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H. 知的財産権の出願・登録状況
(予定を含む)
該当なし

III. 研究成果の刊行一覧

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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IV. 研究成果の刊行物・別冊

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ORIGINAL ARTICLE

Reactivation of hepatitis B virus in HBsAg-negative patients with multiple myeloma: two case reports

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Abstract It was recently reported that hepatitis B virus (HBV) reactivation had occurred in HBsAg-negative lymphoma patients who received rituximab plus steroid combination chemotherapy. HBV reactivation in myeloma patients have not been reported extensively. We describe here two cases of HBV reactivation in HBsAg-negative myeloma patients receiving systemic chemotherapy: one from the medical records of 40 patients and another from 61 patients with prospective HBV-DNA monitoring. In the first case positive for anti-HBs, HBV reactivation was diagnosed when hepatitis developed during conventional chemotherapy such as MP and MCP regimen in a relapsed patient after autologous stem cell transplantation (AP-BSCT); in the second case positive for anti-HBc and anti-HBs, elevation of HBV-DNA was recognized by serial HBV-DNA monitoring performed prospectively following APBSCT. Interestingly, these two cases had the reduction of the titer of anti-HBs during the treatment, followed by HBV reactivation. These clinical data suggest that the HBV-DNA monitoring is necessary for not only HBsAg-positive but also HBsAg-negative myeloma patients with anti-HBc-positive and/or anti-HBs-positive following transplantation and after conventional chemotherapy in the salvage setting. Establishment of a standard strategy to prevent HBV reactivation is important for myeloma patients receiving systemic chemotherapy.

Keywords Reactivation · HBV · Myeloma · Transplantation

Abbreviations

HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
AST	Aspartate transaminase
ALT	Alanine aminotransferase
RTD-PCR	Real-time detection polymerase chain reaction
APBSCT	Autologous peripheral blood stem cell transplantation
VAD	Vincristine, doxorubicin, dexamethasone
MP	Melphalan, prednisolone
MCP	Ranimustine, cyclophosphamide, prednisolone
MMCP	Melphalan, ranimustine, cyclophosphamide, prednisolone
BD	Bortezomib, dexamethasone
TD	Thalidomide, dexamethasone
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone

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1 Introduction

Most cases of hepatitis B virus (HBV) reactivation have been reported in hepatitis B surface antigen (HBsAg)-positive cancer patients receiving systemic chemotherapy [1]. It was recently reported, however, that HBV reactivation also occurred in HBsAg-negative lymphoma patients who received rituximab plus steroid combination chemotherapy [2–5].

The clinical data on HBV reactivation in myeloma patients have not been reported extensively; therefore, we have performed retrospective and prospective analyses of HBV reactivation in 101 myeloma patients who received systemic chemotherapy at Nagoya City University Hospital. Based on these analyses, we report here two cases of HBV reactivation in HBsAg-negative myeloma patients.

2 Patients and methods

Between January 2001 and July 2009, 101 patients were diagnosed as multiple myeloma at Nagoya City University Hospital. We retrospectively analyzed the medical records of 40 patients for the development of hepatitis B who were diagnosed as multiple myeloma between January 2001 and December 2005. In 2006, we instituted the strategy described below to prevent HBV reactivation, and carried it out prospectively in 61 patients between January 2006 and July 2009. The serological markers for HBsAg, hepatitis B core antibody (anti-HBc) and hepatitis B surface antibody (anti-HBs) were tested to establish HBV infection status before the initial chemotherapy. HBsAg and anti-HBs were determined by enzyme immunoassay (EIA) (AxSYM; Abbott Japan, Tokyo, Japan) or chemiluminescence enzyme immunoassay (CLEIA) (Fujirebio, Tokyo, Japan). Anti-HBc of IgG classes was determined by radioimmunoassay (Abbot Japan) or CLEIA (Fujirebio). If the patient was positive for any of the serological markers, plasma HBV-DNA was measured by real-time detection polymerase chain reaction (RTD-PCR). If the patient was HBsAg-positive and/or had HBV-DNA before chemotherapy, prophylactic therapy with an antiviral drug was administered during and for at least 6 months after the chemotherapy. On the other hand, if the patient was HBsAg-negative, but seropositive for anti-HBc and/or anti-HBs (defined as resolved HBV infection), a serial monitoring of HBV-DNA was performed monthly by RTD-PCR during and for at least 1 year after the chemotherapy. If plasma HBV-DNA levels became detectable, antiviral therapy was started as soon as possible.

