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

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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/m^2. 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 Abdulkadyrov[48] and Bessmel'tsev[49] 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"s 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 hypereosinophilia 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-PDGFRA 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/m^2 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/m^2 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, mytomycin 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 O_2 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 subclinical 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/m^2, 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/m^2 vs a total of 450 mg/m^2 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 (±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 cardiac myocytes 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 ½, 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% to1.8%,[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, Fernandez[142] 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 al 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 metylenetetrahydrofolate 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 cardiomyocite 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/m^2 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 μM 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 μM 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 μM 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 show 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 hematologic 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 currentI(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 Cuzick[212] showed a 62% increase in cardiac death in women receiving radiation therapy, although Pistevou-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 myocardiocyte 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 malignity 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, Adiamycin, 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. Multivariate 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 donator 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 posses 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 antineoplastic 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.

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