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The Impact of Hepatitis D Coinfection on the Hepatitis Flare during Chemotherapy for B-Cell Non-Hodgkin Lymphoma

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Objectives: This study was conducted to determine the effect of Hepatitis B infection with or without D coinfection on the hepatitis flare associated with chemotherapy for B-Cell non-Hodgkin lymphoma. **Methods:** The hepatitis flare related to the chemotherapy for newly diagnosed B-Cell non-Hodgkin lymphoma was studied in HBV mono-infected and HBV and HDV coinfected patients between 2015 and 2018. **Results:** Nineteen HBsAg positive patients satisfied the inclusion criteria. In the group with the hepatitis flare, 14.3% were anti-HDV negative and 83.3% were anti-HDV positive ($p<.006$). Also, the hepatitis flare occurred in all patients where HDV-RNA was detected, while it had occurred in 60% of patients where HDV-RNA was not detected. **Conclusion:** The hepatitis flare related to chemotherapy occurred more frequently in B-Cell non-Hodgkin lymphoma patients coinfected with HBV and HDV without antiviral prophylaxis, especially when HDV-RNA was detected.

Keywords: anti-HDV, chemotherapy, hepatitis B virus, hepatitis flare, non-Hodgkin lymphoma.

Introduction

Hepatitis B virus (HBV) infection is a major global health problem, with an estimate of 350 million people living with chronic hepatitis B (CHB) worldwide [1]. HBV has hepatotropic and lymphotropic characteristics, whereas some reports suggest that they may cause the development of malignant lymphoproliferative disorders or lymphoma [2, 3]. The exact mechanism through which HBV and hepatitis C virus (HCV) infection causes B-cell non-Hodgkin's lymphoma (B-NHL) remains unclear. The HBV infection rate in B-NHL patients is significantly higher than that in the general population and patients with other diseases [4, 5].

Hepatic complications occur broadly across a spectrum of individuals with a history of HBV infection, including malignant and nonmalignant disease processes, with some immunosuppressive drugs implicated. For many reasons, especially, related to the immunosuppressive drugs or receiving steroids containing chemotherapy hepatitis activity, an episodic abrupt rise of alanine aminotransferase (ALT) elevation occurs, often measured as a multiple of the upper limit of normal (ULN), resulting in a so-called acute exacerbation of hepatitis B, or flare in CHB [1]. The hepatitis flare was initially defined as "an abrupt elevation of ALT over 300 U/L (normal <40 U/L) in patients with a baseline ALT level <200 U/L" [6, 7]. Both of these definitions agree that "an abrupt ALT elevation >5 ULN" is the minimum criterion of a hepatitis flare [8]. Although rituximab (anti-CD20 receptor monoclonal antibodies) plus cyclophosphamide, doxorubicin, vincristine, and prednisone (standard cancer chemotherapy) are the standard treatment for patients with B-NHL [9, 10], hepatitis flare often occurs in CHB patients during and after this chemotherapy without antiviral prophylaxis [11, 12]the incidence, and the risk factors of hepatitis B in the treatment of malignant lymphoma. PATIENTS AND METHODS: HBV carriers were defined as patients with positive HBs-antigen, either with normal or abnormal serum aminotransferase level at patient presentation. Questionnaires to the members of the Japan Lymphoma Treatment Study Group included general information, details about HBV carriers, and further information about hepatitis B. RESULTS: Among 1380 patients collected from eight institutions, 45 patients (3.26%.

