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Capecitabine-Induced Hypertriglyceridemia and Hyperglycemia: Two Cases

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Key Words
Capecitabine · Hypertriglyceridemia · Breast cancer · Colorectal cancer

Abstract
Capecitabine has shown significant antitumor activity against anthracycline/taxane refractory breast cancer and advanced colorectal carcinoma. The main drug-related adverse effects are palmar-plantar erythrodysesthesia (hand-foot syndrome), diarrhea and stomatitis. Dyslipidemia is a rare but important side effect of this drug. The mechanism of capecitabine-induced hypertriglyceridemia (CI-HTG) is unclear. It may be due to the decreased activities of lipoprotein lipase and hepatic triglyceride lipase. This report is associated with 2 patients who developed severe HTG when receiving capecitabine. Capecitabine was discountinued and antilipemic treatments were given and both cases are in follow-up with normal lipid levels. This report describes CI-HTG and possible pathogenetic mechanisms and the literature is reviewed.

Introduction

Capecitabine is a prodrug of 5-fluorouracil (5-FU) and its antitumor activity has been established in colorectal and breast cancers. The recommended treatment schedule is 2,500 mg/m^2/daily in 2 divided doses for 2 weeks followed by 1 week of rest [1].

Capecitabine is a well-tolerated drug but the main drug-related and dose limiting adverse-effects are palmar-plantar erythrodysesthesia (hand-foot syndrome), diarrhea and stomatitis. Hypertriglyceridemia (HTG) associated with capecitabine has been reported rarely [2]. The delayed onset of HTG supports a possible change in the expression of the enzymes responsible for the metabolism of triglycerides (TGs) such as lipoprotein lipase, hepatic TG lipase and apoproteins, especially apoprotein CII [3].

Here we reported on 2 patients with HTG related to capecitabine therapy.

Case Reports

Case 1

A 47-year-old woman with breast cancer presented with a mass on her right breast. Biopsy revealed invasive ductal carcinoma, grade III, T4N2M0, hormone-receptor-positive and human epidermal growth factor receptor-negative. After surgery, a 4-cycle dose-dense AC-paclitaxel (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 for 4 cycles every 14 days followed by paclitaxel 175 mg/m^2 for 4 cycles every 14 days with filgrastim support) regimen was performed. Radiation therapy and then tamoxifen were administered in the postopeartive period. Bone metastasis was detected 30 months after diagnosis. Zoledronic acid and aromatase inhibitor were started for meta-

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Table 1. Lipid and glucose profile of the cases before and after capecitabine and antilipemic treatment

Lipid and glucose levels mg/dl	Case 1			Case 2		
	before capecitabine	after capecitabine	after antilipemic treament	before capecitabine	after capecitabine	after antilipemic treament
Glucose	90	350	118	95	89	100
Cholesterol	208	678	121	204	212	185
Low-density lipoprotein	108	5	51	40	48	32
High-density lipoprotein	46	4,8	28	114	32	112
TG	270	9,063	207	251	657	202

static disease. One year later, progressive disease was detected and capecitabine (1,000 mg/m^2 twice daily for 14 days in 21 days) was prescribed. The lipid profile obtained at the beginning of chemotherapy was within normal limits. The patient had hypertension for 10 years but she had no history of diabetes mellitus or hyperlipidemia. Body mass index (BMI) was 23. At the 5th cycle of capecitabine treatment, the lipid profile was found to be disturbed. At the same time, the blood glucose level was found to be high. Due to the very high lipid and TG levels, lipid apheresis was performed. Diet, insulin and a lipid-lowering agent (gemfibrozil) were given. After these treatments, modalities i.e. the lipid profile and blood glucose levels returned to normal range. Table 1 shows the lipid and glucose levels before and after capecitabine. Capecitabine was stopped and there was no need to use lipid-lowering agents after that.

