37. Fukushima N, Mizuta T, Tanaka M, et al. Retrospective and prospective studies of hepatitis B virus reactivation in malignant lymphoma with occult HBV carrier. *Ann Oncol*. 2009;20(12):2013-2017.
38. Hsu C, Tsou HH, Lin SJ, et al. Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: a prospective study. *Hepatology*. 2014;59(6):2092-2100.
39. Kusumoto S, Tanaka Y, Suzuki R, et al. Prospective nationwide observational study of hepatitis B virus (HBV) DNA monitoring and preemptive antiviral therapy for HBV reactivation in patients with B-cell non-Hodgkin lymphoma following rituximab containing chemotherapy: results of interim analysis [abstract]. *Blood (ASH Annual Meeting Abstracts)*. 2012;120(21):2641.
40. Huang YH, Hsiao LT, Hong YC, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. *J Clin Oncol*. 2013;31(22):2765-2772.
41. Kusumoto S, Tanaka Y, Mizokami M, Ueda R. Is Antiviral Prophylaxis Necessary to Prevent Hepatitis B Virus (HBV) Reactivation in Patients With HBV-Resolved Infection Receiving Rituximab-Containing Chemotherapy? *J Clin Oncol*. 2013;31(35):4480.

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ORIGINAL ARTICLE

Reactivation of hepatitis B virus (HBV) infection in adult T-cell leukemia–lymphoma patients with resolved HBV infection following systemic chemotherapy

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Abstract Reactivation of hepatitis B virus (HBV) infection may occur in adult T-cell leukemia–lymphoma (ATL) patients with resolved HBV infection who receive monotherapy with the anti-CC chemokine receptor 4 monoclonal antibody, mogamulizumab. However, there is little evidence regarding the incidence and characteristics of HBV reactivation in ATL patients receiving systemic chemotherapy, including the use of this antibody. We conducted a retrospective study for 24 ATL patients with resolved HBV infection underwent regular HBV DNA monitoring to assess HBV reactivation in Nagoya City University Hospital between January 2005 and June 2013. With median HBV DNA follow-up of 238 days (range 57–1420), HBV reactivation (defined as the detection of HBV DNA) was observed in three (12.5 %) of 24 patients with resolved HBV infection. No hepatitis due to HBV reactivation occurred in those patients who were diagnosed with HBV DNA levels below 2.1 log copies/mL and who received antiviral drugs. Mogamulizumab was administered prior to HBV reactivation in two of three HBV-reactivated patients. In the mogamulizumab era, further well-designed prospective studies are warranted to estimate the incidence of HBV reactivation and to establish regular HBV DNA monitoring-guided preemptive antiviral therapy for such patients.

Keywords Reactivation · HBV · CCR4 · Mogamulizumab · ATL

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Abbreviations

HBV	Hepatitis B virus
ATL	Adult T-cell leukemia–lymphoma
HBsAg	Hepatitis B surface antigen
Anti-HBc	Antibodies against hepatitis B core antigen
Anti-HBs	Antibodies against hepatitis B surface antigen
CCR4	CC chemokine receptor 4

Introduction

Reactivation of hepatitis B virus (HBV) infection has been reported as a potentially fatal complication of systemic chemotherapy [1–6]. HBV reactivation may occur not only in hepatitis B surface antigen (HBsAg)-positive patients, but also in patients with resolved HBV infection who are seronegative for HBsAg but seropositive for antibodies

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against hepatitis B core antigen (anti-HBc) and/or antibodies against HBsAg (anti-HBs).

Chemotherapy containing the anti-CD20 monoclonal antibody, rituximab plus steroids has been shown to be an important risk factor for HBV reactivation in B-cell lymphoma patients with resolved HBV infection [2, 3]. Recently, the anti-CC chemokine receptor 4 (CCR4) monoclonal antibody, mogamulizumab, was developed and introduced into the management of adult T-cell leukemia–lymphoma (ATL) [7–12]. A dose-finding study showed that mogamulizumab monotherapy could induce HBV reactivation-related hepatitis in an ATL patient with resolved HBV infection [9, 13].

However, there is little evidence regarding the incidence and characteristics of HBV reactivation in ATL patients with resolved HBV infection who were receiving systemic chemotherapy including this antibody. We conducted here a retrospective study in a single institution to evaluate the risk of HBV reactivation in these patients who underwent regular monitoring of HBV DNA levels during and after chemotherapy.

Patients and methods

Between January 2005 and June 2013, 66 patients were diagnosed with ATL in Nagoya City University Hospital. Baseline serological markers for HBsAg, anti-HBc, and anti-HBs were measured to evaluate their viral status before systemic chemotherapy. Antiviral prophylaxis was provided to the HBsAg-positive patients before the initiation of systemic chemotherapy. HBV DNA levels were assessed in HBsAg-negative patients who were seropositive for anti-HBc and/or anti-HBs. Patients seronegative for HBsAg but with detectable of HBV DNA were considered to have occult HBV infection, and antiviral prophylaxis was provided to those patients. HBsAg-negative patients seropositive for anti-HBc and/or anti-HBs but without detectable of HBV DNA were considered to have resolved HBV infection and their HBV DNA levels were monitored regularly (monthly in principle) for HBV DNA levels during chemotherapy and at least 1 year after chemotherapy; HBV reactivation was defined as the detection of HBV DNA. If HBV reactivation was confirmed, antiviral drugs were given immediately (preemptive antiviral therapy).

All baseline serological markers of HBsAg, anti-HBc and anti-HBs were measured by the laboratory in this hospital, using the following methods and cut-off values: CLEIA with cut-off values for HBsAg, anti-HBc and anti-HBs were 1.0 C.O.I, 1.0 INH % and 10.0 mIU/mL, respectively, from January 2005 to December 2010, CLEIA with cut-off values for HBsAg, anti-HBc and ant-HBs were 0.03 mIU/mL, 1.0 C.O.I, and 10.0 mIU/mL, respectively, from January 2011.

HBV DNA levels were measured by an outside laboratory (SRL, Inc.; Tokyo, Japan) or by the laboratory in this hospital, using the following methods and cut-off values: transcription-mediated amplification test with a cut-off value of 3.7 LGE/mL from January 2005 to April 2006, Amplicor HBV monitor test with a cut-off value of 2.6 log copies/mL from April 2006 to May 2008, COBAS AmpliPrep/COBAS TaqMan HBV test (v1.0) with a cut-off value of 1.8 log copies/mL from May 2008 to July 2009, and COBAS AmpliPrep/COBAS TaqMan HBV test (v2.0) with a cut-off value of 2.1 log copies/mL from July 2009.

For the analysis of HBV sequences, nucleic acids were extracted from the preserved serum specimens (200 μL) and subjected to PCR to amplify HBV genomes within the short S region [nucleotides (nt) 427–607] and the basal core promoter (BCP)/precore (PC) regions [nt 1628–2047] followed by direct sequencing using the ABI Prism Big Dye ver. 3.1 kit in an ABI 3100 DNA automated sequencer (Applied Biosystems, Foster City, CA). HBV genotypes were determined by molecular evolutionary analysis [14].

To compare the baseline characteristics and ATL treatment of the patients with and without HBV reactivation, we used the Chi-square test and two-sided Fisher's exact test for categorical data, and the Mann–Whitney U test for continuous variables. A two-tailed p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (version 22.0) statistical software for Windows, using data fixed on August 31, 2013. This study was approved by the Institutional Review Board of Nagoya City University. All patients gave written informed consent.

Results

The status of HBV infection at baseline was as follows (Fig. 1): HBsAg-positive (n = 2, 3.0 %), HBsAg-negative (n = 63, 95.5 %), and no serological HBV assessment (n = 1, 1.5 %). Of the 63 HBsAg-negative patients, 31 (49.2 %) were anti-HBc positive and/or anti-HBs positive. Of the remaining 32 patients, 31 were anti-HBc negative and anti-HBs negative, and one had no data for anti-HBc and anti-HBs. Because HBV DNA below 1.8 log copies/mL was detected at baseline in one patient who was anti-HBc positive and anti-HBs positive at baseline (and who was therefore judged to have occult HBV infection), antiviral drugs were administered before initiating systemic chemotherapy. Finally, 24 of 31 patients with resolved HBV infection underwent regular HBV DNA monitoring (Fig. 1). For these 24 ATL patients, initial systemic chemotherapy included the following regimens: CHOP (n = 7, 29.2 %), VCAP-AMP-VECP (n = 13, 54.2 %) and others (n = 4, 16.6 %) (Table 1). Systemic chemotherapy was started in 6

