Review

Cardio-Oncology/Onco-Cardiology

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ABSTRACT

An understanding of onco-cardiology or cardio-oncology is critical for the effective care of cancer patients. Virtually all antineoplastic agents are associated with cardiotoxicity, which can be divided into 5 categories: direct cytotoxic effects of chemotherapy and associated cardiac systolic dysfunction, cardiac ischemia, arrhythmias, pericarditis, and chemotherapy-induced repolarization abnormalities. Radiation therapy can also lead to coronary artery disease and fibrotic changes to the valves, pericardium, and myocardium. All patients being considered for chemotherapy, especially those who have prior cardiac history, should undergo detailed cardiovascular evaluation to optimize the treatment. Serial assessment of left ventricular systolic function and cardiac biomarkers might also be considered in selected patient populations. Cardiotoxic effects of chemotherapy might be decreased by the concurrent use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or beta-blockers. Antiplatelet or anticoagulation therapy might be considered in patients with a potential hypercoagulable state associated with chemotherapy or cancer. Open dialogue between both cardiologists and oncologists will be required for optimal patient care.

Introduction

Cardio-oncology or onco-cardiology are terms coined to describe the field of integrative medicine between cardiologists and oncologists. Close interactions between the 2 specialties are required for the optimal care of many patients with cancer. Cancer patients with prior cardiac disease are usually more susceptible to the cardiotoxic effects of oncologic treatment. Careful attention to past cardiac history is required to optimize the treatment of patients undergoing chemotherapy. Many chemotherapeutic agents are potentially directly cardiotoxic and might result in drug-induced cardiomyopathies and heart failure. Chemotherapeutic agents might also result in repolarization changes or patient-drug interactions that might be associated with life-threatening cardiac arrhythmias such as polymorphic ventricular tachycardia. Although cardiologists are expected to have a clear understanding of the potential cardiac effects of chemotherapy, many might not be well versed in this field. It is important that clinical cardiologists acquaint themselves with the cardiac side effects of oncologic therapy. Effective communication between cardiologists and oncologists is critical for the optimal care of cancer patients.

All antineoplastic agents target tumor cell death but might result in collateral injury to other tissues. The effects of chemotherapy on rapidly proliferating cell lines are well recognized by most cardiologists. Myelosuppression and gastrointestinal toxicities associated with chemotherapy are well recognized as side effects of antineoplastic treatment. Less commonly appreciated is that the heart might be injured by cancer treatment. Antineoplastic cardiac injury can manifest in a myriad of ways. Patients with anthracycline-induced cardiomyopathy might present with congestive heart failure. Patients undergoing chemotherapy with 5-fluorouracil or tyrosine kinase inhibitors have been documented to have drug-induced cardiac ischemia. Arrhythmias and conduction abnormalities have been well described to be associated with the use of taxanes. Pericarditis might be seen in the setting of chemotherapy with cyclophosphamide or cytarabine. Interleukin-2 administration often results in enhanced vascular permeability and associated hypotension caused by intravascular volume depletion. It is important that clinical cardiologists recognize the potential cardiovascular side effects of chemotherapy.

In addition to causing cardiac injury and associated arrhythmias, chemotherapeutic treatment might result in electrocardiographic repolarization abnormalities and an enhanced susceptibility to polymorphic ventricular tachycardia. Repolarization abnormalities might occur immediately after chemotherapeutic administration or might present in a delayed fashion. The administration of arsenic affects the trafficking of potassium channels and results in QT prolongation weeks after initial therapy. Antineoplastic agents might also affect hepatic metabolism and the associated clearance of other drugs that might contribute to QT prolongation. A recent review of potential cardiac complications of cancer therapy has been published.[1]

Cardiotoxicities Associated With Antineoplastics Therapy

In general, cardiovascular side effects of antineoplastic therapy can be broken down into 5 categories. These 5 categories include: direct cytotoxic effects of chemotherapy and

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associated cardiac systolic dysfunction, cardiac ischemia, arrhythmias, pericarditis, and chemotherapy-induced repolarization abnormalities.

