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Unexpected outcome (positive or negative) including adverse drug reactions

# Capecitabine (oral 5-fluorouracil pro-drug) treatment for colorectal carcinoma causing ischaemic chest pain

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## Abstract

We present a case of cardiac ischaemia associated with capecitabine chemotherapy. An elderly female receiving capecitabine chemotherapy developed acute onset severe anterior chest pain associated with ischaemic changes on ECG. The pain and ECG changes failed to respond to thrombolysis and she proceeded to coronary angiogram and stenting of a thrombosed right coronary vessel. She inadvertently recommenced her capecitabine with a further episode of chest pain. On cessation of capecitabine she had no further episodes of chest pain.

## BACKGROUND

5-Fluorouracil (5-FU) is among the most commonly used chemotherapy drugs in oncology practice. It is used to treat colorectal cancer, upper gastrointestinal cancers, breast cancer and head and neck cancers, either as a single agent or in combination with other chemotherapy drugs. Capecitabine (Xeloda) is an oral prodrug of 5-FU and is increasingly replacing infusional and bolus intravenous 5-FU. Capecitabine is a tablet formulation and is usually self-administered by patients at home. Common toxicities of 5-FU and capecitabine include diarrhoea, mucositis and myelosuppression. However, an association between 5-FU and cardiac toxicity has also been known for almost 40 years,[1,2] but this toxicity is less common and less well known to general physicians. Cardiac toxicity most commonly manifests as chest pain, but arrhythmias, myocardial infarction, congestive heart failure, cardiogenic shock and sudden death have all been reported. Estimates of the overall incidence of 5-FU cardiotoxicity range from 1% to 18%.[3] Similar cardiac toxicity has also been observed with capecitabine and in one study the incidence was found to be 6.5%.[4] Mortality in symptomatic patients may be as high as 30%.[5,6] Risk factors for 5-FU induced cardiotoxicity include pre-existing ischaemic heart disease and older age, although it may occur in young individuals with no significant past medical history. In symptomatic patients, ECG and myocardial enzymes may show changes consistent with ischaemia or may be normal. Coronary angiograms may also be normal. The mechanism of this toxicity is not fully delineated but may involve coronary artery vasospasm secondary to a cardiotoxic metabolite of 5-FU.[7] It is essential that

capecitabine (or 5-FU infusion) is discontinued in those patients with chest pain and is not restarted without consulting an oncologist.

## CASE PRESENTATION

A 65-year-old female with metastatic colorectal cancer was advised to receive six cycles of palliative combination chemotherapy. She was prescribed three-weekly Cap/Ox chemotherapy (capecitabine tablets 1000 mg/m$^2$ twice daily from days 1 to 14, and oxaliplatin 130 mg/m$^2$ iv infusion over 2 h on day one). She had no significant past medical history and gave no history of cardiac risk factors or pre-existing ischaemic heart disease. Five days after starting cycle 3, she was admitted to the emergency department with chest pain. She gave a history of sudden onset left anterior chest pain associated with autonomic symptoms.

## INVESTIGATIONS

A 12-lead ECG demonstrated ST elevation in leads II, III and aVF with ST depression in lead aVL (fig 1 ).

## DIFFERENTIAL DIAGNOSIS

Ischaemic heart disease presenting with symptomatic angina or myocardial infarct is the most likely cause of chest pain in this case. Other less common causes include spontaneous pneumothorax, dissecting aortic aneurysm and gastro-oesophageal disease.

## TREATMENT

The chest pain was partially relieved by buccal GTN administered by paramedics. The patient was thrombolysed in the coronary care unit with 7000 U Tenecteplase and commenced on heparin infusion. There was no resolution of ST changes after 90 min and she proceeded to coronary angiography, which demonstrated right coronary artery stenosis with distal thrombus (fig 2). This was treated successfully with coronary artery stenting (fig 3).

