



Pierre-Auguste Renoir. *Luncheon*, 1881.

Although rare, cardiotoxicity as an adverse effect of treatment with 5-fluorouracil is a potentially lethal side effect.

5-Fluorouracil–Induced Coronary Vasospasm

Laura K. Shoemaker, DO, Umesh Arora, MD, and Caio Max S. Rocha Lima, MD

Background: *Cardiotoxicity is a rare but well-documented adverse effect of 5-fluorouracil (5-FU). The underlying cause of this side effect of 5-FU is uncertain.*

Methods: *We present a case report of a 63-year-old man treated for metastatic colon cancer who experienced chest pain while being treated with the FOLFIRI regimen. This case report documents coronary artery spasm on catheterization observed with the continuous infusion of 5-FU.*

Results: *Cardiac catheterization obtained within 36 hours of the onset of chest pain revealed marked coronary vasospasm in the obtuse marginal coronary artery and a right coronary artery with a critical obstructive atherosclerotic plaque. Electrocardiogram revealed the myocardium area associated with the event was diffuse rather than localized to the right coronary artery.*

Conclusions: *This observation supports the vasospastic hypothesis for 5-FU-induced angina. Although rare, this type of cardiotoxicity with 5-FU is a potentially lethal side effect. Therapy with 5-FU should be discontinued and patients should be promptly treated.*

Introduction

5-Fluorouracil (5-FU) is an antimetabolite that acts during the S phase of the cell cycle. The active metabolite 5-

From the Department of Internal Medicine at the Cleveland Clinic Foundation, Cleveland, Ohio (LKS), the Interventional Cardiology Program at the University of South Florida, Tampa, Florida (UA), and the University of Miami and Sylvester Comprehensive Cancer Center, Miami, Florida (CMRL).

Submitted September 2, 2003; accepted December 1, 2003.

Address reprint requests to Laura K. Shoemaker, DO, Department of Internal Medicine, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195. E-mail: lauraksboemaker@yahoo.com

No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.

fluorodeoxyuridylate (5-FdUMP) inhibits thymidylate synthase, thus preventing DNA synthesis which leads to imbalanced cell growth and ultimately cell death. 5-FU is also converted to 5-fluorouridine monophosphate (5-FUMP) and can be incorporated into RNA and interfere with RNA processing and function. 5-FU is used in the treatment of a number of solid tumors, including colorectal, breast, gastric, pancreatic, prostate, and bladder cancers. It is metabolized through the liver and has a half-life of approximately 10 minutes.¹

The toxicity of 5-FU, which includes leukopenia, diarrhea, stomatitis, nausea, vomiting, and alopecia, differs with its schedule of administration.¹ Dose-limiting toxicities of bolus 5-FU are diarrhea and myelosuppression. Hand and foot syndrome and stomatitis are also

dose limiting with prolonged infusion. Cardiotoxicity, a rare adverse effect of 5-FU, has a reported incidence ranging from 1.27% to 18%,^{2,3} and it occurs with 5-FU administered either as a single agent or in combination with other chemotherapy agents.³ Cardiotoxicity is observed with both bolus and continuous infusion administration and also at various dose levels.⁴ A prospective clinical study of 367 patients who were given 5-FU (600 to 1000 mg/m² per day) reported cardiotoxicity in 7.6%.⁴ Life-threatening cardiotoxicity (myocardial infarction, ventricular arrhythmias, and cardiac arrest) has been observed with less frequency. In 910 patients at Memorial Sloan-Kettering Cancer Center who received infusion or daily bolus of 5-FU over a 16-month period, the incidence of life-threatening cardiotoxicity was 0.55%.⁵ The cardiac toxicity was observed after day 4 of treatment in patients receiving the bolus 5-FU, while it occurred on approximately day 3 or 4 in those on the infusion administration schedule.

