Case Report

Capecitabine-induced hypertriglyceridemia: a rare but clinically relevant treatment-related adverse event

An Uche[1], Ritika Vankina[1], Jun Gong[1,2], May Cho[3], James J. Yeh[1,4], Phyllis Kim[1,4], Kathy Pan[1,4]

[1]Division of Medical Oncology and Hematology, Department of Medicine, Harbor-UCLA Medical Center, Torrance, CA, USA; [2]Division of Hematology/Oncology, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [3]Division of Hematology and Oncology, Department of Internal Medicine, UC Davis Comprehensive Cancer Center, Sacramento, CA, USA; [4]Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA

Correspondence to: Kathy Pan, MD. Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, 1000 W Carson Street, Bldg N16, Torrance, CA 90509, USA. Email: kathy.pan@labiomed.org.

Abstract: Capecitabine-induced hypertriglyceridemia (CIHT) represents an increasingly significant treatment-related adverse event from capecitabine given its potential for both acute complications (acute pancreatitis) and chronic metabolic complications (cardiovascular disease). The incidence of CIHT is relatively rare and the majority of cases thus far reported have been managed with lipid-lowering therapy and/or discontinuation of capecitabine followed by resumption of the drug upon normalization of triglyceride levels. We present among the first U.S. cases of CIHT to be reported in the published literature and highlight management approaches for this rare but clinically relevant adverse event. Further understanding of the mechanisms of CIHT and its long-term adverse effects as well as effective preventive strategies, interventions, and monitoring strategies are prudent given the widespread and often prolonged use of capecitabine-based chemotherapy in gastrointestinal and other cancers.

Keywords: Capecitabine; hypertriglyceridemia; adverse event (AE); colorectal cancer; breast cancer

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Introduction

Capecitabine (XELODA®) is an oral prodrug of 5'-deoxy-5-fluorouridine that is converted to 5-fluorouracil (5-FU) *in vivo*. It was originally approved by the U.S. Food and Drug Administration (FDA) on April 30, 1998 as monotherapy for metastatic breast cancer (MBC) resistant to both paclitaxel- and anthracycline-based chemotherapy (1). Since then, capecitabine has received additional indications as monotherapy in metastatic colorectal cancer (mCRC), adjuvant colon cancer, and in combination with docetaxel in MBC (2). The most frequently reported grade ≥3 treatment-related adverse events (AEs) of capecitabine in ≥1% of patients include diarrhea, hand-foot syndrome, hyperbilirubinemia, and lymphopenia (2). The incidence of capecitabine-induced hypertriglyceridemia (CIHT) is much rarer, while acute pancreatitis, the most feared complication of hypertriglyceridemia (HT), more likely occurs when serum triglyceride levels exceed 1,000 mg/dL (3). As patients are often treated with capecitabine for extended periods, chronic HT may increase the risk for cardiovascular disease (4). Management strategies for CIHT are unclear but needed. In this report, we present a case series of mCRC patients with CIHT and our management approaches to this rare but clinically relevant AE.

Case presentation

Case 1

A 54-year-old male with recurrent and metastatic rectal adenocarcinoma to the bilateral lungs was treated with first-line capecitabine [850 mg/m^2 twice daily (BID) for 14 days every 21 days], oxaliplatin [130 mg/m^2 intravenous (IV over 2 hours on day 1 every 3 weeks)], and bevacizumab (7.5 mg/kg IV on day 1 every 3 weeks). He had previously

been treated with six months of perioperative therapy comprised of neoadjuvant chemoradiation with capecitabine (825 mg/m^2 BID on days of radiation) and adjuvant capecitabine and oxaliplatin (XELOX) for locally advanced disease. The patient was transitioned to capecitabine and bevacizumab after five cycles of XELOX-bevacizumab due to neuropathy. Before cycle 6, the patient was found to have a triglyceride level of 3,783 mg/dL and chemotherapy was held for this asymptomatic, grade 4 HT. Fifteen days later, the triglyceride level decreased to 259 mg/dL, and capecitabine and bevacizumab was resumed. After cycle 10, triglyceride level rose to 2,765 mg/dL prompting withholding of capecitabine for one week, and the subsequent repeat level was 822 mg/dL. The patient was prescribed fenofibrate 145 mg daily and resumed capecitabine. His subsequent triglyceride levels have remained between 187–279 mg/dL (grade 1) on monthly laboratory monitoring.

