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Hepatitis C Associated B-Cell Non-Hodgkin Lymphoma: Impact of Combination Direct-Acting Antivirals and Chemotherapy

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Objectives: Direct-acting antiviral agents (DAAs) have successfully eradicated chronic hepatitis C virus (HCV) infection. Since chronic HCV is known to have an increased risk of developing B cell non-Hodgkin lymphoma (B-NHL), successful HCV treatment may have virologic, hepatic, and oncologic benefits for B-NHL. Therefore, this study aimed to determine the efficacy of DAAs combined with chemotherapy in B-NHL patients with chronic HCV in Mongolia. **Methods:** This case-control study included newly diagnosed B-NHL patients with chronic HCV who received DAAs before chemotherapy (with DAAs group). The other is comprised of controls who have been treated by chemotherapy without DAAs. Patients who received courses of DAAs were monitored by the virological and hepatic responses. **Results:** Eleven patients received DAAs and none of them developed chemotherapy-associated hepatitis flare. Of the DAAs group, during DAAs treatment, 90.9% were clinically stable. In all cases of DAAs in combination with chemotherapy, the Sustained Viral Response (SVR)12 and 24 were 100%. However, 47.4% of those who received DAAs after chemotherapy developed hepatitis flare during chemotherapy. Patients with hepatitis flare had higher serum level of ALT before chemotherapy (15.7 U/L vs. 40.2 U/L; $p = 0.014$) than those without. **Conclusion:** DAAs administration results in a significant clinical benefit to B-NHL patients with chronic HCV.

Keywords: B Cell Non-Hodgkin's Lymphoma, Chemotherapy, Hepatitis C Virus, Hepatitis Flare

Introduction

Chronic hepatitis C virus (HCV) infection is a global health issue affecting more than 71 million people worldwide [1]. Although, chronic HCV infection is not the only reason for liver diseases which also includes liver cirrhosis and hepatocellular carcinoma, it also strongly correlates with extrahepatic manifestations of HCV such as type 2 diabetes, chronic kidney disease, non-Hodgkin's lymphoma (NHL), and mixed cryoglobulinemia [2].

Epidemiological and interventional studies have shown

that the most common subtype of NHL [3], B-cell non-Hodgkin's lymphoma (B-NHL), is closely related to chronic HCV. [4 - 8]. According to the researchers, many patients with chronic HCV infection in B-NHL developed hepatitis flare during chemotherapy [9]. On the other hand, complete remission of HCV infection has the benefits of preventing further complications, reducing the risk of B-NHL progression, and improving survival rates [10 - 12]. In recent years, the introduction of direct-acting antiviral agents (DAAs) have made a notable contribution to the eradication of chronic HCV infection with almost no adverse effects [13 - 15]. In addition, it has been documented that DAA treatment has remarkable efficacy in preventing extrahepatic manifestations of chronic HCV infection [16, 17].

Many studies reported that the eradication of HCV by DAA treatment prevented chemotherapy induced virus reactivation, hepatitis flare [18], and significantly correlated with the regression of indolent B-NHL [12]. Besides, successful DAA treatment could make it possible to complete chemotherapy as planned, and has long term advantages such as improved survival rate and quality of life, preventing further complications including liver cirrhosis, cancer progression, and secondary cancer [5, 19, 20].

As results of the DAA treatment response in B-NHL patients with chronic HCV infection, the treatment guideline for 2017 of the National Comprehensive Cancer Network recommended that chronic HCV infected patients, who were newly diagnosed with indolent B-NHL must be given DAAs before taking chemotherapy [21]. A few recent studies revealed that even in the cases of chronic HCV infection combined with an aggressive form of B-NHL, DAAs had significant remedial results [22, 23]. This is remarkable because the combination of DAAs with chemotherapy in HCV-associated B-NHL has not yet been fully introduced into clinical practice in all countries due to a variety of factors, including availability. On the other hand, no consensus has been reached on the importance of combining DAAs with chemotherapy during the aggressive form of B-NHL [24, 25] usually deferring AVT. However, an early HCV elimination may reduce the risk of CIT-induced liver toxicity and consequent CIT interruption or withdrawal. To date few data are available on safety and efficacy of concomitant administration of direct-acting antivirals DAA.

