product was purified and sequenced directly by the dideoxy chain termination method, using a BigDye Terminator v1.1 Cycle Sequencing Kit and an ABI PRISM 3100 DNA Genetic Analyzer (Applied Biosystems, Foster City, CA).

Ethical Considerations

This study protocol complied with the ethical guidelines of the Declaration of Helsinki 1975 (2008 revision) and was approved by the Ethics Committee of Osaka City University Graduate School of Medicine (UMIN Clinical Trials Registry, UMIN000009491). Written informed consent was obtained from all enrolled patients.

Results

Prophylactic therapy for patients with HBsAg

In the 8 patients with HBsAg, prophylactic treatment with entecavir was started before cytotoxic therapy (Table 2). All 8 patients were infected with HBV genotype C. In response to entecavir, the HBV DNA load decreased to under 3 log copies/ml in all patients and fell to undetectable levels in all but 1 patient with HBeAg (case 32). Four of the 8 patients died because of progression of hematologic malignancy or infection. Hepatic failure did not occur in any of the patients with HBsAg. Entecavir treatment has continuously prevented HBV-R in the other 4 patients.

Preemptive therapy for patients with HBV resolution

The clinical backgrounds of the 49 HBsAg-negative patients are shown in Table 1. At enrollment, HBV DNA was not detected in patients without HBsAg. At the end of follow-up, HBV-R has occurred in 5 (26%) of 19 patients who received HSCT and 3 (10%) of 30 patients who received rituximab-based chemotherapy. HBV-R occurred a median of 3 months (range, 2-10) after the end of rituximab-based chemotherapy. On the other hand, HBV-R occurred a median of 22 months (range: 9-36) after HSCT.

As compared with patients without HBV-R, anti-HBs titers at enrollment were slightly but not significantly lower in patients with HBV-R ($p = 0.085$). Among patients given rituximab-based chemotherapy, the anti-HBc titer was significantly higher in the presence of HBV-R ($p = 0.02$, Table 3). HBV-R occurred in 1 (17%) of 6 patients without anti-HBs. Reactivation occurred in 6 (26%) of 23 patients with anti-HBs titers below 50 mIU/ml, 1 (13%) of 8 patients with anti-HBs titers between 50 and 200 mIU/ml, and none of 12 patients with anti-HBs titers exceeding 200 mIU/ml. During the screening period, anti-HBs titers gradually decreased in 6 patients with HBV-R.

Anti-HBs titers became negative at the time of HBV-R in 7 patients. Anti-HBs titers remained persistently positive in 36 patients without HBV-R.

Alanine aminotransferase (ALT) levels increased to more than 5 times the upper limit of normal in 3 of 8 patients with HBV-R (Table 4). In one patient (case 4) who had received rituximab-based chemotherapy, the ALT level rose to 452 IU/L after entecavir treatment (Figure 1). At that time, HBV DNA decreased to below 2.1 log copies/ml. It was speculated that HBV-R was not directly related to ALT flare in this patient. Two other patients who underwent HSCT discontinued regular screening for HBV DNA on their own initiative. Briefly, case 30 dropped out of regular screening 15 months after enrollment, and ALT levels rose to 362 IU/L with an increase in HBV viral load at month 22. Another patient (case 205) dropped out of the study 25 months after enrollment, and ALT levels elevated to 1642 IU/L with a concurrent increase in HBV viral load at month 36. Although HBV-R-related hepatitis occurred in these patients, treatment with entecavir fortunately prevented hepatic failure. With the exception of these 2 patients, preemptive therapy prevented hepatitis related to HBV-R. Treatments for hematologic diseases were completed without hepatic failure in all of the enrolled patients without HBsAg. One patient with HBV-R died of infection 43 months after HSCT. At the last follow-up, HBV DNA was not detected on real-time PCR. Among the 7 survivors with HBV-R, 4 patients discontinued treatment with entecavir. After the withdrawal of entecavir, HBV DNA was detected again in 2 patients without anti-HBs. One of the two patients required retreatment with entecavir. On the other hand, HBV DNA has not been detected in 2 other patients who were persistently positive for anti-HBs (Fig. 1).

DNA sequence of reactivated HBV

All reactivated HBV was genotype C. Sequence analysis showed that reactivated HBV did not have mutations associated with resistance to nucleos(t)ide analogues in the reverse transcriptase region.

