Case Report

Successful 5-fluorouracil (5-FU) infusion re-challenge in a metastatic colorectal cancer patient with coronary artery disease who experienced symptoms consistent with coronary vasospasm during first 5-FU infusion

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Abstract: 5-fluorouracil (5-FU) is an important component of chemotherapy for metastatic colon cancer and can be administered as an intravenous infusion or bolus. Coronary vasospasm is a known complication of infusional and bolus 5-FU administration. In patients who experience coronary vasospasm, 5-FU is often discontinued. Several cases of successful re-challenge with bolus 5-FU, utilizing calcium channel blockers (CCBs) and nitrates to prophylaxis against coronary vasospasm recurrence, have been reported in the literature. However, since there is increased variability of time to symptom onset with infusional 5-FU, re-challenge with infusional 5-FU has not been widely studied. Given potential differences in the toxicity profile and exposure time, infusional may be more appropriate than bolus for some patients. Here we report successful re-challenge with infusional 5-FU, following coronary vasospasm during the first cycle of 5-FU plus leucovorin plus oxaliplatin chemotherapy, in a patient with metastatic colon cancer and coronary artery disease (CAD). The 5-FU re-challenge plan included dose reduction, CCB and nitrate prophylaxis, and telemetry monitoring.

Keywords: 5-fluorouracil (5-FU); coronary vasospasm; metastatic colon cancer; 5-fluorouracil rechallenge (5-FU rechallenge); FOLFOX

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Background

5-fluorouracil (5-FU)-based chemotherapy is the standard first-line treatment for metastatic colorectal cancer (mCRC). Regimens include 5-FU plus leucovorin plus oxaliplatin (FOLFOX), 5-FU plus leucovorin plus irinotecan (FOLFIRI) or 5-FU plus oxaliplatin plus irinotecan (FOLFOXIRI). Bevacizumab (anti-vascular endothelial growth factor-targeted monoclonal antibody) is also recommended as an addition to these regimens (1).

The FOLFOX regimen has a response rate of approximately 50% in the first-line setting for mCRC (2-5). Absence of the 5-FU component diminishes activity. The observed response rate for oxaliplatin monotherapy in a phase II study in the first-line mCRC was 24.1% (6) and a single-agent oxaliplatin arm in a phase III study also suggested minimal activity (7). Experience in the second-line mCRC setting indicates that single-agent irinotecan is also not highly active (8).

5-FU is given as an intravenous bolus, intravenous infusion or in its oral prodrug form (capecitabine). Bolus administration is more convenient to administer than infusional which is typically administered over 46–48 hours.

However, a meta-analysis including 6 trials using 5-FU monotherapy suggests that response rates are superior with infusional, compared to bolus, 5-FU. Respectively, objective response rate (ORR) was 22% *vs.* 14%; odds ratio, 0.55; 95% confidence interval (CI), 0.41 to 0.75 (9).

Cardiac toxicity, including coronary vasospasm, acute coronary syndrome, arrhythmias, myocarditis, and heart failure, is one of several systemic toxicities associated with 5-FU. The mechanisms of these toxicities are likely variable for each specific pathology and are incompletely characterized (10). Accumulation of metabolites and direct cellular effects are generally recognized as putative mechanisms. Additionally, cases of possible histamine-mediated cardiac toxicity have been reported (11).

In vitro evidence suggests that coronary vasospasm results from 5-FU-mediated contraction of vascular smooth muscle (12). Clinically, an increase in the incidence of ST changes was seen on continuous telemetry monitoring in a prospective study (13) and 5-FU induced coronary vasospasm can cause myocardial ischemia manifesting as angina (14-16). Observations from small datasets illustrate distinct clinical features seen with infusional versus bolus 5-FU-induced coronary vasospasm. Symptoms of coronary vasospasm occur in close proximity to the timing of bolus administration and may be accompanied by electrocardiogram (ECG) changes. Symptoms can be less pronounced, or clinically silent, with 5-FU infusion. Additionally, symptoms have been known to occur at any time during, and potentially after the infusion. ECG changes are less common (17-20). Currently, expert consensus advises against re-challenge with 5-FU following cardiac toxicity, given risks of toxicity recurrence and nontrivial mortality rates estimated to be as high as 18% (10). Therefore, suspected cardiac toxicity often results in treatment discontinuation.

