Cardiotoxicity and Capecitabine: A Case Report

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As early as 1975, case reports of rare cardiotoxicity associated with IV administration of 5-fluorouracil (5-FU) began to appear in the literature (Roth, Kolaric, & Popovic, 1975). With the development of oral fluoropyrimidines and the continued use of IV fluoropyrimidines to treat a variety of solid tumors in adults, clinicians need to become aware of this toxicity.

The following is a case report of cardiotoxicity related to first-cycle administration of oral capcitabine (Xeloda®, Roche Laboratories, Nutley, NJ), a thymidine phosphorylase-activated fluoropyrimidine, in the treatment of a woman with metastatic breast cancer. Following the case report, a discussion of the possible pathophysiology of fluoropyrimidine-induced cardiotoxicity, literature to date, and implications for practice are presented.

Case Report

Ms. S is a 52-year-old Caucasian woman who initially presented with stage IV breast cancer in September 1998. Computed tomography (CT) scans at presentation revealed a right middle lobe pulmonary mass, internal mammary lymphadenopathy, and left axillary adenopathy. A bone scan was negative for osseous metastatic disease. She received four cycles of cyclophosphamide, doxorubicin, and 5-FU every 21 days, followed by a left simple mastectomy. Pathology at the time of mastectomy revealed a residual tumor measuring 11 cm x 9 cm x 4 cm. Ms. S subsequently received tamoxifen and locoregional radiotherapy for local control. She was disease free for five months and then presented with new left supraclavicular adenopathy outside her previous radiation treatment field. A biopsy revealed metastatic adenocarcinoma consistent with a primary breast cancer. Further evaluation revealed presence of new osseous metastatic disease and asymptomatic bilateral pulmonary nodules. Ms. S received six cycles of paclitaxel and had an initial partial response. When her disease progressed, she was switched to docetaxel, and a radiographic response was observed at all sites. In September 2000, she began letrozole 2.5 mg orally daily. In December 2000, she presented with a new onset of back pain, and CT scans revealed a new left paraspinal mass and progression of pulmonary nodules.

Ms. S’s past medical history included a 60 pack year smoking history, and she now smokes one to two packs per day despite numerous attempts to quit. She has significant emphysema on a chest radiograph and CT scan but no history of cardiac disease, diabetes, or hyperlipidemia.

On January 18, 2001, Ms. S began oral capecitabine at a total of 1875 mg/m² per day x 14 days in two equally divided doses. Each cycle was a 21-day cycle. On the morning of day four of treatment (after three full days of medication), she reported severe, crushing chest pain with increasing dyspnea and was seen in the emergency room. She was admitted to the cardiac care unit to rule out myocardial infarction after an electrocardiogram (ECG) showed ischemic changes (new ST segment elevation). Cardiac enzymes were reported within normal limits, and cardiac troponin I was 0.8 ng/ml on admission and returned to less than 0.5 ng/ml within 24 hours of admission. A ventilation perfusion scan showed moderate perfusion defect and was read as intermediate probability for pulmonary embolus but likely represented perfusion defect from severe chronic obstructive pulmonary disease. An echocardiogram revealed a left ventricular ejection fraction (LVEF) of 40% with mildly reduced global systolic function, a hypokinetik anterior septum, normal valves, and no pericardial effusion. The ECG initially revealed normal sinus rhythm, with normal axis; ST elevations in leads II, III, AVF, V3, and V4; ST depressions in V1; and PR depressions in leads II, III, and AVF. A second ECG later that first day revealed ST elevations in leads II, III,
III, and AVF with T wave inversions in leads V 2–6. These findings were believed to be consistent with inferolateral ischemia. Ms. S underwent cardiac catheterization, which revealed clean coronary arteries with LVEF of 35%, which was thought to be consistent with prior anthracycline cardiotoxicity. Therefore, chest pain was believed to be related to capecitabine-induced coronary artery spasm. Because of her low LVEF, Ms. S began captopril 6.25 mg orally three times daily and the decision was made to not rechallenge her with capecitabine because of potential cardiac risk, which was based on the published literature of cardiotoxicity with fluorouracil. At the time of this case, no reports of acute cardiotoxicity with capecitabine had been reported. Ms. S recovered completely from this event and began treatment with vinorelbine for her breast cancer.