Case 2

A 71-year-old man with history of type 2 diabetes mellitus who was diagnosed with mCRC to the liver was treated with single-agent capecitabine (1,000 mg/m^2 BID for 14 days every 21 days). After cycle 3, a computed tomography (CT) scan of the chest, abdomen, and pelvis was obtained due to rising carcinoembryonic antigen (CEA) levels; this showed progression of disease (PD) with liver metastases. Therapy was changed to capecitabine (850 mg/m^2 BID for 14 days every 21 days), oxaliplatin, and bevacizumab. A lipid panel obtained prior to initiation of XELOX-bevacizumab revealed a triglyceride level of 164 mg/dL. After 3 cycles of XELOX-bevacizumab (6 cycles total of capecitabine), a repeat lipid panel was obtained and showed a triglyceride level of 866 mg/dL. Chemotherapy was held and patient began gemfibrozil 600 mg daily. Serial lipid panels obtained 1 and 2 weeks after showed triglyceride levels of 580 mg/dL and 214 mg/dL, respectively. The patient was asymptomatic during this entire period of grade 3 CIHT. He subsequently resumed XELOX-bevacizumab and remains on gemfibrozil 600 mg daily with triglyceride levels that are currently near-normal on monthly monitoring.

Case 3

A 57-year-old man with recurrent, mCRC to the liver was treated with 6 cycles of XELOX-bevacizumab (capecitabine 850 mg/m^2 BID for 14 days every 21 days) followed by maintenance single-agent capecitabine for nearly 3 years when repeat imaging showed complete response with resolution of liver lesions. Patient subsequently elected for a chemotherapy holiday. Two years later, he developed a local recurrence on surveillance colonoscopy and underwent surgery with a permanent colostomy followed by adjuvant chemoradiation with capecitabine. Four years later, he developed unresectable pulmonary metastases for which he resumed single-agent capecitabine 850 mg/m^2 BID for 14 days every 21 days. After 2 cycles, the patient developed grade 2 HT (triglyceride level of 442 mg/dL). Capecitabine was held and patient began gemfibrozil 600 mg daily. His triglyceride levels peaked at 448 mg/dL. Three months after holding capecitabine and initiating fibrate therapy, this decreased to 225 mg/dL. The patient resumed capecitabine, and he is continuing chemotherapy with gemfibrozil with stable triglyceride levels in the mid-200s.

Discussion

The incidence of treatment-related grade 3–4 HT has been reported to be 0.1–0.2% in the U.S. FDA package inserts for capecitabine as monotherapy or as part of combination therapy (1,2). The relative rarity of CIHT has often resulted in the lack of reporting for this AE in large phase III trials (5). To the best of our knowledge, we are presenting the first U.S. cases of CIHT described in the published literature. There are increasing cases of grade ≥3 CIHT being reported elsewhere around the world (*Table 1*) in patients treated for MBC and mCRC with (6,8,9,11-15) and without preexisting obesity, hyperlipidemia, or diabetes (6,7,10,14,16,17). In many cases, CIHT is accompanied by mixed disturbances of the metabolic profile including: increased very-low-density lipoprotein (VLDL), increased total cholesterol (TC), increased or decreased low-density lipoprotein (LDL), increased or decreased high-density lipoprotein (HDL), increased blood glucose or glycated hemoglobin (HbA1c), or increased lipemic index, when compared to baseline (6-9,11-14,17). The dose-dependency of CIHT remains unclear as it has been shown to develop across a range of capecitabine doses, as monotherapy or as part of combination regimens, and as early as after 2 cycles or as delayed as 12 cycles of therapy (*Table 1*).

