Cardiotoxicity of Cancer Therapy
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The survival rate of cancer patients has improved greatly in recent decades. There are over 12 million cancer survivors in the U.S. Often, cancer can be managed similarly to other chronic illnesses, such as diabetes and hypertension. This requires early diagnosis, regular surveillance and careful decision making. Cancer therapy can be complex, involving a number of modalities.

At the same time, cardiotoxicity is a common complication of chemotherapy and radiation. It may be irreversible (type 1) or reversible (type 2). The severity ranges from mild left ventricular dysfunction to severe heart failure and death. Such complications often are asymptomatic at the outset, and may become manifest late in the course of treatment. 40% of patients develop arrhythmias. Cardiac complications are the second leading cause of death in this group.

The likelihood of toxicity varies with the regimen used. The mechanism is probably related to production of oxygen free radicals that damage the heart. Recent reports offer hope of prevention and even complete reversibility, at least in early stages. An excellent review of the incidence of cardiac toxicity as well as other aspects may be found in the article by Khouri.

Kinases are enzymes that are involved in the development of many cancers. They play a role in transfer of phosphate from ATP and other substances to their substrate molecules. Kinase inhibition is often employed in cancer therapy. Kinases are important in cardiovascular hemostasis. Inhibiting them can result in cardiomyopathy, pulmonary hypertension, and other adverse events.

Risk Factors for Developing Cardiovascular Complications
The cardiotoxicity of a drug depends on the dose and schedule of administration, as well as concomitant therapy (such as radiation and other drugs). Older patients and those with preexisting heart disease are at greater risk. The protocol and sequence of administration of the drugs can have significant impact. Any treatable risk factors should be addressed.

Pretreatment May Mitigate Cardiotoxicity
Bosch et al performed a pilot study of patients with hematologic malignancies (acute leukemia, Hodgkin and non-Hodgkin lymphoma and multiple myeloma). They found a significant reduction in cardiovascular death and left ventricular dysfunction in the group treated with enalapril and carvedilol.

Anthracyclines
These include doxorubicin, daunorubicin and epirubicin. Mitoxantrone is a derivative of the anthracyclines. Subclinical toxicity develops in 1 patient of 7 and 1 in 10 suffer clinically apparent toxicity. It is irreversible. The mechanism is believed to be free radical injury and oxidative stress, with resulting permanent loss of myocytes. It occurs in both children and adults, and may become clinically apparent even several years after completion of therapy. The main risk factors are total dose and concomitant radiation to the chest. Other predisposing
factors are extremes of age, hematologic malignancies, African-American ethnicity, diabetes, hypertension, obesity, low body weight and serious comorbidities.

Early toxicity produces atrial and ventricular arrhythmias, pericarditis, myocarditis, and impaired left ventricular function. Initially, these can be reversible, but later such complications can be fatal. In the long term, there can be left ventricular dysfunction and heart failure. The latter is dose-related and carries a high mortality. It had been believed that this would be minimized by keeping the dose below 550 mg/m\(^2\). More recent indications are that it can occur at lower doses. Base line echocardiography should be done prior to initiating therapy. Early recognition is important. Cardinale (2010) found that early initiation of enalapril and carvedilol made a significant difference in the recovery of cardiac function and prevention of cardiac events.

In addition to converting enzyme inhibitors and beta blockers, dexrazoxane has been recommended for cardioprotection. Phosphodiesterase-5 inhibitors show promise for treatment of doxorubicin cardiotoxicity. This is still being studied.

**Alkylating agents**

Busulfan, cisplatin, cyclophosphamide, ilostamide and mitomycin are members of this group. Heart failure can occur with these compounds. Previous treatment with mediastinal radiation or anthracyclines may increase the risk.

Cisplatin can cause complications such as hypertension, left ventricular hypertrophy, heart block, myocardial ischemia, and myocardial infarction as long as 10 to 20 years after the remission of metastatic testicular cancer. Nephrotoxicity occurs in up to 35% of patients. This can cause hypomagnesemia and hypokalemia, resulting in cardiac arrhythmias. Cisplatin is said to promote venous thromboembolism in up to 18% of patients.

