Clinical Profile and Efficacy of Antivirals in Hepatitis B Virus Reactivation, in Patients With Cancer Receiving Chemotherapy

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Background/Purpose: Hepatitis B virus reactivation (HBVR) is common in patients with cancer. The aim of the present study was to find out clinical profile of patients with cancer receiving chemotherapy with HBVR and to study the efficacy of entecavir (ETV) and tenofovir in the treatment of HBVR. **Methods:** This is a prospective study in which all consecutive patients with cancer with evidence of HBVR were included. HBVR was defined as: New onset transaminitis with alanine aminotransferase (ALT) >3 times upper limit of normal and >10 fold increase in HBV DNA levels from baseline levels or detection of HBV DNA $\geq 100,000$ IU/ml in patients with no baseline HBV DNA. Patients with HBVR were put on ETV or tenofovir and were closely monitored for efficacy and safety for minimum of 1 year. **Results:** Of 204 Hepatitis B surface antigen (HBsAg)-positive patients with different cancers, 92 met the inclusion criteria. Of 92, 46 received ETV 0.5 mg/day and 46 received tenofovir disoproxil fumarate (TDF) 300 mg/day. At 6 months, there was 4.7 log reduction in HBV DNA level in the ETV group and 5.2 log reduction in the TDF group ($P = 0.029$). Proportion of patients with undetectable HBV DNA (75.7% vs 87.5%), ALT normalization (89.2% Vs 87.5%), HBsAg negativity (25% vs 28.1%), and seroconversion (2.8% vs 3.1%) at 1 year were almost similar in both groups with P value > 0.05 for all efficacy end points. There was no HBVR-related mortality in any group. **Conclusion:** Both ETV and tenofovir are very effective in the treatment of HBVR and reduce the liver-related mortality and morbidity in such patients. (J CLIN EXP HEPATOL 2020;10:590–598)

Hepatitis B virus (HBV) infection is the most common chronic viral infection in the world. An estimated 2 billion people have been infected, and about 350 million are chronic carriers of the virus.¹ HBV infection can cause life-threatening complications such as fulminant liver failure, chronic liver disease (CLD) and hepatocellular carcinoma (HCC). Prevalence of HBV infection is higher in hemato-oncological patients ranging from 3.26% to 22% than in general population.^{2–5}

HBV infection in patients with cancer is primarily due to reactivation of a previous infection usually acquired in perinatal period, and due to treatment-related immune suppression.² Reactivation has been shown to occur with chemotherapy (CT) for both solid and hematological cancers^{6–9} particularly when using rituximab.¹⁰ With the introduction of universal screening of blood products for hepatitis B, the proportion of transfusion associated hepatitis B has declined but the risk of transfusion associated hepatitis B still exists because of occult hepatitis B.¹¹

HBV reactivation (HBVR) in patients with cancer is marked by the clinical or biochemical features of hepatitis and surge in HBV DNA in patients with previously occult or resolved HBV infection.^{6,8,12} In patients who are asymptomatic HBV carriers, CT-induced immunosuppression can result in HBV reactivation, causing severe morbidity and mortality.

All the latest hepatitis B guidelines including EASL 2017,¹³ AASLD 2018,¹⁴ and INASL 2018¹⁵ recommend HBV infection screening in all patients with cancer, before starting CT. However, clinical oncology guidelines (ASCO Provisional Clinical Opinion 2010) are unclear and do not recommend routine screening of HBV infection in all patients as the evidence is insufficient to determine the net benefits and harms of routine screening for chronic HBV infection in individuals with cancer who are about to

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Abbreviations: AASLD: American Association of Study of Liver Diseases; ADR: Adverse Drug Reaction; ALT: Alanine Aminotransferase; ANOVA: Analysis of Variance; CHB: Chronic Hepatitis B; CT: Chemotherapy; CXR: Chest X-ray; EASL: European Association of Study of Liver; ETV: Entecavir; HBV: Hepatitis B Virus; HBVR: Hepatitis B Virus reactivation; HCC: Hepatocellular Carcinoma; INASL: Indian National Association of Study of Liver; PCR: Polymerase Chain Reaction; TAF: Tenofovir Alafenamide; TDF: Tenofovir Disoproxil Fumarate; USG: Ultrasonography

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receive cytotoxic or immunosuppressive therapy or who are already receiving therapy.¹⁶ Besides cost effectiveness for screening and monitoring all patients for HBV infection is also controversial.^{17,18} Similar problem exists in other parts of the world also.^{19,20} Because of these reasons, most of the patients are not screened which results in patients being referred to gastroenterologists once the reactivation has already set in.