Fluoropyrimidine Cardiotoxicity

The exact pathophysiologic mechanisms of fluoropyrimidine-induced cardiac toxicity are unknown. Although it is generally considered to be a rare event, various sources cite an incidence of 1%–18% (Becker, Erckenbrecht, Haussinger, & Frieling, 1999; Prunier, Monsegu, Coutant, & Ollivier, 2000), with mortality rates of 2.2%–13.3% (Clavel, Simeone, & Grivet, 1988; de Forni et al., 1992). The incidence of oral fluoropyrimidine-induced cardiotoxicity is similar to that reported with 5-FU (Van Cutsem, Hoff, Blum, Abt, & Osterwalder, 2002).

Fluoropyrimidines have a high relapse rate characterized by recurrent symptoms, and rechallenge should be avoided because of the risk of ischemic injury or sudden death (Becker et al., 1999). Clavel et al. (1988) reported on 28 patients who were rechallenged with 5-FU after presenting with anginal-type symptoms. Myocardial necrosis occurred in four patients and resulted in death from cardiogenic shock. In reviewing these cases, risk factors that may have predicted this outcome were not clearly identified, including age, gender, route of administration, or pre-existing cardiovascular disease (Clavel et al.). Severe, reversible cardiotoxicity has been reported to occur in patients as young as 14 years (Blutters-Sawatzki, Grathwohl, Mertens, & Lampert, 1995).

A number of pathophysiologic hypotheses based on clinical and animal models have been proposed to explain the phenomenon of fluoropyrimidine-induced cardiac toxicity. Whether the coronary arterial endothelium has underlying damage, active metabolite causes a toxic reaction (fluoroacetate is a known cardiototoxic compound), or an autoimmune-mediated response occurs, the exact causes are unknown. Kinhult, Albertsson, Eskilsson, and Cwikiel (2001) designed a study to evaluate the role of antithrombotic treatment with dalteparin as a preventative strategy against the thrombogenic effect of 5-FU. An earlier study found evidence of severe cell damage with accompanying thrombus formation in rabbits (Cwikiel, Eskilsson, Wieslander, Stjernquist, & Albertsson, 1996). Kinhult et al. confirmed this observation of tissue damage and added to the understanding of 5-FU toxicity in the animal model. Using scanning microscopy, the researchers observed severe endothelial damage with intima disruption, denuding of underlying structures, and fibrin formation in the animals treated with 5-FU. Interestingly, the most severe damage was observed on day three of treatment with 5-FU. Although the damage was partly reversible in the rabbits treated with 5-FU alone, the rabbits treated with the combination of 5-FU and dalteparin had fewer thrombotic events but less reversibility of endothelial damage. Concern was raised regarding potential endothelial toxicity from dalteparin alone, at least in this animal model (Kinhult et al.).

In a prospective trial conducted by de Forni et al. (1992), 337 patients were monitored for cardiac function while receiving 5-FU via IV continuous infusion for 96 or 120 hours as a single agent or in combination with other chemotherapeutic agents. Twenty-eight patients experienced cardiac events and only nine of these patients had a prior history of cardiac disease or impairment. Five sudden deaths and three irreversible cardiac collapses occurred. Cardiac events typically were associated with ischemic ECG changes. Echocardiography revealed that partial or global hypokinesia and cardiac enzymes rarely were elevated. In reversible cases, all ECG and clinical parameters returned to baseline within 48 hours of discontinuation of the 5-FU. Of note, fluoroacetate was detected in the urine of 14 patients, half of whom had cardiac symptoms.

One hundred patients receiving 5-FU infusions, either alone or as part of combination chemotherapy, were evaluated for the presence of symptomatic cardiotoxicity in a retrospective study conducted by Akhtar, Salim, and Bano (1993). Researchers excluded patients with a history of cardiac disease or those who had abnormal ECGs or cardiac enzymes. Daily ECGs were performed during treatment. Patients who developed cardiac symptoms had ECGs monitored until they were symptom free for 24 hours. Eight of the 100 patients developed symptoms of cardiotoxicity that included (in order of frequency) pain, palpitations, and diaphoresis. Three patients developed ECG abnormalities, and one developed cardiogenic shock. Serial cardiac enzymes remained within normal levels in all patients, and the symptoms were reversible in all affected patients. Complete recovery with reversal of cardiac dysfunction also was documented in a case report of a patient who developed cardiogenic shock while receiving high-dose 5-FU (1000 mg/m² every 24 hours for 96 hours) (Akhtar, Wani, Bano, Salim, & Handoo, 1996).