In this prospective HBV-DNA monitoring, each case of plasma HBV-DNA was measured at SRL Inc, using methods with the highest sensitivity available at the time in clinical practice; the assays included the following: TaqMan PCR assay (Roche Molecular Systems Inc, between April 2008 and July 2009), or Amplicor-PCR assay (Roche Molecular Systems Inc, between January 2006 and March 2008). The cutoff values of the TaqMan PCR assay and Amplicor-PCR assay were set at 1.8 log copies and 2.6 log copies/mL, respectively. In this retrospective analysis, serum HBV-DNA was measured at our laboratory of Nagoya City University using preserved specimen, and HBV-DNA sequences spanning the S gene were amplified by RTD-PCR in accordance with the previously described protocol with a slight modification; it has a detection limit of 2.0 log copies/mL [6].

The two patients with HBV reactivation provided written informed consent to the publication of this report.

3 Treatment for multiple myeloma

In patients younger than 65 years, autologous peripheral blood stem cell transplantation (APBSCT) was performed using high-dose melphalan (200 mg/m^2) following three courses of a VAD (vincristine, doxorubicin, and dexamethasone) regimen as induction therapy and a high-dose cyclophosphamide regimen as stem cell harvest therapy.

In patients who did not choose the transplantation treatment option, or from whom we could not collect enough hematopoietic stem cells, the initial treatment for symptomatic multiple myeloma was MP (melphalan plus prednisolone) or MMCP (melphalan, ranimustine, cyclophosphamide, prednisolone combination chemotherapy).

Patients over 65 years of age were not candidates for transplantation. The initial treatment regimens for these patients were MP, VAD, MMCP or VAD following MP. In relapsed and refractory patients, BD (bortezomib, dexamethasone: after December 2006), or TD (thalidomide, dexamethasone: after December 2008) or other regimens (MP, VAD, etc.) were administered as salvage treatments for all patients.

4 Results

4.1 A case with HBV reactivation on the basis of the medical records

Based on the retrospective analyses, only one patient developed HBV reactivation among 40 multiple myeloma patients diagnosed from January 2001 to December 2005. The clinical course is shown in Fig. 1. A 59-year-old woman diagnosed as symptomatic multiple myeloma (BJP-κ type) received APBSCT as initial treatment. Before APBSCT, she was seronegative for HBsAg, but no

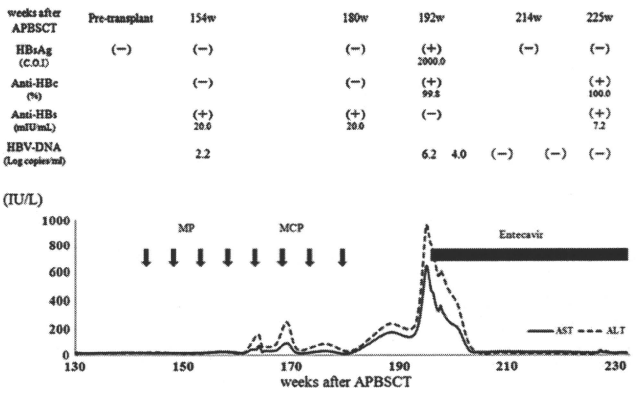

Fig. 1 Clinical course of Case 1. *AST* aspartate transaminase, *ALT* alanine aminotransferase

screening tests for anti-HBc or anti-HBs were performed. Multiple myeloma recurred about 3 years after APBSCT, and MP was administered as salvage treatment. When MP therapy was started, she was seronegative for both HBsAg and anti-HBc, but seropositive for anti-HBs. Because MP could not control the disease, MCP (ranimustine, cyclophosphamide, prednisolone) therapy was administered as the next salvage regimen. Liver damage occurred 32 weeks after the initial salvage chemotherapy was started, and at that time HBsAg changed from negative to positive, and serum HBV-DNA was detectable at 6.2 log copies/mL, so we concluded that the liver damage was caused by hepatitis B virus.

