# Cardiotoxicity of 5-fluorouracil in a young colorectal cancer patient – case report and review of literature

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**Submitted:** 3 March 2008
**Accepted:** 28 April 2008

Arch Med Sci 2009; 5, 2: 277-280


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## Abstract

Pyrimidine analogues such as 5-fluorouracil (5-FU) are widely used in adjuvant and palliative treatment of various solid tumours. However, their administration may be associated with severe adverse events such as myelosuppression, mucositis or cardiotoxicity. Cardiotoxicity is a relatively rare event but its fatal outcomes occur at a rate of 2.2-13.3%. Since 5-fluorouracil is widely used in medical oncology, cardiotoxicity associated with its administration may significantly impair treatment of patients with cancers sensitive to pyrimidine analogues. This article reviews fluoropyrimidine-associated cardiotoxicity and presents a case report of a young woman who experienced this complication during 5-fluorouracil treatment.

**Key words:** cardiotoxicity, 5-fluorouracil, pyrimidine analogues.

## Introduction

Cardiotoxicity is a frequent side effect associated with administration of chemotherapeutic agents to cancer patients, particularly in the case of anthracycline antibiotics such as daunomycin or doxorubicin. Cardiological adverse events can also be induced by fluoropyrimidines such as 5-fluorouracil (5-FU) or capecitabine, which are widely used in adjuvant and palliative treatment of various solid tumours. The first reports describing cardiotoxicity of 5-FU appeared in 1975 [1]. Since then large prospective studies have demonstrated an incidence of 5-FU induced cardiotoxicity ranging from 1.6 to 8% [2, 3]. Cardiotoxicity seems to be dose- and schedule-dependent since its frequency is lower with bolus regimens than with continuous infusion (over 2-4 days) [4].

The most frequent symptom of 5-FU associated cardiotoxicity is chest pain with projection to the left arm or neck. Other clinical symptoms include arrhythmias, myocardial infarction, cardiogenic shock or heart failure leading to hypotension, dyspnoea or sudden death. In many patients receiving pyrimidine antimetabolites ECG may reveal asymptomatic reversible ST segment depressions or transient bradycardia [5]. Fatal outcomes have been reported to occur at a rate of 2.2-13.3% [2, 3].

Patients with a history of cardiac disease, particularly coronary artery disease, are at high risk of developing 5-FU associated cardiotoxicity as compared with patients without a history of cardiac disease [6]. Therefore,

occurrence of 5-FU-induced cardiotoxicity is assumed to be very uncommon in young, otherwise healthy cancer patients. This article presents a case of cardioto-xicity in a young woman treated with an adjuvant FOLFOX regimen following metastasectomy of liver metastasis.

## Case report

A 28-year-old female patient was to be treated with FOLFOX6 regimen. Fourteen months earlier she was diagnosed with a rectal adenocarcinoma pT3N1. Following preoperative, short course (25 Gy/T 5Gy/dose) radiotherapy and surgical excision she received 8 courses of adjuvant capecitabine (1250 mg/m$^2$ bid d1-14 q3w). She completed the adjuvant treatment without any complications. Seven months after completion of adjuvant chemotherapy she was diagnosed with a single resectable liver metastasis. Following metastasectomy she was initiated on adjuvant chemotherapy with FOLFOX6 regimen (Oxaliplatin 100 mg/m$^2$ d1, 5-FU 400 mg/m$^2$ bolus d1, leucovorin 400 mg/m$^2$ d1, 5FU 2400 mg/m$^2$ continuous infusion d 1-2; q2w) on an outpatient basis. On day 14, prior to the start of the next course, she informed about a chest pain incident which occurred 18 h after initiation of the first course (during 5-FU infusion). The pain had been diminishing while resting and had been present for 6 h following a scheduled end of 5-FU infusion (Figure 1). She had no history of heart disease. The ECG and echocardiography performed on day 14 showed no abnormalities. Due to the cardiac symptoms she was admitted to our hospital for observation. Prior to the second course she received along with a standard premedication (intravenous ondansetron 8 mg and dexamethasone 8 mg) 5 mg of calcium channel blocker (amlodipine) *p.o.* 16 h following initiation of the second course she complained of a chest pain. Electrocardiography showed a slight depression of the ST segment while echocardiography and troponin analysis showed no abnormalities. Her blood pressure was 120/70 mm Hg. She received 0.4 mg of glyceryl trinitrate s. l. and 20 min later the pain diminished but was still present (RR 105/60 mm Hg). Therefore she was given additionally 20 mg of isosorbide mononitrate *p.o.* 30 min later the pain almost completely disappeared and the patient reported no additional complaints (RR – 80/40 mm Hg, ECG – no abnormalities). During the next 26 h she received further doses of isosorbide mononitrate 40 mg per day *p.o.* and blood pressure was kept below 90/60 mm Hg. During the next courses of chemotherapy on an outpatient basis she was taking 40 mg of iso-sorbide mononitrate and 5 mg of amlodipine daily, and a sporadic, tolerable, low-intensity chest pain appeared only during intensive walking, while receiving the 48-h 5-FU plus 6 h following the end of infusion. The patient received 12 adjuvant courses of FOLFOX6 regimen within 6 months following the resection of liver metastasis. The management of cardiotoxicity with nitrates and calcium channel blocker turned out to significantly decrease the incidence and intensity of this cardiac adverse event.

