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EDITORIAL COMMENT

More Data to Support a Cardiac-Oncologic Partnership*

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Sarcomas remain challenging to treat, in large part because the mainstay therapy, doxorubicin, has been known since its introduction to cause cardiotoxicity with the development of clinical heart failure in patients.[1] Unfortunately, this chemotherapeutic agent, one of the most active agents for the treatment of sarcoma, comes with a risk of heart failure. Given the dose-dependent cardiotoxicity risk, the management of this problem consumes the attention of oncologists and cardio-oncologists[2] engaged in treating patients with sarcoma.[3]

The need to manage "cancer treatment-related cardiac dysfunction," referred to as CTRCD in patients receiving doxorubicin or other anthracyclines stimulated the birth of cardio-oncology as a subspecialty of cardiology in major centers such as MD Anderson[4] and the European Institute of Oncology.[5] Many years ago, cardiologists at such centers identified the need for early cardiac consultation in patients receiving these medications. Now, programs in cardio-oncology are more common.

The challenge was and remains to identify patients at risk for cardiotoxicity and to institute some form of cardiac protection therapy to mitigate CTRCD in order to permit continuing therapy with anthracyclines. Cardinale et al[6,7] at the European Institute of Oncology showed that it was essential to initiate therapy at the first sign of CTRCD, because later initiation, even 6 months after the development of dysfunction, was less effective. Although doxorubicin is used to treat many tumors in addition to sarcoma, such as breast cancer[8,9] and lymphoma, because of the availability of other effective treatments, the potential cardiotoxicity of doxorubicin can be "managed" by limiting the dose and potentially using another therapy. However, with sarcomas, there is no other treatment as effective as doxorubicin, so treatment of sarcomas can be described as giving doxorubicin until toxicity, cardiac or otherwise, or until there is progression of the tumor from the development of resistance. This was especially common 15 years ago when limited treatment options were available, and led to the use of such agents as dexrazoxane or 72-hour continuous infusion of anthracyclines at some centers to mitigate the risk of heart failure as the dosages escalated.

Thus, it is important to identify patients at increased risk so cardiac protection can be instituted as early as possible to permit continued treatment with doxorubicin and hopefully limit long-term cardiac toxicity.

The University of Leiden in the Netherlands has maintained a registry of patients with sarcoma for many decades. A recent study from this institution utilized this registry to characterize the effect of age at diagnosis of patients with high-grade osteosarcomas on prognosis and showed that patients of an older age had a worse prognosis than patients diagnosed at a younger age.[10] In this issue of *JACC: CardioOncology,* Heemelaar et al[11] use this registry to help characterize the effect of age at diagnosis on the prognosis of these patients, to evaluate the effect of age at diagnosis on the development of heart failure, and to identify factors that risk stratify these patients. After evaluating an extensive list of possible factors,

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the only non-tumor-specific factors associated with heart failure were age at diagnosis, female sex, and lifetime dose of doxorubicin.

Patients with osteosarcoma and Ewing's sarcoma were followed for a median of 5.7 years for the development of heart failure. It should be stated that heart failure is a difficult diagnosis to make, especially in a retrospective study, and in the past, it required symptoms and signs that have a relatively low specificity. However, the recently introduced Universal Definition and Classification of Heart Failure by the major heart failure societies[12] objectifies the definition, basing it on symptoms and objective findings on radiographs, echocardiograms and biomarkers, specifically N-terminal B-type natriuretic peptide (NT-proBNP) or BNP. This can deal with the ambiguousness of shortness of breath, which can be a symptom of other complications of cancer such as pulmonary embolism, pulmonary metastases, pleural effusions, and just frailty. Peripheral edema often develops in patients with low albumin and is more related to cancer rather than to cardiac dysfunction. Unfortunately, in this study, the investigators are unable to evaluate lessor degrees of left ventricular dysfunction short of heart failure. In addition, they could not distinguish between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), which may not be related directly to doxorubicin toxicity and is treated differently. On the other hand, HFpEF needs treatment and has a mortality similar to HFrEF, so a monitoring protocol that does not exclusively focus on ejection fraction should have a role in cardio-oncology management. Moreover, they have also not evaluated lessor degrees of cardiotoxicity that could trigger earlier institution of cardiac protective medication. However, they have called attention to the ongoing risk of heart failure in these patients.