There are only few case reports or case series in literature in which patients receiving CT with HBVR have been treated with entecavir (ETV) or tenofovir.^{21,22} ETV is a carbocyclic analog of 2'-deoxyguanosine. It is more potent than lamivudine and adefovir, and it is effective against lamivudine-resistant HBV.²³ ETV has been successfully used for the treatment of HBVR in patients with cancer in case reports and case series.²⁴⁻²⁶ Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir, and is structurally similar to adefovir. It is more potent than adefovir at suppressing lamivudine-resistant HBV DNA.²⁷ Although it is known that ETV and tenofovir are better antiviral drugs than lamivudine, there are no proper efficacy studies in HBV reactivation.

This study was undertaken with the aim to find out clinical profile of patients with cancer receiving CT with HBVR and the comparative efficacy of ETV and tenofovir in the treatment of HBVR and its outcome in terms of mortality and morbidity, as well as prevention of complications.

MATERIAL AND METHODS

The present study was conducted at a 900 bedded tertiary care center in the Department of Gastroenterology in collaboration with Department of Medical Oncology and Clinical Hematology from October 2012 to January 2015.

Study population

This was a prospective study in which all consecutive patients with different cancers who had received CT or were on CT with evidence of HBVR were included. The study was approved by the local institutional ethics committee. HBVR was defined as: New onset transaminitis [Alanine aminotransferase (ALT)] > 3 times upper limit of normal and >10 fold increase in HBV DNA levels from baseline levels or detection of HBV DNA with level $\geq 100,000$ IU/ml in a person with no baseline HBV DNA.⁹

Exclusion criteria

The exclusion criteria were as follows: (1) Patients who did not give informed consent. (2) Children younger than 18 years of age. (3) Patients with acute hepatitis B and chronic hepatitis B who did not fit in the definition of HBVR. (4) Patients with coinfection with other hepatotropic viruses,

HIV, and patients with HCC. (5) Patients who are pregnant/breast feeding women.

Study design

A written informed consent was taken from the patients before conducting the study. After the detailed history (history of drugs, risk factors, and surgery) and examination, all baseline investigations were sent which included complete blood count, kidney function tests, liver function tests, coagulogram, ECG (Electrocardiogram), chest x-ray, and ultrasonography abdomen. Full panel of hepatitis viral markers were sent which included Hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), IgM anti-HBc, anti-HBe Ab, anti-HBs antibody, HBV DNA levels, IgM anti-HAV, IgM anti-HEV, IgM anti-HDV, and anti-HCV. The address and phone numbers of the patients were recorded for follow-up.

Because all the patients with cancer with hepatitis B infection who were assessed for eligibility did not have baseline HBsAg and Anti-HBc, there was problem of differentiating de novo hepatitis/acute HBV infection from HBVR. This problem was solved by defining acute hepatitis B as follows: hepatic injury characterized by elevated ALT and aspartate aminotransferase (AST), HBsAg positive/IgM anti-HB core positive with HBV DNA level $<10^5$ IU/ml and anti-HBe negative.^{28,29} Hepatitis B carrier was defined by HBsAg-positive, normal ALT and AST, negative HBeAg, and positive anti-Hbe and serum HBV DNA less than 2000 IU/mL.³⁰ Acute severe hepatitis was defined by the presence of high bilirubin (≥ 18 mg/dl), coagulopathy (INR ≥ 1.5), ascites or encephalopathy.

Screening for markers of HBV infection

HBsAg testing was carried out by ELISA (Micro screen, HBsAg ELISA kit, Span Diagnostics). Total and IgM anti-HBc antibody was tested by enzyme immunoassay (EIA-Anti-HBc-MScreen, DSI S.R.I. Serono [VA], Italy). Anti-HBs antibodies were detected by (DS-EIA-Anti-HBsAg kit, DSI S.R.I). Hepatitis B viral DNA quantification was carried out by real-time polymerase chain reaction assay on COBAS Ampliprep/Cobas TaqMan on the patient's plasma. The lower limit of detection of this assay is 20 IU/ml.

Treatment protocol

All patients of HBVR were assessed for symptoms, and thorough examination was carried out to look for complications and were given supportive treatment as needed. Patients were put on either ETV or TDF on the basis of open computer-generated random numbers by the statistical software MiniTab14 and categorized into two groups.

