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Case Report

Ribociclib-Induced Acute Pancreatitis in Metastatic Breast Cancer

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Abstract

Ribociclib is an inhibitor of cyclin-dependent kinase 4 and 6, whose inhibitors are used in treatment of hormone receptor positive and human epidermal growth factor receptor 2 negative advanced breast cancer. They have been recently used widely in breast cancer, and new side effects have emerged with its increased use.

We describe a 57-year-old female with breast cancer treated with ribociclib and letrozole. She presented to our hospital with complaints of back pain and epigastric pain. After she was investigated for these complaints, she was diagnosed with acute pancreatitis.

After ruling out other common causes of acute pancreatitis, ribociclib was considered as a cause of acute pancreatitis. Ribociclib was immediately discontinued and her medical treatment was re-arranged. She was free of symptoms on the third day. One week later, she presented again with the complaints of abdominal and back pain, after which we learned that the patient had continued ribociclib and letrozole. The treatment of the patient was discontinued and the symptoms disappeared again.

We report a case in which the symptoms and laboratory findings of acute pancreatitis emerged twice while on ribociclib; acute pancreatitis were not found as a side effect of ribociclib in previous publications or in the side effect guidelines. Acute pancreatitis in cancer patients is associated with poor prognosis and prolonged hospital stay. Possibility of ribociclib-induced acute pancreatitis should be considered in order to achieve early diagnosis and prevent significant mortality in cancer patients.

Keywords: Acute pancreatitis, breast cancer, CDK4/6 inhibitors, cyclin-dependent kinase 4/6 inhibitors, ribociclib

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Usage of cyclin-dependent kinase (CDK) 4/6 inhibitors for hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (ABC) has increased. A combinatorial strategy of endocrine therapy(ET) plus targeted therapy is the preferred treatment approach for patients with HR-positive and HER2-negative ABC.

Ribociclib was currently approved by the Food and Drug Administration (FDA) as initial endocrine-based therapy or following disease progression on endocrine therapy, whose combination with an aromatase inhibitor is used in premenopausal/perimenopausal or postmenopausal women as an initial ET or with fulvestrant in postmenopausal women as a first- or second-line therapy for HR+/HER2– ABC.[1]

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Ribociclib is a selective inhibitor of CDK4/6 that inhibits the phosphorylation of retinoblastoma(RB) protein, preventing cell-cycle progression and inducing G1 phase arrest.[2] CDK 4 and 6 regulate cell-cycle progression in conjunction with the protein regulator cyclin D1 (encoded by CCND1), a direct transcriptional target of estrogen-receptor(ER) signalling.[3] CDK4/6 overexpression and CCND1 amplification are frequently encountered in HR-positive breast cancers, representing key mediators of endocrine resistance.[4,5] The inhibition of the pathway consisting of cyclin D, CDK4/6, inhibitor of CDK4 (INK4) and RB protein is an effective therapeutic strategy for HR-positive ABC, both as a first-line option[6,7] and in patients with progression while on ET.[8,9]

CDK4/6 inhibitors are subject to interactions mediated by modification of the cytochrome P450 (CYP) pathway because the CDK4/6 inhibitors are all major substrates of the CYP3A4 enzyme.[10] Inhibitors or inducers of CYP3A4 must be avoided, or dose reductions of the appropriate agent should be considered for patients receiving these inhibitors.[1]

The CDK4/6 inhibitors are well tolerated, and adverse events are typically managed with dose modification. Cytopenias are considered an on-target effect of CDK4/6 inhibitors because CDK6 plays a key role in the proliferation of hematological precursors.[11] Common bone marrow toxicity in CDK4/6 inhibitors results from inhibition of the cell cycle, but febrile neutropenia is uncommon. The FDA has issued a warning about rare, but serious cases of pneumonitis.[12] Ribociclib may cause hepatotoxicity, and it has been associated with reversible, concentration-dependent prolongation of the QT interval.[13]

Side effects of ribociclib reported in the literature include hematologic symptoms (neutropenia, lymphpoenia, leucopenia, thrombocytopenia and anemia), fatigue, nausea, vomiting, prolonged QT intervals on electrocardiogram (ECG), increased blood creatinine, decreased appetite, pyrexia, hypophosphatemia, constipation, diarrhea, palmar–plantar erythrodysesthesia, dermatitis acneiform, infections, hypertension and increased alanine aminotransferase and bilirubin levels.[13,14]

Here, we present a patient who had lumbar and epigastric pain after ribociclib therapy and was treated with diagnosis of pancreatitis, representing the first such presentation in the literature.

