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Original Article

Incidence and clinical background of hepatitis B virus reactivation in multiple myeloma in novel agents' era

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Abstract

There are some reports regarding hepatitis B virus (HBV) reactivation in patients with myeloma who are HBV carriers or who have had a resolved HBV infection, and there is no standard prophylaxis strategy for these patients. We performed a retrospective multicenter study to determine the incidence and characteristics of HBV reactivation in patients with multiple myeloma. We identified 641 patients with multiple myeloma who had been treated using novel agents and/or autologous stem cell transplantation with high-dose chemotherapy between January 2006 and June 2014 at 9 Japanese hospitals. The patients' characteristics, laboratory data, and clinical courses were retrieved and statistically analyzed. During a median follow-up of 101 weeks, 1 of 8 (12.5%) HBV carriers developed hepatitis and 9 of 99 (9.1%) patients with resolved HBV infection experienced HBV reactivation; the cumulative incidences of HBV reactivation at 2 years (104 weeks) and 5 years (260 weeks) were 8% and 14%. The 9 cases of reactivation after resolved HBV infection had received entecavir as preemptive therapy or were carefully observed by monitoring their HBV DNA levels, and none of these cases developed hepatitis. Among patients with multiple myeloma, HBV reactivation was not rare. Therefore, long-term monitoring of HBV DNA levels is needed to prevent hepatitis that is related to HBV reactivation in these patients.

Key words: hepatitis B, viral reactivation, multiple myeloma, novel agents

Introduction

An estimated 2 billion people have been or are currently infected with the hepatitis B virus (HBV), and the HBV seroprevalence is particularly high in East Asia [1,2]. HBV reactivation has often been reported among hepatitis B surface antigen (HBsAg)-positive patients with hematological malignancies during or after their cytotoxic chemotherapy [3,4]. In the rituximab era, HBV reactivation has also been reported in some patients with malignant lymphoma and resolved HBV infection who are HBsAg-negative but seropositive for antibodies against the hepatitis B core antigen (anti-HBc) and/or the hepatitis B surface antigen (anti-HBs) [5-7]. Furthermore, initiation of antiviral therapy after acute hepatitis onset is often insufficient to control HBV reactivation, and may lead to death due to fulminant hepatitis [4].

There are several reports regarding HBV reactivation in patients with myeloma and resolved HBV infection, and almost all of these cases had undergone autologous stem cell transplantation (ASCT) with high-dose chemotherapy [8-10]. However, novel agents (e.g., proteasome inhibitors and immunomodulatory drugs) are one of the major advances in the management of multiple myeloma during the past decade. Nevertheless, it is unclear whether these drugs are involved in HBV reactivation. Therefore, we performed a retrospective multicenter study in Japan to investigate the incidence and characteristics of HBV reactivation in patients with multiple myeloma who were treated using novel agents.

Patients and Methods

We identified patients with multiple myeloma who had been treated using novel agents (e.g., bortezomib, thalidomide, and lenalidomide) with or without ASCT between January 2006 and June 2014 at 9 Japanese hospitals. All patients had been diagnosed with symptomatic multiple myeloma using the diagnostic criteria of the International Myeloma Working Group [11]. The patients' baseline levels of serological markers for HBsAg, anti-HBc, and anti-HBs were measured to evaluate their pre-chemotherapy viral status. We classified the serological markers as either positive or negative, as each hospital adopts a different measurement method. We routinely had monitored HBV DNA level by every 1 or 2 months. HBV DNA levels were determined with a real-time polymerase chain reaction (RT-PCR) assay, using the COBAS Amplicor HBV Monitor test, the COBAS TaqMan HBV test (version 1.0), or the COBAS TaqMan HBV test (version 2.0) (Roche Diagnostics, Tokyo, Japan). The cut-off values for each test were 2.6 log copies/mL, 1.8 log copies/mL, and 2.1 log copies/mL, respectively. The following patient data were recorded: age, sex, M-protein levels, stage (using the Durie-Salmon staging system and the international staging system), laboratory findings, treatments, and outcomes. This study was performed in accordance with the ethical principles of the Declaration of Helsinki, and was approved by the ethics review board at each participating institution.