One group received Tab. ETV 0.5 mg once a day (OD) and another TDF 300 mg OD.

Follow-up

Patients with HBVR who were put on treatment were closely monitored, mostly on outdoor patient department basis and were followed for minimum of 1 year. Monitoring at regular intervals was carried out by calling the patients on their cell phones. Liver function tests were repeated at 2, 4, 8, 12 weeks and then at 3 monthly intervals. HBs Ag, HBe Ag, and HBV DNA level were repeated at 3 months, 6 months, 12 months, 18 months, and 24 months. Patients on treatment were reassessed regularly to look for the progression of the liver disease in the form of development of acute liver failure (defined as development of hepatic encephalopathy within 8 weeks of symptom onset), CLD or development of any adverse effects due to drugs.

Outcomes

Efficacy of two drugs was compared by assessing the following end points in each group: reduction in HBV DNA level at 6 months from the baseline, proportion of patients with undetectable HBV DNA at 1 year, proportion of patients with HBsAg loss at 1 year, and proportion of patients who died because of HBV reactivation.

Statistical analysis

Data were analyzed by descriptive statistics such as means, median, range, standard deviations, and percentage. Chi square test was used for studying and comparing the categorical variables. Student independent t-test was used to see the difference in means. Analysis of repeated measures was used to assess the reduction in HBV DNA/ALT level at different time points. *P*-value <0.05 was considered statistically significant. SPSS, version 16.0 was used to carry out the statistical analysis of data.

RESULTS

Study population

Two hundred four patients with different cancers were referred to the Department of Gastroenterology with evidence of HBV infection from October 2012 to August 2015 over a period of 3 years. One hundred twelve patients were excluded. Twenty five patients had acute hepatitis B, 31 had chronic hepatitis B other than HBVR (18 had chronic hepatitis B and 13 were inactive carriers), 28 were children with HBV infection, 8 patients had HCV coinfection, 2 patients had HCC, and 18 patients did not give consent for the study. Screening for HBs Ag and Total Anti-HBc was carried out in 66.3% and 4.4% patients before receiving CT, respectively.

Among 92 patients with HBV reactivation, 46 received ETV and 46 received TDF. Seven patients died, 5 in TDF group and 2 in ETV group. Five patients died due to underlying cancer and 2 died due to sepsis. Sixteen patients were lost to follow-up which included 7 in ETV group and 9 in TDF group. A total of 69 patients completed the study period of at least one year after starting treatment, 37 in ETV and 32 in TDF group [Figure 1].

Relationship of HBVR with type of cancers

Forty three of 92 patients (47.8%) of HBVR, were suffering from hematological cancers (Non-hodgkins lymphoma [NHL]: 13 of 92 [14.1%], acute myeloid leukemia [AML]: 12 [13%], acute lymphoblastic leukemia: 8 [8.7%], multiple myeloma: 7 [7.6%]). NHL was the most common cancer among hematological cancers. Among solid cancers, HBVR was seen in carcinoma colon (9.8%), followed by Ca stomach (8.7%), Ca breast (8.7%) and others (Table 1). As per our Regional Cancer Center Sheri-kashmir Institute of Medical Sciences (SKIMS) data, we received 655 patients of hematological cancers and 2630 patients of solid cancers (ratio of 1:4) during the study period. Presuming that the ratio of hematological cancers versus the solid cancers remains the same, we can conclude that reactivation is 4 times more common in hematological cancers than in solid cancers.

Relationship of HBVR with type of CT received

Most common CT protocol in patients with HBVR was combined with anthracycline- and steroid-based CT (20.6%) followed by anthracycline and Cisplatin+5 Fluracil (FU) based (17.4% each). Nine of 92 (9.8%) had received rituximab-based CT (Table 2).

Timing of HBVR and its impact on the CT schedule

Twenty four of 92 (26.1%) patients developed reactivation on CT and 49 of 92 (53.3%) patients developed reactivation within 6 months of stopping the CT. Eleven of 92 (12%) patients developed HBVR after 1 year of stopping CT. Nineteen (20.7%) patients needed to interrupt CT because of HBVR.

HBV infection screening before CT in patients with HBVR

Screening for HBs Ag and total anti-HBc was carried out in 66.3% and 4.4% patients before receiving CT, respectively.

Clinical and laboratory parameters in patients with HBVR

Forty five of 92 (48.9%) patients with HBVR were asymptomatic on presentation. Thirty six of 92 (39.1%) patients

Figure 1 Flow diagram showing distribution of study population.

presented as acute mild hepatitis and 11 (12%) had severe acute hepatitis.