Case Report

A 57-year-old female patient was found to have invasive ductal carcinoma in a tru-cut biopsy, which was performed in July-2016 because of a palpable mass in the right breast. Modified radical mastectomy and axillary lymph node dissection were performed on the right breast. ER+, progesterone receptor (PR) and c-erbB-2(HER2/neu) were negative in the pathological examination. Pathology results revealed an infiltrative ductal carcinoma and 1/12 metastatic lymph nodes (T1-N1-M0). For the adjuvant therapy, four cycles of cyclophosphamide (600 mg/m^2, repeat every 21 days x 4 cycles) and doxorubicin (60 mg/m^2, repeat every 21 days x 4 cycles) (CA) for 21 days, started on September-2016 and 12 weekly paclitaxel (80 mg/m^2, 12 weeks total) chemotherapy were applied, started on November-2016. After adjuvant chemotherapy, radiotherapy (50 Gy in 25 fractions were given to the right chest wall and lymphatics) were performed to the right chest wall and letrozole(2.5 mg, daily) treatment was started in February-2017. Eight months later, palliative radiotherapy (30 Gy in 12 fractions were given to the thoracic 11 and lumbar 5 vertebrae) treatment were performed to the patient, who had new bone metastases in the vertebra, and then fulvestrant (500 mg, once every 28 days) and zoledronic acid (4 mg, repeat once every 4 weeks) treatments were initiated, December-2017, letrozole treatment was discontinued. A breast cancer (BRCA) 1/2 gene mutation test was performed, and the result was negative. Seven months later, the patient progressed with bone metastases and pleural effusion, and then she approved chemotherapy and received capecitabine (1250 mg/m^2 BID x 14 days (d 1 to 14), repeat every 21 days), July-2018. Four months later, the patient progressed with bone metastases received gemcitabine (800 mg/m^2 once weekly x 3 weeks then 1 week rest (=4 week cycle)) treatment, started on December-2018. The patient refused intravenous chemotherapy during gemcitabine treatment, and she was then treated with tamoxifen (20 mg Daily) and zoledronic acid (4 mg, repeat once every 4 weeks), which was continued due to bone metastasis, June-2019. Five months later, progression was detected, with newly formed liver metastasis and progression of pleural effusion, and vinorelbine (30 mg/m^2 on days 1 and 8) was started after approval of the patient, started on November-2019. A liver biopsy was scheduled due to the newly formed liver metastasis and increase in tumor markers; however, the patient refused biopsy. Three months later, progression in liver metastasis and pleural effusion was observed, and paclitaxel (80 mg/m^2 on days 1, 8 and 15, repeat every 28 days) plus carboplatin (AUC 2, days 1, 8 and 15, repeat every 28 days) was initiated in February-2020.

After 3 months of the follow-up, the size and the number of liver lesions, as well as bone metastases were found to be increased. Ribociclib (600 mg once daily in the morning for 21 days on, 7 days off) and letrozole (2.5 mg once daily continuously) treatments were initiated in May-2020. The drug was discontinued for 2 weeks due to the development of grade 3 neutropenia (0.8 10^3/uL, N 1.5–7.3). After two weeks when neutrophilia was improved, the patient was started

on the drug again and an amylase level of 110 (N 28–100 U/L) and lipase level of 205 (N 13–60 U/L) were additionally detected in her laboratory results. As the patient had no complaints suggesting pancreatitis and her physical examination was normal, it was decided to follow-up the laboratory values (24-June-2020). The patient presented with complaints of back and epigastric pain in the follow-up. Physical and laboratory examination revealed the following: blood pressure, 120/70 mmHg; pulse, 87 beats/minute; fever, 37.4 °C; and epigastric pain (01.07.2020). An amylase level of 137 U/L and lipase level of 212 were found in the laboratory results; Upon this increase, the patient was admitted to the oncology ward with the pre-diagnosis of acute pancreatitis, and her current treatments were discontinued. Other laboratory test results were as follows: total bilirubin (T-BIL): 0.74 (N 0.2–1.2 mg/dL); direct bilirubin (D-BIL): 0.48 (N 0–0.30 mg/dL); alkaline phosphatase (ALP): 295 (N 35–104 U/L); aspartate aminotransferase (SGOT): 111 (N 0–33 U/L); alanine transaminase (SGPT): 43 (N 0–32 U/L); gamma-glutamyl-transferase (GGT): 924 (N 0–40 U/L); white blood cells (WBCs): 4.92 (N 4–10 10^3/uL); neutrophil (NEU): 2.73 10^3/uL; hemoglobin (HGB): 9.7 (N 12.1–17.2 g/dL); and platelet (PLT) count: 166 (N 150–400 10^3/uL).

