# Bolus 5-Fluorouracil as an Alternative Modality to Infusion 5-Fluorouracil in a Patient with Rectal Cancer and Capecitabine-induced Cardiotoxicity

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**Abstract.** *5-Fluorouracil (5-FU) is the backbone of the chemotherapy regimens approved for treatment of colorectal cancer. Incidence of cardiotoxicity associated with 5-FU ranges between 1.5% to 18%; 48% as anginal symptoms and 2% as cardiogenic shock. Cardiotoxicity is unpredictable and no alternatives have been defined so far. A 35-year-old man treated for stage III A rectal cancer developed chest pain typical of angina on treatment with capecetabine initially and 5-FU infusion afterwards. Scheduled dosing of 5-FU was changed from infusion to a bolus type. He was asymptomatic with no electrocardiographic (ECG) changes on 24-h Holter monitoring after changing the mode of administration to bolus 5-FU. Here, we report the first case in the English literature where a change in the mode of 5-FU administration to bolus is an alternative to infusion 5-FU-induced cardiotoxicity. In conclusion, Bolus 5-FU can be used in patients developing cardio-toxicity due to 5-FU infusion.*

Colorectal cancer (CRC) is a common and lethal disease. Approximately 148,810 new cases of large bowel cancer are diagnosed each year in the United States, of which 108,070 are colon and the remainder rectal cancer. Annually, approximately 49,960 Americans die of CRC, accounting for approximately 9% of all cancer deaths (1). 5-Fluorouracil (5-FU) remains the backbone of most regimens used in the treatment of CRC. It may be administered as a bolus injection weekly (b5-FU) or daily for 5 days every 4 weeks, or as a continuous infusion on an outpatient basis. It is modulated by leucovorin (LV), which raises the level of 5,10-methylenetetrahydrofolate and results in the formation of a stable ternary complex of the folate coenzyme thymidylate synthase with 5-FU in the form of the principal metabolite, fluorodeoxyuridine (2). The National Surgical Adjuvant and Bowel Project (NSABP) C-03 trial demonstrated the superiority of bolus 5-FU/LV over methyl-lomustine (MeCCNU), vincristine and 5-FU (MOF) by better three-year disease-free survival (DFS) (73 *versus* 64%) and overall survival (OS) (84 *versus* 77%) (3). The International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) which studied the efficacy of fluorouracil and high-dose folinic acid after surgery for Dukes' B and C colon cancer, reported a significant 22% reduction in death rate, which translated into 5% benefit in three-year OS (83 *versus* 78%) in node positive (Dukes' C) disease (4). The North Central Cancer Treatment Group (NCCTG) trial noted a similar degree of benefit with stage II or III colon cancer patients with lower doses of LV (20 mg/m$^2$) Mayo regimen (5). Based upon these data, a 1990 NIH Consensus Conference reported a standard of care regimen for resectable stage III colon cancer, with 5-FU and either levamisole or LV (6). Subsequent studies showed the inferiority of 6 months compared to 12 months with 5-FU and levamisole, along with adjuvant 5-FU/levamisole compared with LV-modulated 5-FU and the lack of additional benefit for adding levamisole to 5-FU/LV (7, 8, 9). The Mayo regimen (b5-FU at 425 mg/m$^2$ and LV at 20 mg/m$^2$) has fallen out of favor because of its toxicity (diarrhea) secondary to the bolus 5-FU given over 5 days per cycle. As compared to 6 months of 5-FU/LV treatment, 12 months' duration therapy has shown to be similar (7). As reported in the intergroup study 0153, no difference for infusion *versus* bolus 5-FU was shown in terms of DFS or OS, although infusion 5-FU had a better toxicity profile compared to bolus. In this study, levamisole was added to both groups (10). The Pan-European Trials in Adjuvant Colon Cancer (PETACC-2) trial, which included 1601 patients with stage III colon cancer randomly assigned to low dose Mayo regimen and infusion 5- FU, showed no difference in relapse-free survival or OS but demonstrated a better toxicity profile (11).

