International Journal of Clinical Oncology (2021) 26:305–315
https://doi.org/10.1007/s10147-020-01814-7

ORIGINAL ARTICLE

Hepatitis B virus reactivation during temozolomide administration for malignant glioma

Takuhiro Shoji[1] · Masayuki Kanamori[1] · Jun Inoue[2] · Ryuta Saito[1] · Yoshinari Osada[1] · Yoshiteru Shimoda[1] · Masashi Chonan[1] · Hiroshi Uenohara[3] · Atsushi Masamune[2] · Teiji Tominaga[1]

Received: 1 July 2020 / Accepted: 13 October 2020 / Published online: 28 October 2020

Abstract

Introduction The purpose of this study is to clarify the clinical features of temozolomide (TMZ)-related hepatitis B virus (HBV) reactivation and to identify HBV reactivation predictive factors.

Method We retrospectively reviewed the clinical course of 145 patients newly diagnosed or with recurrent malignant glioma treated with TMZ. Before treatment, we screened patients for HB surface antigen (HBsAg) positivity (HBV carrier) and HBsAg negativity. Patients were also screened for antibody for HB core antigen (anti-HBc) positivity and/or for HB surface antigen positivity (resolved HBV infection). The patients were monitored by HBV DNA, alanine, and aspartate aminotransaminase during and after the completion of TMZ. HBV carriers and those with resolved HBV infections with HBV reactivation received preemptive entecavir treatment. In those with resolved HBV infections, we analyzed clinical characters for the predictive factors for HBV reactivation.

Results In one of two HBV carriers, HBV DNA turned positive 8 months after the completion of TMZ and entecavir. In four (16.7%) of 24 resolved HBV infections, HBV DNA turned detectable at completion of concomitant radiation and TMZ or during monthly TMZ. HBV DNA turned negative with entecavir in all patients without liver dysfunction. In resolved HBV infections, those with a high anti-HBc titer had significantly higher incidence of HBV reactivation than those with low anti-HBc titers (60% vs. 5.3%: $p = 0.018$).

Conclusion Screenings, monitoring, and preemptive entecavir were important for preventing TMZ-related HBV reactivations. Anti-HBc titers could be the predictive markers for HBV reactivation in the those with resolved HBV infections.

Keywords Hepatitis B virus reactivation · Temozolomide · Malignant glioma · Entecavir · Predictive factor

Introduction

Hepatitis B virus (HBV) infections are characterized by a variety of clinical features, reflecting the interaction between HBV replication and a host immune response [1]. Infections begin as acute hepatitis, and progresses to an inactive HBV carrier status, then chronic hepatitis, and liver cirrhosis in a small proportion of patients. Those recovering from acute hepatitis B and some patients with chronic hepatitis B will have hepatitis B surface antigen (HBsAg) negativity long after the infection; however, a covalently closed circular DNA (ccc DNA) particle persists in the hepatocytes, in which virus replication is inhibited by innate and adaptive immune responses [2]. Epidemiologically, it is reported that one-third of the world's population has serological characteristics of past or recent HBV infections, and nearly 240 million people are HBsAg positive [1]. In addition, there were a number of asymptomatic cases with chronic HBV infections worldwide [1].

In patients with chronic HBV infections, HBV reactivation is a well-known complication of cytotoxic chemotherapy or immunosuppressive therapy [1–25]. This treatment leads to the escape of HBV particles from immune surveillance and viral replication in hepatocytes. This complication

✉ Masayuki Kanamori
mkanamori@med.tohoku.ac.jp

[1] Department of Neurosurgery, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan

[2] Department of Gastroenterology, Tohoku University Graduate School of Medicine, Sendai, Japan

[3] Department of Neurosurgery, Sendai Medical Center, Sendai, Miyagi, Japan

can cause severe hepatitis and fatal fulminant hepatitis. Additionally, even when patients with cancer recover from liver dysfunction, interruption of chemotherapy may reduce their survival. To prevent this severe complication, risk assessment by estimating HBV status before immunosuppressive therapy and monitoring of HBV during and after these treatments were recommended in the guideline of Japan Society of Hepatology [26].

Glioblastoma and anaplastic glioma were the primary brain tumors with dismal prognosis [27–29]. The overall age-adjusted incidence rate of primary intracranial tumors was 14.09 (11.59 for males, 16.38 for females) per 100,000 population per year [30]. Malignant glioma, including anaplastic glioma and glioblastoma, were composed of 14.8% primary intracranial tumors [31]. In this manner, malignant glioma is considered a rare disease with an estimated incidence of 2.1 per 100,000 population per year. Temozolomide (TMZ) is the alkylating agent and now widely used in combination with radiotherapy as one of few effective drugs in the treatment of malignant gliomas [27, 28]. There were a few case reports of HBV reactivation associated with TMZ treatment [32–36], which suggested that temozolomide could cause HBV reactivation. However, the clinical features of TMZ related-HBV reactivation, including its incidence, timing, outcomes of antiviral therapy and risk factors, remain unclear.

The purpose of this study is to clarify the clinical features of TMZ related-HBV reactivation in patients with malignant glioma and to identify the predictive factors for HBV reactivation in those with resolved HBV infection.

Materials and methods

Patients

We retrospectively reviewed the clinical course of 145 patients newly diagnosed with malignant glioma or with recurrent malignant glioma treated with TMZ at Sendai Medical Center from January 2014 to June 2015 and at Tohoku University Hospital July 2015 to August 2019. This study was conducted after obtaining the necessary ethical clearance from the institutional ethics board for study on human subjects.

