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Journal of Cancer Research and Cellular Therapeutics

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Case Report

Cardiotoxicity Memory, Cardio-Oncology Risk & Predisposing Genetic ¿Who is the Real Evil?

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Received Date: May 03, 2023; **Accepted Date:** June 02, 2023; **Published Date:** June 20, 2023

Citation: Andrés J. Daniele, Vanesa Gregorietti, (2023). Cardiotoxicity Memory, Cardio-oncology Risk & Predisposing Genetic ¿Who is the Real Evil?, *J. Cancer Research and Cellular Therapeutics*. 7(2); **DOI:**10.31579/2640-1053/144

Abstract

For several decades, medicine has tried to establish the risk of people developing cardiovascular disease. (1,2)

Different research groups developed and validated different scores for the assessment of cardiovascular risk in the population. (3,4)

In their development, assessment of cancer patients was not included, and the oncology history or treatments received were not considered. (3,4)

When we use them in daily to evaluate cancer patients in clinical practice, are we making a mistake?

On the other hand, when the cardiovascular assessment of cancer patients is carried out, do we consider the consecutive or simultaneous oncological therapies that the patient receives to define the risk of a cardiovascular adverse event?

We have a challenge, and we're going to try to clarify it.

Keywords: cardiotoxicity, cardiotoxicity memory, cardio-oncology risk, permissive cardiotoxicity

Main Text

Case 1

A 32-year-old female patient. He has a pathological history of non-Hodgkin lymphoma when she was 16 years old, so she was treated with RCHOP for 6 cycles and radiotherapy

9 months ago, she was diagnosed with left breast Cancer HER2 + HR - Ki67 70% in stage III. Neoadjuvant was performed with Trastuzumab followed by mastectomy and axillary nodal emptying.

Prior to the neoadjuvant therapy, a cardiovascular evaluation was conducted where it was found that the patient did not present cardiovascular risk factors, so she presented a SCORE 2 <1%, ASCV 2%. An Echocardiogram was performed which showed a LVEF 64% GLS -20%. Cardiovascular evaluation for non-cardiovascular surgery showed no alterations in physical exam, ECG, cholesterol levels and echocardiogram parameters.

After surgery, adjuvant therapy with double anti-HER2 blockade (Trastuzumab and Pertuzumab) associated with Docetaxel was indicated.

Before the third cycle, the patient reported presenting dyspnea NYHA CF II-III, so she was referred to the cardio-oncology department where clinical signs of global heart failure were observed.

A new echocardiogram was performed that showed a drop in LVEF to a value of 32% with a GLS – 11.

Case 2

A 42-year-old male patient without history of risk factors or cardiovascular disease. SCORE 2 < 1% ASCV 2%.

Diagnosis of chronic myeloid leukemia at 37 years old. Treated with Imatinib, Dasatinib, and Nilotinib sequentially due to lack of therapeutic response

During treatment with Nilotinib, an ultrasound of arteries of the lower limbs was performed, which showed the presence of atherosclerotic lesions in the right superficial femoral artery that caused a 20% obstruction.

Due to treatment failure with nilotinib, the patient was reassessed and tested for the T315i mutation whose was positive, so treatment with Ponatinib 45 mg per day was indicated.

Six months after starting Ponatinib, the patient attends the consultation for intermittent claudication of the right lower limb at 50 meters,

A new ultrasound of arteries of the lower limbs is performed, verifying the evolution of the lesion of the right superficial femoral artery that now generates an obstruction of 85%.

Case 3

A 43-year-old patient who consults for the progressive deterioration of functional degree after mild influenza three months before the consultation. As relevant background Hodking Lymphoma treated at age 19 with ABVD. LVEF 6 months after finishing treatment was 50%

He goes to consult with dyspnea of minimal efforts and bilateral edemas up to the root of limbs. The ECG shows sinus rhythm with left bundle branch block.

The echo shows LVEF 25%. Depletive treatment is initiated and with Sacubitril/ Valsartan, Beta blockers, eplerenone and SLGT2i. Coronary angiography is requested showing absence of significant coronary heart disease and a Magnetic Resonance. That rule out the diagnosis of myocarditis

The patient evolves favorably with improvement of LVEF up to 48% at 6 months of treatment

Discussion

Cardiology was originally limited to describing cardiovascular adverse events after cancer therapy.

