Current trials of cytotoxic and targeted agents in breast cancer: the caveat of radiotherapy

In *Annals of Oncology*, Verma et al. [1] reviewed the way investigators are approaching the assessment of potential cardiotoxicity in adjuvant, metastatic, and neoadjuvant breast cancer setting. In this high-quality paper, authors have...
concluded that only a few studies were including cardiac end points in their pattern. We subsequently highlight another major caveat of most ongoing clinical trials, which fail to incorporate any accurate information regarding radiation-related cardiac hazard.

There is growing biological and clinical evidence that cardiac toxicity should be considered as the result of additive or supra-additive toxic effects, not as the consequence of a specific therapy [2]. Past experiences brought strong evidence that ionizing radiation may cause heart disease, and particularly so when provided concurrently with systemic cardiotoxic agents [3]. The toxicity data reported with adjuvant trastuzumab and/or conventional chemotherapy agents could be amplified by previous exposure to other cardiotoxic agents, such as irradiation. Whereas the long-term effects of such sequential or concurrent association remain unknown, cardiac mortality from breast cancer treatments will develop decades later, while the patient is cured [4].

Although recent irradiation modalities were found to facilitate sparing the heart and coronaries from irradiation, particularly for left-sided patients, those did not annihilate the risk for subsequent cardiotoxicity, which might be increased by concurrent chemotherapy or targeted agents [3]. A substantial amount of relevant information should be mandatory in further clinical assessments, including doses delivered to the coronaries or the left ventricle. Recently, the University of Michigan developed a cardiac atlas that could be incorporated as a useful predictive tool in studies assessing cardiac toxicity from new combinations [5]. Since most breast cancer patients receiving chemotherapy and/or targeted agents are likely to have also received adjuvant radiotherapy, including such dosimetric data could permit better defining the true cardiotoxicity of targeted anticancer therapies.

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