## OUTCOME AND FOLLOW-UP

The patient was discharged 4 days later with no further chest pain. Inadvertently, she continued to take capecitabine, despite it being implicated in her infarct. She developed further chest pain, requiring re-admission to hospital. Her capecitabine was discontinued and she has had no further chest pain. She is being considered for non-5-FU based chemotherapy.

## DISCUSSION

5-FU based chemotherapy is well recognised by oncologists as having the potential to induce cardiotoxicity. As the above case demonstrates, this toxicity may manifest in those with no recognised cardiac risk factors or significant past medical history. In the presented case, cardiotoxicity manifested as infarct associated with coronary artery thrombus, requiring coronary artery stenting. However, a spectrum of cardiovascular toxicities is associated with capecitabine/5-FU. These include exertional ischaemic chest pain with potentially normal ECG and normal angiographic findings. This spectrum of effects reflects observations that 5-FU or its metabolites may induce coronary artery spasm or induce direct damage to endothelial cells with resulting thrombus formation.[8] Although organoplatinum drugs have been implicated in arterial thrombus formation,[9] oxaliplatin is unlikely to be implicated in this case. The chest pain recurred on re-challenge with capecitabine making capecitabine (5-FU) the most

likely cause.

There is no unequivocally effective prophylaxis or treatment for patients who develop 5-FU induced chest pain, although calcium channel blockers, nitric oxide donors and 5-FU dose reduction have anecdotally been reported as reducing or preventing symptoms in some patients.[10] Symptoms are usually reversible following discontinuation of 5-FU although mortality can be as high as 30%.[5] It is now becoming apparent that capecitabine can also cause cardiac toxicity, with an incidence of almost 7%.[4] Approximately 6200 patients are currently receiving capecitabine each month in the UK for colorectal cancer and breast cancer (personal communication with Roche Products Ltd, UK, January 2007), and this figure is likely to increase. Patients who develop chest pain are likely to present to emergency services and therefore all health professionals need to be aware of this potential drug induced toxicity. In patients receiving 5-FU (or taking oral 5-FU prodrugs such as capecitabine) who present with suspected cardiac chest pain, it is essential that these drugs are stopped immediately, cardiac investigations are performed, the patient is advised not to re-start their chemotherapy tablets and the oncology team is informed promptly.

### LEARNING POINTS

- Chest pain may be associated with medications including capecitabine/5-FU.
- A full drug history is essential.
- Capecitabine treatment should be stopped immediately on developing chest pain and only restarted after discussion with an oncologist.