In epidemiologic studies, Mongolia stands as one of the countries with the highest prevalence of HCV infection with 8.5 - 16% of adults positive for the presence of anti-HCV [26, 27] and compare levels of AST, ALT, M2BPGI in the Mongolian population in the age between 40 - 64. Methods: In order to reflect the administrative and geographical features of Mongolia, the sampling was done at three levels: urban, province center, and rural. The immunological test was measured by chemiluminescence enzyme immunoassay (CLEIA. Consequently, among patients with B-NHL, the incidence of anti-HCV is significantly higher as mentioned in the above literature [28]. Our team studied cases of chronic HCV infection among B-NHL patients and complications associated with chemotherapy for the first time in Mongolia. In the study, patients with chronic HCV infection with B-NHL were treated with a combination of DAAs and chemotherapy. Therefore, this study is aimed to determine the efficacy of DAA therapy in treating patients with HCV-associated B-NHL in Mongolia, and how it can be combined with chemotherapy.

Materials and Methods

This study was conducted between June 2016 and June 2019 in the Center of Hematology and Bone Marrow Transplantation (CHBMT) of the First Central Hospital of Mongolia (FCHM), out of 55 patients with chronic HCV infection newly diagnosed with B-NHL. The CHBMT is the only place that is responsible for all Mongolian patients who have a blood cancer diagnosis, requiring treatment and follow-up care.

The inclusion criteria were: more than 2 cycles of chemotherapy preformed; complete CBC and biochemical parameter results before, during, and after chemotherapy; willingly agreed to take DAA treatment before chemotherapy; and haematologists approved initiation of combination DAAs and chemotherapy.

Exclusion criteria were as follows: refusing chemotherapy; co-infection with either hepatitis A or hepatitis B; alcoholic hepatitis or drug induced hepatitis not related to chemotherapy; or hepatocellular carcinoma.

This study was conducted in a case-control study design that included patients who met the study criteria. The DAAs group (case group) included 11 patients newly diagnosed with B-NHL with chronic HCV infection after August 2017 and who had received DAA-therapy. Patients in the DAAs group received DAA therapy according to HCV treatment guidelines

and then underwent chemotherapy. The control group was composed of 19 patients newly diagnosed B-NHL with chronic HCV infection before August 2017. This control group's patients received chemotherapy without DAAs. The general condition of the patients included: type of chemotherapy (with or without rituximab), B-NHL subtypes, the results of serum level of ALT and lactate dehydrogenase (LDH), and HCV ribonucleic acid (RNA) before chemotherapy, and APRI (Aspartate aminotransferase to Platelet Ratio Index), and clinical data collected from electronic medical records and patients' medical paper documents. The assessment of treatment response in the B-NHL group was by Cheson criteria [29]. These criteria measure the size of the patient's lymph nodes before and after treatment by CT scan and analyse the results. In the DAA group, assessment the DAA treatment response also was by Cheson criteria.

The control group was divided into two groups: with and without hepatitis flare. Clinical variables associated with hepatitis flare were investigated in both groups.

The possibility and importance of concomitant chemotherapy and DAA therapy in two patients with diffuse large B-cell lymphoma (DLBCL), an aggressive form of B-NHL that is not included in the two groups, was also investigated. The control group's patients were also treated with DAA treatment after chemotherapy and the virologic outcome was studied. The effective combination of the DAA treatment and chemotherapy (before chemotherapy, during chemotherapy, after chemotherapy) was evaluated by hepatitis flare or not.

During DAA treatment courses (before chemotherapy, during chemotherapy, after chemotherapy) patients were monitored by the HCV treatment guideline, liver function tests, and HCV viral loading. The characteristics of the liver function test before and during chemotherapy, serum level of HCV ribonucleic acid (RNA) before chemotherapy, APRI score, B-NHL subtypes, and type of chemotherapy (with or without rituximab) were compared in the case and control group.