In 2017, Clasen *et al.* reported successful experiences with bolus 5-FU and oral capecitabine re-challenge, employing prophylactic oral calcium channel blockers (CCBs) and/or nitrates in patients who had been diagnosed with 5-FU-associated coronary vasospasm (21). Success with oral diltiazem as secondary prophylaxis for patients with capecitabine-related coronary vasospasm has also been reported (22). To our knowledge, the only report of successful infusional 5-FU re-challenge that exists in the literature involves one CRC patient who received 6 months of adjuvant FOLFOX with prophylactic CCB and nitrates (23). The course was complicated by chest pain requiring IV nitroglycerin, but the authors reported no signs or symptoms of cardiotoxicity 24 months after treatment.

Given the less predictable timing of vasospasm symptoms in relation to 5-FU administration, infusional 5-FU re-challenge in patients with suspected coronary vasospasm carries a higher clinical risk in the unmonitored setting. However, evidence suggests that infusional 5-FU has a better response rate and more favorable hematologic toxicity profile (9). For these reasons, we attempted re-challenge with 5-FU (at 50% of the original dose and with the use of prophylactic CCB and nitrates) in an mCRC patient who had experienced coronary vasospasm during his first cycle of FOLFOX.

Case presentation

A 69-year-old male with a past medical history significant for osteoarthritis, hyperlipidemia, and coronary artery disease (CAD) status post coronary artery bypass graft (CABG) 3 years prior underwent screening colonoscopy. He was diagnosed with mismatch repair-proficient (MMR-proficient), *KRAS* wild-type colon adenocarcinoma of the transverse colon. Staging workup revealed unresectable metastases to the liver. He enrolled in a clinical trial of FOLFOX plus bevacizumab plus immunotherapy (anti-PD-L1 antibody and tumor-targeted vaccine). Bevacizumab was held. The FOLFOX treatment regimen was as follows: oxaliplatin 85 mg/m^2 intravenously (IV) over 2 hours, leucovorin 400 mg/m^2 IV over 2 hours (concurrently with oxaliplatin), then 5-FU 1,200 mg/m^2/day continuous infusion over 23 hours for two doses (total of 2,400 mg/m^2/cycle); each cycle repeated every 2 weeks. Bolus 5-FU was not given, per research protocol.

Approximately 46 hours after the initiation of the cycle one 5-FU infusion, the patient presented to the infusion center to be disconnected from the ambulatory infusion pump. Complaints included mild fever, rhinorrhea, nausea, and severe headache that started on his second day of treatment and continued to progress. At that time, he took ondansetron for nausea without relief and experienced worsening headache. When asked to describe the headache, he stated that it felt similar to the headache that he experienced at the time of his CAD diagnosis. Of note, prior to CABG, this patient had an atypical presentation of CAD that manifested as exertional headache without chest pain or dyspnea. On this occasion, he denied shortness of breath, chest pain or palpitations. Vitals signs and physical exam were unremarkable. A cardiac work-up was

initiated, including a chest X-ray and ECG, which were also unremarkable. Troponin-I was detectable and initially within the reference range but found to be elevated at 0.168 ng/mL (normal range, 0.000–0.056 ng/mL) when a second level was obtained. Serum chemistry and complete blood count were unremarkable. After symptoms had resolved, a repeat ECG was suggestive of inferoposterior ischemia. Serial troponins and ECGs were obtained until normalization. Echocardiogram revealed left ventricular ejection fraction of 58% with equivocal inferior wall motion hypokinesis. Subsequent nuclear medicine exercise stress test did not induce any ischemia. Incidentally, the patient tested positive for coronavirus on nasopharyngeal wash obtained for fever and rhinorrhea workup. The findings of an anginal equivalent, elevated troponin-I and ECG changes suggestive of ischemia were highly suspicious for coronary vasospasm in a patient with known CAD who was receiving infusional 5-FU for the first time. A clinical diagnosis of coronary vasospasm was made.

For cycle 2 of treatment, 5-FU was held and treatment with oxaliplatin and immunotherapy continued, per protocol. The patient tolerated the second cycle without complications. Genetic testing for the dihydropyrimidine dehydrogenase gene (DYPD) revealed no variants known to be associated with impaired 5-FU catabolism. After discussion of the risks and benefits of continuing therapy, the patient expressed his desire to be aggressive with treatment and the 5-FU was resumed with cycle 3 at a 50% dose reduction (1,200 mg/m^2/cycle IV infusion administered over 46 hours). For coronary vasospasm prophylaxis, nifedipine extended release 30 mg orally daily and isosorbide dinitrate 10 mg every 8 hours were administered prior to the start of the 5-FU infusion and continued for 24 hours after the completion. The patient was admitted for observation with telemetry monitoring during this time. He tolerated treatment well and no clinically significant events were seen on telemetry. Cycle 4 proceeded with an increase in 5-FU dosing to 75% of the original dose (1,800 mg/m^2/cycle IV infusion administered over 46 hours) which was tolerated well. Imaging prior to cycle 5 showed a response to treatment. The nifedipine and isosorbide mononitrate regimen was continued for subsequent cycles.

