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Mini Review

Vascular Damage Induced by Chemotherapy and Radiotherapy in Oncological Patients

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Abstract

The growing number of aged patients with cancer and protracted periods of treatment with chemotherapic drugs and radiotheraphy have made the administration of cardiovascular side effects and treatment-related cardiotoxicity an important issue. For these reason, Cardio-oncology has received increasing attention. The number of cases of cardiotoxicity, especially atherosclerotic lesions have increased, making the involvement of onco-cardiologists fundamental for effective pathology management. Monitoring for the cardiovascular side effects of oncological treatment should include evaluation of cardiovascular disease (CVD) risk and the use of imaging to value the extent of any damage.

Keywords: Cardio-oncology, Cardio-vascular toxicity, Chemiotheraphy, Radiotheraphy, Cancer, Atherosclerosis

Introduction

Progress in cancer therapy, particularly the development of chemotherapy, immunotherapy and radiotherapy, have markedly improved outcomes in patients with cancer. However, it's difficult to avoid collateral damage to non-targeted organs with systemic chemotherapies and the capacity to impair the endothelium and vascular system as well as the heart with drug-specific effects has been well recognized. Both chemotherapy and radiotherapy lead to inflammation and endothelial cell activation, crucial for the early stages of atherosclerosis. Numerous conventional chemotherapic drugs, as well as some of the newer antiangiogenic drugs and signalling inhibitors, especially in combination treatments, predispose to cardiovascular complications including hypertension, ischemic heart disease, and arterial and venous thrombosis. In this paper, we describe the mechanisms and the management of vascular damage in patients treated with radiotherapy and chemotherapy.

Radiotherapy

Radiotheraphy is often used for the treatment of different types of cancer and has been proven to increase the risk for Coronary Artery Disease (CAD). Although it is difficult to confirm the exact incidence of radiation-induced accelerated atherosclerosis, it has been documented in patients who did not have the usual risk factors for CAD. The incidence of CAD and the time it takes for it to appear after radiation therapy is dosage dependant. Intimal disruption and luminal stenosis or occlusion are the two main consequences of artery irradiation, according to histological research. Radiotherapy has direct effects on cells in the pathogenesis of vascular damage with endothelial cell involvement as an early sign of radiation-induced vascular injury. It causes endothelial damage with increased expression of interleukins (e.g., IL-6 and IL-8), intercellular cell adhesion molecules (e.g., ICAM-1), fibroblast growth factor and stimulates a neutrophil response with secondary cytokines release.

Furthermore, radiation can induce apoptosis throught p53 in response to DNA damage or mithocondrial-activated apoptosis. Endothelial injury, with changes in the permeability of the endothelium, leads to additional fibrosis and neovascularization in the vessel walls and in patients with previously present atherosclerotic plaques further promoting plaque instability [1]. Patients with preexisting CAD are particularly vulnerable. Those who received thoracic radiation for lung cancer had progression in coronary artery calcium score, a known predictor of CAD, compared with those who did not [2]. Aorta and other peripheral arteries, including the subclavian and iliofemoral, can be also involved with ischaemic limb symptoms. After mediastinal, cervical, or cranial radiation, the risk of stroke is doubled. Irradiation of cerebral small vessels may cause endothelial injury and thrombus development. Three mechanisms have been described in medium and large vessels: vasa vasorum occlusions with necrosis and fibrosis of the medial tunic; fibrosis of the adventitial tunic and accelerated atherosclerosis, leading to increased intima-media thickness (IMT), carotid stiffness and advanced atherosclerosis (occurring 10 years after radiotherapy) [3].

Thus, evaluation of carotid arteries through echocolordoppler to exclude subclinical atherosclerosis could be used for a complete cerebrovascular risk estimation. Management of radiation-related CAD is similar to the atherosclerotic -related one. Coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) have both been used to treat this kind of CAD. CABG may be more difficult in patients with radiation-induced atherosclerosis because of mediastinal fibrosis. Heart-sparing radiation techniques could overcome the problem in part. When there is a history of mediastinal irradiation in the anamnesis, even if patients are asymptomatic, evaluation for CAD and vascular damage is indicated, starting 5 years after the completion of therapy and at least every 5 years thereafter.

