Cardiotoxicity Monitoring in Patients with Breast Cancer: Still a Major Challenge

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"It is difficult to make predictions, especially about the future"

Karl Kristian Steincke, Danish politician, 1937

Medical decision making is a multi-layer process based on a recognized medical problem (diagnosis), ways to mitigate the issue, possible side effects, and the cost to society in terms of financial burden associated with the management of these side effects. Cardiotoxicity, more recently referred to as cancer therapy related cardiac dysfunction (CTRCD), relates to the most feared complication of anti-cancer treatment with high mortality and morbidity rates [1].

CRTCD is a long-recognized side effect of anthracyclines. Adding HER-2 receptor targeted therapies to the oncology armamentarium has significantly improved the survival of breast cancer patients but the problem of increased cardiotoxicity arose after the first excitement surrounding targeted therapy [2]. Strict protocols were implemented by oncologists for prevention and early detection of cardiotoxicity [3,4].

Until recently left ventricular ejection fraction (LVEF) remained the single mostly used parameter in oncology trials to define CTRCD. LVEF is widely accepted due to its simplicity (a single number for easy decision making) but is often criticized for being imprecise and dependant on hemodynamic factors, the operator, and modality in addition to its variable cut-offs [5].

The definition of cardiotoxicity, based on LVEF results, differs profoundly among different reported studies, ranging from < 50% by the ESC and Common Terminology Criteria for Adverse Events (US Departments of Health and Human Services) (CTCAE) definitions [1,4] to < 55% in the European Society of Medical Oncology, American Society of Clinical Oncology, Cardiac Review and Evaluation Committee documents [6-8].

Myocardial longitudinal deformation assessment by speckle tracking technology is becoming increasingly popular due to its increased sensitivity and stronger association with prognosis than LVEF in non-oncology populations [9].

In this issue of the *Israel Medical Association Journal* (*IMAJ*), Laufer et al. [10] reported their results on CTRCD, which is defined according to the American and European Society of Echocardiography Expert Consensus as a LVEF reduction of > 10% to a value below 53%, from a single-center cohort of consecutive breast cancer patients. The researchers used serial echocardiography two-dimensional LVEF and global longitudinal strain (GLS) measurements. They showed that among 103 patients, 5 developed CTRCD, and one developed heart failure. All five were considered at baseline to be of low risk for the development of CRTCD and had lower GLS (-18% vs. -21%, $P < 0.016$) at baseline.

The authors concluded that baseline GLS evaluation may be helpful for CTRCD risk stratification. They should be congratulated for successful routine implementation of GLS in the echocardiography protocol of breast cancer patients, showing that it can be conducted in the real world practice.

The small sample size and low event rate are significant limitations of the study, but we believe that the authors will update their systematic database of this important patient segment.

Should we recommend the routine use of GLS for the follow-up of HER-2 targeted therapy patients? Probably yes, because of the continuous improvement and automatization of the GLS process and its integration in most echocardiography machines puts a lesser burden on the comprehensive echocardiography study [11].

Do GLS parameters give us actionable information? There are a few publications that show that a GLS-guided strategy for cardioprotective medications initiation may be feasible [12] but to a have more definite answer we have to wait for the results of the ongoing SUCCOUR study, which assesses the initiation of cardioprotective medications triggered by the reduction of GLS versus waiting for 3D-derived LVEF decrease [13].

Last, the recent joint position statement of the European Heart Failure Association, the European Association of Cardiovascular Imaging (EACVI), and the Cardio-Oncology Council of the European Society of Cardiology recommends that physicians implement GLS in the routine echocardiography assessment of oncology patients who are evaluated for CTRCD [14].

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Capsule

Interferons interfere with lung repair

Interferons (IFNs) are central to antiviral immunity. Viral recognition elicits IFN production, which in turn triggers the transcription of IFN-stimulated genes (ISGs), which engage in various antiviral functions. Type I IFNs (IFN-α and IFN-β) are widely expressed and can result in immunopathology during viral infections. By contrast, type III IFN (IFN-λ) responses are primarily restricted to mucosal surfaces and are thought to confer antiviral protection without driving damaging proinflammatory responses. Accordingly, IFN-λ has been proposed as a therapeutic in coronavirus disease 2019 (COVID-19) and other such viral respiratory diseases **Broggi** and co-authors reported that COVID-19 patient morbidity correlated with the high expression of type I and III IFNs in the lung. Furthermore, IFN-λ secreted by dendritic cells in the lungs of mice exposed to synthetic viral RNA causes damage to the lung epithelium, which increases susceptibility to lethal bacterial superinfections. Similarly, using a mouse model of influenza infection, **Major** and colleagues found that IFN signaling (especially IFN-λ) hampers lung repair by inducing p53 and inhibiting epithelial proliferation and differentiation. Complicating this picture, **Hadjadj** et al. observed that peripheral blood immune cells from severe and critical COVID-19 patients have diminished type I IFN and enhanced proinflammatory interleukin-6, and tumor necrosis factor-α-fueled responses. These findings suggests that in contrast to local production, systemic production of IFNs may be beneficial. The results of this trio of studies suggest that the location, timing, and duration of IFN exposure are critical parameters underlying the success or failure of therapeutics for viral respiratory infections.

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