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In the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, which included 2,246 patients, statistical significance in stage III colon cancer patients with respect to DFS was proven. The regimen contains oxaliplatin added to the de Gramont scheduled 5-FU/LV administration (12). NSABP C-07 showed improved outcomes from addition of oxaliplatin to b5-FU/LV randomization of 2,407 patients having stage II or III colon cancer. The median follow-up was 43 months. Four-year DFS significantly favored bolus 5-FU/LV/oxaliplatin (bFLOX) over 5-FU/LV (73 *versus* 67%). bFLOX was more toxic than was 5-FU infusion (13). We have shown that capecitabine can be an alternative to 5-FU as a radiosensitizer in the treatment of locally advanced rectal cancer (14).

We report the first case in the English literature where a change in the mode of 5-FU administration to bolus, is an alternative to infusion to overcome 5-FU-induced and capecitabine-induced cardiotoxicity.

## Case Report

A 35-year-old man presented to the hospital in April 2008 because of painless rectal bleeding. Flexible sigmoidoscopy showed a malignant-appearing rectal mass which extended approximately 8-12 cm from the anal verge. Biopsy of the lesion showed moderately differentiated adenocarcinoma without lymphovascular invasion. Staging computed tomography (CT) and positron emission tomography (PET) scans revealed non-specific pulmonary nodules along with splenic hypodensities with moderate PET avidity. Chemoradiation was planned with capecitabine as neo-adjuvant treatment. The patient developed chest pain typical of angina after administration of capecitabine. The pain was described as burning to pressure-like in nature, substernal in location, 8/10 in intensity, radiating to the left jaw and arm, associated with shortness of breath, not relieved by any position, not associated with food intake, occurring at rest, associated with nausea, diaphoresis and palpitations, lasting around 20 minutes and resolving on its own. Pain started after around 20 hours of the capecitabine dose. The pain was not associated with deep breaths. No electrocardiographic (ECG) changes had been recorded, and there was no elevation in cardiac biomarkers. There was no history of heart-burn or similar chest pains, nor was there any history of dyspnea on exertion. He was put on multiple antacid regimens. The patient was then scheduled for infusion 5-FU because of suspected capecitabine-induced cardiotoxicity. After 24 hours of 5-FU continuous infusion pump, the same type of chest pain was described but now lasting for approximately 30 minutes and relieved by 30 minutes after infusion was stopped. Pain occurred at rest, and was not associated with food or any position. Troponin T was negative in the first 2

sets (<0.1 ng/ml) and mildly elevated in the third set (0.14 ng/ml). CK-MB (negative in 3 sets) and creatinine phosphokinase (CPK) (55, 49, 42 U/l respectively) were within normal limits (24-129 U/l). ECG showed sinus tachycardia (Figure 1). Upper endoscopy was carried out to show normal esophagus and chronic gastritis. Biopsy of the stomach wall revealed inflammatory changes with negative cultures for *Helicobacter pylori*, cytomegalovirus and herpes simplex virus. Dihydro-pyrimidine dehydrogenase (*DPYD*) gene was assessed for possible mutation although no bone marrow suppression was noted. The results were negative for any mutation. *DPYD* and thymidylate synthetase (*TYMS*) gene analysis indicated low risk for 5-FU toxicity. Restaging CT scan carried out in July 2008 showed pericaval, portal, peripancreatic and retroperitoneal lymphadenopathy. Rectal wall thickening of 1.7 cm was noted, with hypodense splenic lesions which were larger compared to previous scan. CT chest showed multiple paratracheal, hilar and supraclavicular nodules and lymphadenopathy. Pathology of one of the nodules after biopsy showed granulomatous changes with metastasis.

The patient underwent low anterior resection with an ileostomy on 09/04/08 with a T3N1Mx finding and was diagnosed with stage IIIA rectal adenocarcinoma. 5-FU, LV and oxaliplatin (FOLFOX-6) regimen was planned as first-line adjuvant treatment in the adjuvant setting according to the MOSAIC trial for stage III colorectal cancer. After 20 hours, the chest pain syndrome recurred and the infusion of 5-FU was discontinued. The patient was given aspirin 325 mg and morphine 1 mg. Thirty minutes later, symptoms were relieved. Chest x-ray was normal and cardiac markers were within normal limits. ECG was normal except for tachycardia to 110 beats per minute. Echocardiography showed moderate global hypokinesis, moderately decreased left ventricular systolic function and ejection fraction of 40%. Treatment mode was changed to FLOX according to the NSABP C-07 with the thought that the bolus dosage might decrease the cardiotoxicity. The patient was put on Holter monitoring. He was symptom free after 2 doses of bolus 5-FU and 24-hour Holter monitoring showed sinus rhythm with sinus tachycardia and paroxysmal atrial contractions (PACs) in <1%. Heart rate varied between 65 and 150 beats per minute, with an average of 96 (Figure 2). There were 42 isolated PACs with atrial runs (Figure 3).