Case 2

A 48-year-old woman with breast cancer presented with a mass on her left breast. Biopsy revealed invasive ductal carcinoma, grade II, T2N2M0, hormone-receptor-positive, human epidermal growth factor receptor-negative disease. After surgery, a 4-cycle dose-dense AC-paclitaxel regimen was performed. Radiation therapy was given and aromatase inhibitor was prescribed postoperatively. Fourteen months after diagnosis, bone metastasis developed. Chemotherapy was instituted with oral capecitabine (1,000 mg/m^2 twice daily for 14 days in 21 days) and zoledronic acid. A lipid profile obtained at the beginning of chemotherapy was in normal range. The patient had a 5-year hypertension history. There was no history of diabetes mellitus or hyperlipidemia. BMI was 31. The lipid profile was found to be disturbed at the 8th cycle of capecitabine. The lipid profile can be seen in table 1. Diet and a lipid-lowering agent were given to the patient. The patient is in follow-up with a normal lipid profile and normal glucose levels.

Discussion

Causes of secondary HTG include uncontrolled diabetes mellitus, hypothyroidism, obesity and nephrotic syndrome. Several drugs can also induce an increase in TG levels. These drugs are beta-blockers, glucocorticoids, thiazides, estrogen, antipsychotics and bile acid-binding resins as well as drugs used in oncology cases. Among drugs prescribed for malignant diseases, tamoxifen, protease and mTOR inhibitors, some immunosuppressants, interferon, L-asparaginase and bexarotene can cause lipid disturbances [4]. According to the manufacturer's product information [5], capecitabine is rarely (0.1–1%) associated with grade 3 (5- to 10-fold) or 4 (10-fold increase above the upper normal limit) elevation in serum TG. Acute pancreatitis, as the complication of high triglycerides, has been reported as a side effect of capecitabine [6, 7].

Capecitabine is a cytotoxic drug with acceptable toxicity. The main drug-related adverse effects are palmar-plantar erythrodysesthesia (hand-foot syndrome), diarrhea and stomatitis. Capecitabine-induced (CI)-HTG has been reported rarely [2]. Some reports suggested that 5-FU may interfere with lipid metabolism. A study investigating the effect of 5-FU on plasma lipid levels in patients and in animals showed a significant reduction of the total plasma cholestero and a decrease in TG levels in animals [8]. Although cholesterol constitutes a prodrug of 5-FU, recent reports suggest an influence on lipid metabolism through different pathways and that capecitabine may cause HTG [2, 3, 7–10]. Table 2 shows the reports about the capecitabine-associated dyslipidemia [2, 3, 7, 9–14]. When we looked at the literature findings, we found disruptions in the lipid profile, especially in TG, in 4 cases with breast cancer and in 12 with colorectal cancer [2, 3, 7, 9–13]. Five other cancer cases, but not the origin of the cancer have been reported [11, 14]. The comorbid conditions were diabetes mellitus in 4 cases [2, 11, 12], obesity in 2 [2, 14], hypertension in 2 [3, 11], dyslipidemia in 1 [11] and a genetic

Table 2. CI-HTG patient profiles from literature

First author [ref.]	No of cases	Age/ Gender	Diagnosis	Comorbid disease	TG1[1]	TG2[2]	Cycle No.[3]	Treatment
Koutras [2]	2	69/F	breast cancer	mild obesity, DM	219	1,409	7	omega-3 fatty acid, simvastatin
		45/M	colorectal cancer	–	101	1,510	2	atorvastatin
Kurt [3]	2	73	breast cancer	HT	324	916	7	atorvastatin
		59	colorectal cancer	–	244	1,455	5	atorvastatin
Bar-Sela [12]	1	50	breast cancer	DM	337	3,090	2	bezafibrate, atorvastatin
Garg [13]	1	56	colorectal cancer	–	5,3 mmol/l[a]	41 mmol/l[a]	7	fenofibrate
Orphanos [7]	1	57/F	colorectal cancer	–	89[b]	891	6	omega-3 fatty acid, bezafibrate
Seminara [14]	38[c]/4	n.g.	n.g.	–	130	1,515	6	details n.g.
		n.g.	n.g.	BMI >28	145	3,060	2	
		n.g.	n.g.	–	115	276	n.g.	
		n.g.	n.g.	–	107	280	n.g.	
Michie [11]	212/8[d]	54 (range 44–69)	7 colorectal, 1 unknown primary site	2 DM, 1 HT 1 dyslipidemia	–	31 mmol/l[a]	n.g.	fenofibrate
Javot [10]	1	50/F	breast cancer	–	12 mmol/l[e]	26 mmol/l	6	rosuvastatin, fenofibrate
Polinder-Bos [9]	1	52/M	colorectal cancer	genetic disorder of lipid metabolism		138 mmol/l	3	gemfibrozil

