Capecitabine-induced Hypertriglyceridemia: A Report of Two Cases

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Abstract. *Background: Capecitabine is a tumor-activated oral fluoropyrimidine with established antitumor activity in breast and colorectal cancer. Hypertriglyceridemia associated with this drug has rarely been reported in the literature. Case Report: This is a report of two patients who developed capecitabine-induced severe hypertriglyceridemia, together with an increase in total cholesterol levels. The first patient developed hyperlipidemia during long-term capecitabine treatment in combination with trastuzumab for metastatic breast carcinoma (triglycerides: from 219 mg/dl to 1409 mg/dl, 543% increase; cholesterol: from 239 mg/dl to 363 mg/dl, 52% increase). The second patient developed abnormalities in the lipid profile after the second cycle of chemotherapy with capecitabine and oxaliplatin for metastatic colorectal cancer (triglycerides: from 101 mg/dl to 1510 mg/dl, 1395% increase; cholesterol: from 203 mg/dl to 310 mg/dl, 52% increase). An analysis of the possible underlying pathogeneic mechanisms is provided. Conclusion: Physicians should be aware of the possibility of dyslipidemia, particularly hypertriglyceridemia, following treatment with capecitabine.*

Capecitabine is a new, orally-administered, enzyme-activated fluoropyrimidine carbamate, designed to generate high levels of 5-Fluorouracil (5-FU) in tumor cells (1, 2). Capecitabine has shown considerable activity against breast cancer refractory to anthracyclines and taxanes and also significant antitumor activity in patients with advanced colorectal carcinoma (3-6). Capecitabine tolerance is acceptable. The main drug-related adverse-effects are palmar-plantar erythrodysesthesia (hand-foot syndrome), diarrhea and stomatitis. In this report, two cases of capecitabine-induced hypertriglyceridemia are described.

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Key Words: Capecitabine, hypertriglyceridemia, hypercholesterolemia, hyperlipidemia.

Case Reports

Case 1. A 69-year-old woman with breast cancer had presented with extensive skin metastases in February 2004. The patient had received adjuvant chemotherapy with cyclophosphamide/methotrexate/5-FU (CMF) 10 years earlier. The patient had also been treated with adjuvant chemotherapy (cyclophosphamide/epirubicin) following surgical management of tumor relapse in the axilla, in April 2001. One year later, the patient presented with cutaneous metastases on the left chest wall and the left arm. She received first-line chemotherapy with docetaxel and second-line treatment with the combination of vinorelbine and trastuzumab, with subsequent regression of the skin lesions. Eight months after the completion of treatment, the patient worsened, with extensive skin involvement of the chest wall, the arm and the back. In March 2004, chemotherapy was reinstituted with oral capecitabine (1000 mg/m^2 twice a day for 14 days every 21 days) and trastuzumab (6 mg/kg every 21 days).

A lipid profile obtained at the beginning of chemotherapy revealed a slight elevation of serum triglycerides 219 mg/dl (normal range 50-150 mg/dl) and serum cholesterol 239 mg/dl (normal range 140-220 mg/dl). The serum HDL value was 62 mg/dl (normal range 35-65 mg/dl), while the LDL value was 133 mg/dl (normal range 0-160 mg/dl). Cardiovascular risk factors included mild obesity (BMI 30) and non-insulin-dependent diabetes mellitus, which was not well controlled (glucose 249 mg/dl). Evaluation of the patient after five cycles of chemotherapy revealed almost complete remission of the cutaneous lesions. Because of the impressive response, the patient remained on treatment.

A blood test before the eighth cycle of chemotherapy (July 2004) revealed increased triglycerides (1409 mg/dl) and total cholesterol levels (363 mg/dl). Furthermore, the HDL level was 28 mg/dl and the LDL level 53 mg/dl, while

glucose was 226 mg/dl. The thyroid hormone profile was normal. The patient did not report alcohol consumption or dietary changes and there was no weight gain. She received simvastatin (20 mg/day) and omega-3 fatty acid supplement (3 g/day) for 1 month. The triglyceride and cholesterol levels rapidly decreased to 129 mg/dl and 133 mg/dl, respectively. Given the complete response and the lack of evidence in the literature connecting hyperlipidemia with capecitabine or trastuzumab, the treatment was continued with close monitoring of the lipid profile. The treatment was tolerated fairly well without other serious adverse events. Due to the development of grade 2 hand-foot syndrome, the dose of capecitabine was modified to 750 mg/m^2 twice a day for 14 days every 21 days. A repeat lipid panel, in August 2005, again demonstrated triglyceride elevation (1640 mg/dl). Capecitabine was discontinued and treatment with simvastatin (20 mg/day) and omega-3 fatty acid supplement (3 g/day) was reinstituted for 1 month. The triglycerides were reduced to 208 mg/m^2, while the serum value of cholesterol decreased to 195 mg/m^2. The patient remained on treatment with trastuzumab without clinical or radiographic evidence of disease and without recurrence of dislipidemia, even though the simvastatin was discontinued after a month.

Case 2. Capecitabine-induced hypertriglyceridemia was also recorded in another patient, a 45-year-old man with metastatic colorectal cancer. The patient had received adjuvant chemotherapy with irinotecan / 5-FU / leucovorin (01/2003-10/2003) following colectomy for stage III colon cancer. In October 2004, the patient had relapsed with disease in the abdomen and was started on first-line chemotherapy with capecitabine (1000 mg/m^2 twice a day for 14 days every 21 days) and oxaliplatin (130 mg/m^2 every 21 days).

