



Successful Completion of Adjuvant Chemotherapy in a Patient With Colon Cancer Experiencing 5-Fluorouracil–Induced Cardiac Vasospasm

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Clinical Practice Points

- Fluoropyrimidines are the chemotherapy backbone in the treatment of adenocarcinoma of the colon. Adjuvant 5-fluorouracil (5-FU)/leucovorin (LV) has been shown to significantly increase recurrence-free survival compared to surgery alone for patients with stage III colon cancer.
- Furthermore, the addition of oxaliplatin to 5-FU/LV (FOLFOX) in the adjuvant setting has been shown to provide an improved disease free survival compared to adjuvant 5-FU/LV therapy alone.
- Cardiotoxicity associated with 5-FU or capecitabine is a rare but serious adverse effect that can present as cardiomyopathy, vasospastic angina, coronary thrombosis and dissection, ventricular arrhythmias, and sudden cardiac death.
- We report a case of successful completion of adjuvant FOLFOX therapy in a patient who experienced 5-FU–induced cardiotoxicity.
- This was completed through aggressive inpatient supportive care and cardiac monitoring. The patient showed no signs of delayed cardiotoxicity or colon cancer recurrence at 10-month follow-up.

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Introduction

Fluoropyrimidines are the chemotherapy backbone in the treatment of adenocarcinoma of the colon. Adjuvant fluorouracil (5-FU)/leucovorin (LV) has been shown to significantly increase recurrence-free survival compared to surgery alone for patients with stage III colon cancer.¹⁻³ Furthermore, the addition of oxaliplatin to 5-FU/LV (FOLFOX) in the adjuvant setting has been shown to

provide an improved disease-free survival compared to adjuvant 5-FU/LV therapy alone.⁴ These advances have provided a significant increase in overall survival in patients with colon cancer in the past 20 years. While the addition of adjuvant chemotherapy clearly provides benefit for a majority of patients, it is necessary to identify and understand the risk of the potential toxicities of these therapies.

Cardiotoxicity associated with 5-FU or capecitabine is a rare but serious adverse effect that can present as cardiomyopathy, vasospastic angina, coronary thrombosis and dissection, ventricular arrhythmias, and sudden cardiac death.⁵⁻⁹ Rechallenging with fluoropyrimidine after cardiotoxic events is avoided because the risk of recurrence ranges from 82% to 100% and the risk of death is 18%.^{8,10} Here we report a case of successful completion of adjuvant FOLFOX (oxaliplatin, 5-FU, and LV) therapy in a patient who experienced 5-FU–induced cardiotoxicity.

Case Report

A 48-year-old otherwise healthy woman with no known cardiac risk factors was diagnosed with stage IIIc (pT₃N_{2b}M₀) moderately differentiated adenocarcinoma of the colon and initiated adjuvant chemotherapy with FOLFOX at an outside facility. She was referred

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5-FU—Induced Cardiac Vasospasm

to the James Cancer Hospital at The Ohio State University after experiencing chest pain during her first 5-FU infusion. Outside records revealed that she began experiencing chest pain the second day of treatment during the 46-hour continuous 5-FU infusion, and she was subsequently admitted for cardiac assessment. Serial troponins and electrocardiograms (EKG) were unremarkable.

Transthoracic echocardiogram revealed a left ventricular ejection fraction of 55% with no regional wall motion abnormality. Cardiac catheterization revealed a normal coronary study with widely patent coronary arteries and no flow-limiting stenosis. The patient was diagnosed with 5-FU—induced cardiotoxicity, specifically vasospastic angina. Chest pain continued for several days, and the patient was discharged free of pain after 4 days' therapy with isosorbide mononitrate extended released (ER) 30 mg daily and amlodipine 2.5 mg daily. At this point, the patient was referred to us for further management of her resected colon cancer. We decided to increase the isosorbide mononitrate ER to 60 mg daily and switched the calcium channel blocker from amlodipine to diltiazem 30 mg 4 times daily with plans to escalate to a total dose of diltiazem ER 240 mg once daily (as tolerated with blood pressure monitoring). The decision to switch to diltiazem was more the result of experience and reports in the literature that used this agent over others in its class to manage fluoropyrimidine-induced vasospasms. Further, we postulated that because it is a centrally acting calcium channel blocker, there might be greater potential for smooth muscle relaxation. The patient did not wish to discontinue therapy, given her age and risk-of-recurrence score. After careful consideration and referral to a cardiologist at The Ohio State University Wexner Medical Center, the decision was made to continue treatment with FOLFOX with oxaliplatin 85 mg/m² intravenously over 2 hours and 5-FU 2400 mg/m² intravenously over 48 hours every 2 weeks to complete 6 months of adjuvant therapy. Therapy would be done in an inpatient setting on a cardiology service with continuous cardiac monitoring. The bolus 5-FU and LV were discontinued for all future cycles, as the addition of LV to 5-FU has been reported to increase cardiotoxicity compared to 5-FU alone.¹¹

