Case Report

Severe Hypertriglyceridemia Induced by Docetaxel: A Novel Case Report

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Keywords

Hypertriglyceridemia · Docetaxel · Taxane · Chemotherapy · Triglyceride · Statins

Abstract

Docetaxel (DOC) is one of the most effective agents for breast cancer treatment. Here, we report docetaxel-induced severe hypertriglyceridemia in a patient previously diagnosed with hyperlipidemia and corresponding therapeutic intervention. A postmenopausal woman, with previously controlled hyperlipidemia using rosuvastatin 5 mg daily, was diagnosed with stage IIB breast cancer with human epidermal growth factor receptor-2 overexpression; she received DOC (75 mg/m²), pertuzumab, and trastuzumab treatment as neoadjuvant chemotherapy. The serum triglyceride level was mildly higher than normal, and cholesterol level was normal at baseline. The serum triglyceride level was almost stable after chemotherapy initiation but suddenly increased to grade 3 (770 mg/dL) after the third cycle of the treatment without any symptoms. Sustained-release bezafibrate 400 mg was administered, resulting in a significant decrease to the baseline level; bezafibrate was discontinued on day 28 of the fourth chemotherapy as neoadjuvant chemotherapy was completed. The level was stable around the baseline level during adjuvant chemotherapy with pertuzumab and trastuzumab. Therefore, DOC-induced severe hypertriglyceridemia was strongly indicated in this case. The mechanism underlying the symptoms remains unclear; we speculate that it could be a resultant of a decrease in lipid metabolism as the patient had grade 2 diarrhea. Moreover, her backgrounds, such as mild hypertriglyceridemia, postmenopausal, diabetes, and obesity, in addition to DOC administration might have affected the outcome. Fibrate administration and cessation of treatment were as effective as in previous reports. DOC-induced hypertriglyceridemia presents with the possibility of severe complications. Elucidation of the exact mechanisms and epidemiological features is required for better management.

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Introduction

The prevalence of breast cancer has been increasing. Human epidermal growth factor receptor-2 (HER-2) overexpression is confirmed in up to 30% of all breast cancer cases. Docetaxel (DOC) + pertuzumab + trastuzumab is one of the most effective chemotherapeutic regimens in neoadjuvant, adjuvant, and metastatic settings for breast cancer patients with HER-2 overexpression [1]. Here, we report DOC-induced severe hypertriglyceridemia in a patient with hyperlipidemia as well as the corresponding therapeutic intervention.

Case Presentation

A postmenopausal woman in her 50s, who had previously been affected with hyperlipidemia controlled by rosuvastatin, was diagnosed with stage IIB breast cancer with estrogen receptor positive (>90%), progesterone receptor positive (20%), HER-2 overexpression positive (3+), and Ki-67 (32.1%). The patient was a current smoker (10 cigarettes per day) and a social drinker with normal liver and renal function. She was previously diagnosed with integration disorder syndrome, diabetes mellitus, and hyperlipidemia, all of which were well controlled by aripiprazole 6 mg twice daily, ethyl loflazepate 1 mg twice daily, trihexypenidyl hydrochloride 2 mg twice daily, sitagliptin phosphate hydrate 50 mg once a day, and rosuvastatin 5 mg once a day.

The patient received DOC (75 mg/m²), pertuzumab (840 mg in initial administration and 420 mg in subsequent administration), and trastuzumab (8 mg/kg in initial administration and 6 mg/kg in subsequent administration) treatment (every 3 weeks) after epirubicin and cyclophosphamide (EC; every 3 weeks, 4 times) as neoadjuvant chemotherapy. Dexamethasone 6.6 mg intravenously on day 1 and 8 mg orally on days 2–4 was administered for the prevention of taxane-associated acute pain syndrome and edema. Pegfilgrastim (3.6 mg) was subcutaneously administered on day 3 from the initiation of treatment. Goshajinkigan, a herbal medicine, 2.5 g 3 times a day, was administered for the prevention of peripheral neuropathy from the beginning of the treatment, but stopped on day 7 in the second cycle due to the suspicion of mild liver dysfunction. Metoclopramide 5 mg 3 times a day was administered from day 1 to day 8 at every cycle to prevent nausea.

She experienced grade 2 diarrhea and grade 1 fatigue from the first cycle, grade 1 edema from the second cycle, and grade 1 peripheral neuropathy from the third cycle of the treatment. She received 40 mg of the probiotic *Clostridium butyricum* MIYAIRI, 3 times a day for diarrhea prevention from the second cycle of the treatment, which attenuated the symptoms to grade 1, and loperamide 1 mg per request controlled the breakthrough symptoms well.