We defined HBV carriers as patients who were positive for HBsAg, and cases of resolved HBV infection as patients who were HBsAg-negative but positive for anti-HBc and/or anti-HBs. We defined HBV reactivation as the detection of HBV DNA in the peripheral blood during or after treatment [12,13].

Cases of hepatitis related to HBV were defined as serum alanine aminotransferase (ALT) levels of >3-fold above the upper normal limit at two consecutive evaluations that were >5 days apart, in the absence of other potential causes [6].

All statistical analyses were performed using SAS software (version 9.4.; SAS Institute Inc., Cary, NC, USA). Statistical associations of HBV reactivation with the clinical and laboratory parameters were analyzed using the t-test or the chi-square test. Cumulative incidence was estimated by the Kaplan-Meier method. A p-value of less than 0.05 was considered significant, and all statistical tests were two-tailed.

Results

We included 641 patients from the 9 study hospitals, and detected HBV infection in 16.7% of these patients. Eight patients (1.2%) were HBV carriers and 99 patients (15.4%) exhibited resolved HBV infection (Figure 1). The baseline characteristics of these patients are shown in Tables 1 and 2. During a median follow-up of 101 weeks (range, 1–416 weeks), one of the 8 HBV carriers developed hepatitis. That patient had not received an anti-viral agent during chemotherapy, but was successfully treated using entecavir after the onset of hepatitis. The other patients had received prophylactic anti-viral agents before starting their chemotherapy. Among the 99 patients with resolved HBV infection, HBV DNA was not detected at the start of chemotherapy and no patients had received antiviral prophylaxis. The cumulative rates of HBV reactivation at 2 years (104 weeks) and 5 years (260 weeks) were 8% and 14%.

HBV reactivation occurred in 19.0% (4/21) of the patients in the ASCT group and 6.4% (5/78) of the patients in the non-ASCT group. The relationships between the patients' clinical features and HBV reactivation are shown in Table 2. All 9 cases of HBV reactivation occurred during or after bortezomib treatment. There were no cases of HBV reactivation during thalidomide or lenalidomide treatment. Two cases (patients 1 and 8) experienced HBV reactivation several months after lenalidomide treatment was completed. In the 4 cases with quantifiable HBV DNA levels, 2 patients had received entecavir (patients 4 and 6) and the other patients had not received medication, as they died due to myeloma progression immediately after the HBV reactivation (patients 3 and 9). In the other 5 cases, HBV DNA was detectable but not quantifiable using the RT-PCR method. In these 5 cases, the HBV DNA levels fell to below the detection limit after entecavir treatment (patients 1, 5, and 7) or only observation (patient 2), and the other patient died due to myeloma progression soon after HBV reactivation (patient 8). Although patient 2's HBV DNA levels had fallen below the limit of detection after only observation (Table 3), and he had continued the bortezomib treatment, his HBV DNA levels subsequently became elevated again (2.1 log copies/mL), and he was treated using entecavir. None of the patients with HBV reactivation developed hepatitis. In the univariate analysis, HBV reactivation was not associated with age, sex, stage, laboratory findings (excluding serum albumin levels), or treatment (Table 2). Furthermore, serum IgG levels were not associated with HBV reactivation among patients with non-IgG myeloma.

Discussion

An estimated 240 million people are carriers of HBV, and three-fourths of these people are located in East and Southeast Asia. Patients who are HBV carriers have conventionally been considered to have a high risk of HBV reactivation during chemotherapy or immunosuppressive therapy, and prophylaxis using antiviral agents has been recommended [13,14]. Furthermore, in the rituximab era, HBV reactivation has been reported in prospective studies of Asian patients with lymphoma and resolved HBV infection [15-18]. These studies have also confirmed the usefulness of regular HBV DNA monitoring and the optimal timing of antiviral prophylaxis.

Hsu et al. defined HBV reactivation as HBV DNA levels that were ≥10-fold above baseline levels in their prospective study of malignant lymphoma [15]. In that study, HBV reactivation was observed in 17 cases (11.3%), although liver damage was apparent in 10 cases and 7 of those cases exhibited serious liver damage (ALT levels of 10-fold above the upper normal limit). In contrast, 3 other groups defined HBV reactivation as the detection of HBV DNA in the peripheral blood, regardless of liver biochemistry or HBsAg status, in their prospective studies [16-18]. Furthermore, these studies all successfully used preemptive therapy to prevent HBV-related hepatitis or liver failure during the study periods. Moreover, the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Japan Society of Hepatology guidelines define HBV reactivation as HBV DNA detection, and recommend the administration of anti-viral agents [12,13,19]. Thus, we defined HBV reactivation in the present study as the detection of HBV DNA in the peripheral blood during or after treatment.

