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Increased Awareness of the Possibility of HBV Reactivation Through Use of Patient HBV Caution Cards

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Background: Reactivation of hepatitis B virus (HBV) replication has been frequently reported and can result in severe disease, including acute liver failure and death. However, physicians other than hepatologists have a low awareness of HBV reactivation. The aim of this study was to investigate the efficacy of carrying HBV caution cards from the viewpoint of patients with HBV infection.

Material/Methods: We handed HBV caution cards to 50 HBV-infected patients. When we handed over the card, we tested their knowledge of HBV reactivation and oral administration of nucleic acid analogs. After 3 months, 6 months, and 1 year, we sent a questionnaire to the subjects. The questionnaire addressed the following: the use or nonuse of the card, all instances of diagnosis and treatment using the card, and the physician's response when the patient produced the card.

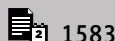
Results: We collected questionnaires from all individuals (100%). Only 30% (15/50) of the patients had knowledge of HBV reactivation; 36 (72%) patients used the card at least once during the year; and 77.8% (28/36) of patients using the HBV caution cards judged it to be good or very good. Among the study patients, there were no cases of HBV reactivation.

Conclusions: In our study, we showed the efficacy of the card which the patients carried to increase awareness of the possibility of HBV reactivation. Patient education, standardization of medical information for non-hepatologists, and the spread of the use of the cards are expected in future.

MeSH Keywords: **Hepatitis B virus • Questionnaires • Virus Activation**

Abbreviations: **HBV** – hepatitis B virus; **HBsAg** – hepatitis B surface antigen; **anti-HBc** – HBV core antibody; **HCV** – hepatitis C virus; **CH-C** – chronic hepatitis C; **LC-C** – liver cirrhosis type C; **CH-B** – chronic hepatitis B; **LC-B** – liver cirrhosis type B; **HCC** – hepatocellular carcinoma; **IFN** – interferon; **SVR** – sustained virological response; **DM** – diabetes mellitus

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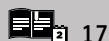
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Background

Reactivation of hepatitis B virus (HBV) associated with chemotherapy has often been reported in patients carrying HBV surface antigen (HBsAg) or HBV core antibody (anti-HBc) [1,2], especially those with malignant lymphoma who receive combination chemotherapy involving rituximab treatment [3–5] and patients undergoing cytotoxic chemotherapy or immunosuppressive therapy [6,7]. Reactivation can lead to clinically apparent acute hepatitis, which can be severe and result in acute liver failure and death [8,9].

Therefore, prophylactic antiviral therapy is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy [10]. Prophylactic antiviral therapy can prevent reactivation and possible fulminant hepatitis in HBsAg-positive patients. We reported previously that prophylactic lamivudine administration prevents exacerbation of liver damage in HBe antigen-positive patients with hepatocellular carcinoma (HCC) undergoing transhepatic arterial infusion chemotherapy [11]. The Japanese Guidelines for HBV reactivation were published in 2009 [12] and the Japan Society of Hepatology established the Drafting Committee for Hepatitis Management Guidelines in November 2011 and have published the Guidelines for the Management of Hepatitis B [13].

Unfortunately, many physicians who regularly prescribe immunosuppressive therapy do not recognize this potentially fatal condition. Notsumata et al. reported an automated system to increase awareness of the possibility of HBV reactivation, using medical record encoding [14]. They showed usefulness in preventing HBV reactivation using an electronic chart inside the hospital. However, this system is not effective when the patients consult a different medical institution.

Therefore, we educated HBV-infected patients about HBV reactivation and each carried an HBV caution card. When the patients consulted any medical institution, we advised them to show the card to the physician or dentist. We made not only the patients but also physicians of various specialties recognize the possibility of HBV reactivation, depending on the treatment regimen, and so sought to prevent HBV reactivation. The purpose of this study was to investigate the efficacy of the HBV caution cards from the viewpoint of the patients.

Material and Methods

Subjects

We handed a personal HBV caution card to 50 HBV-infected patients who consulted Kurume University Hospital from January

15, 2003 to October 29, 2003. The 50 patients ranged in age from 28 to 76 years, with an average age of 54.1 ± 12.6 years. There were 30 men and 20 women (Table 1); 80% (40/50) were HBsAg-positive, and 20% (10/50) had been HBsAg-positive in the past. All patients were anti-HBc-positive.

