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Original Research Article

TELBIVUDINE IN THE TREATMENT OF HEPATITIS B VIRUS REACTIVATION IN CANCER PATIENTS RECEIVING CHEMOTHERAPY

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Abstract

Background & Aims: Hepatitis B virus Reactivation (HBVR) in cancer patients receiving chemotherapy is potentially fatal condition and needs prompt diagnosis and treatment. Treatment of such patients has been attempted with lamivudine, entecavir, and tenofovir with variable success rates. Although a rapidly acting highly potent antiviral, telbivudine has not been studied in HBVR and our aim was to study the efficacy of telbivudine in such patients.

Methods: This prospective study of four patients with HBVR who were suffering from different malignancies was conducted in a tertiary care center. These patients were referred with transaminitis and on investigating proved to be having HBVR. After starting them on Telbivudine 600mg OD, these patients were followed very closely on OPD basis.

Results: 3 out of 4 patients developed HBsAg seroconversion and the drug could be stopped within 1 year of treatment in all three of them. In one patient, HBe seroconversion was achieved.

Conclusions: Telbivudine is an effective alternative to entecavir and tenofovir in cancer patients with HBVR.

Keywords: Transaminitis; Seroconversion; Immunosuppression; Reactivation: Telbuvidine.

Introduction

Hepatitis B infection is a major health problem worldwide and has infected around 2 billion people[1]. Over 350 million have developed chronic HBV infection and more than 620,000 die annually due to long-term sequelae of Hepatitis B virus (HBV) infection like cirrhosis and HCC[2]. 4 stages of chronic hepatitis B have been defined.[3] Immune tolerant phase, Immune reactive or immune clearance phase, inactive HBsAg carrier phase and reactivation phase. Reactivation may occur spontaneously or due to immunosuppression.[3]Hepatitis B virus reactivation is known to occur in immuno-suppressed patients receiving cancer chemotherapy. The frequency of HBV reactivation in immuno-suppressed

patients receiving chemotherapy varies ranging from 14 to 72%[4,5]. HBV reactivation in such patients is life-threatening with a fatality rate of 23-71%[4,6,7]. HBV reactivation needs to be either prevented by giving antiviral prophylaxis(pre-emptive treatment) in patients with evidence of resolved infection and in HBV carriers or treating them promptly as soon as liver function and HBV DNA level deteriorates(deferred treatment)[8]. EASL[9] and AASLD[10] guidelines, therefore, recommend screening all cancer patients for HBV infection who are planned to undergo chemotherapy by doing HBsAg and Total anti-HBc. Treatment of reactivation in such patients has been so far tried with lamivudine and in few cases entecavir[11,12]. Telbivudine is the nucleotide analog which is potent and rapidly acting antiviral drug and decreases HBV DNA level promptly. In some studies, it has been shown that telbivudine is better than entecavir in HBe Ag positive patients and it decreases HBV DNA rapidly[13]. It has been shown that HBe Ag seroconversion rate is higher with telbivudine than entecavir[14]. Considering these observations, telbivudine could be a very good choice in immunosuppressed patients with HBV reactivation, as there is a need to decrease the HBV replication quickly to prevent the complications of HBVR and also to restart the chemotherapy quickly. So far, the role of telbivudine has not been studied in HBVR. We here report successful treatment of 4 cancer patients of HBV reactivation with telbivudine.

Material & Methods:

Four patients with different cancers (Colon, Rectum, Breast, and Lung) were referred to our department for new-onset transaminitis and on evaluation were found to be HBsAg positive. All of them had received or were receiving chemotherapy. On further evaluation, all of them were found to have reactivation of Hepatitis B infection. We defined HBVR as a 3-fold or more increase in alanine aminotransferase (ALT) above the upper limit of normal value plus 10-fold or more increase of HBV DNA level above the baseline, or an absolute increase in the HBV DNA level more than 20,000 IU/ mL (10^5 copies/mL).[15] After proper informed consent, baseline investigations like complete blood count(CBC), Liver function test(LFT), Kidney function test(KFT), coagulogram, Ultrasound abdomen, Hepatitis serology A, B, C, D, E, and HBV DNA levels were done. Patients were put on telbivudine 600mg once daily and followed with LFT weekly, HBV DNA levels at 4 weeks, 12 weeks, 24 weeks, 36 weeks, 48 weeks. HBsAg, HBeAg were repeated monthly.