With respect to 5-FU, the term *cardiotoxicity* has been used to describe a number of conditions including cardiogenic shock, supraventricular and ventricular arrhythmias, aberrant ventricular function documented on echocardiogram and, most commonly, anginal symptoms, and myocardial infarction. The mechanism of 5-FU cardiotoxicity is unclear. The prevalent hypothesis suggests that 5-FU induces coronary vasospasm.^{6,8} In vitro studies by one group of researchers suggest that 5-FU causes direct vasoconstriction of vascular smooth muscle, which is mediated by the activation of protein kinase C (PKC).⁹ A competing hypothesis postulates that cardiotoxicity is due to the uncoupling of the electromechanical mechanisms that underlie normal myocardial function, which could be mediated at the level of the cell membrane.² Another study proposes that 5-FU toxicity is a cardiomyopathic process of undetermined mechanism.⁴

We review a case of 5-FU cardiotoxicity in which a patient undergoing treatment with a 46-hour continuous

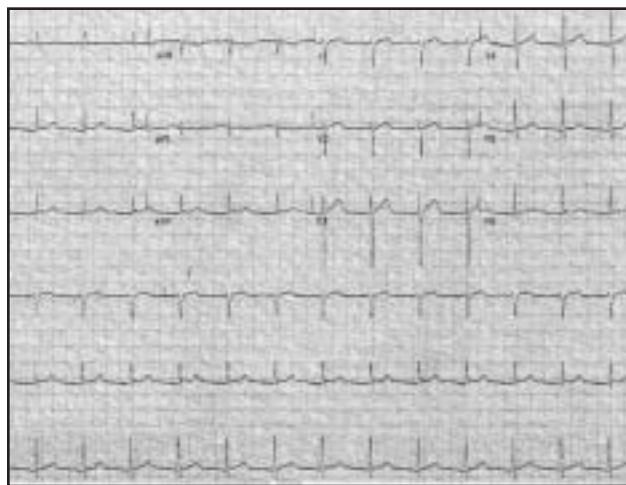


Fig 1. — Normal ECG during therapy before patient had “crushing” substernal chest pain.

infusion of 5-FU presented with typical angina and electrocardiographic changes suggestive of an ischemic coronary event. The patient underwent a cardiac catheterization within 36 hours of this event, and the infusion that showed vasospasm of the obtuse marginal ramus intermedius (OMI-1) was stopped. Notably, there was no critical atherosclerotic plaque observed in that artery.

Case Report

A 63-year-old man was diagnosed with a moderately differentiated adenocarcinoma of the colon and treated with colectomy and adjuvant chemotherapy with bolus 5-FU given on the Mayo Clinic schedule: bolus 5-FU and leucovorin (LV) for 5 days every 4 weeks. The cancer relapsed with metastatic disease to the lungs 5 years later. The three apparent lung lesions were surgically resected. The patient then received chemotherapy with 5-FU, LV, and irinotecan in the FOLFIRI schedule.¹⁰ This regimen consists of irinotecan 180 mg/m² as a 90-minute infusion on day 1 and LV 400 mg/m² as a 2-hour infusion during irinotecan, both of which are immediately followed by a 5-FU 400 mg/m² bolus. 5-FU is then given over 46 hours in a continuous infusion.

The patient had a medical history of coronary artery disease, hypercholesterolemia, peripheral vascular disease, and exertional dyspnea. Two episodes of myocardial infarctions occurred — one in the 1980s and a second in the mid 1990s that was treated with cardiac catheterization and angioplasty of the right coronary artery (RCA). Two months prior to beginning treatment for the metastatic lung disease, he had a normal stress test. His family history is unremarkable, but he has a 70-pack-year smoking history.

The protracted 5-FU infusion in the FOLFIRI regimen was given over 46 hours by continuous infusion. The evening of the first day of the infusion (day 0), he experienced nausea and vomiting that were not relieved by antiemetics. The following day (day 1), he reported an



Fig 2. — ST elevation in leads II, III, aVF, and V₂-V₆ shown on a repeat ECG obtained during the patient's therapy and “crushing” substernal chest pain, diaphoresis, and vomiting.



Fig 3. — Cardiac catheterization demonstrating spasm of the first obtuse marginal artery before intervention.



Fig 4. — Cardiac catheterization demonstrating a critical lesion in the right critical artery with approximately 80% stenosis before intervention.