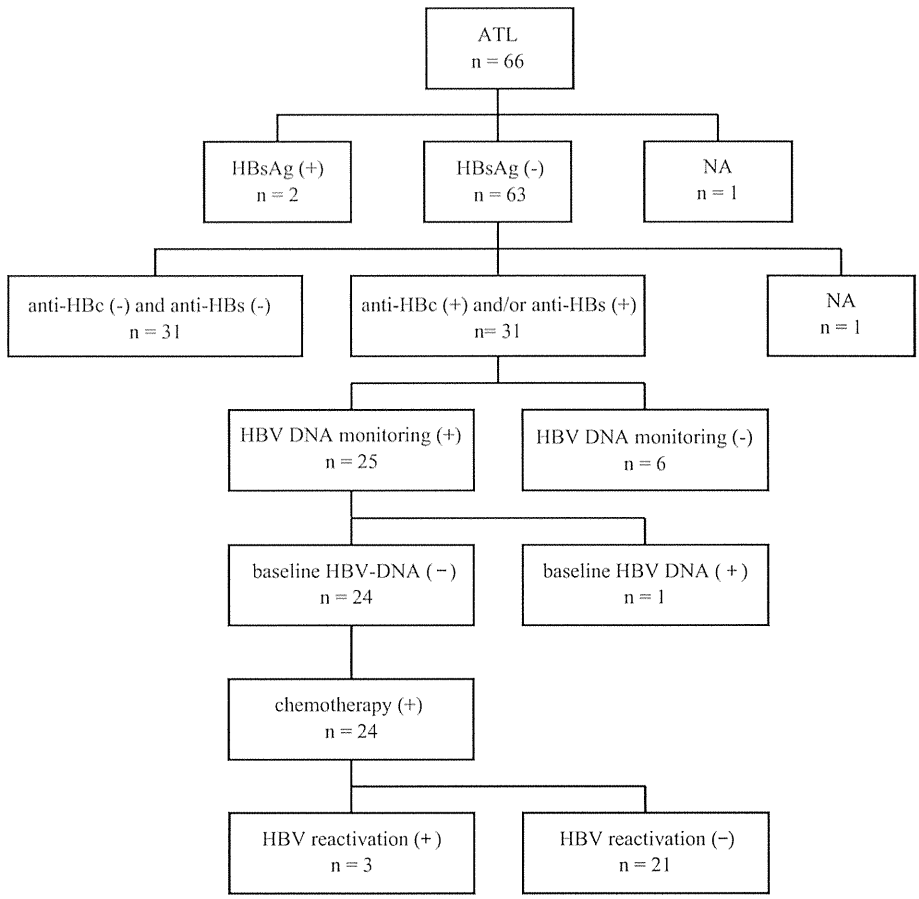

Fig. 1 Baseline serological markers of HBV infection in the 66 ATL patients. Two patients were HBsAg-positive, 63 were HBsAg-negative, the last was not available for serological HBV assessment. Of the 63 HBsAg-negative patients, 31 were anti-HBc-positive and/or anti-HBs-positive. One patient had detectable HBV DNA at baseline, and was judged as having occult HBV infection. Regular HBV DNA monitoring was performed in 24 of 31 patients with resolved HBV infection and 3 patients suffered HBV reactivation. *HBV* hepatitis B virus, *ATL* adult T-cell leukemia–lymphoma, *HBsAg* hepatitis B surface antigen, *anti-HBc* antibodies against hepatitis B core antigen, *anti-HBs* antibodies against hepatitis B surface antigen, *NA* not available

patients before HBV DNA monitoring. For the 24 patients with resolved HBV infection during and after systemic chemotherapy, regular monitoring of HBV DNA was conducted with a median interval of 30 days (range 2–703).

HBV reactivation was observed in 3 (12.5 %) of 24 patients with resolved HBV infection, with a median HBV DNA follow-up of 238 days (range 57–1420). No hepatitis due to HBV reactivation occurred in those patients who were diagnosed with HBV DNA levels below 2.1 log copies/mL and who received antiviral drugs (entecavir, 0.5 mg/day), resulting in no detectable HBV DNA levels during antiviral treatment.

There was no statistically significant difference in baseline characteristics and ATL treatment between patients with and without reactivation in this retrospective analysis (Table 1). The characteristics of 3 patients with HBV reactivation are shown in Table 2; all were male, and seropositive for anti-HBc and anti-HBs at baseline, and received the VCAP-AMP-VECP regimen as initial treatment. Mogamulizumab was administered prior to HBV reactivation in 2 of 3 HBV-reactivated patients. The anti-HBs titers of 3 patients decreased at reactivation compared to baseline titers in 3 patients. Their HBV genotypes were determined as C. HBV mutations were not found in the precore region or basal core promoter. One patient died due to ATL progression.

The clinical course of case 1 is shown in Fig. 2. HBV reactivation was confirmed with HBV DNA levels below 2.1 log copies/mL, 3 months after initiating mogamulizumab-containing chemotherapy as initial treatment for ATL. The patient presented with elevation of transaminase levels after detection of HBV DNA, it considered not viral hepatitis, but drug-induced liver damage because of transient and slight increase of HBV DNA levels. Reemergence of HBV was observed repeatedly after withdrawal of antiviral drugs following the development of drug-induced allergic rash or interstitial pneumonia. The patient maintains complete remission of ATL with undetectable of HBV DNA after withdrawal of antiviral drugs over 3 years after mogamulizumab-containing chemotherapy.

Discussion

This study showed that the incidence of HBV reactivation among ATL patients with resolved HBV infection who received systemic chemotherapy was 12.5 %. Preemptive antiviral therapy, guided by regular HBV DNA monitoring,

Table 1 Baseline characteristics and treatment of 24 ATL patients with resolved HBV infection who underwent HBV DNA monitoring following systemic chemotherapy

	HBV reactivation (+) $n = 3$	HBV reactivation (−) $n = 21$	p value
Median age (range)	59 (58–65)	64 (41–77)	0.822
Sex			0.217
Male	3	9	
Female	0	12	
ATL type of disease			0.090
Acute	1	17	
Lymphoma	2	1	
Chronic	0	2	
Smoldering	0	1	
ECOG performance status			0.530
0 or 1	3	14	
2 or more	0	7	
Baseline HBV status			1.00
Anti-HBc positive and anti-HBs positive	3	18	
Anti-HBc positive and anti-HBs negative	0	3	
Anti-HBc negative and anti-HBs positive	0	0	
Baseline anti-HBs titers (mIU/mL)			0.728
<10	0	3	
≥10, <100	2	8	
≥100	1	10	
Initial chemotherapy regimen[a]			0.396
CHOP	0	7	
VCAP-AMP-VECP	3	10	
Others	0	4	
Mogamulizumab administration[b]			0.576
(+)	2	9	
(−)	1	12	
Allogeneic HSCT[c]			1.00
(+)	1	5	
(−)	2	16	
Year enrolled for HBV DNA monitoring			–
2005–2006	0	0	
2006–2008	0	4	
2008–2009	0	3	
2009–2013	3	14	
Median HBV DNA follow-up time (range)[d]	640 (637–1030)	227 (57–1420)	–

HBV hepatitis B virus, *ATL* adult T-cell leukemia–lymphoma, *ECOG* Eastern Cooperative Oncology Group, *HBsAg* hepatitis B surface antigen, *anti-HBc* antibodies against hepatitis B core antigen, *anti-HBs* antibodies against hepatitis B surface antigen, *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisolone, *VCAP-AMP-VECP* VCAP (vincristine, cyclophosphamide, doxorubicin, prednisolone)-AMP (doxorubicin, ranimustine, prednisolone)-VECP (vindesine, etoposide, carboplatin, prednisolone), *HSCT* hematopoietic stem cell transplantation

[a] Initial chemotherapy regimen for adult T-cell leukemia–lymphoma was given during HBV DNA monitoring

[b] In 2 of 3 HBV-reactivated cases, mogamulizumab was given prior to HBV reactivation

[c] One patient received allogeneic hematopoietic stem transplantation after HBV reactivation

[d] HBV DNA follow-up time indicates the time from the date of baseline HBV DNA measurement until the date of the last HBV DNA measurement

was effective in preventing hepatitis due to HBV reactivation in all three patients. Most of HBV reactivation has been reported to occur in B-cell lymphoma, especially in those who received rituximab-containing chemotherapy [2–4, 6]. This is the first report regarding the risk of HBV reactivation focused on ATL patients with resolved HBV infection, which suggesting that the risk of HBV reactivation in ATL patients may be similar to that in B-cell lymphoma patients [15, 16].

ATL is a mature T-cell lymphoma and human T-cell leukemia virus type-1 plays a role in its pathogenesis. Aggressive ATL has been reported to have a poor prognosis with a median overall survival of approximately 1 year, regardless of intensive chemotherapy [17]. The anti-CCR4 monoclonal antibody, mogamulizumab has been shown recently to be effective and safe for aggressive ATL patients in the setting of monotherapy or combined with conventional chemotherapy [9, 11, 18]. It is expected that mogamulizumab will enable long-term disease control, so more HBV reactivation events may be predicted because CCR4 is a chemokine receptor expressed on T-helper type 2 and regulatory T cells [7, 19], and is thought to have an important

Table 2 Characteristics of 3 patients with HBV reactivation

	Case 1	Case 2	Case 3
Age	65	59	58
Sex	Male	Male	Male
Type of ATL	Lymphoma	Lymphoma	Acute
ECOG performance status	1	1	0
Baseline HBV status			
HBsAg	(−)	(−)	(−)
Anti-HBc titers	98.1 %	3.6 C.O.I	1.5 C.O.I
Anti-HBs titers	20.0 mIU/mL	24.0 mIU/mL	>1000.0 mIU/mL
HBV DNA levels	Not detectable	Not detectable	Not detectable
Chemotherapy regimens before HBV reactivation			
	VCAP-AMP-VECP plus mogamulizumab	VCAP-AMP-VECP	VCAP-AMP-VECP Mogamulizumab CHOP DeVIC etc.
Number of regimens	1	1	7
Allogeneic HSCT[a]	No	Yes	No
After HBV reactivation			
Time to reactivation (day)[b]	90	71	541
HBV DNA levels at reactivation (log copies/mL)	<2.1	<2.1	<2.1
Peak HBV DNA levels (log copies/mL)	2.3	<2.1	<2.1
Anti-HBs titers	17.6 mIU/mL	22.0 mIU/mL	566.5 mIU/mL
HBV genotype	C	C	C
HBV mutation of precore region or basal core promoter	Wild	Wild	NA
Antiviral drugs	Entecavir, lamivudine	Entecavir	Entecavir
Hepatitis due to HBV reactivation	No	No	No
HBV DNA follow-up time (day)[c]	1030	640	637
Outcome	Alive (CR1)	Alive (CR1)	Death due to ATL progression

