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HCV Infection on Lymphoid Neoplasm

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Abstract

Since there is a suggested a link between HCV and liver cancer, attempts are currently being made to discover new drugs that can advance the treatment of hepatitis C and prevent it from progressing to liver cancer. On the other hand, in the treatment of lymphoma, it has been pointed out that HCV is associated with HCV reactivation and lymphoproliferative diseases such as lymphoma. In this review, we will summarize the relationship between lymphoproliferative diseases and hepatitis due to reactivation of HCV during treatment with rituximab.

Keywords: Rituximab; Hepatitis C virus (HCV); Lamivudine; Non-Hodgkin's lymphoma (NHL); Direct-acting anti-viral agents (DAA)

Introduction

HCV is regarded as a causative factor of liver cancer, and is said to increase the incidence of liver cancer by 23 to 35 times compared with healthy people [1,2]. It is known that HCV-positive patients can develop liver cancer without transitioning to cirrhosis, so controlling HCV is essential for suppressing the onset of liver cancer. However, the mechanism whereby HCV contributes to the onset of liver cancer is still not clearly understood [2]. There have been reports suggesting the involvement of lymphoproliferative disease and HCV, but the relationship between HCV and lymphoproliferative disease has not yet been clarified [3,4]. This could be due to the contribution of HCV to lymphoproliferative disease, although this contribution may not always be direct. The reactivation of HBV has also been reported in cases of HBV-positive malignant lymphoma treated with rituximab, and preventive methods for this eventuality are in the process of being established [5,6]. But with regard to lymphoma having HCV as a complication, it has also been reported that reactivation of HCV occurs when treated with rituximab, and it is interesting to see if the HCV reactivation affects the treatment or if it affects the prognosis of lymphoma [7,8]. In this review, we summarize the reports that have been published so far.

Principles of HCV Reactivation in Patients Treated with Rituximab

One factor contributing to the reactivation of HCV is thought to be a model whereby the administration of rituximab causes a reduction in B-cells that decreases the production of antibodies and allows HCV to increase. Stamataki et al. used rituximab against cases of HCV-related cryoglobulinemia, and reported that the depletion of B cells is accompanied by lysis of HCV-infected B cells, the release of HCV, and an increased HCV viral load [9]. One cause of these phenomena is thought to be that HCV attached to B cells becomes disconnected when the B cells are broken down by rituximab, resulting in a rapid increase in HCV viral load [10]. We also used rituximab either on its own or in combination with chemotherapy in cases of B-cell non-Hodgkin's lymphoma with HCV infection as a complication, and we reported that although there was an increase in HCV viral load after administering rituximab, the HCV viral load either decreased or showed no increase when using chemotherapy alone [11]. Although this supports the report of Stamataki et al., it is difficult to explain why the increased amount of HCV virus in the peripheral blood decreases when rituximab is not used. This is because the B-cells are unlikely to be re-infected since B-cells do not recover for at least 6 to 9 months after using rituximab [12,13]. It is possible that an elevated level of HCV in the peripheral blood could spread through the blood stream and cause further infection of hepatocytes, and therefore it is expected to be attacked by cytotoxic T cells (CTL) resulting in hepatitis [14]. However, this is only speculation since insufficient fundamental experiments have been conducted to investigate this decrease. On the other hand, although the lack of reports on severe cases of hepatitis caused by HCV reactivation is thought to be due to the action of a system whereby HCV is likely to be more chronic than HBV, the mechanism for this is not clear. Following the administration of rituximab, there is not only a reduction of B-cells but it is also known that changes in CD4/CD8-positive T-cells occur due to changes in cytokine. There is a reduction of CD8-positive cells, and HCV tends to proliferate even more in the same way as HBV, followed by the production of CD8-positive cells targeting HCV when there is a recovery of CD8-positive T-cells. At the same time, memory T cells are damaged (reduced), giving rise to a phenomenon that is similar to HBV whereby HBV is randomly attacked causing hepatitis, and is liable to become severe when it occurs [15,16]. Regarding HCV, despite the production of HCV-specific CTL by the host, it is known that HCV is not completely excluded [17,18]. Since these systems cause escape mutations that pass through CTL monitoring upon reactivation of HCV following rituximab treatment, they induce immune tolerance to the host and make HCV infections chronic, while on the other hand, they are thought to prevent the onset of acute hepatitis compared with HBV reactivation.

Epidemiology of HCV Reactivation in Patients Treated with Rituximab

There are many reports of HCV reactivation prior to the use of rituximab, but few are actually based on large-scale evaluations. In sporadic reports, there are mentions of HCV reactivation and consequent hepatitis, but this is only mentioned in a few large-scale reports [11,19-23]. These reports have also mentioned fatalities caused by hepatitis following HCV reactivation [19,21]. There are few reports discussing large numbers of cases, but a typical example is the report by Ennishi et al. where the incidence of hepatitis in HCV-positive cases was 27%, but the incidence of hepatitis in HCV-negative cases was only 3%, and it was also reported that there were high levels of transaminase in the HCV-positive cases [22]. Arcaini et al. reported that liver damage was observed in 17.9% of HCV-positive cases when using R-CHOP [23], and together with the report by Ennishi et al., it seems that liver damage occurs in roughly 15–30% of cases. These reports mentioned that lymphoma is exacerbated by lethal hepatitis in HCV-positive cases, and by delayed treatment of liver damage [24]. On the other hand, other reports have stated that although liver damage occurs, there is no need to postpone treatment, and the conclusions of prospective studies are awaited [25-27]. In cases of HCV reactivation where rituximab is used, there have been a few examples where there was more reactivation of HCV genotype II [28,29], and it is thought that differences in severity and the likelihood of reactivation could be due to the HCV genome.