In the present study, we evaluated 641 Japanese patients with myeloma and observed that 12.5% (1/8)

of the HBV carriers developed hepatitis and 9.1% (9/99) of patients with resolved HBV infection experienced HBV reactivation. HBV reactivation occurred in 19.0% (4/21) of the patients in the ASCT group and 6.4% (5/78) of the patients in the non-ASCT group. In the present study, elevated serum albumin levels were a significant risk factor for HBV reactivation (Table 2), although the reason for this association remains unclear.

A total of 58 patients with myeloma who experienced HBV reactivation or hepatitis have been described in 20 reports, which include 8 case reports [8-10,20-36]. Almost all of these patients developed hepatitis and HBV reactivation after undergoing ASCT or allogeneic hematopoietic stem cell transplantation [8-10,20-23,27-31,33-36]. The largest retrospective study of myeloma and resolved HBV infection evaluated 230 Korean patients, and reported that HBV reactivation occurred in 5.2% (12/230) of the patients [8]. HBV reactivation occurred in 9.4% (12/127) of the patients in the ASCT group and none of the patients in the non-ASCT group, indicating that ASCT is a significant risk factor for HBV reactivation. However, although we observed HBV reactivation in 19.0% (4/21) of the patients in the ASCT group, ASCT did not appear to be a significant risk factor for HBV reactivation. These incidences of HBV reactivation were similar to that among patients with malignant lymphoma who underwent hematopoietic stem cell transplantation [37].

Interestingly, HBV reactivation was not observed in myeloma patients without ASCT before the novel agents' era. However, similar to the findings in our study, HBV reactivation was observed in 6 cases that were treated with a bortezomib-containing regimen without ASCT [10,24-26,32], which may indicate

that bortezomib was a risk factor for HBV reactivation [10]. On the other hand, similar to the findings of our study, no previous findings have indicated that thalidomide or lenalidomide treatment can cause HBV reactivation. In addition, new proteasome inhibitors (e.g., carfilzomib or ixazomib) have recently been approved in other countries, and these drugs may increase the incidence of HBV reactivation.

In our present study, the cumulative incidences of HBV reactivation at 2 years (104 weeks) and 5 years (260 weeks) were 8% and 14% (Figure 2). In contrast, the previously described Korean study reported that the 2-year and 5-year cumulative HBV reactivation rates were 5% and 8%, respectively [8]. However, that study defined HBV reactivation as the reappearance of HBsAg with or without HBV DNA detection in the blood [8], which may explain the higher incidence and earlier onset of HBV reactivation in the present study, as we considered detectable HBV DNA in the peripheral blood.

Interestingly, 12 of the Korean patients experienced HBV reactivation, with 8 patients experiencing a biochemical flare (serum ALT levels of >80 IU/L) [8]. In another report, one patient experienced fatal fulminant hepatic failure after HBV reactivation and died [25]. That patient had received entecavir after elevations in their serum ALT and bilirubin levels. In the present study, entecavir had been started when HBV DNA levels were detectable in 5 cases including the 3 cases whose HBV DNA levels were not quantifiable (1 additional case exhibited undetectable HBV DNA levels after careful observation and no entecavir treatment). Thus, our patients with HBV reactivation did not experience elevated serum ALT levels or hepatitis. Nevertheless, multiple myeloma is not curable, and several reports recommend continuous therapy until disease progression [38]. Therefore, it is difficult to select the optimal timing

for anti-viral treatment and to stop anti-viral treatment after HBV reactivation.

In conclusion, we observed that HBV reactivation was not rare among patients with myeloma who were treated with novel agents or ASCT. This phenomenon is relevant and important, as the incidence of HBV reactivation dramatically increased after the introduction of monoclonal antibodies (e.g., rituximab) for treating lymphoma. Furthermore, several monoclonal antibodies (e.g., elotuzumab and daratumumab) will likely be approved for treating myeloma in the near future. Therefore, these treatments are likely to increase the incidence of HBV reactivation, and large well-designed prospective studies are needed to identify the risk factors and optimal preventative strategy for HBV reactivation in patients with myeloma.