HBV hepatitis B virus, *ATL* adult T-cell leukemia–lymphoma, *ECOG* Eastern Cooperative Oncology Group, *HBsAg* hepatitis B surface antigen, *anti-HBc* antibodies against hepatitis B core antigen, *anti-HBs* antibodies against hepatitis B surface antigen, *VCAP-AMP-VECP* VCAP (vincristine, cyclophosphamide, doxorubicin, prednisolone)-AMP (doxorubicin, ranimustine, prednisolone)-VECP (vindesine, etoposide, carboplatin, prednisolone), *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisolone, *DeVIC* dexamethasone, etoposide, ifosfamide, carboplatin, *CR1* first complete response

[a] One patient (case 2) received allogeneic hematopoietic stem transplantation after HBV reactivation

[b] Time to reactivation indicates the time from the date of baseline HBV DNA measurement until the date of the confirmation of HBV reactivation

[c] HBV DNA follow-up time indicates the time from the date of baseline HBV DNA measurement until the date of the last HBV DNA measurement

role in maintaining the balance of the human immune system. The mechanism whereby mogamulizumab causes HBV reactivation is not fully understood; a reduction of numbers of CCR4-expressing cells following this antibody treatment might be associated with an imbalance of antiviral immunity, resulting in the development of HBV reactivation [9, 13]. Although HBV reactivation was confirmed in 2 of 11 patients who received mogamulizumab, this study did not prove that HBV reactivation is associated with mogamulizumab therapy, partly because of the small sample size.

This study has the following limitations: a retrospective study in a single institution with a small sample size, and the diagnosis of HBV reactivation at early stage when only when HBV DNA became detectable (below 2.1 log copies/mL) by PCR. Because antiviral treatments after the onset of hepatitis are often insufficient to control HBV reactivation, preemptive antiviral therapy guided by regular HBV DNA monitoring, whereby the antiviral drug is given immediately when HBV DNA becomes detectable, is recommended by some guidelines to prevent hepatitis due to HBV reactivation [20, 21]. However, the definition of HBV reactivation and cut-off values of HBV DNA levels, along with the timing of initiation of antiviral treatment in patients with resolved HBV infection, have not been fully investigated yet.

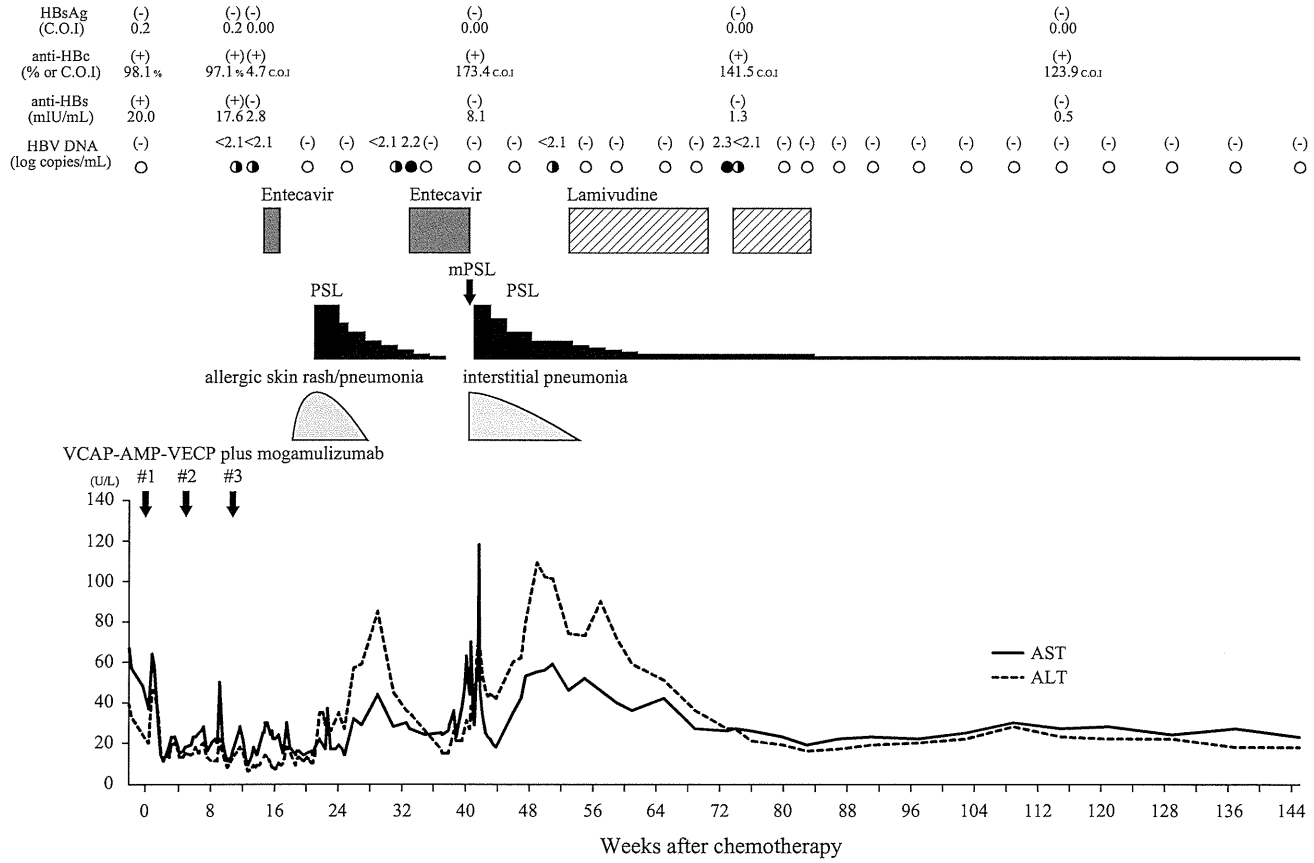

Fig. 2 Clinical course of case 1. A 65-year-old male was diagnosed as having adult T-cell leukemia–lymphoma of lymphoma type and received VCAP-AMP-VECP plus mogamulizumab combined chemotherapy. At 3 months after systemic chemotherapy, HBV reactivation was confirmed with HBV DNA levels below 2.1 log copies/mL and antiviral therapy (entecavir, 0.5 mg/day) was given immediately with no HBV-related hepatitis. He presented with elevation of transaminase levels after detection of HBV DNA, it considered not viral hepatitis but drug-induced liver damage because of transient and slight increase of HBV DNA levels. Because he suffered from an allergic rash and interstitial pneumonia (IP), entecavir could not be continued. Consequently, reemergence of HBV (HBV DNA levels of 2.2 log copies/mL) was observed at 3 months after the first detection of HBV reactivation. However, he discontinued entecavir because of the occurrence of IP, and HBV reactivation was again observed. Lamivudine was given for HBV reactivation, but was discontinued due to mild renal dysfunction, which resulted again in replication of HBV (HBV DNA levels of 2.3 log copies/mL) at 18 months after initiating mogamulizumab-containing chemotherapy. The *open circles* show undetectable PCR signals during HBV DNA monitoring; the *half-filled circles* show PCR signals indicating HBV DNA levels below 2.1 log copies/mL; and the *filled circles* show detectable PCR signals indicating HBV DNA levels of 2.1 log copies/mL or more. *HBV* hepatitis B virus, *PSL* prednisolone, *mPSL* methylprednisolone, *AST* aspartate transaminase, *ALT* alanine aminotransferase, *VCAP-AMP-VECP* VCAP (vincristine, cyclophosphamide, doxorubicin, prednisolone)-AMP (doxorubicin, ranimustine, prednisolone)-VECP (vindesine, etoposide, carboplatin, prednisolone)

In conclusion, the incidence of HBV reactivation was 12.5 % in ATL patients with resolved HBV infection following systemic chemotherapy. In mogamulizumab era, further well-designed prospective studies are warranted to estimate the incidence of HBV reactivation and to establish regular HBV DNA monitoring-guided preemptive antiviral therapy for these patients.

