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EDITORIAL COMMENT

New Cardiotoxicity Risk Assessment Guidelines

Searching for Validation*

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Cancer therapy-related cardiac dysfunction (CTRCD) is one of the most feared side effects of cancer treatment, occurring in approximately 10% of patients.[1] Broadly speaking, clinically significant cardiotoxicity of cancer therapy poses 2 major perils: the morbidity associated with the CTRCD itself and the risk that the toxicity will interrupt the preferred oncologic treatment strategy in order to avoid worsening CTRCD. Efforts to lessen the morbidity of CTRCD have included strategies for better recognition of pretreatment patient risk factors and screening for markers of early CTRCD during cancer treatment. In this context, the recent deployment of new frameworks for risk assessment and disease detection provides opportunities to test their utility while illuminating potential trade-offs associated with efforts to increase the sensitivity of CTRCD detection.

For pretreatment risk assessment, a working group of the Heart Failure Association of the European Society of Cardiology and the International Cardio-Oncology Society (HFA-ICOS) published a set of risk assessment tools in 2020 to assign separate risk levels for each of 7 different classes of cancer treatment.[2] Each risk score proforma is composed of various patient-related and cancer therapy-related factors, and the summary score is calculated based on the cumulative risk and is used to classify patients' risk of cardiotoxicity as low, medium, high, or very high. To endorse and encourage the implementation of the HFA-ICOS risk assessment tools, the 2022 ESC cardio-oncology guidelines[3] included a Class 2a recommendation "to stratify CV [cardiovascular] risk in cancer patients before starting cancer therapies." However, the HFA-ICOS risk assessment tools are based on expert opinion with limited validation to date, with application mainly confined to patients with breast cancer. For example, in 629 women with HER2+ breast cancer treated with trastuzumab with or without anthracycline, Suntheralingam et al[4] demonstrated that the HFA-ICOS risk assessment outperformed 2 other risk scores but did not adequately identify patients at low absolute risk of CTRCD.[4] A similar inability of the HFA-ICOS proforma to identify a truly low risk subpopulation was observed by Battisti et al[5] in 931 HER2-positive breast cancer patients. Better negative predictive values were observed by Cronin et al[6] in 507 breast cancer patients retrospectively divided according to the HFA-ICOS risk proforma. In this cohort, with a follow-up of 5 years, rates of cardiotoxicity were 3.3% in HFA-ICOS low-risk patients, 3.3% in the medium-risk group, 4.4% in the high-risk group, and 38% (n = 6) in the very high-risk group, but overall rates of CTRCD were quite low in this study.

The paper by Glen et al in this issue of *JACC: CardioOncology*[7] is the first study to use the HFA-ICOS risk assessment score in a real-world cohort of 63 melanoma patients treated with rapidly accelerated fibrosarcoma B-type and mitogen-activated extracellular signal-regulated kinase inhibitors, a proforma distinct from the breast cancer cohorts highlighted

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previously. As with the aforementioned studies, the majority of patients fell into the low-risk (46%) and medium-risk (40%) HFA-ICOS subgroups, with only 7 and 2 patients in the high- and very high-risk subgroups. When the analysis is restricted to patients developing moderate CTRCD, defined as a ≥10% decrease in left ventricular ejection fraction (LVEF) to an absolute LVEF of 40% to 49%, the rates were 7% in HFA-ICOS low-risk patients, 8% in medium-risk patients, 14% in high-risk patients, and 50% in very high-risk patients. Although the numbers are small, this gradient of risk for moderate severity toxicity is consistent with expectations and seems to reflect potentially satisfactory performance of the HFA-ICOS proforma in this CTRCD subgroup.

An important feature of the study by Glen et al[7] is its exploration of the rates of mild CTRCD, defined as a decrease in global longitudinal strain of ≥15%, even when unaccompanied by an LVEF <50% or symptoms of heart failure. This definition of mild CTRCD derives from a 2022 consensus statement from the International Cardio-Oncology Society.[8] When Glen et al[7] examined the rate of any severity of CTRCD (mild or moderate) with rapidly accelerated fibrosarcoma B-type inhibitor/mitogen-activated extracellular signal-regulated kinase inhibitor treatment in their cohort, the rate was 24% in the HFA-ICOS low-risk patients, 28% in the medium-risk patients, 29% in the high-risk patients, and 50% in the very high-risk patients. Not surprisingly, these relatively modest differences in the rates of any cardiotoxicity across the risk groups were not statistically significant in this small cohort. Moreover, this analysis begs the question of whether the inclusion of mild severity toxicity is diluting the otherwise satisfactory performance of the HFA-ICOS risk proforma. Relevantly, of those with mild CTRCD who had subsequent echocardiography, none progressed to moderate or severe CTRCD. It is also unclear whether reductions in global longitudinal strain alone are sufficient to diagnose subclinical cardiotoxicity or identify patients who would benefit from cardioprotective treatment to prevent CTRCD. Thus, although Glen et al[7] are to be congratulated for their application of a previously unvalidated HFA-ICOS risk assessment proforma to a real-world cohort, the results in their relatively small study are encouraging but not definitive concerning the prediction of moderate CTRCD using the most commonly used definition. At the same time, the application of the new definition of low-risk CTRCD, based on isolated reductions in left ventricular global longitudinal strain, raises concerns that the increased sensitivity of this metric may come at the price of significantly reduced specificity in this particular cancer treatment population.

More generally, risk assessment guidelines need to be applied to larger populations of cancer patients reflecting the full diversity of treatment strategies reflected in the HFA-ICOS risk assessment proformas. Validation that low-risk pretreatment assignments are indeed associated with low (<5%) rates of moderate severity CTRCD could allow longer intervals between CTRCD screening tests. Conversely, the validation of high-risk assignments could provide a basis for closer surveillance and inform patient selection for CTRCD prevention trials. At the same time, it is important to recognize that the HFA-ICOS proformas were likely designed to assign the risk of cardiotoxicity based on the most commonly used definition—a reduction of LVEF ≥10% to an absolute LVEF <50%. Accordingly, recent recommendations to broaden the threshold for CTRCD by the inclusion of isolated reductions in global longitudinal strain require their own large validation studies with close attention to the trade-offs between efforts to increase diagnostic sensitivity and potential reductions in specificity that may impose an increased burden of follow-up testing without affecting outcomes.

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