Conflict of Interest: SW received scholarship donations from Bristol-Myers Squibb Company and MSD K.K. The other authors have no conflicts of interest to declare.

Authorship statement: YT and MS contributed equally to this work. YT, MS, SS, SW, and NK designed the study. AI, MM, MK, HT, KM, SI, MA, YI, JT, HH, HK, ST, JH, MH, and YY collected the clinical data. TO and HS performed the statistical analysis. The manuscript was written by YT, MS, and NK.

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Figure Legends

Figure 1. Baseline serological markers of hepatitis B virus infection among 641 patients with myeloma
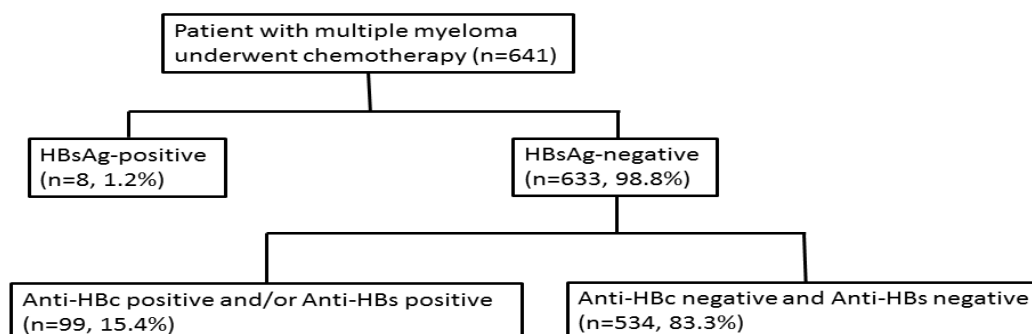
Eight patients were HBsAg-positive and 633 patients were HBsAg-negative. Ninety-nine of these 633 patients were anti-HBc positive and/or anti-HBs positive. Regular hepatitis B virus (HBV) DNA monitoring was performed for the 9 patients who experienced HBV reactivation.

HBsAg, hepatitis B surface antigen; Anti-HBc, antibodies against hepatitis B core antigen; Anti-HBs, antibodies against hepatitis B surface antigen.

Figure 2. Cumulative incidence of hepatitis B virus reactivation among 99 patients with resolved

infection
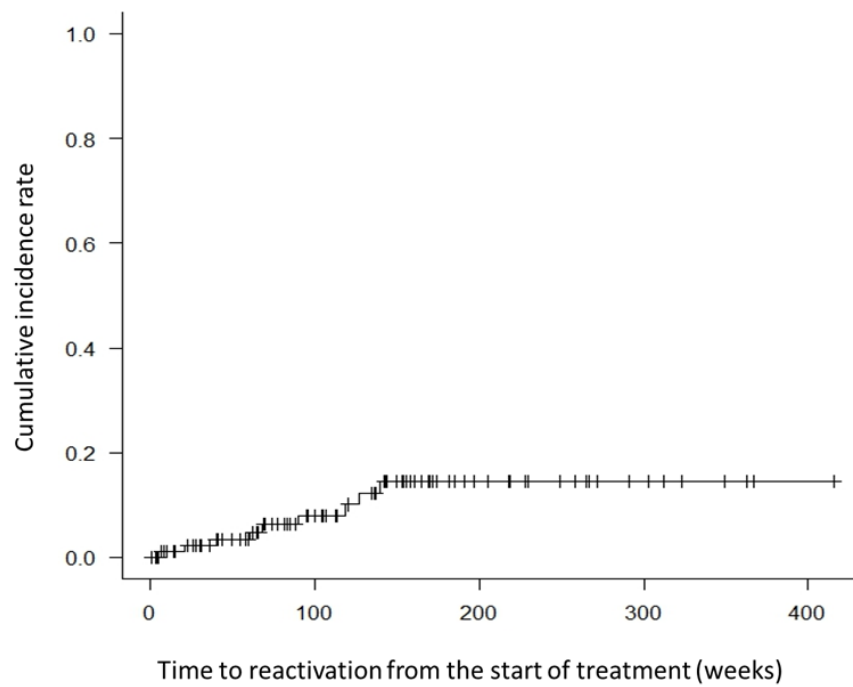
The cumulative incidences of hepatitis B virus reactivation at 2 years (104 weeks) and 5 years (260

weeks) were 8% and 14%, respectively.

