

# Bolus 5-fluorouracil (5-FU) In Combination With Oxaliplatin Is Safe and Well Tolerated in Patients Who Experienced Coronary Vasospasm With Infusional 5-FU or Capecitabine

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## Abstract

**Coronary vasospasm with capecitabine or infusional 5-fluorouracil (5-FU) is a potentially serious complication. We performed a retrospective review to explore the safety of substituting FLOX (bolus 5-FU, oxaliplatin, leucovorin) for capecitabine or infusional 5-FU–based regimens in patients who had coronary vasospasm. FLOX is safe in patients who experienced coronary vasospasm with infusional 5-FU or capecitabine.**

**Introduction:** Coronary vasospasm associated with fluoropyrimidine (FP)-based chemotherapy is a potentially serious complication and reported to occur more often with infusional 5-fluorouracil (5-FU) or capecitabine than with bolus 5-FU. Given the additional benefit of oxaliplatin over FP alone in the management of colorectal cancer, retaining oxaliplatin in the treatment regimen is desirable, but the safety of combining bolus 5-FU with oxaliplatin in patients with FP-induced vasospasm is not well established. We performed a retrospective review to explore the safety of substituting FLOX (bolus 5-FU, oxaliplatin, leucovorin) for FOLFOX (infusional 5-FU, oxaliplatin, leucovorin) and CAPOX (capecitabine, oxaliplatin) in patients who had FP-induced coronary vasospasm. **Patients and Methods:** The pharmacy database of Mayo Clinic was queried to identify patients who developed coronary vasospasm associated with FOLFOX or CAPOX between January 2011 and January 2018 and were subsequently treated with FLOX. Detailed information was obtained on these patients by retrospective electronic chart review. **Results:** A total of 10 patients (median age, 56.5 years; range, 36–77 years) were identified, 9 with FOLFOX and 1 with CAPOX. Among the patients treated with FOLFOX, 8 patients had chest pain as the presenting complaint that had started within 48 hours of beginning of the 5-FU infusion. In 9 of 10 patients, coronary vasospasm occurred with the first cycle of therapy. All patients made full recovery after discontinuation of infusional 5-FU or capecitabine. All patients subsequently received FLOX with 7 median bolus 5-FU doses (range, 2–22 doses) and 7 median oxaliplatin doses (range, 2–12 doses) at 7 days to 18 months after the event, with 7 patients treated within 4 weeks of the event. FLOX did not cause any cardiovascular adverse events in any of the 10 patients. **Conclusion:** Bolus 5-FU in combination with oxaliplatin is safe in patients who have experienced coronary vasospasm with infusional 5-FU or capecitabine.

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## Introduction

5-Fluorouracil (5-FU), a fluoropyrimidine (FP), has been extensively used for several decades to treat a variety of solid tumors including colorectal cancer. The mode of administration of 5-FU has evolved over time. Commonly used 5-FU regimens include its administration as a bolus injection plus leucovorin, either weekly (6 of 8 consecutive weeks in Roswell Park regimen) or daily for 5

consecutive days every 4 weeks (Mayo Clinic regimen), or as a bolus plus short-term infusion over 2 days twice a month (de Gramont schedule)<sup>1</sup> Capecitabine is an oral prodrug of 5-FU that mimics pharmacokinetics of infusional 5-FU and is approved for adjuvant treatment of resected stage III colon cancer,<sup>2,3</sup> metastatic colorectal cancer,<sup>4</sup> and a variety of other solid tumors. Cardiac toxicity of 5-FU has been extensively reported in the literature, and among the chemotherapeutic drugs that cause cardiotoxicity, 5-FU ranks second after anthracyclines.<sup>5</sup> Cardiac toxicity can manifest as chest pain, acute coronary syndrome/myocardial infarction, cardiac arrhythmias, or, rarely, death. A number of mechanisms are thought to be responsible for 5-FU-related cardiotoxicity. The two most likely contributors are ischemia due to coronary vasospasm and drug-related myocardial toxicity.<sup>6</sup>

In colorectal cancer treatment, infusional 5-FU is preferred over bolus administration because of favorable toxicity profile, both in the adjuvant and metastatic setting.<sup>7,8</sup> However, a number of studies have shown that the risk of 5-FU-related cardiotoxicity is higher with infusional 5-FU compared to bolus injection.<sup>8-11</sup> In a literature review of 377 reported cases of 5-FU-induced cardiotoxicity, 72% of the cases were associated with infusional 5-FU.<sup>12</sup> Capecitabine is also known to cause cardiotoxicity and may be associated with higher incidence of cardiotoxicity compared to 5-FU.<sup>13-15</sup>