“abnormal sensation” in his left arm but attributed it to his peripheral infusion port site. On day 2, he noted left and right arm “pain” that radiated up both sides of his neck. An electrocardiogram (ECG) showed no notable changes (Fig 1). Later that day just before discontinuing the 5-FU infusion, he reported “crushing” substernal pain accompanied by diaphoresis and vomiting. A repeat ECG revealed ST elevation in leads II, III, aVF, and V₂ to V₆ (Fig 2), and the 5-FU infusion was stopped. He was given intravenous nitroglycerin and heparin and was transferred to a tertiary care facility. Because of recurrent chest pain, he was evaluated by catheterization at the tertiary care facility on an emergency basis. Prior to reaching the catheterization laboratory, he was treated with a nitroglycerin drip at 0.5 µg/kg per minute, a diltiazem drip at 10 mg per minute, and aspirin 325 mg orally, which provided partial relief of his symptoms and ECG changes. Cardiac catheterization revealed that the first obtuse marginal (OM-1) artery, a branch of the left circumflex coronary artery, was in severe spasm with a subcritical lesion at approximately 60% to 65% (Fig 3). Also, the RCA had an 80% obstructing eccentric lesion (Fig 4). Multiple boluses of 100 µg of intracoronary nitroglycerin and 100 µg of intracoronary nitroprusside promptly resolved the spasm (Fig 5). Subsequently, a stent was placed in the proximal RCA critical lesion (Fig 6).

While the intravenous nitroglycerin and diltiazem were being administered, the chest pain disappeared and the patient was trans-



Fig 5. — Cardiac catheterization demonstrating dilation of the first obtuse marginal artery OMI-1 following administration of intracoronary nitroglycerin and nitroprusside.

ferred to the coronary care unit. He was discharged the next day but continued taking the calcium channel blocker (diltiazem CD) at 240 mg daily and isosorbide mononitrate at 60 mg orally daily, and he has experienced no further chest pain. Throughout these events, blood levels of creatinine kinase and troponin were within the normal ranges. Following these events, he was given a combination of oxaliplatin and irinotecan (without 5-FU) for 6 months. He is currently under surveillance due to his high risk for tumor relapse.

Discussion

5-FU is a chemotherapeutic agent used to treat many solid tumors.¹ Coronary events induced by 5-FU are rare, but considering the potentially lethal nature of this toxicity, physicians should be aware of this possible side effect. Early intervention is important since stopping 5-FU and subsequently starting appropriate treatment in a timely manner are associated with successful outcomes.

Many mechanisms have been hypothesized for 5-FU-induced coronary toxicity. Our case supports a vasospastic theory. Although a number of case reports have documented cardiac toxicity with symptomatology, electrocardiographic findings, cardiac enzyme elevations, and echocardiographic evidence, this case documents coronary vasospasm by cardiac catheterization. In addition, our patient’s ECG demonstrated diffuse ST-segment elevation, which is more consistent with diffuse coronary vasospasm than with isolated myocardial infarction sec-



Fig 6. — Cardiac catheterization demonstrating dilation of the right critical artery following stent placement.

ondary to a critical atherosclerotic lesion. The absence of troponin and creatine kinase (CK)-MB elevation suggests that the insult to the myocardium from the coronary spasm was not sufficient to induce significant necrosis.

Our patient had an extensive history of cardiac problems but had been symptom-free and had a normal stress test 2 months prior to beginning treatment with 5-FU. Also, he had received adjuvant bolus 5-FU and LV after his earlier colectomy. It has been suggested that a history of coronary artery disease may increase the risk of 5-FU-induced cardiotoxicity, although a history of coronary artery disease is not a prerequisite for toxicity.^{2,5}

Our patient was receiving concurrent treatment with two other agents, LV and irinotecan. The cardiotoxic side effects of 5-FU have been noted in patients receiving 5-FU as either a single agent or as part of a chemotherapy regimen.² Some studies suggest that multiple drug regimens increase the risk of 5-FU-induced cardiotoxicity, while others note no apparent difference in the incidence of toxicity between monotherapies and polytherapies.² One study explored the combination of 5-FU and LV and found no difference between this combination and 5-FU as a single agent relative to the frequency and type of cardiotoxicity observed.³ Despite this observation, the use of combinations of antitumor agents in modern oncology raises concern for the potential synergism of overlapping toxicities. Cardiotoxicity is a complication associated with several chemotherapy agents, including anthracyclines, ifosfamide, and cyclophosphamide. Furthermore, newer agents used for advanced colorectal cancer, such as bevacizumab, which causes hypertension, also are associated with cardiac toxicities. A better understanding of cardiotoxicity induced by 5-FU and other fluoropyrimidines is needed and should be explored in clinical trials.