Treatment for malignant glioma

Newly diagnosed anaplastic glioma and glioblastoma was treated by Stupp's regimen [27]. Briefly, after maximal safe resection or biopsy, they received concomitant radiation therapy and TMZ 75 mg/m^2, followed by monthly adjuvant TMZ up to 12 cycles or until progression. Recurrent glioblastoma or progressive lower grade glioma patients received TMZ 100–200 mg/m^2 for recurrent or progressive glioma up to 12 cycles or until progression.

Screening, monitoring, and treatment of HBV reactivation

We screened each patient's HBV status, and monitored and treated any HBV reactivation according to the guidelines for hepatitis B treatment of Japan Society of Hepatology [20] (Fig. 1). Briefly, each patient's HBV status was evaluated by assessing HBsAg status, antibodies for hepatitis B core antigen (anti-HBc) and anti-HBs. The anti-HBc titers were measured using chemiluminescent immunoassays (LSI Medience, Tokyo, Japan). The titer was expressed as the ratio of sample/cutoff (S/CO). The anti-HBs titers were measured using chemiluminescent microparticle immunoassay (Abbott Japan LLC, Tokyo, Japan). The titer was expressed as mIU/ml. HBsAg-positive patients are defined as HBV carriers, and HBsAg-negative and anti-HBc positive and/or anti-HBs positive patients are considered to have resolved HBV infections. Because the incidence of HBV reactivation was highest in HBV carriers, and HBV reactivation could develop in the cases of resolved HBV infection [1–3, 7, 9–11, 13, 17, 24–26], these patients were surveyed for HBV reactivation with HBV DNA quantification through real-time PCR (LSI Medience, Tokyo, Japan). The minimum detection limit was 2.1 log copies/ml until March 2017, and 1.0 log IU/ml after April 2017. HBV DNA, and alanine and aspartate aminotransaminase were monitored every 1–3 months during TMZ treatment and 12 months after TMZ completion. HBV carriers received entecavir before TMZ administration, and the others did if HBV DNA was found to be detectable (Fig. 1).

HBV reactivation was defined as HBV DNA detection in patients with previously undetectable HBV DNA or those with more than a tenfold increase in the HBV DNA level as compared with baseline or nadir levels [3, 14–16]. Having a greater than threefold increase in alanine aminotransaminase (ALT) or aspartate aminotransaminase (AST) was regarded as acute exacerbation of liver function [2].

Predictive factors for HBV reactivation in resolved HBV infections

To elucidate the predictive factors for HBV reactivation during and after TMZ administration in the resolved HBV infection cases, we compared age at onset, gender, the use of corticosteroids, histological diagnosis, newly diagnosed or recurrent disease, anti-HBs positivity status and anti-HBc titers between the cases with and without HBV reactivation.

Categorical and continuous variables were compared using Fisher's exact test and Student's t test, respectively. A receiver operating characteristic (ROC) analysis was

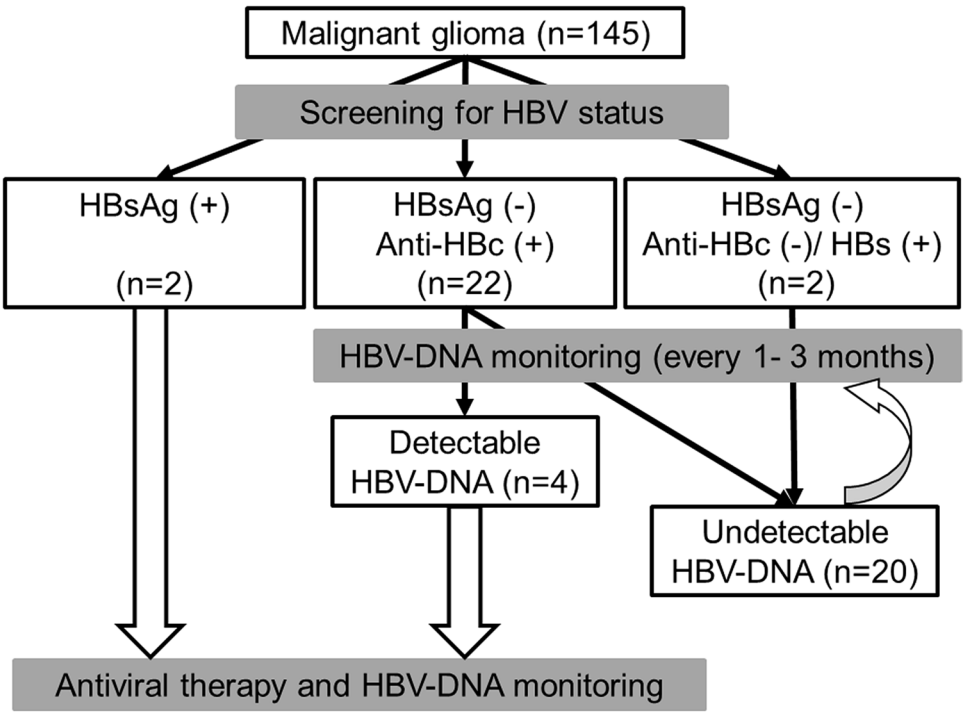

Fig. 1 Summary diagram and management of hepatitis B virus (HBV) carriers and those with resolved HBV infections

preformed to evaluate the efficiency of baseline anti-HBc for predicting the HBV reactivation and to determine the optimal cutoff value of anti-HBc titers. The Youden index was used to determine the optimal cutoff levels of anti-HBc to measure the maximal difference between the true-positive rate and false-positive rate for the prediction of HBV reactivation in the cases of resolved HBV infections. All analyses were performed using GraphPad Prism 5 software (GraphPad Software, San Diego, CA).