A number of reports have confirmed that bolus 5-FU is safe in patients who have developed cardiotoxicity with infusional 5-FU or capecitabine.<sup>12,16,17</sup> For colorectal cancer, both in the adjuvant and metastatic setting, it is important to retain oxaliplatin in the treatment regimen because the combination has shown improved outcome over FP alone.<sup>18-20</sup> However, it has been suspected that the combination of oxaliplatin and FP, especially capecitabine, may increase the risk of cardiotoxicity,<sup>21</sup> although this has not been validated prospectively. On the basis of the safety data of NSABP C-07 trial<sup>20</sup> as well as the reported safety of bolus 5-FU-based regimens in patients who developed cardiotoxicity with capecitabine or infusional 5-FU, we hypothesized that patients could safely be treated with the FLOX (bolus 5-FU, oxaliplatin, leucovorin) regimen when prior cardiotoxicity with FOLFOX (infusional 5-FU, oxaliplatin, leucovorin) or CAPOX (capecitabine, oxaliplatin) was encountered.

We thus conducted a retrospective review to verify the safety of this approach. To our knowledge, this is the first report in the literature to analyze the safety of the FLOX regimen in patients who developed cardiovascular toxicity with FOLFOX or CAPOX.

## Patients and Methods

A pharmacy database query was performed to identify patients who received FLOX. From this group, a cohort of patients was identified by retrospective electronic chart review who were treated with the FLOX regimen as a result of cardiovascular adverse events associated with FOLFOX or CAPOX. The FLOX regimen consisted of 5-FU 500 mg/m<sup>2</sup> intravenous (I.V.) bolus weekly for 6 weeks, leucovorin 500 mg/m<sup>2</sup> I.V. weekly for 6 weeks, and oxaliplatin 85 mg/m<sup>2</sup> I.V. administered on weeks 1, 3, and 5 of each 8-week cycle.<sup>22</sup> Detailed information regarding cardiac events was obtained by chart review. Cardiovascular toxicity was suspected when patients complained of angina-like symptoms including chest pain, shortness of breath, and palpitations. The following data were collected on each patient: age, sex, comorbidities, medications before chemotherapy, underlying

cancer diagnosis, indication of treatment, dose and schedule of FP and other associated chemotherapy drugs, predisposing risk factors for ischemic heart disease, presenting symptoms, cardiac enzyme results, electrocardiograms (EKGs), echocardiograms, stress tests, and cardiac catheterizations when available. Data collected on risk factors for ischemic heart disease were history of smoking, diabetes mellitus, hypertension, hypercholesterolemia, and family history of ischemic heart disease. Information about discontinuation of FP and the management of cardiac adverse events including therapies with aspirin, nitrates,  $\beta$ -blockers, anticoagulation, and calcium antagonist were recorded. When patients were provided FLOX, time to first FLOX therapy, total number of treatments, and toxicities after FLOX administration, including cardiovascular toxicities, were recorded. This study was approved by Mayo Clinic's institutional review board.

## Results

Between January 2011 and January 2018, a total of 9 patients receiving FOLFOX and 1 patient receiving CAPOX experienced cardiovascular toxicity (Table 1). Three patients (30%) were male, and the median age was 56.5 years (range, 36-77 years). All patients had at least one traditional risk factor for ischemic heart disease: 3 were current smokers and 4 had a history of smoking; 3 had a diagnosis of hypertension; 1 had diabetes mellitus; and 1 had a family history of coronary artery disease. Only 1 patient had a history of coronary heart disease. Two patients were receiving  $\beta$ -blockers, and one other patient was receiving a calcium channel blocker (diltiazem) before beginning chemotherapy. None of the patients was receiving long-acting nitrates. Eight patients were treated for adenocarcinoma of the colon, 6 of whom received FOLFOX in the adjuvant setting with curative intent; the other 2 patients were being treated with palliative intent. The remaining 2 patients were treated with FOLFOX for a diagnosis of adenocarcinoma with unknown primary lesion.

