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Editorial Comment

EDITORIAL COMMENT

The intriguing triangle of cancer, chemotherapy and takotsubo syndrome

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Chemotherapy is the mainstay of cancer management, and cardiologists are increasingly confronted with referrals of patients who have suffered cardiotoxic side effects from the employed drugs [1]. Among the many cardiac morbidities encountered is that of chemotherapy-induced cardiomyopathy (CIC) phenotype, with a varying response to therapy in terms of eventual full recovery, and the time required for its attainment. Prevalence of a diagnosis of cancer per se, irrespective of chemotherapeutic drugs used in its management, has been found to be high in patients presenting with takotsubo syndrome (TTS) [2], the mysterious acquired acute cardiomyopathy, which as a rule is completely reversible [3]. Increasingly cases of TTS are reported, which are attributed to a variety of chemotherapeutic agents, particularly 5-fluorouracil (5-FU) [4], raising concerns among clinicians as to how to proceed with the management of their cancer patients, i.e. to continue employment of their choice combination chemotherapeutic regimen, or seek an alternative. These CIC and TTS conundrums will occupy us all increasingly in the time to come.

Cases in point are the two reports that have been recently published in the *Journal* [5, 6]. The first case by Malley and Watson [5] described a 73-year-old woman who suffered TTS on the final day of her 7-day course of chemotherapy with lomustine, cytarabine, cyclophosphomide and etoposide, which she had received for a diffuse large B-cell lymphoma. The authors appropriately noted that in such cases of chemotherapy-induced TTS, the 'causality remains to be established and the mechanism of action is not yet fully understood' [5]. The authors refer to the rarity of TTS in patients receiving anthracyclines (contrary to the rather frequent occurrence of CIC) with the more frequent occurrence of TTS with 5-FU [5], and the association of cytarabine, cyclophosphamide and etoposide with CIC, and cytarabine and cyclophosphamide with TTS [5]. In the absence of specific guidelines to inform a decision about the choice of further chemotherapy (rechallenge with a different drug) in patients who had suffered TTS, avoidance of known cardiotoxic agents appears advisable, and employment of a drug like busulfan [5] may be a good choice.

The second case was reported by Abdulrahman *et al.* [6] on a 41-year-old woman with metastatic esophageal cancer who suffered TTS on Cycle 1, Day 3 of FOLFOX (leucovorin, 5-FU and oxaliplatin) chemotherapy, after disconnection of the infusion pump ('it is of interest that symptoms occurred following pump disconnection, and that previous doses had been well tolerated'), with symptoms resolving over 2 days, and a return to normal of her transiently compromised left ventricular function (LVF) within 2 weeks [6]. The seemingly offending drug (5-FU) was replaced by another fluoropyrimidine agent (capecitabine), commencing in 3 weeks after Cycle 1, without untoward incident, as also noted in a previous report. It is conceivable that the combination of 5-FU and leucovorin is implicated herein, considering the intensified cardiotoxicity when these two agents are administered together [6]. Also, the third ingredient of FOLFOX (i.e. oxaliplatin) has been linked to TTS [7]. The authors make a distinction between CIC and TTS resulting by chemotherapeutic agents, refer to CIC recurring in about half of those rechallenged with 5-FU, and provide examples from the literature of many cases of 5-FU associating with CIC or TTS [6].

There are many things we do not know and need to delineate in these *perceived* associations among cancer, chemotherapy and TTS (and this also applies to CIC): (i) The physical stresses of procedures and surgeries, and the internal turmoil of having cancer, often nor apparent or verbalized [5], may be at the roots of TTS [7, 8]. (ii) The increased sympathetic tone and catecholamine

release promoted by cancer and chemotherapy [5] have not been explored. (iii) Using β-blockers in patients with cancer and/or undergoing chemotherapy has not been systematically considered [5]. (iv) The fuzzy boundaries between CIC and chemotherapy-triggered TTS need exploration. Although the clinical course in TTS is more short-lived in comparison with CIC, this is not always the case since there are cases of CIC with rapid recovery and incidences of TTS with marked delays in the restoration of the LVF to the baseline. (v) It is conceivable that if we start being proactive in checking for rise of catecholamines and cardiac biomarkers and implementing echocardiography and cardiac magnetic resonance imaging, we may find that atypical or milder cases of TTS are more frequent than currently thought [9,10] in patients with cancer and those receiving chemotherapy. (vi) For patients with cancer and/or receiving chemotherapy, cardiac complaints communicated to their physicians can be further characterized using a patient-operated, 'smart-phone'-based technology [11] in their ambient ambulatory environment. All the above will teach us a lot about cancer, chemotherapy, CIC and TTS, which we do not currently comprehend.

CONFLICT OF INTEREST STATEMENT

None declared.

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