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Hepatitis B Virus Reactivation in Oncological Patients who Underwent Chemotherapy. Filantropia Clinical Hospital Five Years' Experience

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ABSTRACT

Objectives: *The aim of the current study is to assess the prevalence of hepatitis B and the risk of hepatitis reactivation in carriers of hepatitis B virus (HBV) cancer patients who underwent chemotherapy for gynecologic and/or breast cancers in a single institution, during a period of five years, and to identify a relationship to some particular chemotherapy regimen, more prone to lead to reactivation.*

Materials and methods: *We conducted a retrospective chart review on all consecutive oncological patients treated for a gynecologic and/or breast cancers who presented for the first time to the Gynecologic Oncology Department of Filantropia Hospital, Bucharest, Romania, between January 2016 and December 2020.*

Results: *A total of 1 895 patients diagnosed with ovarian, cervical, endometrial or breast cancers were admitted to hospital for systemic therapy during the mentioned period. Among these, only four patients (two patients with breast cancers, one cervical cancer and one endometrial carcinoma) were chronic carriers of HBV surface antigen (HBsAg positive). Patients received a variety of chemotherapeutic regimens including corticosteroids, gemcitabine, cisplatin, carboplatin, taxanes and anthracyclines. We report one reactivation that occurred in one occult carrier of hepatitis B virus diagnosed with breast cancer (HBsAg negative, hepatitis B core antibody positive – HBcAb), initially excluded from this study, as being screened negative for HBV, treated with taxanes-based chemotherapy and corticosteroids.*

Conclusion: *HBV reactivation had a low incidence in our population of patients diagnosed with gynecologic or breast cancer who received systemic chemotherapy. The HBV reactivation risk was positively correlated with breast cancer and to taxanes-based regimens and glucocorticoids. Further studies to identify additional risk factors of HBV infection reactivation in gynecologic oncology patients and possible risk reducing measures are warranted.*

Keywords: HBV reactivation, gynecologic cancer, breast cancer, taxanes, glucocorticoids.

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INTRODUCTION

For more than the last two decades, Romania has been on top of the list when talking about the incidence of hepatitis B infection (HBV) in Europe, with a prevalence of 4.4% for chronic HBV infection and 27.0% of the general population having a history of previous HBV (1). Additionally, according to Globocan (2), breast cancer is the most frequent female malignancy worldwide (in terms of incidence and mortality), cervical cancer is on the 4th place and uterine cancer on 8th. Data for Romania shows that cervical cancer ranks third for incidence, followed by uterine cancer (fifth) and ovarian cancer (sixth), with breast cancer still ranking first for incidence and mortality.

Chemotherapy-induced hepatitis B reactivation is reported in several papers (4, 5). When occurring, manifestations can vary largely from asymptomatic and self-limiting hepatitis to potentially life-threatening hepatic failure (6). Clinical trials correlate the risk of HBV reactivation to both the serological profile of the infected patient and immunosuppressive potential of the chemotherapy regimen received (7). Thus, the more aggressive the immunosuppressive effect of the chemotherapy regimen, the higher the viral reactivation risk is (e.g., hematological malignancies) (8-12). But the real magnitude of the risk for hepatitis B virus reactivation with chemotherapy for solid malignant tumors is yet to be established.

Despite the minor effect on the immune system of the chemotherapy regimens used in solid cancers when compared to those used in hematologic malignancies, a higher rate of HBV reactivation has been reported for patients with breast cancer (41-56%) (13-16) and a lower rate for other solid tumors (14-21%) (17-19). Moreover, an increased risk of HBV reactivation has been observed when using chemotherapy regimens that contain corticosteroids, rituximab or anthracycline (17, 20-23).