Analyses of specimens preserved during and after salvage therapy showed that serum HBV-DNA was detectable at 2.2 log copies/mL at base line when MP therapy was started, as shown in Fig. 1. In other words, the patient had an occult HBV infection (defined as HBsAg-negative, but HBV-DNA detectable) before salvage chemotherapy.

Furthermore, the HBV gene sequences before and after salvage chemotherapy were confirmed identical in Case 1, so we judged that the liver damage was caused by HBV reactivation. HBV reactivation was reduced after entecavir (0.5 mg, once daily) was administered as an anti-HBV nucleotide analog, and HBV-DNA levels decreased to below the limit of detection.

4.2 HBV-DNA monitoring to prevent HBV reactivation (Fig. 2)

Among 61 patients with symptomatic multiple myeloma diagnosed between January 2006 and July 2009, 1 patient was seropositive for HBsAg, 15 patients were seropositive for anti-HBc and/or anti-HBs (indicating resolved HBV infection), and the remaining 45 patients were seronegative for either anti-HBc or anti-HBs according to the screening tests shown in Fig. 2. One HBsAg-positive patient was given an antiviral drug for prophylaxis before initial treatment. On the other hand, we prospectively performed serial HBV-DNA monitoring during and after myeloma treatment in the 15 patients with resolved HBV infection who had no occult infection.

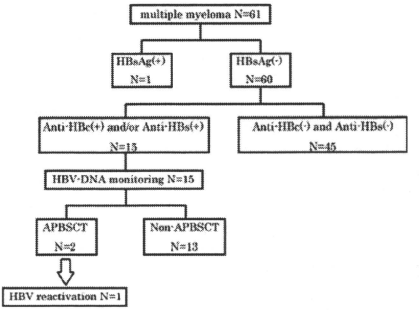

Fig. 2 Screening tests for serological markers of HBV infection and the strategy to prevent HBV reactivation in 61 myeloma patients diagnosed between January 2006 and July 2009 at Nagoya City University Hospital. One patient was seropositive for HBsAg, 15 patients were seropositive for anti-HBc and/or anti-HBs (defined as resolved HBV infection), the remaining 45 patients were seronegative for either anti-HBc or anti-HBs. We prospectively performed serial HBV-DNA monitoring during and after myeloma treatment in 15 patients with resolved HBV infection: following APBSCT, 1 of 15 patients developed HBV reactivation without hepatitis and prior to liver damage because elevation of HBV-DNA was confirmed at an early stage

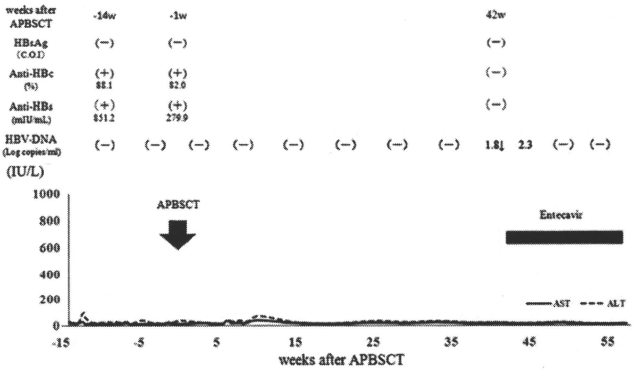

Fig. 3 Clinical course of Case 2

In 8 of these 15 patients, the initial treatment was MP. Following VAD therapy, three patients received MP. Two patients underwent APBSCT. Each of the remaining two patients received MMCP therapy but no further treatment. For salvage treatment, 4 of the 15 patients received BD and/or TD.