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References

1. 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):182–8.
2. Hui CK, Cheung WW, Zhang HY, Au WY, Yueng YH, Leung AY, et al. Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. Gastroenterology. 2006;131(1):59–68.
3. Yeo W, Chan TC, Leung NW, Lam WY, Mo FK, Chu MT, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol. 2009;27(4):605–11 (Epub 2008/12/17).
4. Kusumoto S, Tanaka Y, Mizokami M, Ueda R. Reactivation of hepatitis B virus following systemic chemotherapy for malignant lymphoma. Int J Hematol. 2009;90(1):13–23 (Epub 2009/06/23).
5. Kusumoto S, Tanaka Y, Ueda R, Mizokami M. Reactivation of hepatitis B virus following rituximab-plus-steroid combination chemotherapy. J Gastroenterol. 2011;46(1):9–16 (Epub 2010/10/07).
6. Mitka M. FDA: increased HBV reactivation risk with ofatumumab or rituximab. JAMA. 2013;310(16):1664.
7. Ishida T, Utsunomiya A, Iida S, Inagaki H, Takatsuka Y, Kusumoto S, et al. Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: its close association with skin involvement and unfavorable outcome. Clin Cancer Res. 2003;9(10 Pt 1):3625–34.
8. Ishii T, Ishida T, Utsunomiya A, Inagaki A, Yano H, Komatsu H, et al. Defucosylated humanized anti-CCR4 monoclonal antibody KW-0761 as a novel immunotherapeutic agent for adult T-cell leukemia/lymphoma. Clin Cancer Res. 2010;16(5):1520–31.
9. Yamamoto K, Utsunomiya A, Tobinai K, Tsukasaki K, Uike N, Uozumi K, et al. Phase I study of KW-0761, a defucosylated humanized anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia–lymphoma and peripheral T-cell lymphoma. J Clin Oncol. 2010;28(9):1591–8.
10. Ishida T, Ueda R. Antibody therapy for Adult T-cell leukemia–lymphoma. Int J Hematol. 2011;94(5):443–52.
11. Ishida T, Joh T, Uike N, Yamamoto K, Utsunomiya A, Yoshida S, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia–lymphoma: a multicenter phase II study. J Clin Oncol. 2012;30(8):837–42.
12. Motohashi K, Suzuki T, Kishimoto K, Numata A, Nakajima Y, Tachibana T, et al. Successful treatment of a patient with adult T cell leukemia/lymphoma using anti-CC chemokine receptor 4 monoclonal antibody mogamulizumab followed by allogeneic hematopoietic stem cell transplantation. Int J Hematol. 2013;98(2):258–60.
13. Nakano N, Kusumoto S, Tanaka Y, Ishida T, Takeuchi S, Takatsuka Y, et al. Reactivation of hepatitis B virus in a patient with adult T-cell leukemia–lymphoma receiving the anti-CC chemokine receptor 4 antibody mogamulizumab. Hepatol Res. 2014;44(3):354–7.
14. Shin IT, Tanaka Y, Tateno Y, Mizokami M. Development and public release of a comprehensive hepatitis virus database. Hepatol Res. 2008;38(3):234–43.
15. Hsu C, Tsou HH, Lin SJ, Wang MC, Yao M, Hwang WL, et al. Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: a prospective study. Hepatology. 2014;59(6):2092–100.
16. Kusumoto S, Tanaka Y, Suzuki R, Watanabe T, Nakata M, Takasaki H, et al. Prospective nationwide observational study of hepatitis B virus (HBV) DNA monitoring and preemptive antiviral therapy for HBV reactivation in patients with B-cell non-Hodgkin lymphoma following rituximab containing chemotherapy: results of interim analysis. Blood. 2012; 120(21):abstract 2641.
17. Tsukasaki K, Utsunomiya A, Fukuda H, Shibata T, Fukushima T, Takatsuka Y, et al. VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia–lymphoma: Japan Clinical Oncology Group Study JCOG9801. J Clin Oncol. 2007;25(34):5458–64.
18. Jo T, Ishida T, Takemoto S, Suzushima H, Uozumi K, Yamamoto K, et al. Randomized phase II study of mogamulizumab (KW-0761) plus VCAP-AMP-VECP (mLSG15) versus mLSG15 alone for newly diagnosed aggressive adult T-cell leukemia–lymphoma (ATL). J Clin Oncol 2013; 31: (suppl; abstr 8506).
19. Ishida T, Ueda R. Immunopathogenesis of lymphoma: focus on CCR4. Cancer Sci. 2011;102(1):44–50.
20. Oketani M, Ido A, Uto H, Tsubouchi H. Prevention of hepatitis B virus reactivation in patients receiving immunosuppressive therapy or chemotherapy. Hepatol Res. 2012;42(7):627–36 Epub 2012/06/13.
21. EASL clinical practice guidelines. Management of chronic hepatitis B virus infection. J Hepatol. 2012;57(1):167–85 Epub 2012/03/23.

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Original Article

Multicenter cooperative case survey of hepatitis B virus reactivation by chemotherapeutic agents

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Aim: The purpose of this multicenter cooperative study was to elucidate the clinical features of hepatitis B virus (HBV) reactivation by chemotherapeutic agents and the patient outcomes after HBV reactivation by a retrospective review of accumulated patients' medical records.

Methods: Records of a total of 27 patients (hematological malignancy, 14 patients; solid tumor, 13 patients) from 11 institutions who were diagnosed between June 2005 and October 2010 as having HBV reactivation following chemotherapy were reviewed.

Results: Of the 27 patients with reactivation, 16 patients were hepatitis B surface antigen (HBsAg) positive and 11 were HBsAg negative prior to the commencement of chemotherapy. Of the 11 patients who were HBsAg negative prior to the chemotherapy, 10 had hematological malignancies and one had a solid tumor. Of the 14 patients with hematological malignancies with HBV reactivation enrolled in the study, the reactivation occurred more than 12 months after the completion of chemotherapy in five patients (36%); on the other hand, none of the patients (0%) with solid tumors developed HBV reactivation more than 12 months after the completion of chemotherapy. Of the 24 patients who had acute liver dysfunction at the diagnosis of HBV reactivation, nine (38%) had severe hepatitis and seven (29%) died of liver failure.

Conclusion: Most of the patients with HBV reactivation who were HBsAg negative prior to the chemotherapy had underlying hematological malignancies. Furthermore, patients with hematological malignancies often developed late-onset HBV reactivation. The prognosis of patients who develop acute liver dysfunction as a complication of HBV reactivation is extremely dismal.

Key words: case survey, chemotherapy, hepatitis B virus, hepatitis B virus DNA, reactivation

INTRODUCTION

A VARIETY OF anticancer drugs and their metabolites are known to cause liver dysfunction. In addition, chemotherapy can trigger rapid multiplication of the virus in patients harboring hepatitis B virus (HBV), that can result in fatal liver dysfunction. Such rapid increase in the hepatitis virus load is referred to as viral hepatitis reactivation.[1–4] The frequency and risk of HBV reactivation have been reported to depend on the degree of immunosuppression and the HBV infection status prior to the start of the treatment causing immunosuppression. Immunosuppression of varying degrees is known to occur with

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Table 1 Patient characteristics

Patient no.	Before chemotherapy						Underlying malignancy	Chemotherapy	
	Age	Sex	HBsAg	HBs Antibody	HBc Antibody	HBV DNA (log copies/mL)		Regimen	Combined use of glucocorticoid
1	50	Female	+	–	+	NA	Malignant lymphoma	R + cyclophosphamide + vincristine	–
2	53	Female	+	–	+	NA	Malignant lymphoma	R-CHOP + methotrexate intrathecal	+
3	84	Male	+	NA	NA	NA	Malignant lymphoma	R-THP-COP	+
4	57	Male	+	–	+	5.3	AML	Idarubicin + Ara-C, HD-Ara-C	+
5	62	Male	+	NA	NA	NA	Brain tumor	Temozolomide + RT	–
6	49	Female	+	NA	NA	NA	Breast cancer	Doxorubicin + CPA	+
7	53	Female	+	NA	NA	NA	Colorectal cancer	FOLFOX	+
8	51	Female	+	NA	+	NA	Gastric cancer	Cisplatin + S-1	+
9	58	Female	+	+	+	NA	HCC	Cisplatin (intra-arterial infusion)	–
10	71	Male	+	NA	+	6.9	HCC	TACE with epirubicin	–
11	68	Male	+	–	+	NA	HCC	UFT + mitoxantrone	–
12	53	Male	+	+	+	4.4	ICC	Gemcitabine + RT	+
13	62	Male	+	–	+	NA	ICC	Gemcitabine + S-1	+
14	60	Male	+	NA	NA	NA	Lung cancer	Cisplatin + irinotecan	+
15	78	Male	+	NA	NA	NA	Pancreatic cancer	Gemcitabine	+
16	64	Male	+	–	+	<2.1	Rectal carcinoid	Experimental drug*	–
17	39	Male	–	+	+	UDL	Malignant lymphoma	HD CPA, whole-body RT, AlloUCBT	–
18	65	Female	–	NA	NA	NA	Malignant lymphoma	R-CHOP	+
19	76	Male	–	NA	NA	NA	Malignant lymphoma	R-CHOP	+
20	84	Female	–	NA	NA	NA	Malignant lymphoma	R-THP-COP	+
21	84	Female	–	NA	NA	NA	Malignant lymphoma	THP-COP	+
22	70	Male	–	+	+	UDL	Multiple myeloma	Melphalan +cisplatin +thalidomide	+
23	87	Female	–	+	+	<1.8	Multiple myeloma	Melphalan +prednisolone	+
24	60	Female	–	+	–	NA	Multiple myeloma	MP, MCP, AutoPBSCT	+
25	61	Female	–	+	+	<2.6	Multiple myeloma	VAD, HD-CPA, HD-Melphalan, AutoPBSCT	+
26	48	Male	–	–	+	NA	ALL	HD CPA, whole-body RT, AlloUCBT	–
27	67	Male	–	NA	NA	NA	HCC	TACE followed by TSU-68	–

*the name is not opened because it is under development.
Clinical diagnosis: Elevation of the serum aspartate aminotransferase and/or alanine aminotransferase levels with the detection of HBV DNA positivity and improvement observed in response to antiviral therapy
Complete recovery: complete recovery of AST/ALT and HBV DNA, Incomplete recovery: incomplete recovery of AST/ALT and HBV DNA
ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; AlloBMT, allogenic bone marrow transplantation; AlloUCBT, allogenic umbilical cord blood transplantation; AML, acute myeloblastic leukemia; AST, aspartate aminotransferase; Ara-C; xxx; AutoPBSCT, autologous peripheral blood stem cell transplantation; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisolone; CPA, cyclophosphamide; CVP, cyclophosphamide + vincristine + prednisolone; FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HD, high dose; ICC, intrahepatic cholangiocarcinoma; MCP, ranimustine + cyclophosphamide + prednisolone; MP, melphalan + prednisolone; NA, not assessed; R, rituximab; RT, radiation therapy; S-1, tegafur + gimeracil + oteracil; TACE, transarterial chemoembolization; THP-COP, pirarubicin + cyclophosphamide + vincristine + prednisolone; TSU-68, xxx; UDL, under detected limit; UFD, xxx; UFT, xxx; VAD, vincristine + doxorubicin + dexamethasone.