Four of 8 reactivated HBVs had mutations in the 'a' determinant region of the S gene region with amino-acid replacement (Fig. 2). In detail, case 121 had two mutations: 113 threonine to serine and 143 serine to threonine. In case 128, two mutations were detected (129 glutamine to arginine and 130 glycine to asparagine), and anti-HBs was positive at HBV-R (Fig. 1, case 128). An amino-acid replacement of 145 glycine to arginine was detected in cases 150 and 205. In both cases, anti-HBs was negative at the time of HBV-R. At the time of HBV-R, HBsAg was not detectable in 2 (case 121, and 128) of 4 patients with HBV mutated in the 'a' determinant region.

Discussion

In the present prospective study, the rates of HBV-R in patients with resolved HBV infection were 26% after HSCT and 10% after rituximab-based chemotherapy. Previous studies reported that HBV-R occurred in 12% to 20% of patients who had undergone HCST [6, 7, 20-22] and 4.1% to 17.9% of those who had received rituximab-based chemotherapy for malignant lymphoma [4, 23-25]. The rate of HBV-R in our study is consistent with these previous finding. In retrospective studies of patients who underwent HSCT, HBV-R was defined as seroreversion in HBsAg-negative patients [6, 7, 20]. This is quite a difference from the present study, which used real-time PCR to measure HBV DNA. During follow-up, HBV DNA was detected earlier than HBsAg. In addition, HBsAg did not turn positive in 3 of the 8 patients with HBV-R. Two of the 5 patients in whom HBsAg was consistently negative had mutations in the S determinant region of HBV DNA. Our data confirmed that detection of the viral genome was the most specific and sensitive screening tool for HBV-R, particularly as compared with serological tests. A recent large-scale prospective study using HBV DNA test showed that HBV-R occurred in 17 (11.3%) of 150 HBV resolved patients who had received rituximab-based chemotherapy [26].

In our patients with resolved HBV infection, HBV-R occurred within 1 year after the end of rituximab-based chemotherapy and more than 1 year after HSCT. Although HBV-R rarely occurs more than 3 years after HSCT [27, 28], the longest reported period to HBV-R after HSCT was 47 months [22]. In the 2 patients in the present study who discontinued HBV monitoring more than 15 months after enrollment, HBV-R-associated ALT flare occurred. These results might be useful for establishing follow-up periods for HBV-R according to treatment. Recently, careful monitoring for

HBV-R has been broadly recommended for anti-HBc-positive patients who receive immunosuppressive or cytotoxic therapy. However, the incidence and timing of reactivation might differ according to the details of treatment, such as the drugs used or procedures performed. Cost-benefit analyses should be performed according to specific diseases and treatments to assess the value of screening for HBV-R.

Several studies have suggested that decreased levels or loss of anti-HBs is a predictor of HBV-R in anti-HBs-positive patients [22, 29]. In our study, anti-HBs had become negative at the time of HBV-R in 7 of 8 patients. However, the other patient (case 128) was positive for anti-HBs at HBV-R. A case report has documented the development of fatal hepatitis in a patient with HBV-R who had a high titer of anti-HBs [30]. It is well known that HBV vaccination provides no protection against HBV with mutations in the HBsAg coding region (i.e., 'escape mutant HBV'). Consequently, escape mutant HBV can increase in anti-HBs-positive patients. In our patient who was positive for anti-HBs at the time of HBV-R, two mutations in the 'a' determinant region of the S gene were detected. Borentain et al. showed that reactivated HBV is associated with several mutations in the 'a' determinant region of the S gene [21]. Interestingly, 4 reactivated HBVs in our study had mutations with amino-acid replacement in 'a' determinant region. This finding suggests that the mutated HBV might persist in some patients who have HBV-R without serum HBsAg and/or that such HBV might preferentially increase during immunosuppressive or cytotoxic therapy. Taken together, although patients with low anti-HBs titers might have an increased risk of HBV-R, assessment of anti-HBs alone without screening for HBV DNA may fail to identify some patients at high risk for HBV-R.

Our study showed that prophylactic therapy in HBsAg-positive patients and preemptive

therapy in HBV-resolved patients could prevent hepatic failure related to HBV-R associated with cytotoxic or immunosuppressive therapy for hematologic malignancies. Specifically, entecavir reduced HBV viral load in both patients with HBsAg and 8 patients with HBV-R and maintained it below 2.1 log copies/ml for more than 6 months; the duration of entecavir treatment ranged from 3 to 35 months. The emergence of lamivudine-resistant HBV mutants has been reported in patients who received prophylactic treatment for HBV-R [16, 31]. No entecavir-resistant mutants emerged in our study, suggesting that entecavir might be better suited for patients who require longer periods of prophylactic or preemptive treatment.

