Capecitabine-Induced Hypertriglyceridemia (CIHT): Case Report of an Unsuspected and Misunderstood Adverse Event!

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Abstract

Severe adverse events with both 5-Fluorouracile (5-FU) and capecitabine, one of its prodrugs, have been extensively studied and primarily related to a partial or complete Dihydropyrimidine Dehydrogenase (DPD) deficiency. However, rare and atypical side effects such as hypertriglyceridemia might still occur in the absence of DPD deficiency. We report the case of a 61-year-old woman with early-stage triple negative breast cancer treated with adjuvant capecitabine. While having no phenotypic DPD deficiency, she developed severe Capecitabine-Induced Hypertriglyceridemia (CIHT, 49 g/L) after four treatment cycles at a reduced dose (1000 mg/m^2). Notably, the patient experienced only grade I hand-foot syndrome at initiation with no other capecitabine-associated toxicities. CIHT spontaneously resolved after interrupting treatment with no relapse and no further treatment. We suggest that Carboxylesterase (CES1), an enzyme involved in both capecitabine and lipid metabolism, might contribute to such toxicity. Further studies are required to validate this hypothesis.

Keywords: Capecitabine • 5FU • Hypertriglyceridemia • Case report

Introduction

Capecitabine (CAP) is an oral antimetabolite chemotherapy and a prodrug of active cytotoxic 5-Fluorouracil (5-FU). Current guidelines recommend the use of CAP primarily in digestive cancers (colorectal, pancreatic). CAP is also a key drug in treating metastatic breast cancers. Prior to indications of the KEYNOTE-522 study, adjuvant CAP was recommended in case of residual disease for patients with high-risk early-stage triple-negative breast cancer [1].

Given the potential fatal adverse events in case of total and/or partial Dihydropyrimidine Dehydrogenase (DPD) deficiency, phenotypic screening is necessary before initiating CAP [2]. In France, this screening has been mandatory since 2019, setting plasma uracilemia at a 16 ng/mL threshold to discriminate partial (between 16 ng/ml and 150 ng/ml) from complete DPD deficiency (above 150 ng/ml) [3].

Although involved in the same therapeutic pathway, CAP and 5-FU have distinct tolerance profiles [4]. CAP metabolization involves additional enzymatic steps, catalyzed among others by Carboxylesterase (CES), Cytidine Deaminase (CD) and Thymidine Phosphorylase (TYMS) [5].

Intravenous 5-FU is metabolized independently of these three enzymes. Nevertheless, each of them may theoretically be associated with specific CAP toxicities. Aside from classic toxicities associated with CAP such as hand-foot syndrome, mucositis, diarrhea and cytopenia, atypical and rarer adverse events are also possible such as Capecitabine-Induced Hypertriglyceridemia (CIHT) [6]. This unusual complication is rarely described with intravenous 5-FU therapy and might be under-diagnosed in the absence of systematic lipid monitoring during CAP therapy. To the best of our knowledge, this rare adverse event has been scarcely studied, and no biological explanation has thus far been proposed. We present the case of a patient who developed severe biological CIHT on CAP therapy and discuss the possible involvement of carboxylesterase polymorphism, offering insight to understand and prevent this possibly not-so-rare and potentially dangerous adverse event.

Case Presentation

A non-Caucasian 61-year-old woman, diagnosed in early 2022 with a localized grade III triple negative ductal invasive breast carcinoma, had no germline BRCA pathogenic variant. Her medical history included mainly ulcerative colitis, hypothyroidism, and cutaneous psoriasis, with no evidence of diabetes melitus, obesity, dyslipidemia or endocrine disorders. Given her auto-immune background, she first received neoadjuvant chemotherapy without immune checkpoint inhibitors. Conservative breast surgery with axillary dissection was performed on December 2022. Pathological response was good quality (ypTis ypN1mi, or residual cancer burden class-I) but incomplete, indicating adjuvant CAP therapy1. DPD deficiency screening reported non-elevated uracil plasma concentration (12.5 ng/mL, below the 16 ng/mL threshold) and a normal UH2/U ratio (9.4, where a pathological UH2/U ratio is below 6) [3,7]. The patient took only L-Thyroxine as daily medication. A thin woman had a consistent body mass index of 19.4 and a well-balanced diet.