Interval from initiation of chemotherapy to HBV reactivation (days)	Interval from completion of chemotherapy to HBV reactivation (days)	At occurrence of reactivation				Outcome after reactivation
		Diagnosis of reactivation	HBV DNA (log copies/mL)	Severity of liver dysfunction	Antiviral drug	Complete recovery
637	441	Clinical diagnosis	6.9	Acute hepatitis	Entecavir	Incomplete recovery
760	539	Clinical diagnosis	5.3	Acute hepatitis	Lamivudine	Liver failure and death
1317	1210	HBV DNA titer elevation	8.8	Severe hepatitis	Entecavir	Complete recovery
147	55	Clinical diagnosis	7.6	Acute hepatitis	Lamivudine → entecavir	Complete recovery
448	319	Clinical diagnosis	5.8	Acute hepatitis	Entecavir	Complete recovery
42	23	Clinical diagnosis	5.7	Severe hepatitis	Lamivudine	Liver failure and death
209	34	Clinical diagnosis	8.6	Fulminant hepatitis	Lamivudine	Complete recovery
87	25	Clinical diagnosis	9.0	Acute hepatitis	Entecavir	Incomplete recovery
143	40	Clinical diagnosis	7.1	Acute hepatitis	Lamivudine	Incomplete recovery
309	309	Clinical diagnosis	6.9	Acute hepatitis	Entecavir	Incomplete recovery
93	37	Clinical diagnosis	5.9	Acute hepatitis	Lamivudine	Liver failure and death
130	16	HBV DNA titer elevation	8.0	Fulminant hepatitis	Entecavir	Incomplete recovery
103	17	Clinical diagnosis	5.7	Acute hepatitis	Entecavir	Complete recovery
103	18	Clinical diagnosis	5.5	Acute hepatitis	Entecavir	Incomplete recovery
28	14	Clinical diagnosis	2.8	Acute hepatitis	Entecavir	Complete recovery
51	9	Clinical diagnosis	2.6	Acute hepatitis	None	Complete recovery
340	339	HBV DNA(−) → (+)	6.0	Without hepatitis	Lamivudine → entecavir	Liver failure and death
309	182	HBsAg(−) → (+)	7.4	Severe hepatitis	Lamivudine	Liver failure and death
407	202	HBsAg(−) → (+)	9.7	Fulminant hepatitis	Entecavir	Liver failure and death
528	79	HBsAg(−) → (+)	6.5	Fulminant hepatitis	Entecavir	Complete recovery
721	69	HBsAg(−) → (+)	7.7	Acute hepatitis	Entecavir	Incomplete recovery
937	155	HBV DNA(−) → (+)	<2.1 (+)	Without hepatitis	Entecavir	Liver failure and death
700	553	HBsAg(−) → (+)	8.5	Severe hepatitis	Entecavir	Complete recovery
355	84	HBsAg(−) → (+)	6.2	Acute hepatitis	Entecavir	Complete recovery
354	233	HBV DNA(−) → (+)	2.4	Without hepatitis	Entecavir	Incomplete recovery
416	415	HBsAg(−) → (+)	8.6	Severe hepatitis	Entecavir	Complete recovery
132	14	HBsAg(−) → (+)	6.9	Acute hepatitis	Entecavir	

chemotherapy, such as that following hematopoietic stem cell transplantation and organ transplantation, rituximab-based chemotherapy and chemotherapy for solid tumors. The HBV infection status prior to chemotherapy is determined by the serum profile of HBV-associated markers (hepatitis B surface antigen [HBsAg], hepatitis B e-antigen [HBeAg], hepatitis B core antibody [HBcAb], hepatitis B surface antibody [HBsAb]) and the viral load of HBV DNA.[1–4] However, there have been few comprehensive reports on HBV reactivation, and the clinical background factors involved in HBV reactivation, including the circumstances of the chemotherapy AND the characteristics of the

reactivation, and the clinical outcomes following HBV reactivation have not yet been clearly elucidated. We therefore conducted a retrospective clinical review of the medical records of patients who developed HBV reactivation following treatment with chemotherapeutic agents. The purpose of this multicenter cooperative study was to elucidate the clinical features of HBV reactivation and the patient outcomes after HBV reactivation.

METHODS

Patients

WE CONDUCTED A retrospective clinical review of the medical records of patients with HBV reactivation induced by anticancer drugs accumulated at each institution. This clinical study was conducted with the approval of the ethics committee of the National Cancer Center, and in accordance with epidemiological research guidelines.

We defined HBV reactivation as follows: (i) increase of the HBV DNA titer by more than 10-fold or conversion to a HBeAg positive from HBeAg negative status in patients determined to be HBsAg positive after the commencement of chemotherapy; (ii) conversion from a HBsAg negative to HBsAg positive status after the commencement of chemotherapy; and (iii) increase of the HBV DNA titer to above the detection limit in patients with HBV DNA titers below the detection limit of the assay after the commencement of chemotherapy.[1,2] In addition, elevation of the serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels along with HBV DNA positivity and improvement in response to antiviral therapy was also defined as HBV reactivation in this study.

Variables examined

The variables examined in the patients with HBV reactivation are listed below. Patient background factors were age, sex, the underlying malignancy, presence/absence of liver metastasis, presence/absence of concomitant liver disease and history of alcohol consumption.

Factors related to the chemotherapy inducing the HBV reactivation were chemotherapeutic regimen used, the day of commencement of chemotherapy, the day of discontinuation of chemotherapy and concomitant use of glucocorticoid.

Status at the occurrence of reactivation included date of diagnosis of HBV reactivation, symptoms associated with the HBV reactivation, the antiviral drugs used for treating the HBV reactivation, date of start of antiviral drug administration, concomitant treatments for HBV reactivation, severity of the liver dysfunction caused by the reactivation and outcome after the reactivation.

Laboratory tests before and after the HBV reactivation consisted of hemogram (leukocytes, neutrophils, lymphocytes, hemoglobin, platelets), serum biochemistry (total bilirubin, AST, ALT, alkaline phosphatase), coagulation parameters (prothrombin time) and hepatitis B virus marker profile (HBsAg, HBsAb, HBeAg, hepatitis B e antibody, HBcAb, HBV DNA load).

RESULTS

Patient characteristics before the commencement of chemotherapy

THE RECORDS OF a total of 27 patients with HBV reactivation diagnosed between June 2005 and October 2010 were accumulated from 11 institutions (Table 1). The patient characteristics before the commencement of chemotherapy are shown in Table 2. The patients consisted of 15 men and 12 women, with a median age of 62 years (range, 39–87). Among the patients with HBV reactivation, 16 were HBsAg positive and 11 patients were HBsAg negative prior to the commencement of chemotherapy. The underlying malignancies were hematological malignancies in 14 patients and solid tumors in 13 patients; among the hematological malignancies, malignant lymphoma was the most common, while among the solid tumors, hepatocellular carcinoma was the most common. Among the 11 patients who were HBsAg negative prior to the chemotherapy, 10 had underlying hematological malignancies and only one had a solid tumor. The chemotherapy inducing the HBV reactivation was the chemotherapeutic regimen administrated with hematopoietic stem cell transplantation in four patients, a rituximab-based regimen in five patients, platinum combination regimen in four patients and gemcitabine alone or combination regimen in three patients. A glucocorticoid was used concomitantly in 18 patients.

Findings at the time of HBV reactivation

At the time of reactivation, 12 patients presented with symptoms, including fatigue, anorexia, nausea/vomiting, jaundice, pyrexia and drowsiness (Table 3). Of the 27 patients, in 24, the HBV reactivation was diagnosed by checking for elevation of the HBV DNA titers after detection of increase of the serum AST and/or ALT level, while in the remaining three patients, reactivation was diagnosed by observing conversion from HBsAg negative to HBsAg positive or an increase of the HBV DNA load in the absence of elevation of the serum AST and/or ALT levels (patients

Table 2 Patient characteristics before chemotherapy

Variables		*n*	(%)
All patients		27	–
Age (years)	Median [range]	62	39–87
Sex	Male	15	(56)
	Female	12	(44)
Serological marker of hepatitis B viral infection	HBsAg (+)	16	(59)
	HBsAg (–)	11	(41)
	HBsAg (–), and anti-HBs or anti-HBc (+)	6	(22)
	HBsAg (–), no data on anti-HBs and anti-HBc	5	(19)
Tumor type			
Hematological tumor	All	14	(52)
	Malignant lymphoma	8	(30)
	Multiple myeloma	4	(15)
	Leukemia	2	(7)
Solid tumor	All	13	(48)
	Hepatocellular carcinoma	4	(15)
	Bile duct cancer	2	(7)
	Others	7	(26)
Chemotherapeutic regimen	Hematopoietic stem cells transplant	4	(15)
	R-CHOP	5	(19)
	Platinum combination	4	(15)
	Gemcitabine alone or combination	3	(11)
	Others	11	(40)
Concomitant use of a glucocorticoid	Present	18	(67)
Liver metastases	Present	3	(11)
Complication of liver disease	Chronic hepatitis type C	1	(4)
Alcohol abuse	Habitual drinker	6	(22)
	Social drinker	10	(37)

Anti-HBs, hepatitis B surface antibody; anti-HBc antibody, hepatitis B core antibody; HBsAg, hepatitis B surface antigen, R-CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone combined with rituximab

17, 22 and 25). All of the three latter patients with underlying hematological malignancies were HBsAg negative and HBcAb positive prior to the commencement of chemotherapy, and HBV reactivation was detected by monthly measurements of the HBsAg or HBV DNA. The median interval from completion of chemotherapy to HBV reactivation and median interval from initiation of chemotherapy to HBV reactivation were 79 days (range, 9–1210) and 309 days (range, 28–1317), respectively. In none of the 13 patients (0%) with solid tumors did HBV develop more than 12 months after the completion of chemotherapy, while in five of the 14 patients (36%) with underlying hematological malignancy, it developed more than 12 months after the completion of chemotherapy.