HBV is not directly cytopathic by itself and the hepatocellular injuries are considered to be the results of a complex interplay among HBV, hepatocytes and immune cells of the host [1, 13]. When patients receive immunosuppressants or chemotherapy, there is an upsurge of serum hepatitis B virus deoxyribonucleic acid (HBV-DNA) prior to the abrupt elevation of ALT [14]. There is also a parallel elevation of the serum hepatitis B surface antigen (HbsAg) level along with the upsurge of serum HBV DNA. In addition, there is a subsequent increase in hepatitis B e-antibody (anti-HBe) production and hepatitis B e antigen/anti-HBe immune complex formation, implicating the important role of the immune response to HBV in initiating the hepatitis flare [15]. Then, the host immune response rebounds and a hepatitis flare develops after the withdrawal of such treatments [16]. Immunohistologic studies during the hepatitis flare have shown CD8+ T cells in the mononuclear cell infiltrates, with the strong membranous expression of human leukocyte antigen class I [17]. Interleukin 10 (IL-10) production is the primary mechanism by which B cells modulate other immune cells; however, the excessive quantity of IL-10-producing B cells in B-NHL suppresses the immune system, allowing reactivation of HBV. This leads to liver damage and high levels of ALT [18]. As part of the same process, serum interferon alfa and IL-8 concentrations with peak, coinciding with a sharp increase in viral load preceding the onset of the hepatitis flare. Thus, the rapid increase in HBV disease activity associated with chemotherapy for B-NHL provides a unique opportunity to study the relationship between immune and clinical parameters governing viral control and liver damage [19]. Therefore, the host's immune response against HBV with resultant apoptosis and necrosis, resulting in higher ALT concentrations, usually indicate a vigorous immune response against the HBV and more extensive hepatocyte damage [1].

Mongolia is a country with a high burden of HBV [20-22] and hepatitis D virus (HDV) infection and their complications [23]. HDV causes aggressive viral hepatitis with a virulent course of progression to cirrhosis and hepatic decompensation [24]. The motivation for this research is the paucity of information regarding the hepatitis flare during chemotherapy for B-NHL in patients co-infected or double infected with HBV and HDV, while there are a number of studies about the hepatitis flare or acute exacerbation related to chemotherapy for HBV or HCV with B-NHL. Thus, the aim of our study was to determine the prevalence of hepatitis B surface antigen (HBsAg) among newly diagnosed B-NHL patients and to study whether the hepatitis flare related to the standard chemotherapy differs depending on HBV (mono-infection) or HBV + HDV (double infection or coinfection) for B-NHL patients.

Materials and Methods

We performed a retrospective observational study of the 256 patients newly diagnosed with B-NHL at the Center of Hematology and Bone Marrow Transplantation of the First Central Hospital of Mongolia, between January 2015 and December 2018. There were 37 HBsAg positive cases. Three of the 37 were also anti-HCV positive and these were excluded. The clinical information from the medical history and the electronic medical record system of the First Central Hospital was gathered

in strict compliance with research ethics (approved by the Ethics Committee of the Ministry of Health, No. 4 on June 19, 2017).

The inclusion criteria were as follows: (1) diagnosis of B-NHL based on histologic and immunophenotypic criteria; (2) ≥20 years of age, (2) HBsAg positive, (3) received at least one cycle of chemotherapy, (4) did not receive antiviral prophylaxis at the onset of the chemotherapy, (5) tested for hepatitis delta antibody (Anti-HDV), (6) tested for HBV-DNA, and (7) tested for hepatitis D virus ribonucleic acid (HDV-RNA). Patients were excluded if they previously had received antiviral prophylaxis, liver injury due to hepatitis A, C, alcoholic liver disease, autoimmune hepatitis, drug hepatitis or major systemic events (e.g., shock, hypoxia, hemolytic anemia). Nineteen patients fulfilled these exclusion criteria.

The chemotherapy for patients with B-NHL, cytotoxic chemotherapy consisted of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), and CHOP plus rituximab (R-CHOP) was used based on the guidance of The National Comprehensive Cancer Network [10].

Serum biochemistry, which included ALT and aspartate aminotransferase transaminase (AST), was performed before each cycle of chemotherapy. All patients were observed every three weeks during chemotherapy and every 8 to 10 weeks for nine months after chemotherapy.

HBsAg and anti-HCV marker results of every patient diagnosed with B-NHL were collected from their medical record.

HBV-DNA and HDV-RNA examinations were done before the chemotherapy and the sensitivity of detectable HBV-DNA was >15 IU/ml, HDV-RNA 20 IU/mL using real-time quantitative PCR (polymerase chain reaction).

Because a complete data set of HBV DNA levels for all patients was not available, the incidence of hepatitis flare in patients could not be included an outcome measure.