Cardiac Systolic Dysfunction

Although any chemotherapeutic agent might result in cardiac injury, the therapies most commonly associated with direct cytotoxic cardiac injury include: anthracyclines, anthraquinones, monoclonal antibodies, tyrosine kinase inhibitors, alkylating agents, and interferon alpha administration. Anthracyclines, such as doxorubicin or epirubicin, cause inhibition of DNA polymerases and DNA fragmentation. Cardiotoxic effects of anthracyclines are felt to be related to myocyte injury by oxygen free radicals and lipid peroxidation. This effect appears to be dose dependent and is noted in up to a quarter of patients receiving a cumulative doxorubicin dose of 550 mg/m^2. The cardiotoxic effects of anthracycline therapy appear to be increased in patients with pre-existing heart disease or advanced age.[2] Cardiotoxicity might also be increased when anthracyclines are used in combination with other chemotherapeutic agents with potential cardiotoxicity, such as trastuzumab (Herceptin) or taxanes.[3,4] The use of a chelating agent, such as dexrazoxane, appears to reduce the cardiotoxicity associated with anthracyclines.[5] As the cardiotoxicity associated with anthracyclines has been predominantly dose dependent, the use of dexrazoxane has been considered in patients receiving greater than 300 mg/m^2 of doxorubicin.[6]

Mitoxantrone, an anthraquinone with properties similar to anthracyclines, has also been associated with a dose-dependent cardiotoxic effect.[7] Trastuzumab, an inhibitor of the HER2/neu receptor, is frequently used in patients with receptor-positive metastatic breast cancer. Up to a third of patients treated with trastuzumab might develop a drug-induced cardiomyopathy.[8] Interestingly, trastuzumab-induced cardiotoxicity does not appear to be dose dependent and often is reversible with discontinuation of this agent. The continuation or reinitiation of trastuzumab after recovery of cardiac systolic function in patients with documented impaired left ventricular function might be remarkably well tolerated.[9] Tyrosine kinase inhibitors, such as imatinib, dasatinib, sunitinib, and lapatinib might be associated with the development of heart failure in up to 8% of patients treated with these agents.[10–14] Cyclophosphamide has also been described to cause an acute cardiomyopathy with high-dose therapy.[15] Interferon alpha administration has been described to be associated with a cardiomyopathy that might be reversible upon cessation of its use.[16] Bevacizumab, an inhibitor of vascular endothelial growth factor, is similarly associated with heart failure in up to 0.3% of patients.[17] With all agents, chemotherapy-induced cardiotoxicity appears to be enhanced in patients with antecedent impairment of left ventricular function. Although these agents are most commonly associated with direct cardiotoxicity, it is likely that all antineoplastic agents might have some potential cardiotoxic effects.

Cardiac Ischemia

Chemotherapeutic treatment might also result in cardiac ischemia. Cardiac ischemia associated with antineoplastic therapy has been most commonly described in patients who received purine analogues, such as 5-fluorouracil, topoisomerase inhibitors, and antitumor antibiotics. Patients treated with high-dose 5-fluorouracil might develop coronary vascular endothelial dysfunction and coronary thrombosis. Rare deaths related to myocardial infarction have been noted.[18] Coronary vasospasm has been proposed to cause the cardiac ischemia associated with 5-fluorouracil, but this concept has been debated recently.[19] The risk of cardiac ischemia appears to vary, ranging from 1%–68% in the patients treated with high-dose infusions of 5-fluorouracil.[20,21] Still, patients with a history of ischemic heart disease should be followed more closely as cardiac ischemic events appear to be enhanced in patients with coronary artery disease who are treated with high-dose 5-fluorouracil.[22] Etoposide, a topoisomerase inhibitor, has also been described to be associated with vasospastic angina and myocardial infarction.[23–25] The use of bleomycin has also been described to possibly result in cardiac ischemia and in rare instances chest pain caused by pericarditis.[26,27] Vinblastine therapy has also been associated with myocardial ischemia, vaso-occlusive complications, and myocardial infarction.[28] Ischemic events have also been described with the use of bevacizumab, sorafenib, and taxanes.[29–31] Again, although the above agents have been most commonly described to be associated with cardiac ischemia, it is possible that any antimitotic agent could result in vascular endothelial damage and cardiac ischemia. As it is recognized that vascular endothelial damage might serve as a substrate for progressive atherogenesis, it would be expected that atherosclerotic vascular disease might be enhanced in patients treated with cancer chemotherapy. The potential atherogenic effects of chemotherapy, however, have not been clearly established.