Outcome after HBV reactivation

Of the 27 patients, 26 were treated with antiviral drugs such as entecavir or lamivudine at the time of HBV reactivation, while one patient improved spontaneously (patient 16) (Table 3). Acute liver dysfunction developed at the time of the reactivation in 24 patients, while the remaining three patients showed no evidence of liver dysfunction (patients 17, 22 and 25). Of the 27 patients, five (28%) and four (15%) had severe hepatitis and fulminant hepatitis, respectively, and seven patients (26%) died of liver failure.

DISCUSSION

IN 2001, DERVITE *et al.* reported, for the first time, HBV reactivation in a HBsAg negative patient who had received rituximab-based chemotherapy.[5] It became clear then that reactivation could occur not only in HBsAg positive patients, but also in HBsAg negative and HBcAb/HBsAb positive patients. Since then, HBV reactivation has begun to attract much interest in clinical practice. However, the factors associated with, and the outcomes of, reactivation have not yet been sufficiently characterized. Therefore, we conducted a clinical survey of the data of patients with HBV reactivation, and case reports of 27 patients with HBV reactivation occurring following chemotherapy were collected from 11 institutions. This study focused on the clinical courses of the patients who developed HBV reactivation, and both patients who

Table 3 Condition at occurrence and outcomes in patients with reactivation of hepatitis B viral infection

Variables		*n*	(%)
Symptom	Present	12	(44)
	Malaise	7	(26)
	Anorexia	7	(26)
	Nausea/vomiting	2	(7)
	Jaundice	1	(4)
	Fever	1	(4)
	Somnolence	1	(4)
Criteria for diagnosis of HBV reactivation	Clinical Diagnosis*	14	(52)
	Positive conversion of HBsAg	8	(30)
	Increase of the HBV DNA titer to above the detection limit	3	(11)
	Increase of the HBV DNA titer by more than 10-fold	2	(7)
Interval from completion of chemotherapy to HBV reactivation	Median [range], days	79	[9–1210]
	Solid tumor, median [range], days	23	[9–319]
	Hematological malignancy, median [range], days	218	[55–1210]
Treatment for HBV reactivation	Antiviral drug	26	(96)
	Entecavir	20	(74)
	Lamivudine	8	(30)
	Glycyrrhizin	12	(44)
	Ursodeoxycholic acid	4	(15)
	Interferon	4	(15)
	Steroids	2	(17)
	Plasma exchange	1	(4)
Type of liver dysfunction	Acute hepatitis	15	(55)
	Severe hepatitis	5	(19)
	Fulminant hepatitis	4	(15)
	None	3	(11)
Outcome after reactivation	Complete improvement of the serum AST/ALT and HBV DNA titer to normal range	12	(44)
	Incomplete improvement of the serum AST/ALT and/or HBV DNA titer	8	(30)
	Liver failure and death	7	(26)

*Clinical diagnosis: Elevation of the serum aspartate aminotransferase and/or alanine aminotransferase levels with the detection of HBV DNA positivity and improvement observed in response to antiviral therapy

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus infection.

underwent adequate screening and follow up for HBV reactivation and those who did not undergo adequate screening and follow up were included in this study. In addition, patients with various malignant diseases, receiving various treatment regimens, and any HBsAg status were included in this study. Furthermore, not only patients in whom the HBV reactivation was diagnosed on the basis of increased HBV DNA titers and conversion of the HBeAg or HBsAg status, but also those in whom the diagnosis was made based on elevation of the serum AST and/or ALT levels along with HBV DNA positivity and improvement in response to antiviral therapy were included. Therefore, we obtained comprehensive data on patients developing HBV reactivation in actual clinical practice. Thus, even though the number of patients with HBV reactivation was limited in this study, accumulation of such patients with HBV reactivation may be expected to contribute to a further understanding of HBV reactivation and also lead to the development of some novel countermeasures against HBV reactivation.

In this study, while reactivation in patients with a HBsAg positive status prior to chemotherapy was observed in both patients with underlying hematological malignancies and solid tumors, reactivation in patients with a HBsAg negative status prior to chemotherapy occurred predominantly in patients with underlying hematological malignancies. Previous reports of HBV reactivation in HBsAg negative patients have rarely been reported in the patients with solid tumors, including breast cancer,[6] hepatocellular carcinoma,[7,8] brain tumors,[9] rectal cancer,[10] pharynx and esophageal cancer,[11] and lung cancer,[11] and in patients receiving drug regimens including cyclophosphamide, doxorubicin plus 5-fluorouracil, temozolomide, and mitomycin plus hydroxycamptothecin.[7] Our present report serves to emphasize that caution against reactivation must be exercised even in HBsAg negative patients with

solid tumors. Glucocorticoids were used in combination with the chemotherapy to increase the therapeutic efficacy and/or prevent emetic reaction in 18 of the 27 patients in our study. Glucocorticoids have been mentioned as risk factors for HBV reactivation,[12] and it appears indeed that glucocorticoid use may influence the risk of HBV reactivation. It is necessary to pay attention not only to the anticancer drugs used, but also to whether glucocorticoids were also used in combination with the drugs as antiemetics.

In regard to the interval from completion of chemotherapy to HBV reactivation, HBV reactivation developed within 12 months after the completion of chemotherapy in all 13 patients (100%) with solid tumors. However, in five of the 14 (36%) patients with hematological malignancies, HBV reactivation occurred more than 12 months after the completion of chemotherapy. The maximum interval from completion of chemotherapy to HBV reactivation in this series was 3.3 years in a patient with malignant lymphoma treated with THP-COP therapy (pirarubicin, cyclophosphamide, vincristine plus prednisolone). This late onset was thought to be related to a delayed immune recovery because of prolonged suppressive effects of the intensive chemotherapy for hematological malignancy and glucocorticoid treatment, although some patients might have been due to discontinue prophylactic antiviral drug treatment. On the other hand, the immunosuppressive effects of chemotherapy for solid tumors may not be so prolonged,[1–3,13] although almost all patients with solid tumors may die before the late onset of HBV reactivation because of the generally dismal prognosis. Thus, follow up for HBV reactivation is obviously necessary for a long period of time after completion of chemotherapy in patients with hematological malignancies, although the follow up for HBV reactivation is recommended for limited periods, such as 12 months, at least 12 months and 2–6 months, after the completion of chemotherapy by some guidelines and consensus statement.[14–16]

Among the 24 patients who developed acute liver dysfunction at the time of the reactivation, nine patients (38%) had severe or fulminant hepatitis and seven patients (29%) died of liver failure. As previously reported,[17,18] the prognosis of patients who develop liver dysfunction as a complication of HBV reactivation remains poor. This finding suggests that periodic monitoring of liver function is insufficient to prevent liver function-related deaths associated with HBV reactivation, and countermeasures to prevent liver dysfunction due to HBV reactivation, such as prophylactic administration of antiviral drug(s) before the commencement of chemotherapy and periodic monitoring of the HBV DNA levels, is important in patients receiving chemotherapy.

Consensus statements regarding HBV reactivation were published by the Asian Pacific Association for the Study of the Liver (APASL) in 2005,[19] the Practice Guidelines by the American Association for the Study of Liver Diseases (AASLD) in 2007,[20] the Consensus Development Conference Management of Hepatitis B by the National Institutes of Health (NIH) in 2008,[16] and the Clinical Practice Guideline by the European Association for the Study of the Liver (EASL) in 2009,[12] and, in Japan, the Guidelines for Countermeasures against the Onset of Hepatitis B due to Immunosuppression and Chemotherapy were published in 2009.[13] In all of these guidelines, preventive treatments with antiviral drugs for HBsAg positive patients receiving chemotherapy are recommended. Furthermore, all guidelines, except the AASLD guideline, recommend periodic monitoring for HBV DNA and deferred preemptive administration of antiviral drug(s) after positive conversion of HBV DNA in HBsAg negative HBcAb/HBsAb positive patients. However, evidence is yet to be established to support these recommendations, and these recommendations were based on clinical experiences and ideal aspects. Therefore, some clinical studies to clarify their usefulness have been conducted both in Japan and abroad.[1] In the future, even firmer evidence of countermeasures for HBV reactivation is expected to be demonstrated.

