

## HCV in Lymphoid Neoplasms

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### Abstract

In some HBV carrier cases, there have been reports of HBV reactivation and liver damage occurring during rituximab combination chemotherapy. Recently, with regard to the use of rituximab combination chemotherapy to treat non-Hodgkin's lymphoma in people infected with HCV, it has been suggested that there may be a connection between HCV and the severity and frequency of liver damage. Although these studies have mainly been retrospective, it is still debatable as to whether liver damage increases or becomes more severe when using rituximab combination chemotherapy to treat non-Hodgkin's lymphoma with HCV infection. In these HCV infected non-Hodgkin's lymphoma cases, the difference in prognosis compared with patients without HCV infection is also a key issue. On the other hand, it was recently reported that in some cases of B-cell non-Hodgkin's lymphoma, the use of interferon or a direct-acting antiviral agent against cases of HCV infection either reduced the lymphoma or brought about remission in combination with rituximab, which raises the possibility that treating HCV with antiviral therapy may be effective against lymphoma and may contribute to the vital prognosis. In this review, we present an outline of the current findings relating to non-Hodgkin's lymphoma with HCV infection based on these reports.

**Keywords:** Rituximab; Hepatitis C virus; Non-Hodgkin's lymphoma

**List of Abbreviations:** HCV: Hepatitis C virus; NHL: Non-Hodgkin's lymphoma

### Introduction

HCV is one of the causative factors of liver cancer, which has an incidence 25-35 times higher in HCV positive patients compared to healthy individuals [1,2]. Furthermore, it has been reported that liver cancer can develop without cirrhosis in HCV positive patients. Thus, it is important to control HCV to prevent development of liver cancer. On the other hand, exactly how HCV is involved in causing liver cancer remains unclear [2]. It has been reported that HCV may also play a role in lymphoproliferative disease, although the correlation between the two is still unclear [3,4], and its effects may be indirect. HBV reactivation has been reported during the treatment of malignant lymphoma and autoimmune disease with rituximab in patients who are HBV positive, and preventive measures against HBV reactivation are being developed [5,6]. With regard to cases of HCV infection, a sizeable review of cases of severe liver damage in chemotherapy and rituximab combination chemotherapy has been conducted [7]. It is debatable whether the liver damage was caused by reactivation of HCV or was facilitated by the HCV infection. It is of interest to determine whether HCV affects the treatment and prognosis of lymphoma [8,9]. In this review, these points are outlined based on previously published studies.

### Mechanism of HCV reactivation during rituximab treatment

One proposed model for HCV reactivation is that during rituximab treatment, the HCV viral load increases due to a reduction in the number of B cells and a subsequent decrease in antibody production. However, the hypothesis that antibody production is reduced due to a reduction of B cells is not temporally consistent when considered alongside the time taken for HCV viral growth. In our study, although HCV-RNA increases after administering rituximab, and HCV continues to increase while rituximab is

administered, when rituximab is not administered, it is claimed that HCV-RNA does not increase even when an anti-cancer agent is administered [10]. This may be because of problems caused by HCV proliferating by repeated replication due to the immunosuppressive effects of rituximab. Stamatakis *et al.* reported that the rapid increase of HCV-RNA is not necessarily directly related to the proliferation of B cells themselves, but that the virus is carried to the liver due to HCV infection. They discovered that reinfection of the liver with HCV is likely to have an important bearing on in cases such as liver transplants, and that — according to in vitro studies — if HCV infected liver cells are incubated together with healthy peripheral B cells to cause antibody dependent cellular cytotoxicity (ADCC), then the increase of HCV-RNA in the experimental group not using rituximab where the B cells are not destroyed is unchanged from the control group, but when ADCC is brought about by using rituximab, the B cells are destroyed and as a result the HCV-RNA increases compared with the control group [11,12]. These reports seem to explain the phenomenon whereby HCV-RNA increases rapidly after administering rituximab. However, it is difficult to explain the decline in HCV during treatment without rituximab, although the amount of virus initially increased in peripheral blood. Recovery of B cells following rituximab treatment takes at least 6-9 months and it is therefore unlikely that B cells are infected with HCV during this period [13,14]. It is possible that HCV replicates in peripheral blood and subsequently moves through the bloodstream to re-infect liver cells, where it is attacked by cytotoxic T cells (CTL) resulting in hepatitis [15]. However, basic studies on the mechanism of HCV reduction are lacking. Treatment with rituximab not only causes a decline in B-cells but also changes the balance of CD4 and CD8 T cells due to changes in the cytokine profile. HCV replicates more efficiently as the number of CD8 positive cells decreases, and once the cells recover, CD8 positive cells specific for HCV are then synthesized. After treatment with rituximab, the CD4/8 balance changes and the B cells decrease, resulting in immune suppression and proliferation of the HCV virus [16,17]. Furthermore, in the case of HCV infection, it is known that the virus cannot be eliminated even though HCV specific CTLs are produced [18,19]. It is speculated that upon HCV growth following rituximab treatment, the T-cells and B-cells are both affected, resulting in the production of escape mutants that evade HCV specific CTLs and establish immune tolerance against the host. This may promote chronic infection with HCV and prevent more severe hepatitis compared with HBV reactivation. However, it has been reported that liver damage in HCV-positive cases has no connection with the quantity of HCV virus so an increased quantity of HCV virus may not necessarily be needed, and it has been suggested that increased HCV virus, unlike HBV, may not be a factor behind liver damage occurring in chemotherapy when using rituximab in HCV-positive cases [9,20-22].