Results:

The baseline characteristics of the 4 patients are described in Table 1. HBeAg was negative in 1 patient and positive in 3 patients. IgM anti-HBc was negative in 3 and positive in one patient with Ca Lung. In all 4 patients, HBV DNA level was very high at the time of reactivation. No patient had features of the chronic liver disease and all other viral serology was negative. After starting telbivudine, all 4 patients showed a good response as the LFT normalized quickly and DNA levels came down at a very rapid pace as shown in Table 2. This allowed chemotherapy to be restarted quickly in 2 patients. Surprisingly HBe and HBs seroconversion occurred very rapidly in 3 patients and in one only HBe seroconversion was seen. There were no undesirable effects in any of the patients. In 3 patients, telbivudine could be stopped 6 months after HBs Ag seroconversion as the HBs Ag remained negative. Patients were followed for 10 months and HBs Ag and HBV DNA level was repeated which was negative in 3 patients. The patient with Ca lung achieved HBe seroconversion after 9 months and has completed 15 months of

telbivudine and is still HBsAg positive. None of the patients had any complication of reactivation like liver failure or death.

Discussion and brief review of literature:

Reactivation of hepatitis B virus has no clear and uniform definition. A widely accepted definition of reactivation of HBV has 2 components: clinical or biochemical features of hepatitis and surge in HBV DNA.[15]Hepatitis is defined by a 3-fold or more increase in alanine aminotransferase (ALT) above the upper limit of normal value; reactivation hepatitis is defined by a 10-fold or more increase of HBV DNA level above the baseline, or an absolute increase in the HBV DNA level more than 20,000 IU/ mL (10^5 copies/mL) in the absence of other systemic infection. Clinically, reactivation varies from asymptomatic elevation of serum ALT to acute liver failure and death.[15]Hoofnagle has described the reactivation process in 3 phases: increase in HBV replication, appearance of biochemical/histologic evidence of hepatic injury, and recovery.[15]Hepatitis B virus reactivation(HBV-R) is well known in patients receiving chemotherapy with incidence varying depending on the type of malignancy and chemotherapy received.[8] Although reactivation has been seen in almost all types of malignancies after cytotoxic chemotherapy, it is more common in patients with hematological malignancies(like lymphoma, ALL etc) on polychemotherapy, Anti-CD 20(Rituximab)[8]. The EASL and AASLD guidelines support the routine screening for hepatitis B markers including HBsAg, total anti-HBc in all patients planned for chemotherapy.If HBsAg or total anti-HBc is positive prior to chemotherapy, it is suggested to further do HBV DNA levels. If the HBV DNA levels are low the patients should be given preemptive antivirals in the form of lamuvidine or entecavir, especially in patients who are planned to undergo chemotherapy containing steroids or rituximab.[9,10] But ASCO guidelines are yet unsure about the routine screening for HBV markers and giving preemptive antivirals in all patients planned for chemotherapy.[17]

There is little literature about what is the natural history of reactivation and how to treat reactivation in cancer patients. Recently American Gastroenterological Association (AGA)[16] did a risk stratification of patients receiving different immunosuppressants into three groups: 1. High risk group (HBVR risk >10%) 2. Moderate risk group (HBVR risk 1%-10%) 3. Low risk group (HBVR risk <1%). These guidelines recommend screening for HBV (HBsAg and anti-HBc, followed by a HBV DNA test if positive) in patients at moderate or high risk who will undergo immunosuppressive drug therapy. They suggest against routinely screening for HBV in low risk patients. They recommended antiviral prophylaxis (prefers entecavir over lamivudine) over no prophylaxis for patients at high risk and moderate risk undergoing immunosuppressive drug therapy. Treatment should be continued for at least 6 months after discontinuation of immunosuppressive therapy (at least 12 months for B cell–depleting agents). The AGA recommends antiviral drugs with a high barrier to resistance (Entecavir and Tenofovir) over lamivudine for established HBVR in patients undergoing immunosuppressive drug therapy.[16]