During each 5-FU infusion admission, the patient experienced substernal chest pain radiating to both shoulders and arms, as well as occasional pain to the jaw. The pain was partially relieved by sublingual (S.L.) nitroglycerin (NTG), intravenous (I.V.) morphine, and bed rest and ranged from 10 to 30 minutes in length. After cycle 2 of therapy, the cardiology service transitioned the patient from diltiazem ER 240 mg daily to nifedipine ER 60 mg daily to attempt to provide better protection through coronary vasodilation. During cycle 3, day 3, the patient required I.V. NTG for symptom relief that had become refractory to S.L. NTG and I.V. morphine. The median time from the initiation of 5-FU infusion to the first and last NTG administration was 40.9 hours (range: 36.0-43.1) and 61.6 hours (range: 58.4-66.0), respectively. The patient's chest pain continued for a median of 13.1 hours (range: 10.1-17.2) after completion of the 5-FU infusion. The average number of doses of S.L. NTG administrations per 5-FU infusion was 10 (range: 0-16). With each inpatient therapy, the patient was followed with continuous cardiac monitoring, and an EKG was performed with each episode of chest pain. All EKGs revealed normal sinus rhythm with no acute ST/T wave changes, and no troponin leaks were

observed throughout therapy. A repeat transthoracic echocardiogram was obtained on her fourth admission that revealed a left ventricular ejection fraction of 60% to 65% with trace aortic regurgitation. The patient experienced vasospastic angina during all 10 of her remaining 5-FU infusions and was supported through therapy with S.L. and/or I.V. NTG and I.V. morphine. Upon completion of therapy, the patient discontinued isosorbide mononitrate ER and was tapered off nifedipine ER. At 24 months after treatment with close observation, the patient has exhibited no signs or symptoms of cardiotoxicity.

Conclusion

We here present a case of successful completion of adjuvant infusional 5-FU—based therapy for adenocarcinoma of the colon in a patient experiencing severe 5-FU—induced vasospastic angina. This was completed through aggressive inpatient supportive care and cardiac monitoring. Continuous nitrate and calcium channel blockade, S.L. and I.V. NTG, and I.V. morphine were used to relieve symptoms during angina episodes without sequelae. The mechanism of 5-FU—induced vasospasms is not completely understood but has been hypothesized to be due to activation of protein kinase C, leading to vasoconstriction of vascular smooth muscle.⁶ Thus, the use of vasodilator therapy with nitrates and calcium channel blockers has been debated as potential preventative treatment during 5-FU therapy.¹²⁻¹⁴ Other potential mechanisms for 5-FU—induced cardiotoxicity include endothelial dysfunction, direct myocardial injury, and possibly accumulation of 5-FU metabolites.¹⁵⁻¹⁹

The incidence of 5-FU— and capecitabine-induced symptomatic cardiotoxicity ranges from 1.2% to 4.3%. Cardiac comorbidities, renal insufficiency, prior symptoms with 5-FU, higher doses of 5-FU, continuous-infusion 5-FU, and concomitant cisplatin therapy have been described as risk factors for 5-FU—induced cardiotoxicity.^{5,20-22} However, 5-FU cardiotoxicity has been largely reported in patients with no known risk factors.²³⁻²⁵

Rechallenge with fluoropyrimidines after the occurrence of cardiotoxicity is controversial.⁹ However, in the curative-intent setting, such as stage III colon cancer, the risk versus benefit must be evaluated by the provider and discussed with the patient. In a typical patient with stage III colon cancer, fluoropyrimidine therapy in the adjuvant setting reduces the risk of mortality by approximately 33%.^{2,3} Further, even in the event of disease recurrence, fluoropyrimidines remain the mainstay of therapy. In this patient, we thought that the benefit of administering FOLFOX outweighed the risk associated with completing adjuvant chemotherapy in a controlled setting and for a finite amount of time. Part of the rationale for this included the patient's age, her desire to pursue aggressive therapy, and the limited therapeutic options that would be available for her in that setting.

In the case of reintroduction of 5-FU, careful inpatient monitoring of the patient should be performed during the next, and potentially for all, subsequent infusions as a result of the high risk of recurrence of symptoms and potentially fatal outcome. Preventative strategies that have been suggested include decreasing the 5-FU dose and providing calcium channel blockers and nitrates.^{8,11,26} Our patient reintitiated 5-FU therapy and continued to experience vasospastic angina with each infusion of 5-FU. Her chief complaint was pain during the 5-FU

infusions; the patient did not experience troponin leak or ST segment changes indicating cardiac tissue damage. She was supported through the vasospastic angina symptoms with continued nitrate and calcium channel blockade and aggressive therapy as an inpatient with continuous cardiac monitoring. She showed no signs of delayed cardiotoxicity at 10-month follow-up.

Our case illustrates the successful completion of adjuvant therapy in a patient with 5-FU–induced cardiotoxicity. In patients with a chief complaint of angina and no signs of cardiac tissue damage, physicians should weigh the risks and benefits when reintroducing 5-FU. We utilized aggressive supportive care with nitrates and calcium channel blockers as well as treatment occurring under the inpatient care of cardiology specialists to ensure timely supportive care and continuous cardiac monitoring. If the benefits outweigh the risks of rechallenge with 5-FU, our case details effective treatment strategies to avoid the acute and long-term risks of 5-FU–induced cardiotoxicity.

Disclosure

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

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