Cyclophosphamide can induce pericarditis, myocarditis, irreversible heart failure atrial arrhythmias, and bradycardia.

**Antimetabolites**

5-fluorouracil (5-FU), methotrexate and capecitabine are capable of causing ischemia. This can manifest as angina or a myocardial infarction, sometimes even in the absence of prior coronary disease. Heart failure and arrhythmias may also occur. In the case of 5-FU, the ischemia is usually reversible when the drug is stopped. Nitroglycerine and calcium channel blockers can prevent and treat ischemia.

**Antimicrotubules**

Paclitaxel has been reported to cause coronary artery spasm, sinus bradycardia, heart block, premature ventricular contractions, and ventricular tachycardia. Thromboembolism has also been reported.

Vinca alkaloids have been reported to cause angina with ECG changes, ischemia, and myocardial infarction.
Monoclonal Antibodies
Infusion of these agents commonly causes hypotension due to massive release of cytokines, as well as fever, dyspnea, hypoxia, or even death.

Alemtuzumab can also cause left ventricular dysfunction.

Bevacizumab may induce or worsen hypertension and even hypertensive encephalopathy. 70% of patients on this drug become hypertensive, sometimes within hours of initiation of therap. Subarachnoid hemorrhage may occur. Prior radiation or prior or concomitant anthracycline therapy may result in heart failure. Angina, myocardial infarction and other thrombotic events can occur.

Cetuximab sometimes causes severe, potentially fatal infusion reactions characterized by bronchospasm, urticaria, and hypotension (3% of patients). Rare cases of interstitial pneumonitis with noncardiogenic pulmonary edema have also been reported.

Rituximab infusions can cause hypotension, hypoxia, angioedema, bronchospasm, arrhythmias and rarely heart failure.

Trastuzumab (Herceptin) can cause cardiac dysfunction and heart failure. It interferes with crucial molecular pathways that are involved in cardiac homeostasis. It is especially concerning when it is used in combination with other cardiotoxic chemotherapy, such as anthracycline. The incidence of toxicity is about 2-4%. Preexisting cardiac disease, older age, prior cardiotoxic therapy, and radiation to the chest may increase the incidence. Baseline echocardiography should be done before its use. Pertuzumab and lapatinib carry the same risks. Trastuzumab cardiotoxicity is often reversible.

Cytokines
Interleukin-2 (IL-2 in high-dose IL-2 treatment results in adverse cardiovascular and hemodynamic effects similar to septic shock, such as hypotension, vascular leak syndrome, and respiratory insufficiency. Pressors and mechanical ventilation support may be required. Severe cases may result in cardiac arrhythmias, myocardial infarction, cardiomyopathy, and myocarditis.

Denileukin diftitox (Ontak) can cause vascular leak syndrome (hypotension, edema, hypoalbuminemia), as well as dyspnea, chest pain, dizziness, and syncope. Deep vein thrombosis, pulmonary embolism, and arterial thrombosis have been reported in approximately 11% of patients.

Tyrosine kinase inhibitors
This group of drugs has been shown to increase the risk of arterial and venous thrombosis, including myocardial infarction and pulmonary embolism.
Interferons
Interferon-alpha usually causes acute symptoms during the first 2 to 8 hours after treatment, including flu-like symptoms, hypotension or hypertension, tachycardia, and nausea and vomiting. In severe cases, angina and myocardial infarction have been reported.

Endocrine therapy
Endocrine therapy (e.g. tamoxifen and aromatase inhibitors) may increase the risk of cardiovascular complications.

Miscellaneous

All-trans Retinoic Acid
The retinoic acid syndrome appears in approximately 26% of cases, typically within the first 21 days of treatment. This syndrome is manifested by fever, dyspnea, hypotension, and pericardial and pleural effusions. Other major manifestations of retinoic acid syndrome have included respiratory distress, pulmonary infiltrates, pulmonary edema, and acute renal failure. Approximately 17% of patients also showed substantial decline in the left ventricular ejection fraction. Fatal myocardial infarction and thrombosis have also been noted after use of all-trans retinoic acid.