At cycle 7, oxaliplatin dose was reduced to 65 mg/m^2 IV for neutropenia and growth factor support was added to his regimen. In addition, 5-FU was dose-reduced to 1,200 mg/m^2/cycle continuous infusion over 46 hours. He exhibited signs of oxaliplatin hypersensitivity in cycles 10 and 11, characterized by transient tachycardia and mild hypoxemia during the oxaliplatin administration. Oxaliplatin was therefore held during cycle 12 and the patient received 5-FU alone.

Following 12 cycles of chemotherapy, maintenance capecitabine was initiated during an inpatient stay at a reduced dose of 310 mg/m^2 orally twice daily (approximately a 50% dose reduction). No adverse cardiac symptoms occurred, and the patient was discharged after 48 hours of monitoring. Nifedipine extended release 30 mg orally daily and isosorbide dinitrate 10 mg orally every 8 hours were continued on an outpatient basis. At a follow up appointment after 13 days on capecitabine, the patient reported bilateral jaw pain while walking earlier that day. The pain completely resolved with rest and he complained of no other symptoms. ECG and troponin were unremarkable. Capecitabine was then permanently discontinued after a discussion with the patient regarding the risks and benefits of continuing treatment in an unmonitored outpatient setting.

Discussion

Given the significant benefit that 5-FU provides to regimens (i.e., FOLFOX and FOLFIRI) used for mCRC (2-5), methods for safe re-challenge with 5-FU following suspected coronary vasospasm can preserve what is the most effective chemotherapy-based treatment option for MMR-proficient patients. Chakrabarti and colleagues reported successful treatment with FLOX (bolus 5-FU, oxaliplatin, and leucovorin) in patients who had experienced 5-FU-related coronary vasospasm on FOLFOX (24). However, the diarrhea and marrow suppression associated with FLOX can limit treatment. Additionally, a meta-analysis (9) suggests that an advantage of infusional 5-FU versus bolus is a superior response rate. While it is unknown whether this trend continues despite a reduced dose of infusional 5-FU, as was required in this case, the ability to safely continue FOLFOX in this patient population is appealing.

A significant caveat to re-challenge with infusional 5-FU over bolus is the temporal unpredictability of vasospasm symptoms in relation to dosing. The case presented here demonstrates proof of principle that inpatient cardiac monitoring can enhance safety during infusional 5-FU re-challenge. However, the use of inpatient cardiac monitoring and the associated consumption of resources is a significant barrier to widespread implementation of this approach.

Secondary coronary vasospasm prophylaxis with CCBs and nitrates was included in the approach to infusional 5-FU

re-challenge in this case. A small non-randomized study (58 patients) gave verapamil to patients receiving infusional 5-FU for the primary prophylaxis of coronary vasospasm and showed no difference in rates of coronary vasospasm compared to historical controls (25). However, the use of secondary prophylaxis during 5-FU infusion re-challenge has not been widely studied. This case demonstrates that nitrates and CCBs, coupled with inpatient cardiac telemetry monitoring, allowed this patient to continue with standard of care FOLFOX for mCRC without recurrence of coronary vasospasm. However, it is important to note that this patient incurred minimal cardiac damage (evidenced by preserved left ventricular ejection fraction) during the coronary vasospasm event. Therefore, it is unknown if use of prophylactic medications can be safely applied in patients who have sustained serious cardiac damage after experiencing coronary vasospasm.

Conclusions

Infusional 5-FU is a key component of therapy for CRC but can induce coronary vasospasm during or after infusion. While there are published reports of successful bolus 5-FU re-challenge in patients who experienced coronary vasospasm attributed to 5-FU (21,24), to the authors' knowledge, only one case report of successful re-challenge with infusional 5-FU exists in the literature (23). In light of evidence that infusional 5-FU is more active than bolus (9), safe re-challenge with infusional 5-FU is desirable not only in the metastatic setting, but also in the adjuvant setting, for CRC patients who had experienced coronary vasospasm before completing the prescribed chemotherapy course. Here, we demonstrate proof of principle that infusional 5-FU re-challenge can be carried out safely, using coronary vasodilators (i.e., CCB and nitrates) along with inpatient cardiac telemetry monitoring.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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