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EDITORIAL COMMENT

Second Malignancies and Cardiovascular Disease in Childhood Cancer Survivors

Double Trouble*

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Survivors of childhood cancer are at increased risk of chronic health conditions compared with the general population, experiencing 3-fold the number of severe or life-threatening conditions by age 50 years (4.7 vs 1.6 per person, respectively).[1] Among the most prevalent of these conditions are "second," or subsequent, malignant neoplasms (SMNs) and cardiovascular diseases (CVDs), both of which significantly contribute to survivor morbidity and mortality.[2,3] Shared risk factors for both SMNs and CVDs, including demographic (eg, female) and clinical factors related to the primary cancer (eg, young age at diagnosis, chest-directed radiation, and anthracyclines), leave subgroups of survivors at substantial risk of both. In addition to shared risk factors, SMN treatment, which may be cardiotoxic, and the other potential adverse consequences of having a SMN, can further increase the risk of subsequent CVD. Some studies have suggested an association between SMN and subsequent CVD in childhood cancer survivors; however, these findings have not been consistent or definitive due to limitations in sample sizes and follow-up methods.[4-6] Therefore, larger cohort studies designed to evaluate these associations are critical to better understanding CVD risk after SMN and to developing optimal treatment approaches for high-risk patients.

In this issue of *JACC: CardioOncology*, Charrier et al[7] present an observational analysis of cardiac events occurring in 7,670 survivors of pediatric solid tumors treated at 5 French cancer centers over a 55-year span with a median follow-up of 30 years. Primary cancer treatment data were abstracted from charts, and follow-up data including SMNs, CVD, and mortality were obtained via a combination of chart abstraction and linkage to relevant administrative databases. An additive regression analysis was used to estimate the association between SMNs and the cumulative incidence of Common Terminology Criteria for Adverse Advents grade ≥3 cardiovascular events. A competing risk, time-to-event regression model was used to estimate the association of SMN with the cause-specific hazard of cardiac events.

The investigators found that having a SMN at 15 to 25 years post-diagnosis conferred an increased risk of subsequent CVD. Specifically, having a SMN at 25 years after the initial cancer diagnosis was associated with a 3.8% higher cumulative incidence of subsequent CVD. This association was not observed for SMNs occurring beyond 25 years from cancer diagnosis, which may be attributable to the substantial increases in mortality and reduction in the study population over time. In time-to-event analysis, SMN was associated with a 2-fold higher hazard of subsequent CVD (cause-specific HR of 2.0 [95% CI: 1.4 to 2.8]).

The major contribution of this study is to establish an association between SMN and subsequent CVD in childhood cancer survivors. In comparison with prior studies that were primarily conducted in acute myeloid leukemia populations, Charrier et al[7]

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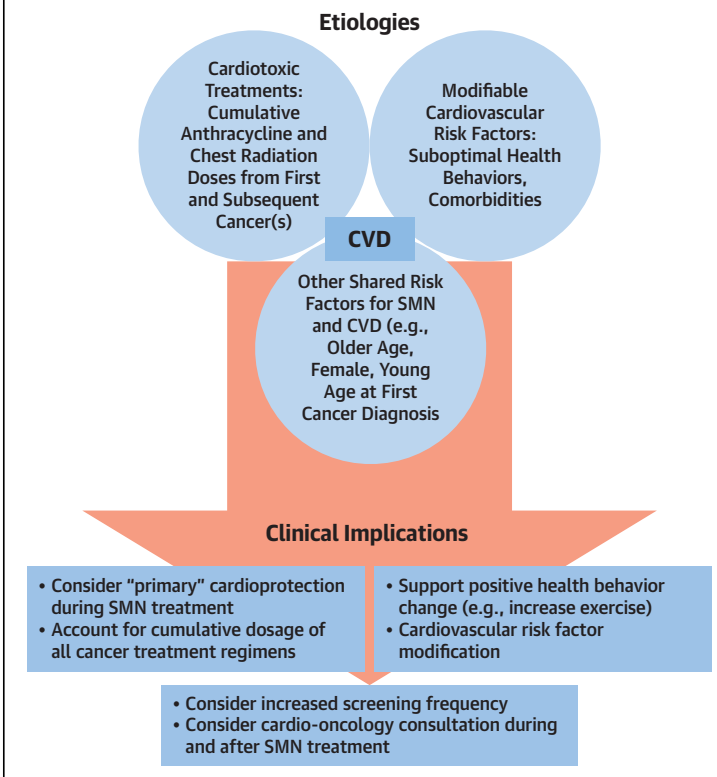
examined a much larger cohort with longitudinal follow-up to provide more precise quantification of risk and to draw more definitive conclusions.