Our patient received 5-FU as a continuous infusion. The effect of dosage and delivery system on the risk of developing 5-FU-related cardiotoxicity remains unclear. A review of 5-FU-related cardiotoxicity suggests that cardiac events are associated more often with infusional schedules than with bolus schedules.⁵ Our patient had received 6 months of adjuvant chemotherapy with bolus 5-FU and LV with no cardiac toxicity.

The coronary event in this patient was treated with intravenous nitroglycerin, an intravenous calcium channel blocker (diltiazem), and oral aspirin prior to his catheterization. During catheterization, he received intracoronary nitroglycerin and nitroprusside; following catheterization, he received an oral calcium channel blocker, long-acting nitrates, and aspirin. Other than stopping administration of 5-FU, the management of 5-FU-related cardiac toxicity is not defined. Appropriate therapy may depend on the institutional protocol for the management of acute coronary events, but a definitive approach has not yet been established.² If the mechanism of toxicity is vasospastic in origin, use of a calcium channel blocker would be reasonable. A number of reports have supported the use of a cal-

cium channel blocker,^{6,7,11} while another reported no benefit.¹² In vitro studies demonstrated no improved response of vasospasm with either calcium channel blockers or beta-blockers.⁹ Finally, a number of reports have shown that in most cases, 5-FU-induced toxicity is reversible with supportive care.²

References

1. Sobrero AF, Aschele C, Bertino JR. Fluorouracil in colorectal cancer: a tale of two drugs. Implications for biochemical modulation. *J Clin Oncol.* 1997;15:368-381.
2. Robben NC, Pippas AW, Moore JO. The syndrome of 5-fluorouracil cardiotoxicity: an elusive cardiopathy. *Cancer.* 1993;71:493-509.
3. Schober C, Papageorgiou E, Harstrick A, et al. Cardiotoxicity of 5-fluorouracil in combination with folinic acid in patients with gastrointestinal cancer. *Cancer.* 1993;72:2242-2247.
4. de Forni M, Malet-Martino MC, Jaillais P, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. *J Clin Oncol.* 1992;10:1795-1801.
5. Keefe DL, Roistacher N, Pierri MK. Clinical cardiotoxicity of 5-fluorouracil. *J Clin Pharmacol.* 1993;33:1060-1070.
6. Kleiman NS, Lehane DE, Geyer CE Jr, et al. Prinzmetal's angina during 5-fluorouracil chemotherapy. *Am J Med.* 1987;82:566-568.
7. Lestuzzi C, Viel E, Picano E, et al. Coronary vasospasm as a cause of effort-related myocardial ischemia during low-dose chronic continuous infusion of 5-fluorouracil. *Am J Med.* 2001;111:316-318.
8. Maseri A, Lanza G. Fluorouracil-induced coronary artery spasm. *Am J Med.* 2001;111:326-327.
9. Mosseri M, Fingert HJ, Varticovski L, et al. In vitro evidence that myocardial ischemia resulting from 5-fluorouracil chemotherapy is due to protein kinase C-mediated vasoconstriction of vascular smooth muscle. *Cancer Res.* 1993;53:3028-3033.
10. André T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. GERCOR. *Eur J Cancer.* 1999;35:1343-1347.
11. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med.* 1994;331:502-507.
12. Akpek G, Hartshorn KL. Failure of oral nitrate and calcium channel blocker therapy to prevent 5-fluorouracil-related myocardial ischemia: a case report. *Cancer Chemother Pharmacol.* 1999;43:157-161.