Clinical staging: The clinical-stage of B-NHL was determined by the Ann Arbor staging classification. The Ann Arbor staging system is determined by clinical presentation, imaging and laboratory tests, and initial biopsy reports [25]. The clinical-stages of our patients were based on their medical records.

Fibrosis Biomarker APRI Score (AST to Platelet Ratio Index): The APRI Score = [(AST / ULN AST) x 100] / Platelet Count. The value of 35 IU/L was used for the AST upper limit of normal (ULN). APRI scores greater than 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis. In addition, they concluded that APRI score greater than 0.7 had a sensitivity of 77% and specificity of 72% for predicting significant hepatic fibrosis [26].

Statistical analysis: Patient characteristics were analyzed using descriptive statistics and were presented as frequencies, percentages, and medians. The chi-square and Fisher's exact test (if the frequency of any cell was less than 5) were used to compare categorical variables, while the Mann-Whitney U test was used to compare differences between two independent groups when the continuous dependent variable was not normally distributed. The one-way ANOVA analysis was used to determine whether there was any difference between the mean values of more than two normally distributed groups, followed by a post-hoc multiple comparison test when a difference was identified. All statistical analyses were performed using STATA 14 software (StataCorp.2015, USA) and $p<.05$ was considered statistically significant.

Results

Patient characteristics

A total of 253 Mongolian adults were newly diagnosed with B-NHL between 2015 and 2018, including 123 males (48.6%) and 130 females (51.4%). The average age was 54.6±15.5 years and all patients were HIV-negative. Of the 253 patients newly diagnosed with B-NHL, 34 (13.4%) patients were positive for HBsAg. Of the 34 HBsAg positive patients, 25 had an anti-HDV test. Of the 25 patients with an anti-HDV test, 19 subjects fulfilled the study inclusion criterion and participated in the study. Of those 19 subjects, 12 (63.2%) were anti-HDV-positive cases and 7 were negative, and these 19 were the primary focus of our attention. For the 253 B-NHL patients we studied, the prevalence of HBsAg was 13.4%, and this did not differ from 11.1% reported by Dashtseren et al. among the Mongolian population ($p\geq.05$).

The characteristics of the B-NHL patients were shown in Table 1. B-NHL patients were divided into four sub-groups: (1) anti-HCV positive, (2) HBsAg positive, (3) eligible for hepatitis flare study, and (4) HBsAg negative and anti-HCV negative. The subgroups were compared by age, gender, and the Ann-Arbor NHL staging.

The nineteen subjects who satisfied the study inclusion

criterion were statistically indistinguishable from the 34 patients with HBsAg positive regarding age, gender, and Ann Arbor stage (p≥.05). Anti-HCV positive patients were older than the other sub-groups (p<.05). Also, there were no statistically significant differences between gender and Ann Arbor stage for the four subgroups by (p≥.05).

Baseline characteristics of HBV-related hepatitis flare

The characteristics of patients with and without hepatitis flare related the chemotherapy are presented in Table 2. Nineteen subjects who fulfilled study inclusion criteria were compared as 2 groups: those who had a hepatitis flare and patients who did not develop hepatitis flare. Overall, 11 patients developed HBV-related hepatitis flare with an incidence of 57.9%. The hepatitis flare occurred in 6 of 10 males and 5 of 9 females. Noteably, it occurred in 14.3% of the anti-HDV negative sub-group compared in 83.3% of the anti-HDV-positive sub-group (p<.05). Moreover, hepatitis flare occurred in 100% of the HDV-RNA detected sub-group versus 60% of the HDV-RNA not detected sub-group in the anti-HDV-positive sub-group. On the other hand, it occurred in 20% of the HBV-DNA detected sub-group and did not occur in the subgroup in which HBV-DNA was not detected (mono-infection).

There were no patients with hepatic fibrosis and cirrhosis in either group based on their APRI scores and their APRI scores did not differ based on whether or not they had a hepatitis flare (0.42 vs. 0.28, p≥.05). The hepatitis flare occurred in 64.3% of the patients during R-CHOP chemotherapy, while it has occurred in 40% during CHOP chemotherapy (p≥.05).