The patient's medical history was unremarkable with no history of hyperlipidemia, obesity or diabetes mellitus. Before the initiation of chemotherapy, the triglyceride serum level was 101 mg/dl (normal range 60-170 mg/dl), while the cholesterol level was 203 mg/dl (normal range 150-200 mg/dl). The patient's blood glucose was 97 mg/dl. After the second cycle of chemotherapy (January 2005), the lipid profile evaluation revealed elevation of triglycerides (1510 mg/dl) and total cholesterol levels (310 mg/dl), while glucose was normal (99 mg/dl). Changes in diet, weight gain, alcohol intake and other causes of acute hyperlipidemia were excluded. The patient was treated with atorvastatin (20 mg/day for 2 months) with subsequent rapid decreases of triglycerides and cholesterol to levels of 320 mg/dl and 150 mg/dl, respectively. Chemotherapy was continued and the patient's triglycerides remained under control during the following four cycles. The treatment was well tolerated without any other serious adverse events. However, due to disease progression, the patient started a second-line chemotherapy with irinotecan / 5-FU / leucovorin, in September 2005. Close monitoring of the lipid panel did not reveal any recurrence of hyperlipidemia. Moreover, the patient did not receive atorvastatin for lipid control after being taken off capecitabine.

Discussion

In this report, an association between capecitabine treatment and the development of significant hypertriglyceridemia, together with increase of the total cholesterol levels were described. Hypertriglyceridemia associated with this drug has rarely been reported. Recently, Kurt *et al.* described hypertriglyceridemia in two patients with slightly elevated baseline triglycerides following treatment with capecitabine (7). Moreover, earlier reports suggested that 5-FU might also interfere with lipid metabolism. A study investigating the effect of 5-FU on plasma lipid levels in patients and animals showed a significant reduction of the total plasma cholesterol in both patients and animals, while in animals the triglyceride levels were also reduced (8). Although capecitabine constitutes a pro-drug of 5-FU, our observations are in contrast with the above findings, suggesting an influence on lipid metabolism through different pathways.

In our patients, hypertriglyceridemia could mainly be attributed to the effect of capecitabine, which was the common component of the two different chemotherapeutic regimens. Moreover, other causes of acute elevation of triglyceride levels, such as dietary changes, weight gain, alcohol abuse and other medications were excluded in both patients. However, the presence of diabetes mellitus in the first case constituted a medical risk factor, since the diabetes was not well controlled. The appearance of hypertriglyceridemia in the second patient, a young, otherwise healthy, man without apparent causal risk, strongly suggested a connection with the drug capecitabine. Moreover, the development of hypertriglyceridemia in the first patient could also be related to her prolonged exposure to capecitabine, although the early appearance of the disorder in the second patient does not support this hypothesis.

The hyperlipidemia observed in our patients was of mixed type (high cholesterol and triglycerides), with a striking elevation of triglycerides to levels potentially precipitating acute pancreatitis. The well-known secondary causes of dyslipidemia were excluded on the basis of either patient history or laboratory tests. The fast and significant response to statins is also worth mentioning since it might shed light onto the mechanism of action of capecitabine in causing hyperlipidemia. It is well established that statins, as inhibitors of the rate-limiting enzyme of cholesterol biosynthesis (HMG CoA reductase), activate the transcription factors (notably

SREBP2) that control the expression of LDL receptors on hepatocyte cell membranes. At high doses, the rate of VLDL production by the liver may decrease and the rate of VLDL and chylomicron clearance by activating lipoprotein lipase may increase. Our patients probably developed mixed hyperlipidemia due to increased VLDL production by the liver. Alternatively, action at the periphery with increased production of free fatty acids, which serve as a substrate for VLDL production by the liver, is possible. Finally, the drug could interfere with lipoprotein lipase activity, causing interference with the clearance of triglyceride-rich lipoproteins (VLDL and chylomicrons) (9).

It is widely accepted that capecitabine is metabolized to 5-deoxy-5-fluorocytidine by carboxylesterase (expressed mainly in the liver), which is converted to 5-deoxy-5-fluorouridine by cytidine deaminase (principally located in the liver and tumor tissue), before its final conversion to 5-FU by thymidine phosphorylase (up-regulated in solid tumors) (2). The observed effect could be attributed either to capecitabine itself or to metabolites prior to the formation of 5-FU. Differences in the metabolism of capecitabine among people, or in the genetic susceptibility of the complicated molecular machinery that controls lipid metabolism, might account for the observed effects on lipid metabolism.

Although we are not able to provide a definitive explanation of the pathogenesis of capecitabine-induced dyslipidemia, our observations suggest that capecitabine might disrupt normal metabolic processes under certain circumstances. The development of hypertriglyceridemia in two patients in our institution raises concerns about the incidence and possible underestimation of similar events, considering that close monitoring of the lipid profile is not common practice for cancer patients treated with chemotherapy.

In conclusion, elevations of the triglyceride and cholesterol levels could be considered to be an additional, albeit rare, adverse event of capecitabine therapy. Since increases in the serum triglyceride levels can lead to severe consequences, such as acute pancreatitis, it is important to include the measurement of lipid concentration in patients being treated with capecitabine, particularly in those with dyslipidemia. The efficacy of capecitabine in breast and colorectal carcinoma is now well documented and, with the increasing use of this agent, it is important for physicians to be aware of possible dyslipidemia, particularly hypertriglyceridemia.

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Received January 30, 2006
Accepted March 30, 2006