Arrhythmias

Cardiac arrhythmias have been described with many chemotherapeutic protocols. These arrhythmias might be the direct result of cardiotoxicity, as with the use of anthracyclines, caused by cardiac ischemia or related to metabolic changes associated with the use of chemotherapy. As an example of the last category, interleukin-2 administration is associated with enhanced capillary permeability and intravascular volume depletion. The vascular leak syndrome caused by interleukin-2 administration might be associated with a variety of supraventricular and ventricular arrhythmias in up to 10% of patients treated.[32] The use of cisplatin similarly might result in renal failure and metabolic

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fluxes associated with vigorous hydration that enhances the development of arrhythmias.

Repolarization abnormalities with QT prolongation might be the direct result of chemotherapy induced by ion channel block. Arsenic trioxide is used in the treatment of acute promyelocytic leukemia. The use of arsenic has been associated with QT prolongation in up to 40% of patients.[33] Arsenic inhibits cellular ion channel trafficking, specifically inhibiting unwrapping of membrane channels synthesized by the Golgi complex. Accordingly, there is a time delay between exposure to arsenic trioxide and electrophysiologic effects.

Repolarization abnormalities induced by chemotherapy might also be the result of changes in hepatic metabolism caused by chemotherapy and a change in clearance of other drugs associated with QT prolongation. Imatinib, a tyrosine kinase inhibitor, inhibits hepatic drug metabolism performed by the CYP3A4, CYP1A2, CYP2D6, CYP2C9, and CYP2C19 systems. The concurrent use of imatinib and other drugs, such as ketoconazole, phenothiazines, or quinolones, might result in progressive QT prolongation directly related to impaired hepatic metabolism of these other agents.[34,35] Careful attention to potential drug-drug interactions is required with the use of imatinib.

Pericarditis

Pericarditis has been well described in patients undergoing therapy with cyclophosphamide, cytarabine, and bleomycin.[15,26,36] Inflammatory pericarditis, however, might be expected in a patient with significant myocardial injury and associated chemotherapy-induced myopericarditis.

Thrombophilia

Cancer chemotherapy might also result in thrombophilia. Thromboembolic complications have been associated with the use of thalidomide, lenalidomide, vorinostat, and erlotinib.[37–39] Although neoplastic conditions might be associated with a hypercoagulable state, chemotherapeutic agents might result in vascular injury and a locally hypercoagulable state. The routine use of aspirin in patients treated with these agents has been suggested by several authors. Warfarin anticoagulation, however, is usually recommended for patients with documented thromboembolic complications.[37]

Effects of Radiation Therapy

The use of radiation therapy for cancer treatment might also increase the risk of cardiac toxicity. Radiation injury to the heart includes not only constrictive pericarditis and myocardial fibrosis, but also valvular and coronary artery lesions.

Radiation therapy causes fibrous thickening of the pericardium, which might lead to pericarditis, pericardial effusion, and rarely, cardiac tamponade.[40] The right side of the heart is usually more frequently involved.[40,41] However, the incidence of pericarditis has decreased with the changes in methods of radiation therapy administration.[42]

There is a high prevalence of diastolic dysfunction in asymptomatic patients after mediastinal irradiation, most likely due to myocardial fibrosis. The presence of diastolic dysfunction is associated with stress-induced ischemia and a worse prognosis.[41,43]

The valves might also undergo fibrotic changes; changes to valves on the left side are more common than those on the right.[40,41]

