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Original Article

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

Hideaki Takahashi,[1] Masafumi Ikeda,[1] Takashi Kumada,[2] Yukio Osaki,[3] Shunsuke Kondo,[4] Shigeru Kusumoto,[5] Kazuyoshi Ohkawa,[6] Seijin Nadano,[7] Junji Furuse,[8] Masatoshi Kudo,[9] Kiyoaki Ito,[10,11] Masahiro Yokoyama,[12] Takuji Okusaka,[4] Masanori Shimoyama[13] and Masashi Mizokami[10]

[1]*Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa,* [2]*Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki,* [3]*Departments of Gastroenterology and Hepatology, Osaka Red Cross Hospital,* [4]*Department of Hepatobiliary and Pancreatic Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases,* [5]*Department of Gastroenterology and Hepatology, Kinki University School of Medicine, Osaka,* [6]*Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital,* [7]*Department of Internal Medicine, Medical Oncology, Kyorin University School of Medicine,* [8]*Division of Medical Oncology and Hematology, Cancer Institute Hospital, Tokyo,* [9]*Multi-institutional Clinical Trial Support Center, National Cancer Center, Tokyo,* [10]*Department of Medical Oncology and Immunology, Nagoya City University Graduate School of Medical Sciences, Nagoya,* [11]*Department of Gastroenterology, National Hospital Organization Shikoku Cancer Center, Matsuyama,* [12]*The Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Ichikawa and* [13]*Department of Gastroenterology, Aichi Medical University School of Medicine, Nagakute, Japan*

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

Correspondence: Dr Masafumi Ikeda, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-8577, Japan. Email: masikeda@east.ncc.go.jp
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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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