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EDITORIAL COMMENT

5-Fluorouracil Cardiotoxicity

Known But Unknown*

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Cardiotoxicity from the anti-neoplastic, antimetabolite 5-fluorouracil (5-FU) has been established for decades, yet it remains poorly defined. The incidence of cardiotoxicity, based on case reports, retrospective studies, and a few prospective trials ranges from 0% to 30% (1–3). The most commonly reported symptom is chest pain, thought to be due to coronary artery vasospasm. Currently 5-FU is an essential active agent against multiple types of malignancies prescribed as part of dozens of chemotherapy regimens. When administered in the adjuvant setting, the goal of therapy is cancer cure. Given its ubiquitous role, development of equivalent agents with less cardiotoxicity would be a viable alternative. Raltitrexed, an anti-folate thymidylate synthase inhibitor, has been used in Europe (4) but has little traction in the United States given high rates of severe myelosuppression. With the potential for fatal cardiac outcomes and chemotherapy dose reductions, delineating the full extent of 5-FU cardiotoxicity is an unmet clinical need.

The research by Zafar et al. (5) in this issue of *JACC: CardioOncology* is remarkable as one of the largest patient denominators in retrospective studies of typical chest pain syndrome temporally associated with 5-FU. In an approximately 10-year span, a pool of more than 4,000 patients who received 5-FU were reviewed for key word "vasospasm" to indicate typical chest pain syndrome at rest, resulting in a 2.16% incidence of vasospasm during the time they were receiving 5-FU therapy. Patients with preexisting myocardial infarction were excluded. As a comparison, 174 patients without vasospasm were randomly selected from 3,932 patients. The 87 patients diagnosed with vasospasm were reported as statistically younger in age with fewer premorbid cardiac risk factors than the comparison group, although there were no significant differences in the individual risk factors, such as tobacco use or hypertension. Accordingly, those with chest pain had less use of beta blockers or calcium channel blockers compared with those without chest pain. Overall, the 87 patients received less 5-FU with a nonsignificant hazard ratio for cancer-related death and progression of disease compared with the other 174 patients receiving 5-FU.

The incidence of typical chest pain syndrome during 5-FU dosing from Zafar et al. (5) aligns with the published literature. As with other reports, the numbers reported here are too small to make precise conclusions. Nonetheless, 5-FU-associated cardiotoxicity is a clinically challenging and underdiagnosed adverse event. 5-FU appears to induce various pathophysiologic effects, resulting in distinct clinical manifestations including arrhythmias, blood pressure alterations, and even cardiogenic shock (1,2). Preclinical work suggests vasospasm as an important cause of these, with supporting hypotheses including an increase in protein kinase C activation, nitric oxide, cardiac arterial thrombosis, and also mismatched demand and oxygen supply (6–8). As well, direct myocardial toxic effects may be responsible for cardiomyopathy and myocarditis (9). Arrhythmias are reported in those undergoing electrocardiograms or continuous monitoring (1,2,10). Antimetabolites are recognized as initiators of atrial arrhythmias (11). However, cardiotoxicity mechanisms are not well defined; in particular, the roles of

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dihydropyrimidine dehydrogenase and 5-FU metabolites need further clarification.

The clinical identification of patients at high risk for cardiotoxicity will permit pre-chemotherapy risk-reduction strategies. There are conflicting reports of both the presence and the absence of established cardiovascular disease risk factors in patients with 5-FU–associated cardiotoxicity. In patients with asymptomatic or undiagnosed coronary vascular disease, even minor vasospasm could be expected to incite chest pain, and not all patients undergo cardiac catheterization at presentation. Likely confounders of risk factor enumeration are accurate co-morbid diagnoses, method and source of data collection, and severity of the condition. For example, recording a diagnosis of diabetes does not indicate if it is diet controlled or if the hemoglobin A1c is in the double digits. More recent publications using electronic medical records with ICD-10 coding should be more precise. It is also plausible that other patient factors, such as obesity and lack of physical activity or exercise, may be influential risk factors (12,13).

Zafar et al. (5) present the cancer outcome data of dose received, progression-free survival, and cancer-specific survival. These cancer outcomes related to decreased dosing or discontinuation are critical to describing the clinical significance of 5-FU cardiotoxicity. However, in clinical practice, there are not enough vasospasm cases to differentiate between various 5-FU–based regimens; potentially the inclusion of vascular endothelial growth factor inhibitors such as bevacizumab could increase risk. All concomitant medications should be assessed for drug interactions with chemotherapy that predispose patients to cardiotoxicity. Other medical conditions such as electrolyte disturbances are common with chemotherapy and can predispose to arrhythmias. Valuable long-term outcomes include subacute and chronic cardiac-related morbidity in survivors, especially with the suggestions of high rates of silent ischemia.

Large National Cancer Institute–sponsored clinical trials comparing efficacy of fluoropyrimidines have been conducted for decades with a wealth of data. Nonetheless, cardiotoxicity of long-established agents has rarely been recorded on case report forms, evidenced by at least 1 National Clinical Trials Network group (14). Per standard drug development, most trials exclude pre-morbid cardiovascular disease, although it is feasible to obtain prospective real-world data from a broader patient population (2). These National Clinical Trials Network studies provide an opportunity to collect prospective cardiotoxicity data as secondary outcomes, as with the ongoing EA2182 Lower-Dose Chemoradiation in Treating Patients With Early-Stage Anal Cancer, the DECREASE Study (NCT04166318) comparing lower fluoropyrimidine and radiation therapy doses for early-stage anal canal carcinoma.

The paper by Zafar et al. (5) adds to the body of retrospective evidence that has been very consistent over time. Elucidating the incidence, mechanisms, and manifestation of anticancer drug toxicity is critical to monitor the associated cancer outcomes. If typical chest pain syndrome associated with 5-FU does decrease the receipt of standard of care treatment and possibly is associated with increased cancer mortality, especially in the curative setting, then urgent solutions are needed. Knowledge of the exact cardiotoxicity incidence depends on the various clinical manifestations reported, making future focus on other forms of cardiac toxicities, such as arrhythmias, crucial. More prospective data are required to comprehend and mitigate potentially poor outcomes from therapy-induced cardiotoxicity for cancer patients.

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