Table 2 lists cardiovascular toxicity and clinical outcome. Eight patients experienced chest pain, 2 of whom had shortness of breath in addition to pain; 1 patient experienced shortness of breath and diaphoresis; and 1 patient experienced severe abdominal pain. In all but one patient, symptoms started with first cycle. Eight of 9 patients treated with FOLFOX experienced symptoms within 2 to 48 hours of onset of 5-FU infusion with the first cycle. The patient treated with CAPOX experienced chest pain on day 14. Cardiovascular symptoms resolved on discontinuation of infusional 5-FU or capecitabine in all patients. EKGs were performed immediately after the event in 7 patients, one of whom demonstrated diffuse ST-segment elevation without elevation of cardiac enzyme levels; one showed T wave inversion in the anterior-septal leads but with normal cardiac enzyme levels; and in one was revealed ectopy without specific ischemic changes, but the patient had elevated cardiac enzyme levels. The remaining 4 patients had unremarkable EKGs.

Seven patients underwent echocardiography. Of the patients with elevated cardiac enzymes, 2 had ejection fractions of 40% to 45%, with one demonstrating no wall motion abnormalities and the other showing global hypokinesia. An additional patient had an ejection fraction of 30%, anterior wall motion hypokinesia, and a mural thrombus. Three patients had normal echocardiogram. Three patients underwent invasive coronary catheterization and 2 underwent computed tomographic coronary angiography; all the results indicated normal coronary arteries.

**Table 1** Characteristics of Patients Who Developed Cardiovascular Toxicity With 5-FU or Capecitabine

Patient No.	Age (Years)	Gender	Risk Factor for CAD	Cancer Type	Treatment Goal (Palliative vs. Curative)	Chemotherapy Regimen	Prior $\beta$ -Blocker or Calcium Channel Blocker Use
1	59	M	Smoking	Colon adenocarcinoma	Palliative	FOLFOX	No
2	54	M	Smoking	Colon adenocarcinoma	Palliative	CAPOX	No
3	51	F	HTN	Colon adenocarcinoma	Curative	FOLFOX	Yes, diltiazem
4	67	F	Smoking	Colon adenocarcinoma	Curative	FOLFOX	No
5	50	F	Smoking	Colon adenocarcinoma	Curative	FOLFOX	No
6	64	F	Smoking, HTN	Adenocarcinoma with unknown primary site	Palliative	FOLFOX	Yes, metoprolol
7	67	F	Family history of CAD	Adenocarcinoma with unknown primary site	Palliative	FOLFOX	No
8	52	F	DM, HTN	Colon adenocarcinoma	Curative	FOLFOX	No
9	77	F	Known CAD, Smoking	Colon adenocarcinoma	Curative	FOLFOX	Yes, metoprolol
10	36	M	Smoking	Colon adenocarcinoma	Curative	FOLFOX	No

Abbreviations: 5-FU = 5-fluorouracil; CAD = coronary artery disease; CAPOX = capecitabine and oxaliplatin; DM = diabetes mellitus; FOLFOX = oxaliplatin, 5-FU, and leucovorin; HTN = hypertension.

Patient 10 had chest pain with the first cycle of FOLFOX 36 hours into the 5-FU infusion, but his EKG changes were suggestive of acute pericarditis (diffuse ST-T elevation). He was rechallenged with FOLFOX, and he developed chest pain within 24 hours of onset of 5-FU infusion, which completely resolved with discontinuation of 5-FU.

Patient 9 developed severe acute abdominal pain within 2 hours of onset of 5-FU infusion, which resolved within 1 hour of discontinuation of 5-FU. She was rechallenged because of uncertainty regarding association between 5-FU infusion and abdominal pain. She again developed abdominal pain within 1 hour. Her pain resolved completely after discontinuation of 5-FU infusion. In both cases, FLOX did not cause any chest or abdominal pain.

All patients received the 5-FU bolus-based FLOX regimen after recovery. The time interval between the cardiac event and first dose of FLOX ranged between 7 days to 18 months. Seven of 10 patients received the first dose of FLOX within 28 days of their cardiac event.

The total number of 5-FU bolus doses provided as a part of the FLOX regimen ranged from 2 to 22. Seven of 10 patients received 5 or more doses. The total number of oxaliplatin doses provided as a part of FLOX ranged from 2 to 12 (median, 7 doses). The patient with an ejection fraction of 30% with anterior wall motion hypokinesia and a mural thrombus (patient 1) received 20 doses of bolus 5-FU and 12 doses of oxaliplatin. None of the patients experienced any cardiac event with FLOX. FLOX was discontinued because of disease progression in 4 patients, severe diarrhea in 2 patients, and completion of adjuvant therapy in 3 patients. One patient was lost to follow-up.