## Epidemiology of HCV reactivation during rituximab treatment

Few large scale studies on HCV reactivation have been conducted and most studies were undertaken before rituximab was introduced as a treatment. Although a few sporadic reports on HCV reactivation and hepatitis exist, most are small in scale [9,10,23-26]. Several fatal cases due to hepatitis following HCV reactivation have been described in these reports [23,25]. Although the number of cases analyzed was small, Ennishi *et al.* reported a rate of hepatitis of 27% and 3% in HCV positive patients and HCV negative patients, respectively, along with a relatively high level of transaminase in HCV positive patients [26]. It was also reported by Arcaini *et al.* that 17.9% of patients who were HCV positive showed liver damage during R-CHOP (R: Rituximab, C: cyclophosphamide, H: hydroxyl doxorubicin, O: vincristine, and P: prednisone) treatment [9]. Together with the report by Ennishi, it appears that approximately 15-30% of HCV positive patients develop liver damage. Additionally, it was reported that progressive lymphoma was caused by fatal hepatitis and a delay in treatment due to liver damage [22]. On the other hand, a number of reports have indicated that it is not necessary to delay treatment despite the presence of liver damage, although more studies are necessary to confirm these results [23,27,28]. It has also been reported that reactivation of HCV is more frequently seen with HCV genotype II [29]. Therefore, HCV genotype may influence disease severity and reactivation rate. On the other hand, since the HCV viral load is not correlated with the severity of hepatitis requiring treatment as mentioned above, this means that the onset of severe hepatitis may be observed while hinting at the possibility of there being no correlation between the increased amount of virus after HCV treatment and the amount of liver damage after treatment. Further studies are necessary to confirm these observations [8,9,20-22].

## Relationship between HCV and non-Hodgkin's lymphoma

HCV was reported to have a strong correlation with cryoglobulinemia [30-33]. However, cryoglobulinemia is rare in Japan, while non-Hodgkin lymphoma in HCV positive patients is more common. Therefore, this review will discuss HCV as a cause of B cell non-Hodgkin lymphoma.

Although several reports exist suggesting a correlation between HCV and B cell non-Hodgkin lymphoma [34-40], no conclusive evidence has been forthcoming. The incidence of lymphoma in HCV positive patients is approximately 0.5-25% [7,8,41]. It also depends on the type of lymphoma. It was reported that marginal zone lymphoma (MZL), diffuse large B cell lymphoma (DLBCL) and lymphoplasmacytic lymphoma are strongly correlated with HCV [42]. Interestingly, there are reports of cases where HCV antiviral therapy has been used to achieve complete remission or partial remission, albeit with low-grade lymphomas [43-45]. Also, a variety of meta-analysis studies have found that at least 10% of non-Hodgkin's lymphoma cases are correlated with HCV in HCV endemic regions such as Italy and Japan [3,35,40,45-47], and Nieters *et al.* reported that people infected with HCV are more likely than healthy individuals to develop B-cell non-Hodgkin's lymphoma with a relative risk of 2-4 times [45]. Marcucci *et al.* summarized the possible mechanisms of HCV-induced lymphoma as follows: 1. Proliferation of lymphoma due to antigen stimulation; 2. Immune suppressive effect due to HCV infection; 3. Co-infection with an unidentified virus; 4. Direct oncogenic

role of HCV [48]. We first recognized the correlation between HCV and lymphoma upon encountering an HCV positive patient with DLBCL whose peripheral blood HCV-RNA rapidly increased before DLBCL recurrence [49]. Based on this observation, we stained lymphoma samples from HCV positive DLBCL patients using HCV-specific antibody. About 76.9% of samples were found to be HCV positive (either “strong positive” or “weakly positive”). However, this analysis found no significant correlation between the degree of HCV staining and the rate of recurrence or resistance to treatment [50]. Correlation between HCV and lymphoma was indicated epidemiologically as well as pathologically, as described in our study. HCV is nonetheless likely to play a role in B cell lymphoma; further evaluation of this hypothesis is needed.

