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EDITORIAL COMMENT

Risk of Myocardial Infarction in Patients Treated With 5-Fluorouracil

Balancing the Evidence With Black Boxes*

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Fluoropyrimidines such as 5-fluorouracil (5-FU) and its orally available prodrug capecitabine are cornerstone treatment for a wide range of solid tumors (gastrointestinal [GI], breast, colorectal, head and neck). Regrettably, however, fluoropyrimidines have long been known to be associate with significant risk for chest pain, angina on exertion or at rest, and acute coronary syndromes including myocardial infarction (MI). Mechanisms of fluoropyrimidine-associated ischemia remain a matter of debate. Patients diagnosed with fluoropyrimidine-related chest pain, angina, or even MI have consistently been shown to lack coronary obstruction on angiography.[1] The most popular theory of fluoropyrimidine-related ischemia therefore invokes coronary vasospasm due to either endothelial dysfunction with defective formation of nitric oxide or endothelium-independent primary dysfunction of smooth muscle cells.[2,3] Others have reported ancillary mechanisms that may include changes of erythrocyte oxygen storage and transport or abnormal adenosine triphosphate consumption in cardiomyocytes, with either mechanism resulting in an acute imbalance between oxygen demand and supply.[3]

The incidence of fluoropyrimidine-related ischemia is controversial. Published research revea an incidence ranging from 1% to 35%, which may well be explained by heterogeneity in the sample sizes of different studies, broad definitions of cardiac events, patient-related factors (age or cardiovascular [CV] risk factors), or treatment-related factors (dose, mode of administration, combination with other cardiotoxic drugs).[3] Notwithstanding these uncertainties, the overall incidence of ischemic events is high enough to make 5-FU the second most cardiotoxic chemotherapeutic after anthracyclines.[4]

In this issue of *JACC: CardioOncology*, Shanmuganathan et al[5] contribute the largest published analysis of the incidence of MI in patients receiving 5-FU for treatment of GI cancers. Data were retrieved from the 2004-2016 frame of the Danish National Patient Registry. A total of 30,870 subjects were included in the final analysis, of whom 10,290 were patients with GI cancer treated with 5-FU and 20,580 were control subjects. A dilemma here is how to select proper control subjects. Both tumor-matched patients not treated with 5-FU and patients with other cancer types were considered inappropriate because of the burden of disease-related competing risks. The investigators therefore compared 5-FU-treated patients with subjects from the general population, carefully matched for demographic and clinical characteristics, including CV risk factors and antianginal medications. The most intriguing finding of the analysis was the cumulative incidence of MI, which was significantly higher in 5-FU-treated patients than control subjects at 6 months (0.7% vs 0.3%), and when considering the competing risk for deelevatedas also significant at 1 year (0.9% vs 0.6% for control subjects). The investigators considered that both GI cancer alone and GI cancer in the constellation of treatment-related hemorrhagic or thrombotic complications introduced competing risks for death.

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The work by Shanmuganathan et al[5] shows remarkable strengths, including a robust sample size and an excellent balance of demographic and clinical characteristics between control subjects and 5-FU-treated patients. Equally meritorious is the investigators' effort to characterize the time from treatment initiation to MI occurrence. They showed that as many as 55% of all patients diagnosed with MI (36 of 67) experienced MI within 5 days of 5-FU initiation. At 1 month, the percentage of patients with MI increased to 75% (49 of 65), but this trend was indicative of MI risk reaching a plateau. These data confirm, with the added value of a credible sample size, the early timing of manifestations of 5-FU cardiotoxicity. Previous small case series reported a median time to chest pain of approximately 12 hours following infusion initiation, with a time window of 1 to 2 days that is well encircled by the 5-day MI incidence reported in this study.[6] The impact of pre-existing ischemic heart disease (IHD) on extending MI risk from 6 months to 1 year represents another strength of this work. Although being of intuitive importance for the clinical management of patients with IHD who are candidates for 5-FU treatment, this observation sheds light on unsettled issues about CV risk factors aggravating (or not) 5-FU cardiotoxicity. Small case series have not resolved these issues; in contrast, a retrospective analysis of some 4,000 patients treated with 5-FU showed that as many as 2.2% developed vasospasm with typical chest pain, and those who developed vasospasm were younger and less likely to have CV risk factors than those who did not.[7] Here Shanmuganathan et al[5] show that MI incidence was much lower than that reported for vasospasm but were able to show that IHD increased MI risk over time. On balance, studies with significant sample sizes seem to reveal multifaceted effects of CV comorbidities on aggravating the risk for a relatively infrequent and serious event such as MI but not the risk for a perhaps more frequent and benign event such as uncomplicated chest pain. This will require further investigation.

This work also has limitations, among which the investigators judiciously recognize not only the competing risks that cancer itself may have introduced but also a lack of information about cancer stage in patients with or without MI. Additional black boxes merit consideration. In other studies, younger age was a hallmark of patients developing vasospasm, but here a precise analysis of how age influenced MI risk is lacking. IHD aggravation of MI risk was determined by comparing the subgroup of patients with IHD treated with 5-FU against the whole cohort of control subjects, but one may wonder what the figures might have been if only control subjects with pre-existing IHD were considered for comparisons. One more black box exists with regard to 5-FU administration. The investigators acknowledge a lack of information about dose, but mode of administration is even more important. Cardiotoxicity induced by 5-FU is determined by plasma exposure over time rather than plasma peak, which makes slow infusions more cardiotoxic than bolus infusions.[3] Most common 5-FU-based regimens for colorectal cancer, such as FOLFOX, FOLFIRI, and FOLFOXIRI, have undergone modifications over the years, and variability across cancer centers with respect to 5-FU infusion modalities is more than plausible.[8] How this influenced these analyses is not known at this point in time. Another black box pertains to the role concomitant cancer drugs may have played. All were said to cause minor changes in 5-FU-related MI incidence, but data scrutiny actually reveals a trend toward higher MI incidence in patients who did not receive bevacizumab compared with those who received it. This is a counterintuitive finding, as bevacizumab and other angiogenesis inhibitors can cause cardiac ischemic events including MI.[9] Finally, the investigators note that 23 of 65 patients diagnosed with MI continued with 5-FU treatment and did not experience reinfarction. On one hand, this fact nicely illuminates how patients with cancer should always be given the best possible oncological treatment, provided that pre-existing risk factors or on-treatment cardiac events are properly managed.[10] In contrast, however, these facts raise questions about the definition and diagnosis of MI and do not help understand whether treatment was momentarily held or not, although one might guess that it was.

In conclusion, the work by Shanmuganathan et al[5] marks an important improvement of our understanding of 5-FU cardiotoxicity. However, 5-FU is difficult to decipher, and much remains to be done in terms of refining patient- and treatment-related determinants of what appears to be a relatively modest risk for MI. Things will be clarified with further large and detailed CV analyses of patients treated with 5-FU.

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