Larger clinical studies outside of the U.S. have provided further understanding that CIHT represents an AE that may not be as rare as once thought (*Table 2*). For example, one retrospective study reported an incidence of CIHT

Table 1 Available case reports/series of capecitabine-induced hypertriglyceridemia (grade ≥3)

Country/ location (n)	Dose/regimen	Baseline-peak	Treatment	Symptoms, post-tx levels, continued C?	Ref.
Greece [2]	1,000 mg/m^2 BID ×14 d Q21d + trastuzumab 6 mg/kg Q21d	TG 219→1,409 mg/dL (after 7 cycles)	Hold C, simvastatin 20 mg/d, omega-3 3 g/d	None, TG 129 mg/dL after 1-month LLT, yes	(6)
	1,000 mg/m^2 BID ×14 d Q21d + oxaliplatin 130 mg/m^2 Q21d	TC 239→363 mg/dL	Hold C, atorvastatin 20 mg/dc	None, TG 320 mg/dL after 2 months LLT, yes	
		TG 101→1,510 mg/dL (after 2 cycles)			
		TC 203→310 mg/dL			
Turkey [2]	1,250 mg/m^2 BID ×14 d Q21d	TG 324→1,782 mg/dL (after 7 cycles)	Hold C, atorvastatin 20 mg/d	None, TG 118 mg/dL after 8 weeks LLT, no due to PD	(7)
	1,250 mg/m^2 BID ×14 d Q21d	TG 244→1,445 mg/dL (after 5 cycles)	Atorvastatin 20 mg/d	None, TG 154 mg/dL 11 weeks after cycle 10, no due to PD	
Israel [1]	2,500 mg/m^2 BID ×14 d Q21d	TG 337→3,090 mg/dL (after 2 cycles)	Hold C, bezafibrate increased from 400 to 800 mg/d, atorvastatin 20 mg/d	None, TG 298 mg/dL and TC 310 mg/dL after 2 weeks LLT, yes with DR 25% but after cycle 3 discontinued due to grade 3 HT	(8)
		TC 212→691 mg/dL			
United Kingdom [1]	Monotherapy, dose NR	TG 5.3 mmol/L→ 41 mmol/L	Hold C, fenofibrate 160 mg/d, metformin	Polydipsia, polyuria, and weakness, TG 2.36 mmol/L and TC 3.5 mmol/L after 1-week LLT, HbA1C 6.4% after 6 months metformin	(9)
		TC 5.4→11.6 mmol/L			
		HbA1C 5.9→9.7% (after 6 cycles)			
Cyprus [1]	Adjuvant 1,250 mg/m^2 BID ×14 d Q21d for 8 cycles	TG 89→891 mg/dL (after 6 cycles)	Omega-3 3 g/d→ bezafibrate 400 mg BID	None, TG 152 mg/dL 1 month after cycle 8, yes	(10)
Turkey [1]	1,250 mg/m^2 BID ×14 d Q21d + oxaliplatin 130 mg/m^2 Q21d	TG 120→1,768 mg/dL (after 8 cycles)	Hold C, gemfibrozil 1,200 mg/d (lipopheresis was performed after TG rose to 4,115 mg/dL with a 2nd fluoropyrimidine)	Fatigue, TG 149 mg/dL after 5 weeks LLT, no due to PD	(11)
		TC 229→497 mg/dL			
France [1]	Dose NR + bevacizumab (dose NR)	TG 2.51→26.77 mmol/L (after 6 cycles)	Fenofibrate (dose NR)	None, TG 6.26 mmol/L after 1-week LLT, no due to PD	(12)
		TC 6.68→ 8.75 mmol/L			
Hong Kong [1]	1,500 mg/m^2 BID ×14 d Q21d	No baseline TG→ 111.2 mmol/L (after 5 cycles)	Hold C, gemfibrozil (dose NR), plasmapheresis ×2	Pancreatitis and septic shock, lipemic index normalized after plasmapheresis, TG normal 2 months after discontinuation of LLT, no	(13)
Turkey [2]	1,000 mg/m^2 BID ×14 d Q21d	TG 270→9,063 mg/dL (after 5 cycles)	Lipid pheresis, gemfibrozil (dose NR)	None, 207 mg/dL after LLT, no	(14)
	1,000 mg/m^2 BID ×14 d Q21d	TG 251→657 mg/dL (after 8 cycles)	LLT (agent and dose NR)	None, 202 mg/dL after LLT, NR if C resumed	
Netherlands [1]	Dose NR + oxaliplatin (dose NR)	No baseline TG→138 mmol/L (after 3 cycles)	Hold C, gemfibrozil (dose NR)	None, TG normalized but details NR	(15)

