Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil

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Capecitabine is a member of a new class of oral fluoropyrimidines. It is a 5-fluorouracil (5-FU) prodrug, activated by a series of enzymes. Activation has been demonstrated to occur preferentially in tumor tissue, which may explain the favorable balance of efficacy and toxicity of this drug. Cardiotoxicity, a rare but potentially serious adverse effect of 5-FU, has not been reported for capecitabine to date. Here we report a patient who experienced a severe and prolonged acute coronary syndrome during treatment with capecitabine. He had previously developed similar symptoms during treatment with infusional 5-FU. Capecitabine should thus be considered an agent with cardiotoxic potential. This adverse effect should be specifically monitored in all patients treated with capecitabine. Patients with symptoms suggestive of cardiotoxicity during previous treatment with a fluoropyrimidine should not be treated with capecitabine.

Key words: adverse effects, capecitabine, cardiotoxicity, case report, chemically induced, thymidine phosphorylase

Introduction

Capecitabine is an orally administered prodrug of 5-fluorouracil (5-FU). It is currently approved for the treatment of metastatic breast cancer refractory to anthracyclines and paclitaxel, and for first-line treatment of metastatic colorectal cancer.

The drug belongs to a new and rapidly expanding class of therapeutics, specifically designed for oral treatment of cancer. Oral treatment has several advantages over i.v. treatment, especially in patients with incurable cancer. It can lead to prolonged exposure of tumor cells to the antineoplastic effects of anticancer agents, mimicking the more cumbersome continuous i.v. infusions; it is more convenient for patients, of whom >80% would prefer oral to i.v. treatment; and it may be less expensive, considering costs saved in drug administration [1].

An additional advantage, which makes capecitabine an attractive compound, is its assumed targeting of tumor tissue [2]. The parent drug is first converted to 5′-deoxy-5-fluorouridine (5′-DFUR) by the enzyme carboxylesterase, which is present predominantly in the liver. 5′-DFCR is then converted to 5′-deoxy-5-fluorouracil (5′-DFUR) by the enzyme cytidine deaminase, which is more widely distributed including the liver and various tumor tissues. Finally, 5′-DFUR is converted to 5-FU by thymidine phosphorylase (TP). TP is identical to the angiogenic agent ‘platelet derived endothelial cell growth factor’ (PD-ECGF) [3]. Expression of TP is increased in tumor tissue compared with normal tissue [4]. The proposed accumulation of 5-FU in tumors by metabolic targeting has been confirmed by measurement of 5-FU concentrations in colorectal cancer tissue compared with adjacent normal tissue [5].

Targeting of tumor tissue by capecitabine may result in a favorable balance of treatment efficacy and toxicity. Cardiotoxicity, a rare but potentially serious toxicity of fluoropyrimidines [6, 7], has not been reported for capecitabine to date. Here we report a patient without evidence of cardiomyopathy or coronary heart disease, who developed cardiac ischemia with severe angina after oral administration of capecitabine. This observation suggests the need for caution when treating patients considered at risk of fluoropyrimidine-associated cardiac toxicity.

Case report

A 60-year-old male patient was diagnosed with stage III (pT3, pN1, M0) rectal cancer in 1997. He was treated with abdominoperineal resection and colostomy, followed by adjuvant radio-chemotherapy with weekly 5-FU/folinic acid (FA) and standard pelvic radiotherapy. 5-FU was given by 10 min-
infusion at a dose of 500 mg/m², preceded by FA 30 mg/m², before and after radiotherapy. During radiation treatment, the dose of 5-FU was reduced to 300 mg/m², again given weekly with FA. Twenty-four weekly courses of 5-FU/FA were tolerated without adverse effects exceeding grade 1 CTC toxicity. In particular, there was no excessive mucosal or cardiac toxicity.

One year later, pelvic relapse and a solitary liver metastasis were diagnosed. The loco-regional relapse was resected. The solitary liver metastasis was not resected since laparotomy 2 months later revealed diffuse peritoneal metastasis. In February 1999, palliative chemotherapy with weekly infusional 5-FU and FA (2600 mg/m²/24 h and 500 mg/m², respectively) was started. Approximately 3 h after the start of the second infusion of 5-FU, the patient developed severe chest pain, suggestive of cardiac ischemia. Electrocardiography (ECG) showed ST-segment elevation in the lateral leads. Angiography did not reveal significant coronary artery disease. There was also no angiographic evidence of coronary spasm, even though the patient had persisting chest pain at the time of angiography. Beta-blockers, given at high doses, were effective for control of the chest pain. Since the clinical suspicion of 5-FU induced cardiotoxicity was high, treatment was switched to irinotecan, 350 mg/m² every 3 weeks. Partial remission was documented after nine courses.