In a recent randomized controlled study of HBV-resolved patients with lymphoma, prophylactic entecavir treatment before rituximab-based chemotherapy prevented HBV-R in all but 1 (2.4%) of 41 [25]. As compared with preemptive treatment at the time of HBV-R, prophylactic treatment with entecavir more effectively prevented HBsAg reverse seroconversion. However, ALT levels increased to above 100 IU/ml in each patient who received prophylactic or preemptive treatment. Fatal hepatitis did not occur in that trial. Our study also showed that preemptive therapy prevented fatal hepatitis in patients with HBV-R who continued to undergo regular screening. Further studies are needed to establish whether prophylactic therapy should be started before cytotoxic or immunosuppressive treatment in all patients with resolved HBV infection. Another important issue is whether entecavir treatment can be safely discontinued in patients with HBV-R. Fatal hepatic failure has been reported after the withdrawal of prophylactic lamivudine therapy in HBsAg-positive patients with HSCT [32]. In general, nucleot(s)ide analogue treatment should be continued in HBsAg-positive patients. However, there are no firm recommendations for patients who have HBV-R without

HBsAg. We withdrew entecavir after more than 6 months after the disappearance of both HBV DNA and HBsAg in 4 patients with HBV-R who had received preemptive therapy. After the withdrawal of entecavir, HBV DNA was detectable in 2 patients without anti-HBs. On the other hand, HBV-R has not occurred in the other patients whose anti-HBs turned positive after preemptive therapy. Our findings suggest that entecavir can be safely discontinued in patients with HBV-R after anti-HBs has become consistently positive. To confirm our speculations, longer-term studies in larger groups of patients are necessary.

In conclusion, this prospective study confirmed that current recommendations for patients with HBsAg and those with resolved HBV infection can prevent fatal hepatitis related to HBV-R in patients who receive immunosuppressive or cytotoxic therapy. To improve cost-benefit ratios, futures studies should attempt to find other reliable markers and to establish optimal screening periods for HBV-R according to specific diseases or treatments. Finally, we speculated that entecavir can be safely discontinued in patients with HBV-R who have acquired anti-HBs.

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Figure legends

Figure 1 Clinical course of 4 patients with HBV reactivation in whom entecavir was withdrawn.

After entecavir treatment, HBV DNA was detected again in patients 4 and 128. On the other hand, HBV DNA has not been detected in patients 37 and 68, in whom anti-HBs remains above 20 mIU/ml.

CHOP-R: combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab, PBSCT: peripheral blood stem-cell transplantation.

Figure 2 Alignment of amino acids codes from the 111th to 156th amino acids of HB surface antigen, the 'a' determinant region.

Comparison of the modified HBV ADR [33] and the 8 reactivated HBV revealed several point mutations in 'a' determinant region. Point mutations with amino-acid replacement were detected in cases 121, 128, 150, and 205.

Table 1. Clinical characteristics of the enrolled patients.

	Age	Gender	Anti-HB marker	Disease	Treatment
HBsAg-positive					
n = 8	62 (53-79)	Male: 7	Anti-HBs positive: 7	ML: 7	CHOP-R: 6
		Female: 1	Anti-HBc positive: 8	Leukemia: 1	HSCT: 2
HBsAg-negative					
n = 49	60 (23-82)	Male: 27	Anti-HBs positive: 43	ML: 29	CHOP-R: 28
		Female: 22	Anti-HBc positive: 49	Leukemia: 14	HSCT: 19
				MDS: 6	R-Hyper CVAD: 2

CHOP-R: combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab, HSCT: hematopoietic stem-cell transplantation, ML: malignant lymphoma, MDS; myelodysplastic syndromes, R-Hyper CVAD: combination chemotherapy with cyclophosphamide, vincristine, doxorubicin, dexamethasone, and rituximab.

Table 2. Baseline characteristics and outcomes of HBsAg-positive patients.