HBVR usually develops during or after chemotherapy and if HBVR develops, it poses few challenges to the clinician. Firstly, chemotherapy needs to be stopped and there is a delay in restarting chemotherapy resulting in chances of disease recurrence. Second, the patient may develop liver failure which can be fatal. So, both the diagnosis and the treatment of HBVR should be prompt. The antiviral used should be potent and rapidly acting to

decrease the HBV replication quickly. This will decrease the chances of liver failure and also will make it possible to restart the chemotherapy. Besides entecavir and tenofovir, which are approved for the long-term treatment of chronic hepatitis B because of their proven potency and very low resistance, telbivudine is a very potent antiviral with rapid onset of action and very early HBe seroconversion in chronic hepatitis B patients.[13,14] Only problem with telbivudine is the development of resistance after 1 year. The problem of resistance may be irrelevant in HBVR as once the viral replication is controlled, the patient may recover spontaneously and the majority may not need long-term treatment. We treated 4 patients with different solid malignancies with HBVR with telbivudine 600mg OD. All 4 patients had very high baseline HBV DNA level which decreased very rapidly at 4 weeks,12 weeks and 24 weeks. Moreover, HBsAg seroconversion was seen in 3 patients and HBe Ag seroconversion in one. None of the patients had any complication related to HBVR. Small case series with entecavir and tenofovir has also shown a high rate of HBsAg seroconversion in HBVR in immunosuppressed patients.[11,18] Reason for high HBsAg seroconversion in such patients may be spontaneous resolution after initial rapid control of viral replication as shown by Hoofnagle[15]. Chances of recovery may also be dependent on the type of malignancy and the amount of immunosuppression.

We conclude that in immunosuppressed patients with HBVR, telbivudine is a very good antiviral drug and can be used as first-line as an effective alternative to entecavir and tenofovir. However, larger randomized controlled trials are needed to compare the efficacy of telbivudine, entecavir, and tenofovir in such patients.

References:

1. World Health Organization. Hepatitis B Factsheet, July 2012. Available at: http://www.who.int/mediacentre/factsheets/fs204/en/.
2. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine 2012;30(12): 2212–2219
3. Hepatitis B virus infection. Trépo C, Chan HLY, Lok AS. Lancet 2014 Dec;384(9959): p2053–2063.
4. Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology 1991; 100(1):182–188
5. Torres HA, Davila M. Reactivation of hepatitis B virus and hepatitis C virus in patients with cancer. Nat Rev Clin Oncol 2012;9(3):156–166
6. Kumagai, K., Takagi, T., Nakamura, S., Sawada, U., Kura, U., Kodama, F., Shimano, S., Kudoh, I., Nakamura, H., Sawada, K. & Ohnoshi, T. Hepatitis B virus carriers in the treatment of malignant lymphomas: an epidemiological study in Japan. Annals of Oncology,1997;8 (Suppl. 1), 107–109.
7.Vassiliadis T, Garipidou V, Tziomalos K, Perifanis V, Giouleme O, Vakalopoulou S. Prevention of hepatitis B reactivation with lamivudine in hepatitis B virus carriers with hematologic malignancies treated with chemotherapy: a prospective case series. *Am J Hematol*. 2005;80:197-203.
8. Lalazar G, Rund D, Shouval D. Screening, prevention and treatment of viral hepatitis B reactivation in patients with hematological malignancies. Br J Haematol 2007;136(5):699–712

9. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol 2012;57:167–185.
10. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661–662.
11. Brost S, Schnitzler P, Stremmel W, Eisenbach W. Entecavir as a treatment for reactivation of hepatitis B in immunosuppressed patients. *World J Gastroenterol* 2010 November 21; 16(43): 5447-5451
12. Sanchez MJ, Buti M, Homs M, Palacios A, Rodriguez-Frias F, Esteban R. Successful use of entecavir for a severe case of reactivation of hepatitis B virus following polychemotherapy containing rituximab. *J Hepatol*. 2009;51:1091-1096.
13. Zheng MH, Shi KQ, Dai ZJ, Ye C, Chen YP. A 24-week, parallel-group, open-label, randomized clinical trial comparing the early antiviral efficacy of telbivudine and entecavir in the treatment of hepatitis B e antigen positive chronic hepatitis B virus infection in adult Chinese patients. Clin Ther. 2010 Apr;32(4):649-58.
14. Liang J, Jiang MJ, Deng X, Xiao Zhou X. Efficacy and Safety of Telbivudine Compared to Entecavir Among HBeAg+ Chronic Hepatitis B Patients: a Meta-Analysis Study. Hepat Mon. 2013.13(6): e7862.
15. Hoofnagle JH. Reactivation of hepatitis B. *Hepatology*. 2009;49: S156-S165.
16. Reddy KR, Beavers KL, Hammond SP, Lim JK, and Falck-Ytter YT. American Gastroenterological Association Institute Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy. Gastroenterology 2015;148:215–219.
17. Artz AS, Somerfield MR, Feld JJ, et al. American Society of Clinical Oncology provisional clinical opinion: chronic hepatitis B virus infection screening in patients receiving cytotoxic chemotherapy for treatment of malignant diseases. J Clin Oncol 2010;28:3199–3202.
18. Koskinas JS, Deutsch M, Adamidi S, et al. The role of tenofovir in preventing and treating hepatitis B virus (HBV) reactivation in immunosuppressed patients. A real-life experience from a tertiary center. Eur J Intern Med. 2014 Oct; 25(8),768–771.

Table 1: Baseline characteristics and clinical outcome of the patients with reactivation on telbivudine.

	Patient 1	Patient 2	Patient 3	Patient 4
Diagnosis	CA Colon	CA rectum	CA Breast	CA Lung
Age/Sex	23/F	40/F	36/F	56/M
Baseline HBsAg	Negative	Negative	Negative	Negative
Baseline Total Anti HBc	Positive	Not done	Positive	Not done
Transfusions	Nil	1	Nil	4
Chemo received	FOLFOX	5-FU/CLV/Radio	FEC	Paclitaxol/carboplatin

Reactivation time	6	5	5	12
Peak ALT	341	771	1285	184
Peak Bili	7.24	20.6	8.66	2.1
INR	1.3	1.4	1.2	1
HBe Ag	Negative	Positive	Positive	Positive
IgM AntiHBc	Negative	Negative	Negative	Positive
HBV DNA level	1.7×10^8	5.02×10^7	1.7×10^8	7.2×10^8
HBe Ag loss	-	Yes	Yes	Yes
HBs Ag negativity time	9 months	9 months	9 months	-
Withdrawal of Telbivudine	Yes	Yes	Yes	No
Clinical Outcome	Alive	Alive	Alive	Alive

*CA= Carcinoma, FOLFOX=Folinic Acid, Fluorouracil,Oxaliplatin;5-FU= 5 fluorouracil,CLV=calcium leucovorine; FEC=5Fluorouracil,Epirubicin,Cyclophosphamide

Table 2: Follow up of patients with reactivation on telbivudine.

Patient	**1**	**2**	**3**	**4**
ALT 0	341	771	1285	256
ALT at 2 wks	54	376	500	80
ALT at 4 wks	50	100	89	42
ALT at 8 wks	40	48	50	42
HBV DNA 0	170000000	50250000	170000000	720000000
HBV DNA at 1 mnth	167600	530000	146700	1980000
HBV DNA at 3 mnth	730	5300	7900	68260
HBV DNA at 6 mnth	70	99	123	2500
HBV DNA at 9 mnth	ND	ND	ND	63
HBV DNA at 12 mnth	ND	ND	ND	ND