

Management of Hepatitis B Virus Reactivation after the Completion of Cancer Chemotherapy using a Plan-do-Check-Act Cycle

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Abstract: The reactivation of the hepatitis B virus (HBV) following systemic chemotherapy reportedly caused acute liver dysfunction as a fatal complication. HBV reactivation sometimes occurs even after the cessation of chemotherapy, especially in the patients with hematological malignancies. A retrospective survey of patients with hepatitis B surface (HBs) antigen-negative cancer with HBs and/or Hbc antibodies was conducted by a multidisciplinary chemotherapy team to determine the examination rate of the HBV DNA test after the completion of chemotherapy. Among 83 patients with a resolved HBV infection, who were followed up for more than 3 months, only 17 patients underwent HBV DNA monitoring every 1-3 months (17/83; 20.5%). Since September, 2022, the chemotherapy team has informed the attending physician regarding the continuous HBV DNA monitoring in patients with cancer with a resolved HBV infection until 12 months after the cessation of chemotherapy.

Keywords: Chemotherapy, Hepatitis B virus reactivation, HBV DNA, PDCA cycle, Multidisciplinary chemotherapy team.

INTRODUCTION

The reactivation of the hepatitis B virus (HBV) is a well-recognized complication of systemic chemotherapy in patients with cancer [1-3]. HBV reactivation is defined as a sudden and rapid increase in the HBV DNA levels among HBV-infected individuals, undergoing either immunosuppressive therapy or chemotherapy [4]. The clinical manifestations of HBV reactivation range from asymptomatic self-limiting hepatitis to fatal, severe, and progressive liver failure [5]. According to Japanese guidelines [6], the hepatitis B surface antibody (HBsAb) and hepatitis B core antibody (HBcAb) levels should be measured in patients receiving immunosuppressive agents or chemotherapeutic drugs even when the status of hepatitis B surface antigen (HBsAg) is negative.

Prophylaxis with antiviral drugs is essential for preventing liver failure in patients who are HBsAg-positive. However, for patients with a resolved HBV

infection, who are negative for HBsAg but seropositive for antibodies against HBc and/or HBs, no standard strategy has been established to prevent HBV reactivation. In patients with a resolved HBV infection, HBV DNA monitoring should be performed every 1-3 months from the treatment period until 12 months after the completion of chemotherapy.

We previously reported that the application of the plan-do-check-act (PDCA) cycle successfully improved the examination rate of HBsAb and HBcAb in patients with cancer before the initiation of chemotherapy [7]. However, there have been few investigations on HBV DNA monitoring after the completion of chemotherapy to detect HBV reactivation.

In the present study, a multidisciplinary chemotherapy team applied the PDCA cycle to improve quality management and prevent HBV reactivation in patients with cancer with a resolved HBV infection. A retrospective survey was conducted to analyze the status of HBV DNA monitoring among patients with cancer with a resolved HBV infection. The study aimed to increase the examination rates of HBV DNA tests until 12 months after the cessation of chemotherapy.

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METHODS

The study procedures were approved by the institutional review board of Nagoya Memorial Hospital (#2013-010). The chemotherapy team reviewed the medical records of patients with cancer with a resolved HBV infection until 12 months after the end of treatment, and the PDCA cycle was implemented.

Plan

- (I) A system was created to calculate the duration from the date of the last HBV DNA measurement. This provided information regarding the timing of HBV DNA examination after the end of chemotherapy.
- (II) The examination rates of HBV DNA testing were determined.

Moreover, the occurrence of HBV reactivation after the completion of chemotherapy was investigated among patients with a resolved HBV infection, who were negative for HBsAg but seropositive for antibodies against HBc and/or HBs.

Do

- (I) The above system was created by a chemotherapy team in collaboration with system engineers.
- (II) Plan (II) was implemented using this system and electronic medical records.

Check

- (I) The examination rates of HBV DNA tests were assessed and then compared among the clinical departments.

Act

- (I) Based on the results, the chemotherapy team improved the quality of the management of patients with a resolved HBV infection by continuing HBV DNA monitoring even after the cessation of chemotherapy.

The statistical analysis software eZR ver. 1.36 [8] was used to compare the groups. Fisher's accuracy test analysis was performed, and a *p*-value of less than 0.05 was considered significant.