## Discussion

5-FU is reported as the second most common chemo-therapeutic agent after anthracyclines causing cardiotoxicity (15). 5-FU cardiotoxicity ranges from asymptomatic ECG abnormalities to fatal myocardial infarction (16). The relative incidence of symptoms induced by 5-FU is illustrated by a
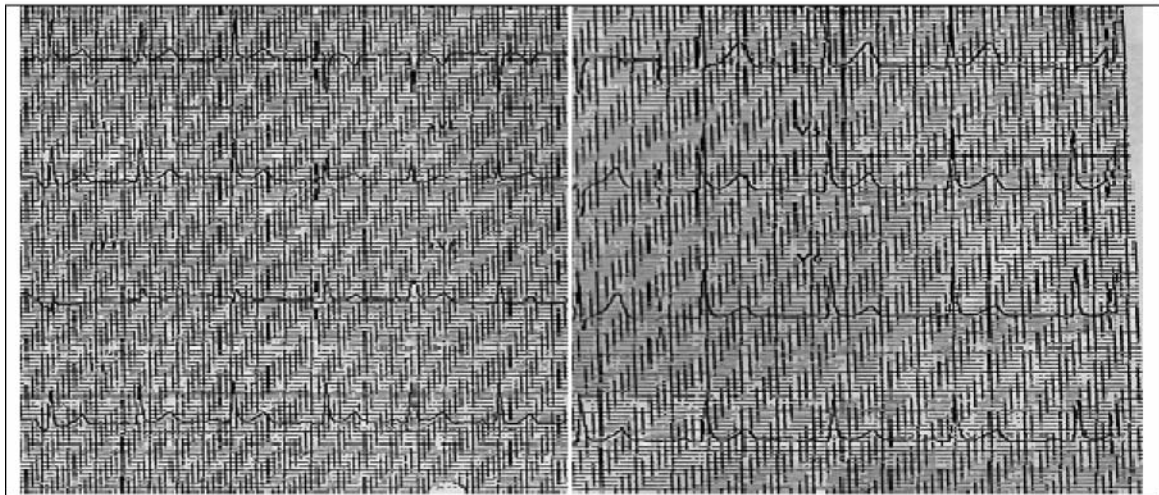
Figure 1. *Electrocardiogram showing sinus tachycardia. ECG taken at onset of symptoms.*
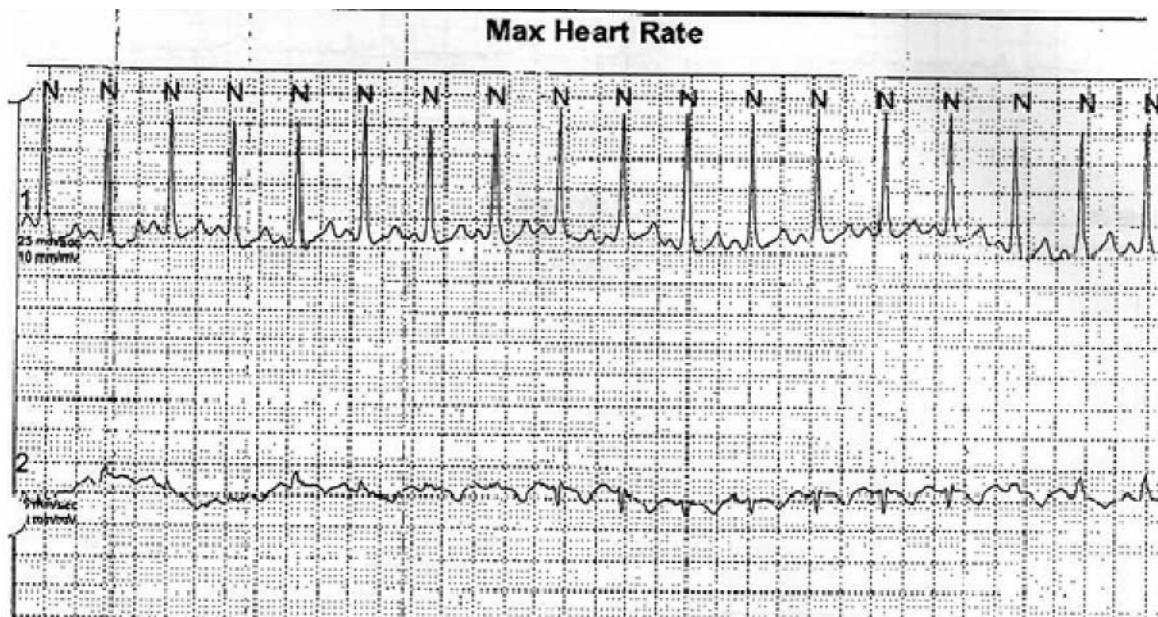