Results

Patients demographics

We screened the HBV status of 145 patients with newly diagnosed or recurrent gliomas before TMZ administration. Their age ranged from 4 to 81 years of age, and median age was 61 years. There were 85 males and 60 females.

Among the 145 patients, 2 (1.4%) were HBV carriers (Case 1 and 2 in Table 1) and 24 (16.6%) had resolved HBV infections (Case 3–26 in Table 1). In the latter group, there were two HBsAg and anti-HBc negative and anti-HBs positive cases without the history of vaccination (Case 25 and 26 in Table 1). HBV DNA was detected in only one HBV carrier (Case 2, Table 1), and all 24 patients with resolved HB infection had undetectable HBV DNA before treatment and temozolomide administration. The demographics of these 26 patients are demonstrated in Table 1. Their ages ranged from 23 to 80 years, and median age was 66 years. All but one patient was over 40 years. Histological characteristics of 20 newly diagnosed patients included glioblastoma in 18 and anaplastic oligodendroglioma in two. In five of six recurrent cases, histological diagnosis of recurrent disease was not verified and 20 patients received concomitant radiation therapy and TMZ for newly diagnosed malignant glioma, and 17 of them did receive subsequent adjuvant TMZ, ranging from 1 to 12 cycles (median: 7 cycles). 6 patients received monthly TMZ for recurrent or progressive glioma on day 1–5 every 4 weeks, ranging from 2 to 12 cycles (median: 9.5 cycles). Overall, 16 (66.7%) of 24 patients with resolved HBV infections were positive for anti-HBs. They were monitored for HBV reactivation during and after TMZ administration. Intervals between the initial TMZ administration and last examination of HBV DNA ranged from 1–29 months (median: 8.5 months). HBV DNA was examined after discontinuing TMZ in 17 of 26 cases. Intervals between the discontinuation of TMZ administration and last examination of HBV DNA ranged from 1 to 18 months (median: 3 months).

HBV reactivation and response to entecavir

One of two HBV carriers and four (16.7%) of 24 patients with resolved HBV infections experienced HBV reactivation. The clinical features of these patients are demonstrated in Tables 1 and 2.

HBV carriers received preemptive entecavir administration before TMZ administration, but one of the HBV carriers experienced HBV reactivation. In case 1, HBV DNA turned

Table 1 Demographics of the HBV carrier and patients with resolved HBV infection

Case number	Age/sex	Diagnosis	Timing of TMZ	HBsAg	Anti-HBs	Anti-HBs titer (mIU/ml)	Anti-HBc titer (S/CO)	HBV infection status	Corticosteroid use	TMZ administration[b]	Intervals from the start of TMZ (months)[c]	Intervals from the discontinuation of TMZ (months)[d]	HBV Reactivation
1	44/M	progressive AA	R	+	–		9.48	HBV carrier	–	3	15	13	+
2	64/M	progressive O	R	+	–		12.13	HBV carrier	–	12	25	14	–
3	51/F	AO	N	–	+	N.A	10.34	Resolved HBV infection	+	15	27	During treatment	–
4	72/M	GB	N	–	+	455.8	10.24	Resolved HBV infection	–	12	28	14	–
5	69/M	progressive AA	R	–	+	N.A	9.76	Resolved HBV infection	–	12	29	18	+
6	69/F	GB	N	–	+	235.9	9.37	Resolved HBV infection	–	8	12	2	–
7	61/F	GB	N	–	+	192.1	8.73	Resolved HBV infection	+	3	4	No evaluation	–
8	79/F	GB	N	–	+	N.A	6.98	Resolved HBV infection	–	5	8	2	–
9	72/M	GB	N	–	+	N.A	6.7	Resolved HBV infection	–	Concomitant[a]	1	During treatment	–
10	80/F	GB	N	–	+	N.A	6.31	Resolved HBV infection	–	2	2	During treatment	–
11	66/M	GB	N	–	+	N.A	5.67	Resolved HBV infection	–	Concomitant[a]	3	During treatment	–
12	68/M	GB	N	–	+	4.3	8,23	Resolved HBV infection	–	12	19	5	+
13	44/M	progressive DA	R	–	+	N.A	2.55	Resolved HBV infection	–	2	2	During treatment	–
14	69/F	GB	N	–	+	99.4	2.17	Resolved HBV infection	+	1	3	No evaluation	–
15	62/F	AO	N	–	+	N.A	2.02	Resolved HBV infection	–	6	7	During treatment	–
16	75/F	GB	N	–	+	N.A	1.01	Resolved HBV infection	–	7	14	1	–
17	57/M	GB	N	–	–		10.6	Resolved HBV infection	–	10	15	4	+
18	66/M	GB	N	–	–		9.99	Resolved HBV infection	+	1	3	No evaluation	+
19	56/M	GB	N	–	–		9.1	Resolved HBV infection	–	2	3	No evaluation	–

Table 1 (continued)