This study had some limitations. HBcAb and HBsAb were measured in only 59% and 52% of patients, respectively. Therefore, the diagnostic basis for HBV reactivation may be inadequate, because patients with HBV reactivation diagnosed clinically, based on elevation of the serum AST and/or ALT followed by detection of HBV DNA positivity and improvement observed in response to antiviral therapy, were also included in this study. In addition, there were some missing data in this study, inevitable on account of the retrospective nature of the study. Finally, we could not clarify the frequency of HBV reactivation in patients under chemotherapy who were HBsAg positive or HBsAg negative and HBcAb/HBsAb positive, because the number of such patients during the study period could not be determined in all of the institutions. However, the frequency of HBV reactivation according to the HBsAg status could be clarified from the results of some prospective studies on the risk of HBV reactivation in patients with solid tumors or hematological malignancies receiving chemotherapy conducted by our colleagues (UMIN no. 000005369 and 000001299). However, despite these limitations, the analyses were meaningful, because

information about HBV reactivation following chemotherapy available to date is rather limited.

In conclusion, HBV reactivation has been observed in patients with a variety of malignancies, but almost all of the patients who developed HBV reactivation from a HBsAg negative status had underlying hematological malignancies. Because late onset of HBV reactivation was often observed in patients with hematological malignancies, follow up for HBV reactivation is obviously necessary for a long period of time after completion of chemotherapy in patients with hematological malignancies. As the prognosis of patients who develop liver dysfunction as a complication of HBV reactivation remains poor, countermeasures to prevent liver dysfunction due to HBV reactivation is important in patients receiving chemotherapy. To establish firm evidence of HBV reactivation, further well-designed clinical trials are warranted.

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REFERENCES

1 Ikeda M. Reactivation of hepatitis B virus in patients receiving chemotherapy. *Jpn J Clin Oncol* 2013; **43**: 8–16.
2 Kusumoto S, Tanaka Y, Mizokami M *et al.* Reactivation of hepatitis B virus following systemic chemotherapy for malignant lymphoma. *Int J Hematol* 2009; **90**: 13–23.
3 Hui CK, Cheung WW, Zhang HY *et al.* Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. *Gastroenterology* 2006; **131**: 59–68.
4 Ohtsu T, Sai T, Oka M *et al.* Activation of hepatitis B virus infection by chemotherapy containing glucocorticoid in hepatitis B virus carriers with hematologic malignancies. *Jpn J Clin Oncol* 1991; **21**: 360–365.
5 Dervite I, Hober D, Morel P. Acute hepatitis B in a patient with antibodies to hepatitis B surface antigen who was receiving rituximab. *N Engl J Med* 2001; **344**: 68–69.
6 Ide Y, Ito Y, Takahashi S *et al.* Hepatitis B virus reactivation in adjuvant chemotherapy for breast cancer. *Breast Cancer* 2013; **20**: 367–70.
7 Peng JW, Lin GN, Xiao JJ *et al.* Hepatitis B virus reactivation in hepatocellular carcinoma patients undergoing transcatheter arterial chemoembolization therapy. *Asia Pac J Clin Oncol* 2012; **8**: 356–61.
8 Shiba S, Kondo S, Ueno H *et al.* Hepatitis B Virus Reactivation during Treatment with Multi-Tyrosine Kinase Inhibitor for Hepatocellular Carcinoma. *Case Rep Oncol* 2012; **5**: 515–9.
9 Ohno M, Narita Y, Miyakita Y *et al.* Reactivation of hepatitis B virus after glioblastoma treatment with temozolomide--case report. *Neurol Med Chir (Tokyo)* 2011; **51**: 728–31.
10 Noguchi Y, Tsurushima M, Tamura Y *et al.* A case of hepatitis B virus reactivation in a patient with prior resolved hepatitis B infection during bevacizumab plus FOLFIRI treatment. *Gan To Kagaku Ryoho* 2013; **40**: 1561–3. (In Japanese)
11 Hagiwara S, Sakurai T, Nishina S *et al.* Characteristic pattern of reactivation of hepatitis B virus during chemotherapy for solid cancers. *Dig Dis* 2012; **30**: 541–6.
12 Cheng AL, Hsiung CA, Su IJ *et al.* Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. *Hepatology* 2003; **37**: 1320–8.
13 Lau GK, Liang R, Chiu EK *et al.* Hepatic events after bone marrow transplantation in patients with hepatitis B infection: a case controlled study. *Bone Marrow Transplant* 1997; **19**: 795–9.
14 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B. *J Hepatol* 2009; **50**: 227–242.
15 Tsubouchi H, Kumada H, Kiyosawa K *et al.* Prevention of immunosuppressive therapy or chemotherapy-induced reactivation of hepatitis B virus infection—Joint report of the Intractable Liver Diseases Study Group of Japan and the Japanese Study Group of the Standard Antiviral Therapy for Viral Hepatitis. *Kanzo* 2009; **50**: 38–42 (In Japanese).
16 NIH Consensus Development Conference Statement on Management of Hepatitis B. NIH Consensus and State-of-the-Science Statements. Volume 25, Number 2. October 20–22, 2008.
17 Yeo W, Lam KC, Zee B *et al.* Hepatitis B reactivation in patients with hepatocellular carcinoma undergoing systemic chemotherapy. *Ann Oncol* 2004; **15**: 1661–6.
18 Umemura T, Tanaka E, Kiyosawa K *et al.* Mortality secondary to fulminant hepatic failure in patients with prior resolution of hepatitis B virus infection in Japan. *Clin Infect Dis* 2008; **47**: e52–6.
19 Liaw YF, Leung N, Guan R *et al.* Asian-Pacific consensus statement on the management ofchronic hepatitis B: a 2005 update. *Liver Int* 2005; **25**: 472–489.
20 Lok AS, McMahon BJ. Chronic Hepatitis B. *Hepatology* 2007; **45**: 507–539.

JOHNS 特集○大きく変わりつつある頭頸部癌化学療法

化学療法施行時のB型肝炎の再活性化と留意点

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● Key Words ●頭頸部癌，化学療法，B型肝炎，再活性化，HBV DNA●

はじめに

化学療法を施行する際に，B型肝炎ウイルス（HBV）が再活性化し，時には劇症化する報告が散見されている。HBs抗原陽性例のみならず，HBs抗原陰性で，HBs抗体またはHBc抗体陽性のいわゆる既往感染と考えられている例でも再活性化の報告がある[1]。HBVが再活性化し肝障害を起こした症例は，化学療法を中止せざるを得なくなり，時には重症肝炎や劇症肝炎を起こし，生命が脅かされることもある。このHBVの再活性化による肝障害はきちんと対策をとることで，未然に防ぐことが可能な場合が多く，HBVの再活性化のリスク，対応策を熟知しておくことが必要である。本稿では，HBV再活性化の現状や留意すべき対応策を中心に概説する。

HBVの再活性化の現状

1．HBVの再活性化とは

HBVを有する患者に化学療法を施行した場合，急激なHBVの増殖が生じ，致死的な肝障害が起こることがある。このように，化学療法による免疫抑制状態などが誘因となり，HBVの急激な増殖を再活性化という[1]。このHBVの再活性化は，HBs抗原陽性のいわゆるキャリア/慢性肝炎の患者のみならず，HBs抗原陰性で，HBc抗体またはHBs抗体陽性のいわゆる一過性感染してHBVは排除されたと考えられていた患者（既往感染例）においても，HBVの再活性化のリスクがあることが言われている。それは，HBVは肝臓や末梢血単核球中に存在し，低レベルながらHBV DNAの複製が長期間持続していることが原因と言われている[1]。

2．HBVの再活性化の定義

HBV再活性化の定義は，一般的に次のように定義されることが多い[1]。

1）HBs抗原陽性例
- ①HBV DNAが10倍以上の上昇
- ②HBe抗原陰性例で，HBe抗原が陽性化

2）HBs抗原陰性で，HBc抗体またはHBs抗体陽性例
- ①HBs抗原が陽性化
- ②HBV DNA検出感度以下の例でHBV DNAの陽性化

3．HBs抗原，HBc抗体またはHBs抗体の陽性率

国立がん研究センター東病院で2010年8月から2012年5月の間，初回化学療法を施行した1,129例を対象として検討したところ，HBs抗原の陽性率，HBs抗原は陰性でHBc抗体またはHBs抗体の陽性率は，それぞれ3.3%，25.2%であった。その他の報告も同様に，本邦の成人でのHBs抗原陽性の割合は1～3%，HBs抗体またはHBc抗体の陽性の割合は20～30%前後である（表1）。したがって，本邦で化学療法を施行する際にHBVの再活性化のリスクがある症例は4人に1人ぐらいの割合で存在すると言われている。

4．HBs抗原陽性例からのHBVの再活性化の報告

これまでにHBs抗原陽性例からのHBVの再活性化は，ほとんどすべての癌腫，さまざまな抗が

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表 1　HBs 抗原，HBc 抗体，HBc 抗体または HBs 抗体の陽性率

	n	HBs 抗原（+）	HBc 抗体（+）	HBc 抗体（+）または HBs 抗体（+）	著者	報告年
香　港	244	NA	62.0%	72.0%	Hui CK	2006
香　港	626	12.0%	NA	NA	Yeo W	2000
アメリカ	3,343	1.3%	9.0%	NA	Ludwig E	2010
名古屋	3,874	1.5%	20.0%	23.2%	Kusumoto S	2009
東　京	1,031	NA	16.9%	NA	Matsue K	2010
千　葉	261	3.4%	24.3%	NA	Hattori M	2010
青　森	428	1.4%	29.1%	31.5%	Urata Y	2011
千葉（当院）	1,129	3.3%	22.3%	25.2%	—	—

