CASE REPORT

Successful capecitabine rechallenge following 5-fluorouracil-induced Takotsubo syndrome

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Abstract
Cardiac toxicity is a widely reported complication of fluoropyrimidine chemotherapies (5-fluorouracil and capecitabine); however, Takotsubo syndrome (TS) is less widely reported. There is little data available describing the viability of fluoropyrimidine rechallenge after fluoropyrimidine-induced TS. We report the case of Ms X, a 41-year-old woman with metastatic oesophageal cancer, who developed acute onset left ventricular dysfunction, with a measured left ventricular ejection fraction of 15% on cycle 1 day 3 of FOLFOX chemotherapy, after disconnection of the 5-fluorouracil infusion pump. Her symptoms resolved over 2 days, and an echocardiogram returned to normal within 2 weeks. 5-Fluorouracil was discontinued, and replaced with capecitabine, without recurrence of symptoms. The remainder of her treatment was uneventful. This is the second case to describe successful capecitabine retreatment following 5-fluorouracil-induced TS.

INTRODUCTION
The fluoropyrimidine chemotherapeutic drugs 5-fluorouracil and capecitabine have therapeutic activity in a wide range of cancers and are extensively employed in clinical practice. Cardiotoxicity—in the form of ischaemic events—is a well-described adverse effect of fluoropyrimidine therapy (reviewed by Sorrentino et al. [1]). Takotsubo syndrome (TS), the sudden onset of reversible left ventricular dysfunction, is less well documented, and only one previous case of successful capecitabine rechallenge following TS has been described in the literature [2]. Here, we report a second case of successful retreatment with oral capecitabine following resolution of 5-fluorouracil-induced TS, without the recurrence of cardiotoxicity.

CASE REPORT
Ms X, a previously healthy 41-year-old woman, was diagnosed with metastatic oesophageal adenocarcinoma 2 months preceding this acute episode. She completed a course of palliative radiotherapy (30 Gy in 10 fractions) to the primary tumour for local symptom control, before commencing systemic therapy with FOLFOX chemotherapy. On day 3 of her first chemotherapy cycle, 8 h following disconnection of the 5-fluorouracil infusion pump, she presented acutely, complaining of progressive central chest pain, shortness of breath, palpitations and diaphoresis. Her blood pressure was 92/60, and her heart rate was 110, with a regular pulse. Systemic examination was otherwise normal.

Blood tests revealed a troponin-T of 29 ng/l (twice the upper limit of normal) and D-dimers of 2.0 μg/ml (four times the upper limit of normal). A biochemistry profile and full blood count were otherwise unremarkable. An electrocardiogram (ECG) demonstrated T-wave inversion in the lateral leads, which was new compared with her baseline pre-chemotherapy ECG (Fig. 1). A transthoracic echocardiogram showed impaired left ventricular systolic function, with mid- and apical left ventricular hypokinesis, and an estimated ejection fraction of 25% (Fig. 2). Later that day, she
proceeded to coronary artery catheterization, which demonstrated normal coronary arteries, severe left ventricular dysfunction and a measured ejection fraction of 15%. A CT pulmonary angiogram examination showed no evidence of pulmonary embolus.

Ms X was treated with bisoprolol and ramipril, and analgesia as required for the chest pain, along with supportive measures. No further cardiac medications were indicated. Serial cardiac data demonstrated normalization of ECG changes and troponin within 2 days of presentation. Ms X’s symptoms resolved over the same time period. A repeat echocardiogram carried out 2 weeks later demonstrated normal left ventricular function.

For her second chemotherapy cycle—commenced 3 weeks after cycle 1—5-fluorouracil was discontinued and replaced with capecitabine, which was well tolerated. Two weeks after commencing capecitabine, an echocardiogram demonstrated normal left ventricular function. She remained symptom free for the duration of her treatment.

DISCUSSION

Fluorouracil- and capecitabine-induced cardiotoxicity is recognized in the literature, affecting between 1.2 and 18% of individuals treated with these drugs [1]. Cardiotoxicity is more common with infusional regimes, and rates of cardiotoxicity are higher in patients who also receive leucovorin [3]. Symptoms of cardiotoxicity recur in about half of those rechallenged with the drug [4]. The mechanism of cardiotoxicity remains unclear (reviewed by Polk et al. [5]).

The majority of adverse cardiac events is described as acute coronary syndrome (ACS), likely induced by vasospasm [3]. However, cases of TS are increasingly reported. TS is characterized by the onset of reversible left ventricular dysfunction. While TS is often aetiologically associated with intense emotional stress [6], chemotherapy-induced TS is now a recognized entity. In particular, TS has been reported in individuals treated with both capecitabine [7] and 5-fluorouracil [2, 8, 9]. The mechanism underlying the induction of TS by chemotherapy is unclear. Similar to fluoropyrimidine-induced ACS, coronary artery vasospasm had been proposed as a possible pathogenetic feature of fluoropyrimidine-induced TS [2]. However, coronary angiography during an acute episode of capecitabine-induced TS has demonstrated slow coronary artery blood flow in the absence of coronary artery vasospasm [7]. Current hypotheses include coronary microvascular dysfunction or catecholamine-induced cardiotoxicity [7]. Further evidence
will be needed to clarify the importance of these mechanisms in the pathogenesis of fluoropyrimidine-induced TS.

There is little evidence describing the likely outcomes of fluoropyrimidine rechallenge following TS. Successful capecitabine administration in individuals following 5-fluorouracil-induced ACS \[10\] and TS \[2\] has been reported previously. Similarly, our patient tolerated capecitabine well, with no recurrence of cardiac symptoms, and a normal echocardiogram after one complete cycle of capecitabine therapy. It is also of note that onset of symptoms occurred following pump disconnection, and that previous doses had been well tolerated. While data supporting fluoropyrimidine challenge following TS remains limited, our case demonstrates that cautious rechallenge with capecitabine under close clinical supervision might be reasonable in this setting.

CONFLICT OF INTEREST STATEMENT

None declared.

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ETHICAL APPROVAL

No ethical approval was sought.

CONSENT

The patient has signed consent for publication of this case.

GUARANTOR

N.O. is guarantor of this study.

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Figure 2: Resolution of left ventricular dilatation on echocardiogram. During the acute presentation, an echocardiogram revealed left ventricular dysfunction with marked apical and mid-left ventricular hypokinesis and an estimated left ventricular ejection fraction of 20% (A and B). Two weeks following discharge, a repeat echocardiogram demonstrated normal left ventricular function, with an estimated ejection fraction of 55% (C and D).
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