As the investigators point out, there are several potential explanations for this finding. First, there is a significant overlap between the clinical and demographic risk factors for SMN and CVD. Though a specific analysis of these shared factors was not performed, the diminished association between SMN and CVD after adjustment for some of these factors was suggestive of their role in this association. Second, CVD risk is known to be highly dependent on anthracycline and chest radiation dosage during primary cancer therapy; it is intuitive that additional doses of cardiotoxic therapies for SMN would result in additional risk. The investigators examined SMN type as a surrogate for treatment data and observed the strongest associations between breast, bone, and soft tissue cancers with subsequent cardiac events. Given that these cancers are routinely treated with anthracyclines, the results support the hypothesis that the cumulative effects of additional cardiotoxic SMN-directed therapy played a role as well. Third, there may be other complications of SMN apart from cardiotoxic therapy that increase the risk of CVD, such as altered lifestyle and health behaviors, and a potentially higher risk of developing other comorbidities. These potential factors could not be assessed with the available data.

The findings of this study have clinical implications for survivorship care (Figure 1), the most important being that clinicians should be aware that patients with SMNs may be at substantially higher risk of cardiovascular complications. During survivorship after both the first and subsequent cancer(s), risk factors should be proactively assessed and used to help guide management, including frequency of screening. When assessing cardiotoxicity risk, cumulative anthracycline and chest radiation dosage for both primary and subsequent cancer(s) should be included. Further study may determine whether "primary" cardioprotective interventions during SMN treatment, such as dexrazoxane or cardiac medications, may benefit this high-risk population. Although recent data have supported the use of dexrazoxane in certain pediatric cancer treatment regimens,[8] its use during adulthood has been largely restricted to women with metastatic breast cancer, perhaps missing an opportunity to mitigate risk in vulnerable adult survivors in whom many of these SMNs occur. Finally, care should be taken to address cardiovascular risk factors and support should be given to patients to improve health behaviors, with even greater emphasis after subsequent cancer(s). Cardio-oncology consultation and management should be considered during and after SMN therapy. In addition, close collaboration between pediatric and adult survivorship programs could facilitate care of high-risk patients who are transitioning from a pediatric to an adult care setting. Finally, improved integration of electronic medical records between health care organizations is needed to make cancer treatment data more accessible to providers within different hospital systems.

It should be noted that there are limitations to this study, most importantly the lack of SMN treatment information. Although the SMN type analysis provides some insight, it is insufficient to accurately assess the role of cumulative dosages between first and subsequent cancer(s). Furthermore, there was a lack of information about patient cardiovascular risk factors and health behaviors. In sum, the absence of these data preclude a mediation analysis to determine the relative contribution of the various

FIGURE 1 CVD After SMN in Childhood Cancer Survivors



Schematic depicting the potential etiologies of the association between subsequent malignant neoplasms (SMNs) and cardiovascular disease (CVD) (top) and clinical implications for the care of high-risk childhood cancer survivors (bottom).

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etiologies of increased cardiovascular risk, thereby limiting the ability to inform specific clinical intervention strategies. Finally, the outcome measures were grade ≥3 cardiac events from administrative data, albeit with efforts to ensure confirmation; core laboratory analysis of primary imaging data could have improved detection of lower grade events and the precision of risk estimates.

This study highlights the need for further research into the etiologies of increased cardiac risk after SMN, with more robust treatment and clinical data. Unfortunately, existing long-term survivor cohorts such as the Childhood Cancer Survivor Study similarly lack SMN treatment data. New strategies for data collection, such as linkages between cohort studies, registries, and medical expenditures data should be considered. In addition, studies to assess alternate monitoring and treatment strategies during and after SMNs could improve cardiovascular care.

In summary, this study by Charrier et al[7] demonstrates that SMNs may be associated with a significantly increased risk of CVD in survivors of pediatric cancer. Their findings emphasize the need to optimize cardiovascular management in this high-risk population.

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