Palbociclib-induced severe hepatitis: A case study and literature review

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ABSTRACT
Palbociclib is a selective and reversible CDK4/6 inhibitor approved for patients presenting with HR+ HER2– locally advanced or metastatic breast cancer. Its adverse effect (AE) is mainly reported on the occurrence of leukopenia and fatigue. Even though palbociclib has an extensive hepatic metabolism, there are rare reports about significant liver toxicity. We present the case of a 61-year-old female with metastatic breast cancer treated with palbociclib and an aromatase inhibitor (letrozole). The patient developed a rare AE of severe acute drug-induced hepatitis but improved dramatically after stopping the palbociclib and receiving treatment with N-acetylcysteine (NAC). The treatment with NAC may be a proof of concept for the mechanism of palbociclib liver injury.

KEYWORDS: drug-induced liver injury; necro-inflammatory hepatitis; palbociclib

INTRODUCTION
There has been a great deal of interest in the development of inhibitors of cyclin-dependent kinases (CDKs) since they were identified as potential regulators of the cell cycle in cancer tissues, more specifically CDK 1, 2, 4, and 6 (1). They work by blocking the transition from G1 to the S phase of the cell cycle. Therefore, they prevent cancer cell progression (1). Palbociclib is a known selective and reversible CDK 4/6 inhibitor approved for patients presenting with hormone receptor-positive (HR+), human epidermal growth factor receptor 2–negative (HER2–), and locally advanced or metastatic breast cancer. It is part of the arsenal for endocrine therapy (2). Palbociclib has an extensive hepatic metabolism, mainly via CYP3A4 and sulfotransferase 2A1 enzymes. Its adverse effect (AE) is mainly
reported on the occurrence of leukopenia and fatigue, and its overall tolerability is considered manageable (3). In the PALOMA-3 trial, increased aspartate aminotransferase (AST) was observed in 11.6% of patients in the palbociclib and fulvestrant arm compared with 7.6% in the placebo with fulvestrant arm (4). In most of the cases, the liver enzymes did not increase above 5 times the limit of the normal range.

We present herein a case of a 61-year-old female with metastatic breast cancer who was treated with palbociclib and an aromatase inhibitor (letrozole). The patient developed a rare AE of severe acute drug-induced hepatitis but improved dramatically after stopping the palbociclib and receiving treatment with N-acetylcysteine (NAC).

CASE PRESENTATION

The patient was a 61-year-old female who immigrated to Canada from Latin America. In December 2008, she was diagnosed with left breast cancer. After surgery, it was determined that she had stage II cancer: invasive ductal carcinoma <2cm, positive estrogen-receptor, and positive axillary sentinel lymph node. She had no risk factors for breast cancer, and her personal medical history was negative for any chronic diseases up to the finding of the tumour. She was initially treated with neoadjuvant chemotherapy. A few months later, in May 2009, she underwent a left mastectomy, and in September 2009, she received adjuvant tamoxifen along with radiotherapy. Due to AE, tamoxifen was switched to anastrozole, then to letrozole from May 2012 through March 2018.

During the period of remission (2012–2018), the patient had had bilateral breast prostheses. In February 2020, she presented at the hospital for an upper respiratory tract infection. Chest X-rays showed mild infiltrate on the right middle lobe and a small right pleural effusion. Following a 10-day course of antibiotics, she underwent a computed tomography (CT) of the chest, which showed enlarged mediastinal lymph nodes. Biopsy of the lymph node through endobronchial ultrasound revealed adenocarcinoma. Subsequently, two subcutaneous nodules suspicious for metastases were located near the breast implants and confirmed the recurrence of the cancer.

The patient started treatment with palbociclib and letrozole on August 3, 2020. A basic blood panel before treatment showed normal creatinine, electrolytes, liver enzymes and liver synthetic function, CBC, and TSH. She had a good clinical response to the treatment, as the nodules’ sizes decreased. Yet, on August 17, her liver function tests (LFTs) started to rise, with alanine aminotransferase (ALT) at 615 IU/mL and AST at 417 IU/mL. On August 21, 2020, the LFT values were as follows: ALT at 1,713 IU/mL and AST at 1,052 IU/mL. Creatinine kinase, alkaline phosphatase, total bilirubin, and albumin levels were all in the normal range. The patient also denied having nausea, vomiting, or abdominal pain. Abdominal echography conducted at the time of transaminitis showed hepatic steatosis and a few simple hepatic cysts without abnormal flow in the portal and hepatic veins.

An abdominal CT showed no biliary tree dilatation, no suspicious lesions, and no evidence of liver metastases. An extensive workup was done and ruled out viral, autoimmune, genetic, and metabolic liver diseases (ANA, AMA, ASMA, and LKM), complement, immunoglobulin, ferritin, ceruloplasmin, serology for HAV, HBV, HCV, HEV, CMV, and EBV were all normal. A FibroScan demonstrated very mild fibrosis, 0–1/4.

Hepatocellular drug-induced liver-injury (DILI) due to palbociclib was diagnosed. Palbociclib was discontinued. The patient was treated with IV fluids and IV NAC 300 mg/kg over a period of 21 hours. The treatment included three steps: 150 mg/kg in 200 mL D5W over 1 h, then 50 mg/kg in 500 mL D5W over 4 h, then 150 mg/kg in 1,000 mL D5W over 16 h. The level of ALT dropped by 50% in 4 days. Then, the levels decreased gradually to a normal range (Table 1).