Then, only patients in cancer remission who evolved with advanced stages of heart failure were treated and assessed for a heart transplant.

Since the advent of anthracyclines and the first descriptions of cardiac involvement secondary to them we have advanced in the study of the various predisposing factors of the occurrence of different types of cardiotoxicities. [1,2,3]

For many years we tried to predict the probability of the presentation of a cardiotoxic events through the assessment of the cardiovascular risk of our patients using cardiovascular risk scores developed for the general population. [3,4]

Clinical experience has shown us that, although with them, we have achieved an approach in the prediction of cardiovascular adverse events in cancer patients, but they are not effective enough to measure the certain probability of their occurrence.

Based on this finding, different groups began to study and publish risk scores that incorporated factors related to the patient's cancer history and their treatment. [5]

Some of these scores have been validated, demonstrating the highest precision in the prediction of the occurrence of cardiovascular adverse events secondary to cancer therapies. [6,7]

For this reason, we are tempted to suggest that when we talk about risk assessment for our cancer patients, we are no longer talking about cardiovascular risk.

We must use the term of cardio-oncology risk, since it would be more comprehensive, and it would conceptualize the basis of our specialty where the patient is the center of a multidisciplinary approach and the abode of different morbidities coexistence.

In addition, for several years, the scientific community has been studying the pathophysiology of cardiac toxicities and the biomolecular mechanisms associated with them. [8,9]

It has been possible to elucidate some of the mechanisms underlying cardiovascular adverse events secondary to certain drug groups, whereas with others we have only speculated. [10]

In this uncertain situation, clinical practice has shown that the implementation of successive cancer therapies predisposes patients to have a higher incidence of cardiovascular adverse events. [7,11]

And is it possible that when our patient is treated with specific cancer therapy, they create an indelible imprint on their cardiovascular system?

Our conviction, based on the demonstration of numerous studies on the increase in the incidence of cardiotoxicities with the achievement of consecutive specific cancer therapies, is that each therapy generates that footprint in the cardiovascular system and therefore we have coined the term cardiotoxicity memory.

Cardiotoxic memory presents us with the challenge of minimizing, through cardioprotective treatments, the impact that oncology therapies have on our patients.

But we have another question. Does this imprint have any relation to the presence of certain predisposing genes in the DNA?

In recent days, Purmina Singh et al. published the relationship between the haptoglobin gene and anthracycline-related cardiomyopathy. [12,13]

In addition, Wang et al. describe the association between CELF4 and GSMT1 and anthracycline-related cardiomyopathy. [13, 14,15]

It is valid to think that the presence of certain genes predisposes a patient to present a greater susceptibility to presenting vascular endothelial dysfunction secondary to cancer therapy and thus increasing the probability that a consecutive treatment increases the possibility of the occurrence of a cardiovascular adverse event.

Otherwise, in a context where therapies are increasingly effective in achieving remission or "chronicity" of oncological pathology; we must consider what is, in the event of cardiotoxicity, the precise indication to limit them.

Understanding that suspending specific cancer treatments to determine our patient's prognosis is that we need to open to a new concept described recently: permissive cardiotoxicity. [16]

When we ask ourselves who the real devil is, we consider that the concept of cardiotoxic memory should be anchored in our day-to-day cardio-oncology practice, because the achievement of therapies for cancer, often despised in the baseline evaluation of approval of a new line of oncological treatment, is the basis of the cardio-oncology risk of our patients.

Therefore, we must increase our efforts to understand the pathophysiological basis by which the various drugs for cancer and, especially, their combination simultaneously or sequentially produce damage to the cardiovascular system.

Otherwise, based on the above, we can also conclude that the assessment of cardio-oncology risk and permissive cardiotoxicity are two tools that, in the context of an adequate baseline evaluation and rigorous monitoring at follow-up, will allow us to improve the oncological prognosis of our patients benefiting their accessibility to effective cancer therapies.

Conclusion

Cardio-oncology is a young and fertile field of research where we still have a long way to go to achieve a complete understanding how the patient´s cardiovascular system responding to different cancer therapies

and how, through this, we can develop targeted prevention strategies; therefore, being able to apply precision medicine in our specialty.

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DOI: 10.31579/2640-1053/144