Case number	Age/sex	Diagnosis	Timing of TMZ	HBsAg	Anti-HBs	Anti-HBs titer (mIU/ml)	Anti-HBc titer (S/CO)	HBV infection status	Corticosteroid use	TMZ administration[b]	Intervals from the start of TMZ (months)[c]	Intervals from the discontinuation of TMZ (months)[d]	HBV Reactivation
20	59/M	GB	N	–	–		8.7	Resolved HBV infection	–	2	6	2	–
21	79/M	GB	N	–	–		8.58	Resolved HBV infection	–	4	8	1	–
22	73/F	GB	N	–	–		4.02	Resolved HBV infection	–	7	12	3	–
23	66/M	GB	N	–	–		2.29	Resolved HBV infection	+	Concomitant[a]	2	During treatment	–
24	55/M	GB	N	–	–		2.1	Resolved HBV infection	–	7	9	1	–
25	66/F	progressive O	R	–	+	N.A	0.16	Resolved HBV infection	–	12	14	2	–
26	23/M	GB	R	–	+	N.A	0.16	Resolved HBV infection	–	7	12	3	–

HBV hepatitis B virus; *TMZ* temozolomide; *HBsAg* hepatitis B surface antigen; *Anti-HBs* antibody for hepatitis B surface antigen; *anti-HBc* antibody for hepatitis B core antigen; *S/CO* the ratio of sample/ cutoff; *AA* anaplastic astrocytoma; *O* oligodendroglioma; *AO* anaplastic oligodendroglioma; *GB* glioblastoma; *DA* diffuse astrocytoma; *N* newly diagnosed; *R* recurrent; *N.A.* not analyzed

[a]Completion of concomitant radiation therapy and temozolomide and before maintenance TMZ

[b]Cycles of TMZ maintenance at last follow-up

[c]Months between the initial temozolomide administration and last examination of HBV-DNA

[d]Months between the termination of temozolomide administration and last examination of HBV-DNA

Table 2 Clinical demographics of patients with HBV reactivation

Case number	HBV status	Corti-costeroid use	HBV-DNA titer at presentation	HBV-DNA titer before TMZ	HBV-DNA titer at HBV reactivation	Timing of HBV reactivation	Increase in AST/ALT at HBV reactivation[a]	Treatment	Outcomes after antiviral treatment	Increase in AST/ALT until last follow- up
1	HBV carrier	–	< 1.0 log IU/ml	< 1.0 log IU/ml	1.5 log IU/ml	8 months after completion of TMZ[a]	No	Entecavir	Undetectable (2 months)	No
5	Resolved HBV infection	–	Not examined	< 1.0 log IU/ml	1.0 log IU/ml	Before 3rd cycle of TMZ	No	Entecavir	Undetectable (2 months)	No
12	Resolved HBV infection	–	< 1.0 log IU/ml	< 1.0 log IU/ml	1.3 log IU/ml	At completion of concomitant RT/TMZ	No	Entecavir	Undetectable (2 months)	No
17	Resolved HBV infection	–	< 2.1 log copies/ml	< 2.1 log copies/ml	3.7 log copies/ml	At completion of concomitant RT/TMZ	No	Entecavir	Undetectable (4 months)	No
18	Resolved HBV infection	+	< 2.1 log copies/ml	< 2.1 log copies/ml	2.3 log copies/ml	at completion of concomitant RT/TMZ	No	Entecavir	Undetectable (2 months)	No

HBV hepatitis B virus; *TMZ* temozolomide; *AST/ALT* aspartate aminotransaminase/alanine aminotransaminase; *RT* radiation therapy

[a]More than 3 times the baseline value; a, entecavir were discontinued at the completion of monthly TMZ

detectable 8 months after simultaneous discontinuation of TMZ and entecavir (Table 2). In 24 who had a resolved HBV infection, HBV DNA turned detectable in 4 (16.7%) cases. HBV reactivation occurred at the completion of concomitant radiation therapy and TMZ and before adjuvant TMZ in 3 patients and just before third cycle of adjuvant TMZ in one patient (Table 2).

With evidence of HBV reactivation, entecavir was started in all patients. HBV DNA subsequently turned undetectable within 2–4 months. None of the patients had acute exacerbation of liver function because of the HBV reactivation (Table 2).

Two HBsAg and anti-HBc negative and anti-HBs positive patients did not experience HBV reactivation.

Predictive factors for HBV reactivation in patients with resolved HBV infections

We did not find a statistically significant difference in patient clinical backgrounds, characteristics of tumors between those with and without HBV reactivation (Table 3). However, anti-HBc titers in those with HBV reactivation were significantly higher than those without HBV reactivation (8.23–10.6 S/CO: median 9.87 S/CO vs. 0.16–10.34 S/CO: median 5.99 S/CO: $p=0.027$) (Fig. 2a). The ROC analysis of anti-HBc titers indicated that the optimal cutoff value for the prediction of HBV reactivation was 9.57 S/CO, and that the area under the curve was 0.86. With this cutoff value, the sensitivity, specificity, positive predictive rate, and negative predictive rate for the prediction of HBV reactivation were 75.0%, 90%, 60.0%, and 94.7%, respectively. When we divided the cases according to anti-HBc titers, those with high anti-HBc titers (> 9.57 S/CO) had a significantly higher incidence than those with a low-HBc titer (60% vs. 5.3%: $p=0.018$). With regard to anti-HBs, there was no statistically significant difference in the incidence of HBV reactivation between anti-HBs positive and negative patients from qualitative examination (Table 3). The titer of anti-HBs at baseline was measured in only one patient with anti-HBs positive, and HBV reactivation was measured in only four