Arsenic trioxide is used in the treatment of refractory or relapsed acute promyelocytic leukemia. Arsenic is commonly known to cause ECG abnormalities, producing QT prolongation in >50% of patients. Other side effects include sinus tachycardia, nonspecific ST-T changes, and torsades de pointes. In one study, the most common acute side effect was fluid retention with pleural and pericardial effusions. In addition to prolonged QT interval, complete heart block and sudden death have also been reported. In these cases, the infusion of arsenic had been completed 7 to 22 hours before the event, underscoring the importance of continuous monitoring after the infusion has been completed.

Imatinib mesylate is associated with a significant incidence of edema, which can progress to severe fluid retention and result in pericardial or pleural effusions or generalized third-space fluid accumulation.

Pentostatin may have several cardiotoxic effects, including myocardial infarction, heart failure, and arrhythmias. Cardiotoxicity is particularly prominent when pentostatin is given with high doses of cyclophosphamide in preparation for bone marrow transplantation.

Thalidomide currently is relatively safe with regard to cardiovascular complications and is generally well tolerated. The major cardiotoxic effects of thalidomide are edema and sinus bradycardia and, rarely, deep venous thrombosis.

Etoposide
The most common cardiac side effect is hypotension, although myocardial ischemia and myocardial infarction have also been noted. Patients who have previously undergone chemotherapy or mediastinal radiation may be at increased risk for myocardial infarction after etoposide treatment. Concomitant chemotherapy with other agents may also be a predisposing factor.
Homoharringtonine can be associated with severe hypotension—a dose-related and occasionally rate-limiting effect that may be related to its calcium channel–blocking activity. Premature ventricular contractions, ventricular tachycardia, and atrial fibrillation have been reported.

Taxanes may cause bradycardia, atrioventricular block, atrial and ventricular arrhythmias, heart failure or myocardial ischemia.

Everolimus and tensirolimus can case hypertension.

Dasatanib, which is used for treatment of Philadelphia Chromosome positive leukemia can induce pulmonary hypertension, which may become permanent.

Bleomycin can induce pulmonary hypertension due to lung injury. This can be mitigated by therapy with statins, rho kinase inhibitors, endothelin receptor antagonists, arginase inhibition, inhaled NO or sildenafil.

Cardiotoxicity Associated With Radiation Therapy

Radiation to the thorax can damage the pericardium, myocardium, valves, and coronary vessels or conduction system. The pericardium is the most commonly involved. Constrictive pericarditis can result. High doses of radiation, inadequate shielding, preexisting cardiovascular risk factors and concurrent doxorubicin increase the risk. The presentation may be angina, dyspnea, or heart failure, or even sudden death. Vascular injury can also be silent and show up only as a new myocardial perfusion defect. The mean interval for developing coronary artery disease after radiation therapy is approximately 82 months. Radiation cardiotoxicity rarely develops during the radiation therapy. The risk is lifelong and requires long-term followup. An annual history and physical is recommended, as well as an echocardiogram if a murmur is detected. An echocardiogram is also advised at 5 to 10 year intervals as well as periodic stress testing. This should preferably be a stress echocardiogram or a stress MRI, rather than a nuclear study, in order to avoid additional radiation.

Lancellotti et al recommend a baseline echocardiogram before starting radiation. Afterward, patients should be monitored annually for evidence of heart disease. Patients at risk should have echocardiograms every 5 years, and others every 10 years. Cardiac risk factors should be addressed in all. In equivocal cases, additional imaging (computed tomography, magnetic resonance imaging, nuclear imaging) is advised (Donnellan et al).

Percutaneous intervention or coronary artery bypass grafting are used. Radiation causes mediastinal fibrosis, which makes surgery more difficult and prone to complications. Radiation therapy also causes pericardial thickening effusion or pericarditis. The interval between radiation therapy and symptom development in patients with radiation-induced pericardial disease is variable, ranging from 2 to 145 months. Pericardial effusion is typically an early presentation, whereas pericardial constriction usually appears after 18 months. Myocardial fibrosis is also a side effect of radiation therapy. Valvular heart disease often develops due to fibrous thickening of cardiac valves. The mean time from radiation to onset of symptoms is approximately 98 months.
Radiation to the neck (e.g. for thyroid or laryngeal cancer) carries a risk of carotid artery stenosis. These patients should be monitored by doppler imaging for prevention of stroke or transient ischemic attacks. Radiation-induced carotid disease produces carotid lesions that are more extensive than that due to atherosclerosis. These are less amenable to conventional carotid endarterectomy, but can be treated with stenting.

