


# CASE REPORT

## Rapidly developing heart failure from capecitabine cardiotoxicity: a case study

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### Introduction

**Capecitabine** is a pyrimidine analogue used as an anti-neoplastic agent. It is a fluoropyrimidine-based oral prodrug of **5-fluorouracil** (5-FU). It exerts its effect by selectively activating a three step enzymatic pathway. The last step is catalysed by the enzyme **thymidine** phosphorylase [1].

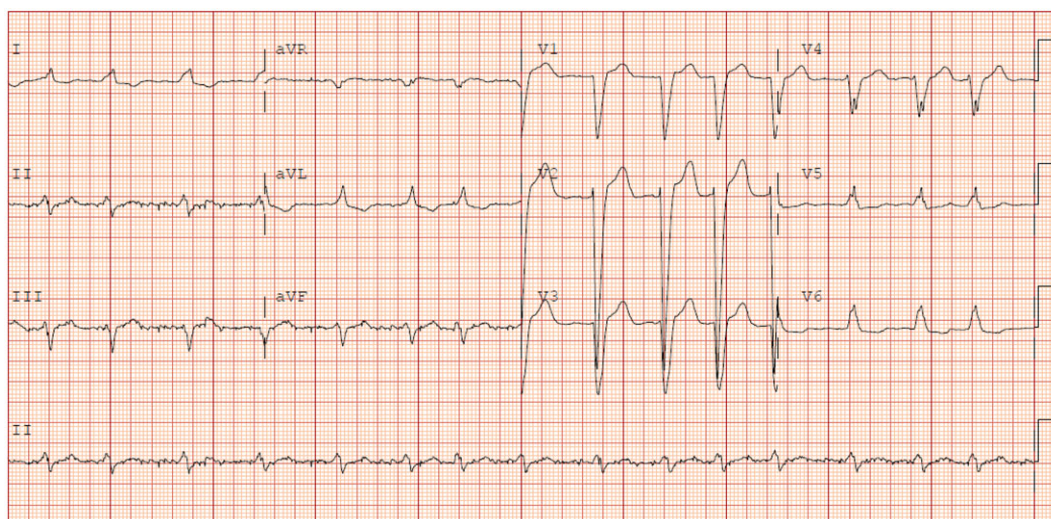
As compared to normal tissues, this enzyme has higher activity in neoplasms than in normal tissues. Hence, 5-FU tends to accumulate in tumour cells. Capecitabine is currently approved for treatment of metastatic breast cancer and is included in the WHO list of essential medicines. Though 5-FU has been associated with cardiotoxicity, there have only been a handful of reports linking capecitabine to cardiac dysfunction. Generally speaking, capecitabine is known as a relatively safe drug. However, the most common reversible side effects are hand-foot syndrome (17%), gastrointestinal upset (17%), and nausea (15%) [1]. Though 5-FU has been associated with cardiotoxic effects, capecitabine-induced myocardial toxicity is rare and has not been much reported. Its incidence is on the rise due to a burgeoning geriatric population and more widespread use of capecitabine [2]. In this case report, we describe a male with metastatic breast cancer and no pre-existing heart disease, who was being treated with capecitabine. Before initiation of chemotherapy, his cardiac function was normal with an ejection fraction of 70%. However, over the next 12 months, he developed progressive exertional dyspnoea. Repeat Transthoracic Echocardiography (TTE) revealed an ejection fraction of 10%.

### Case presentation

A 76-year-old man with metastatic right-sided breast cancer, atrial fibrillation, and benign prostatic hyperplasia presented with shortness of breath (SOB) and fatigue. In the emergency room, he was afebrile, respiratory rate was 16/min, pulse

88/min irregular, and blood pressure 140/92 mm Hg. Examination revealed distended neck veins, pedal oedema, and peripheral skin mottling. Rales were heard in bilateral lower lung zones. Cardiac auscultation revealed a Grade 3+ Holosystolic murmur over the left parasternal region with radiation to left axilla. An audible S3 was also appreciated. Patient reported that 1 year back, he could walk a block without SOB. However, over the last 12 months, his exercise tolerance had dramatically decreased to the extent that he was now breathless at rest [New York Heart Association (NYHA) Class IV].