Table 3 Analysis of the predictive factors of HBV reactivation

Clinical variables	HBV reactivation (−) ($n=20$)	HBV reactivation (+) ($n=4$)	p value*
Age at TMZ administration (median)	23–80 (66)	57–69 (67)	0.87
Female proportion (%)	10 (50%)	0 (0%)	0.11
Histological diagnosis of glioblastoma (%)	16 (80%)	3 (75%)	1.00
Newly diagnosed glioma (%)	17 (85%)	3 (75%)	0.54
anti-HBs positive (%)	14 (70%)	2 (50%)	0.57
Use of corticosteroid (%)	4 (20%)	1 (25%)	1.00

HBV hepatitis B virus; *TMZ* temozolomide; *anti-HBs* antibody for hepatitis B virus surface antigen

*Student t test for age at TMZ administration and titer of anti-HBc and Fisher's exact test for other categorical variables

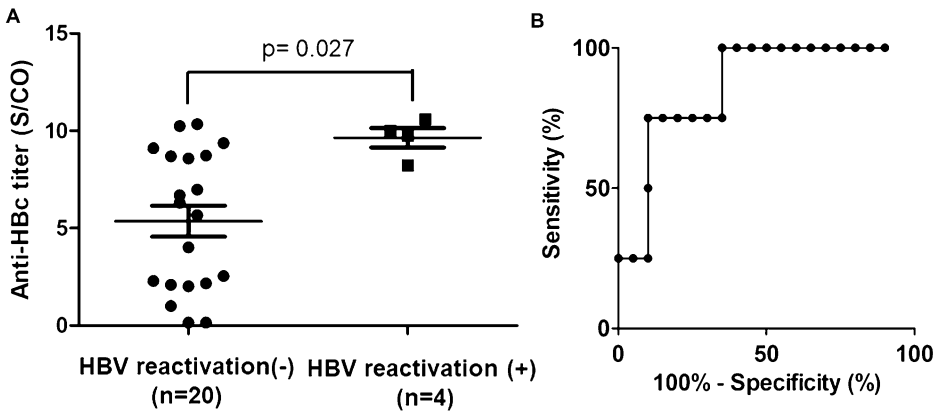

Fig. 2 Correlations between antibody for hepatitis B core antigen (anti-HBc) titers and hepatitis B virus (HBV) reactivation. **a** Scatter plots demonstrating the tendency of higher anti-HBc titers in cases with HBV reactivation. $p=0.027$ (Student's t test). **b** The receiver operating characteristic analysis indicated that baseline anti-HBc titers were useful for predicting HBV reactivation with an optimal cutoff value of 9.57 ratio of sample/cutoff (S/CO) (Area under the curve: 0.86)

of 12 patients with anti-HBs positive and without HBV reactivation. The titer was 4.3 mIU/ml in the former and 99.4, 192.1, 235.9, and 455.8 mIU/ml in the latter (Table 1).

Discussion

In this report, we demonstrated a high incidence of HBV reactivation in HBV carriers (50%) and those with resolved HBV infections (16.7%) with a median follow-up period of 8.5 months. The results also showed that HBV reactivation could develop from the end of concomitant radiation and TMZ to follow-up period after the completion of maintenance TMZ.

So far, five patients with TMZ-related HBV reactivation in those with glioblastoma have been reported. Four of them were positive for HBsAg before TMZ administration, one had remote history HBV hepatitis and positivity for HBsAg at the time of HBV reactivation. None of these patients received preemptive antivirus treatment, and all of them developed severe acute exacerbation of liver function. These results and our findings suggest the importance of preemptive antivirus treatment especially among those with HBsAg positivity before TMZ administration. In contrast, there were no reports of TMZ-related HBV reactivation in those with resolved HBV infections. Although those with resolved HBV infections have a lower risk for HBV reactivation compared to HBV carriers [7, 17], the prevalence of resolved HBV infection was much higher than that of HBV carriers [1]. In this study, 16.6% of cases and 22.6% of cases more than 50 years of age had resolved HBV infection. Therefore, screening for the presence of resolved HBV infections and monitoring of HBV DNA reappearance during and after TMZ administration is important. A recent systematic review and guidelines of the Japan Society of Hepatology suggest that the preemptive antiviral treatment might not be required for those with non-hematological disease and/or rituximab-free regimens for those with resolved HBV infections due to the low risk of HBV reactivation, whereas it may be required in the rituximab-containing regimens or in those with hematological diseases [3, 26]. However, the incidence of HBV reactivation during and after TMZ administration among those with malignant glioma in this study was comparable to that of other high risk conditions, estimated using the definition of HBV reactivation mentioned above; 3.0–4.9% in those with malignant lymphoma treated with a rituximab containing regimen [14, 15], and 10% in those with hematologic malignancies, including those lymphoma, leukemia, and myelodysplastic syndromes [16]. From these findings, the necessity of preemptive antiviral treatments before TMZ administration in the resolved HBV infections should be examined prospectively in the future.