**Monitoring Cardiovascular Toxicity**

Prior to initiating therapy, the patient should undergo a complete history and physical examination, as well as baseline ECG, echocardiogram, and biomarkers. Patients considered to be at higher risk warrant consideration of less cardiotoxic regimens.

Traditionally, oncologists order echocardiograms prior to starting treatment and periodically thereafter. This is a relatively insensitive test of cardiotoxicity. Echocardiographic estimation of left ventricular ejection fraction is somewhat imprecise, particularly in the case of small changes. Serial studies could thus be misleading in either direction. The development of diastolic dysfunction may be an earlier manifestation of anthracycline toxicity. A reduction in ejection fraction of 20% from baseline should prompt consideration of stopping therapy. Another concern is that, once left ventricular ejection fraction has been found to be reduced by conventional methods, it may be too late to reverse it. More sensitive are the Doppler derived diastolic indexes and other measures of diastolic dysfunction, which precede systolic dysfunction (Bovelli). Tissue doppler imaging is a promising method that may provide an earlier warning signal. Strain imaging is also a more sensitive tool (Smiseth, Vejpongsa).

Other methods of detecting cardiac toxicity have included the electrocardiogram, magnetic resonance imaging, radionucleide ventriculography, exercise or dobutamine stress echocardiography, and endomyocardial biopsy. Some of the findings of interest include ejection fraction, pulmonary artery pressure, and pericardial disease. Cardiac monitoring is used to detect arrhythmias.

While these tools are valuable, they are generally insensitive to early cardiac involvement. They do not necessarily predict the eventual development of heart failure. In contrast, Cardinale et al have shown the measurement of troponin I can effectively risk-stratify these patients, and potentially allow reversal of early stages of cardiotoxicity. They found this biomarker useful in patients undergoing treatment with a many different regimens for various types of cancer. Patients with normal troponin level had a good prognosis and did not develop a significant reduction of left ventricular ejection fraction. Those with elevated troponins required careful monitoring and prophylactic therapy. The more persistent the rise, the more likely was late cardiac dysfunction. If the increase persisted for a month, over 80% of patients developed left ventricular dysfunction.

B-type natriuretic peptide has also emerged as a useful biomarker to detect and even predict left ventricular dysfunction. It was much more sensitive than measurement of ejection fraction. It appears to be less reliable than troponin.
Sawaya et al conducted a small study of patients with breast cancer who were receiving chemotherapy. In their trial, three biomarkers were used: troponin I, NT-proBNP and the interleukin family member (ST2). They also employed echocardiography with peak systolic strain measured by speckle tracking. Changes in left ventricular ejection fraction alone on completion of therapy did not predict the development of cardiotoxicity. However, measurement of troponin I and of strain did anticipate its development.

**Strategies to Reduce Cardiovascular Toxicity and Manage Complications**

A baseline cardiovascular assessment, including echocardiography, should be done on patients who are to undergo cancer therapy. All cardiovascular risk factors should be addressed, probably even more aggressively than in the average patient. Obesity should be corrected, and regular exercise is recommended. Higher risk patients should ideally be monitored by a cardiologist during and after therapy.

A number of changes in the techniques of drug delivery have been shown to reduce the incidence of cardiac toxicity. The rate of infusion may be important. A total dose of anthracycline of <400 mg/m² seems to be safer, but even this precaution often fails. There is no consensus as to the best approach for detecting, preventing or managing anthracycline toxicity. One strategy is to administer the drug by continuous infusion. Liposome encapsulation of the drug is another method. This alters the distribution in a way that distributes more of the drug to the tumor while restricting its access to the heart and other organs. Epirubicin and idarubicin are less toxic congeners, which could be employed. Finally, several drugs (ACE inhibitors, ARB's and beta-blockers) have been thought to be cardioprotective. The only FDA approved drug for this purpose is dexrazoxane an iron chelating agent. However, there is concern that it could interfere with the antitumor effect of anthracycline if given concurrently (Vejpongsa).