An abdominal computed tomography (CT) was performed to rule out other pathological causes (Fig. 1). CT showed a parenchymal hypodense, edematous changes of the pancreatic body and tail, associated with dilatation of the pancreatic duct related to pancreatitis. The pancreatic duct was dilated up to the head of the pancreas, and the head of the pancreas had normal density. No dilation was observed in the intrahepatic biliary ducts.

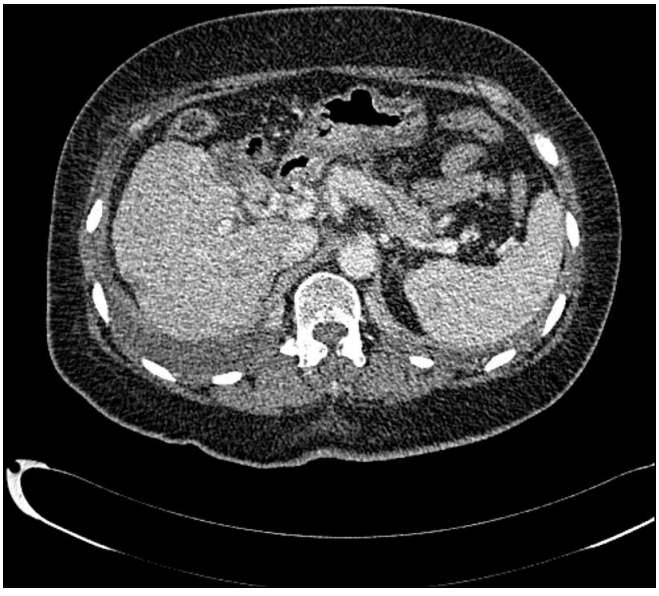

Figure 1. Axial computed tomography (CT) image obtained after administration of intravenous contrast material demonstrates parenchymal hypodense, edematous changes of the pancreatic body and the tail associated with dilatation of the pancreatic duct related to pancreatitis. The pancreatic duct is dilated up to the body of the pancreas (arrow). The head of the pancreas is normal in density. No intrahepatic bile duct dilatation is seen.

Laboratory tests requested on the second day of hospitalization revealed the following results: amylase: 141 U/L; lipase: 367.8 U/L; GGT: 754 U/L; ALP: 295 U/L; T-BIL: 0.74 mg/dL; and D-BIL: 0.48 mg/dL. No significant improvement was observed in symptoms.

There were no symptoms on the third day, and no findings were evident on physical examination. The patient was discharged on the third day from the hospital on her own will.

One week later, she presented again with the complaints of abdominal and back pain. It was learned that the patient had continued the treatment. Physical and laboratory examination revealed the following results: blood pressure: 125/60 mmHg; pulse:92 beats/minute; temperature: 37.5 °C; and epigastric and periumbilical pain. Laboratory tests were as follows: WBCs: 4.99 10^3/uL; NEU: 3.44 10^3/uL; HGB: 9.4 g/dL; PLT: 177 10^3/uL; T-BIL: 1.13 mg/dL; D-BIL: 0.69 mg/dL; ALP: 355 U/L; SGOT: 117.1 U/L; SGPT: 44.2 U/L; GGT: 1103 U/L; amylase: 200 U/L; and lipase: 424.5 U/L. There was no history of alcohol use or trauma. The patient's current treatment was discontinued, and she was admitted to the oncology ward with the diagnosis of acute pancreatitis. The medical treatment was arranged.