The remaining characteristics, such as gender, age, stage of NHL, the extranodal disease only, CHOP, R-CHOP chemotherapy, and pre-chemotherapy ALT level, APRI score, and LDH levels were not significantly different between the two groups (p≥.05) (Table 2).

Seventeen patients (89.5%) had normal serum levels of ALT at the onset of chemotherapy. With progression of the hepatitis flare in patients, the median peak serum ALT levels were 700.3 U/L (range, 208.2-3385 U/L). However, HBV-DNA and HDV-RNA information at the moment hepatitis flare were unavailable for 17 of the 19 patients.

The occurrence of hepatitis flare in the period of the chemotherapy

During this study, the hepatitis flare occurred in 11 subjects

Table 1. Characteristics of all B-NHL patients and patients eligible for hepatitis flare study.

Characteristics	Anti-HCV positive (I)	HBsAg positive (II)	Eligible for study (III)	HBsAg negative & anti-HCV negative (IV)	p-value
Age (ys), mean±SD	59.2±12.8	50.7±14.3	48±12.6	51.6±17.0	.000* (I: II) - .027 (I: III) - .002 (I: IV) - .018
Gender n (%)					
Male	42 (44.2)	20 (58.8)	10 (52.6)	51 (48.6)	.517**
Female	53 (55.8)	14 (41.2)	9 (47.4)	54 (51.4)	
Stage (NHL) n (%)					
Ann Arbor 1-2	31 (32.6)	12 (35.3)	8 (42.1)	40 (38.1)	.805**
Ann Arbor 3-4	64 (67.4)	22 (64.7)	11 (57.9)	65 (61.9)	
Total n (%)	95 (100.0)	34 (100.0)	19 (100.0)	105 (100.0)	

Notes: *The mean age was statistically significantly different between four sub-groups by one-way ANOVA test with Bonferroni multiple comparisons. For instance, anti-HCV positive patients were older than other sub-groups. **There was no statistically significant difference between four sub-groups regarding their gender and Ann Arbor stage using the Chi-square test. Notably, there were no statistically significant differences in characteristics between HBsAg positive group and the other sub-groups which are were eligible for the study.

Table 2. Baseline characteristics of patients with and without hepatitis flare-related chemotherapy.

Characteristics n=11		Patients who had hepatitis flare n=8	%	Patients who did not develop hepatitis flare	%	p-value
Gender						
Male		6	60.0	4	40.0	1.000
Female		5	55.6	4	44.4	
Mean age, years (range)		48.0 (25-70)		47.9 (31-62)		.124*
Stage of Ann-Arbor						
II		5	62.5	3	37.5	
III		3	42.9	4	57.1	.696*
IV		3	75.0	1	25.0	
Extra nodal disease only		3	75.0	1	25.0	.603
Pre-chemotherapy status						
Anti-HDV negative		1	14.3	6	85.7	.006
HBV-DNA	detected	1	20.0	4	80.0	
	undetected			2	100.0	
Anti-HDV positive		10	83.3	2	16.7	.006
HDV-RNA	detected	7	100.0			.000
	undetected	3	60.0	2	40.0	
ALT level (U/L)						
Median		48.7		22.5		.147*
Range		(15.2-149.4)		(10.2-37.6)		
APRI score						
Median		0.42		0.28		.162*
Range		(0.11-0.73)		(0.09-0.5)		
LDH level (normal, 87-250 U/L)						
Median		418.5		446.4		.968*
Range		(139.4-1954.8)		(135.8-1816.7)		
Type chemotherapy						
R-CHOP		9	64.3	5	35.7	.603
CHOP		2	40.0	3	60.0	

Notes: APRI-Aspartate Aminotransferase to Platelet Ratio Index, LDH-Lactate dehydrogenase, CHOP-cyclophosphamide doxorubicin vincristine and prednisone, R-rituximab, p-value by Fisher exact test, *p-value by Mann-Whitney U test. The hepatitis flare was observed much more commonly in the anti-HDV-positive cases compared to that in anti-HDV negative cases (p=.006), and of those in the anti-HDV-positive group, the hepatitis flare of was even more pronounced in the HDV-RNA detected subgroup compared to that in HDV-RNA undetected group (p=.000).

of 19 who have enrolled in the study and had standard chemotherapy. The time to hepatitis flare was different for them depending on whether they had mono-infection or coinfection and undetectable viral load or detectable. In Table 3, the clinical outcomes of hepatitis flare in the period of chemotherapy for anti-HDV-positive and negative patients.

