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First case of hepatitis B virus (HBV) reactivation in a patient with breast cancer receiving CDK4/6 inhibitor drugs

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Background

Reactivation of overt or occult Hepatitis B virus (HBV) infection due to the use of immune-suppressive therapy for solid tumors is a significant cause of liver-related morbidity and mortality, even in low endemic countries.
Although international oncological societies suggest HBV screening in all patients, anticipating systemic anticancer therapy, suboptimal testing rates constitute an issue[1].
As chemotherapy is often part of breast cancer treatment, HBV reactivation has become a significant clinical problem for oncological patients with chronic HBV infection.
HBV reactivation can result in a pause in the systemic therapy administration, with uncertain consequences on prognosis [2].
Moreover, new oncological drugs that affect the immune system are constantly being tested and approved, and getting hard evidence on the actual risk of HBV reactivation can be a challenge.
Palbociclib and ribociclib are CDK4/6 inhibitors recently approved for metastatic luminal breast cancer.
They represent the standard of care for Estrogen Receptor (ER) and Progesterone Receptor (PgR) positive and human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer, combined with endocrine therapy[3].
In previous randomized controlled trials, acceptable liver function was part of the eligibility criteria; instead , HBV/HCV screening was not mandatory, and no specific data are available regarding liver toxicity in chronic carriers of viral hepatitis[4].
Hence, HBV reactivation can pose a real clinical problem in the management of oncological patients.

Case report

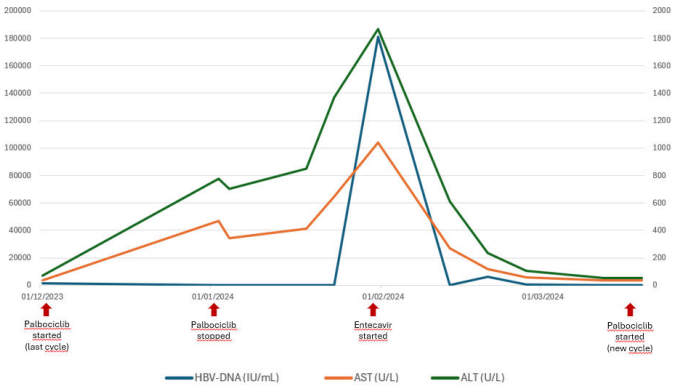
A 71-year-old Italian woman was diagnosed with breast cancer in 2001.
She underwent surgery and was treated with adjuvant endocrine therapy and radiotherapy, with a complete response.
In 2010, she was admitted to Infectious Diseases Unit for osteomyelitis of the toe. Her results were compatible with a profile of chronic HBV inactive infection (HBsAg and anti-HBc positive with negative IgM, HBV-DNA 1530 IU/mL), with normal transaminase levels.
At that time, an ultrasound showed moderate liver fibrosis.
As a result, we initiated a follow-up program without starting any prophylactic regimen.
In 2014, she was diagnosed with skull and vertebral metastasis, treated with cycles of radiotherapy and hormone agents, with a partial response.
Right after the treatment, she discontinued coming the scheduled appointments in our clinic.
In December 2022, disease progression was radiologically documented, with the metastatic lesions increasing in size and metabolic activity.
Combination treatment with palbociclib in association with fulvestrant, an anti-estrogen drug, was started, monitoring her liver and kidney function, without any significant modifications.
In December 2023, a short cycle of low-dose oral corticosteroids (two weeks, prednisone 7.5 mg daily) was administered for pain management.
In January 2024, a sudden increase in the transaminase and the gamma-glutammyl transpeptidase levels were reported (ALT 645 IU/L, AST 726 IU/L, GGT 267 IU/L respectively).
A virological test was again, performed showing HBV reactivation with a three-log increase in HBV DNA, compared to baseline (HBV-DNA 1810000 IU/mL), without any serological change.
The detailed lab values at the time of the reactivation are shown in Table 1.

Table 1 - Laboratoy values at time of HBV-reactivation

HAV-Ab IgG	+	WBC (K/mcl)	9,01
HAV-Ab IgM	-	Hb (g/dL)	12
HBsAg	+	Platelets (K/mcl)	184
HBsAb	-	AST (U/L)	645
Total HBcAb	+	ALT (U/L)	726
HBcAb IgM	-	Gamma-glutamyl transpeptidase (U/L)	267
HBeAg	-	Alkaline phosphatase (U/L)	176
HBeAb	+	Albumin (g/dL)	3,8
HBV-DNA PCR (IU/mL)	1.810.000	Total Bilirubin (mg/dL)	0,7
HCV-Ab	-	INR	0,99
HEV-Ab IgG	-	Creatinine (mg/dL)	1
HEV-Ab IgM	-	Sodium (mEq/L)	141
HDV-Ab	-	Potassium (mEq/L)	4,1
		LDH (U/L)	478

The oncological regimen was immediately stopped, and liver function kept getting worse (AST 1040 IU/mL, ALT 826 IU/mL, GGT 375 IU/L, total bilirubin 1,1 mg/dL).
Then, we initiated antiviral therapy with entecavir.
Two months later, liver functionality tests returned to normal, with low levels of HBV-DNA (172 IU/mL).
US and transient elastography showed moderate liver fibrosis (7.9 kPa), with no significant change from previous radiological tests.
Thus, we started the oncological therapy again, keeping the antiviral treatment.
US and transient elastography showed moderate liver fibrosis (7.9 kPa), with no significant change from previous radiological tests.
Therefore, we initiated the oncological therapy again, while keeping the antiviral treatment.
At the moment, the patient is stable, her liver function is normal, HBV-DNA level is under the test limit of detection and her performance status (PS) is 1.
Changes in HBV-DNA during the course are presented in Fig. 1, as well as transaminase levels.

Figure 1. HBV-DNA, AST/ALT trends over time



Conclusion

According to international guidelines, low dose, short term steroid treatment, is not a risk for HBV reactivation.
Although, we cannot exclude an additive role for this treatment, CDK 4/6 inhibitor should be considered the main causative agent for reactivation in our patient.
It is suggested that chronic carriers of HBV - like the patient studied here- following treatment on CDK 4/6 inhibitor may experience hepatitis reactivation.
These findings need to be further investigated by larger trials.
However, this case highlights the importance of HBV screening and prophylaxis for people receiving this new drug class.

References

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