Comment to Moady et al. *A Comparative Retrospective Study of Patients with Takotsubo Syndrome and Acute Coronary Syndrome*

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TO THE EDITOR,

We read with great interest the article by Moady et al. [1]. We focus on an additional etiologic factor that may induce both of these syndromes, namely 5-Fluorouracil (5-FU).

While the most commonly described cardiac adverse event from 5-FU is coronary artery spasm resulting in ischemia, the occurrence of Takotsubo cardiomyopathy has been described as well.

We report a patient who developed an acute cardiomyopathy while receiving 5-FU as a continuous infusion (CI).

CASE PRESENTATION

A 53-year-old-male patient, with a past medical history of diabetes mellitus and dyslipidemia in addition to an episode of atrial fibrillation in the distant past, was diagnosed with squamous cell carcinoma of the middle third of the esophagus, T3, N+, M0. He was admitted to our in-hospital unit in February 2021 for the administration of his first cycle of systemic therapy including cisplatin, 5-FU as a CI (1000 mg/m^2 daily for 5 consecutive days), and cetuximab.

On the second day of the administration of 5-FU the patient complained of bilateral shoulder and neck pain, which resolved promptly on discontinuation of the drug. An electrocardiogram did not show ischemic changes and was unchanged from previous traces. The troponin level increased to 22 ng/ml (N ≤ 13 ng/ml) and decreased thereafter. An echocardiogram revealed severe left ventricular dysfunction with an estimated left ventricular ejection fraction (LVEF) of 30% (the LVEF was 69% in June 2020). A computed tomography (CT) coronography showed no evidence of stenosis or occlusion. A cardiac magnetic resonance imaging (MRI), which was performed a week later, revealed an increase in LVEF to 49%, a normal sized left ventricle with septal hypertrophy and mild diffuse dysfunction with no signs of an infarction or myocarditis. The patient was then considered to have experienced a 5-FU induced acute cardiomyopathy. Treatment was continued with cisplatin and cetuximab without 5-FU, and he had no further complications. A repeat positron-emission tomography (PET)/CT showed a partial regression of the esophageal lesion.

COMMENT

5-FU is one of the oldest and most widely used chemotherapeutic agents worldwide. It is, after doxorubicin, the most common cytotoxic drug associated with cardiotoxicity. This may present in a wide range of events including coronary spasm, myocardial infarction (MI), myocarditis, arrhythmias, QT prolongation, atrioventricular node dysfunction, and cardiomyopathy [2].

The reported incidence of 5-FU-related cardiac events varies widely and is dependent on several factors, including pre-existing coronary artery disease, other cardiovascular risk factors, age, the schedule in which 5-FU is given, and the concomitant administration of other potentially cardiotoxic drugs. In fact, when 5-FU is given as a bolus injection the incidence of cardiotoxicity is less than 3%, increasing to up to 8% for short-term infusions and to as high as 18% for CI of 5 days or more.

Cardiotoxicity usually, but not always, occurs during the first cycle of 5-FU administration. It may take place at any time during the infusion and up to 1 to 2 days later, but rarely more.

The mechanisms underlying cardiac injury from 5-FU are not fully understood and may include endothelial and smooth muscle dysfunction, incorporation of the drug into cardiomyocytes resulting in cellular damage, protein kinase C mediated vasoconstriction, DPD (dihydropyrimidine dehydrogenase) deficiency and increased levels of catecholamines as a result of stress [3].

The most common clinical manifestation of 5-FU cardiotoxicity is coronary artery spasm presenting as chest pain; ECG may suggest a MI with ST elevations, an increase in troponin level, without evidence of significant coronary stenosis or occlusion on angiography or CT. Typically, the symptomatology subsides upon discontinuation of the drug.

5-FU-induced Takotsubo cardiomyopathy has been infrequently reported [4], manifested with ST depression on ECG, and echocardiographically with left ventricular hypokinesia and a profound decrease in LVEF, apical ballooning, a normal coronary angiography and a cardiac MRI without evidence of myocardial edema or necrosis, with prompt recovery upon discontinuation of the drug, as observed in our patient. In fact, considerable improvement in his LVEF was documented shortly thereafter.

An important issue is that of re-challenge with 5-FU after recovery from the cardiac event. Recurrence rates are high even with the prophylactic administration of calcium channel blockers, aspirin, and long-acting nitrates and may lead to severe cardiac injury and even death.

Oncologists should be aware of the potential cardiotoxicity of 5-FU, including relatively rare conditions such as the cardiomyopathy described in our patient. This caution is especially important since 5-FU remains an essential and extensively used integral component of our cytotoxic armamentarium, even six decades after its introduction into clinical practice.

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Response to the letter by Sulkes et al. Regarding the Article: *A Comparative Retrospective Study of Patients with Takotsubo Syndrome and Acute Coronary Syndrome*

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TO THE EDITOR,

Takotsubo syndrome (TTS) may be induced by several drugs, mainly those with sympathomimetic properties by catecholamine mediated pathways [2,3]. TTS and other forms of unspecified transient left ventricular dysfunction have also been reported following anti-neoplastic therapy, including 5-Fluorouracil (5-FU), and by non-catecholamine mechanisms. In the case of 5-FU, these mechanisms include microvascular spasm, endothelial dysfunction and myocardial ischemia [3]. The majority of 5-FU related TTS cases have been described during or immediately after the infusion of the drug. The re-administration of 5-FU after cardiac recovery has been a topic of debate.

Sulkes et al. [1] described an interesting and rare case of TTS following 5-FU administration in a patient with squamous cell carcinoma of the middle third of the esophagus. The diagnosis was assumed based on echocardiography, cardiac computed tomography (CT), and cardiac magnetic resonance (CMR). The measurement of natriuretic peptides (NPs) is recommended in such cases since high levels of NPs in additional to modest troponin elevation are indicative of the diagnosis. Moreover, the description of the specific type of TTS (i.e., typical, reverse, or median) may be clarified using ventriculography during coronary angiogram, or cardiac MRI. In general, the exclusion of obstructive coronary disease by cardiac CT and the absence of tissue edema and other signs of myocarditis along with the significant improvement in cardiac function by CMR a week later, make the diagnosis of TTS very reasonable. The use of the interTAK score may be helpful to estimate the probability of TTS with high sensitivity and specificity in equivocal cases [4]. Takotsubo and transient left ventricular dysfunction may be encountered in oncologic patients following the administration of different antineoplastic drugs or due to the overwhelming stress and fear secondary to the underlying disease. One of the evolving forms of cardiac toxicity in the oncologic arena is autoimmune myocarditis, particularly with the increasing use of the immune checkpoint inhibitors (ICIs). Fulminant autoimmune myocarditis has been reported following different ICIs and as associated with high reported mortality [5]. Among the currently available non-invasive imaging modalities to diagnose myocarditis, CMR is the most validated one.

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