Unusual Hepatotoxicity With Ribociclib in Premenopausal Patient

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BACKGROUND: The introduction of cyclin inhibitors in the treatment of metastatic breast cancer has completely changed the natural history of this disease. In premenopausal women, the use of ovarian suppression + aromatase inhibitor or tamoxifen associated with ribociclib has shown not only a gain in disease-free survival, but also in overall survival, and it became the first choice of treatment for premenopausal women with HER2 negative hormone receptor-positive metastatic breast cancer. Ribociclib is a very well tolerated drug. Neutropenia, the main side effect, is easily manageable in clinical practice. However, one study showed elevation of ALT and AST grade 3 or 4 in 9.3% of patients, while other studies observed that liver dysfunction was dose-limited, and therefore should always be evaluated when using this drug. The pathophysiology of liver injury, not yet fully understood, is attributed to hepatotoxic metabolites or immunogenic effects with damage to hepatocytes similar to the ones triggered by autoimmune hepatitis. There are successful case reports with re-exposure to either the same drug or another CDK4/6 inhibitor

METHODS: We describe a case of a premenopausal woman with metastatic breast cancer who experienced severe hepatotoxicity with ribociclib. When her liver function was back to normal, a rechallenge with a lower dose of ribociclib was tried and had another liver disfunction.

RESULTS: A 34-year-old premenopausal and nulliparous woman, was diagnosed in 2020 with hepatic and lymph nodes metastatic HER2 negative, hormone receptor-positive invasive breast carcinoma, (ER 90%, PR 90%, HER2 negative, KI-67: 20%). Genetic evaluation showed pathogenic mutation in ATM and VUS in RET, and positive PIK3CA in the tumor. Her first-line treatment was according to Monaleesa-7 trial with gosserelin 3.6 mg every 28 days + letrozole 2.5 mg daily + ribociclib 600 mg/day for 21 days and a break for 7 days, without delays or dose reductions. After 3 months of treatment, with monthly laboratory tests showing normal results, a new PET-CT was performe and it showed a complete metabolic response, both in lymph nodes and in liver lesions (attached figures). In the 4th month of treatment, the patient presented symptoms of malaise, nausea, vomiting, epigastric pain, and jaundice. Laboratory tests showed: ALT 1439 (Reference value – RV: 13-35); AST 1946 (RV:10-49), Total Bilirubin 5 (RV: 1.1), INR 1.8, GGT 500 (RV<38), ALP 651 (RV: 46-116). After extensive laboratory investigation, the hypothesis of toxicity by ribociclib was raised, which was suspended. She was started with prednisone 60 mg daily associated with ursodeoxycholic acid 300 mg BID with normalization of the hepatic profile after2 months, when PET-CT was repeated, maintaining response in all lesion foci. It was decided to reintroduce ribociclib, this time at a dose of 200 mg daily, with further laboratory worsening after 2 weeks and definitive suspension of the drug. The patient is currently with non-evidence of disease, using gosserelin 3.6 mg every 28 days associated with letrozole 2.5 mg daily. Last PET-CT was performed 20 months after ribociclib discontinuation, maintaining response in all lesions.

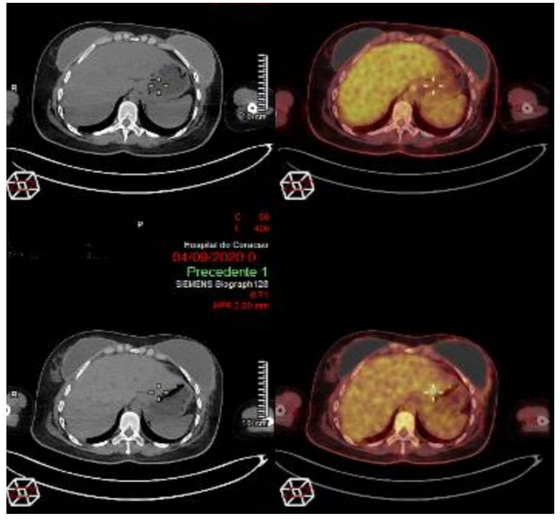

Figure 1

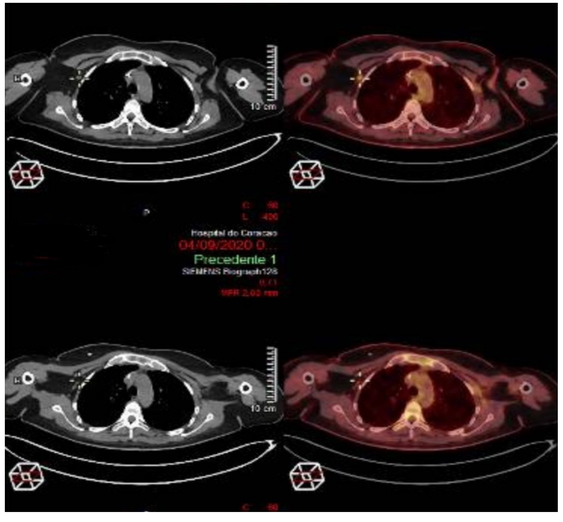

Figure 2

Figures 1 and 2: PET-TC with complete response in liver lesion and lymph nodes after 3 months of Ribociclib + Letrozole treatment

CONCLUSION: Ribociclib is a great therapeutic option for the treatment of HER2 negative HR+ metastatic breast cancer. It is generally well tolerated, however laboratory monitoring should be performed throughout the treatment period. Hepatotoxicity, although rare, may occur, with improvement after discontinuation of the drug.

REFERENCES:

- Seock-ah IM, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. N Engl J Med 2019, 381:307-316
- Hortobagy GN, et al. Ribociclib as first-line therapy for HR-positive advanced breast cancer. J Engl J Med 2016;375(18):predict1738-1748.
- Yap Y-S, et al. Ribociclib, a CDK4/6 inhibitor, plus endocrine therapy in Asian women with advanced breast cancer. Cancer sci.2020; 111(9):3313-3326
- Finnsdottir S et al. Hepatotoxicity associated with ribociclib among breast cancer patients. Acta Oncologica. Volum 60, 2021, issue 2: 195-198
- Fuentes-Antrás J, et al. Safety and efficacy of cyclin-dependent kinase inhibitor rechallenge following ribociclib-induced limiting hypertransaminasemia. The Breast, 2020: 160-163.
- Raschi E, et al. Strategies for early ion and timely recognition of drug-induces lives injury: The case of cycline-dependent Kinase 4/6 inhibitors. Front Pharmacol.2019;10:1-15.
- Meynard L at al. CDK 4/6 inhibitor successful rechallenge after limiting hepatic toxicity. Breast J 2020: 255-257.