### Discussion

Cardiac adverse events with 5-FU and capecitabine are well documented in the literature.<sup>15,23,24</sup> Anginal chest pain is the most common presentation of 5-FU-induced cardiotoxicity, comprising 40% to 60% of all initial presentations.<sup>10,25-28</sup> Less common presentations include palpitations, dyspnea, hypotension, and, rarely, severe clinical events such as myocardial infarction, cardiogenic shock, and cardiac arrest.<sup>15</sup> There is a wide variation in reported incidence of FP-induced cardiotoxicity, ranging from 1% to 19% with a 0 to 13% mortality rate.<sup>11,15,29,30</sup> A large meta-analysis reported a 3% incidence of all-grade cardiac adverse events with both capecitabine and the bolus 5-FU-based Mayo Clinic regimen but less than 1% grade 3/4 events.<sup>28</sup> However, a surveillance study reported anginal symptoms in 19% patients treated with 5-FU.<sup>30</sup> The primary mechanism of 5-FU-induced cardiotoxicity involves coronary artery vasospasm, which has been demonstrated in coronary angiography.<sup>31,32</sup> As a result, chest pain is the most frequent presenting symptom, as was confirmed in our case series.

Infusional 5-FU is preferred for the treatment of colorectal cancer, both in the metastatic and adjuvant setting, over bolus 5-FU. In metastatic colorectal cancer, the infusional 5-FU schedule has shown statistically significant improved response rate, disease-free survival and fewer grade 3/4 toxicities compared to the monthly 5-FU bolus-based Mayo Clinic regimen.<sup>8</sup> In adjuvant treatment of resected colon cancer, an infusional 5-FU-based regimen has demonstrated similar disease-free survival and overall survival compared to the Mayo Clinic regimen, but neutropenia,

**Table 2** Pattern of Cardiovascular Toxicity and Outcome With FLOX

Patient No.	Onset of Symptom	Clinical Presentation	Pain Resolution With Discontinuation of 5-FU	Cardiac Enzyme Elevation	EKG Finding	Echocardiogram Finding	Coronary Angiogram Finding	Time to First FLOX	Total Doses of Bolus 5-FU/ Oxaliplatin	Reason for Discontinuation	Cardiac Symptoms With FLOX
1	First cycle, 24 hours	CP	Yes	NA	Normal	EF 30%, anterior wall hypokinesis, thrombus	NA	13 days	20/12	Disease progression	None
2	First cycle, 14 days	CP	Yes	positive	Normal	EF 40-45%	Negative for coronary artery stenosis	18 months	12/7	Disease progression	None
3	First cycle, 48 hours	CP	Yes	Normal	NA	NA	NA	19 days	18/9	completed course of adjuvant treatment	None
4	First cycle, 24 hours	CP, SOB	Yes	Mild elevation	normal	Mild left ventricular dysfunction	Negative for coronary artery stenosis	13 days	Lost to follow-up after 4 doses of 5-FU and 2 doses of oxaliplatin	Lost to follow-up	None
5	First cycle, 48 hours	CP, SOB	Yes	Positive	Ectopy, no ST-T changes	40% EF, global hypokinesia	Negative for coronary artery stenosis	56 days	6/3	Severe diarrhea	None
6	2 hours with second cycle	SOB, diaphoresis	Yes	Normal	T-wave inversion—V1-V3	Normal	Negative for coronary artery stenosis	21 days	3/3	Disease progression	None
7	First cycle, 48 hours	CP	Yes	Normal	Normal	Normal	Negative for coronary artery stenosis	12 days	7/7	Disease progression	None
8	First cycle, 48 hours	CP	Yes	NA	NA	NA	NA	28 days	22/11	completed course of adjuvant treatment	None
9	First cycle, 2 hours	Abdominal pain	Yes	NA	NA	NA	NA	7 days	2/2	Severe diarrhea	None
10	First cycle, 36 hours	CP	Yes	Normal	Diffuse ST elevation	Normal	NA	41 days	15/9	completed course of adjuvant treatment	None

Abbreviations: 5-FU = 5-fluorouracil; CP = chest pain; EF = ejection fraction; FLOX = bolus 5-FU, oxaliplatin, leucovorin; NA = not available; SOB = shortness of breath.