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## Footnotes

**Competing interests:** none.

**Patient consent:** Patient/guardian consent was obtained for publication.

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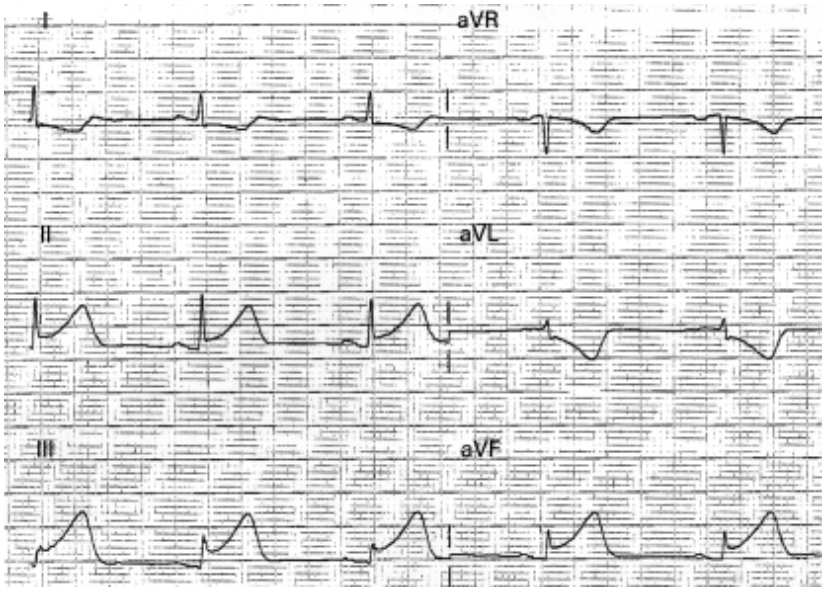
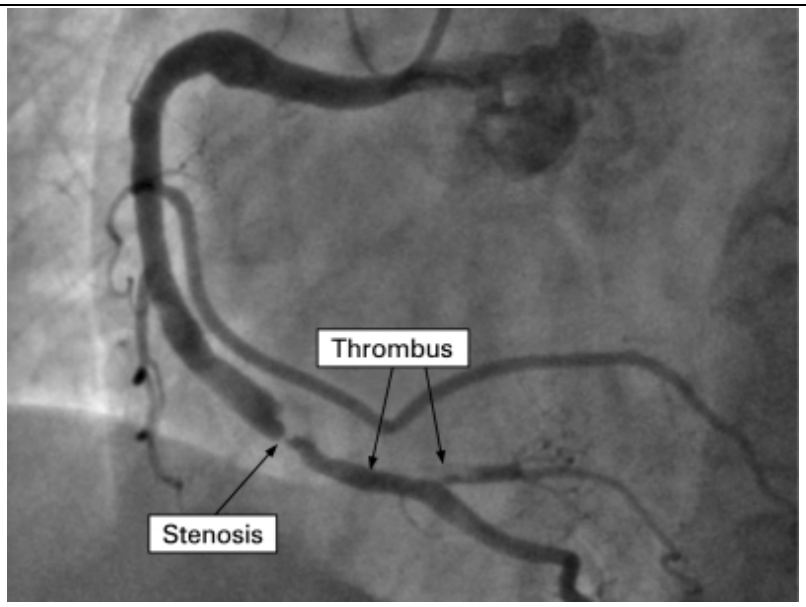
## Figures and Tables

### Figure 1



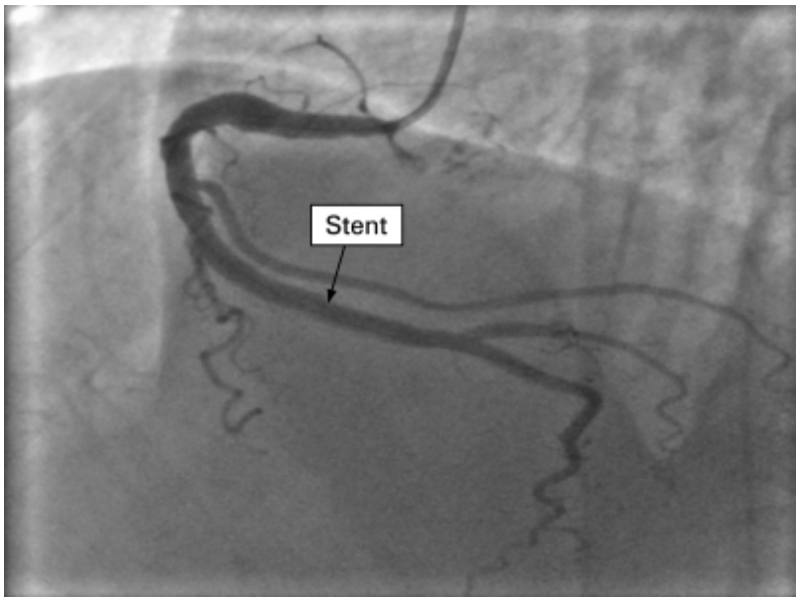

A 12-lead ECG demonstrating ST elevation in leads II, III and aVF with ST depression in lead aVL.

### Figure 2




Coronary angiogram showing right coronary artery stenosis with distal thrombus.

**Figure 3**




Coronary angiogram after angioplasty, demonstrating deployed stent and restoration of blood flow in right coronary vessels.