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The intriguing issue of genetic predisposition and the importance of identification of pre-clinical markers of endothelial damage in radiotherapy-induced cardiotoxicity

We have read with great interest the article ‘Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography’ by Lancellotti et al.1 Late cardiovascular complications after chest radiotherapy (RT), even modern RT techniques, are a remarkably increasing problem. Care of cancer survivors is becoming an emergent and topic issue especially after chest irradiation and more so for left breast cancer patients.2 In this subset of patients, RT should be addressed a risk factor for coronary artery disease (CAD) and since vascular endothelium seems to be the first target of radiation, it should be our duty to detect early marker of endothelial damage long before clinical coronary events. In our institution, we are enrolling early left breast cancer patients in a protocol study to estimate coronary flow reserve (CFR) by Tc-99m-tc-tetrofosmin SPECT Myocardial Perfusion Imaging before and after RT. Regional CFR is defined as the ratio between dipyridamole and baseline myocardial blood flow.3 In preliminary data, we have found ST segment and T wave of ventricular repolarization abnormalities registered soon after RT, coupled with myocardial perfusion defects (mostly in the apical region of the left ventricle) and with reduction of estimated values of CFR even in patients with no other risk factors for CAD besides chest RT. Our patients were all treated according to the Quanetc constraints.4 We do not know yet the predicting role of CFR reduction for clinical coronary events, but while following up very closely our patients, we are aggressively treating their risk factors for CAD.

We are also intrigued by the genetic issue of RT-induced cardiotoxicity, and we are also trying to identify the genetic marker of increased risk. We have read the editorial by Kelsey et al.5 and the paper by Hilbers et al.6 about the association between genetic variants in Transforming Growth Factor β-1 and Plasminogen activator inhibitor-1 and an increased risk for cardiovascular diseases after RT for breast cancer. The authors say that, for the great majority of individuals, the normal tissue toxicity is influenced by the cumulative effect of multiple genetic polymorphisms. If these assumption are proved to be true, then we will be able to predict which patient are more exposed to toxicity and we can improve our ‘tailored therapies’ maximizing the therapeutic ratio of cancer therapies.

We would like to ask two questions:

(1) What is your opinion on genetic determinants of RT-induced toxicity? The search for polymorphisms should be encouraged in Oncology Departments to modify therapeutic strategies. (For example, left mastectomy instead of breast-conserving surgery plus adjuvant RT if the risk of RT-induced cardiotoxicity is genetically increased.)

(2) Do you think it is worthy to search for a suitable early marker of endothelial damage? And do you think CFR reduction could be such a preclinical marker? Would you suggest an ECG recording soon after RT to screen high-risk patients?

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References

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increase in cancer survivors who have received old radiotherapy regimens.

The pathophysiology of RIHD remains poorly understood. Genetic and exogenous factors certainly enhance the risk of RIHD and contribute to inter-patient disease expression differences. As exogenous factors have been shown to result in genomic instability, and as low-dose radiation induces long-lasting genomic instability, synergistic interaction between radiation-induced effects and pathogenic events unrelated to radiation exposure is highly probable. When normal tissues are irradiated, identifying factors modulating their sensitivity to radiation is paramount but challenging. Little is known about the genetic variants of RIHD. Recently, single-nucleotide polymorphisms in a series of genes associated with DNA repair pathways, damage response, and angiogenesis regulating genes associated with DNA repair pathways, single-nucleotide polymorphisms in a series of about the genetic variants of RIHD. Recently, unreported.

Several imaging methods, including MIBI SPECT-MPI (single-photon emission computed tomography myocardial perfusion imaging), can be used to identify reduced CFR. Dr Gallucci also reported her preliminary data regarding an ongoing study in which CFR was assessed before and after radiotherapy in patients with left breast cancers. After treatment, a set of abnormalities (ST-T changes, myocardial perfusion defects in the left ventricular apical region, and reduction in estimated values of CFR) was found even in patients with no other risk factors for coronary artery disease other than chest irradiation. However, as the monitoring data are still ongoing, the impact of a reduced CFR on the outcome was not reported. In the meantime, these patients have been followed up closely and treated aggressively to correct any risk factor.

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References

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