In our study, the timing of the hepatitis flare in relation to the chemotherapy was stratified into two groups: occurring during 2-6 cycles of chemotherapy (peri-chemotherapy) and 2-6 months after finishing the last cycle of chemotherapy (post-chemotherapy). Hepatitis flare occurrences were more common during the peri-chemotherapy period compared to post-chemotherapy (9 vs. 2, p<.05), respectively. While the hepatitis flare was observed all HDV-RNA and

HBV-DNA detected patients (7/7 vs. 1/1) during the peri-chemotherapy period, it was observed in only 1 (33.3%) of the

Table 3. The comparison of the timing of the hepatitis flare in relation to chemotherapy for anti-HDV-positive and negative patients.

Characteristics		Timing of hepatitis flare				Total
		peri-chemotherapy		post-chemotherapy		
		n	%	n	%	n (%)
Anti-HDV positive						
HDV-RNA	detected	7	100.0	0		7 (100.0)
	undetected	1	33.3	2	66.6	3 (100.0)
Anti-HDV negative						
HBV-DNA	detected	1	100.0	0		1 (100.0)
	undetected	0		0		0 (0)
Total		9	81.8	2	18.2	11 (100.0)

Notes: Peri-chemotherapy: flare occurred during cycles 2-6 of chemotherapy; post-chemotherapy: flare occurred 2-6 months after finishing the last cycle of chemotherapy. The hepatitis flare was observed in the peri-chemotherapy period in patients with HDV-RNA and HBV-DNA, including 100% (7/7) of patients with detectable HDV-RNA .

patients in which HDV-RNA was not detected.

Discussion

The hepatitis flare among B-NHL patients with CHB (mono-infection) and its prevention has been extensively studied in other countries. However, information about hepatitis flare in B-NHL patients with HBV/HDV coinfection is rare; thus, we performed this study. Also, to our knowledge, our study is the first hepatitis flare study in B-NHL patients with HBV in Mongolia. We demonstrated that the hepatitis flare related to chemotherapy in B-NHL patients occurred much more commonly in patients with HBV/HDV coinfection compared with HBV mono-infection.

Hepatitis B flare is an important complication of immunosuppressive or anti-cancer chemotherapy. It is a clinically important disorder because it can result in significant morbidity, liver failure, and even death [13and this may have no identifiable cause or be triggered by an increase in viral replication or genotypic change. It is important to keep in mind the clinical situations in which patients are at increased risk of reactivated infection and secondary exacerbations. Reactivation is frequently induced by medical treatments such as cancer chemotherapy, antirejection drugs used in organ transplantation, and corticosteroids. The immunologic flares that often result from sudden withdrawal of these medications can be life-threatening unless recognized and treated promptly with antivirals, and there is increasing experience that preemptive antiviral treatment can diminish their occurrence and improve the outcome. The experience with lamivudine and other nucleoside analogues has increased our understanding of the molecular events behind hepatitis flares that occur when chronic hepatitis B is treated with drugs that potently inhibit HBV DNA polymerase. However, not all flares are explainable by events related to HBV infection alone. Depending on the population studied, as many as 20%-30% of flares may be caused by infection with other hepatotropic viruses, and this situation may inhibit HBV replication. Proper understanding of the etiology and effective treatment of acute flares in chronic hepatitis B requires an appreciation of high-risk clinical situations, assessment of HBV replication status, and testing for other viruses when HBV persists in the body of all patients with infection, even those with evidence of serological recovery. Thus, individuals with a history of HBV infection without antiviral prophylaxis who receive immunosuppressive therapy are at risk for HBV reactivation and hepatitis flare of their HBV disease [28]. The recently published guidelines of the American, European, and Asian liver disease associations recommend that not only HBsAg positive, but also HBsAg negative hepatitis B core antigen (anti-HBc) positive patients undergoing chemotherapy receive antiviral prophylaxis [8, 29, 30](II.