Kuropkat et al. (1999) reported a case of sudden, severe cardiac failure in a 23-year-old man with squamous cell carcinoma of the tongue receiving 5-FU. Previously, he had been healthy and showed no signs of ischemic changes at the time of the event. Endomyocardial biopsy revealed proliferation of the sarcolemmal reticulum with marked vacuolization, which is typical of myocardial injury seen with anthracycline-induced cardiotoxicity. This case study suggests a different mechanism of cardiac injury unrelated to coronary artery spasm, which had been previously reported with 5-FU.

Gamelin et al. (1991) reported data on a cohort of 133 patients who had undergone treatment with high-dose, continuous-infusion 5-FU (1,000 mg/m² per day x 4 days) plus cisplatinum (20 mg/m² per day x 4 days) for a variety of solid tumor malignancies. Daily ECG and 5-FU plasma assays were measured. Twenty-eight patients experienced 36 ischemic cardiac events, 29 of which were asymptomatic. The researchers found that cardiac events occurred most frequently after 5-FU plasma levels reached a level greater than 450 ng/mL. Increased toxicity because of the combination of cisplatinum and 5-FU was suggested. Although this study does not describe any risks associated with mediastinal or chest wall irradiation, other authors have suggested that concomitant radiation may increase cardiotoxicity associated with fluoropyrimidines (Pottage, Holt, Ludgate, & Langlands, 1978).

In a prospective cohort study involving 483 patients from 35 hospitals, Meyer, Calis, Burke, Walawander, and Grasela (1997) evaluated the incidence of symptomatic cardiotoxicity and identified associated risk factors for cardiotoxicity in patients receiving 5-FU via continuous infusion. Cardiotoxicity occurred in 7 of 209 patients receiving their first cycle of 5-FU. In this sample of patients, risk factors identified were pre-existing cardiac disease and use of calcium channel blockers, nitrates, and etoposide (concomitant).

Although many of the clinical reports in the literature have focused on continuous infusion 5-FU therapy as a risk factor, patients...
also have experienced cardiotoxicity from bolus 5-FU infusions as well as intraperitoneal 5-FU infusions (El-Attar, Skeel, & Howard, 1999; Lomeo, Avolio, Iacobellis, & Manzione, 1990).

Oatl fluoropyrimidines, such as capcitabine, recently have been used to treat breast, pancreatic, and gastrointestinal tumors (Twelves, 2001). The first case report of capcitabine-induced cardiotoxicity was published in June 2001 and involved a 39-year-old patient who received 2,000 mg/m² per day of capcitabine for advanced gastric cancer and developed anginal-type chest pain. Cardiotoxicity was completely reversible with cessation of capcitabine therapy (Bertolini et al., 2002). In 2002, another case report of capcitabine-induced cardiotoxicity was published. A male patient experienced a severe and prolonged acute coronary syndrome during capcitabine treatment; he previously had developed similar symptoms during treatment with continuous infusion 5-FU (Frickhofen et al., 2002). To date, clinical trial data have not found any cardiotoxicity associated with capcitabine administration. Recent data based on the U.S. Food and Drug Administration’s (FDA’s) approval of combination therapy of docetaxel and capcitabine for the treatment of metastatic breast cancer report supraventricular tachycardia and edema as the only cardiotoxicities associated with this therapy (FDA, 2001).

Similar cardiotoxicity was observed in Spain in four patients receiving p�能化, a dihydropyrimidine dehydrogenase (DPD)-inhibitory fluoropyrimidine also known as UFT® (uracil/tegafur, Bristol-Myers Squibb, Waterloo, Belgium). The patients experienced symptoms of myocardial ischemia and had complete resolution of symptoms following withdrawal of the offending medication, p�能化 (Camps, Godes, & Soler, 1990).