The aim of our retrospective study was to evaluate the prevalence of hepatitis B and the risk of HBV reactivation in women who underwent chemotherapy for gynecologic cancers, including breast cancer, and to assess which chemotherapy regimen was more prone for reactivation. ❑

MATERIAL AND METHODS

We performed a retrospective chart review of newly consecutive diagnosed cancer patients with gynecologic malignant tumors, including breast cancer, who received chemotherapy between 2016 and 2020 in the Gynecologic Oncology Department of Filantropia Clinical Hospital, Bucharest, Romania. Only women who were positive for HBsAg at the onset of chemotherapy were included in this report. Patients were completely evaluated prior to chemotherapy administration through blood tests. Liver function tests, which included alanine aminotransferases (ALT) and aspartate aminotransferases (AST), were evaluated before each chemotherapy cycle. HBV-DNA detection tests followed if any rise in transaminase levels occurred.

Data we recorded from patients' charts included the year of first admission to hospital, age, type of malignancy, tumor stage, chemotherapy agents, viral marker HBsAg, HBV load when needed and result of serum liver biochemical test prior to the beginning of the chemotherapy and at end of treatment or any time a rise was observed. HBV DNA level was not available at baseline for all patients.

We considered HBV reactivation the reappearance of HBV DNA in a patient who previously had undetectable HBV DNA and hepatitis flare – an increase greater than five-fold the upper limit of normal (ULN) in ALT that exceeded 100 IU/L (without any other identifiable cause) or the reverse seroconversion (reappearance of HBsAg in a patient with a history of past HBV infection and who was negative for HBsAg at baseline). ❑

RESULTS

A total of 1 895 new patients were admitted to hospital for chemotherapy during the mentioned period. Among these, we identified four patients (0.21%) who had hepatitis B infection (HBsAg positive) at baseline and a gynecologic malignant tumor, including breast cancer. The fifth patient was HBsAg negative. Table 1 shows the main characteristics of patients at baseline, including the year of the first presentation, age,

TABLE 1. Baseline patient characteristics

No	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Year	2017	2018	2018	2019	2020
Age (years)	48	57	63	66	64
Type of cancer	Cervix	Endometrium	Breast	Breast	Breast
Stage	FIGO III B	FIGO III A	T1cN0M0	T4dN1Mx	T4bN0M1x

P – patients.

TABLE 2. Chemotherapy regimens and duration of chemotherapy

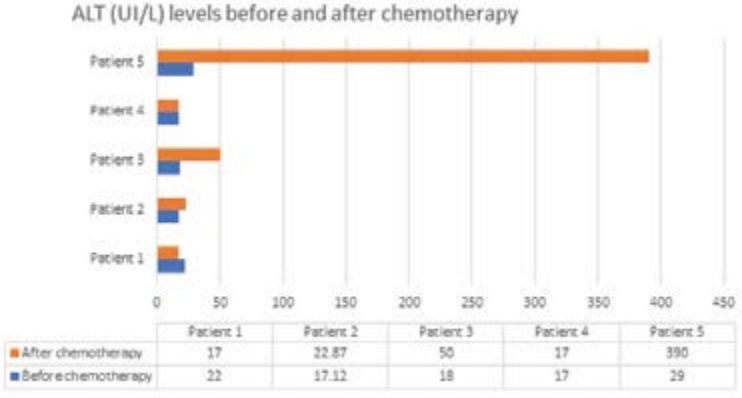
	Diagnosis of cancer	Treatment regimen	No of cycles	Anti-viral treatment
P1	Cervix uteri	Corticosteroids/Gemcitabine/Cisplatin	6	Yes
P2	Endometrium	Corticosteroids/Taxanes/Carboplatin		Yes
P3	Breast	Corticosteroids/Anthracyclines/Taxanes	6	No
P4	Breast	Anthracyclines	8	No
P5	Breast	Corticosteroids/Taxanes	6	No

+ positive; - negative

TABLE 3. Serologic profile of each patient

Nr	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Ag HBs	+	+	+	+	-
Ac HBc					
Ac HBc Ig M	-	-			
Ac HBc Ig G	+	+	+	+	
Anti HBs	-	-			
HBV DNA	Undetected	Undetected	Undetected		

TABLE 4. ALT (UI/L) levels before and after chemotherapy



type of cancer and stage. The median age was 63 years. Out of the five patients, three (60%) had breast cancer, one (20%) had cervix cancer and one (20%) had endometrial carcinoma.