HCV as a Cause of B-cell Lymphoproliferative Disease

The question of whether or not HCV contributes to lymphoproliferative disorders has been studied in the same way as liver cancer, and it has been reported to be strongly associated with cryoglobulinemia [30-34]. However, it is rare in Japan. Since the possibility of HCV combined with non-Hodgkin's lymphoma has been recognized, we will look at the possibility of HCV contributing to B-cell non-Hodgkin's lymphoma in this review.

There have already been reports describing the relationship between HCV and B-cell non-Hodgkin's lymphoma [34-40], but although they are possibly related, this has not yet been confirmed. In previous reports, the proportion of HCV-positive lymphomas is estimated to be roughly 0.5–25% [8,41,42]. The incidence is also said to vary depending on the type of lymphoma, with a high incidence occurring for marginal zone lymphoma (MZL), diffuse large B-cell lymphoma (DLBCL) and lymphoplasmacytic lymphoma [43]. A study by Nieters et al. also showed that many HCV carriers have B-cell lymphoma that is impossible to distinguish from DLBCL [44]. Also, Dai Maso et al. examined 15 studies and reported that the relative risk of lymphoma is 2–2.5 times greater in HCV-positive cases, with a similar trend being observed for each type of lymphoma [35]. Marcucci et al. summarized the possibility of HCV-induced lymphoma, and put forward four hypotheses: 1. Proliferation of lymphoma by antigen stimulation, 2. Suppression of tumor immunity by HCV infection, 3. Co-infection with an unknown oncogenic virus, and 4. Direct tumor antigenicity of HCV [45]. We first became aware of a connection between HCV and lymphoma after seeing cases where HCV-positive patients with large-cell lymphoma showed a rapid increase of HCV-RNA in peripheral blood prior to recurrence. Subsequently, based on these cases, we found that when lymphoma specimens from HCV-positive lymphoma cases were stained with HCV-specific antibodies, 76.9% of the HCV-specific antibodies (including strong positive and weak positive) were positive in the lymphoma specimens. However, in this analysis there was no difference in the strength of HCV-specific antibody staining in lymphoma specimens in cases of treatment resistance or recurrence [46,47]. This suggests an epidemiological possibility that HCV is associated with lymphoma. This is also thought to be pathologically relevant as mentioned in our report, but since not all the pathological specimens of HCV-positive lymphoma cases all tested positive for HCV antibodies, it is still unknown whether HCV is the direct cause of the onset of lymphoma in all cases that test positive for HCV antibodies. It is thought that HCV is somehow related to B-cell lymphoma, but further examination of this hypothesis (and its correctness) is awaited.

Prognosis of HCV Positive Lymphoma

Although this is only a retrospective analysis of studies on the prognosis of HCV-positive B-cell malignant lymphoma and HCV-negative B-cell lymphoma, some reports have stated that HCV-positive lymphoma has a poor prognosis [41,25], while others have found no difference [8,48], and it has even been reported to have a better prognosis [26]. At present, therefore, it is unclear if there is any difference in prognosis. In these reports, many of the cases in the favorable prognosis group were young patients and patients with low-grade lymphoma, while many of the cases in the poor prognosis group had high LDH. Due to this pronounced variation of cases, it is difficult to draw any definite conclusions [42]. A retrospective analysis we conducted in 2011 also found that the prognosis was worse for HCV-positive lymphoma cases, but found no significant difference due to the small number of cases [47].

Also, with regard to the investigation of prognostic factors, Merli et al. analyzed the prognostic factors of 535 HCV-positive lymphoma patients who had received anthracycline-based treatment, and reported that the prognostic risk factors include an ECOG score of 2 or more, an albumin level of less than 3.5, and an HCV-RNA load of more than 1000 KIU/ml. It was proposed that these risk factors should be classified into three groups-0=low, 1=intermediate, and 2=high risk-in terms of OS and progression-free survival (PFS), and verification by other groups is awaited [49].