2 years back, he was diagnosed with right sided breast cancer. Ultrasonography of chest revealed a 15 × 10 × 16 mm right breast solid mass at 8:00 posterior peri-areolar region. Biopsy of mass showed invasive ductal carcinoma with hormone receptor positivity. Positron Emission Tomography (PET) scan showed metastases to right axillary nodes and the left iliac wing. Tamoxifen was initiated, but after a year, his primary tumour site had progressed to 2 cm. Hence, due to treatment resistant metastatic breast cancer, he was switched to capecitabine, a prodrug of 5-FU. Before capecitabine initiation, a TTE had been obtained to record baseline cardiac function. Baseline EF had been recorded as 70%, with a normal diastolic filling and relaxation pattern. Electrocardiogram (EKG) revealed atrial fibrillation and a new left bundle branch block (Figure 1). Cardiac enzymes were within normal limits. Lab results showed an elevated B type natriuretic peptide at 1355 pg ml<sup>-1</sup>. Complete blood count and chemistry panel were within normal range. Chest X-ray showed pulmonary congestion. The patient was given intravenous furosemide to achieve adequate diuresis. The next day, his dyspnoea was markedly improved. A new TTE was obtained which revealed a precipitous drop of the EF to 10%. Spectral Doppler showed impaired relaxation pattern of left ventricular diastolic filling (Video S1). There was moderate mitral regurgitation and severe left ventricular systolic dysfunction. Since suspicion for ischaemic heart disease was



**Figure 1**

12 Lead ECG showing Left bundle branch block

high, urgent coronary angiography was performed. However, angiography revealed no evidence of coronary artery disease. Hence, a diagnosis of nonischaemic cardiomyopathy was made. After discussion with the oncology team, capecitabine was discontinued with no plans of re-initiation. Patient was discharged with a life vest to reduce risk of sudden cardiac death. He continues to follow up in the cardiology outpatient clinic regularly. After 8 months of stopping capecitabine, the EF continues to be 6–10%.

## Discussion

Capecitabine is a selectively active prodrug of 5-FU against tumour cells. This makes it more tolerable for the patients. It is a relatively safe drug. The most common reversible side effects are hand–foot syndrome (17%), gastrointestinal upset (17%), and nausea (15%) [1]. However, the parental salt of capecitabine may induce dose dependent cardiotoxicity [3]. It is hypothesized that 5-FU acts on the endothelium and produces **endothelin-1** which results in coronary vasospasm [4]. Fluoropyrimidines-based therapy regimens are associated with a cardiac complication rate ranging from 1.2% to 18% and a mortality rate from 2.2% to 13.3% [5]. One meta-analysis showed a 3% incidence of symptomatic 5-FU and capecitabine-related cardiac events [6]. Pharmacokinetic studies have shown that the active metabolites of 5-FU are retained at cellular level, both in cardiac and in normal tissue [7]. The aetiology of 5-FU-induced cardiotoxicity is not clearly understood. One mechanism of 5-FU action is inhibition of endothelial **nitric oxide (NO) synthase**. 5-FU causes direct vasoconstriction in smooth muscle cells [8]. A decreased NO level causes coronary vasoconstriction through the protein kinase pathway [9]. Neither nitrates nor calcium channel blockers have shown to reduce incidence of 5-FU-induced cardiotoxicity [10, 11]. On the contrary, concomitant therapy with both categories of drugs has shown greater risk of

cardiotoxicity [12]. Another study has found association of 5-FU with direct oxidation mediated cardiotoxicity [7].

In our patient, the absence of chest pain, and normal cardiac enzymes ruled out a myocardial infarction. The new onset LBBB was most likely a result of capecitabine-induced cardiotoxicity. Curiously, a higher prevalence of capecitabine-induced cardiotoxicity has been found in patients with pre-existing CAD. There have been a handful of previously reported cases of capecitabine-induced coronary artery disease, systemic hypertension, and sudden death [13]. However, our patient had no history of CAD. In general, capecitabine cardiotoxicity is not uncommon but does typically present in the first cycle of therapy [14]. For the sake of objectivity, we employed the Naranjo Score to ascertain the likelihood of capecitabine causing the heart failure [15]. A calculated score of 8 was highly predictive of capecitabine being the culprit.

## Conclusion

Capecitabine has major potential to cause cardiac toxicity. As demonstrated in our case, we see how the cardiac systolic function in normal hearts can decompensate over a very short period of time. Therefore, in patients with or without CAD, it is imperative to be mindful of the baseline cardiac function before capecitabine initiation. Watchful monitoring of cardiac function over the course of the treatment is highly recommended.

## Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [16], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [17].

## Competing Interests

There are no competing interests to declare.

*Our institution does not require ethics committee approval for publication of individual case reports.*

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## Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

<http://onlinelibrary.wiley.com/doi/10.1111/bcp.13509/supinfo>

**Video S1** Transthoracic Echocardiogram showing severely depressed systolic function