Comparison of baseline clinical and demographic parameters in patients of HBVR receiving ETV and tenofovir (Tables 3 and 4)

All the parameters in two groups were similar, and there was no statistically significant difference between the two groups. IgM anti-HBc was positive in significantly higher number of patients in the ETV group than in the TDF group ($P = 0.01$).

Comparison of efficacy end points in patients with HBVR

1. Reduction in HBV DNA level (Figure 2):

HBV DNA level decreased from a mean of $7.749 (\pm 1.19)$ log IU/ml at baseline to $3.175 (\pm 0.89)$ log IU/ml at 6 months in the ETV group with reduction of 4.7 logs, whereas HBV DNA level decreased from a mean of $7.879 (\pm 1.08)$ log IU/ml at baseline to $2.655 (\pm 0.58)$ log IU/ml in the TDF group with a reduction of 5.224 logs. This dif-

ference at 6 months was significant ($P = 0.029$). At 6 months, HBV DNA was undetectable in 11 (29.7%) patients in the ETV group and 13 patients in the TDF group (40.6%), and this difference was not significant (P value = 0.178).

2. Reduction of mean ALT (Figure 3):

Mean ALT level decreased from mean of $397.9 (\pm 292.8)$ IU/L to $43.34 (\pm 16.7)$ IU/L in the ETV group at 6 months, and it decreased from $422.65 (\pm 300.49)$ IU/L to $50.04 (\pm 23.71)$ in the TDF group, and this difference was not significant ($P = 0.219$). ALT normalization happened in 33 (89.2%) patients in the ETV group and 28 (87.75%) patients in the TDF group at 1 year. This difference was not significant ($P = 0.827$).

3. Efficacy end points at 1 year (Table 5):

At 1 year of treatment, 28 patients (75.7%) in the ETV group and 28 patients in the TDF group (80%) had undetectable HBV DNA. Nine (25%) patients in the ETV group and 9 (28.1%) patients in the TDF group had loss of HBs Ag ($P = 0.77$). However HBsAg seroconversion was achieved

Table 1 Frequency of Different Cancers in Patients With HBV Reactivation.

Diagnosis	Frequency	Percentage
ALL	8	8.7
AML	12	13
CA bladder	1	1.1
CA breast	8	8.7
CA colon	9	9.8
CA esophagus	4	4.3
CA GB	1	1.1
CA lung	4	4.3
CA OVARY	2	2.2
CA pancreas	1	1.1
CA rectum	4	4.3
CA stomach	8	8.7
CLL	1	1.1
EWING sarcoma	1	1.1
GCT	1	1.1
GIST	2	2.2
Hodgkins	3	3.3
Myeloma	7	7.6
NHL	13	14.1
Sarcoma	1	1.1
Thymoma	1	1.1
Total	92	100.0

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CLL = chronic lymphocytic leukemia, GCT = germ cell tumor, GIST = gastrointestinal stromal tumors, NHL = non-Hodgkins lymphoma, CA = carcinoma, GB = gall Bladder.

Table 2 Frequency of Patients With HBVR Receiving Different Chemotherapy Protocols.

Chemotherapy Received	Antiviral Drug Received		Total
	Entecavir	Tenofovir	
	N (%)	N (%)	N (%)
Anthracycline based	5 (10.9)	11 (23.9)	16 (17.4)
Steroid based	4 (8.7)	3 (6.5)	7 (7.6)
Cisplatinum+5FU based	8 (17.4)	8 (17.4)	16 (17.4)
5FU based	4 (8.7)	3 (6.5)	7 (7.6)
Cytarabine based	2 (4.3)	4 (8.7)	6 (6.5)
Anthracycline + steroid	11 (23.9)	8 (17.4)	19 (20.6)
Rituximab based	4 (8.7)	5 (10.9)	9 (9.8)
Platinum based	7 (15.2)	5 (10.9)	12 (13.0)
Total	46 (100)	46 (100)	92 (100)

5 FU = 5-fluorouracil. HBVR, hepatitis B virus reactivation.

Table 3 Comparison of Baseline Parameters in Two Groups of Patients With HBVR.