Table 1 (*continued*)

Table 1 (*continued*)

Country/ location (n)	Dose/regimen	Baseline-peak	Treatment	Symptoms, post-tx levels, continued C?	Ref.
Lebanon [1]	1,250 mg/m^2 BID ×14 d Q21d	No baseline TG→ 2,322 mg/dL (after 9 months therapy)	Fenofibrate 200 mg/d	None, TG 312 mg/dL after 1-month LLT, yes	(16)
China [2]	1,000 mg/m^2 BID ×14 d Q21d + oxaliplatin 130 mg/m^2 Q21d	Normal baseline TG→ 2.47 mmol/L (after 2 cycles)	Hold C	None, 1.45 mmol/L 2 months after discontinuation, no	(17)
	1,000 mg/m^2 BID ×14 d Q21d + oxaliplatin 130 mg/m^2 Q21d	Normal baseline TC→6.93 mmol/L	DR C 25%, hold oxaliplatin	None, TG normalized within 2 months dose modification, yes	
		Normal baseline TG→2.41 mmol/L (after 6 cycles)			
		Normal baseline TC→7.73 mmol/L			

C, capecitabine; BID, twice daily; TG, triglycerides; TC, total cholesterol; LLT, lipid-lowering therapy; PD, progressive disease; DR, dose-reduced; NR, not reported; HbA1c, hemoglobin A1c; tx, treatment.

as high as 10% in treated patients, while another reported an incidence of grade ≥3 CIHT in 4% (20,22). Median triglyceride levels and average TC levels have been shown to increase over time in capecitabine-treated patients, and more so in those with preexisting diabetes or lipid disorders (23). In patients treated with capecitabine as monotherapy or as part of combination therapy, the median time to development of grade ≥2 CIHT was 79 days (range, 16–243 days) (22). Reassuringly, the overwhelming majority of CIHT cases are asymptomatic with only a few cases resulting in clinically significant manifestations such as acute pancreatitis (*Tables 1*,*2*).

The mechanisms by which CIHT develops remain unclear. Several reports have postulated that HT is induced by capecitabine itself or its generated metabolites prior to formation of 5-fluorouracil by thymidine phosphorylase (8,18,19,22,23). Enzymatic interference by capecitabine of lipid metabolism pathways involving lipoprotein lipase (LPL), hepatic triglyceride lipase, and apoproteins has also been described as a potential mechanism of HT, suggesting that CIHT may be more prevalent in individuals with susceptible genetic polymorphisms resulting in differential drug metabolism or hereditary defects in lipid metabolism such as inherited LPL deficiency (6-8,11,18,22,23). Impaired activity of LPL results in accumulation of chylomicrons and VLDL, whereas statins activate LPL and increase clearance of such triglyceride-rich lipoproteins, providing a basis for the often rapid and significant responses of CIHT to statin therapy (6,22). Notably, a LPL defect can also occur with increases in its inhibitor, apolipoprotein CIII, and/or decreases in its activator, apolipoprotein CII, although the relationship between capecitabine and apolipoprotein CII/CIII levels has yet to be formally explored (12,22,23). In one report of CIHT, tests for apolipoprotein B and LPL activity were normal while genetic disorders of lipid metabolism including apolipoprotein CII deficiency and familial dysbetalipoproteinemia (apolipoprotein E genotype was E3/E3) were excluded during the work-up (15).