Their liver diseases included asymptomatic HBV carriers (n=13, 26%), asymptomatic HBV carrier with constitutional jaundice (n=1, 2%), asymptomatic HBV carrier with chronic hepatitis C (CH-C) post-interferon (IFN), sustained virological response (SVR) (n=1, 2%), chronic hepatitis B (CH-B) (n=25, 50%), CH-B and post-HCC (n=3, 6%), CH-B and CH-C (n=1, 2%), CH-B and CH-C post-IFN SVR (n=1, 2%), CH-B and past HCV infection (n=1, 2%), CH-B and CH-C & post-HCC (n=1, 2%), liver cirrhosis type B (LC-B) (n=2, 4%), and LC-B and post-HCC (n=1, 2%).

Evaluation of extrahepatic diseases

Diagnosis of type II diabetes mellitus (DM) was based on the American Diabetic Association (ADA) criteria of 1997. Hypertension was defined as a systolic blood pressure (SBP) of 140 mmHg or higher or a diastolic blood pressure (DBP) of 90 mmHg or higher, according to the criteria of JNC-VI of the International Hypertension Society. Examination of the upper and lower gastrointestinal tract was performed. The diagnosis of lichen planus was made by an oral surgeon on the basis of the typical clinical appearance. Oral biopsy confirmed the diagnosis in some patients.

Methods

We asked our patients about their knowledge of HBV reactivation and examined the oral administration of nucleic acid analogs, such as adefovir, entecavir, and lamivudine, when we handed them their cards. In addition, we carried out the following important tasks: (i) We explained HBV reactivation to each patient for 30 minutes and then handed them the document; (ii) the patients signed the front of the caution card (entry part of the patients) for HBV infection (Figure 1); (iii) the hepatologist signed the reverse of the card (entry part of the physician) and provided an address and telephone number (Figure 2); (iv) the patients were asked to carry their card on a daily basis and to show the card to the physician or dentist when they consulted a medical institution of any kind. After 3 months, 6 months, and 1 year, we sent a questionnaire to the subjects. The contents of the questionnaire included: the use or nonuse of the card, all instances of diagnosis and treatment using the card, and the physician's response when the patient produced the card.

Ethical considerations

The investigation was explained to all participants. The study was conducted in full accordance with the ethical principles

Table 1. Characteristics of the 50 subjects.

Age (mean \pm SD) (yr)		54.1 \pm 12.6	
Sex (Males/Females) (n)		30/20	
Knowledge of HBV reactivation (n,%)		15	30%
Oral administration of nucleic acid analogs (n, %)		23	46%
HBsAg positive (n, %)		40	80%
Anti-HBc positive (n, %)		50	100%
Use or nonuse of the card (n, %)	In the first 3 months	30	60%
	During 3 months to 6 months	19	38%
	During 6 months to 1 year	22	44%
	At least one time of card during the year	36	72%
Liver diseases (n, %)	Asymptomatic HBV carrier	13	26%
	Asymptomatic HBV carrier with constitutional jaundice	1	2%
	Asymptomatic HBV carrier with CH-C post-IFN SVR	1	2%
	CH-B	25	50%
	CH-B & post-HCC	3	6%
	CH-B & CH-C	1	2%
	CH-B & CH-C post-IFN SVR	1	2%
	CH-B & past HCV infection	1	2%
	CH-B & CH-C & post-HCC	1	2%
	LC-B	2	4%
Extrahepatic manifestations	LC-B & post-HCC	1	2%
	Hypertension	5	10%
	Heart disorder	3	6%
	Diabetes mellitus	3	6%
	Lichen planus	2	4%
	Thyroid disease	1	2%
	Extrahepatic malignant tumor	1	2%
	Other	27	54%
None	17	34%	

CH-C – chronic hepatitis C; IFN – interferon; SVR – sustained virological response; CH-B – chronic hepatitis B; LC-B – liver cirrhosis type B; HCC – hepatocellular carcinoma.

