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Hepatitis B and/or C virus reactivation in patients receiving chemotherapy: An observational study

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ABSTRACT

Background: Viral hepatitis reactivation occurs during various chemotherapy treatments. Patients with high serum titer levels of Hepatitis B virus (HBV) DNA before chemotherapy and those receiving intensive chemotherapy for hematological malignancies are particularly at risk. **Aims and Objectives:** This study aimed to determine the incidence, predictors, and clinical significance of HBV and hepatitis C virus reactivations during chemotherapy. **Materials and Methods:** This prospective observational study was conducted at a tertiary care center. Hepatitis B and C virus status was identified before the initiation of cancer treatment. Liver function was monitored in all patients before each cycle of chemotherapy. Patients with deranged liver function were subjected to repeated viral antigen tests and DNA/RNA titer levels. **Results:** A total of 110 patients were identified as having hepatitis virus reactivation out of 1190 patients. The sites of malignancy were breast, 39.1% (43 patients); colorectal, 11.8% (13 patients); upper gastrointestinal, 10% (11 patients); ovary, 9.1% (10 patients); hematological malignancies, 8.2% (9 patients); lung, 5.6% (6 patients); genitourinary, 4.5% (5 patients); head-and-neck, 4.5% (5 patients); biliary tract, 3.6% (4 patients); brain tumor, 1.8% (2 patients); and others, 1.8% (2 patients). Most of the patients with reactivation received 5-FU/Capecitabine-based chemotherapy 37.3%, (41 patients), taxane plus platinum (10.9%, 12 patients), taxane only (10%, 11 patients), trastuzumab (8.2%, 9 patients), platinum-based (6.4%, 7 patients), tyrosine kinase inhibitors (6.4%, 7 patients), monoclonal antibodies (MABs) (3.6%, 4 patients), anthracyclines (2.7%, 3 patients), immunomodulators (2.7%, 3 patients), and other agents (11.8%, 13 patients). **Conclusion:** We recommend that Hepatitis B and C virus Screening must me performed before chemotherapy and that non-reactive patients should be vaccinated.

Key words: Reactivation; Hepatitis virus; Chemotherapy; Malignancy; Hepatitis B virus

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\INTRODUCTION

Viral hepatitis reactivation is a treatment challenge encountered during various chemotherapy regimens. Hepatitis B virus (HBV) or Hepatitis C virus (HCV) reactivation may result in treatment break and liver failure posing a major problem.[1,2] There is a clear association between Hepatitis B virus reactivation and some anticancer drugs, such as MABs and immune checkpoint inhibitors.[3-7] In contrast, the incidence and consequences of Hepatitis C virus reactivation during cancer treatment remain poorly defined. HCV reactivation is less common and has less severe consequences than HBV reactivation.[2,8,9] In most cases, reactivation occurs in patients with chronic HBV infection and is positive for Hepatitis B surface antigen (HBsAg). Reactivation may also occur in patients with resolved infection who are HBsAg-negative, anti-HBs-positive, and anti-Hepatitis B core positive. Patients with high serum titer levels of HBV DNA before chemotherapy and those receiving intensive chemotherapy for hematological malignancies are particularly at risk.

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The pathogenesis of hepatitis virus reactivation can be divided into three stages.[10] First stage begins with an increase in viral replication on starting immunosuppressive agents. The second stage occurs after the discontinuation of treatment when the immune system starts recovering and attacking infected hepatocytes. The final stage is the recovery phase when hepatitis resolves and viral replication returns to baseline levels. The pathogenesis of Hepatitis B and C viral reactivation seems to be similar.

The conventional definition of HBV reactivation during chemotherapy is the development of hepatitis with a serum alanine transaminase (ALT) level >3 times the upper limit of normal, and/or an increase in HBV DNA by at least 10-fold, or an absolute increase to >108 IU/mL. Similarly, HCV reactivation can be defined as an increase of HCV-RNA viral load >1 log10 IU/mL and/or at least a threefold increase in serum ALT in HCV-infected patients.[11]

However, the American Association for the Study of Liver Diseases 2018 updated guidelines defined HBV reactivation in HBsAg positive patients as at least 2 log (or 100 fold) increase in HBV DNA level compared to baseline. Moreover, for HBsAg negative but anti-HBc positive patients, HBV reactivation is defined as detectable HBV DNA level or reappearance of HBsAg.[12]

Aims and objectives

This study aimed to determine the incidence, predictors, and clinical significance of HBV and HCV reactivations during chemotherapy.