DISCUSSION

We describe a case of a 61-year-old female who developed severe necro-inflammatory liver disease 14 days after starting treatment with palbociclib and letrozole for metastatic breast carcinoma. The patient was asymptomatic. Extensive investigation, which included blood tests and imaging, was negative. She was diagnosed as having palbociclib-triggered DILI. This was based on the lack of any other identifiable causes of acute liver injury, an excellent response to stopping the palbociclib, and treatment with NAC, as well as based on a DILI-specific assessment score. Based on the foregoing, a liver biopsy was unnecessary.

Several DILI-specific causality assessment scores have been developed over the past few decades, but none have been formally validated (5). When we applied the Roussel–Uclaf Causality
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Assessment Method (RUCAM) scale for DILI to our patient, the score suggested “probable association” (RUCAM score of 8). Rechallenging the patient with palbociclib was not an option based on data from case reports.

Most DILI events are idiosyncratic, meaning they are unexpected based on the pharmacologic actions of the drug. Idiosyncratic DILI (iDILI) is uncommon, with an incidence of 19 per 100,000 people per year (6). There is a higher risk of iDILI in women than men, in the range of 56%–59% versus 41%–44%, respectively (7). Apart from gender, other patient factors have been implicated in increased susceptibility to iDILI, namely genetic factors, aging, hormonal and nutritional status, gut microbiome, and pre-existing liver disease (8). Polymorphisms of drug-metabolizing enzymes such as NAT2, CYP2E1, GSTM1, and GSTT1 are major contributors to risk of iDILI, as are lifestyle factors such as alcohol use and high-fat diets, which can induce CYP2E1 and 4A (9).

The most common pattern of liver injury is hepatocellular (57.8%), as was seen in our patient. However, the presentation can be cholestatic (18.3%) or mixed (23.2%), particularly in older individuals (5,8).

The PAOLUMA-1 study reported elevated LFTs in 7.2% of the palbociclib-treated patients (10). In most of the cases, the liver enzymes did not increase above 5 times the limit of the normal range. Case reports discussed the occurrence of palbociclib-induced DILI. The authors of the case reports have mentioned an occurrence of acute hepatotoxicity after two to three cycles. It was managed with alternative endocrine therapy after an attempt to withhold the medication or by initiating treatment with steroids. Rechallenge with palbociclib led to re-elevation of enzymes up to 10 times the upper limit of the normal range (11–14).

The mechanism of the liver injury from palbociclib therapy is unknown. Palbociclib is metabolized in the liver largely through the CYP 3A4 pathway, and liver injury may be caused by production of a toxic or immunogenic intermediate (14). Because it is a substrate for CYP 3A4, palbociclib is susceptible to drug–drug interactions with agents that inhibit or induce this specific hepatic microsomal activity. Based on the possibility that the injury was caused by a significant increase of free radicals in the hepatocytes, we treated the patient with NAC. It is not entirely clear whether the NAC had a major role in the rapid decline of her liver enzymes and in avoiding liver damage, or whether it was the stopping of the palbociclib or a combination of the two. This success in treating the patient may be a proof of concept for the mechanism of palbociclib liver injury.

If this is the case, it is possible that our patient has polymorphisms of drug-metabolizing enzymes, namely the CYP 3A4 pathway. This is the first time, as far as we know, that the above treatment was given in palbociclib-induced DILI.

It is not clear whether letrozole contributed to the acute hepatocellular injury. Letrozole is metabolized in the liver mainly by CYP 2A6 and has less affinity to CYP 3A4. However, in higher dosage, it may block the CYP 2A6, and then the metabolic pathway is diverted to CYP 3A4 (15). It is possible that polymorphism and competition over CYP 3A4 with letrozole led to significant liver toxicity in the case of our patient.

Treating patients with NAC for non-acetaminophen-induced DILI is controversial. In our opinion, the benefit of NAC therapy outweighs its risk in two particular scenarios. First, NAC should be considered in patients who develop DILI, and there is insufficient data about the response to holding the suspected medication. Second, NAC should also be considered when the patient’s liver function continues to deteriorate toward acute liver failure, despite holding the suspected medication. It is particularly appropriate when the suspected

### Table 1: Changes in ALT levels over time

| Date (D/M/YY) | 7/7/20 | 10/8/20 | 17/8/20 | 19/8/20 | 21/8/20 | 25/8/20 | 26/8/20 | 27/8/20 | 28/8/20 | 9/9/20 | 9/12/20 |
|---------------|--------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| ALT level (U/L) | 14     | 18      | 613     | 1,313   | 1,713   | 1,114   | 1,084   | 806     | 551     | 75      | 17      |
| Palbociclib started 3/8/2020 |         |         |         |         |         |         |         |         |         |         |         |
| Palbociclib stopped 24/8/2020 |         |         |         |         |         |         |         |         |         |         |         |
| NAC started 25/8/2020 |         |         |         |         |         |         |         |         |         |         |         |

NAC = N-acetylcysteine

Palbociclib started 3/8/2020 Palbociclib stopped 24/8/2020 NAC started 25/8/2020
medication is known to be metabolized mainly through cytochrome P450. In summary, palbociclib is a selective and reversible CDK4/6 inhibitor approved for patients presenting with HR+, HER2– locally advanced or metastatic breast cancer. It rarely causes significant DILI. Our patient represents a case of severe hepatic cellular injury (× 65 ULN) 14 days after initiating treatment with palbociclib and letrozole. The necro-inflammatory process was without symptoms and did not induce hepatic synthetic malfunction. As far as we know, it is the first report that the treatment with NAC led to rapid improvement in ALT levels, up to its normalization. This should be added to the therapeutic options.

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