We investigated the variation of HCV-RNA before and after treatment, and reported that cases where HCV-RNA falls below pre-treatment levels are unlikely to relapse, while cases where it exceeds the pre-treatment level are more susceptible to recurrence or resistance to treatment [47]. In particular, cases in which patients became HCV-negative due to being administered interferon following treatment of malignant lymphoma showed no subsequent recurrence [46]. A recent report discussed the prognosis of patients following the treatment of HCV-positive lymphoma with this antiviral therapy, and it was reported that patients receiving antiviral therapy such as interferon have a better overall survival rate [47,48]. A report by Arcaini et al. was the first to describe clinical trials of the treatment of low-grade lymphoma, and hinted at the possibility of extending OS through the use of interferon on at least low-grade HCV-positive lymphoma [50]. There have also been reports of cases in which improvements of cases such as splenic marginal zone lymphoma are obtained through the use of antiviral therapy alone, and it is expected that the use of antiviral therapy on HCV-positive lymphoma will result in an improved prognosis [51–53].

On the other hand, studies of whether treatment of HCV with antiviral drugs after treatment for diffuse large-cell lymphoma contributes to the prognosis are being conducted either retrospectively

or through a combination of retrospective and prospective methods [54,55]. It has been reported that the five-year OS and PFS can both be improved [54,55]. However, a report by Michot et al. mentioned the possibility of including cases where diffuse large B-cell lymphoma is thought to have transformed from splenic marginal zone lymphoma [54]. In Europe and the US, there are many cases where splenic marginal zone lymphoma is associated with HCV. These cases are highly responsive to HCV antiviral therapy, suggesting the possibility of an improved prognosis. On the other hand, in the report by Michot et al., the antiviral therapy group included cases where SVR could not be achieved, and the report by Hosry et al. included many cases of cirrhosis, where it is thought that these factors could have a negative effect on OS and PFS [54,55].

Since we consider that prospective studies are always important, we conducted a study of antiviral therapy against HCV after remission using CHOP or CHOP-like chemotherapy in combination with rituximab in five successive cases of HCV-RNA-positive diffuse large cell lymphoma. The control groups consisted of a group of HCV-RNA-positive diffuse large-cell lymphoma cases prior to this trial (control-1), and a group of cases that tested negative for HIV, HCV and HBV (control-2). All the cases were in remission at the time of initial treatment. As a result, the DAA group contained more genotype 2 cases, and control group 1 contained more genotype 1 cases. This difference in genotypes is liable to affect the treatment outcomes, but in all five of the cases receiving DAA treatment, there were no recurrences and the two-year overall survival and progression-free survival rates were significantly better than in the control-2 group where HCV antiviral therapy was performed following treatment for diffuse large-cell lymphoma (P=0.029) [56].

Although analysis has only been performed in a few cases, it seems that HCV-RNA-positive cases have a poorer prognosis than non-HCV-infected diffuse large-cell lymphoma cases, and although there are signs that the prognosis is improved for cases treated with direct-acting anti-viral agents (DAA), it is recommended that DAA treatment is performed after remission in HCV-RNA-positive diffuse large-cell lymphoma. In addition, R-THP-COP therapy was performed in one case of HCV-RNA-positive follicular lymphoma and one case of marginal zone lymphoma. In both cases, remission was followed by DAA therapy. Although maintenance therapy with rituximab was not performed at all in these two cases, the patients continued to survive without showing further signs of disease for 5 years and 2 years respectively following R-THP-COP treatment, and it is possible that rituximab maintenance therapy as an addition to DAA therapy could perhaps be omitted in cases of low-grade HCV-RNA-positive lymphoma. Further investigation of this issue is awaited.

In Japan, DAA therapy can only be performed in chronic hepatitis cases, so DAA was used in cases that had been confirmed as chronic HCV-positive hepatitis by performing a liver biopsy. For this reason, the patients were treated with anticancer drugs, followed by DAA therapy after about 6 weeks. But on the other hand, there are no clear guidelines on the appropriate timing of DAA therapy, such as whether antiviral therapy should be administered after or simultaneously with lymphoma treatment, whether it should be preceded by lymphoma anticancer drug treatment, and so on. In a recent report, DAA was administered at the same time as various anticancer drugs to cancer patients with HCV infections, and the resulting interactions were studied. Although this report only considered blood toxicity and gastrointestinal toxicity, the DAA therapy caused a change of no more than 10%, while the SVR changed by 95%. This suggests that DAA therapy can be used simultaneously with anticancer drugs [57,58]. However, in this analysis there were no cases where DAA therapy was performed simultaneously with the anticancer drug treatment, either due to difficulties in continuing with DAA treatment, or because no complications requiring a change of medication were observed. In the future, it may be necessary to investigate the optimal timing of DAA therapy, including simultaneous administration with anticancer drugs.

Future Prospects

We have reviewed whether of nor rituximab can be used to reactivate HCV-positive B-cell lymphoma, and whether or not it can become pathogenic. Hepatitis due to reactivation of HCV may not need to be taken too seriously, but it is possible that HCV reactivation may decrease the prognosis of lymphoma in cases of hepatitis, so regular monitoring and prompt countermeasures are required. On the other hand, regarding HCV as a pathogen of B-cell lymphoma, it may be relevant to pathological and epidemiological searches, and the prognosis of HCV-positive B-cell lymphoma is improved by the addition of DAA therapy. With low grade lymphoma, it is possible that rituximab maintenance therapy is not always necessary. We await the results of studies that examine large numbers of cases.

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