MATERIALS AND METHODS

Study design and setting

This prospective observational study was conducted on 1190 patients in a tertiary care center from June 2022 to May 2023. The study was approved by the Institutional Ethics Committee before initiation, and informed consent was obtained from all patients.

Inclusion criteria

Patients with histologically proven hematological or solid malignancy, age: 18–65 years, performance status (Karnofsky performance status [KPS] ≥70% or Eastern cooperative oncology group [ECOG] ≤2), and planned for chemotherapy or targeted agents were included in the study.

Exclusion criteria

Patients with performance status (KPS <70% or ECOG >2), hepatocellular carcinoma, and metastasis to the liver were excluded from the study.

Methods and data collections

Hepatitis B and C virus status was identified before the initiation of cancer treatment. Liver function was monitored in all patients before each cycle of chemotherapy. Patients with deranged liver function were subjected to repeated viral antigen tests and DNA/RNA titer levels. Predictors of reactivation, such as the nutritional status of the patient, type of malignancy, chemotherapy agent, dose, and frequency, were identified.

The patients with reactivation were treated with antiviral drugs and supportive care. Chemotherapy was stopped during the acute phase and was resumed on normalization of liver function. All patients were followed up according to the guidelines. All data are presented as frequencies and percentages.

RESULTS

Among the 1190 patients, 110 (9.24%) were identified with hepatitis viral reactivation during the study period of 1 year. Among the patients with reactivation, the sites of malignancy were identified as breast, 39.1% (43 patients); colorectal, 11.8% (13 patients); upper gastrointestinal, 10% (11 patients); ovary, 9.1% (10 patients); hematological malignancies, 8.2% (9 patients); lung, 5.6% (6 patients); genitourinary, 4.5% (5 patients); head-–and-neck, 4.5% (5 patients); biliary tract, 3.6% (4 patients); brain tumor, 1.8% (2 patients); and others 1.8% (2 patients) (Table 1).

Most of the patients with reactivation received 5-FU/Capecitabine-based chemotherapy 37.3% (41 patients), taxane plus platinum 10.9% (12 patients), taxane only 10% (11 patients), trastuzumab 8.2% (9 patients), platinum-based 6.4% (7 patients), tyrosine kinase inhibitor (TKI) 6.4% (7 patients), MABs 3.6% (4 patients), anthracyclines 2.7% (3 patients), immunomodulators 2.7% (3 patients), and other agents 11.8% (13 patients) (Figure 1).

Most patients with reactivation have already received multiple lines of chemotherapy. Furthermore, 79.1% of patients showing reactivation had advanced-stage cancer (79.1%), and chemotherapy was stopped for a median period of 2 months (range, 1–3 months) due to reactivation.

DISCUSSION

Hepatitis virus reactivation is a known phenomenon in cancer patients undergoing chemotherapy. However, the exact frequency and associated risk factors for hepatitis virus reactivation are not well understood. The reported rates of HBV reactivation in hepatitis virus carriers undergoing chemotherapy vary from 20% to 57%.[13]

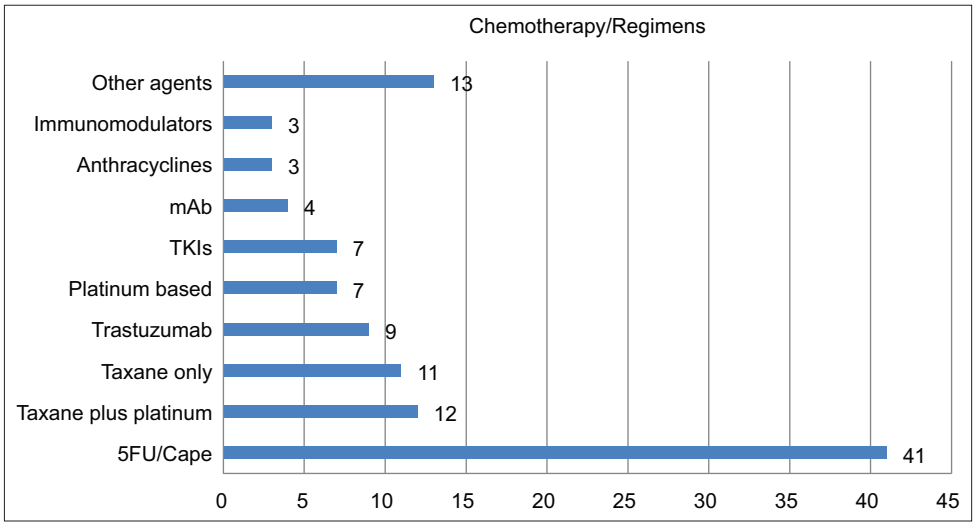

Figure 1: Distribution of chemotherapy

Table 1: Patient characteristics (n=110)