Figure 2. *Holter monitor tracing at highest heart rate of 150 after bolus 5-FU administration. The tracing shows a brief episode of sinus tachycardia.*

review of Saif *et al*. that included 262 reported cases. Cardiac events occurred within 72 hours of the first cycle of 5-FU in 76% of cases, ECG changes in 69%, and elevated cardiac markers in 14%. Clinical symptoms included angina in 48%, myocardial infarction in 23%, arrhythmias in 16%, acute pulmonary edema in 7% and cardiac arrest and pericarditis in 2% of the cases (17). An overall incidence of 1.2-18% for 5-FU-associated cardiotoxicity was reported previously (18).

The pathogenesis of this induced cardiotoxicity is not well understood. Coronary vasospasm has been suggested to be involved in the pathophysiology of this syndrome. Interference with myocyte metabolism is another proposed mechanism. This was demonstrated on echocardiography by reduced ejection fraction and significant akinesis of the left myocardium during the attacks. This did not correspond to the major coronary artery distribution, suggesting a direct
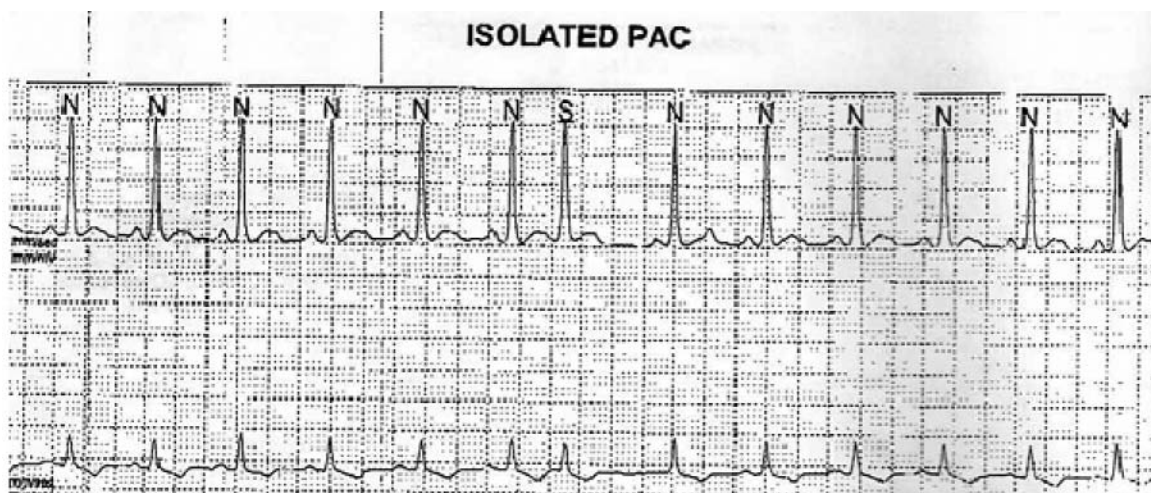
Figure 3. *Isolated paroxysmal atrial contraction (PAC) beat (seventh beat) during 24-hour Holter monitoring after bolus 5-FU was given. Forty-two PACs were recorded over a period of 24 hours after bolus 5-FU administration.*

drug or drug metabolite-mediated toxic action on myocytes (19). Südhoff *et al.* demonstrated that the first step in 5-FU-induced cardiotoxicity could be vasospasm by measuring the diameter of the brachial artery using high resolution ultrasound in patients on 5-FU-based chemotherapy (20). Moreover, Shoemaker *et al.* documented that coronary artery spasm on catheterization was observed with a continuous 5-FU infusion 36 hours after onset of angina (21). Cwikiel *et al.* observed injuries of the vascular endothelium in the central ear arteries of rabbits that could result in arterial thrombosis due to platelet aggregation (22). In another study comparing the effects of methotrexate to those of 5-FU on cultured bovine endothelial cells, 5-FU, but not methotrexate, was found to activate prostacyclin release by endothelial cells (23). The hypothesis that endothelin-1 release could be involved was put forward but has never been substantiated (24). An immuno-allergic reaction after a sensitization period is also mentioned in the literature (25).