In this series and previous reports of TMZ related HBV reactivation, HBV reactivation occurred most frequently at the completion of concomitant radiation therapy and TMZ (case 15,16,17) [32, 33, 35], followed by during the monthly adjuvant TMZ (case 14) [34, 36]. In addition, one HBV carrier (case 1 in this series) experienced late HBV reactivation 8 months after discontinuation. He did not take any potential drugs after discontinuation of TMZ, but entecavir was improperly discontinued at the completion of TMZ. The recent guideline for HBV reactivation and chronic hepatitis does not recommend simultaneous discontinuation, but rather extended administration of antiviral drugs including entecavir. Similarly, late HBV reactivation was reported in patients with HBsAg negativity treated with rituximab- containing regimens [24]. From these results, regular monitoring of HBV DNA and liver function should cover the entire period of TMZ administration and an additional period after the completion of TMZ.

Several factors associated with the host, treatment, and HBV status have been reported as the predictors for HBV reactivation. High risk factors were found to be male [18], elevated baseline ALT [19], lymphoma and hematologic malignancies [18] as host factors. Some cytotoxic chemotherapies, including anthracyclines [20], high-dose corticosteroids [20, 21], anti-CD20 monoclonal antibody, rituximab [4, 5, 7, 10, 12, 13], and a combination of rituximab and corticosteroid [6, 8, 13] were identified as treatment factors, and HBsAg or HBeAg positivity [7, 17, 18], negative or low anti-HBs titers [9, 22, 29, 37], decrease in anti-HBs titer during chemotherapy [37], high titers of anti-HBc [25, 37], and amount of HBV DNA [9, 22] were factors associated with HBV status. In this study, we demonstrated a high incidence of HBV reactivation in the TMZ-treated patients with malignant glioma. Although glioblastoma of itself could be associated with the onset of HBV reactivation through systemic immunosuppression [38], there were no reports of patients with HBV reactivation treated with medications other than a TMZ regimen. In addition, HBV reactivation was reported in only one patient with primary central nervous system lymphoma (PCNSL) [23]. Considering that there was a very high incidence of HBV reactivation in those with systemic lymphoma treated with [12] and without [20] rituximab containing regimens, those with intracranial neoplasms including glioblastoma and PCNSL, could have a lower incidence of HBV reactivations than those with systemic diseases through unknown reason.

Among host factors, tumor characteristics, and HBV status, we demonstrated that anti- HBc titers were predictive factors with high specificity and negative predictive value. Previous reports also suggested that baseline anti-HBc levels can predict HBV reactivation in those with non-Hodgkin's lymphoma [25]. Because hepatitis B core antigens (HBcAg) are produced from cccDNA, which is the transcriptional and

replicative template of HBV, high baseline anti-HBc levels can reflect a high amount of HBcAg produced by replication-competent cccDNAs in hepatocytes [39]. In addition, anti-HBc was associated with host immune response to HBV through T-cell responses typical of protective memory [40], and patients in active hepatitis phases have higher anti-HBc titers than that with immune tolerance [41]. These conditions of HBV and host immunity could explain the correlation between anti-HBc titers and HBV reactivation. In addition, the patient with the lowest titer of anti-HBs developed HBV reactivation in this study. Although the number of the patients analyzed was too small to draw a conclusion, low titer anti-HBs may be predictive for HBV reactivation in the malignant glioma patients treated with TMZ. This finding was consistent with previous reports [37, 42], and indicated the role of anti-HBs in neutralizing HBV. Based on these results, a combination of anti-HBc and anti HBs titer can predict HBV reactivation, as reported previously in other types of cancer and chemotherapies [37].

There were limitations in this study. First, this study included 22 resolved HBV infection patients with short-term follow-up (< 12 months) or no evaluation for HBV reactivation after completion of TMZ. The median follow-up period was as short as 3 months. 19 patients had simultaneous examination of HBV DNA and AST/ALT until the last follow-up. The reason for the short-term follow-up was progression of disease in 7 patients, completion of the study in 11, and transfer to another hospital in one. To compensate for this situation, we reviewed three patients who had evaluation of only AST/ALT after the last HBV DNA examination. These three patients (Cases 19, 22, and 24) did not have acute exacerbation of liver function defined more than 3 times AST/ALT elevation for 2, 6, and 11 months after the last HBV DNA examination. However, this study could not clarify the incidence of HBV reactivation after discontinuation of TMZ. One previous study demonstrated that 53% of rituximab- related HBV reactivation in those with resolved HBV infections and lymphoma developed after the completion of rituximab [11]. Although the outcomes associated with rituximab might not apply to that of TMZ, late onset of HBV reactivation could occur more frequently than observed. Second, although this report provided a definitive finding that HBV reactivation could develop during and after completion of TMZ, the number of the patients who were HBV carriers and those with resolved HB infections in this study was too small to draw definitive conclusions regarding its precise incidence and the effect of entecavir. This limitation attributed to the rarity of malignant gliomas and the decline of the patients with HBV infections owing to the improvement of public health in Japan. However, this report is valuable in light of the fact that clinicians cannot help with carrying out temozolomide treatment for patients with HBV infection in clinical practice and recent ongoing clinical trials assessing the effect of TMZ in a situation in which there were no reports based on even a few patients.

In conclusion, not only HBV carriers, but also patients with resolved HBV infections had a high incidence of HBV reactivation during and after the completion of TMZ administration. Therefore, we should perform screening of HBV status before TMZ administration in all cases along with regular HBV DNA monitoring and alanine and aspartate aminotransaminase assessments during concomitant radiation and TMZ, monthly TMZ, and after the completion of TMZ in HBV carriers and those with resolved HBV infections. During resolved HBV infection monitoring, anti-HBc titers could be predictive markers for HBV reactivation in those with resolved HBV infections. Preemptive antiviral therapy for HBV carriers and for those with HBV DNA reappearance in patients with resolved HBV infections was necessary to prevent TMZ related HBV reactivation.

