

Cardio-Protection Against Cancer Treatment-Related Cardiac Dysfunction: Who is at Risk?

Ariane Vieira Scarlatelli Macedo^{1,2}  and Wolney de Andrade Martins^{3,4} 

Instituto Brasileiro de Pesquisas Clínicas,¹ São Paulo, SP – Brazil

Santa Casa de Misericórdia de São Paulo,² São Paulo, SP – Brazil

Universidade Federal Fluminense,³ Niterói, RJ – Brazil

DASA Centro de Pesquisa Clínica do Complexo Hospitalar de Niterói,⁴ Niterói, RJ – Brazil

Long-term survival of cancer patients has improved, and the sequelae of treatment have become more evident. Mortality rates of cancer patients, adjusted for age, have decreased globally, with a reduction by 17% from 1990 to 2019.¹

The prevention of left ventricular dysfunction secondary to cancer treatment is still a medical challenge.² Drug-induced cardiotoxicity is the main limiting factor for the administration of higher doses of anthracyclines. Addressing the anthracycline-induced cardiotoxicity is particularly important for pediatric cancer survivors, as it remains one of the main causes of morbidity and mortality in this population.³

Other classes of antineoplastic agents, such as tyrosine kinase inhibitors, anti-HER2 therapies, and immunotherapy can also have a negative impact on myocardial function.⁴ Thus, there is a need for (a) the development of strategies to identify and control cardiotoxicity; (b) further data on the long-term risk in these patients; and (c) effective primary and secondary prevention strategies. It is known that the precise evaluation of baseline characteristics and cardiovascular risk factors allow an individualized approach to each patient.⁵

Cardioprotective therapies represent an important way to reduce the cardiotoxicity secondary to cancer treatment. However, the ideal duration, the strategy and the long-term efficacy of empiric cardio-protection remain unknown.⁶ There is still no clear consensus on recommendations for cardioprotective pharmacotherapy. However, it is known that the first step in preventing cardiotoxicity is to be aware of the cardiovascular risk, and to identify the high-risk patients. A pro-active approach is essential, towards the identification of risk factors and pre-existing cardiovascular diseases in oncologic patients.^{4,5} This is a continuous process that must be applied during the whole treatment period. In patients who require high doses of anthracyclines, continuous infusion of anthracyclines, the use of liposomal doxorubicin and dexrazoxane have been shown to attenuate cardiotoxicity.⁷ Current data do not support the routine use of neuro-humoral antagonists as cardioprotective agents in patients treated

with cardiotoxic chemotherapy.⁶ This lack of evidence on cardioprotective therapies may be attributed to the high heterogeneity and modest size of the samples in most studies.⁶ Although small studies have been included in the meta-analyses, the considerable heterogeneity in the study design and method, as well as in patients' risk makes interpretation and generalization of results quite challenging.⁸

In the absence of definite results from large-scale studies, the question about which patients are most likely to benefit from cardioprotective treatment with neurohormonal antagonists remains unanswered.⁶ Although risk-based strategies may be attractive, currently available randomized trials do not support the use of interventions guided by images or biomarkers. This may be explained by the fact that the effect of interventions with neurohormonal antagonists may be lower in the absence of an elevated neurohormonal activation. Besides, in general, neurohormonal antagonists are not specifically targeted to the cardiotoxic effects of anti-cancer treatments, but rather, used to attenuate potential negative effects of neurohormonal activation in response to myocardial lesion. Future studies should develop new targeted cardioprotective agents.⁶ In contrast, there is a strong consensus on the importance of a strict control and treatment of risk factors. In this context, the interaction and collaboration among oncologists, cardiologists, and cardio-oncologists play a key role.⁹

The design of larger, collaborative, multicentric studies have been a high priority in cardio-oncology. Fortunately, there is currently an international effort to develop multicentric, randomized trials on cardioprotection.⁶ In addition, it is important to incorporate cardiovascular outcomes into pivotal studies in oncology. The design of conventional clinical trials in oncology has been mostly focused on the efficacy of anti-cancer therapy to the detriment of valuable information on cardiovascular risk factors and outcomes. To achieve a balance between efficacy and potential risk of cardiotoxicity of oncologic treatment, research in oncology should integrate baseline cardiovascular data with pre-established cardiovascular outcomes.⁶

The improvement of survival rates in several types of cancer should not be accompanied by an increased risk of treatment-related cardiotoxicity. A continuous search for methods to identify more precisely those patients at higher risk should continue, together with the development of interventions directed at cardio-protection in oncology.

Keywords

Cardiology; Cardiovascular Diseases; Neoplasms; Medical Oncology.

Mailing Address: Ariane Vieira Scarlatelli Macedo •

Irmandade da Santa Casa de Misericórdia de São Paulo – Cardiologia – Rua Dr. Cesário da Mota Junior, 112. CEP 01221-020, Santa Cecília, São Paulo, SP – Brasil
E-mail: arianevsm@yahoo.com.br

DOI: <https://doi.org/10.36660/abchf.20230006>

References

1. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results [Internet]. Seattle: Institute for Health Metrics and Evaluation; 2021. [cited 2023 Jan 15]. Available from: <https://www.healthdata.org/gbd/2019>.
2. Hajjar LA, Costa IBSDSD, Lopes MACQ, Hoff PMG, Diz MDPE, Fonseca SMR, et al. Brazilian Cardio-Oncology Guideline - 2020. *Arq Bras Cardiol*. 2020;115(5):1006-43. doi: 10.36660/abc.20201006.
3. Lipshultz SE, Karnik R, Sambatakis P, Franco VI, Ross SW, Miller TL. Anthracycline-Related Cardiotoxicity in Childhood Cancer Survivors. *Curr Opin Cardiol*. 2014;29(1):103-12. doi: 10.1097/HCO.0000000000000034.
4. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on Cardio-Oncology Developed in Collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43(41):4229-61. doi: 10.1093/eurheartj/ehac244.
5. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, et al. Baseline Cardiovascular Risk Assessment in Cancer Patients Scheduled to Receive Cardiotoxic Cancer Therapies: A Position Statement and New Risk Assessment Tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in Collaboration with the International Cardio-Oncology Society. *Eur J Heart Fail*. 2020;22(11):1945-60. doi: 10.1002/ehf.1920.
6. Omland T, Heck SL, Gulati G. The Role of Cardioprotection in Cancer Therapy Cardiotoxicity: JACC: CardioOncology State-of-the-Art Review. *JACC CardioOncol*. 2022;4(1):19-37. doi: 10.1016/j.jacc.2022.01.101.
7. Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2017;35(8):893-911. doi: 10.1200/JCO.2016.70.5400.
8. Sayed A, Abdelfattah OM, Munir M, Shazly O, Awad AK, Ghaith HS, et al. Long-Term Effectiveness of Empiric Cardio-Protection in Patients Receiving Cardiotoxic Chemotherapies: A Systematic Review & Bayesian Network Meta-Analysis. *Eur J Cancer*. 2022;169:82-92. doi: 10.1016/j.ejca.2022.03.024.
9. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, et al. Management of Cardiac Disease in Cancer Patients Throughout Oncological Treatment: ESMO Consensus Recommendations. *Ann Oncol*. 2020;31(2):171-90. doi: 10.1016/j.annonc.2019.10.023.



This is an open-access article distributed under the terms of the Creative Commons Attribution License