Daily administration of oral DPD-inhibitory fluoropyrimidine results in similar serum concentrations of 5-FU achieved with continuous infusions of 5-FU. UFT combined with oral leukovorin (Orzel®, Bristol-Myers Squibb, New York, NY) is being evaluated as a treatment for colorectal and non-small cell lung cancer in clinical trials (Carmichael et al., 2002; Langer, 2001).

Clinical Symptoms

Chest pain is the most common presenting symptom of cardiotoxicity in patients receiving fluoropyrimidines, either orally or via IV. Other signs and symptoms include dysrhythmia, dyspnea, ST-T wave changes on ECG, myocardial infarction, pulmonary edema, cardiogenic shock, and sudden death (Gradishar & Vokes, 1990). Supportive care should include immediate cessation of fluoropyrimidine therapy, intensive cardiac monitoring, and treatment based on the specific signs and symptoms observed. As Ms. S’s case study demonstrated, patients experiencing cardiotoxicity from either oral or IV fluoropyrimidines may present with classic myocardial infarction-type chest pain syndrome with crushing chest pain, dyspnea, diaphoresis, and nausea. Full cardiac work-up should ensue. As noted in this case, cardiac catheterization revealed no evidence of coronary artery disease and no cardiac enzyme elevation occurred, although a transient increase in troponin I level did occur, with complete resolution within 24 hours. Ms. S was heavily pretreated with prior anthracycline-based therapy as well as chest wall irradiation, and her chronic lung disease likely played a significant role in her symptoms.

Treatment

Attempts to prevent cardiotoxicity, based on assumption of coronary artery spasm as the mechanism or manifestation of injury, have been unsuccessful. Prophylactic treatment with verapamil may reduce supraventricular tachycardia but did not alter the incidence of cardiotoxicity in patients receiving continuous infusion 5-FU with cisplatinum for aerodigestive cancer (Eskilsson & Albertsson, 1990). Other authors have suggested, based on case studies of cardiotoxicity, that the mechanism of injury is more consistent with acute myocardial tissue injury not associated with ischemia and more likely a direct toxicity to myocardial cells by a metabolite, such as fluorocacetate, or an autoimmune process that, to date, has not been clearly defined (de Forni et al., 1992; Kuropkat et al., 1999).

Careful monitoring for potential cardiac symptoms, prompt recognition of the potential for drug-induced toxicity, and prevention of further myocardial injury are the best patient management strategies at the current time. See Figure 1 for assessment, monitoring, and patient teaching points.

In summary, cardiotoxicity is a rare but potentially fatal complication associated with the use of IV fluoropyrimidines. With the advent of oral fluoropyrimidines such as UFT and capcitabine, clinicians should carefully monitor patients receiving these agents for this potential side effect and instruct them about symptoms to report and actions to take in the event that such symptoms occur. Although cardiotoxicity with oral fluoropyrimidines has been reported infrequently, this incidence likely will increase with wider use of these medications.

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References


Pre-treatment assessment

• Assess at baseline previous cardiac disease, cardiac risk factors, prior cardiotoxic medication exposure, and chest wall or mediastinal radiotherapy (concurrent or prior).
• Assess baseline weight.
• Perform baseline electrocardiogram (EGG).

Treatment monitoring

• Monitor for any cardiovascular symptoms: chest pain, dyspnea, hypo- or hypertension, cardiac irregularities or dysrhythmias, or fluid overload.
• Weigh patients daily or have patients monitor weight daily at home. Instruct patients to contact their healthcare providers if they gain more than 1 kg or notice peripheral edema or dyspnea.
• If chest pain occurs, stop drug immediately, have patient go to emergency room, or, if hospitalized, obtain ECG, maintain IV access, and proceed with evaluation to rule out myocardial infarction.

Patient education

• Instruct patients to report any chest pain, discomfort, or pressure; any shortness of breath; or edema.
• Make patients aware that chest pain or discomfort is not a common side effect of this therapy and it warrants urgent attention should it occur.

Figure 1. Assessment, Monitoring, and Teaching Points for Patients Receiving Fluoropyrimidines

Note. Based on information from Pederssen et al., 1997.