RESULTS

From January, 2015 to June, 2022, 1,416 patients with cancer were treated with antineoplastic agents at

Nagoya Memorial Hospital, and 133 patients were negative for HBsAg but seropositive for antibodies against HBc and/or HBs. There were 83 eligible patients, while 50 patients were excluded because they died or were transferred to a hospital for palliative care within 3 months of the last chemotherapy. Thus, their clinical outcomes were not followed up (Figure 1). While 43 patients (51.8%) with a resolved HBV infection underwent HBV DNA testing at least once after the cessation of anticancer treatment, only 17 patients (20.5%) underwent HBV DNA monitoring every 1-3 months. The examination rate of the HBV DNA test was demonstrated for each clinical department and type of malignancy (Table 1). In the Department of Hematology HBV DNA monitoring was performed after the completion of chemotherapy in 14 patients according to Japanese guidelines. The examination rate of HBV DNA monitoring was 40% (14/35) in this department. This was significantly higher than those in the other departments (6.3%, 3/48) (Table 2): Department of Medical Oncology, 1; Department of Respiratory Internal Medicine, 1; Department of Gynecology, 1; Department of Gastrointestinal Medicine, 0; Department of Orthopedic Surgery, 0; Department of Pediatrics, 0.

Five patients (malignant lymphoma; 2, myeloma; 1, gastric cancer; 1, and colorectal cancer; 1) experienced HBV reactivation during the chemotherapeutic treatment, but none experienced reactivation after the cessation of chemotherapy.

DISCUSSION

HBV reactivation is a recognized complication of chemotherapy [1-5]. A multidisciplinary chemotherapy team investigated the medical records of patients with cancer with a resolved HBV infection, who were negative for HBsAg but seropositive for antibodies against HBc and/or HBs. The study aimed to improve the management of HBV reactivation during and after the completion of chemotherapy.

In the present study, a system that provided information on HBV DNA monitoring was developed to ensure its availability even after the end of cancer chemotherapy (**Plan**). A retrospective survey of patients with cancer with a resolved HBV infection who completed chemotherapy was conducted using this system (**Do**). While 51.8% of the above patients underwent HBV DNA testing at least once after completing the anticancer regimen, the rate of patients who underwent HBV DNA monitoring every 1-3 months decreased to 20.5% (**Check**). The monitoring rate of