An opinion regarding the etiology of pancreatitis was obtained from department of gastroenterology, and the recommended tests for liver and biliary tract ultrasonography were performed. On ultrasonography, multiple metastases were seen in the liver; the intrahepatic and extrahepatic biliary ducts were normal, with gallstones detected in the gallbladder. Magnetic resonance cholangiopancreatography (MRCP) was recommended for the patient, but she did not accept this imaging procedure. Laboratory tests revealed the following results: calcium: 8.58 (N 8.4–10.2 mg/dL); cholesterol: 146.9 (N 0–200 mg/dL); triglycerides: 102.1 (N 0–150 mg/dL); very low density lipoprotein (VLDL): 20.42 (N 0–30 mg/dL); high-density lipoprotein (HDL): 22.8 (N 0–60 mg/dL); and low-density lipoprotein (LDL): 103.68 (N <100 mg/dL). Furthermore, anti-nuclear antibodies (ANAs) and immunoglobulin-G4(IgG4) were negative. Viral causes of pancreatitis were checked, and the results were found to be negative (Table 1). After discontinuation of the treatment, improvement in laboratory tests were observed with medical treatment; amylase (Fig. 2) and lipase (Fig. 3) were decreased, and there was no abdominal or back pain. The treatment of the patient having liver and bone metastases was switched to eribulin treatment due to the detection of ribociclib-induced pancreatitis.

Table 1. Viral laboratory tests to determine the etiology of pancreatitis

Laboratory Test	Result
EBV IG-M	Negative
CMV IG-M	Negative
Parvovirus B19 IG-M	Negative
Toxoplasmosis IG-M	Negative
Rubella IG-M	Negative
Mumps IG-G	Negative
Measles IG-G	Negative

EBV: Epstein–Barr virus; IG: Immunoglobulin; CMV: cytomegalovirus.

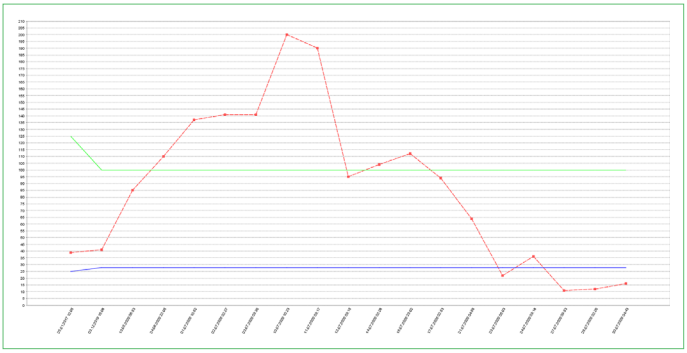

Figure 2. Graphic of amylase level by day. Ribociclib treatment started on 12.05.2020, and an increase was detected in amylase testing for the first time on 24.06.2020. The first symptom arose on 01.07.2020, and the second symptom emerged on 10.07.2020. Ribociclib was first discontinued on 01.07.2020 and not used until 03.07.2020. On 04.07.2020, the patient resumed ribociclib at her request; the use of ribociclib was discontinued after the recurrence of symptoms on 10.07.2020.

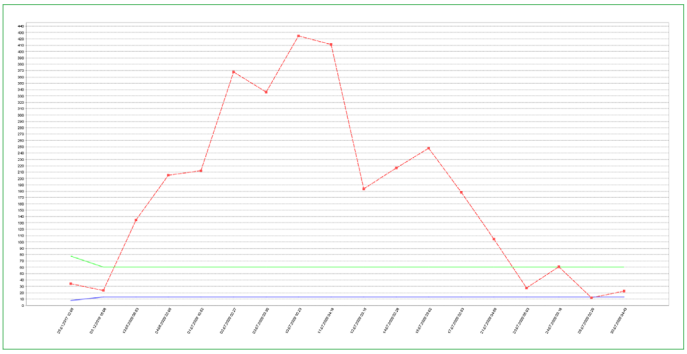

Figure 3. Graphic of lipase level by day. Ribociclib treatment started on 12.05.2020, and an increase was detected in amylase testing for the first time on 24.06.2020.The first symptom emerged on 01.07.2020, and the second symptom arose on 10.07.2020. Ribociclib was first discontinued on 01.07.2020 and not used until 03.07.2020. On 04.07.2020, the patient resumed ribociclib at her request; the use of ribociclib was discontinued after the recurrence of symptoms on 10.07.2020.