One of the 15 patients developed HBV reactivation without hepatitis following APBSCT, after elevation of HBV-DNA was confirmed at an early stage prior to liver damage (Fig. 3). A 61-year-old woman was diagnosed as symptomatic multiple myeloma (BJP-λ type). In screening tests before treatment, HBsAg was negative, both anti-HBc and anti-HBs were positive, and plasma HBV-DNA was below the limit of detection. Therefore, the patient's HBV status was confirmed as a resolved infection. Prospective serial HBV-DNA monitoring was performed monthly, but the testing was sometimes postponed up to 3 months on account of the patient.

Forty-two weeks (about 10 months) after APBSCT, the plasma HBV-DNA level was less than 1.8 log copies/mL but an amplification signal was detectable by the TaqMan PCR assay, and during the following month the HBV-DNA level became detectable with up to 2.3 log copies/mL, as shown in Fig. 2. HBV reactivation was diagnosed at that time, and entecavir (0.5 mg, once daily) was administered immediately as an anti-HBV nucleotide analogue. The plasma HBV-DNA decreased to an undetectable level without liver damage. At the time of HBV reactivation, all HBV serological markers (HBsAg, anti-HBc and anti-HBs) were negative, which suggested that the antibody titers may be reduced by the myeloma treatment. We performed a retrospective search of blood transfusions (red cells and platelets) received by this patient during the previous chemotherapy using the stored specimens from all the blood donors. As a result, it was concluded that the possibility of HBV infection through blood transfusion was extremely low.

5 Discussion

We reported two cases of HBV reactivation in myeloma patients who were seronegative for HBsAg before treatment. HBV was reactivated in a patient with occult infection and definitely diagnosed by a retrospective analysis of preserved specimens when the onset of liver damage occurred after salvage treatment 3 years after APBSCT. In another patient with resolved HBV infection, HBV reactivation at an early stage was detected by the serial HBV-DNA monitoring performed prospectively, and an antiviral drug was administered before liver damage had occurred.

Some HBsAg-negative patients have recently been reported to develop fatal hepatitis by HBV reactivation in the rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) or R-CHOP-like regimens, which combine rituximab and steroid for treatment of CD20-positive malignant lymphoma [2–5]. In 2006, Hui et al. [3] reported that 8 of 244 HBsAg-negative lymphoma patients receiving systemic chemotherapy developed hepatitis by HBV reactivation, and these eight patients were seropositive for either anti-HBc or anti-HBs. It was shown that rituximab plus steroid combination chemotherapy was a risk factor by multivariate analysis. Most recently, Yeo et al. [4] reported that 5 of 80 HBsAg-negative patients diagnosed as diffuse large B cell lymphoma and receiving R-CHOP or CHOP-like regimens had reactivated HBV. All five had received R-CHOP and all were positive for anti-HBc and negative for anti-HBs.

The HBV reactivation following APBSCT in patients with multiple myeloma has been reported sporadically.

Endo et al. [7] reported that 3 of 24 HBsAg-negative patients with resolved HBV infection developed new-onset hepatitis B following APBSCT, and all three patients were multiple myeloma patients. Uhm et al. [8] performed a retrospective analysis of the change of HBV serologic markers following APBSCT. Seven of 129 HBsAg-negative patients became HBsAg-positive after transplantation. All seven patients were seropositive for both anti-HBs and anti-HBc before treatment, and six of the seven patients had multiple myeloma. Furthermore, at reactivation after transplantation, it was shown that the titers of anti-HBs decreased in six of the seven patients. This phenomenon was also shown in our both cases. These data suggested that the decreased titer of anti-HBs may be associated with HBV reactivation, and that the pathophysiology of reactivation may be affected by the dysfunction of humoral immunity in multiple myeloma.