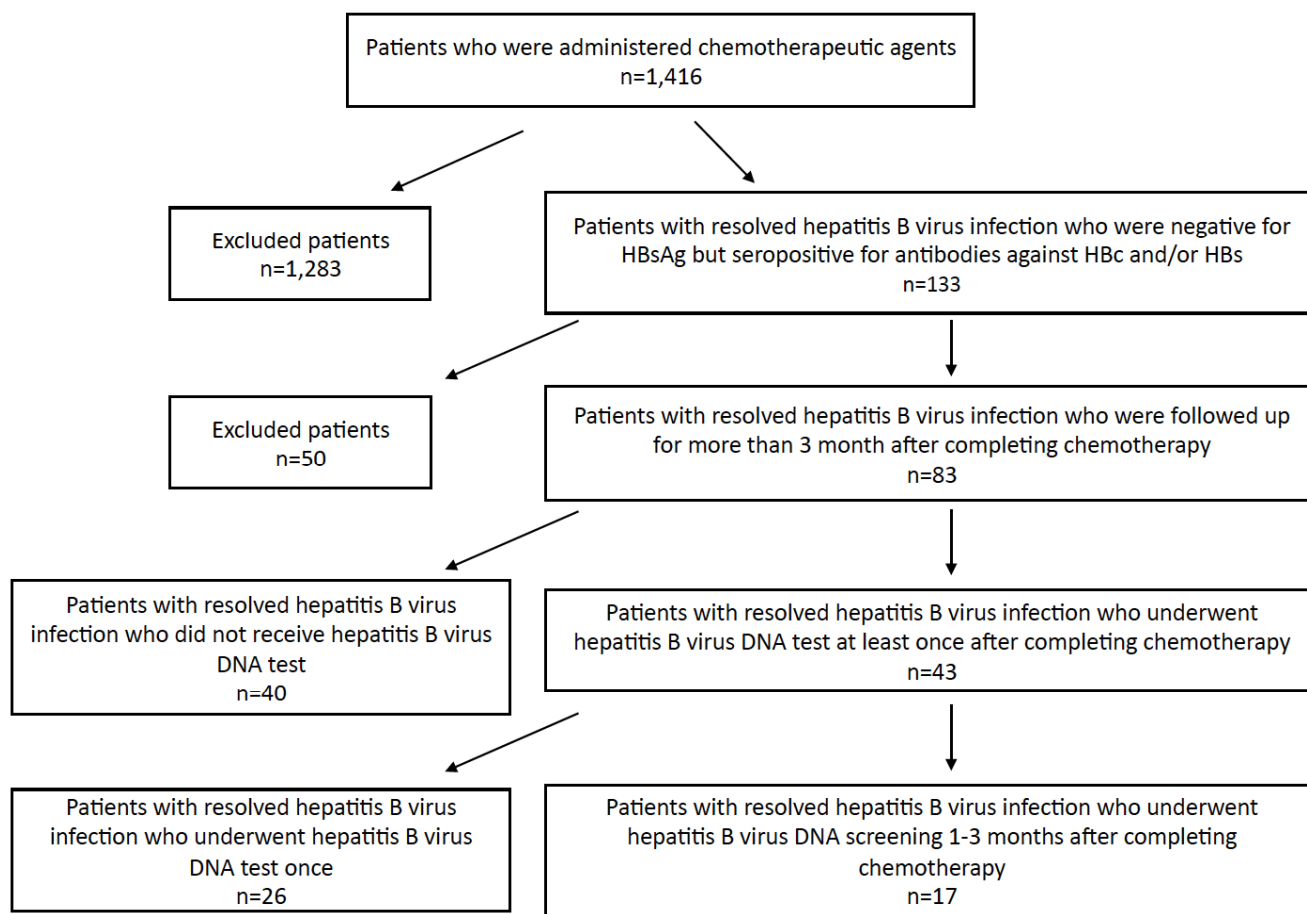


Figure 1: Flow chart of the patients who were administered chemotherapeutic agents and underwent hepatitis B virus DNA testing from January, 2015 to June, 2022.

Table 1: Examination Rates of Hepatitis B Virus DNA Screening Test

Department	A	B	C	Type of malignancy	A	B	C
Hematology	35	26 (74.3)	14 (40)	hematological	32	25(78.1)	14(43.8)
				breast	3	1(33.3)	0 (0)
Medical Oncology	25	8 (32.0)	1 (4.0)	gastric	5	1(20)	0 (0)
				colorectal	15	6(40)	1 (6.7)
				bladder	4	1(25)	0 (0)
				prostate	1	0	0 (0)
Respiratory Internal Medicine	11	4 (36.4)	1(9.1)	lung	11	4(36.4)	1 (9.1)
Gynecology	7	4 (57.1)	1(14.3)	ovarian	6	3(50)	1 (16.7)
				cervical	1	1(100)	0 (0)
Gastrointestinal Medicine	3	0	0	esophageal	3	0	0 (0)
Orthopedic Surgery	1	0	0	soft tissue tumor	1	0	0 (0)
Pediatrics	1	0	0	hematological	1	0	0 (0)
Total	83	43 (51.8)	17 (20.5)		83	43	17

A: Patients with resolved hepatitis B virus infection who were followed up over 3 months after the end of chemotherapy (%).

B: Patients with resolved hepatitis B virus infection who underwent hepatitis B virus DNA testing at least once after the end of chemotherapy (%).

C: Patients with resolved hepatitis B virus infection who underwent hepatitis B virus DNA monitoring every 1-3 months (%).

Table 2: Comparison of the Rate of Hepatitis B Virus DNA Monitoring in Patients with Resolved Hepatitis B Virus Infection following the Japanese Guidelines between the Department of Hematology and the other Departments

	A	B	B/A	
Department of Hematology	35	14	40%	p = 0.0003
Other Departments	48	3	6.30%	

A: Patients with resolved hepatitis B virus infection who were followed up over 3 months after the end of chemotherapy.

B: Patients with resolved hepatitis B virus infection who underwent hepatitis B virus DNA monitoring every 1-3 months.

HBV DNA in the hematology department was 40%, which was significantly higher than those in the other clinical departments. This was associated with the high prevalence of HBV reactivation in lymphoma patients [9]. Since chemotherapeutic regimens containing rituximab or steroids reportedly increased the risk of viral reactivation [10, 11], hematologists recognized the importance of HBV DNA testing to prevent HBV reactivation (**Check**).

Although five patients developed HBV reactivation during treatment, they successfully continued receiving treatment with antineoplastic agents by taking nucleoside analogs and undergoing HBV DNA status monitoring. However, after the completion of chemotherapy, HBV reactivation did not occur in any patients whose HBV DNA was monitored.

Since the rate of HBV DNA monitoring among patients with a resolved HBV infection was significantly low in Nagoya Memorial Hospital (20.5%), the chemotherapy team started an action, which recommended HBV DNA testing every 1-3 months until 1 year after the end of chemotherapy, in September, 2022 (**Act**). In addition, the interval of HBV DNA monitoring was shortened to every month for patients with hematopoietic malignancies because the 3-month interval sometimes failed to detect HBV reactivation. Currently, the chemotherapy team is following up for HBV reactivation until 1 year after the end of chemotherapy using the PDCA cycle.

The multidisciplinary chemotherapy team applied the PDCA cycle method to improve the quality of management of HBV reactivation after the completion of cancer chemotherapy.

CONCLUSIONS

We conducted quality improvement activities for managing HBV reactivation following systemic chemotherapy. Use of the PDCA cycle method will contribute to the continuous HBV DNA monitoring in

patients with cancer with a resolved HBV infection until 12 months after the cessation of chemotherapy.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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