DM = Diabetes mellitus; HT = hypertension; n.g. = not given.

[1] Before capecitabine; [2] after capecitabine; [3] capecitabine-induced dyslipidemia cycle.

[a] Conversion from mmol/l to mg/dl: mg/dl = 88,57 × mmol/l.

[b] Pretreatment level of TG levels were not measured. This is the level before 1 year after treatment.

[c] The study included 38 patients [median age: 68 (34–81) years, 24 female, 11 male, 22 breast cancer, 10 colorectal cancer, 6 gastric cancer, 6 type II DM and 11 with a family history of lipidic disorders].

[d] From 304 colon carcinoma cases treated with capecitabine, 212 patients were screened and 8 (3,7%) developed significant HTG, 2 of 8 patients had DM and 1 had preexisting dyslipidemia. Treatment: capecitabine was discontinued and lipid-lowering agents were administered. The highest level of TG was approximately 31 mmol/l.

[e] Approximately 3 months before the beginning of treatment.

disorder of lipid metabolism in 1 [9]. In 8 cases, there was no underlying comorbid condition [2, 3, 7, 10, 13, 14]. CI-HTG occurred between the 2nd and the 8th cycle of capecitabine treatment and most of the patients were treated with statins or fibrates [2, 3, 7, 9–14]. In most of the cases, capecitabine was stopped due to high TG levels. In both of our cases there was a history of hypertension. We stopped the capecitabine and started antilipemic treatment. In our first case, the TG level was very high and lipid apheresis was performed; we did not find similar cases requiring aggressive treatment for CI-HTG.

The etiology of CI-HTG is basically unknown. 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 (essentially located

in the liver and tumor tissue), before its final conversion to 5-FU by thymidine phosphorylase (upregulated in solid tumors). This effect may be attributed either to capecitabine itself or to metabolites prior to the formation of 5-FU [15]. Differences in the metabolism of capecitabine or the genetic susceptibility of the complicated molecular machinery regulating lipid metabolism may be the cause of disturbances in lipid metabolism [2]. Hereditary lipoprotein lipase deficiency due to genetic polymorphisms or a drug-enzyme interaction may be the underlying pathogenic mechanism. Alterations in the lipid profile and glucose levels observed in some patients raises the suspicion that these abnormalities may represent part of the metabolic syndrome. Besides, it is possible that high levels of TG caused low-grade undetected pancreatic inflammation and this inflammation may be the cause of overt diabetes and HTG [13]. This adverse event was seen in the later cycles of capecitabine use in both of our cases. It seems that HTG is a chronic adverse effect of capecitabine treatment. The delayed onset of HTG also supports a possible change in the expression of the enzymes responsible for the metabolism of TG, including lipoprotein lipase, hepatic TG lipase, and apoprotein CII [12]. In our first case, hyperglycemia was detected simultaneously with HTG. This mechanism can be speculated on as the cause of this adverse event, but the exact mechanism is not clear enough.

In the case of CI-HTG, the treatment choices are the discontinuation of capecitabine and the use of lipid-lowering agents such as fenofibrate, gemfibrozil, statins and fish oil [2, 3, 7–14]. Our first case was treated with lipid apheresis due to the very high level of TG, with the result that pancreatitis could be prevented probably before overt disease occurred.

Conclusion

This report represents an underdiagnosed side effect of capecitabine. Diabetes and HTG have serious acute and chronic metabolic complications and patients receiving capecitabine therapy should undergo regular monitoring of lipid and glucose levels.

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