Definitions

Partial remission-by Cheson criteria is defined as lymph node reduction of > 50% when compared to before treatment.

Chronic HCV infection-is is marked by the persistence of HCV RNA in the blood for at least 6 months after the acute infection [30].

Sustained virologic response (SVR)12 and 24 is defined as the absence of detectable HCV-RNA on blood testing 24 weeks after the completion of antiviral therapy [31, 32].

A hepatitis flare was defined as an increase in ALT level to ≥ 3 times (>110 U/L) the upper limit of the normal value (35 U/L) [33 data on DAAs used during or after salvage treatments are still lacking. In this study we assessed clinical and virological outcome in 11 patients with relapsed (n = 7, 34].

B-NHL staging: The clinical-stage of B-NHL is defined by the Ann Arbor staging classification. The Ann Arbor staging system is determined by clinical presentation, imaging and laboratory tests, and initial biopsy reports. The clinical stages in this study were based on the medical history of the patients.

Statistical analysis

The distribution, mean, standard deviation, median, and interquartile range of patient characteristics were calculated using descriptive statistics. We used a Chi-square or Fisher's (if the frequency of any cell is less than 5) exact test to compare categorical variables (gender, Ann-Arbor stage, B-NHL type, chemotherapy type, cases of hepatitis flare) and the Mann-Whitney U test to compare differences in continuous variables (age, serum level of ALT, LDH, and HCV-RNA, APRI score) between two groups. A p-value of less than 0.05 ($p < 0.05$) is considered statistically significant. Different variables ($p < 0.05$) for hepatitis flare were included in the final analysis by logistic regression. All statistical tests were made using the STATA 14 software program (StataCorp.2015, USA).

Ethical statement

The study was approved by the Mongolian Ministry of Health's Ethical committee resolution. (No.4; June 19th, 2017). After providing study information, each patient signed a consent form if they allowed to participate in this study.

Results

This study included 32 patients who had chronic HCV associated with B-NHL who were treated with DAA, all of whom had HCV genotype 1b, so they were treated with Sofosbuvir/Ledipasvir. DAAs was administered to 11 patients (6 females and 5 males) before chemotherapy (the DAAs group), 2 patients (1 female and 1 male) were treated concurrently with chemotherapy, and 19 patients (13 females and 6 males) after chemotherapy (control

group). As shown in Table 1, a total of 30 chemotherapy patients were enrolled. Prior to the administration of chemotherapy, 11 patients had DAAs and 19 did not.

Table 1 shows that the baseline clinical and laboratory characteristics between these two groups were similar, except that those in the control group had higher serum ALT level (30.1 vs. 13.9; p = 0.043). None of the patients developed hepatitis flare in the DAAs group in chemotherapy. In contrast, 9 patients (47.4%) developed hepatitis flare among those who did not receive antiviral treatment (control group). This difference was statistically significant (p = 0.011) between the two groups. During the chemotherapy, the control group had higher average peak value of ALT (121.5 and 28.7; p = 0.001) than the with DAAs group.

Table 2 shows the clinical characteristics of individuals who did not receive DAAs before chemotherapy. Analysis was performed in two groups of with and without hepatitis flare to determine the important factors contributing to hepatitis flare.

Table 2 shows that patients with hepatitis flare had higher serum level of ALT before chemotherapy (15.7 U/L vs. 40.2 U/L; p = 0.014) than those without. However, there were no significant differences between the two groups in terms of age, gender, Ann-Arbor stage, B-NHL type, chemotherapy type, LDH, HCV-RNA levels, and APRI score. There were no two or more statistically significant variables in the two groups, therefore, bivariate logistic regression was not calculated.

Table 3 shows some clinical changes in lymph nodes pre-chemotherapy during DAA treatment.