In January 2000, progression of the disease in the pelvis and liver and new lung metastases were found. The patient was treated with irinotecan and oxaliplatin within a phase II study. Irinotecan was given at a dose of 80 mg/m² on days 1, 8 and 15 and oxaliplatin was given at 85 mg/m² on days 1 and 15, both to be repeated on day 29. Because of oral mucositis and severe diarrhea after one course of this regimen, irinotecan was replaced by raltitrexed, 3 mg/m² every 3 weeks. Oxaliplatin was continued at a dose of 130 mg/m² every 3 weeks. Treatment was again discontinued after only two courses due to neurotoxicity attributed to oxaliplatin.

Since the patient was in good shape and willing to continue treatment, we decided to go back to use of a fluoropyrimidine, since he had never been given a significant amount of 5-FU (and only two infusions of raltitrexed). Capecitabine was chosen because of the ease of administration and our speculation that low systemic peak levels of 5-FU, due to tumor-associated activation, would decrease the risk of cardiotoxic effects.

In the morning of 20 September 2000, he began taking capecitabine at a total daily dose of 2500 mg/m², divided in two doses during meals. There were no adverse effects on the first day of treatment. After the third dose of capecitabine at 10:00 a.m. on 21 September, he did not notice any adverse effects. However, with a delay of 11.75 h (9:45 p.m.), immediately before the planned fourth dose of capecitabine, the patient noticed acute chest pain accompanied by nausea and later vomiting. Since the character of these symptoms reminded him of the episode after infusional 5-FU in 1999, he did not take the fourth dose of capecitabine, called emergency, and was transferred to this hospital.

During transfer to the emergency department, chest pain was unresponsive to treatment with nitroglycerine (0.4 mg s.i.), metoprolol (5 mg i.v.), morphine (10 mg i.v.), acetylsalicylic acid (500 mg i.v.) and heparin (5000 IU). Only after initiating continuous infusion of nitroglycerine (4 mg/h) did the pain subside. At the time of admission (11:10 p.m. 21 September) the patient was not symptomatic. Admission ECG showed no ST-segment elevation, but new negative T-waves in leads AVL, I and V4–V6. Only ~4 h later, at 3:00 a.m. September 22, chest pain recurred. It persisted despite treatment with nitroglycerine (4 mg/h continuous i.v.), metoprolol (cumulative dose 15 mg i.v.), diazepam (5 mg i.v.) and morphine (cumulative dose 20 mg i.v.). ECG now showed ST-segment elevations in leads I, II, AVL, AVF and V3–V6, suggestive of transmural ischemia (Figure 1). Angiography, performed while the patient’s symptoms slowly subsided, did not reveal significant coronary artery disease and no coronary artery spasm. The picture was essentially unchanged compared with the angiography in 1999. ECG immediately after angiography (5:00 a.m. 22 September) and with the patient still not symptomatic, again demonstrated normal ST-segments and negative T-waves in leads AVL, I and V4–V6.

Since intermittent coronary artery spasms were considered the most likely cause of chest pain, treatment with continuous infusion nitroglycerine (6 mg/h) was continued and nifedipine (1.2 mg/h continuous i.v.) was added to the treatment. Nevertheless, the patient experienced repeated episodes of chest pain at 8:30 a.m., 4:00 p.m., 11:00 p.m. (22 September), 4:00 a.m. and 11:00 a.m. (23 September). All these episodes lasted ~1 h and were essentially unresponsive to treatment. The pain was so severe that the patient had to be treated with short-term general anesthesia using propofole during one of these episodes. During the time of chest pain, ST-segments and T-waves always returned to the pattern suggestive of myocardial infarction as shown in Figure 1. Serial analysis of creatine kinase (including the CK-MB subforms), troponin T and lactate dehydrogenase was negative. Symptoms finally subsided in the afternoon of 23 September. ECG returned to normal in the morning of 24 September and there was no laboratory evidence of myocardial infarction.

After recovery from the cardiac events, the patient decided to try raltitrexed again. There were again no adverse events after a single dose of 3 mg/m². Because of deterioration of his performance status, he did not continue antineoplastic treatment. After 1 month of palliative care, he died in December 2000.

Discussion

This case report demonstrates that capecitabine can induce cardiac ischemia accompanied by severe chest pain. Cardiac symptoms after ingestion of capecitabine were similar to the
symptoms experienced by our patient after treatment with infusional 5-FU/FA 18 months earlier. They also matched symptoms of 5-FU induced cardiotoxicity reported in the literature [6, 7]. Capecitabine is metabolized to 5-FU in vivo; this implies that 5-FU or 5-FU metabolites, rather than capecitabine or metabolites upstream of 5-FU (5′-DFCR or 5′-DFUR), caused cardiotoxicity in our patient. Similar to most reports of 5-FU-induced cardiotoxicity, symptoms did not occur after the first dose of capecitabine. It took three doses of capecitabine (7500 mg/m² total dose) and ~12 h after the last ingestion of capecitabine before chest pain developed. This argues against a peak dose effect and in favor of a cumulative dose effect.