No.	Gender	Age	Hematologic Disease	Treatment	HBeAg	Anti-HBe (% inh)	HBV DNA (log/ml)	ALT (IU/L)	Observation period (month)	Out-come
32	M	79	ML	CHOP-R	1600	-	8.5	78	26	Dead
66	M	63	ML	CHOP-R	-	100	ND*	10	37	Alive
77	M	57	ML	CHOP-R	-	97	2.8	22	40	Alive
87	M	62	ML	HSCT	419	-	3.6	10	16	Dead
80	M	62	ML	CHOP-R	-	100	4	106	5	Dead
120	M	53	AML	HSCT	-	89	2.3	155	3	Dead
141	M	58	ML	CHOP-R	-	100	3.7	18	26	Alive
211	F	58	ML	CHOP-R	-	100	4	106	5	Alive

AML: acute myeloid leukemia, ML: malignant lymphoma

Table 3. Comparison between patients with or without HBV reactivation in the HBsAg-negative group.

	All patients (n = 49)		Patients with HSCT (n = 19)		Patients with chemotherapy(n = 30)	
	with reactivation	without reactivation	with reactivation	without reactivation	with reactivation	without reactivation
Age	55 (44-64)	64 (23-82)	55 (44-60)	49 (23-66)	60 (53-64)	67 (49-82)
Gender; M/F	2/6	21/20	2/3	8/6	3/0	13/14
Anti-HBs	35 ± 48	243 ± 366	41 ± 63	151 ± 210	25 ± 5	295 ± 420
Anti-HBc	77 ± 33	63 ± 38	80 ± 13	67 ± 36	99 ± 1*	69 ± 36*
Observation period	37 (24-63)	12 (4-61)	41 (32-52)	9 (4-55)	32 (24-63)	13 (4-61)

Data were shown mean ± SD.

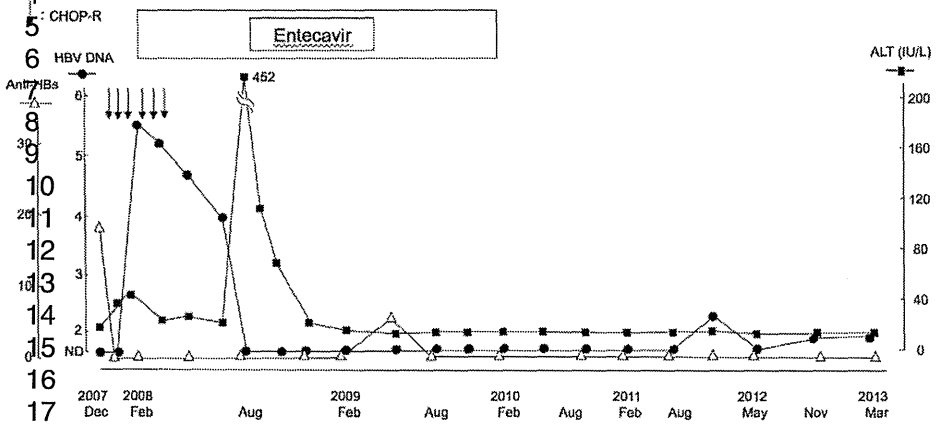
*$p = 0.02$, There were no differences in anti-HBs between the two groups.

Table 4. Clinical characteristics of patients with HBV reactivation.

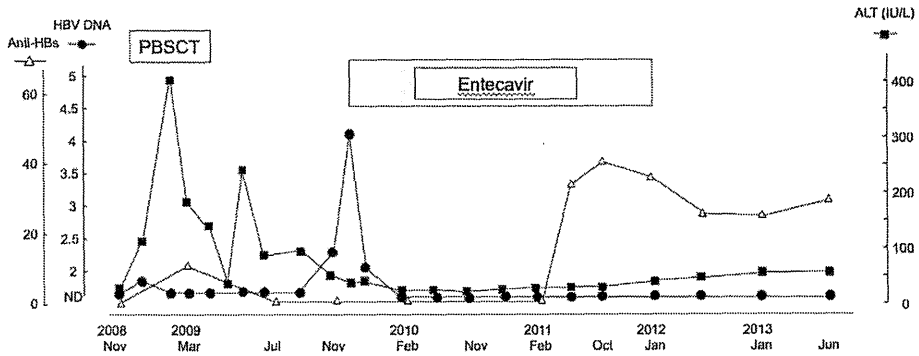
No.	Gender	Age	Hematological Disease	Treatment	Anti-HBs/Anti-HBc at the enrollment	At the tme of HBV reactivation	HBV DNA at reactivation (Log/ml)	HBsAg at or after reactivation (IU/ml)	ALT peak after reactivation (IU/L)	Outcome
4	M	53	ML	CHOP-R	19.6/98.4	2 mon	5.4	1047	452	alive
30	M	59	Chronic leukemia	HSCT	30.2/70	22 mon*	6.6	2000	362	death
37	M	60	ML	CHOP-R	28.5/97.9	10 mon	3.6	negative	28	alive
68	F	46	MDS	HSCT	ND/97.4	10 mon	4.1	45.7	49	alive
121	M	55	Acute leukemia	HSCT	151.7/71	22 mon	2.8	negative	58	alive
128	M	64	ML	R-Hyper CVAD	26.9/99.2	3 mon	3.1	negative	45	alive
150	F	60	MDS	HSCT	14/ND	9 mon	5.4	63.4	22	alive
205	M	44	MDS	HSCT	7.4/81.5	36 mon*	5.4	145	1642	alive