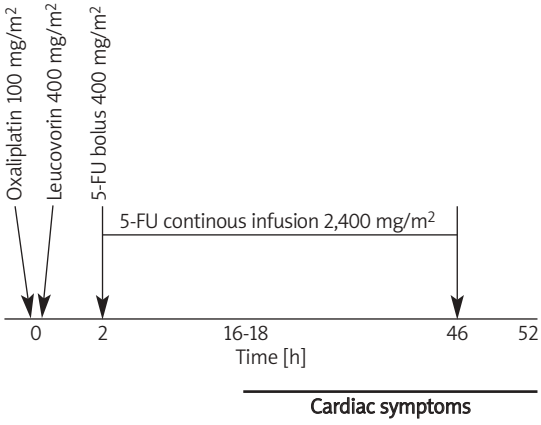


**Figure 1.** Time course of FOLFOX6 regimen and the treatment-associated cardiac adverse event

## Discussion

Cardiotoxicity is a rare adverse event associated with 5-FU-based chemotherapy. The pathogenesis of cardiotoxicity induced by pyrimidine antimetabolites is still unknown. However, there are several proposed mechanisms of this phenomenon, which include coronary vasospasm [7], toxicity on the myocardium [8, 9], activation of autoimmune responses [10] or production of fluoroacetaldehyde generated in the alkaline solution of 5-FU vials during storage, which undergoes conversion *in vivo* into the cardiotoxic fluoroacetate [11].

Characteristic electrocardiographic findings and clinical similarities to a reversible ischaemic heart disease indicate coronary vasospasm to be involved in the pathophysiology of this phenomenon [2, 3, 12]. In a study of Südhoff *et al*. 5-FU was shown to induce brachial artery vasocontraction in 50% of 5-FU-treated patient compared to 0% of patients treated with non-5-FU containing chemotherapy [9]. However, in many patients coronary angiography performed during symptomatic attacks of cardiotoxicity did not reveal spasm of coronary arteries [13]. Cardiotoxicity of 5FU is sometimes associated with reduced ejection fraction and significant akinesia of the left myocardium during attacks. However, De Froni *et al.* demonstrated that the akinetic area did not correspond to a segmental distribution of major coronary arteries [3]. Another possible mechanism

is direct toxicity on coronary endothelial cells. Electron microscopy evaluation of rabbit arterial endothelium following infusion of 5-FU revealed significant degradation of endothelial cells often accompanied by platelet accumulation and fibrin formation [14]. The toxic effect of 5-FU on endothelial cells may be associated with generation of free oxygen radicals. In a study of Kinhult *et al*. administration of probucol, which possesses strong antioxidant properties, prevented 5-FU-mediated endothelial injury [15]. Some new data indicate that toxic myocarditis is responsible for the pathological findings associated with 5-FU infusion [16]. Myocarditis may thus explain the observed clinical symptoms such as: chest pain, reversible ST segment depression, left ventricular dysfunction and elevation of cardiac enzymes. In an animal model Tsibiribi *et al*. demonstrated several mechanisms of 5-FU cardiotoxicity [17]. High-dose 5-FU (50 mg/kg) given intravenously to rabbits induced massive haemorrhagic myocardial infarcts associated with spasm of proximal coronary arteries. However, repeated infusions of lower doses of 5-FU (15 mg/kg) induced left ventricular hypertrophy, myocardial necrosis, thickening of intra-myocardial arterioles and apoptosis of endothelial and myocardial cells [17].

There are several risk factors for occurrence of 5-FU-induced cardiotoxicity. Pre-existing heart disease is one of them. In a study evaluating 390 patients receiving 5-FU based chemotherapy 13 adverse cardiac events were observed. The incidence of cardiotoxicity was higher in patients with previous cardiac disease than in otherwise healthy counterparts (15.1 vs. 1.5%) [18]. In another prospective study silent ischaemia-like ECG changes occurred at higher frequency in patients with heart disease [6]. Recently, Jensen and Sorensen evaluated the frequency of cardiac events in 668 patients treated with 5-FU or capecitabine. Cardiotoxicity was observed in 29 (4.3%) patients [19]. There were no significant differences in the occurrence of grade 2-3 cardiotoxicity between patients with and without pre-existing heart disease (12 vs. 17 cases). Moreover, in their study Jensen and Sorensen noticed that in a few cases patients with impaired renal function were more susceptible to chemotherapy-induced cardiotoxicity [19]. However, some other studies have not confirmed a casual relationship between renal function and 5-FU-associated cardiotoxicity [7, 20, 21].

Prevention of recurrence of 5-FU associated cardiotoxicity involves dose reduction during subsequent chemotherapy courses, administration of calcium channel blockers, β-blockers and long-acting nitrates. In a small, prospective study administration of calcium channel blockers to patients receiving 5-FU did not decrease the incidence of ischaemia-like changes in ECG as compared to a control group [22]. In a review of 134 patients receiving 5-FU-based chemotherapy administration of calcium channel blockers or nitrates did not prevent the occurrence of adverse cardiac events [21]. In the study of Jensen and Sørensen administration of calcium channel blockers and nitrates along with reduction of 5-FU dose significantly prevented symptoms of cardiotoxicity [19].

In conclusion, 5-FU-mediated cardiotoxicity is a relatively rare event which, however, may occur even in very young patients without a prior history of cardiac disease. In our patient a combination of two drugs – calcium channel blocker and long-acting nitrates – effectively protected her against treatment-associated cardiotoxicity and made possible continuation of chemotherapy according to the planned schedule.

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