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ORIGINAL ARTICLE

Uncontrolled hypertriglyceridemia induced by capecitabine: case report and review of the literature

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Abstract
Introduction Capecitabine, a prodrug of 5-fluorouracil (5-FU), is rarely associated with severe hypertriglyceridemia. We present a patient with severe capcitabine-induced hypertriglyceridemia, with the literature review.
Case report A 50-year-old woman with metastatic breast carcinoma was treated with oral capecitabine. She was also receiving bezafibrate due to hyperglycenemia. Pretreatment lipid profile revealed slight elevation of serum triglycerides and total cholesterol. A repeat lipid profile performed 5 weeks after the start of capecitabine treatment revealed a marked increase in the serum triglyceride and cholesterol levels. The dose of bezafibrate was increased, atorvastatin was added, and the next cycle of capecitabine was withheld. When the triglyceride and cholesterol levels had decreased, capecitabine was started with reduced dose. However, at the end of this cycle, the triglyceride and the cholesterol levels increased again.
Conclusion Monitoring of the lipid profile should be considered in cancer patients receiving capecitabine, particularly those with a known diagnosis of dyslipidemia.

Keywords Capecitabine · Hypertriglyceridemia · Cholesterol · Breast cancer

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Introduction

Capecitabine is a prodrug of 5-fluorouracil (5-FU), approved by the Food and Drug Administration for adjuvant treatment in colorectal cancer and in patients with metastatic colon, breast or gastric carcinoma. The recommended schedule is a daily dosage of 2,500 mg/m^2/day, given orally in two divided doses for 2 weeks followed by 1-week rest period [1]. According to the manufacturer's product information, Capecitabine is rarely (≥0.1 to <1%) associated with grade 3 or 4 hypertriglyceridemia, i.e., >5–10 or >10-fold increase in serum triglyceride (TG) levels above the upper normal limits [2]. A search of the literature revealed only four reported cases of capecitabine-induced hypertriglyceridemia [3, 4], all with a severe increase in serum TG level, i.e., >500 mg/dL [5].

We present another case of severe capecitabine-induced hypertriglyceridemia where hypertriglyceridemia developed in spite of concomitant therapy with a fibrate drug (bezafibrate) given due to pre-existing hyperlipidemia, requiring interruption of capecitabine.

Case report

A 50-year-old woman developed acute hypertriglyceridemia during capecitabine therapy given in January 2008. Her history included a diagnosis of stage IIA invasive carcinoma of the left breast 10 years earlier, treated with left lumpectomy and axillary lymph node dissection, followed by adjuvant therapy with cyclophosphamide, methotrexate, and 5-fluorouracil. Bilateral salpingo-oophorectomy was performed in October 1999 due to BRCA1 mutation. In November 2004, she was diagnosed with stage IIA invasive carcinoma of the right breast. This time she underwent

bilateral mastectomy and breast reconstruction. Adjuvant therapy at this time included doxorubicin with cyclophosphamide followed by paclitaxel and radiotherapy to the right axilla. Seven months before capecitabine treatment was initiated, metastatic spread to the right axillary, supraclavicular and cervical lymph nodes was noted. Her disease further progressed despite treatment with docetaxel and bevacizumab for 5 months, followed by letrozole for 2 months. Therefore, oral capecitabine (2,500 mg/m^2/day, in two divided doses given on days 1–14 every 3 weeks) was commenced. Whole body CT scan performed prior to the start of capecitabine did not reveal metastatic spread other than the above-mentioned nodal sites. She was in a good general condition (WHO performance status 1) and her BMI was 28.9. Complete blood count and routine serum chemistry studies including all liver functions and thyroid-stimulating hormone (TSH) tests were unremarkable.

Other medications included atenolol 25 mg daily for hypertension, ibuprofen 200 mg daily for painful metastatic lymph nodes, and bezafibrate 400 mg daily that had been given for 5 years due to hyperglycenemia. A lipid profile performed at the beginning of capecitabine therapy revealed a slight elevation of serum TG (337 mg/dL; normal range: 10–200) and total cholesterol (212 mg/dL: normal range 110–200). HDL cholesterol was 46 mg/dL (normal range: 35–120) and LDL cholesterol was not calculated due to the high level of TGs. She also had borderline diabetes, well controlled with diet.

A repeat lipid profile, performed 5 weeks after the start of capecitabine (i.e., at the end of the second cycle) revealed a marked increase in the TG serum level (3,090 mg/dL) and in the serum cholesterol level (691 mg/dL) (HDL cholesterol, 38 mg/dL). The dose of bezafibrate was increased to 800 mg/day and atorvastatin 20 mg daily was added, in addition to a low-fat diet, and the next cycle of capecitabine was withheld. Two weeks later, TG level decreased to 298 mg/dL and cholesterol to 310 mg/dL, and a third cycle of capecitabine was started with daily doses reduced to 75% of the original dose. However, at the end of this cycle (i.e., 2 weeks later), TG plasma level increased to 1,183 mg/dL and cholesterol level increased to 595 mg/dL (HDL 50 mg/dL).

Possible risk factors for acute hyperlipidemia, including changes in diet, weight gain, alcohol intake, and uncontrolled diabetes, were excluded. Because of the uncontrolled hyperlipidemia and also due to tumor progression, it was decided to stop the capecitabine. The same lipid lowering drug therapy was continued and anti-tumoral therapy with vinorelbine 25 mg/m^2 once a week was initiated.

After 4 weeks, TG serum level decreased to 218 mg/dL and cholesterol to 160 mg/dL.