The hepatitis flare is defined as a rise of ALT levels to greater than 5 times the upper normal ALT limit and ALT levels rising over 10 times above the upper normal are not rare [31]. The mortality after cancer chemotherapy is more related to the serum ALT levels than HBV-DNA [32, 33]. In patients with CHB, elevated ALT levels at baseline or during follow-up are associated with a greater risk of liver cirrhosis or hepatocellular carcinoma [34].

Dashtseren et al. found no statistically significant difference in HBV prevalence, as determined by the presence of HBsAg, between B-NHL patients and the general population of Mongolia [22]. However, other investigators have found the HBV infection rate among B-NHL patients to be significantly higher than in the general population in other countries [11, 35, 36]. Like Dashtseren et al., we did not find a higher prevalence in the Mongolian people. Not having a higher prevalence of HBsAg among our B-NHL patients compared to the general population may depend on several reasons. Perhaps one of the reasons is HDV. More than 60% of the Mongolian HBsAg positive population with are co-infected with HDV [23including higher rates of hepatocellular carcinoma (HCC, 37HBV, HCV, HDV, and HEV was evaluated in 249 apparently healthy individuals, including 122 inhabitants in Ulaanbaatar, the capital city of Mongolia, and 127 age- and sex-matched members of nomadic tribes who lived around the capital city. Overall, hepatitis B surface antigen (HBsAg, 38] hepatitis C virus (HCV and 56% of the HBsAg-positive patients with B-NHL were anti-HDV-positive in our study. Also, many in-vitro and in-vivo studies, as well as clinical observations, have indicated that the HDV can suppress the replication of the HBV at a certain time point of the coinfection [39].

Even though the total population of HBsAg positive cases was not the subject of this study, we considered that the 19 patients who fulfilled the study inclusion criterion could represent them, because, the characteristics their age, gender, and Ann-Arbor stage were statistically indistinguishable.

The hepatitis flare with chemotherapy for B-NHL occurs commonly without antiviral prophylaxis therapy for the prevention of CHB. For instance, Nakamura et al. [40] found 72.2% of patients had hepatic complications without antiviral prophylaxis therapy, and Kumagai et al. [12]the incidence, and the risk factors of hepatitis B in the treatment of malignant lymphoma. PATIENTS AND METHODS: HBV carriers were defined as patients with positive HBs-antigen, either with normal or abnormal serum aminotransferase level at patient presentation. Questionnaires to the members of the Japan Lymphoma Treatment Study Group included general information, details about HBV carriers, and further information about hepatitis B. RESULTS: Among 1380 patients collected from eight institutions, 45 patients (3.26% reported hepatitis B developed in 37.8% of the HBV carrying patients without antiviral prophylaxis therapy, while Chen et al. [11] reported about 52.4% occurrence of hepatitis flare without it. In our study, eleven (57.9%) of 19 patients who enrolled in the study had hepatitis flare without antiviral prophylaxis therapy, and this is similar to the above-mentioned reports.

The number of cases of hepatitis flare in the anti-HDV-positive sub-group was significantly higher compared to that in anti-HDV negative sub-group (14.3% vs. 83.3% p=.006). In the anti-HDV-positive sub-group, the hepatitis flare has occurred in 60% of HDV-RNA undetected patients, while it has occurred in 100% of HDV-RNA detected patients. It can be concluded that the hepatitis flare is significantly higher when the patient is anti-HDV positive and HDV-RNA is detected. But it occurred in only 20% in HBV-DNA detected patients.

HDV remains a potential risk factor for serious liver damage, either for HBV chronic carriers or for all those still susceptible to HBV infection [41]leading more frequently to cirrhosis, increased risk of liver decompensation and hepatocellular carcinoma (HCC. It is well known that in patients with HDV, HBV can be reactivated during immunosuppressive treatment [42]. Therefore, HBV and HDV co-infected patients may have a higher chance of hepatitis flare compared to HBV mono-infected patients and, hepatitis flare may occur in more than 90% of patients if HDV-RNA is detected.