It is necessary to pay attention to the onset of HBV reactivation during salvage treatment; thus, if immunologic inhibition is strong over a longer period, the risk of HBV reactivation may be increased more in patients on second-line or third-line chemotherapy than in those undergoing chemotherapy for the first time [9]. As mentioned above, APBSCT may be one of the important risk factors for HBV reactivation in myeloma patients; however, the reactivation may occur even if the salvage treatment was performed with a mild myelosuppressive regimen such as MP and MCP after the autologous transplantation shown in Case 1. New molecular target drugs such as bortezomib, thalidomide, and lenalidomide improve the survival of myeloma patients remarkably [10–12], so the number of patients who will receive the immunosuppressive therapy for longer periods may increase in the future. Therefore, a standard strategy to prevent HBV reactivation may also become more important in myeloma treatment.

HBV reactivation may lead to fatal fulminant hepatitis, so we hematologists and oncologists should identify high-risk groups in advance before chemotherapy. The latest CDC and Japanese guidelines recommend that patients receiving cytotoxic or immunosuppressive therapy should be tested for serologic markers of HBV infection (i.e., HBsAg, anti-HBc, anti-HBs) [13, 14]. HBV infection status should be established before any chemotherapy or immunosuppressive therapy is initiated (when there is no immunologic inhibition), because antibody titers may be reduced by the treatment, as shown in Case 2. For patients positive for any of the HBV serological markers, the presence of HBV-DNA should be confirmed by RTD-PCR [5, 14].

Prophylaxis with antiviral drugs is essential for HBsAg-positive patients undergoing systemic chemotherapy as recommended by the latest American and Japanese guidelines [14, 15]. Because patients with serum HBV-DNA have more potential risk factors for HBV reactivation, they should be given antiviral drugs as well [5, 14].

If a patient is seropositive for anti-HBc and/or anti-HBs, no standard strategy to prevent HBV reactivation has been established, but making an early diagnosis of HBV reactivation is critical to enable early initiation of active antiviral therapy. Preemptive therapy by serial HBV-DNA monitoring is a reasonable strategy recommended by the latest Japanese guidelines [14]. If HBV-DNA levels become detectable, antiviral therapy should be started as soon as possible.

Only a few studies have reported on the optimal frequency and duration of HBV-DNA monitoring. Hui et al. [3] reported on malignant lymphoma patients that the median time from the elevation of serum HBV-DNA to hepatitis onset was 18.5 weeks (range 12–28 weeks). Most recently, Fukushima et al. [16] conducted a prospective study to monitor HBsAg monthly and HBV-DNA every 3 months during and after systemic chemotherapy in HBsAg-negative but anti-HBc-positive patients with malignant lymphoma; they found that 1 of 24 patients developed HBV reactivation, which was diagnosed by elevation of HBV-DNA level, while their HBsAg was still negative. In fact, as shown in Case 2, we were able to diagnose HBV reactivation at an early stage by the monthly HBV-DNA monitoring and avoid liver damage and decrease plasma HBV-DNA to below the limit of detection by starting the antiviral drug administration.

It is also necessary to make a differential diagnosis in order to distinguish transmission of HBV by blood transfusion from HBV reactivation, because blood transfusion may be received during systemic chemotherapy. In Case 2, we performed a retrospective search of blood transfusion (red cells and platelets) received during previous chemotherapy, using the stored specimens of all blood donors. It was concluded that the possibility of HBV infection through blood transfusion was extremely low.

In conclusion, these clinical data suggest that the HBV-DNA monitoring is necessary for not only HBsAg-positive but also HBsAg-negative myeloma patients with anti-HBc-positive and/or anti-HBs-positive following transplantation and after conventional chemotherapy in the salvage setting. Preemptive therapy by serial HBV-DNA monitoring may be a useful and cost-effective option for preventing HBV reactivation in patients with resolved HBV infection. Establishment of a standard strategy to prevent HBV reactivation is important for myeloma patients receiving systemic chemotherapy.

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