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EDITORIAL COMMENT

Aortic Inflammation

A Predictor of Cardiovascular Disease Risk in Lymphoma Patients?*

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At the cornerstone of cancer and cardiovascular disease (CVD) pathophysiology is inflammation. Numerous studies have demonstrated associations of markers of inflammation with increased risk of cancer, CVD events, and mortality.[1-3] In the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), the use of statins in patients with low levels of cholesterol but elevated levels of C-reactive protein was associated with reductions in cardiovascular events, suggesting measures of inflammation may be useful tools for cardiovascular risk stratification with implications for statin therapy allocation.[4-6] Most recently, the CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) showed for the first time that the use of direct anti-inflammatory therapies leads to reductions in C-reactive protein levels, cardiovascular events, and cancer mortality.[7]

Not surprisingly, many cancer patients are at increased risk of CVD compared to those of similar risk profiles who do not have cancer.[8] In fact, for Hodgkin lymphoma (HL) patients, CVD is the most common cause of noncancer death.[9] Several factors may contribute to the increased CVD risk in cancer patients. In HL and non-Hodgkin lymphoma (NHL) patients, direct cardiac toxicities of cancer therapy, including anthracycline-based regimens and chest radiation therapy, are thought to play important roles.[9] Anthracyclines are known to cause cardiomyopathy largely due to mitochondrial-dysfunction-generated oxidative stress leading to cardiomyocyte dysfunction and death.[10] Radiation therapy may cause arterial disease by direct endothelial injury leading to a chronic pro-inflammatory state that accelerates atherosclerosis.[11]

Inflammation may additionally contribute to CVD risk in HL and NHL patients. In a recent study, Vlachopoulous et al demonstrated that 18-flourodeoxyglucose (18-FDG) uptake by the aortic wall, a marker of vascular inflammation, atherosclerosis, and CVD risk, correlated with cancer severity in chemotherapy-naive lymphoma patients.[12-14] Importantly, studies have shown that treatment of conditions that cause chronic inflammation is associated with a reduction in aortic 18-FDG uptake suggesting a reduction in arterial inflammation and, possibly, in CVD risk.[15,16] However, to date, no prior studies had assessed the net effect of cancer therapies on markers of vascular inflammation.

In this issue of *JACC: Advances*, Vlachopoulos et al[17] report findings from a prospective, 3-center study that aimed to examine the effects of first-line chemotherapy on aortic inflammation in 65 consecutive patients with a new diagnosis of HL (n = 33) or NHL (n = 32). Aortic inflammation was measured via aortic wall 18-FDG and global aortic target-to-background ratio (GLA-TBR) on positron emission tomography/computed tomography (PET/CT) imaging obtained at baseline, during, and after the completion of first-line therapy. First-line therapy for both groups included anthracycline and alkylating-agent-based regimens, specifically ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) for HL and RCHOP (rituximab, cyclophosphamide,

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doxorubicin hydrochloride, vincristine, prednisolone) for NHL. The principal finding was that aortic inflammation was reduced after first-line therapy in HL patients, but not in NHL patients. The authors also found that serum biomarkers of inflammation, interleukin-6, and interleukin-1b were both significantly reduced after treatment in HL, patients, whereas only serum interleukin-6 was significantly reduced in NHL patients.

These findings imply that aortic inflammation may be predominantly driven by cancer in HL, serving as a marker of disease activity that is reduced by therapy. Conversely, in NHL patients, other factors that are not affected by cancer therapy may underlie the increased aortic inflammation. In fact, there were important differences in the patient populations, with NHL patients being older and having a higher burden of CVD risk factors. Notably, there was no significant interaction between GLA-TBR and response to first-line treatment in both groups. While this is likely due to the small number of participants in the study with few patients being classified as nonresponders, it is also possible the different changes observed in the 2 groups reflect different effects of the 2 chemotherapeutic regimens on the vasculature.

The authors should be congratulated on their efforts in this thoughtfully designed and well-executed study, as this is the first prospectively designed study to assess aortic inflammation in lymphoma patients before and after therapy. The findings in this study could have important clinical implications for assessing future CVD risk in lymphoma patients. It is increasingly recognized that traditional CVD risk scores underperform in cancer populations, and incorporation of tools such as aortic FDG uptake may improve risk prediction in this population.

However, several additional questions remain that will hopefully be addressed by future studies. Studies with a longer follow-up period would be useful to determine if lack of decrease in aortic inflammation after treatment correlates with increased CVD risk. Furthermore, as the authors astutely point out, in order to obtain aortic 18-FDG uptake and GLA-TBR, a second PET/CT at 120 minutes is required, in addition to the 60-minute PET/CT completed to assess lymphoma burden. This in turn requires double the amount of examination time, more radiation exposure, and higher cost. Longer-term follow-up studies would also be useful to assess whether the additional radiation exposure from the additional PET/CTs could have a negative health impact.

Ultimately, this study highlights the complex pathophysiology of CVD in cancer patients. Factors that predate cancer diagnosis such as obesity and diabetes may contribute to both cancer and CVD risk. Cancer itself, as well as cancer therapies, may further contribute to CVD risk through indirect mechanisms such as promotion of inflammation, weight gain, decreases in physical activity, or by causing direct cardiovascular damage. The relative contributions of these factors may vary in cancer patients, but there ought to be better studies for the development of effective CVD screening and preventative strategies for this population.

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