Parameter	Entecavir	Tenofovir	P value
	N = 46	N = 46	
Males n (%)	31 (67.4)	26 (56.5)	0.28
HBe Ag-positive n (%)	32 (69.6)	31 (67.4)	0.82
IgM anti-HBc positive n (%)	12 (26.1)	3 (6.5)	0.01
Severe acute hepatitis n (%)	6 (14.3)	5 (11.9)	0.94
Baseline HBsAg-positive n (%)	3 (6.52)	2 (4.35)	0.64
Baseline anti-HBc-positive n (%)	2 (4.35)	2 (4.35)	1.00
Cirrhosis n (%)	2 (4.35)	1 (2.1)	0.55

HBVR, hepatitis B virus reactivation;

in 2.8% in the ETV group and 3.1% in the TDF group ($P = 0.95$). Nine (40.9%) HBe Ag-positive patients in the ETV group and 10 (47.6%) in the TDF group achieved HBe Ag seroconversion. There was no HBVR-related mortality in any group.

Adverse drug effects

Only 1 patient in the TDF group with AML developed severe peripheral neuropathy and after stopping the drug, neuropathy improved. The patient died due to relapse of AML before completing the study period. No adverse effect was seen in the ETV group.

DISCUSSION

Prevalence of hepatitis B is higher in patients with cancer than in the general population which has been attributed to increasing exposure to blood products, surgeries, and importantly hepatitis B reactivation.^{3,4} We observed that HBVR was 4 times more common in hematological malignancies than solid malignancies. Majority of the patients with HBVR received polychemotherapy (47.8%) which was mostly anthracycline based, anthracycline plus steroid based, and rituximab based. Other common CT protocol in HBVR was platinum based and cisplatin+5FU based. Similar data has been seen in other studies which have observed anthracycline based,³¹⁻³⁴ steroid based,³¹ and rituximab-based chemotherapies³⁵⁻³⁷ to be commonly associated with HBVR. The reason of HBVR being more common in hematologic malignancies may be the more aggressive immune suppression with multiple chemotherapeutic agents in hematological malignancies and more exposure to blood and blood products than solid malignancies. More number of blood transfusions increases the chances of acquiring hepatitis B even after HBs Ag screening of donors because of the presence of occult hepatitis B in donors.¹¹

Most of the patients (73.9%) developed reactivation after stopping CT. Twelve % of patients developed

Table 4 Comparison of Baseline Biochemical Parameters in Two Groups of Patients With HBVR.

Parameter	Entecavir	Tenofovir	P value
	Mean (SD)	Mean (SD)	
Age (years)	44.7 (15.4)	42.5 (14.7)	0.48
HBV DNA Baseline (IU/ml)	4.29×10^8 (1.17×10^9)	5.85×10^8 (1.38×10^9)	0.56
Bilirubin (mg/dl)	2.76 (3.1)	3.85 (5.6)	0.25
ALT (IU/l)	393.6 (296.9)	422.6 (300.5)	0.64
INR	1.15 (0.25)	1.11 (0.21)	0.39
Creatinine(mg/dl)	0.88 (0.25)	0.88 (0.21)	0.97
HB(g/dl)	11.2 (1.9)	11.8 (1.4)	0.10
Platelet	168.6 (89.1)	170.1 (63.2)	0.93

ALT, alanine aminotransferase.

reactivation after 1 year of stopping CT. Reactivation most frequently follows cessation of CT but may occur during CT.^{2,38,39} The reported interval usually ranges from 1 to 12 months from initiation of CT but has also been upto 39 months as seen in some of our patients.⁴⁰⁻⁴³ We observed that 20.7% of patients needed to interrupt CT because of HBVR. Interruption of CT owing to HBVR has been seen with different frequencies ranging upto maximum of 71%.^{44,45}

Only 66.3% of patients were screened for HBs Ag before the start of CT and only 4 patients were screened for total anti-HBc. In patients who developed reactivation, 68.5% patients were HBe Ag-positive and 16.3% patients with HBVR were IgM anti-HBc-positive. IgM anti-HBc can be positive in patients of HBVR but the titers are lower than the patients with acute hepatitis B.^{28,29} HBVR can occur in both HBe Ag-negative and HBe Ag-positive patients,

and reactivation can result in conversion of HBe Ag-negative to HBe Ag-positive status.^{9,31} We observed that 48.9% patients with HBVR were asymptomatic on presentation. Twelve % of patients developed severe acute hepatitis, and the rest had mild icteric hepatitis. HBVR is known to present as asymptomatic transaminitis, severe acute hepatitis, fulminant liver failure, and death. Almost similar results have been shown by previous studies.^{6,40}

We compared the efficacy of ETV and tenofovir in patients with HBVR receiving CT. We observed that overall ETV and tenofovir were equally effective in reducing ALT and HBV DNA levels. We observed that HBs Ag loss was 25% and 28.1% with ETV and tenofovir, respectively, at 1 year of treatment. High rate of HBsAg loss in patients with cancer with HBVR has also been seen other smaller reports which have used ETV or tenofovir.^{22,24-26} One of the

Figure 2 Graph showing almost similar reduction of mean log HBV DNA with entecavir and tenofovir at different intervals.