The FDA package insert for capecitabine does not provide specific dosing and management guidelines for CIHT. In general, for grade 2 treatment-related AEs it is recommended to hold the drug until resolution of the AE to grade 0–1 and resume the drug at 100% of the starting dose (for first occurrences), 25–50% of the starting dose (for second and third occurrences), or discontinue the drug (for the fourth occurrence) (1,2). For grade 3 AEs, it is also recommended to hold capecitabine until resolution of the AE to grade 0–1 and resume at 75% (if first occurrence) or 50% of the starting dose (if second occurrence); if a grade 3 AE occurs for the third time, it is recommended to discontinue capecitabine. For grade 4 AEs, it is recommended to discontinue or hold capecitabine until resolution of the AE to grade 0–1 followed by a dose reduction to 50% of the starting dose.

Table 2 Retrospective/clinical studies of capecitabine-induced hypertriglyceridemia

Country/ location (n)	n (tumor subtypes)	Dose/regimen	Findings	Ref.
Greece	5/42 (24 breast, 17 colon, and 1 pancreatic)	1,200 mg/m^2 BID ×14 d Q21d	1 breast cancer patient: baseline TG 150→1,100 mg/dL within 6 months, TG 200 mg/dL after holding C for 6 weeks 4 remaining patients: TG increased 3–4× normal	(18)
United Kingdom	8/110 (all colorectal)	XELOX (dose NR)	Comorbidities: 1 with lipid disorder, 2 with diabetes In all but 1 case, TG normalized with continuing C and fenofibrate 267 mg daily and sustained at 3-month follow-up, 3 patients remained on fenofibrate, 5 discontinued after 3 months with normal TG 1 patient had cerebral infarction after cycle 2 (baseline TG 10.25→16.6 mmol/L since starting XELOX) No cases of acute pancreatitis	(19)
Italy	4/38 (22 breast, 10 colorectal, and 6 gastric cancer)	NR	Comorbidities: 11 patients with lipid disorder, 6 with DM2 In 2 patients: TG 107–145→280–3,060 mg/dL after 2 or 6 cycles of C In remaining 2 patients: TG increased to 2.4 and 2.61 times baseline after treatment with C In all cases, CIHT was reversible by holding C ± LLT	(20)
Israel	54 (all breast)	47 monotherapy, 7 with lapatinib (dose NR)	Comorbidities: Mean BMI 27.8±5.3, 16 patients with lipid disorder, 7 with diabetes Mean baseline TG 165±100 mg/dL and mean baseline TC 212±49 mg/dL 22/54 had >20% increase in TG post-treatment *vs*. pre-treatment 16/54 had >20% decrease in TG post-treatment *vs*. pre-treatment Only concurrent lapatinib was predictive for CIHT (P=0.01)	(21)
Israel	102 (72 colorectal, 20 breast, and 10 upper GI)	40 monotherapy, 24 XELOX, 10 XELOX-bevacizumab, 28 others (dose NR)	Comorbidities: 59 patients with BMI 25.0–34.9, 45 with lipid disorder, 25 with diabetes, 14 with IHD, 13 with BMI ≥35 Grade ≥2 CIHT in 19 patients (19%), median time to development of grade ≥2 CIHT was 79 days (range, 16–243 days) Grade ≥3 CIHT in 4 patients (4%): 1 patient with TG 272→2,041 mg/dL after 3 cycles of C 2,000 mg/m^2 BID ×14 d Q21d (died 4 days after latest TG test from PE) Average increase of 92.97±213.0 mg/dL from baseline TG with C treatment (P<0.001) Only IHD was risk factor for grade ≥3 CIHT (P=0.02)	(22)
Turkey	57 (37 breast, 9 colorectal, and 13 other)	20 monotherapy, 37 in combination therapy (dose NR)	Comorbidities: 21 patients with lipid disorder, 13 with diabetes After 5 treatment cycles: ❖ Median TG increased from 170 (range, 69–657) mg/dL to 321 (range, 228–871) mg/dL and average TC; ❖ Increased from 187.7±50.0 to 242.3±52.7 mg/dL (P<0.01); ❖ Median TG increased from 187.5 to 668.5 mg/dL (with diabetes) *vs.* median TG increased from 161.5 to 292.0 mg/dL (without diabetes); ❖ Median TG increased from 223 to 466 mg/DL (with lipid disorder) *vs.* median TG increased from 137 to 292 mg/dL (without lipid disorder)	(23)

BID, twice daily; CIHT, capecitabine-induced hypertriglyceridemia; TG, triglycerides; C, capecitabine; XELOX, capecitabine and oxaliplatin; NR, not reported; DM2, type 2 diabetes mellitus; LLT, lipid-lowering therapy; BMI, body mass index; TC, total cholesterol; GI, gastrointestinal; IHD, ischemic heart disease; PE, pulmonary embolism.

