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EDITORIAL COMMENT

Assessing STEMI Outcomes in Patients With Cancer

A Call for Integrated Cardiovascular and Cancer Phenotyping*

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Across the globe, nearly 20 million patients receive new diagnoses of cancer each year, and the incidence of cancer is predicted to increase by 47% over the next 20 years.[1] Common risk factors for cancer, such as age and obesity, are also key contributors to cardiovascular disease. Increasingly, cardiologists will be faced with patients presenting with acute coronary syndromes, such as ST-segment elevation myocardial infarction (STEMI), who are concurrently receiving active treatment for cancer. Decision making in this scenario is complex and requires detailed knowledge of the patient's cancer stage, response to cancer treatment, and overall prognosis. In parallel with the increasing incidence of cancer, the landscape of cancer treatment has changed dramatically over the past few decades. Oral targeted therapies and immunotherapies are now available in addition to traditional cytotoxic chemotherapy regimens. The array of options for cancer treatment has undoubtedly resulted in increased quality of life and improved longevity but further contributes to patient complexity when acute cardiovascular issues arise. These factors have led to the development of the burgeoning field of cardio-oncology, which aims to seamlessly integrate expertise in both cardiovascular disease and cancer to improve outcomes in this challenging patient population.

In a study reported in this issue of *JACC: CardioOncology*, Dafaalla et al[2] investigated heart failure readmission rates following diagnoses of STEMI in patients with cancer living in the United Kingdom. More than 326,000 patients were identified from a linked data set derived from the UK Myocardial Infarction National Audit Project registry, the UK Hospital Episode Statistics registry, and the National Deaths Registry from the Office for National Statistics. Approximately 7,000 patients (2.2%) had diagnoses of cancer on the basis of billing claims. After adjustment for key covariates relevant to heart failure outcomes, such as age and cardiovascular comorbidities, cancer was not independently associated with heart failure readmission within 30 days or 1 year following STEMI. However, patients with cancer were less likely to be admitted to a cardiology service and had lower rates of coronary intervention, including percutaneous coronary intervention and coronary artery bypass grafting. Patients with cancer were also less likely to received guideline-directed medical therapy for heart failure during their hospitalizations, and fewer were referred to cardiac rehabilitation programs at the time of discharge.

The investigators' study provides insights on how cancer may influence post-myocardial infarction (MI) treatment and outcomes, leveraging a large national registry in which detailed cardiovascular phenotyping is available. STEMI and heart failure are important contributors to morbidity and mortality in the cardio-oncology patient population; however, patients with active cancer have traditionally been excluded from large cardiology clinical trials, leading to a knowledge gap in how best to care for these patients. The present study demonstrates that patients with cancer and STEMI received fewer coronary interventions and

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guideline-directed therapies, and they were more frequently readmitted for heart failure. However, the association of cancer with readmissions was no longer present after risk adjustment, leading the investigators to conclude that differences in heart failure readmissions between patients with and those without cancer were driven primarily by age and other comorbid conditions, rather than the presence or absence of cancer itself.

This study highlights the difficulty of elucidating a causal role for cancer in influencing cardiovascular outcomes on the basis of retrospective data alone. It could be informative to assess whether these quality-of-care measures differed between patients with and those without cancer after risk adjustment for comorbidities, similar to the primary analysis performed on heart failure readmission rates. If cancer were to remain associated with worse performance on quality measures after risk adjustment, the underuse of quality-of-care interventions may nonetheless be appropriate because of other unmeasured factors associated with cancer. Low blood counts, frailty, and poor oncologic prognosis may change the balance of risk and benefit for standard interventions, including invasive cardiovascular procedures.

Similarly, reliance on billing codes alone to diagnose "active cancer" could result in a heterogeneous population, with strikingly different stages and prognoses from one patient to another. A patient with non-small-cell lung cancer treated with an oral targeted therapy may have indolent disease for several years; in this setting, revascularization, initiation of dual antiplatelet therapy, and referral to a cardiac rehabilitation program are more likely to be indicated. In contrast, medical management of STEMI could be most consistent with the goals of care established for a patient with a relapsed hematological malignancy complicated by severe thrombocytopenia, given the prohibitive risk for bleeding and poor cancer prognosis. In the study by Dafaalla et al,[2] patients with hematologic and colon cancers had higher heart failure readmission rates. These malignancies are typically treated with high doses of cytotoxic chemotherapies that can lead to decreased blood counts, potentially contributing to lower rates of revascularization. In cardio-oncology studies in particular, data sets that capture granular information may be necessary to obtain a more comprehensive understanding of important covariates, as well as insights into the mechanisms driving clinical observations.

Given the complexity of disentangling a diagnosis of cancer with its associated comorbidities, it remains unclear whether increased surveillance post-MI (eg, with biomarkers or echocardiography) would be beneficial in patients with cancer. More comprehensive risk adjustment, paired with detailed information about cancer stage and treatments, would enable the development of targeted approaches to improve STEMI and heart failure outcomes in patients with cancer. In parallel, studies in preclinical models can offer insights into the molecular mechanisms driving crosstalk between the tumor and cardiovascular system. For instance, MI in mice accelerated breast tumor growth by reprogramming inflammatory responses driven by bone marrow–derived monocytes, an effect that occurred in the absence of heart failure.[3] In another mouse model, postinfarct heart failure led to the release of proteins secreted by the heart into the circulation and exacerbated the growth of intestinal tumors.[4] The extent to which molecular mechanisms of tumor-heart crosstalk may affect outcomes in patients with cancer and STEMI remains to be determined and represents a rich opportunity for translational investigation.

The study by Dafaalla et al[2] included patients diagnosed with STEMI between 2005 and 2019. Cancer treatment paradigms changed significantly during that time, with the introduction of new therapies carrying cardiovascular toxicity profiles that include STEMI and heart failure. These range from vascular endothelial growth factor pathway inhibitors, commonly used for renal cell carcinoma and other solid tumors, to androgen deprivation therapy for prostate cancer. For traditional cytotoxic chemotherapies such as anthracyclines, detailed information on cumulative lifetime exposure is essential to quantify the risk for subsequent cardiomyopathy and heart failure. In the present study, a higher percentage of patients with cancer had moderate or poor left ventricular function, an effect that could be due to cancer treatments such anthracyclines or, alternatively, the presence of cancer itself.

To improve outcomes in patients with cancer and STEMI, one solution may be to involve those with dedicated cardio-oncology expertise in decisions around revascularization and post-MI care. Although direct communication between interventional cardiologists and primary oncologists may be sufficient in many circumstances, cardio-oncologists have increased familiarity and experience with the unique issues facing patients with cancer. Modern cancer treatment regimens are often complex and associated with idiosyncratic cardiovascular toxicities. Newer agents may be administered as part of a cancer

clinical trial, in which the diagnosis and management of cardiovascular events has implications for current and future cancer treatment options. Cardio-oncologists typically have established relationships with treating oncologists and can facilitate conversations around cancer prognosis, particularly in the urgent setting of an acute coronary syndrome. Moving forward, an interdisciplinary approach will be critical to elucidate the effects of cancer itself on cardiovascular outcomes and to optimize these outcomes in the cardio-oncology patient population.

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