of the World Medical Association Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Kurume University (reference number: 12260) and Saga University (reference number: 27–14) in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Results

Patient's knowledge of HBV reactivation

Only 30% (15/50) of the patients had knowledge of HBV reactivation; 23 patients (46%) were taking nucleic acid analogs

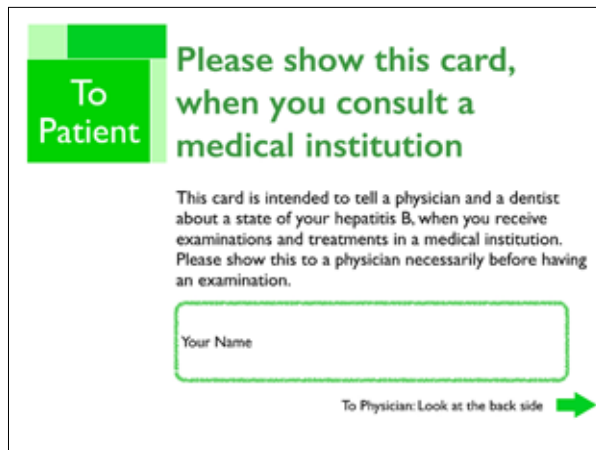


Figure 1. The face of the caution card which the patients carry. The patients sign the card (entry part of the patients) for HBV infection. The size of the card is the same as a credit card (width: 8.56 cm; height: 5.4 cm). The patients carry their card on a daily basis and show the card to the physician or dentist when they attend another medical institution.

as antiviral therapy when we handed out the card (Table 1).

Collection rate of questionnaires

We collected the questionnaires from all subjects (100%) after 3 months, 6 months, and 1 year.

Use or nonuse of the card

Thirty (60%) patients used the card during the first 3 months, 19 (38%) during the period of 3 months to 6 months, and 22 (44%) during the period of 6 months to 1 year (Table 1). Thirty-six (72%) patients used their card at least once during the first year; 14 (28%) patients did not use the card at all because they did not consult a medical institution, other than this hospital, during the first year.

Characteristics of the 36 subjects using the HBV caution card (Table 2)

The evaluations of the card by the patients through 1 year were as follows: “very good”, n=16 (44.4%); “good”, n=12 (33.3%); “average”, n=8 (22.2%); “no good”, n=0 (0%); “very bad”, n=0 (0%).

Instances of diagnosis and treatment using the card throughout the year were as follows: general internal medicine, n=20 (55.6%), dentistry, n=13 (36.1%), orthopedics, n=9 (25.0%), dermatology, n=9 (25.0%), otolaryngology, n=4 (11.1%), urology, n=4 (11.1%), ophthalmology, n=3 (8.3%), psychiatry, n=2 (5.6%), and surgery, n=1 (2.8%).

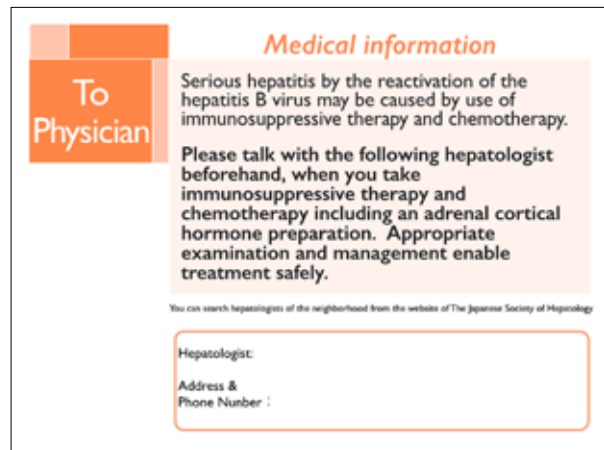


Figure 2. The reverse of the caution card. The hepatologist signs the back of the card (entry part of the physician), and provides an address and telephone number.

The responses of the physicians when the patients presented the card are shown in Table 2. There were no patients for whom the relationship with the physician became difficult.

There were 3 patients who consulted us before the physician gave treatment and medication, after the physician from another medical institution looked at the HBV caution card. Two patients had inquiries from dermatologists and 1 had an inquiry from a dentist. One was an inquiry about medications for eczema, another was an inquiry about medications for oral-labial herpes, and the last was an inquiry about treatment and medication for tooth extraction. Among the study patients, there were no patients with HBV reactivation.