## 5-FU With Oxaliplatin

diarrhea, and mucositis were significantly reduced with the infusional schedule.<sup>7</sup> As a result, the infusional schedule evolved as the preferred mode of 5-FU administration. The addition of oxaliplatin to infusional 5-FU in the FOLFOX regimen (which consists of oxaliplatin, leucovorin, short-term infusional and bolus 5-FU) has been shown to increase 10-year overall survival from 59% to 67.1% in resected stage III colon cancer patients compared to 5-FU alone (de Gramont schedule).<sup>18</sup> An overall survival advantage was also confirmed with the addition of oxaliplatin to capecitabine (CAPOX) compared to bolus 5-FU-based regimens in stage III colon cancer, with 7-year overall survival rates improving from 67% to 73%.<sup>33</sup> Thus, it is of paramount importance to include both oxaliplatin and an FP in the treatment of colorectal cancer. FOLFOX and CAPOX are the current preferred chemotherapy regimens for adjuvant treatment of resected stage III and high-risk stage II colon cancer based on data from MOSAIC,<sup>18,34</sup> updated NO16968,<sup>33</sup> and IDEA.<sup>35</sup> Similarly, infusional 5-FU or capecitabine plus oxaliplatin-based schedules are the standard of care in metastatic colorectal cancer.<sup>19</sup>

A number of studies have shown that the risk of 5-FU-related cardiotoxicity is higher with protracted administration of FP compared to bolus 5-FU.<sup>8-11</sup> Capecitabine, which is an oral prodrug of 5-FU and mimics the pharmacokinetics of infusional 5-FU, has shown a similar pattern of cardiotoxicity.<sup>15,28</sup> It has been reported that bolus 5-FU is safe in patients who developed cardiotoxicity with infusional 5-FU or capecitabine.<sup>12,16,17</sup> The FLOX regimen has been compared in a randomized trial (NSABP C-07) with the Mayo Clinic regimen in resected stage II and III colon cancer patients. This trial demonstrated significantly improved 5-year disease-free survival with FLOX in resected stage III colon cancer patients.<sup>20</sup> Moreover, the incidence of cardiac toxicity with the FLOX regimen is extremely low (4 of 1234 patients experienced grade 3 or higher chest pain in NSABP C-07 trial who received the FLOX regimen; personal communication, Greg Yothers, Research Associate Professor of Biostatistics, Director, Division of Biostatistics and Science, NRG Oncology Statistics and Data Management Center, Pittsburgh). Hence, if the short-term infusional 5-FU schedule or capecitabine could not be used because of cardiotoxicity, it might be preferable to use the bolus 5-FU-based FLOX regimen.

Independent of FP, platinum compounds are known to cause vascular toxicity and chest pain. Cisplatin can cause chest pain at an incidence as high as 40%, and endothelial dysfunction is the key mechanism of altered vasoreactivity.<sup>36</sup> Incidence of cardiotoxicity in patients treated with capecitabine and oxaliplatin has been reported to be 6.5%, and potential additive cardiotoxicity with oxaliplatin and capecitabine has been suggested in 2 retrospective studies.<sup>21,37</sup> We did not observe any cardiotoxicity with the 5-FU bolus- and oxaliplatin-based FLOX regimen.

Several alternative approaches have been reported in the literature when patients developed 5-FU infusion- or capecitabine-induced cardiotoxicity. In 2 case reports, patients were switched to capecitabine when they developed cardiotoxicity to infusional 5-FU without recurrence of cardiac symptoms.<sup>38,39</sup> However, in a case series of 6 patients who developed cardiotoxicity to infusional 5-FU, 5 patients were rechallenged with oral capecitabine, and all patients developed clinical and/or diagnostic features suggestive of cardiotoxicity.<sup>16</sup> The

effectiveness of prophylactic transdermal nitroglycerine to prevent 5-FU-induced cardiotoxicity is controversial.<sup>40</sup> A number of case reports have suggested the efficacy of a prophylactic calcium channel blocker in preventing 5-FU-related cardiotoxicity,<sup>41-43</sup> but a prospective study showed lack of efficacy of verapamil in preventing 5-FU-induced cardiotoxicity.<sup>44</sup> Our series suggests that the bolus 5-FU-based FLOX regimen is safe in patients who have experienced symptoms consistent with coronary vasospasm while receiving either infusional 5-FU or capecitabine.

## Conclusion

Our retrospective review confirms that the 5-FU bolus-based FLOX regimen is safe in patients who have previously experienced cardiovascular adverse events with infusional 5-FU (FOLFOX)- or capecitabine (CAPOX)-based regimens.

## Clinical Practice Points

- Oxaliplatin-containing chemotherapy regimens such as FOLFOX and CAPOX have shown superiority compared to FP-only regimens in the treatment of adjuvant and metastatic colorectal cancer. Oxaliplatin is therefore an important component of therapy.
- In the event of cardiotoxicity with infusional 5-FU or capecitabine, a FLOX regimen is an appropriate alternative for colorectal cancer treatment.

## Disclosure

The authors have stated that they have no conflict of interest.

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