In the DAAs group, 5 (45.5%) of the 11 patients who underwent DAA's resulted in lymph nodes diminished or reached "partial remission" level. Also 5 (45.5%) the patient's lymph nodes size was not enlarged or diminished, just stable from the previous period of DAA treatment. Thus, 10 patients (90.9%) of the chronic HCV infected with B-NHL were clinically stable (lymph nodes maintained or decreased), and there was clinical progressive in 1 patient (9.1%). However, it should be noted

Table 1. Comparison of baseline data and clinical parameters between control and with DAAs groups prior to chemotherapy

	Control group (n = 19)	With DAAs group (n = 11)	Total (n = 30)	p-value
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Age, years	55.4 ± 12.6	55.2 ± 11.5	55.3 ± 12.0	0.897[1]
	N (%)	**N (%)**	**N (%)**	
Male	6 (31.6)	5 (45.5)	11 (36.7)	0.447[2]
Female	13 (68.4)	6 (54.5)	14 (63.3)	
B-NHL stage				
I-II	4 (21.0)	4 (36.4)	8 (26.7)	0.417[3]
III-IV	15 (79.0)	7 (63.6)	19 (73.3)	
Aggressive type of B-NHL				
No	9 (47.4)	2 (18.2)	12 (40.0)	0.140[3]
Yes	10 (52.6)	9 (81.8)	18 (60.0)	
Treatment type				
CHOP	4 (21.0)	4 (36.4)	8 (26.7)	0.417[3]
R-CHOP	15 (79.0)	7 (63.6)	19 (73.3)	
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	
LDH (U/L)	280 (138)	180 (110.1)	225 (130.1)	0.175[1]
ALT (U/L)	30.1 (25.3)	13.9 (11.3)	21.8 (22.9)	0.043[1]
APRI score	0.248 (0.267)	0.253 (0.423)	0.251 (0.269)	0.948[1]
HCV-RNA (log10 U/L)	6.2 (1.3)	6.4 (1.2)	6.3 (1.2)	0.344[1]
Hepatitis flare	9 (47.4)	0	9 (30.0)	0.011[3]

DAAs, direct-acting antiviral agents; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index – AST enzyme, the platelet ratio is a non-invasive method to determine hepatic liver fibrosis; IQR, interquartile range. [1]p-value was calculated by Mann-Whitney U test; [2] by Chi-square test; [3] by Fisher's exact test.

Table 2. Demographic data of B-NHL patients with chronic HCV infection receiving chemotherapy without DAAs.

	Without hepatitis flare (n = 10)	With hepatitis flare (n = 9)	Total (n = 19)	p-value
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Age, years	56.0 ± 13.5	54.8 ± 12.3	55.4 ± 12.6	0.683[1]
Gender	**N (%)**	**N (%)**	**N (%)**	
Male	1 (10.0)	5 (55.6)	6 (31.6)	0.057[2]
Female	9 (90.0)	4 (44.4)	13 (68.4)	
B-NHL stage				
I-II	3 (30.0)	1 (11.1)	4 (21.0)	0.582[2]
III-IV	7 (70.0)	8 (88.9)	15 (79.0)	
Treatment type				
CHOP	2 (20.0)	2 (22.2)	4 (21.0)	1.000[2]
R-CHOP	8 (80.0)	7 (77.8)	15 (79.0)	
B-NHL type				
Indolent	3 (30.0)	6 (66.7)	9 (47.4)	0.179[2]
Aggressive	7 (70.0)	3 (33.3)	10 (52.6)	
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	
LDH U/L	245.5 (151)	280 (61)	280 (138)	0.807[1]
ALT U/L	15.7 (19.5)	40.2 (22.1)	30 (25.3)	0.014[1]
APRI score	0.237 (0.102)	0.303 (0.240)	0.248 (0.267)	0.350[1]
HCV-RNA log10 U/L	6.56 (1.26)	6.06 (0.8)	6.2 (1.26)	0.086[1]

DAAs, direct-acting antiviral agents; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index – AST enzyme, the platelet ratio is a non-invasive method to determine hepatic liver fibrosis; [1]p-value was calculated by Mann-Whitney U test; [2]by Fisher's exact test.