Author contributions Conceptualization and design: M.K. and J.I. Acquisition of data: T.S., R.S., Y.S., and M.C. Manuscript writing: T.S., M.K, and J.I. Final editing and approval of the manuscript: T.S., M.K., J.I., R.S., Y.O., Y.S.,M.C., H.U., M.A., and T.T.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest All of the authors declare no conflicts of interest pertaining to this work.

Ethical approval This study was conducted after obtaining the necessary ethical clearance from the institutional ethics board for study on human subjects of Tohoku University hospital and Sendai Medical Center.

References

1. European Association for the Study of the Liver (2017) EASL 2017 Clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 67:370–398. https://doi.org/10.1016/j.jhep.2017.03.021
2. Sagnelli C, Pisaturo M, Calò F et al (2019) Reactivation of hepatitis B virus infection in patients with hemo-lymphoproliferative diseases, and its prevention. World J Gastroenterol 25:3299–3312. https://doi.org/10.3748/wjg.v25.i26.3299
3. Cholongitas E, Haidich AB, Apostolidou-Kiouti F et al (2018) Hepatitis B virus reactivation in HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy: a systematic review. Ann Gastroenterol 31:480–490
4. Dong HJ, Ni LN, Sheng GF et al (2013) Risk of hepatitis B virus (HBV) reactivation in non-Hodgkin lymphoma patients receiving rituximab-chemotherapy: a metaanalysis. J Clin Virol 57:209–214. https://doi.org/10.1016/j.jcv.2013.03.010
5. Evens AM, Jovanovic BD, Su YC et al (2011) Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports.