ん薬で報告がある。おおよそ 20～50% 前後の HBV の再活性化の報告があり，そのリスク因子として，男性，若年者，HBe 抗原陽性，HBV DNA 高用量，乳癌の患者，ステロイドの併用，アンスラサイクリン系の抗がん薬の使用，リツキシマブの使用，リンパ腫の患者などが言われている[1,2]。

5．HBs 抗原陰性で，HBc 抗体陽性または HBs 抗体陽性例からの HBV の再活性化の報告

2001 年に Dervite らがリツキシマブ併用化学療法例における症例報告に始まり，2006 年 Hui らによる悪性リンパ腫の患者 3.3% に HBV の再活性化を認めたという報告[4]，2009 年に Yeo らによるリツキシマブとステロイド併用化学療法を施行した患者 6.25% に HBV の再活性化を認めたという報告[5]など，悪性リンパ腫に対するリツキシマブなどでは，よく報告されている。しかし，その他のがんに関しては，まだ頻度は低く，レジメンも限られており，症例報告レベルである。頻度は低いが，HBs 抗原陰性で，HBs 抗体または HBc 抗体陽性例でも再活性化は起こっており，やはり注意が必要である。

6．HBV の再活性化症例の転帰

HBV の再活性化による肝障害を併発した症例の予後は不良と報告されている。Yeo らは HBV 再活性化による肝炎を併発した 32 例に対して，ラミブジンにて治療したが，全身化学療法の中止を余儀なくされた症例は 22 例（69%）で，5 例（16%）で肝障害によって死亡されたと報告した[6]。

また，Umemura らは，HBV の再活性化を認めた 23 例のうち，劇症化した症例は 5 例（22%）で，肝関連死亡率は 26%，劇症化例での死亡率は 100% であったのに対して，急性肝炎の患者 529 例では劇症化した症例は 45 例（9%）で，肝関連死亡率は 4%，劇症化例での死亡率は 47% であり，HBV の再活性化による劇症化率ならびに肝関連死亡率，劇症化例での死亡率は有意に高率であったことを報告した[7]。このように HBV の再活性化による肝障害を起こしてからでは予後不良であり，肝障害を起こす前に再活性化を抑え込むことが重要である。

HBV 再活性化に対する留意すべき対応策

HBV 再活性化のモニタリングと対応は，HBs 抗原陽性例と HBs 抗原陰性で HBs 抗体または HBc 抗体陽性例で異なっている。

1．HBs 抗原陽性例に対する対応策

HBs 抗原陽性例に対しては，抗ウイルス薬であるラミブシンの予防投与に関するランダム化比較試験がいくつか報告されており，どの試験も再活性化の頻度，再活性化による肝障害の頻度の頻度は，ラミブシンの予防投与群で良好な結果であった。また，これらのメタアナリシス[8]でも，ラミブジン予防投与群において，HBV の再活性化の頻度，再活性化による死亡割合，化学療法の中止割合が低いことが報告されている。このように HBs 抗原陽性例には，抗ウイルス薬の予防投与の有用性が示されている。

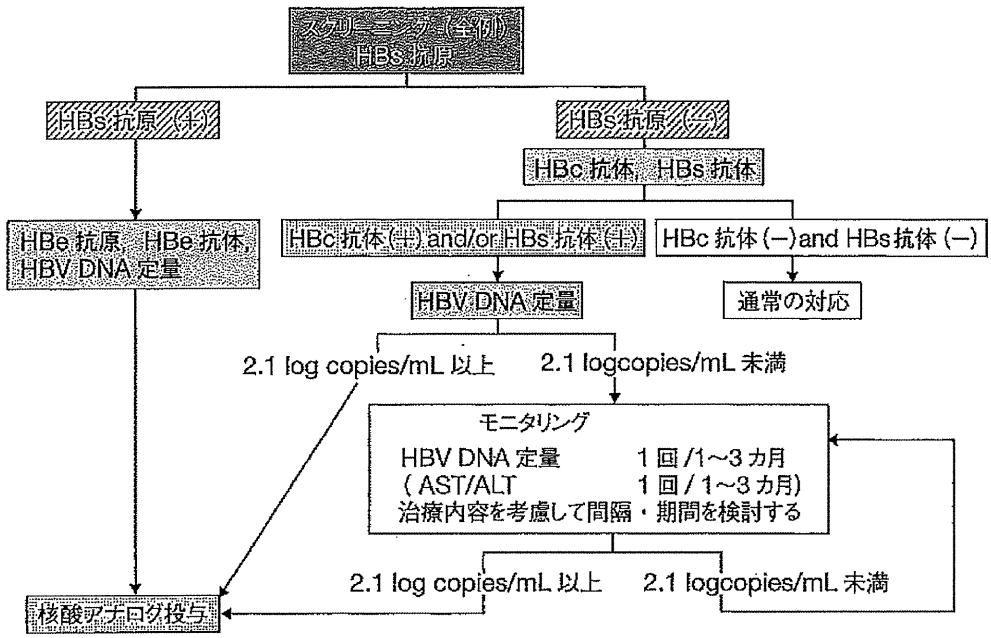

図1　免疫抑制・化学療法により発症するB型肝炎に対する診療ガイドライン

2．HBs抗原陰性で，HBc抗体またはHBs抗体陽性例に対する対応策

HBVの再活性化の予防に関する十分な検討は行われていない。ただし，HBV DNAが陽性化してから肝障害・肝炎が出現するまでに平均4〜5カ月ほど先行すると言われており[4]，HBV DNAを1〜3カ月に1回，モニタリングして，HBV DNAが陽性化してから抗ウイルス薬の投与を行っても，肝炎の重症化は予防可能と推察されている。

3．本邦でのHBV再活性のガイドライン

2009年2月に「免疫抑制・化学療法により発症するB型肝炎対策のガイドライン」（図1）が発表された。その後，改訂されたガイドラインの概要[9]を下記に示す。

1）スクリーニング検査

化学療法を施行する場合，全例にスクリーニング検査として，HBs抗原を測定し，HBV再活性化の高リスク群を同定する。

2）HBs抗原陽性の場合

HBe抗原，HBe抗体，HBV DNA定量を測定し，治療前の状態を確認する。再活性化のリスクが高いので，原則，抗ウイルス薬の予防投与を行う。予防投与すべき抗ウイルス薬としては，ランダム化比較試験などで有用性が示されているのはラミブジンであるが，HBVに対する治療効果，薬剤耐性の問題より，本邦では，エンテカビルが推奨されている。

3）HBs抗原陰性の場合

HBc抗体とHBs抗体を測定し，どちらかが陽性であれば，再活性化のリスクがあると判断し，HBV DNAの定量を行う。HBV DNAが陽性であれば，抗ウイルス薬の投与を行う。陰性（検出感度以下）であれば，HBV DNAを1〜3カ月ごとにモニタリングしながら，陽性化したら抗ウイルス薬の投与を開始する。

HBc抗体とHBs抗体がともに陰性であれば，再活性化のリスクはないと判断して，定期的なHBV DNAの経過観察は必要ないとされている。

おわりに

化学療法施行時のHBVの再活性化は，実際の診療においてあまり経験することがないために，軽視されがちである。初回化学療法例3,302人を対象とした本邦でのスクリーニング率は，HBs抗原で66.3%，HBc抗体/HBs抗体の測定率は19.9%

と低値であり，十分に行われていない状況であった[10]。しかし，HBV再活性化を起こし，肝障害まできたしてしまうと，化学療法の継続が困難となったり，劇症化して生命を落としてしまうこともある。そして，HBVの再活性化で裁判になると，敗訴になる可能性は高い。

もとより，HBV再活性のガイドラインに従ってきちんと対応することで重篤な肝障害を起こさせずに管理することが可能であり，患者のためにも有益である。化学療法施行時のHBVの再活性化は軽視され，忘れられがちであるが，意識してHBVの再活性化の予防に取り組むことが必要である。

文　献

1) Ikeda M：Reactivation of hepatitis B virus in patients receiving chemotherapy. Jpn J Clin Oncol 43：8-16, 2013.
2) Kusumoto S, et al：Reactivation of hepatitis B virus following systemic chemotherapy for malignant lymphoma. Int J Hematol 90：13-23, 2009.
3) Dervite I, et al：Acute hepatitis B in a patient with antibodies to hepatitis B surface antigen who was receiving rituximab. N Engl J Med 344：68-69, 2001.
4) Hui CK, et al：Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. Gastroenterology 131：59-68, 2006.
5) Yeo W, et al：Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol 27：605-611, 2009.
6) Yeo W, et al：Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. J Clin Oncol 22：927-934, 2004.
7) Umemura T, et al：Mortality secondary to fulminant hepatic failure in patients with prior resolution of hepatitis B virus infection in Japan. Clin Infect Dis 47：e52-56, 2008.
8) Martyak LA, et al：Lamivudine prophylaxis is effective in reducing hepatitis B reactivation and reactivation-related mortality in chemotherapy patients：a meta-analysis. Liver Int 28：28-38, 2008.
9) 日本肝臓学会：肝炎診療ガイドライン作成委員会．B型肝炎治療ガイドライン，第1.2版，2013.
10) Ikeda M, et al：Current status of screening of hepatitis B virus infection in patients with undergo chemotherapy in Japan. Asian Pacific Association for the Study of the Liver, Brisbane, 2014（Abstract）.

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