The Issue of Radiation-induced Cardiovascular Toxicity: Preclinical Highlights and Perspectives on Preventive Strategies

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About one-half of all cancer patients will receive external beam radiation therapy in the course of their disease, either as neoadjuvant or as adjuvant or as exclusive therapy in case of locally advanced disease. Although the true incidence of radiation-induced vascular disease is uncertain, it is a significant concern in long-term survivors because it will potentially alleviate the survival benefit of radiation therapy.[1] Based on the experience of adjuvant irradiation for breast cancer, numerous papers have investigated the impact of irradiation on heart coronaries.[2,3] In a recent study published few weeks ago in the New England Journal of Medicine, Darby *et al*. provided meaningful insights on the risk of ischemic coronary heart disease in breast cancer patients receiving radiotherapy, based on dosimetric parameters.[2] The authors incorporated systemic agents or individual risk factors at time of radiotherapy and established correlations between dose to the heart and the risk of coronary disease. They found that there was a linear correlation between the mean dose to the heart and the risk of coronary event, which increased by 7.4% per Gray (95% confidence interval: 2.9-14.5, $p < 0.001$). In this study, the estimated dose to the whole heart was 4.9 Gy (range, 0.03-27.72). Of interest, the authors did not evidence a threshold for cardiac toxicity, suggesting that even low doses can generate cardiovascular morbidity. The increase in coronary events began within the first 5 years after radiation therapy and continued into the third decade after completion of the treatment course.[2]

Actually, the physiopathology of cardiovascular toxicity is not fully understood. It is usually alleged that large vessels, such as the carotids, are relatively more resistant to ionizing radiation. Few data corroborate this assumption. Moreover, for patients with head and neck carcinoma, the dose delivered to the carotid is usually much higher, ranging from 50 to 70 Gy. Although the vascular remodeling after such high doses could be somewhat different, irradiation generates functional changes that are relatively common to most vessels. Early cardiovascular toxicity from radiotherapy results from direct cellular toxicity against endothelial cells through apoptosis and necrosis. These events increase vascular permeability and generate stromal edema. Later, irradiated vascular tissues show nuclear atypia within endethelium and stroma fibroblasts. Morphological analysis reveals that the vascular intima is thickened. Other pathological changes within vessels include the development of a fibrinoid necrosis, medial hyalinization, inflammation, thrombosis, arterial fibrosis, and accelerated atherosclerosis.[4] From a molecular point of view, it seems that there are some similarities between radiation-induced vasculopathy and fibrotic process, mediated by an inappropriate secretion of components of the extracellular matrix. Thus, the transcription factor nuclear factor kappa-B (NF-κB) is activated after irradiation. As an actor of the vascular inflammation, it contributes to the risk of future adverse cardiovascular events.[5] Transforming growth factor beta 1 (TGFβ1) is also produced in various mesenchymal or epithelial cells in response to irradiation through generation of reactive oxygen species. TGFβ1 may convert fibroblasts into myofibroblasts, which also generates inappropriate matrix secretion.[6] Some strategies aimed at decreasing radiation-induced vascular toxicity have emerged. In preclinical studies, the phosphodiesterase inhibitor, pentoxifylline, was shown to reduce skin radiation fibrosis, when given alone or combined with α-tocopherol.[7] This agent inhibits the translocation of NF-κB in vascular smooth muscle cells and downregulates inflammatory cytokines mediated by NF-κB, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6,[8] and this effect is associated with modulation of collagen deposition.[9] It seems that pentoxifylline could also inhibit the expression of TGFβ1 in models of heart toxicity.[9-11] A better understanding of the underlying mechanism of radiation-induced toxicity could help in developing protective strategies to avoid clinically relevant cardiovascular side effects. Furthermore, the incidence of vasculopathy is probably multifactorial and should be analyzed in the light of not only the total delivered dose, fractionation, but also of several other factors such as the use of concurrent radiosensitizers (chemotherapeutic agents, cetuximab), and associated morbidities such as preexisting atherosclerosis, hypertensive disease, or smoking.

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In clinical practice, no preventive strategy has been validated yet. Although most recent irradiation modalities were found to facilitate sparing the heart and coronaries from irradiation, it is impossible to spare the carotids from irradiation of head and neck carcinoma because large vessels within the neck are included into the target volumes. Thus, it is of great importance that clinicians are aware of the vascular risk after irradiation. Few studies have investigated the therapeutic management of radiation-induced stenoses of the carotid artery. Although fibrosis of the arterial layers is a concern for surgical treatment, some studies have highlighted that carotid stenting is feasible and effective for the treatment of radiation-induced carotid occlusive disease.[12-14] However, those included only a few patients and, consequently, the study by Min-Ping Huang is an important contribution to the field of treatment of radiation-induced vascular pathology.[15] In particular, the finding that there were more frequent intrastent restenosis in the group of irradiated patients suggests that the fibrotic process could remain active several years after the completion of irradiation. Halle *et al*., have investigated gene expression networks related to cardiovascular disease in irradiated human arteries. The authors found that several genes related to the NF-κB signaling pathway were deregulated even years after irradiation and that NF-κB was activated itself, suggesting that inflammatory response dose not disappear years after exposure to the causal event.[16] Further research on the molecular pathways underlying this phenomenon might allow designing strategies aimed at modulating the disease process, either as prophylactic or for the regression of an established radiation-induced vascular occlusive disease.

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