In our study, all B-NHL patients (100%) with positive anti-HDV and detectable HDV-RNA experienced hepatitis flare during the peri-chemotherapy, while it was observed only in 33.3% of patients without detectable HDV-RNA during the peri-chemotherapy. , In the remaining two patients without detectable HDV-RNA, the hepatitis flare occurred in the post-chemotherapy period. A previous study reported that the hepatitis flare related to B-NHL chemotherapy usually occurred within the post-chemotherapy [43], whereas we found that the hepatitis flare 100% occurred during the peri-chemotherapy when HDV-RNA was detected. All of these findings might enhance the rapid progression of liver failure for patients with HDV.

Although some studies on HBsAg-positive cancer patients on chemotherapy have reported male gender to be significantly associated with the risk of developing HBV (reactivation and hepatitis flare) [44HBV reactivation during cytotoxic treatment may become a more common problem. In lymphoma patients, the incidence of chronic HBV infection has been reported to be 26%, of whom 47% developed HBV reactivation during chemotherapy. However, corresponding data for patients with

other malignancies undergoing cytotoxic chemotherapy are not known. In this prospective study, hepatitis B surface antigen (HBsAg, 45]even those with resolved HBV infection. Since anti-HBV prophylaxis for patients with resolved HBV infection is not covered by national health insurance in Taiwan, a proportion of these patients receive no prophylaxis. In addition, late HBV reactivation has emerged as a new issue in recent reports, and no consensus has been reached for the optimal duration of antiviral prophylaxis. Thus, the aim of our study was to investigate the incidence and outcomes of HBV reactivation in NHL patients in a real-world setting and to study the frequency of late HBV reactivation. MATERIALS: Non-Hodgkin lymphoma patients who received rituximab and/or chemotherapy at our institute between January 2011 and December 2015 and who were hepatitis B surface antigen (HBsAg, no gender difference was identified for our study.

During the course of our study, one of two patients who had hepatitis flare in 2016, and all nine patients had hepatitis flare between 2017 and 2018 are still alive. All of them were received oral nucleos(t)ide analogs after hepatitis flare. In 2019, the hepatitis flare did not occur in newly diagnosed B-NHL patients treated with chemotherapy who had mono-infection (4) and coinfection (4) due to the oral nucleos(t)ide analog antiviral prophylaxis which effectively prevented it.

As a result of oral nucleos(t)ide analogs therapy, ALT decreased and the health condition improved not only for HBV patients but also for HBV/HDV coinfection patients. Also, we consider that antiviral prophylaxis therapy can prevent patients with mono and coinfection from having the hepatitis flare related to chemotherapy.

Limitations and future study

There were several B-NHL patients for which no viral markers found could in the clinical record during our retrospective review. Also, many patients were excluded by the study inclusion criteria. For this study, only the B-cell major category NHL, which was 85% of cases, was studied. Our numbers were limited by the rarity of NHL in the Mongolian population and that immunohistochemistry has been used to determine NHL subtypes since only 2013. Also, it was challenging to compile the statistics and evaluate the results on so few patients who met the inclusion criteria. Yet, we consider that we can study several NHL subtypes and study HBsAg positive and anti-HBc positive cases in the future.

Eventually, compared to mono-infection, HDV coinfection with B-NHL has a higher chance of hepatitis flare or acute exacerbation with chemotherapy and its recurrence might be earlier or during the chemotherapy. Thus, it is necessary to perform routine anti-HDV, HBV-DNA and HDV-RNA examination for HBsAg positive patients before the chemotherapy.

Conclusions

The occurrence of hepatitis flare related to chemotherapy in B-NHL patients was high among HBsAg positive patients without antiviral prophylaxis and most of them were coinfected with HBV and HDV. For B-NHL patients coinfected with HBV and HDV, especially those with where HDV-RNA was detected, hepatitis flare was more common. Because of this, it is necessary to improve virus marker control in the peri and post-chemotherapy periods. We concluded that antiviral prophylaxis possibly can prevent patients with coinfection from having the hepatitis flare.

Conflict of Interest

The authors declare that they have no competing interests.

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