In this study, the investigators also showed an increased risk of heart failure in women as well as a role for increased dosing of doxorubicin. The type of heart failure (HFpEF vs HFrEF), however, deserves clarification, especially given the increased prevalence of HFpEF in women.[13] Dexrazoxane was not used in the University of Leiden medical system, though infusional doxorubicin was used for some patients.

Strategies for treating heart failure are available with neurohormonal therapy with angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists,[14] whereas other, more specific approaches with dexrazoxane or modified slow administration of the doxorubicin to limit cardiotoxicity can be considered. Newer treatments with SGLT2 inhibitors are effective in both HFrEF and HFpEF,[15] so there is a premium on identification of patients at risk for heart failure from either cause, because the risk factors may differ.

In summary, this well-executed study uses a unique database to lay a foundation for identifying patients at risk of heart failure and also for calling attention to the potential for treatment. The increased incidence of heart failure in women raises a question of the role of HFpEF in this development. Monitoring for the development of heart failure remains important in survivors of sarcoma, and the data from this study are helpful in focusing efforts on the older patients and women treated with higher doses of doxorubicin, although some monitoring of all patients exposed to doxorubicin is essential.[2] Overall, this study suggests that cardio-oncologists should be more involved with older patients at high risk for heart failure and that strategies such as dexrazoxane or infusional doxorubicin are important to consider as preventative measures in this patient population.

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REFERENCES

1. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer*. 2003;97:2869–2879.

2. Curigliano G, Lenihan D, Fradley M, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol*. 2020;31:171–190.

3. Cardinale D, Biasillo G, Cipolla CM. Curing cancer, saving the heart: a challenge that cardioncology should not miss. *Curr Cardiol Rep*. 2016;18:51.

4. Yeh ET. Onco-cardiology: the time has come. *Tex Heart Inst J*. 2011;38:246–247.

5. Cardinale D. A new frontier: cardio-oncology. Article in Italian. *Cardiologia*. 1996;41(9):887–891.

6. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation*. 2015;131:1981–1988.

7. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol*. 2010;55:213–220.

8. Ewer MS, Swain SM, Cardinale D, et al. Cardiac dysfunction after cancer treatment. *Tex Heart Inst J*. 2011;38:248–252.

9. Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. *Clin Cancer Res*. 2008;14:14–24.

10. Evenhuis RE, Acem I, Rueten-Budde AJ, et al. Survival analysis of 3 different age groups and prognostic factors among 402 patients with skeletal high-grade osteosarcoma. real world data from a single tertiary sarcoma center. *Cancers (Basel)*. 2021;13(3):486. https://doi.org/10.3390/cancers13030486

11. Heemelaar JC, Speetjens FM, al Jaff AAM, et al. Impact of age at diagnosis on cardiotoxicity in high-grade osteosarcoma and Ewing sarcoma patients. *J Am Coll Cardiol CardioOnc*. 2023;5(1):117–127.

12. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *Eur J Heart Fail*. 2021;23:352–380.

13. Lam CSP, Arnott C, Beale AL, et al. Sex differences in heart failure. *Eur Heart J*. 2019;40(47):3859–3868c. https://doi.org/10.1093/eurheartj/ehz835

14. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79:e263–e421.

15. Tsampasian V, Elghazaly H, Chattopadhyay R, et al. Sodium glucose co-transporter 2 inhibitors in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2022;29(6):e227–e229. https://doi.org/10.1093/eurjpc/zwab189

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