Table 3. The clinical changes of DAA therapy on lymph nodes of B-NHL patients.

	Lymph nodes			
Gender	**Decreased [a]**	**Maintained [b]**	**Increased [c]**	**Total**
Male	2 (40.0%)	3 (60.0%)	0 (0.0%)	5
Female	3 (50.0%)	2 (33.3%)	1 (16.7%)	6
Total	5 (45.5%)	5 (45.5%)	1 (9.1%)	11

DAA, Direct-acting antiviral. [a] Enlarged lymph nodes size regressed by >50% from pre-treatment; [b] enlarged lymph nodes size did not regressed and progressed from pre-treatment; [c] enlarged lymph nodes progressed by >50% from pre-treatment.

Table 4. Brief results of combination variants of DAAs and chemotherapy.

	Combination variants			
Variables	**Sequential [a] (n = 11)**	**Concomitant [b] (n = 2)**	**DAAs after chemotherapy [c] (n = 19)**	**Total (n = 32)**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Hepatitis flare				
Yes	-	-	9 (47.4)	9 (28.1)
No	11 (100.0)	2 (100.0)	10 (52.6)	23 (71.9)
SVR12 and 24*				
Yes	11 (100.0)	2 (100.0)	19 (100.0)	32 (100.0)
No	-	-	-	-

DAAs, Direct-acting antiviral agents. [a] Received DAAs before chemotherapy; [b] Received simultaneous treatment with DAAs and chemotherapy; [c] Received DAAs after chemotherapy. *Absence of detectable HCV RNA on blood testing 12 and 24 weeks after the completion of DAAs.

that these patients developed virological and hepatic responses during DAA therapy.

Of the 32 participants in the study, the virological response to DAA treatment in combination with chemotherapy was similar. However, there were differences in hepatitis flare, a complication of chemotherapy.

Table 4 show the brief results of combination variants of DAAs and chemotherapy.

Table 4 show that 100% SVR12 and 24 occurred in all cases of DAA treatment in combination with chemotherapy in patients with chronic HCV infection who were newly diagnosed with B-NHL. When DAA treatment was given before or at the same time as chemotherapy, there was no elevation in the levels of liver enzymes. However, 47.4% of those who received chemotherapy without DAA treatment discontinued treatment due to hepatitis flare during chemotherapy.

Discussion

Here we report a study of the characteristics and outcomes of DAA treatment in newly diagnosed B-NHL patients with chronic HCV infection who had received chemotherapy in Mongolia.

According to a meta-analysis of epidemiological studies, anti-HCV positive in B-NHL patients is 5 to 10 times higher than that of the general population [5, 6, 35]. This suggests that chronic HCV infection significantly increased the risk of developing B-NHL [4, 8, 36]. Consequently, interferon treatments indicate that B-NHL remission was observed in some subtypes of B-NHL with chronic HCV only after administering DAAs [11, 12], and our recent SVR treatments also confirm these results [7, 37 - 39]. Another issue is that chemotherapy-induced immunosuppression increases the risk of hepatitis flare (26.2%) in B-NHL patients with chronic HCV infection [40]. It is common for an HCV-related hepatitis flare to result in the patient's planned chemotherapy being halted, and their prognosis worsen.

In our clinical investigation, administrating DAAs before chemotherapy had clinical significance in patients who were newly diagnosed with B-NHL having chronic HCV (possible prevention from hepatitis flare and clinical remission). There were no elevated liver enzymes during chemotherapy, and all patients completed the treatment as planned. Also, our results were similar to H. Torres et al., as receiving DAAs prior to chemotherapy showed significant hepatic outcomes for blood cancer patients [23].