This patient received adjuvant oral CAP from January 2023 at 1650 mg twice daily (1000 mg/m^2 instead of 1250 mg/m^2 according to our institutional regimen) for 14 days in a 21-day cycle. Clinical tolerance was acceptable with grade I asthenia and hand-foot syndrome. At the end of the fourth cycle, a lipid profile systematically prescribed by the patient's general practitioner revealed an asymptomatic hypertriglyceridemia (23 g/L) without concomitant hypercholesterolemia.

Capecitabine therapy was not discontinued, given manageable clinical tolerance, and a dosage error was even suspected. Plasma triglycerides were monitored every three weeks and showed an initial spontaneous decrease (5.47 g/L on May 2023), before again increasing to 21 g/L on early July and 49 g/L three days after (Figure 1).

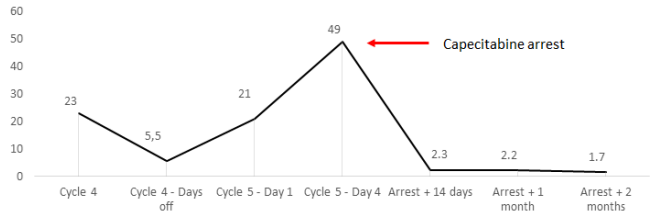

Figure 1. Triglyceride evolution depending on capecitabin therapy.

Finally, hypertriglyceridemia became symptomatic with epigastric abdominal pain leading to suspect acute pancreatitis. Plasma lipase was normal and abdominal ultrasound showed hepatic steatosis with no direct or indirect sign of pancreatitis. Neither a thromboembolic event, oral mucositis, cytopenia nor diarrhea ever occurred. CAP was immediately – and definitively – discontinued after six cycles. This complication required no hospitalization, and no pharmacologic interaction with L-Thyroxine was deemed relevant. Declaration to our post-marketing surveillance agency revealed no similar cases for CAP. Based on semiotic and chronologic criteria, hypertriglyceridemia was strongly attributed to CAP (15/16 according to Bregaud's classification) [8].

The patient was advised to follow a strict fat-free diet and was prescribed oral fenofibrate. The medication was not taken, but CAP discontinuation and diet alone lowered triglycerides to normal plasma concentration within 15 days (2.2 g/L on August 2023). It remained normal, and the patient has remained free of local or metastatic recurrence.

Discussion

Cases of CAP-Induced Hypertriglyceridemia (CIHT) have been reported since 2006, and the number of retrospective series studied has been increasing. Its incidence has been reported to vary from 3.4% to 10% of patients, raising obvious concerns about this rare and possibly life-threatening adverse event [9,10]. A recent update provided by Zhou *cr _j.* reported 22 patients developing CIHT after a median of five cycles [6]. Two cases were symptomatic (angina, pancreatitis) with no fatal events. Notably, all patients received CAP-based regimens, but none received CAP as monotherapy. To the best of our knowledge, the case reported here is the first describing severe CIHT resulting from CAP alone.

Induced hypertriglyceridemia has also been reported with two other 5-FU prodrugs, respectively tegafur and doxifluridine, but rarely with 5-FU itself [11-13]. This specificity for 5-FU prodrugs suggests a shared metabolic process of metabolites, independently of 5-FU itself. This is consistent with the fact that all patients experiencing CIHT exhibited no DPD deficiency (partial or complete).

Despite the absence of personal or familial history of hyperlipidemia or hypertriglyceridemia, our patient showed hepatic steatohepatitis on ultrasound check-up, possibly reflecting chronic impairment in lipid metabolism. This may, however, have resulted from neoadjuvant chemotherapy, but may also be attributed to an individual polymorphism/impairment in lipid metabolism.