A significantly higher risk of death due to ischemic heart disease has been reported for patients treated with radiation for Hodgkin's disease and breast cancer, although a fair number of patients might remain asymptomatic.[44,45] Damage to endothelial cells is a central event in the pathogenesis of damage to the coronary arteries. Coronary artery disease can be reasonably ascribed to the effects of chest irradiation when the patients are young and free from risk factors, especially if the obstructions are ostial and there is important damage to other cardiac structures.[40]

In addition, it is suspected that the concurrent use of radiation therapy and chemotherapy might have additive cardiotoxic effects.[46]

Clinical Evaluation

All patients being considered for chemotherapy should undergo a detailed cardiovascular evaluation. Appropriate documentation of cardiac disease, including an analysis of left ventricular function or arrhythmias, should be performed as part of routine oncologic evaluation. Patients with a history of heart failure or arrhythmias should undergo cardiac evaluation prior to initiation of chemotherapy. Patients being considered for chemotherapy are advised to undergo a baseline electrocardiogram and should be evaluated for conduction block or repolarization abnormalities.[47–49]

Serial assessment of left ventricular function is suggested in patients in whom treatment with anthracyclines, trastuzumab (Herceptin), tyrosine kinase inhibitors, or antitumor antibiotics is being considered, although standards for surveillance screening intervals have not been established. It is reasonable to consider at least a single baseline assessment and repeat evaluation of left ventricular function after the administration of a total dose of >150 mg/m^2 of doxorubicin, although recommendations widely vary among the literature.[50,51] Similar recommendations for screening intervals of cardiac function with trastuzumab cannot be made as cardiotoxicity might occur in a non–dose-dependent fashion.[47]

When combined chemotherapy with potential cardiotoxicity is utilized, repeat assessment of left ventricular function might be considered at an earlier interval. There is evidence that the combined use of anthracycline-based chemotherapy

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and the concurrent use of trastuzumab increases the risk of potential cardiotoxicity.[3]

Routine assessment of cardiac function, even in asymptomatic individuals, is helpful as there is evidence that in asymptomatic patients the discontinuation of cardiotoxic chemotherapy when left ventricular systolic dysfunction is first identified might allow for reversible improvement in cardiac function.[52]

Routine evaluation of cardiac biomarkers, including troponin I and B-type natriuretic peptide (BNP), might be considered in patients undergoing chemotherapy with cardiotoxic agents such as anthracyclines. Elevated biomarker levels have been shown to correlate with the development of progressive cardiotoxicity. In a series of 703 patients receiving high-dose chemotherapy, those documented to have elevated levels of troponin I 1 month after initiation of chemotherapy had a higher rate of cardiovascular events or impairment of left ventricular function.[53] Similarly, persistent elevations in BNP have been documented to correlate with anthracycline-induced cardiotoxicity.[54]

Potential Treatments

Cardiotoxic effects of chemotherapy might be decreased by the concurrent use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or beta-blockers.[55–57] In a study of patients undergoing high-dose chemotherapy, the routine use of enalapril appeared to be associated with preservation of left ventricular systolic function.[55] Similarly, in a smaller study addressing prevention of cardiotoxicity associated with anthracycline use, carvedilol administration appeared to prevent progressive impairment of left ventricular function associated with anthracycline use.[56] Most interesting is the recent finding that stem cell therapy might be useful in the treatment of anthracycline-induced cardiomyopathy.[58]

Issues regarding a potential hypercoagulable state associated with chemotherapy or cancer have been previously addressed. There is no clear recommendation for a prophylactic anticoagulation strategy in patients undergoing chemotherapy. The risk of thromboembolic complications is clear but appears to be relatively low.[37–39] It would be reasonable to consider aspirin therapy in selected patients undergoing chemotherapy.[37]

Conclusion

An understanding of onco-cardiology or cardio-oncology is critical for effective patient care of the cancer patient. It is clear that with the advent of newer chemotherapeutic protocols and the increased incidence of cardiovascular disease and population, open dialogue between both cardiologists and oncologists will be required for optimal patient care.

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