Table 1. Baseline characteristics of hepatitis B virus carriers

	hepatitis n=1	no hepatitis n=7
Age		
Median (range)	83 (-)	73 (67-82)
Male, n	1	5
MM subtype, n		
IgG	0	5
IgA	1	1
Light chain only	0	1
Durie-Salmon staging system, n		
IA	0	0
IB	0	0
IIA	0	1
IIB	0	0
IIIA	1	5
IIIB	0	1
International Staging System, n		
I	0	0
II	1	2
III	0	5
WBC ($\times 10^9$/μL)		
Median (range)	4.9 (-)	5.4 (3.8-10.5)
Lymphocyte ($\times 10^9$/μL)		
Median (range)	1.793 (-)	1.296 (0.912-1.995)
ALT (IU/L)		
Median (range)	16 (-)	17 (5-74)
Novel agent, n		
Bortezomib	1	5
Lenalidomide	1	2
Thalidomide	1	3
ASCT, n	0	0
Follow up (week)		
Median (range)	305 (-)	79 (15-250)

One of 8 hepatitis B virus carriers developed hepatitis. That patient had not received an anti-viral agent

during their chemotherapy, and the other 7 patients had received prophylactic anti-viral agents before

starting chemotherapy.

MM, multiple myeloma; WBC, white blood cells; ALT, alanine aminotransferase; ASCT, autologous stem

cell transplantation with high-dose chemotherapy.

Table 2. Baseline characteristics of patients with resolved hepatitis B virus infection

	HBV reactivation n=9	No HBV reactivation n=90	*P*-value
Age			n.s.
Median (range)	64 (42-82)	68.5 (43-90)	
Male, n (%)	3 (33.3)	50 (55.6)	n.s.
MM subtype, n (%)			n.s.
IgG	5 (55.6)	52 (57.8)	
IgA	1 (11.1)	21 (23.3)	
Light chain only	1 (11.1)	13 (14.4)	
Others*	2 (22.2)	4 (4.4)	
Durie-Salmon staging system, n (%)			n.s.
IA	1 (11.1)	9 (10.0)	
IB	0 (0.0)	0 (0.0)	
IIA	3 (33.3)	17 (18.9)	
IIB	0 (0.0)	6 (6.7)	
IIIA	4 (44.4)	42 (46.7)	
IIIB	1 (11.1)	13 (14.4)	
unknown	0 (0.0)	3 (3.3)	
International Staging System, n (%)			n.s.
I	3 (33.3)	19 (21.1)	
II	4 (44.4)	33 (36.7)	
III	2 (22.2)	36 (40.0)	
unknown	0 (0.0)	2 (2.2)	
HBV serological marker, n (%)			
Anti-HBc(+) and anti-HBs(+)	4 (44.4)	43 (47.8)	
Anti-HBc(+) and anti-HBs(-)	4 (44.4)	26 (28.9)	
Anti-HBc(-) and anti-HBs(+)	1 (11.1)	19 (21.1)	
Anti-HBc unknown and anti-HBs(+)	0 (0.0)	1 (1.1)	
Anti-HBc(+) and anti-HBs unknown	0 (0.0)	1 (1.1)	
WBC ($\times 10^9$/μL)			n.s.
Median (range)	4.0 (2.4-7.0)	4.5 (2.2-11.04)	
Lymphocyte ($\times 10^9$/μL)			n.s.
Median (range)	1.456 (0.604-2.201)	1.148 (0.144-4.536)	
Albumin (mg/dL)			0.017
Median (range)	4.4 (3.0-5.0)	3.5 (1.8-5.3)	
ALT (IU/L)			n.s.
Median (range)	16 (10-73)	17 (5-74)	
Serum IgG level (mg/dL) [†]			n.s.
Median (range)	549 (281-731)	446 (100-847)	
Novel agent, n (%)			
Bortezomib	9 (100)	79 (87.8)	n.s.
Lenalidomide	4 (44.4)	46 (51.1)	n.s.
Thalidomide	1 (11.1)	20 (22.2)	n.s.
ASCT, n (%)	4 (44.4)	21 (23.3)	n.s.
Follow up (week)			n.s.
Median (range)	122 (23-233)	105 (1-416)	

Among 641 patients with myeloma, 9 of 99 (9.1%) patients with resolved hepatitis B virus (HBV) infection experienced HBV reactivation. Elevated serum albumin levels were the only significant risk factor for HBV reactivation.

