

The impact of radiotherapy, trastuzumab and hormonal therapy on cardiac fibrosis. More is worse?

Radiotherapy (RT) for early breast cancer (EBC) has proven capable of reducing the rates of recurrence and death from the disease. Similarly, trastuzumab, an anti-human epidermal growth factor receptor 2 (HER2) antibody, has significantly improved the prognosis of breast cancer patients in both the adjuvant and metastatic settings. However, major concerns have arisen about these treatments because both have been linked to cardiac toxicity, the former increasing the risk of ischemic heart disease, the latter, heart failure.

Before the era of 3-dimensional CT-based treatment planning it was observed that rates of major coronary events increased linearly for the first 5 years after radiotherapy (1). It has also been seen that cardiac side-effects may occur after adjuvant treatment with trastuzumab, with an absolute 12.0% higher adjusted incidence rate for heart failure over 3 years (2). Although preclinical data originally pointed towards a radiosensitizing effect of trastuzumab, more recent clinical studies have demonstrated that concurrent RT and trastuzumab for EBC is not associated with increased acute adverse events, including those of a cardiological nature (3, 4).

Having said that, cardiotoxicity is becoming an increasingly important issue in modern medical practice as more and more patients are being treated with RT or chemotherapy and targeted therapies and are surviving longer. Moreover, the widely used definition of cardiotoxicity, originally created by oncologists decades ago and based on the development of heart failure symptoms and/or left ventricular ejection fraction reduction, has become obsolete. In fact, it refers to the detection of cardiac damage only after the onset of cardiac dysfunction and does not take into consideration the possibility of taking timely preventive measures. Finally, the survival rate of cancer patients has greatly increased over the past twenty years (5), making those who recover at higher risk for cardiovascular events.

In this context, Cihan et al. (6) published in this issue evaluated the effect of RT, trastuzumab and hormone therapy sequencing on cardiac function in animal models. A single 12-Gy fraction to the rats caused increased fibrosis of the atrium, left ventricle and aorta after 6 months with respect to the control group. The trastuzumab-only treated arm also had higher fibrosis scores than the control group. Interestingly, this study highlighted a difference in the effect of the hormonal agents used, i.e. anastrozole and exemestane reduced the severity of the fibrosis, whereas letrozole and tamoxifen showed no impact on the myocardial damage induced after RT and trastuzumab administration.

In Azria et al. (7) preclinical study of breast cancer cells transfected with an aromatase gene, letrozole showed a strong radiosensitising effect. However, the same authors did not observe a clinically meaningful effect in terms of the occurrence of acute or late adverse events when concurrent or sequential letrozole and adjuvant RT were given after breast-conserving surgery (8). Nevertheless, some doubt remains about the potential cardiac toxicity of administering hormone treatment concurrently with radiotherapy (9), especially in association with another potentially cardiotoxic drug such as trastuzumab.

Although the paper focuses on an area of great current interest, it is somewhat limited by the fact that it only evaluates the short-term effect of a single 12-Gy fraction to the whole thorax on the heart, raising concerns about the transferability of the results to current clinical practice where modern 3-dimensional conformal RT is used in breast cancer. Moreover, it is becoming increasingly clear that, whilst preclinical models are helpful, they are not adequate to truly predict cardiotoxicity or to define mechanisms of injury. In fact, real-life patients are much more complex than preclinical models for many reasons, one of which is the lack of co-morbidities (hypertension, ischemic heart disease, etc). The above limitation does not, however, diminish the impact of the finding that adjuvant hormone therapy following concomitant RT and trastuzumab treatment does not increase acute cardiotoxicity (cardiac fibrosis) with respect to RT alone. Clinical validation of these results is now needed.

Alberto Farolfi, MD
Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS; Meldola-Italy

References

1. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; 368: 987-98. [\[CrossRef\]](#)
2. Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP, et al. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *J Am Coll Cardiol* 2012; 60: 2504-12. [\[CrossRef\]](#)
3. Halyard MY, Pisansky TM, Dueck AC, Suman V, Pierce L, Solin L, et al. Radiotherapy and adjuvant trastuzumab in operable breast

Address for Correspondence: Dr. Alberto Farolfi, MD, Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Via P. Maroncelli 40, 47014 Meldola-Italy
 Phone: +39 0543 73 91 00 Fax: +39 0543 73 92 49 E-mail: alberto.farolfi@irst.emr.it

Accepted Date: 25.03.2014 **Available Online Date:** 02.05.2014

© Copyright 2014 by Turkish Society of Cardiology - Available online at www.anakarder.com
 DOI:10.5152/akd.2014.1233812014



- cancer: tolerability and adverse event data from the NCCTG Phase III Trial N9831. *J Clin Oncol* 2009; 27: 2638-44. [\[CrossRef\]](#)
4. Farolfi A, Melegari M, Aquilina M, Scarpi E, Ibrahim T, Maltoni R, et al. Trastuzumab-induced cardiotoxicity in early breast cancer patients: a retrospective study of possible risk and protective factors. *Heart* 2013; 99: 634-9. [\[CrossRef\]](#)
 5. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: results of EURO-CARE-5-a population-based study. *Lancet Oncol* 2014; 15: 23-34. [\[CrossRef\]](#)
 6. Cihan YB, Arsav V. The effects of hormonotherapy administered concurrent radiotherapy and trastuzumab on cardiac toxicity in rats. *Anadolu Kardiyol Derg* 2014; 14: 00-00.
 7. Azria D, Larbouret C, Cunat S, Özşahin M, Gourgou S, Martineau P, et al. Letrozole sensitizes breast cancer cells to ionizing radiation. *Breast Cancer Res* 2005; 7: 156-63. [\[CrossRef\]](#)
 8. Azria D, Belkacemi Y, Romieu G, Gourgou S, Gutowski M, Zaman K, et al. Concurrent or sequential adjuvant letrozole and radiotherapy after conservative surgery for early-stage breast cancer (CO-HO-RT): a phase 2 randomised trial. *Lancet Oncol* 2010; 11: 258-65. [\[CrossRef\]](#)
 9. Chargari C, Toillon RA, Macdermed D, Castadot P, Magne N. Concurrent hormone and radiation therapy in patients with breast cancer: what is the rationale? *Lancet Oncol* 2009; 10: 53-60. [\[CrossRef\]](#)