The variations in serum triglyceride and cholesterol levels are shown in Figure 1. The serum triglyceride level was higher than normal, whereas the cholesterol level was normal at baseline. She had no history of severe hyperlipidemia prior to chemotherapy. The serum triglyceride level mildly increased after the first cycle of EC treatment, which decreased again after the second cycle of EC and was stable until the second cycle of DOC + pertuzumab + trastuzumab without any countermeasures. However, the level suddenly increased to grade 3 (770 mg/dL) without any symptoms after the third cycle. Fourth-cycle treatment was conducted, and sustained-release bezafibrate 200 mg twice a day was administered from the day, resulting in a significant decrease of serum triglyceride level to grade 1 (287 mg/dL) after 16 days. Administration of bezafibrate was stopped on day 28 of the fourth cycle as neoadjuvant chemotherapy was completed, and the level further decreased to the baseline level (212 mg/dL) on day 39. Surgery was conducted on day 39 of the last chemotherapy cycle, and adjuvant chemotherapy consisting of pertuzumab + trastuzumab was resumed 52

Fig. 1. Variations in the serum lipid level of the patient. (1) Baseline, (2) after the first administration of EC as neoadjuvant chemotherapy, (3) after the second EC administration, (4) after the fourth EC administration, (5) after the second DOC + pertuzumab + trastuzumab administration, (6) after the third DOC + pertuzumab + trastuzumab administration, (7) after the fourth DOC + pertuzumab + trastuzumab administration, (8) at surgery, (9) after the first pertuzumab + trastuzumab administration as adjuvant chemotherapy, (10) after the second pertuzumab + trastuzumab administration, (11) after the third pertuzumab + trastuzumab administration, (12) after the fourth pertuzumab + trastuzumab administration, and (13) after the fifth pertuzumab + trastuzumab administration. EC, epirubicin and cyclophosphamide.

days after the surgery. The lipid levels did not change during adjuvant chemotherapy. Grade 1 aspartate aminotransferase, alanine aminotransferase, and γ -glutamyltransferase elevation was confirmed in the second cycle of EC and continued to be around the same level till the end of neoadjuvant chemotherapy. No other new medications were administered during chemotherapy.

Discussion

Combination therapy of chemotherapy and surgery is the first line of treatment for locally advanced breast cancer, and DOC is one of the most effective chemotherapeutic drugs used in the treatment [1]. We encountered a patient who was previously affected with hyperlipidemia and developed severe hypertriglyceridemia after DOC + pertuzumab + trastuzumab treatment. There are no reports regarding hypertriglyceridemia caused by pertuzumab, trastuzumab, pegfilgrastim, ethyl loflazepate, or trihexyphenidyl hydrochloride. Sitagliptin has been reported to improve lipid profiles, including serum triglycerides, in patients with diabetes [2]. Aripiprazole, unlike olanzapine, has been reported not to affect serum triglyceride levels [3], whereas another report suggested that some patients experienced mild to severe hypertriglyceridemia by its intake, experiencing this elevation by 8 weeks from the initiation of aripiprazole treatment [4]. In this case, as the patient was administered aripiprazole for at least 4 months prior to the induction of neoadjuvant chemotherapy, its association would be low. A previous report has suggested a relationship between glucocorticoids

and lipid levels [5]; the patient was temporarily administered dexamethasone 6 times before the development of the symptoms; hence, the possibility of hypertriglyceridemia induction would also be low.

There are no reports regarding DOC-induced severe hypertriglyceridemia. In contrast, paclitaxel, which possesses an antitumor mechanism similar to that of DOC, in combination with carboplatin or cisplatin, has been reported to induce hypertriglyceridemia; however, the underlying mechanism has not been understood [6–8]. Lander et al. [6] have reported that a patient developed grade 3 hypertriglyceridemia (769 mg/dL) after the fourth cycle of cisplatin and paclitaxel, and its level significantly increased to grade 4 (1,871 mg/dL) 10 days later. Watanabe et al. [7] also reported that patients developed serum triglyceride elevation at the time of 2.8 ± 0.6 courses of carboplatin + paclitaxel treatment. In contrast, Wang et al. [8] have reported that 3 cases of temporary hypertriglyceridemia occurred in every cisplatin + paclitaxel treatment cycle. The course of the symptoms in our patient was similar to the initial 2 reports described above, which suggested that the level increased after several treatment cycles. As the serum triglyceride level decreased after the completion of neoadjuvant chemotherapy and did not increase after the recommencement of the pertuzumab + trastuzumab treatment, DOC-induced hypertriglyceridemia was strongly indicated in this case. We evaluated it using the Naranjo adverse drug reaction probability scale, and a score of 6, which is classified as “probable,” was obtained (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000518684).