Bolus 5-FU as an alternative to infusion, in cases of cardiotoxicity, was rarely referred to in the literature. However, it is mentioned that vasoconstriction was more frequent during infusion as compared to bolus 5-FU (20). Wijesinghe *et al.* reported that capecitabine should be discontinued once cardiovascular adverse effects are noted. Bolus administration of 5-FU maybe tried with co-treatment with nitrates and calcium channel blockers (CCB) is noted although the safety and efficacy of this approach was not tested (26). In another case report where capecitabine was the drug which induced the angina, the patient tolerated a reduction of the dose (27). Mosseri *et al.* confirmed this finding by investigating the effect of 5-FU on aortic rings

isolated from rabbits in *in vitro* experiments and concluded that the toxicity is dose dependent (28).

Risk factors are not well described. Previous chest radiation, cardiovascular disease and concurrent chemotherapy with other cardiotoxic agents have been reported to be risk factors (26). The prognostic value of pre-existing heart disease for severity of cardiotoxicity is unclear. Some report an increased risk with previous coronary artery disease (CAD) (29). In a study of more than 1,000 patients, the incidence of myocardial ischemia associated with 5-FU infusion was reported to be 1.1% in those patients lacking prior history of ischemic heart disease compared to 4.5% in those with a prior history (30). In contrast, a meta-analysis found that the prevalence of cardiac disease in patients with 5-FU cardiotoxicity did not differ significantly in an age-matched and gender-matched study. The treatment for this condition is suggested to be a combination of anti-anginal drugs with the chemotherapy since there are few alternatives to 5-FU and capecitabine (31, 32, 33). Pre-existing history of coronary artery disease or chest irradiation, concomitant medications, age and sex do not consistently correlate with 5-FU-associated cardiac toxicity (34).

Other modalities of treatment in this condition are described. Soren *et al.* reported that 5-FU cardiotoxicity may be associated with the dose, route of administration and medical prevention with CCB, beta-blockers, long-acting nitrates and intervention with nitroglycerine. Benefit from nitroglycerine intervention was demonstrated in this study (18). Eskilsson *et al.* showed failure of CCB to prevent ECG signs of ischemia during 5-FU treatment as compared to a control group in a 58 patients (32). In contrast to the study

by Rezkalla *et al*. which showed increased cardiotoxicity of 5-FU when used with cis- and carboplatin (35), Südhoff *et al*. did not find any correlation with this combination (20). Kosmas *et al*., in a study which included 640 patients, observed that an increase incidence of cardiac related events was encountered in patients with continuous 24-h 5-FU+LV infusion for 5 days rather than patients with the same schedule without LV (*p*<0.027), as well as in patient with short 5-FU+LV administration (*p*<0.019). In the analysis of the results, continuous 5-FU infusion proved to be much more toxic than bolus infusion (*p*<0.012) (36). Other drugs which also target thymidylate synthase, such as raltitrexed, have been recommended as a replacement for 5-FU in patients after the first cardiotoxic event (37).

As no specific treatment has yet been identified, and according to the few reports that suggested lower toxicity with bolus 5-FU, we decided to treat our patient with a bolus regimen according to the Mayo regimen. We do not know if the exposure to capecitabine influenced the 5-FU toxicity. This needs to be further studied even with other chemotherapeutic agents and different exposure to these agents. In addition to that, our patient had a 24-hour cardiac monitoring which had non-specific changes after the bolus. We report successful treatment with bolus 5-FU as an alternative to the infusion route in patients developing 5-FU cardiotoxicity, without changing the chemotherapy regimen. *DPYD* mutation study was negative in our patient. The pathophysiology of this syndrome needs to be defined. An algorithm of alternatives in cases of cardiotoxicity should be set because 5-FU is an essential backbone in the treatment of colorectal cancer.

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