi S, et al. Metalloproteinases 2 and 9 are increased in plasma of patients with heart failure. *Eur J Clin Invest.* 2003;33:648–656.
241. Bolignano D, Basile G, Parisi P, et al. Increased plasma neutrophil gelatinase-associated lipocalin levels predict mortality in elderly patients with chronic heart failure. *Rejuvenation Res.* 2009;12:7–14. [Epub ahead of print].
242. Zhang F, Pasumarthi KBS. Embryonic stem cell transplantation: promise and progress in the treatment of heart disease. *BioDrugs.* 2008;22:361–374.
243. Srivastava D, Ivey KN. Potential of stem-cell-based therapies for heart disease. *Nature.* 2006;441:1097–1099.
244. Laflamme MA, Murry CE. Regenerating the heart. *Nat Biotechnol.* 2005;23:845–856.
245. Murry CE, Field LJ, Menasche P. Cell-based cardiac repair: reflections at the 10-year point. *Circulation.* 2005;112:3174–3183.
246. Reinecke H, Zhang M, Bartosek T, et al. Survival, integration, and differentiation of cardiomyocyte grafts: a study in normal and injured rat hearts. *Circulation.* 1999;100:193–202.
247. Taylor DA, Atkins BZ, Hungspreugs P, et al. Regenerating functional myocardium: improved performance after skeletal myoblast transplantation. *Nat Med.* 1998;4:929–933.
248. Shake JG, Gruber PJ, Baumgartner WA, et al. Mesenchymal stem cell implantation in a swine myocardial infarct model: engraftment and functional effects. *Ann Thorac Surg.* 2002;73:1919–1925.
249. Yamada Y, Wang XD, Yokoyama S, et al. Cardiac progenitor cells in brown adipose tissue repaired damaged myocardium. *Biochem Biophys Res Commun.* 2006;342:662–670.
250. Orlic D, Kajstura J, Chimenti S, et al. Bone marrow cells regenerate infarcted myocardium. *Nature.* 2001;410:701–705.
251. Kawamoto A, Tkebuchava T, Yamaguchi J, et al. Intramyocardial transplantation of autologous endothelial progenitor cells for therapeutic neovascularization of myocardial ischemia. *Circulation.* 2003;107:461–468.
252. Wollert KC, Meyer GP, Lotz J, et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet.* 2004;364:141–148.
253. Pfannkuche K, Neuss S, Pillekamp F, et al. Fibroblasts facilitate the engraftment of embryonic stem cell-derived cardiomyocytes on three-dimensional collagen matrices and aggregation in hanging drops. *Stem Cell Dev.* 2010. [Epub ahead of print].
254. Gulbins H, Meiser BM, Reichenspurner H, et al. Cell transplantation—a potential therapy for cardiac repair in the future? *Heart Surg Forum.* 2002;5:28–34.
255. Siu CW, Moore JC, Li RA. Human embryonic stem cell-derived cardiomyocytes for heart therapies. *Cardiovasc Hematol Disord Drug Targets.* 2007;7:145–152.
256. Stamm C, Westphal B, Kleine HD, et al. Autologous bone-marrow stem-cell transplantation for myocardial regeneration. *Lancet.* 2003;361:45–46.
257. Fernandez-Aviles F, San Roman JA, Garcia-Frade J, et al. Experimental and clinical regenerative capability of human bone marrow cells after myocardial infarction. *Circ Res.* 2004;95:742–748.
258. Janssens S, Dubois C, Bogaert J, et al. Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. *Lancet.* 2006;367:113–121.
259. Sanchez PL, San Roman JA, Villa A, et al. Contemplating the bright future of stem cell therapy for cardiovascular disease. *Nat Clin Pract Cardiovasc Med.* 2006;3:138–151.
260. Schachinger V, Elsasser A, Haberbosch W, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med.* 2006;355:1210–1221.
261. Urbanek K, Torella D, Sheikh F, et al. Myocardial regeneration by activation of multipotent cardiac stem cells in ischemic heart failure. *Proc Natl Acad Sci U S A.* 2005;102:8692–8697.
262. Reinecke H, Minami E, Poppa V, et al. Evidence for fusion between cardiac and skeletal muscle cells. *Circ Res.* 2004;94:56–60.
263. Gavira JJ, Perez-Illarbe M, Abizanda G, et al. A comparison between percutaneous and surgical transplantation of autologous skeletal myoblasts in a swine model of chronic myocardial infarction. *Cardiovasc Res.* 2006;71:744–753.
264. Wollert KC, Drexler H. Cell therapy for the treatment of coronary

- heart disease: a critical appraisal. *Nat Rev Cardiol.* 2010;7:204–215. [Epub ahead of print].
265. Beltrami AP, Barlucchi L, Torella D, et al. Adult cardiac stem cells are multipotent and support myocardial regeneration. *Cell.* 2003;114:763–776.
266. Messina E, De Angelis L, Frati G, et al. Isolation and expansion of adult cardiac stem cells from human and murine heart. *Circ Res.* 2004;95:911–921.
267. Laugwitz KL, Moretti A, Lam J, et al. Postnatal *Isl1*+ cardioblasts enter fully differentiated cardiomyocyte lineages. *Nature.* 2005;433:647–653.
268. Oh H, Bradfute SB, Gallardo TD, et al. Cardiac progenitor cells from adult myocardium: homing, differentiation, and fusion after infarction. *Proc Natl Acad Sci U S A.* 2003;100:12313–12318.
269. Martin CM, Meeson AP, Robertson SM, et al. Persistent expression of the ATP-binding cassette transporter, *Abcg2*, identifies cardiac SP cells in the developing and adult heart. *Dev Biol.* 2004;265:262–275.
270. Moretti A, Caron L, Nakano A, et al. Multipotent embryonic *Isl1*+ progenitor cells lead to cardiac, smooth muscle, and endothelial cell diversification. *Cell.* 2006;127:1151–1165.
271. Cai CL, Liang X, Shi Y, et al. *Isl1* identifies a cardiac progenitor population that proliferates prior to differentiation and contributes a majority of cells to the heart. *Dev Cell.* 2003;5:877–889.
272. Shi X, Garry DJ. Muscle stem cells in development, regeneration, and disease. *Genes Dev.* 2006;20:1692–1708.
273. Cowan CA, Atienza J, Melton DA, et al. Nuclear reprogramming of somating cells after fusion with human embryonic stem cell. *Science.* 2005;309:1369–1373.