A key enzyme involved in the first metabolism step of CAP is carboxylesterase (CES1 and CES2) that catalyze CAP transformation into 5-DFCR (5'-deoxy-5-fluorocytidine) [14]. Aside from their key role in detoxification, both CES1 and CES2 are also physiologically involved in lipid metabolism, lipoprotein secretion, obesity and atherosclerosis. In mouse models, the role of CES isoforms have contradictory effects on lipidemia and lipid trafficking [15]. On the one hand, CES1d knock-down or inhibition is associated with reduced hypertriglyceridemia and is a current therapeutic target for evaluation [16]. On the other hand, CES1g deficiency is associated with postabsorptive and postprandial hyperlipidemia, an increased level of chylomicrons and liver steatosis16. Gan et al. demonstrated in a murine model with CES1 knock-down (CES1-/) that CES1 inhibition was associated with a 63-fold higher plasma CAP concentration, excess weight and increased adipose tissue [17]. Rescue with human CES1 transgenic hepatic expression (TgCES1) partially reversed the phenotype but was still associated with increased CAP concentration, suggesting the role of extra-hepatic CES1 in CAP metabolism. Notably, the TgCES1 model was associated with increased triglyceride secretion and hypertriglyceridemia compared with control and CES1-/ models. These findings suggest that hepatic expression of human CES1 is necessary for CAP metabolism even if peripheral CES1 expression might still be involved and is associated with onset of hypertriglyceridemia. Surprisingly, both in CES1-/ and TgCES1 models, 5-FU plasmatic concentrations remained normal, suggesting alternative metabolization regulation. This concurs with Xu et al.'s mouse model where CES1 knock-down was associated with decreased triglyceridemia, suggesting that CES1 physiologically increases plasma triglyceride concentration [18].

We may speculate that CAP therapy induces a positive recontrol on CES1 to assure CAP detoxification, possibly increasing TG intestinal absorption and inducing CIHT (Figure 2).

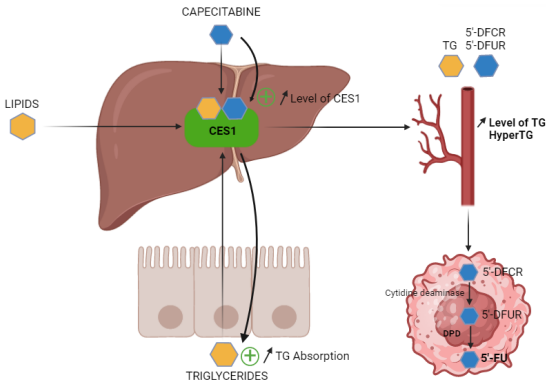

Figure 2. Hypothesized path.

However, this hypothesis needs to be more fully explored. Finally, independently of the CES hypothesis, a Japanese database analysis including 29,000 fluoropyrimidine users suggests that patients with breast cancers might run a higher risk of developing CIHT compared with patients with gastric and colorectal cancers. The use of tamoxifen in this population, however, might be a cofounding factor [11]. Given these data, it cannot be presumed that the primitive breast cancer localization played a significant role in the advent of CIHT for our patient.

Conclusion

CIHT is a rare but potentially serious, yet unscreened adverse event occurring with CAP monotherapy. Initial presentation may be asymptomatic despite extremely high plasma concentration. It would appear that CIHT occurs independently of DPD activity and does not resemble adverse events classically associated with partial or complete DPD deficiency. Carboxylesterase a key enzyme involved in both CAP and lipid metabolism may play a role in CIHT, but this remains to be shown. Further, CIHT characterization and pathophysiology research are necessary to identify both at-risk populations and possible screening biomarkers. For patient safety, we would recommend including initial and/or subsequent lipid monitoring with CAP therapy.

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