Table 2 summarizes the chemotherapy regimens administered to each patient, depending on the type of diagnosed cancer, number of cycles and whether the patient has received an anti-HBV treatment. The fifth patient was HBsAg negative at the beginning of chemotherapy, therefore no further investigations were conducted.

Table 3 presents the serologic profile of each patient at the beginning of the oncologic treatment. All patients were tested for HBsAg, yet further investigations were conducted only for two patients who had been recently detected with the viral infection and were already under antiviral treatment, medication that was administered simultaneously with the chemotherapy, as the viral load was undetectable. All patients were negative for hepatitis D.

Table 4 shows the ALT (IU/L) levels at the beginning and at the end of the chemotherapy regimens administration. All four HBsAg positive patients had no rise in serum alanine aminotransferase; two of them were simultaneously administered anti-viral treatment and chemotherapy. However, the fifth patient, who was initially HBsAg negative, developed an increase of ALT level up to 390 UI/L (x 11 ULN) throughout the course of chemotherapy. Further investigations identified the presence of HBsAg at that moment. The patient was diagnosed with HBV reactivation, although no previous history of HBV infection was documented, and an oral antiviral drug (entecavir) was immediately administered. ALT values normalized within the next couple of weeks. Fortunately, the increase was noticed during the 6th chemotherapeutic cycle and no treatment postponement was required. The patient was a 64-year-old woman diagnosed with advanced breast cancer and received both corticosteroids and taxanes. ❑

DISCUSSION

HBV reactivation subsequent to the administration of chemotherapy in HBsAg positive oncologic patients is a matter of concern and has been widely studied, especially in hematologic malignancies (24-28). This is the main reason why patients who are positive during the HBV screening tests receive prophylactic antiviral treatment according to the Centers for Disease Control and Prevention (CDC) and American As-

sociation for the Study of Liver Diseases (AASLD) recommendations (29). However, data remains less clear for solid tumors. Yet, there is limited medical information regarding a higher risk of HBV reactivation particularly in breast cancer patients receiving anthracycline-based regimens (30). One study reported a 41% HVB reactivation rate in breast cancer patients who underwent chemotherapy (30). Another retrospective study, published in 2015, demonstrated that the incidences of severe acute exacerbation of chronic HBV in HBsAg positive patients with breast cancer and gynecological cancer were 9% and 16.7%, respectively (31). Yeo et al. reported that pre-chemotherapy HBV DNA level, the use of steroids and a diagnosis of lymphoma or breast cancer were risk factors associated with viral reactivation in oncologic patients whoo needed chemotherapy (20).

Literature data were confirmed in our study by the patient with breast cancer treated with corticosteroids and taxanes that reactivated HBV infection.

As stated before, the HBV reactivation in gynecologic cancer patients has not been completely clarified. Type of anticancer drugs and type of cancer that facilitate HBV reactivation are still to be addressed. However, breast cancer and concomitant steroid treatment or treatment with anthracyclines have been stated to be risk factors for HBV reactivation in many studies (17, 20, 24-25, 32-35). ❑

CONCLUSIONS

HBV reactivation had a low incidence in our population of patients diagnosed with gynecologic or breast cancer that received systemic chemotherapy. However, we have to keep a high index of suspicion and continue to investigate all patients prior to initiating chemotherapy, including occult carriers. The risk of HBV reactivation was positively correlated to breast cancer and taxanes-based regimens and glucocorticoids. Nevertheless, further studies to identify additional risk factors for HBV infection reactivation in gynecologic oncology patients and possible risk reducing measures are mandatory. ❑

Conflicts of interest: none declared.

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