Chemotherapy

Chemotherapy-induced vascular toxicity is related to the initiation and progression of atherosclerosis. Vascular damage related to chemotherapy frequently reflects endothelial dysfunction, with loss of vasodilatation effects and suppressed anti-inflammatory and vasoreparative functions. Platelets are a link between atherosclerosis and cancer. Activated platelets contribute to the inflammatory burden in atherosclerosis by releasing their inflammatory mediators. Platelets have been demonstrated to oxidize low-density lipoprotein (LDL), which is a primary contributor to the formation of atherosclerotic plaques. Platelets also interact with neutrophils and eosinophils to promote the formation, expansion, and thrombosis of atherosclerotic plaques, just as they do in atherosclerosis. Platelets contribute to the recruitment of inflammatory cells to tumors, which promotes tumor growth. Furthermore, the procoagulant effect of cancer per se, enhances platelet activity and decreases endothelial nitric oxide (NO) production, which may enhance atherosclerotic plaque formation and raise the risk of cardiovascular events [4].

Various classes of chemotherapic drugs have been known to cause cardiotoxicity and vascular toxicity. It has been proved that Cisplatin and other platinum-based drugs can increase the risk of CAD due to endothelial damage, atherosclerosis and plaque erosion [3]. Long-term patients treated with cisplatin are associated with an increased risk of developing dyslipidemia, hypertension, metabolic syndrome and obesity. In these patients cisplatin showed a significant increase in IMT after 12 weeks. Cisplatin may also increase the risk of arterial thrombosis with consequent myocardial and cerebrovascular ischemia. Mechanisms involved in 5-FU-induced cardiotoxicity include interstitial fibrosis, myocardial inflammation, endothelial damage, arterial vasoconstriction and procoagulant changes including increased platelet aggregation [5]. In healthy adults, vascular-endothelial growth factor (VEGF) plays an important role in wound healing and the repair of vascular endothelial injury by promoting the production of nitric oxide (NO) and prostacyclin (PGI2) to maintain normal blood flow. In pathological settings like CAD, VEGF production is stimulated by hypoxia-inducible factors (HIFs) associated with tissue ischemia, promoting compensatory angiogenesis.

Furthermore, VEGF can be produced by cancer cells, which promotes angiogenesis and proliferation needed for the extension of cancer. VEGF inhibition is associated with decreased endothelial NO production, vasoconstriction, rarefaction of capillary beds and increases in arterial stiffness [6]. On the other hand, endothelial dysfunction and hypoxia cause vasoconstriction with the promotion of endothelin-1 (ET-1) production. Inhibition of tumor angiogenesis through the block of VEGF with anti–VEGF monoclonal antibody (bevacizumab) or tyrosine kinase inhibitors (TKIs) (sorafenib, sunitinib or pazopanib) is associated with increased arterial thrombotic events, including myocardial infarction (MI). Angiogenesis inhibitors cardiotoxicity is dose-dependently [7]. Chronic treatment with angiogenesis inhibitors can lead to a capillary rarefaction and a reduction in the peripheral arteriolar bed, associated with microthrombus formation, thromboembolism and microangiopathy. In a murine model, inhibition of VEGF led to endothelial dysfunction and accelerated atherosclerosis.

Although the risk of cardiovascular events is reasonably low with imatinib, newer TKIs, like ponatinib and nilotinib, have shown to have a higher incidence of cardiovascular events compared to imatinib. Severe peripheral artery disease (PAD), atherosclerotic and non-atherosclerotic, can occur in 30% of the patients treated

with TKIs, particularly with ponatinib. PAD can appear during the first months of treatment or after many years. The management of the cardiovascular side effects caused by chemotherapic drugs has become an important concern. Currently, there is no recommendation about primary prevention for cardiotoxicity caused by chemotherapy-related atherosclerosis. A reasonable pharmacological treatment, especially in secondary prevention, could be represented by aspirin and statins.

Patients with multiple risk factors for atherosclerosis who are at a high risk for thrombosis should benefit from treatment with aspirin and statins, which are considered relatively safe in patients with cancer. In patients treated by percutaneous coronary intervention who are subsequently found to have a malignancy, the minimal duration of dual antiplatelet therapy should be pursued as far as reasonable, according to the most recent guidelines, to limit bleeding risk. However, traditional platelet inhibitors may be limited in their usage in cancer patients due to an increased risk of bleeding. Patients should also have repeat investigations to ascertain the rate of progression of any atherosclerotic disease as well as regular echocardiographic monitoring [4].

Conclusions

Both radiotherapy and chemotherapy regimens are associated with increased rates of atherosclerotic CVD. Monitoring for the cardiovascular consequences of oncological treatment should include assessment of CVD risk and the use of imaging to ascertain the extent of any damage. The threshold for initiation of cardiovascular preventive therapies needs to be lower than that predicted by classical CVD risk factor-based calculators.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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