Figure 3 Graph showing almost similar reduction of mean ALT with entecavir and tenofovir at different intervals. ALT, Alanine Aminotransferase.

Table 5 Comparison of Efficacy End Points at 1 year in Two Groups.

Outcome	Entecavir	Tenofovir	P value
Undetectable HBV DNA n(%)	28 (75.7)	28 (87.5)	0.21
HBsAg loss n(%)	9 (25)	9 (28.1)	0.77
ALT normalization n(%)	32 (89.2)	28 (87.5)	0.82
HBe seroconversion n(%)	9 (40.9)	10 (47.6)	0.65
HBs seroconversion n(%)	1 (2.8)	1 (3.1)	0.95

HBVR, hepatitis B virus reactivation; ALT, alanine aminotransferase.

reasons may be that once the CT effect is over, the immunity recovers and tries to clear the virus which may add to the clearance rate of HBsAg. There was no HBV infection-related mortality in any group. However, at 6 months, there was 4.579 log IU/ml reduction in mean DNA level in the ETV group and 5.229 log IU/ml reduction in mean HBV DNA level in the tenofovir group. This difference was statistically significant ($P = 0.029$). This means that tenofovir was more effective in rapidly decreasing the HBV DNA level at 6 months. This can be very important observation in patients of HBVR because of the need to decrease the HBV replication rapidly to prevent the life-threatening complications and also to restart CT quickly. Similar observations have been seen in one of the studies in patients with HBeAg-positive chronic hepatitis B with high HBV DNA levels.⁴⁶ However in most of the studies, the two drugs have been shown to be almost equally effective in the treatment of chronic hepatitis B.⁴⁷

Majority of the previous studies have used lamivudine in the treatment of HBVR. Although lamivudine is effective as prophylaxis but it is not as effective for the treatment of hepatitis B as the mortality has been high even after starting treatment with lamivudine in patients with HBVR as shown in previous studies.^{39,40,42} The result is that more stress is given on preventing HBVR rather than treating it. There are no large studies in which ETV or tenofovir has been used for patients of HBVR during immunosuppressive therapy. ETV has been used in case reports and small case series with very good results in patients with cancer with HBVR due to CT.^{24–26} We did not observe any HBV-related mortality in our cohort as was observed in other small studies with ETV.⁴⁸ One small study of 13 patients with HBVR,²² showed that tenofovir was very effective in the treatment of reactivation in patients who underwent immunosuppressive treatment with complete biochemical and virological response within 6 months with no liver-related death.

Our study had some major limitations. The sample size is small and may not be adequate to compare the efficacy of two drugs in the present population and needs studies with larger sample size to confirm our findings. The reason may be that patients with cancer with HBVR are far less in number and getting a proper sample size is difficult. Sec-

ond major drawback is that baseline HBV markers were not available in all the patients which may have resulted in including some patients with acute hepatitis B as HBVR. Follow-up was only for 1 year. Histologic parameters were not compared as liver biopsy was not performed.

We conclude that hepatitis B is a common problem in patients with cancer receiving CT especially HBV reactivation which can be life-threatening if not properly managed. Both ETV and tenofovir are very effective in the treatment of HBVR decreasing liver-related mortality and morbidity. HBVR may not be as fatal as shown in previous studies if treated on time and with newer antivirals, and antiviral prophylaxis may not be cost-effective in all the patients with cancer.

CONFLICTS OF INTEREST

The authors have none to declare.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Manzoor A. Wani: Data curation, Writing - original draft, Software. **Jaswinder S. Sodhi:** Conceptualization, Methodology. **Ghulam N. Yatoo:** Conceptualization, Writing - review & editing. **Altat Shah:** Resources, Project administration. **Sajad Geelani:** Visualization, Investigation. **Showkat A. Zargar:** Supervision, Methodology. **Ghulam M. Gulzar:** Software, Validation. **Mushtaq Khan:** Resources, Supervision. **Sheikh A. Aziz:** Investigation, Resources, Supervision.

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