Whereas the nature of symptoms after capecitabine was similar to those our patient previously experienced after 5-FU, the pattern of events was different. Symptoms persisted for 38 h with repeated bouts of pain, each lasting ~1 h and separated by 5–7 h. One obvious explanation for the prolonged toxicity is the fact that parenteral 5-FU can be and has been stopped in patients experiencing cardiac toxicity, whereas exposure to capecitabine cannot be interrupted after oral ingestion of the drug. In addition, it is reasonable to speculate that there is a prolonged generation of cardiotoxic agents in vascular or par-enchymal cells of the heart. The plasma AUC for 5-FU generated from oral capecitabine at a daily dose of 1657 mg/m² has been reported to be ~30 times lower than from an i.v. bolus of 5-FU at 600 mg/m². However, capecitabine generates a prolonged high concentration of 5′-DFUR in the plasma and thus provides ample substrate for the generation of 5-FU in cells over a prolonged period of time [8]. This might be the key to the cumulative dose effects of 5-FU or its metabolites after administration of capecitabine.

If it is assumed that 5-FU or its metabolites were responsible for cardiotoxicity after capecitabine, the events finally causing cardiac ischemia should be similar. Coronary artery vasospasm [9, 10], direct toxicity to the myocardium [11], thrombogenic effects [12] and autoimmune phenomena [13] have been proposed.

This report may help to narrow down the spectrum of hypotheses. Acute thrombosis of the large coronary arteries could be excluded in our patient and in several cases reported in the literature (reviewed by Robben [6] and Meyer [7]). Obviously, small vessel thrombosis is a possibility, which cannot be excluded by angiography. Autoimmunity is unlikely as no data to support this hypothesis have emerged since it was first proposed in 1990 [13].

Figure 1. ECG during an episode of capecitabine induced severe chest pain, suggestive of transmural cardiac ischemia.
Vasospasm is a reasonable mechanism, since it would explain reports of the efficacy of vasodilating drugs given prophylactically to patients who experienced a previous episode of chest pain during 5-FU treatment. However, the efficacy of these drugs is variable [14–17] and they were not apparently effective in our patient. Vasospasm cannot formally be ruled out in our patient, since angiography was performed when he was not symptomatic, between two bouts of capecitabine-induced chest pain. However, at the time of 5-FU induced cardiotoxicity 18 months earlier, there was no anatomic evidence of vasospasm when the patient was symptomatic. This argues against vasospasms of large coronary arteries, but it cannot exclude transient spasms and spasms of small coronary vessels, not visible by angiography.

The final hypothesis, direct damage to the myocardial cells or the blood vessels of the heart by 5-FU or 5-FU metabolites, is attractive. In the patient reported here, as well as in several patients reported in the literature, angiography and echocardiography could best be interpreted as diffuse ischemia, suggestive of a transient cardiomyopathic process without myocardial necrosis [18].

Exactly how 5-FU or 5-FU metabolites might damage the myocardium or the vessels of the heart remains elusive. Accumulation of 5-FU or cardioxic 5-FU metabolites due to dihydronpyrimidine dehydrogenase deficiency is highly unlikely, since there is no correlation between mucosal toxicity and cardiotoxicity. This deficiency was not evaluated in our patient, but he never developed excessive mucosal toxicity during previous treatment with 5-FU. Preclinical data demonstrate the potential for 5-FU to induce dose- and time-dependent depletion of high-energy phosphates in heart tissue [11, 19]. Biochemical data indicated the accumulation of citrate in the myocardium of 5-FU-treated guinea pigs [11]. Fluoroacetate has been incriminated in interference with the tricarboxylic acid cycle [11]. This compound can be generated in vivo from fluoroacetalddehyde, a spontaneous degradation product of parenteral 5-FU preparations [20]. Since capecitabine preparations do not contain fluoroacetalddehyde, this mechanism of cytotoxicity is unlikely.

Could it be that the very advantage of tissue targeting is also responsible for targeting the heart of some patients? TP, the enzyme converting 5’-DFUR to 5-FU, has been found in higher concentrations in tumor tissue compared with normal tissue [4]. However, it is not derived from the tumor cells, but rather from infiltrating non-neoplastic cells [21]. Its expression is increased in hypoxic cell lines in vitro and in vivo [22], compatible with its role as an angiogenic agent (PD-ECGF). One could therefore speculate that the expression of this critical enzyme is also increased in the hypoxic myocardium of a patient with subclinical coronary heart disease. This hypothesis is worth investigating. Expression of TP has not been evaluated in normal, as opposed to ischemic, myocardium [23].

In summary, capecitabine should be considered a drug with cardiotoxic potential. The fact that this adverse effect has not been reported to date suggests that the incidence of cardioxicity of capecitabine may be lower than 1.5–2% reported for 5-FU [7, 24]. The experience with the patient reported here strongly suggests that a history of cardiotoxicity associated with 5-FU should be considered a risk factor for similar cardiotoxicity after administration of capecitabine. Whether other risk factors for 5-FU-associated cardiotoxic events [7] also apply to capecitabine remains to be demonstrated.

References