During administration of chemotherapy, particularly with 5-FU or paclitaxel, the vital signs should be monitored frequently.

The combination of trastuzumab, anthracyclines, and cyclophosphamide can lead to severe heart failure in up to 16% of patients with breast cancer. These drugs are no longer given simultaneously.

As in other forms of systolic heart failure, treatment of cardiomyopathy due to chemotherapy should usually include ACE inhibitors and beta-blockers. Other causes of heart failure should, of course be considered. Cardinale also found that early treatment with enalapril in high-risk patients dramatically reduced the incidence of cardiotoxicity (both heart failure and arrhythmias). She started with 5 mg. daily dose, which was slowly titrated either to 20 mg. or the highest tolerated dose. This may be a class effect, since lisinopril has also been shown to be effective. A variety of mechanisms have been proposed, such as scavenging of free radicals and antioxidant effects. In selected patients with refractory heart failure implanted devices or even cardiac transplantation could be indicated. Life style modification, including exercise training, is also beneficial to these patients.

Carvedilol has recently been reported to significantly protect against anthracycline toxicity. It is initiated simultaneously with chemotherapy. This is believed to be due to its antioxidant effects. The dose is controversial, ranging from 12.5 to 50 mg daily. Patients in heart failure
might best be started at 3.125 mg twice daily. Metoprolol does not appear to share this protective effect.

Schroeder recommends that both ACE inhibitors and carvedilol should be administered to these patients. Neither is approved for this indication, but the safety of these drugs and mounting evidence favors this approach.

Hypertension can be managed with ACE inhibitors, and calcium channel blockers. However, nondihydropyridine calcium channel blockers should not be used with VEGF inhibitors, as they raise the blood level. Severe hypertension may require interruption of chemotherapy.

While chemotherapy itself usually poses little risk for arrhythmias, vomiting and diarrhea which may accompany their use can cause electrolyte imbalance. This could be a problem if other agents are used, which also prolong the QT interval (such as arsenic, ondansetron, many psychotropic drugs, some antibiotics, etc.).

In some cases, consideration of revising or even withdrawing chemotherapy should be considered. The conflicting goals of curing or suppressing the cancer versus avoiding serious cardiotoxicity requires a dialog between the oncologist and the cardiologist.

The use of statins is recommended to achieve low-density lipoprotein cholesterol <100 mg/dl. Recently initiation of statin therapy prior to chemotherapy protected against the development of heart failure in women receiving anthracyclines for breast cancer. The authors did not specify which statin was used (presumably various ones) or the dose employed. Some of the patients were also on ACE inhibitors and/or beta blockers. Desrazoxane, an intravenous drug, is approved for mitigating cardiotoxicity associated with doxorubicin in selected patients.

The use of sulfonylurea or biguanide (metformin) is recommended for women with type II diabetes mellitus to achieve a glycosylated hemoglobin (HbA1c) <7%.

Following treatment, patients who have received radiation and/or chemotherapy with cardiotoxic agents should continue to be monitored clinically, probably for years, if not indefinitely.

A very comprehensive and detailed discussion of cardiovascular effects of chemotherapy may be found in the article by Herrmann et al.

**Tumor lysis syndrome**

The tumor lysis syndrome has been seen with every type of tumor, usually a leukemia or lymphoma. It typically occurs as a result of chemotherapy, but has been seen with radiation and even spontaneously. Early recognition is important, since it has high rate of serious complications, including hyperkalemia, hyperphosphatemia, hypocalcemia and kidney failure. The hyperkalemia can induce a variety of serious arrhythmias. Heart failure can result from overzealous rehydration.
References


Kalay N et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. JACC 2006; 48:2258-2262


Cardinale D et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. JACC 2000; 36:517-5220


Vejpongsa P and Yeh ETH. Prevention of anthracycline-induced cardiotoxicity. J Am Coll Cardiol 2014; 64:938-945
Sutter TM and Ewer MS. Cancer drugs and the heart: importance and management. Eur Heart J 2013; 34:1102-1111
Donnellan E et al. Radiation-induced heart disease: a practical guide to diagnosis and management. Cleveland Clinic J Med. 2016; 83:914-922