## Prognosis of HCV positive lymphoma

So far, the outcome of HCV positive malignant B-cell lymphoma and HCV negative B-cell lymphoma has only been addressed through retrospective analyses. Some have reported poor prognosis [27,41] while others reported good prognosis [28]; thus, no clear conclusions can be drawn on whether any difference in prognosis between these two types of lymphomas exist. In some cases, it was reported that younger patients with low-grade lymphoma were observed in the group with a favorable prognosis, whereas patients in the poor prognosis group had a tendency to have high LDH values. Thus, from currently available data, it is not possible to draw clear conclusions on prognosis since the disease status of patients in each group is varied and inconsistent [7]. Our previous study found a poorer prognosis in an HCV positive patient group; although the number of cases was small and statistical significance was not attained. Further studies and analyses are needed [7].

Merli *et al.* analyzed prognosis factors for 535 patients with HCV positive lymphoma who received anthracycline-based treatment and reported the following three prognosis factors: ECOG score of 2 or higher, albumin less than 3.5g/dl, and HCV-RNA load >1,000KIU/ml. Using these factors, it is possible to categorize both OS and progression free survival (PFS) into 3 groups as follows: 0=low, 1=intermediate, 2=high risk [20]. Furthermore, it has been reported that treatment times are longer in cases of HCV-positive NHL combined with liver cirrhosis than in cases of HCV-negative NHL, which suggests the treatment is less effective and has an adverse effect on the prognosis [51,52]. Further studies by other groups are necessary to confirm this method.

## DAA treatment in HCV positive NHL patients

The treatment of hepatitis C is currently changing: the conventional treatment with interferon is being replaced by a regimen of internal medication. In both the United States and Japan, it is recommended that treatment is performed by combining various DAAs according to the current HCV genotype [53-56]. In Japan, the HCV genotype is thought to be 70% genotype 1b, with genotypes 2a and 2b being the next most common [19]. Treatment with a combination of DAAs is said to achieve a sustained virologic response (SVR) of roughly 75-95%. Since therapeutic effects can be achieved without burdening the patient with inconveniences such as having to self-inject, the use of interferon is being dropped from the treatment of hepatitis C. Recent reports on the prognosis of patients with HCV positive lymphoma who received anti-viral treatment such as interferon showed better overall survival rate [50,57]. We also evaluated changes in HCV-RNA before and after treatment and found that patients whose HCV-RNA load decreased after treatment had fewer reactivation episodes than those with increased HCV-RNA after treatment [49]. Patients who received treatment for malignant lymphoma and became HCV negative with interferon treatment in particular showed no recurrence [50]. A report by Arcaini *et al.* reported that, at least in case of low-grade lymphoma, interferon treatment could extend OS [58]. This was the first report based on a clinical study, although the number of low-grade lymphoma cases was limited. Furthermore, according to recent reports, complete remission has been achieved using direct antiviral agents on low-grade lymphomas such as HCV-positive marginal zone lymphomas in combination with rituximab, which is very promising for the future [53,59-61]. Further studies on the effect of interferon post-lymphoma treatment on improvement of prognosis in patients with HCV-positive B cell lymphomas, including DLBCL, are awaited.

Based on this information, we designed an intervention trial where R-CHOP therapy was used to treat B-cell non-Hodgkin lymphoma with hepatitis C (genotypes 1 and 2) as a complication, following which the hepatitis C was treated with these antiviral medicines, and the patients are monitored for any improvement in the prognosis or reduction of recurrence. We started registration after gaining the approval of the ethics committee in June 2015. Although the number of patients is still small, there have been no cases of recurrence or death without additional treatment, such as rituximab, and we are awaiting the accumulation of results from further cases. We plan to conduct an interim analysis in the second year of the study. In the future, we expect that the combination of antiviral therapies will suppress the recurrence of malignant lymphoma, leading to a reduction in liver cancer and liver sclerosis.

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