ALT flare occurred in 3 patients with HBV reactivation. *2 patients with HSCT dropped out of regular screening for HBV DNA 1 year after enrollment. In another patient who had received rituximab-based chemotherapy, ALT increased to 452 IU/L during entecavir treatment.

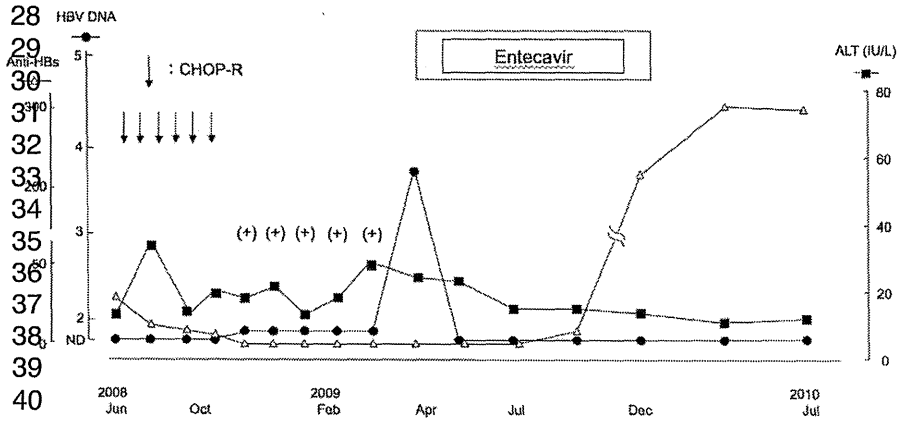
Case 4



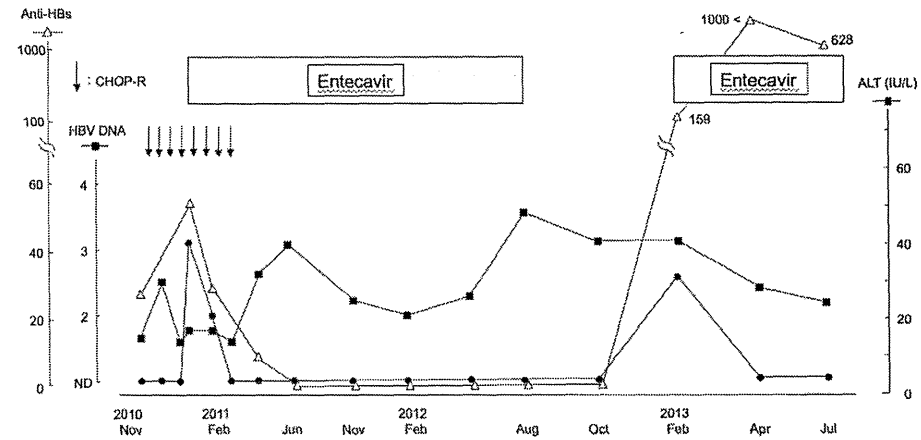
Case 68



Case 37



Case 128



111 120 130 140 150

HBV DNA ; P G T S T T S T G P C K T C T I/T P A Q G T S M F P S C C C T K L S D G N C T C I P I P S S W

case 4 ; -

case 30 ; -

case 37 ; -

case 68 ; -

113 143

case 121 ; - - S - T - - - - - - - - - - - - -

130

case 128 ; - - - - - - - - - - - - - - - - - - R N -

145

case 150 ; - R - - - - - - - - - - -

145

case 205 ; - R - - - - - - - - - - -