Discussion

Approximately 350 million people in the world are persistently infected with HBV [15] and in Japan the HBV infection rate is around 1% [13]. HBV reactivation after chemotherapy or immunosuppressive therapy is a serious issue, with the possibility of liver-related morbidity and mortality. Yeo et al. concluded that the significant predictive factors for the development of HBV reactivation were high HBV viral load prior to chemotherapy, the use of steroids, and a diagnosis of lymphoma or breast cancer [16].

The Japan Society of Hepatology recommends the following: (i) Monthly HBV DNA monitoring should be performed for patients undergoing hematopoietic stem cell transplantation or chemotherapy, including rituximab, corticosteroids, or fludarabine, during treatment and for at least 12 months after its completion. (ii) HBV DNA monitoring should be performed every 1–3 months for patients undergoing chemotherapy for hematological malignancies, not including rituximab, and standard

Table 2. Characteristics of the 36 subjects using the HBV caution card.

Evaluation of the card by patients through one year	Very good	16	44.4%
	Good	12	33.3%
	Average	8	22.2%
	No good	0	0.0%
	Very bad	0	0.0%
Instances of diagnosis and department using the card throughout one year	General internal medicine	20	55.6%
	Dentistry	13	36.1%
	Orthopedics	9	25.0%
	Dermatology	9	25.0%
	Otolaryngology	7	19.4%
	Urology	4	11.1%
	Ophthalmology	3	8.3%
	Psychiatry	2	5.6%
The response of the physician when the patient presented the card (in the first 3 months) n=30	Physicians understood HBV-infected liver disease well	9	30.0%
	Opportunities for questioning and recognition of liver disease by the physician increased	7	23.3%
	Not changed	14	46.7%
	The relationship with the physician became difficult	0	0.0%
The response of the physician when the patient presented the card (during 3 months to 6 months) n=19	Physicians understood HBV-infected liver disease well	8	42.1%
	Opportunities for questioning and recognition of liver disease by the physician increased	3	15.8%
	Not changed	8	42.1%
	The relationship with the physician became difficult	0	0.0%
The response of the physician when the patient presented the card (during 6 months to 1 year) n=22	Physicians understood HBV-infected liver disease well	7	31.8%
	Opportunities for questioning and recognition of liver disease by the physician increased	4	18.2%
	Not changed	11	50.0%
	The relationship with the physician became difficult	0	0.0%

chemotherapy for solid malignancies, although the duration of monitoring and intervals can be adjusted in accordance with the nature of the treatment. (iii) HBV DNA monitoring should be performed at monthly intervals for patients undergoing immunosuppressive therapy for rheumatic or connective tissue diseases, for at least 6 months after commencement or alteration of treatment. After 6 months, the duration of monitoring and intervals should be decided in accordance with the nature of the treatment. (iv) If HBV reactivation occurs during chemotherapy or immunosuppressive therapy, it is preferable to consult a hepatologist and not immediately cease use of

the anti-neoplastic agent with immunosuppressive activity or immunosuppressant agent [13].

However, immunosuppressive drugs are widely prevalent and used in various medical fields. Non-hepatologists, including dentists, may not be aware of the Japanese guidelines. The card that we suggested the HBV patients carry was effective in providing medical information to non-hepatologists, as well as to the patients.

Only 30% of HBV-infected patients were aware of the possibility of HBV reactivation. Education of the patient is essential

to prevent reactivation. In Japan there are few reports regarding the impact of education of patients with liver disease on their awareness and behavior. Most recently, repeated participation in seminars led to advancement of knowledge and active behavior regarding liver disease [17].

Conclusions

Our study shows the effectiveness of carrying the card from the viewpoint of the patients; 77.8% (28/36) of the patients

using the HBV caution card judged it to be very good or good. Patient education, standardization of medical information for non-hepatologists, and the spread of use of the cards are expected in future.

Competing interests

Prof. Nagao, Dr. Kawahigashi, and Dr. Kimura belong to a department funded by Nishinohon Hospital.

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