Editorial

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Cardiotoxicity and Cancer Therapy

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A fundamental concept of treatment is to do no harm. However, with cancer treatment this is not always possible.

Chemotherapy is associated with cardiovascular (CV) complications.[1,2] This risk is even greater in the elderly patients and patients with established CV disease. More specifically, tachyarrhythmias (eg, cisplatin), bradyarrythmias (eg, paclitaxel), or QT prolongation (eg, dasatinib) have been reported. Furthermore, myocardial necrosis, coronary vaso-occlusion or vasospasm, pericardial disease (eg, cytarabine), endocardial fibrosis (eg, busulfan), and heart failure can occur. Hypotension (eg, fludarabine) or hypertension (eg, vinca alkaloids) has also been reported.[1,2] Cardiotoxicity, endothelial injury, and Takotsubo syndrome have been reported in patients treated with 5-fluorouracil (5-FU).[3-5] Cardiotoxicity to 5-FU was reported 35 years ago.[3-5] Cardiotoxicity of chemotherapy has been reported in patients ranging from children through adults (eg, with anthracyclines or cisplatin).[6] Adriamycin-induced myocyte damage has been attributed to the production of toxic oxygen free radicals.[7] This can cause lipid peroxidation of membranes resulting in vacuolation, irreversible damage, and myocyte replacement by fibrous tissue.[7]

The use of angiogenesis inhibitors in cancer therapy is expanding as are the associated adverse CV effects (eg, hypertension, thromboembolism, left ventricular dysfunction, and QTc prolongation).[2,8] Vascular endothelial growth factor (VEGF) plays a role in maintaining vascular homeostasis via the production of the vasodilator nitric oxide (NO) and decreased vascular resistance through the generation of new blood vessels.[2,8] Therefore, it is not surprising that inhibition of VEGF signaling (eg, by bevacizumab, aflibercept, sorafenib, sunitinib, pazopanib, vandetanib, axitinib, regorafenib, or cabozantinib) can be associated with hypertension.[2,8] An increased risk of arterial thromboembolic events has also been linked to the use of bevacizumab, aflibercept, and a number of the antiangiogenic tyrosine kinase inhibitors.[2,8]

The risk of thrombotic events is increased in patients with malignant disease.[9] The proposed mechanisms include release of procoagulants by tumor cells (tissue factor or tumor cells dying as a result of treatment) and expression of procoagulant activity by normal host cells such as monocytes, platelets, and endothelial cells.[9] Furthermore, surgery, chemotherapy, indwelling central venous catheters, platelet activation, reduced fibrinolytic activity, decreases in proteins C and S, endothelial cell injury as well as disease- and patient-specific risk factors may contribute to the risk of thrombosis.

Hormonal agents are used for the treatment of cancer.[10] Compared with aromatase inhibitors, tamoxifen use is associated with a higher rate of venous thromboembolic events but possibly with decreased odds of developing CV disease.[11] Tamoxifen is an antiestrogen with weak estrogenic effects that may contribute to its prothrombotic activity. Tamoxifen raises triglyceride (TG) levels and increases the risk of acute pancreatitis.[10] Other agents used in estrogen receptor-positive breast cancer such as toremifene (a selective estrogen receptor modulator) show reduction in total cholesterol, low-density lipoprotein cholesterol, and TGs.[12] The lipid effects of these drugs and their potential effect on the risk of cardiac events are complex and beyond the scope of this editorial.

Mediastinal radiotherapy (especially to the left chest) can damage virtually any component of the heart, including the pericardium, myocardium, valves, coronary arteries, capillaries, and conducting system.[13-17] Pericarditis is the typical acute manifestation of radiation injury, while chronic pericardial disease, coronary heart disease (CHD), cardiomyopathy, valvular disease, and conduction abnormalities can appear years or decades later.[13-17] The lesions leading to diseases exhibit typical features of atherosclerosis, including lipid accumulation, inflammation, and thrombosis.[13-17] Moreover, the presence of vascular risk factors (eg, smoking and dyslipidemia) may increase the risk of cardiotoxicity following radiation therapy.[15] The pathophysiologic pathway responsible for most manifestations of cardiotoxicity appears to involve damage to blood vessels.[13-17] The histological hallmarks of radiation-associated cardiotoxicity are diffuse fibrosis in the interstitium of the myocardium with normal-appearing myocytes and narrowing of capillary and arterial lumens.[13-17] Conduction

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system fibrosis may predispose to dysrhythmias.[13-17] Therefore, it is not surprising that recent guidelines state that radiotherapy may increase the incidence of CHD and stroke.[14] Surprisingly, these guidelines do not consider the possibility of increased cardiac harm when patients receive chemotherapy or both radiotherapy and chemotherapy.[15]

The effect of radiation on arteries extends beyond the heart, since similarities between irradiation-induced, plaque-like carotid artery stenosis and arterial changes occurring in hypercholesterolemia have been reported.[18,19] Furthermore, Kilicaslan et al in this issue of *Angiology* report that radiotherapy is associated with impaired aortic elasticity and stiffness in patients with breast cancer.[20] The authors also link this effect with an increased risk of CHD.

It is also clinically relevant that patients with peripheral arterial disease, abdominal aortic aneurysms, and carotid artery stenosis are at increased risk of developing lung and other cancers.[21] This may be due to sharing risk factors such as age and smoking while delaying vascular death.[21] Thus, these patients combine a high risk for vascular event as well as cancer.[21] The vascular risk may be further aggravated by chemotherapy and/or radiotherapy.[21]

Regarding the prevention of adverse CV events, the early recognition of subclinical cardiotoxicity by noninvasive monitoring (eg, echocardiography, Holter monitoring, cardiac magnetic resonance imaging, brain natriuretic peptide, and troponin levels) may prove useful.[1] The presence of other risk factors for CHD (eg, hypertension and smoking) as well as the younger age of the patients, in relation to the total radiation dose, the dose per fraction, volume of heart irradiated, and the concomitant administration of cardiotoxic systemic agents, influence the probability of cardiotoxicity after radiation therapy.[13-17] Because established CHD risk factors (eg, smoking, dyslipidemia, and hypertension) may increase the risk of radiation-induced heart disease, efforts should be made to screen for and manage these risk factors. There is even an interest in the prevention of chemotherapy-induced left ventricular systolic dysfunction by administering carvedilol together with enalapril just before starting chemotherapy in patients with hematological malignancies.[22]

Diabetes and metabolic syndrome are associated with an increased risk of cancer and vascular events.[23,24] In turn, some drugs used to treat vascular risk (eg, statins, aspirin, and metformin) may have anticancer effects while other drugs may potentially increase that risk.[25,26] However, a detailed discussion of the interplay between diseases (and their treatment) associated with an increased risk of cancer as well as vascular events is beyond the scope of this editorial.

We suggest that there is a need for specific guidelines for the management of vascular risk in patients who have malignant disease and have been treated with chemotherapy and/or radiotherapy. In this context, others have suggested the need for improved interaction between cardiology and oncology and creating a cardio-oncologist "specialty."[27] As treatment for malignant disease becomes more successful, there will be an increased number of patients at a higher risk of vascular events. We need to avoid patients surviving cancer only to die soon after from "iatrogenic" vascular disease!

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