Discussion

Drugs causing pancreatitis in oncology practice are frequently seen and include tamoxifen, vemurafenib, thalidomide, paclitaxel, prednisolone, lanreotide, octreotide, lenvatinib, sirolimus, pazopanib, sunitinib, 5-fluorouracil, ifosfamide, vincristine, doxorubicin, capecitabine and cisplatin.[17,18] Letrozole, anastrozole, exemestane and tamoxifen are commonly used hormonal therapies in HR-positive breast cancer. Tamoxifen causes acute pancreatitis by causing severe hypertriglyceridemia.[19] No articles suggesting that letrozole, anastrozole or exemestane cause acute pancreatitis have been found.

In our patient, amylase and lipase levels found to be elevated in the tests performed after the diagnosis of acute pancreatitis. In the tests performed for determining etiology, bilirubin levels were found to be normal, whereas SGOT, SGPT, ALP and GGT levels were elevated. It was thought that these high levels may be primarily due to liver and bone metastases. There was no dilatation in the biliary ducts and an appearance consistent with pancreatitis on abdominal CT. Investigation of the etiology of acute pancreatitis was planned because the patient's symptoms recurred with continued treatment. There was no history of alcohol use or trauma. MRCP was scheduled, but the patient refused due to anxiety. Multiple metastases in the liver and biliary ducts were found to be normal on abdominal ultrasonography. Calcium, lipid panel, viral screening, ANA, and IgG4 tests were requested for etiology and found to be normal. The patient was diagnosed with drug-related pancreatitis as a result of the normal findings on the etiology studies and the normal appearance of the biliary tract in the imaging, which was consistent with pancreatitis. For the treatment, ribociclib and letrozole were discontinued at first, and then fluid balance, pain relief and nutrition were addressed.

Ribociclib and letrozole have not been reported to cause acute pancreatitis. Ribociclib-induced pancreatitis was first considered because the patient had used letrozole before, and no letrozole-induced pancreatitis has been previously reported previously. When both drugs were evaluated, it was considered that ribociclin was more likely to be responsible for the pancreatitis due to its effect on the cell cycle. Growth inhibition in sensitive cell lines was consistent with a cytostatic effect stemming from the ribociclib inhibition of CDK4/6. CDK4/6 inhibition is primarily cytostatic and mediated by G1 cell-cycle arrest and cellular senescence.[20] In our case, ribociclib may have caused acute pancreatitis due to its cytotoxic effect. Thus, ribociclib was discontinued and acute pancreatitis treatment was administered; the patient's symptoms and laboratory tests became normal after drug discontinuation.

Naranjo scale[21] total score 8, probable adverse drug reaction; there were no previous conclusive reports about this reaction (0 points), adverse event occurred after suspected drug was administered (2 points), adverse reaction resolved when drug was discontinued (1 points), adverse event reoccurred when drug was re-administered (2 points), there were no alternative causes other than medication (2 points), no placebo used (0 points), there was no method to detect drug at concentrations known to be toxic in blood (or other fluids) (0 points), no dose escalation or dose reduction applied (0 points), the patient had a similar reaction to the same drug on previous exposure (1 points), adverse event not confirmed by any objective evidence (0 points).

Conclusion

We reported a patient who developed acute pancreatitis due to ribociclib treatment. To the best of our knowledge, this is the first case of ribociclib-induced acute pancreatitis described in the literature. Drug-induced acute pancreatitis presents with symptoms of epigastric and lumbar pain following drug intake, and it results in increased amylase and lipase levels in the laboratory. Other causes of pancreatitis must be ruled out before diagnosing drug-induced acute pancreatitis. Gallstones, biliary obstruction, viral causes, lipid metabolism disorders, hypercalcemia, immunological causes, pancreatic head pathologies, other drugs causing pancreatitis, alcohol use and trauma should be excluded. Recovery from drug-induced acute pancreatitis occurs after the discontinuation of the causative drug. Symptoms and laboratory values regress during patient follow-up.

Disclosures

Informed Consent: Written informed consent was obtained from the patients' family for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.U.; Design – M.U.; Supervision – M.A.; Materials – Ü.K., M.A.; Data collection and/or processing – M.K., M.K.E., M.A., M.A.; Analysis and/or interpretation – M.A.; Literature search – M.U., E.H., M.M.E.; Writing – M.U.; Critical review – M.A.

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