Ann Oncol 22:1170–1180. https://doi.org/10.1093/annonc/mdq583
6. Hui CK, Cheung WW, Zhang HY et al (2006) (2006) Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. Gastroenterology 131:59–68. https://doi.org/10.1053/j.gastro.2006.04.015
7. Kim SJ, Hsu C, Song YQ et al (2013) Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: analysis from the Asia Lymphoma Study Group. Eur J Cancer 49:3486–3496. https://doi.org/10.1016/j.ejca.2013.07.006
8. Kusumoto S, Tobinai K (2014) Screening for and management of hepatitis B virus reactivation in patients treated with anti-B-cell therapy. Hematol Am Soc Hematol Educ Progr 2014:576–583. https://doi.org/10.1182/asheducation-2014.1.576
9. Kusumoto S, Tanaka Y, Suzuki R et al (2015) Monitoring of hepatitis B virus (HBV) DNA and risk of HBV reactivation in B-cell lymphoma: a prospective observational study. Clin Infect Dis 61:719–729. https://doi.org/10.1093/cid/civ344
10. Mozessohn L, Chan KK, Feld JJ et al (2015) Hepatitis B reactivation in HbsAgnegative/ HbcAb-positive patients receiving rituximab for lymphoma: a meta-analysis. J Viral Hepat 22:842–849. https://doi.org/10.1111/jvh.12402
11. Seto WK, Chan TS, Hwang YY et al (2014) Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. J Clin Oncol 20(32):3736–3743. https://doi.org/10.1200/JCO.2014.56.7081
12. Tsutsumi Y, Yamamoto Y, Ito S et al (2015) Hepatitis B virus reactivation with a rituximab-containing regimen. World J Hepatol 28(7):2344–2351. https://doi.org/10.4254/wjh.v7.i21.2344
13. Yeo W, Chan TC, Leung NW et al (2009) 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. https://doi.org/10.1200/JCO.2008.18.0182
14. Matsui T, Kang JH, Nojima M et al (2013) Reactivation of hepatitis B virus in patients with undetectable HBsAg undergoing chemotherapy for malignant lymphoma or multiple myeloma. J Med Virol 85:1900–1906. https://doi.org/10.1002/jmv.23694
15. Oh MJ, Lee HJ (2013) A study of hepatitis B virus reactivation associated with rituximab therapy in real-world clinical practice: a single-center experience. Clin Mol Hepatol 19:51–59. https://doi.org/10.3350/cmh.2013.19.1.51
16. Tamori A, Hino M, Kawamura E et al (2014) Prospective long-term study of hepatitis B virus reactivation in patients with hematologic malignancy. J Gastroenterol Hepatol 29:1715–1721. https://doi.org/10.1111/jgh.12604
17. Tamori A, Koike T, Goto H et al (2011) Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both HBsAg-positive and HBsAg-negative cohorts. J Gastroenterol 46:556–564. https://doi.org/10.1007/s00535-010-0367-5
18. Yeo W, Chan PK, Zhong S et al (2000) Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. J Med Virol 62:299–307
19. Yeo W, Lam KC, Zee B et al (2004) Hepatitis B reactivation in patients with hepatocellular carcinoma undergoing systemic chemotherapy. Ann Oncol 15:1661–1666. https://doi.org/10.1093/annonc/mdh430
20. Yeo W, Zee B, Zhong S et al (2004) Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. Br J Cancer 5(90):1306–1311. https://doi.org/10.1038/sj.bjc.6601699
21. Cheng AL, Hsiung CA, Su IJ et al (2003) Lymphoma Committee of Taiwan Cooperative Oncology Group. Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. Hepatology 37:1320–1328. https://doi.org/10.1053/jhep.2003.50220
22. Zhong S, Yeo W, Schroder C et al (2004) High hepatitis B virus (HBV) DNA viral load is an important risk factor for HBV reactivation in breast cancer patients undergoing cytotoxic chemotherapy. J Viral Hepat 11:55–59. https://doi.org/10.1046/j.1352-0504.2003.00467.x
23. Kim MG, Park SY, Kim EJ et al (2011) Hepatitis B virus reactivation in a primary central nervous system lymphoma patient following intrathecal rituximab treatment. Acta Haematol 125:121–124. https://doi.org/10.1159/000321792
24. Ceccarelli L, Salpini R, Sarmati L et al (2012) Late hepatitis B virus reactivation after lamivudine prophylaxis interruption in an anti-HBspositive and anti-HBc-negative patient treated with rituximab-containing therapy. J Infect 65:180–183. https://doi.org/10.1016/j.jinf.2011.11.021
25. Yang HC, Tsou HH, Pei SN et al (2018) Quantification of HBV core antibodies may help predict HBV reactivation in patients with lymphoma and resolved HBV infection. J Hepatol 69:286–292. https://doi.org/10.1016/j.jhep.2018.02.033
26. Tanaka A et al. (2019) The guidelines for hepatitis B treatment of Japan Society of Hepatology. https://www.jsh.or.jp/files/uploads/HBV_GL_ver3.1_v1.2-1.pdf. Accessed 29 Sept 2019
27. Stupp R, Mason WP, van den Bent MJ et al (2005) European organisation for research and treatment of cancer brain tumor and radiotherapy groups; National Cancer Institute of Canada Clinical trials group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987–996. https://doi.org/10.1056/NEJMoa043330
28. Kumabe T, Saito R, Kanamori M et al (2013) Treatment results of glioblastoma during the last 30 years in a single institute. Neurol Med Chir (Tokyo). 53:786–796. https://doi.org/10.2176/nmc.oa2013-0212
29. van den Bent MJ, Baumert B, Erridge SC et al (2017) Interim results from the CATNON trial (EORTC study 26053–22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomized, open-label intergroup study. Lancet 390:1645–1653. https://doi.org/10.1016/S0140-6736(17)31442-3
30. Nakamura H, Makino K, Yano S et al (2011) Kumamoto Brain Tumor Research Group. Epidemiological study of primary intracranial tumors: a regional survey in Kumamoto prefecture in southern Japan–20-year study. Int J Clin Oncol 16:314–321. https://doi.org/10.1007/s10147-010-0178-y
31. The Committee of Brain Tumor Registry of Japan (2013) Report of Brain Tumor Registry of Japan (2005–2008). Neurol Med Chir (Tokyo) 57:14–16
32. Chheda MG, Drappatz J, Greenberger NJ et al (2007) Hepatitis B reactivation during glioblastoma treatment with temozolomide: a cautionary note. Neurology 68:955–956. https://doi.org/10.1212/01.wnl.0000259430.48835.b5
33. Fujimoto Y, Hashimoto N, Kinoshita M et al (2012) Hepatitis B virus reactivation associated with temozolomide for malignant glioma: a case report and recommendation for prophylaxis. Int J Clin Oncol 17:290–293. https://doi.org/10.1007/s10147-011-0294-3
34. Grewal J, Dellinger CA, Yung WK (2007) Fatal reactivation of hepatitis B with temozolomide. N Engl J Med 356:1591–1592. https://doi.org/10.1056/NEJMc063696
35. Ohno M, Narita Y, Miyakita Y et al (2011) Reactivation of hepatitis B virus after glioblastoma treatment with temozolomide–case report. Neurol Med Chir (Tokyo) 51:728–731. https://doi.org/10.2176/nmc.51.728
36. Purchiaroni F, Begini P, Minniti G et al (2014) Glioblastoma multiforme and hepatitis B: do the right thing(s). Eur Rev Med Pharmacol Sci 18:3629–3631

37. Nishida T, Matsubara T, Yakushijin T et al (2019) Prediction and clinical implications of HBV reactivation in lymphoma patients with resolved HBV infection: focus on anti-HBs and anti-HBc antibody titers. Hepatol Int 13:407–415. https://doi.org/10.1007/s12072-019-09966-z
38. Alban TJ, Alvarado AG, Sorensen MD et al (2018) Global immune fingerprinting in glioblastoma patient peripheral blood reveals immune-suppression signatures associated with prognosis. JCI Insight. https://doi.org/10.1172/jci.insight.122264
39. Yuan Q, Song LW, Liu CJ et al (2013) Quantitative hepatitis B core antibody level may help predict treatment response in chronic hepatitis B patients. Gut 62:182–184. https://doi.org/10.1136/gutjnl-2012-302656
40. Zerbini A, Pilli M, Boni C et al (2008) The characteristics of the cell-mediated immune response identify different profiles of occult hepatitis B virus infection. Gastroenterology 134:1470–1481. https://doi.org/10.1053/j.gastro.2008.02.017
41. Yuan Q, Song LW, Cavallone D et al (2015) Total hepatitis B core antigen antibody, a quantitative non-invasive marker of hepatitis B virus induced liver disease. PLoS ONE 10:e0130209. https://doi.org/10.1371/journal.pone.0130209
42. Pei SN, Ma MC, Wang MC et al (2012) Analysis of hepatitis B surface antibody titers in B cell lymphoma patients after rituximab therapy. Ann Hematol 91:1007–1012. https://doi.org/10.1007/s00277-012-1405-6