Discontinuation of capecitabine results in reduction of triglyceride levels, although increases in triglycerides after resumption of capecitabine have been observed (7). Aside from holding capecitabine and awaiting normalization of triglycerides prior to restarting the drug as recommended by the FDA dosing guidelines, a growing body of evidence supports that dietary modification and addition of lipid-lowering therapy are effective in mitigating CIHT and allowing timely resumption of capecitabine (*Tables 1,2*). Fibrates are often the preferred first-line treatment in patients with severe HT (24). Omega-3 fatty acids and niacin are also useful agents in HT, whereas statins at high doses exhibit significant hypotriglyceridemic activity.

Indeed, a recent prospective United Kingdom study on CIHT implemented a protocol when CIHT was detected; this entailed referral to the general practitioner (or metabolic disease team for severe HT) and initiation of first-line fenofibrate 267 mg daily for triglyceride levels >5 mmol/L while continuing capecitabine (19). This important study demonstrated the feasibility of treating CIHT while continuing capecitabine without any significant clinical consequences detected.

Notably, other reports have shown that when capecitabine is not withheld, resistance of HT to lipid-lowering therapy may develop (10). In patients with preexisting hyperlipidemia, resistance to lipid-lowering therapy has similarly been observed (8). In mild cases of CIHT, dose reduction of capecitabine without lipid-lowering therapy may be sufficient enough to reverse CIHT (17). In resistant cases of CIHT, increasing the fibrate dose and/or addition of a statin may be needed to resolve the AE (8). At our institution, we have favored the practice of holding capecitabine and initiating fibrate therapy for grade ≥2 CIHT, which has resulted in normalization of HT in our series of patients and allowed timely and safe resumption of an important chemotherapeutic agent in the treatment paradigm of our cancer patients.

We are in agreement with the recommendations of several groups for the regular monitoring of lipid profiles in patients treated with capecitabine, particularly in those with risk factors for cardiovascular disease, including dyslipidemia, diabetes, hypertension, obesity, and coronary heart disease (8,11,12,18,20-23). Others groups have mandated checking of a lipid panel before initiation of capecitabine or other 5-fluorouracil prodrugs (12). Importantly, preexisting lipid disorder and diabetes mellitus have increasingly been shown to be risk factors for development of clinically significant HT from capecitabine (21,23). In patients at risk, it is reasonable to perform a baseline lipid survey prior to initiation of capecitabine therapy or at the least by cycle 2 or 3 of capecitabine to allow early intervention (19,22). In the United Kingdom, one protocol necessitated fasting serum lipids pre-chemotherapy, at cycle 3 or 4 of capecitabine, and before the final cycle with initiation of lipid-lowering therapy and healthcare referrals when CIHT was detected (19). Persistently abnormal levels were monitored for up to 3 months after chemotherapy, or more often as indicated, and fenofibrate was discontinued 3 months after the end of chemotherapy if HT normalized with further repeat lipid profiling 3 months after discontinuation of fenofibrate. It is worthwhile to mention that the authors concluded that continuous routine lipid screening of all patients on capecitabine-containing chemotherapy is not justified, and an agreed upon management plan between physician and patient should be reached when CIHT is detected.

In conclusion, CIHT is an increasingly recognized treatment-related AE of capecitabine with potentially significant acute and chronic metabolic complications. Most cases of CIHT are asymptomatic and can be resolved with lipid-lowering therapy and/or holding of the drug with resumption following improvement in triglyceride levels. Given the widespread and more prolonged use of capecitabine-containing chemotherapy across a spectrum of cancers, further understanding of the mechanisms of CIHT, its long-term effects on outcome, preventative strategies, effective interventions, monitoring practices are warranted.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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