*Others, includes IgD and biclonal gammopathy (IgG and IgA)

†Serum IgG level was evaluated in non-IgG myeloma patients.

MM, multiple myeloma; WBC, white blood cells; ALT, alanine aminotransferase; ASCT, autologous stem cell transplantation with high-dose chemotherapy; n.s., no significant.

Table 3. Characteristics and clinical courses of patients with hepatitis B virus reactivation

	Pt#1	Pt#2	Pt#3	Pt#4	Pt#5	Pt#6	Pt#7	Pt#8	Pt#9
Age/Gender	63/female	82/male	73/female	57/female	64/female	79/male	44/female	73/male	56/female
MM subtype	IgG-λ	IgG-κ	LC-κ	IgG-κ	IgD-λ	IgG-κ	IgA-κ	IgG-κ	IgD-λ
Durie-Salmon staging system/ International Staging System	IIA/I	IA/II	IIIB/III	IIIA/II	IIIA/I	IIA/II	IIA/II	IIIA/I	IIIA/III
Baseline HBV serological marker									
Anti-HBc/Anti-HBs	(+)/(+)	(+)/(-)	(+)/(+)	(+)/(+)	(+)/(+)	(+)/(-)	(+)/(+)	(+)/(-)	(+)/(-)
HBV DNA	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Treatment (cycles)	BD(3), LD(3), ASCT, Len maintenance	MPB(4), Bor maintenance	PSL, HD-DEX, BD(3)	BD(4), ASCT, Len consolidation, Bor maintenance	BD(8), ASCT, Bor maintenance	MPB(2)	VAD(2), BD(1)	MPB(6), BD(1), LCd(8), Len maintenance, CTD(4), Ld(1)	BD(3), ASCT, Len maintenance, CHOP(5), VL(D)(1), bendamustine(1)
HBV reactivation									
Duration from initial treatment (weeks)	140	61	21	68	90	7	40	127	119
HBV DNA*	<2.1 Log copies/mL	<2.1 Log copies/mL	2.8 Log copies/mL	2.3 Log copies/mL	<2.1 Log copies/mL	2.7 Log copies/mL	<2.1 Log copies/mL	<2.1 Log copies/mL	2.1 Log copies/mL
HBsAg reverse seroconversion	(-)	(-)	ND	(-)	(-)	(-)	(+)	(+)	ND
Antiviral agent	entecavir	(-)	(-)	entecavir	entecavir	entecavir	entecavir	(-)	(-)
Hepatitis due to reactivation	No	No	No	No	No	No	No	No	No
Outcome	alive	alive	died of pneumonia	alive	alive	alive	alive	died of myeloma	died of myeloma

Hepatitis B virus (HBV) reactivation occurred in 9 patients. In 5 patients, entecavir was started after the detection of HBV DNA (patients 1, 4, 5, 6, and 7). One of the 9 patients with detectable (but not quantifiable) HBV DNA levels only underwent observation (patient 2). The 3 remaining patients died due to pneumonia or myeloma progression soon after HBV reactivation (patients 3, 8, and 9).

* HBV DNA levels of all patients were measured using the COBAS TaqMan HBV test (version 2.0).

BD, bortezomib, dexamethasone; LD, lenalidomide, dexamethasone; MPB, melphalan, prednisolone, bortezomib; HD-DEX, high-dose dexamethasone; VAD, vincristine, doxorubicin, dexamethasone; LCd, lenalidomide, cyclophosphamide, dexamethasone; CTD, cyclophosphamide, thalidomide, dexamethasone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; VLD, bortezomib, lenalidomide, dexamethasone; ND, not done.