On the other hand, in the control group 47.4% of the cases experienced hepatitis flare during chemotherapy. In reports of most researchers, during the R-CHOP treatment for B-NHL with HCV-positive patients, there were 13 - 27% who experienced hepatitis flare [41, 42] but characteristics and outcome of these patients remain undefined. PATIENTS AND METHODS: We analyzed 156 previously untreated consecutive HCV-positive patients with DLBCL observed between 1994 and 2004 in three major institutions from northern Italy. RESULTS: Median age at presentation was 63 years and 8% of patients had DLBCL transformed from low-grade lymphomas. Spleen was the most frequently involved extranodal site, followed by liver and stomach. Treatment was delivered with cure-intent in 132 patients, while the remaining 24 patients received monochemotherapy or radiotherapy alone due to old age or seriously impaired hepatic function. Only five patients (4%). The incidence of hepatitis flare in our study was higher than that of the following researchers. It is especially noteworthy that the incidence is high in men. This may be due to the small number of participants. On the other hand, it could be the result of insufficient detailed viral hepatitis screening prior to chemotherapy. We believe that early DAAs in combination with chemotherapy in high-risk groups will reduce the incidence of hepatitis C flare. Alone in a report by C Besson et al., hepatitis flare was observed in 15 (65.0%) out of 23 cases of DLBCL with chronic HCV who were under R-CHOP treatment [43], an identical treatment outcome with our studies.

Clinical response was 45.5% (n = 5) in the DAAs group after DAA treatment. However, in Italy, the result was less than 77% clinical response of B-NHL in HCV-infected patients [44] HCV-positive patients with indolent NHL diagnosed and treated from 1993 to 2009 in 39 centers of the Fondazione Italiana Linfomi; 134 patients were managed with AT for lymphoma control. For entire cohort, 5-year overall survival (OS. This finding could be explained by the fact that those researchers included participants with indolent B-NHL, whereas most of our study group (72.7%) had aggressive B-NHL.

A small number of studies have been conducted on the concurrent strategy of chemotherapy and DAA treatment in patients with chronic HCV and an aggressive form of B-NHL (such as DLBCL). We administered DAAs and chemotherapy concurrently to two patients who had chronic HCV and were newly diagnosed with DLBCL. Their liver enzymes did not exceed

normal levels during chemotherapy, like the with case group. Our finding regarding the DAA treatment response in DLBCL with chronic HCV had the same result with 7 cases who were reported in the study of O.Vincenzo et al. from Italy [25] usually deferring AVT. However, an early HCV elimination may reduce the risk of CIT-induced liver toxicity and consequent CIT interruption or withdrawal. To date few data are available on safety and efficacy of concomitant administration of direct-acting antivirals (DAA).

The control group's patients who received DAAs after chemotherapy in a reverse sequence, resulting in SVR12 and 24. However, the cohort study of Italy and France has demonstrated that the concurrent strategy may be ideally preferred to the sequential strategy to prevent hepatic toxicity during chemotherapy [45] although limited experiences substantiate this recommendation. Moreover, only a few data concerning concurrent administration of DAAs with I-CT have been reported. SUBJECTS, MATERIALS, AND METHODS: We analyzed hematological and virological outcome and survival of 47 consecutive patients with HCV-positive DLBCL treated at 23 Italian and French centers with DAAs either concurrently (concurrent cohort [ConC]: n = 9.

When combining DAA therapy and chemotherapy in chronic HCV-infected patients who are newly diagnosed with B-NHL, each patient must be individually evaluated to determine which approach is more efficient for their case. Patients with elevated normal levels of ALT should be treated with special care.

Limitations and future study

At the start of the study, the public, as well as all physicians (except hepatologists), had a limited understanding of HCV treatment marked by a low interest in DAA therapy and it was common to receive chemotherapy without first taking an HCV-RNA count test. Because of this, fewer patients were included in this study. A comprehensive baseline assessment of liver status and viral hepatitis screening before the onset of chemotherapy should be improved. In the future, larger scales of studies are suggested to be done regarding the combination usage of DAA therapy and chemotherapy in chronic HCV infected patients who are newly diagnosed with B-NHL.

Conclusion

Our results suggested that DAAs in combination with chemotherapy showed significant therapeutic improvement in chronic HCV-infected patients with newly diagnosed B-NHL.

Conflict of Interest

The authors declare no conflict of interest

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