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Case report

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Capecitabine induced hypertriglyceridaemia: An underreported and potentially severe side effect

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Abstract

A 57 year-old-woman, with no previous history of dyslipedemia, developed severe hypertriglyceridemia while being treated with capecitabine for metastatic breast cancer. Capecitabine was not discontinued and serum triglyceride levels were normalized after 4 weeks of treatment with fenofibrate. Capecitabine induced hypertriglyceridemia, as a rare drug-related side effect, seems to be often overlooked by clinicians.

Keywords: breast cancer; capecitabine; fenofibrate; hypertriglyceridemia; serum triglyceride levels; chemotherapy

Introduction

Capecitabine is a third generation oral fluoropyrimidine frequently used alone or as part of combination chemotherapy in the adjuvant and metastatic breast, gastric and colorectal cancer [1]. The most frequent adverse events associated with capecitabine are diarrhea, hand-foot syndrome and asymptomatic elevation of indirect bilirubin; whereas stomatitis, myelosuppresion and alopecia are more commonly seen with the use of bolus 5-fluorouracil rather than capecitabine [2]. There have been several reports documenting capecitabine induced hypertriglyceridaemia [1, 3-7, 9].

Case report

A 57 year-old-woman, with no known history of dyslipedemia, underwent a partial mastectomy for a stage IIB invasive lobular carcinoma of the left breast in September 1998. Surgery was followed by adjuvant chemotherapy (doxorubicin, cyclophosphamide and 5-fluorouracil), radiotherapy, and 5 years of adjuvant tamoxifen.

In January 2010, she presented a subcutaneous relapse to the left chest wall with multiple bone metastases. Excision of the local relapse confirmed the same lobular histology with over-expression of hormone receptors and negative erb2 staining. She was treated with letrozole until the reappearance of bone pain in July 2012. Three months of chemotherapy with docetaxel failed, and second-line capecitabine monotherapy was initiated in November 2012. The patient was receiving capecitabine 1250mg/m^2 bid for two weeks every three weeks along with intravenous biphosphonates.

In August 2013, after 9 months of capecitabine therapy, the laboratory technicians notified the attending physician that the patient had a lipemic serum during a routine blood examination. Triglyceride levels were severely elevated i.e., 2 322 mg/dl (with a normal value of less than 150 mg/dl). Capecitabine was not discontinued and the patient was treated with fenofibrate 200 mg per day orally. After one month of fenofibrate therapy, triglyceride assessment showed a drop to a blood level of 312 mg/dl.

Discussion

Metabolic abnormalities associated with the use of capecitabine are most commonly associated with bilirubin elevation. However, capecitabine also causes hypertriglyceridaemia, which is underestimated and

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almost ignored by physicians. While intravenous 5-fluorouracil was never incriminated with such toxicity [8], several reported cases have incriminated capecitabine.

In fact, Sela and Haim reported the case of a woman with metastatic breast cancer who developed severe hypertriglyceridaemia (3 090 mg/dl) after two cycles of capecitabine chemotherapy [3].

Koutras et al. reported two cases (breast and colon cancer each) with triglyceride levels (1 409 mg/dl and 1 510 mg/dl) after seven and two cycles of treatment, respectively [4]. Kurt et al. presented another two cases of breast and colon cancer with triglyceride levels of 916 mg/dl and 1 455 mg/dl after two and five cycles of chemotherapy, respectively [5]. They also retrospectively reviewed the data of 40 patients treated with capecitabine and found that average triglyceride levels increased significantly (137.1 ± 76.3 vs. 204.5 ± 125.2 mg/dl; $p < 0.001$) before and after capecitabine respectively.

Michie et al. prospectively reviewed the data of 212 patients treated for colorectal cancer and found that 8 (3,7%) patients developed clinically significant hypertriglyceridaemia requiring lipid-lowering therapy; this study also found that triglyceride levels safely returned to normal with therapy and without discontinuation of capecitabine [6]. While, Seminara et al. found that the incidence of hypertriglyceridaemia reached 10% [7].

Finally, Stathopoulos et al. observed hypertriglyceridaemia in five of 12 patients whose triglyceride levels were tested, who were treated for advanced breast and colon cancer with capecitabine monotherapy [1].

The etiology of capecitabine induced hypertriglyceridaemia is unknown but seems to be due to the molecule of capecitabine rather than 5-fluorouracil, which actually lowers serum cholesterol and triglycerides [8]. One theory states that capecitabine may reduce the activity of lipoprotein lipase and hepatic TG lipase [1]. Javot et al. suggested a link between the thymidine metabolic pathways and the phospholipids metabolism that may explain this side effect [9].

Unexpected increase of serum triglyceride can have severe consequences such as acute pancreatitis, especially when the levels reach 15 times the normal value, as was the case with our patient. She presented this complication after 12 cycles of capecitabine, and serum levels of triglycerides were almost normalized with fenofibrate without discontinuation of capecitabine. It is important that oncology teams should be aware of this potentially life threatening side effect. Therefore, a lipid survey, including a cholesterol panel as well as triglyceride blood levels, should be conducted before initiation of capecitabine and also lipid sampling should be monitored during treatment. Detection of lipid abnormalities associated with the use of capecitabine can be safely managed without discontinuation of chemotherapy [1, 9].

Conclusion

Several authors have encountered capecitabine induced hypertriglyceridaemia in their clinical practice. This side effect can have potentially fatal consequences for oncology patients and we believe that clinicians should be prompted to order a lipid panel during routine follow-ups with patients receiving capecitabine.

Conflict of interest

The authors wish to express that they have no conflict of interest.

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