We have previously reported that S-1, a medical compound containing tegafur, gimeracil, and oteracil potassium, induced severe hypertriglyceridemia [9]. In that case, the serum triglyceride level increased with increasing administration dose and finally reached grade 4. In addition, the serum triglyceride level in a cisplatin + paclitaxel-treated patient was significantly elevated from 769 mg/dL to 1,871 mg/dL within 10 days [6]. These results suggest that early intervention is necessary for the management of severe hypertriglyceridemia. We consider that medications should be started with the incidence of grade 3 or higher symptoms. The general treatment regimens for severe hypertriglyceridemia include dietary restrictions and lipid-lowering drug treatment such as the use of fibrates, medium-chain triglycerides, omega-3-fatty acids, and nicotinic acid. We and Michie et al. [10] have also reported that treatment of fluoropyrimidine-induced severe hypertriglyceridemia is the cessation of suspect-drug administration, fibrate and/or statin administration, or plasmapheresis [9]. We considered fibrate as the first option to lower serum triglyceride levels in this case, as the patient was already administered rosuvastatin. Therefore, we decided to administer sustained-release bezafibrate in addition to rosuvastatin with careful attention to rhabdomyolysis as an early countermeasure in this case, resulting in significant reduction of serum triglyceride levels.

In addition to the treatment, it is important to detect severe hypertriglyceridemia as it is asymptomatic in most cases. It is correlated with arteriosclerotic disease, especially coronary artery disease, and the possibility of acute pancreatitis induction [9], which is life threatening in severe cases. Observation at baseline and periodic evaluation of lipid profiles would be necessary in patients receiving chemotherapeutic agents that may result in the development of hypertriglyceridemia. In particular, we strongly recommend monitoring patients with cardiovascular disease or those who are at risk, such as individuals with dyslipidemia, obesity, diabetes, hypertension, and coronary heart disease, as described in a previous report [9].

Mechanisms underlying chemotherapy-induced hypertriglyceridemia are still unclear, but it could result from a decrease in lipid metabolism, as the patient had grade 2 diarrhea in this case. She and her family reported that her food intake was stable, suggesting that her lipid intake did not change. It has been reported that serum lipid levels, such as triglyceride, total cholesterol, and low-density lipoprotein, were significantly but not severely elevated after

chemotherapy in breast cancer treatment [11]. He et al. [11] speculated that chemotherapy itself can directly cause endothelial dysfunction and insulin resistance, leading to cytokine alterations, resulting in elevated serum lipid levels. They also proposed another possibility that suggests that the enhancement of systemic oxidative stress causes lipid peroxidation, leading to liver dysfunction, and resulting in a decrease in lipid metabolism [11]. In addition, paclitaxel has been reported to be sufficient to trigger significant alterations in lipid metabolism by increasing hydroperoxide [12]. We believe that these mechanisms compositely induced the symptoms observed in our patient.

Moreover, the risk factors for chemotherapy-induced dyslipidemia in breast cancer patients are older age, postmenopausal status, weight gain or overweight/obese status, taxane-based regimens, and corticosteroid premedication, although it is unknown whether they are suitable risk factors for severe hypertriglyceridemia [13]. He et al. [11] have also reported that BMI >24 kg/m² was an independent risk factor. Furthermore, Murase et al. [14] have reported that obesity, diabetes mellitus, and heavy alcohol intake could be involved in the incidence of severe hypertriglyceridemia. As the patient was affected with mild hypertriglyceridemia and diabetes and was postmenopausal and obese (BMI was 32.4 kg/m²), her baseline characteristics in addition to DOC administration might have affected the outcome.

The prevalence of general severe hypertriglyceridemia in Japan is 0.3% [15]. Michie et al. [10] have reported that capecitabine-induced hypertriglyceridemia occurs in 3.7% of the patients, although the epidemiology of the symptoms caused by other chemotherapeutic drugs remains unknown. Therefore, it is important to reveal the epidemiological features of chemotherapy-induced severe hypertriglyceridemia for early detection and adequate preventative treatment.

In conclusion, herein, we have reported DOC-induced severe hypertriglyceridemia in a breast cancer patient previously affected with hyperlipidemia treated with statins. Severe hypertriglyceridemia caused by DOC is uncommon, but presents the possibility of severe complications such as pancreatitis and arteriosclerotic disease. Hence, early detection with appropriate pre-emptive treatment is required. The mechanisms and epidemiology remain unclear, and further studies pertaining to their elucidation are necessary for better management.

Statement of Ethics

We have reported this case in compliance with the Declaration of Helsinki. Informed written consent was obtained from the patient for the publication of the clinical data. Case reports are granted an exemption from requiring ethical approval at Hokkaido University Hospital.

Conflict of Interest Statement

All authors have no conflicts of interest.

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Author Contributions

Y.S. contributed to the design of the report, collected the data, and drafted the manuscript. Y.T., T.T., and M.S. revised the manuscript. All authors have read and approved the final manuscript.

Data Availability Statement

All data generated during this study are included in this article and its online supplemental files.

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