Discussion

While the manufacturer mentions hypertriglyceridemia as a rare side effect of capecitabine, only nine cases of such a metabolic complication have been reported. Four cases were fully described, while the other five cases were reported as part of the evaluation of the side effects of capecitabine [6]. Table 1 summarizes the fully described cases and the present case. Included are three females and two males, aged between 45 and 73 years. All had metastatic disease (breast cancer in three, colorectal cancer in two). Severe hypertriglyceridemia (916–3090 mg/dL; 2.8–15.0-fold increase above baseline level) was documented after two treatment cycles of capecitabine (three cases), after five cycles and after seven cycles (one case each). Total cholesterol levels, when acute hypertriglyceridemia was reported in three cases (Nos. 3, 4, and 5), were increased in all (1.5-, 1.6-, and 3.3-fold of baseline, respectively).

Other possible causes for acute elevation of triglyceride levels were ruled out in all cases. A unique feature of the present case is that hypertriglyceridemia developed despite concomitant therapy with a fibrate, bezafibrate 400 mg/day that had been given due to pre-existing hyperlipidemia.

After the serum TG levels had been normalized, capecitabine therapy was renewed in all five patients with concomitant lipid-lowering therapy that included statins. In our patient, the dose of bezafibrate was increased and atrovastatin 20 mg/day was added. While the TG levels remained under control in one case (No. 4), during four subsequent cycles of capecitabine, a marked increase in the TG levels was again noticed in the remaining four patients. In the current case, capecitabine was stopped due to a striking increase in TG and cholesterol levels (1,183 and 595 mg/dL, respectively) observed 2 weeks after renewal of capecitabine.

Other than the reported cases, only scarce data regarding capecitabine-induced hypertriglyceridemia have been published. Kurt et al. [3] retrospectively analyzed the TG levels in 40 patients with breast cancer whose TG levels were measured before and after capecitabine administration; they found a significant increase in TG levels following a median number of six cycles. Stathopoulos et al. [6], who evaluated capecitabine as monotherapy in advanced breast and colorectal cancer, observed hypertriglyceridemia in 5 of the 12 patients whose TG levels were tested. A partial description of one of these cases is given, with a TG level of 1,100 mg/dl before capecitabine withdrawal; the other four cases are reported as having TG levels 3–4 times higher than normal. Since monitoring lipid profile is not routinely performed in cancer patients undergoing chemotherapy, the real incidence of TG level elevation due to capecitabine could be much higher than appreciated.

Table 1 Reported cases of severe hypertriglyceridemia induced by capecitabine

No. [Ref]	Age/gender	Metastatic malignancy	Capecitabine schedule	Baseline TG and total C/lipid lowering therapy	Time to severe hypertriglyceridemia	Serum level of TG and C (fold increase of baseline)
1 [3]	73/F	Breast	SD[a]	TG = 324/no	After 2 cycles	TG = 916 (2.83)
2 [3]	59/M	Colorectal	SD[a]	TG = 244/no	After 5 cycles	TG = 1,455 (5.96)
3 [4]	69/F	Breast	67% SD[a] + trastuzumab	TG = 219 (50–150), C = 239/no	After 7 cycles	TG = 1,409 (6.43) C = 363 (1.52)
4 [4]	45/M	Colorectal	67% SD[a] + oxaliplatin	TG = 101 (60–170), C = 203/no	After 2 cycles	TG = 1,510 (14.95) C = 320 (1.58)
5 [current]	50/F	Breast	SD[a]	TG = 337 (10–200), C = 212/yes	After 2 cycles	TG = 3,090 (9.17) C = 691 (3.26)

TG Triglycerides, *C* cholesterol

[a] SD = standard dose, i.e., 2,500 mg/m^2/day, in two divided doses given orally on days 1–14 every 3 weeks

Hypertriglyceridemia can lead to acute pancreatitis, which was reported as a rare side effect of capecitabine [7]. Although none of the five reported patients had clinical signs of acute pancreatitis, it is possible that capecitabine-induced hypertriglyceridemia could be complicated by pancreatitis.

The etiology of capecitabine-induced hypertriglyceridemia is unknown. Since hypertriglyceridemia has not been reported as a side effect of 5-fluorouracil, the observed effect of capecitabine could be attributed to capecitabine itself or to its metabolites prior to the formation of 5-fluorouracil. Differences in the metabolism of the drug or genetic susceptibility of lipid metabolism are probably the reason for the rarity of this adverse event.

In this context, it is worth mentioning other anti-cancer drugs. Tamoxifen causes a reduction in the activity of lipoprotein lipase and hepatic triglyceride lipase, the key enzymes of TG metabolism [8]. In new drugs, like the mammalian target of rapamycin (mTOR) inhibitors, hypertriglyceridemia is one of the common grade 3–4 adverse events [9]. The suspected mechanism is interference with TG metabolism by altering the insulin-signaling pathway, inducing increased secretion of VLDL [10]. Recently, a correlation between grade 3–4 hypertriglyceridemia and response to treatment with bexarotene, a retinoid X receptor-selective retinoid was found in non-small cell lung patients [11]. Probably due to the rarity of hypertriglyceridemia caused by capecitabine, the underlying mechanism was never studied.

Since an increase in serum TGs levels can be associated with severe consequences, including acute pancreatitis, clinicians should be aware of this potential complication of capecitabine. Monitoring the lipid profile should be considered in cancer patients receiving capecitabine, particularly in those with a known diagnosis of dyslipidemia, as was the current patient.

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