Variable	Frequency (%) n=110
Age in years (median, range)	51 (21–71)
Gender	
Male	42 (38)
Female	68 (62)
Performance status	
PS 1	73 (66)
PS 2	37 (34)
Tumor type	
Breast	43 (39.1)
Colorectal	13 (11.8)
Upper GI	11 (10)
Ovary	10 (9.1)
Hematological malignancy	9 (8.2)
Lung	6 (5.6)
Genitourinary	5 (4.5)
Head-and-neck	5 (4.5)
Biliary tract	4 (3.6)
Brain tumor	2 (1.8)
Others	2 (1.8)
Stage	
I	5 (4.5)
II	18 (16.4)
III	48 (43.6)
IV	39 (35.5)
Lines of chemotherapy	
1st line	34 (30.9)
Multiple lines	76 (69.1)

In our study, 9.24% of the patients showed hepatitis viral reactivation. HCV reactivation seems less common than HBV reactivation. Only eight patients tested positive for HCV, among which four patients were also positive for HBV. Multiple risk factors for hepatitis virus reactivation in cancer patients have been identified, such as treatment for hematologic malignancies, type of cancer treatment, and high levels of pre-chemotherapy HBV DNA.[14] However, the exact mechanism of risk is not clearly defined.

The possible reason for hepatitis viral reactivation in cancer patients receiving chemotherapy is the decreased level of immunity which is further enhanced by chemotherapy or targeted therapy. The reactivation can occur during the course of chemotherapy or after discontinuation of treatment. The risk of HBV reactivation can be classified based on the potency of immunosuppressive agents such as (a) high risk (>10% chance) – MABs, doxorubicin; (b) moderate risk (1% to 10% chance) – TKs like imatinib; and (c) low risk (<1% chance) – other conventional chemotherapeutic agents.[15]

HBV reactivation is observed mainly in patients who are HBsAg positive. However, viral reactivation can also occur in previously infected patients who have cleared of the virus. These patients can be identified based on the presence of antibodies against the Hepatitis B core antigen or HBsAg. Patients with HBV reactivation may be asymptomatic or have symptoms of hepatitis. Hepatitis reactivation may progress to liver failure or even death. Two patients with HBV reactivation died of liver failure. Therefore, patients with cancer should undergo Hepatitis B and C virus screening before commencing specific therapy.

Among patients with solid tumors, rising trends in hepatitis virus reactivation have been observed in breast cancer patients (as high as 41–56%).[16,17] We also observed similar findings in this study because of the high incidence of female breast cancer. Reactivation typically starts with a rise in viral replication.[10] The rise in viral replication can be measured by the serum HBV DNA levels. This increase can precede an increase in liver enzyme levels. The risk of HBV reactivation depends on both the specific type of cancer and the chemotherapy drugs administered.

All patients planned for chemotherapy or any immunosuppressive therapy should be screened for HBV and HCV serological status and patients with moderate to high risk for reactivation shall be considered for antiviral prophylaxis.[18]

Disruption of chemotherapy due to hepatitis virus reactivation can have a detrimental impact on the overall survival. The median duration of the treatment break observed in this study was 2 months (Range, 1–3 months). The maximum number of patients with viral reactivation in the present study was treated with 5FU/Capecitabine followed by taxane plus platinum chemotherapy. However, other agents, such as trastuzumab, platinum compounds, anthracyclines, TKIs, MABs, and immunomodulators, are involved in HBV/HCV reactivation. Older age and previous exposure to multiple lines of chemotherapy were associated with a higher risk of hepatitis virus reactivation.

HBV reactivation can be prevented by antiviral drugs and should be initiated before cancer therapy. Entecavir or tenofovir are preferred over lamivudine for prophylaxis of HBV reactivation and current international guidelines suggest continuation of antiviral therapy for at least 6–12 months after the discontinuation of cancer treatment.[19]

Limitations of the study

A limitation of this study is that we did not compare hepatitis virus reactivation among patients diagnosed with different types of cancer and who received various chemotherapy regimens.

CONCLUSION

Hepatitis virus reactivation leads to interruption of cancer treatment, causing tumor progression or mortality, and may ultimately affect clinical outcomes. We recommend that Hepatitis B and C virus screening must be performed before chemotherapy, and non-reactive patients should be vaccinated.

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