A significant association between hepatitis C virus (HCV) infection and B-cell lymphoma has been reported by epidemiological studies, most of them describing a strong relationship between indolent lymphomas and HCV. Furthermore, the curative potential of antiviral therapy on HCV related indolent lymphomas supports a specific role for the virus in lymphomagenesis. These observations are reinforced by numerous laboratory experiments that led to several hypothetical models of B-cell transformation by HCV. Diffuse large B-cell lymphoma (DLBCL), the most common lymphoma subtype in the western countries, has been associated to HCV infection despite its aggressive nature. This association seems particularly prominent in some geographical areas. Clinical presentation of HCV-associated DLBCL has consistently been reported to differ from the HCV-negative counterpart. Nevertheless, histopathology, tolerance to standard-of-care chemo-immunotherapy (R-CHOP or CHOP-like regimens) and final outcome of HCV-positive DLBCL patients is still matter of debate. Addition of rituximab has been described to enhance viral replication but the probability of severe hepatic complications remains low, with some exceptions (i.e., hepatitis B virus or immune immunodeficiency virus co-infected patients, presence of grade > 2 transaminases elevation, cirrhosis or hepatocarcinoma). HCV viral load in this setting is not necessarily directly associated with liver damage. Overall, treatment of HCV associated DLBCL should be performed in an interdisciplinary approach with hepatologists and hematologists with close monitoring of liver function. Available reports reveal that the final outcome of HCV-positive DLBCL that receive standard immunochemotherapy is not inferior to their HCV-negative counterpart. This review summarizes data on epidemiology, pathogenesis and therapeutic approach on HCV-associated DLBCL. Several issues that are matter of debate like clinical management of patients with transaminase elevation, criteria for discontinuing or starting immuno-chemotherapy, as well as the exact role of monoclonal antibodies will be analyzed.

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Key words: Hepatitis C virus; Non-Hodgkin lymphoma; Liver; Toxicity; Diffuse large B-cell lymphoma; Rituximab; Cyclophosphamide; Hydroxydaunorubicin; Vincristine; Prednisolone; Immuno-chemotherapy; Antiviral treatment

Core tip: Patients with hepatitis C virus-positive diffuse large B-cell lymphoma should be managed in a multidisciplinary setting. Initial evaluation of liver status and comorbidities is essential to establish if the patient is candidate to curative approaches. Unless contraindicated by adverse clinical conditions, patients should be treated with standard immuno-chemotherapy. Concomitant hepatitis B virus infection and liver failure or cirrhosis confer a significantly higher risk of viral reactivation or therapy related complications. These patients
should be managed cautiously and treated with less intense approaches at least for the initial cycles. Antiviral treatment should be considered after the end of immuno-chemotherapy, when lymphoma remission has been achieved.

Visco C, Finotto S. Hepatitis C virus and diffuse large B-cell lymphoma: Pathogenesis, behavior and treatment. World J Gastroenterol 2014; 20(32): 11054-11061 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i32/11054.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i32.11054

**INTRODUCTION**

Several reports from countries with relatively high prevalence of hepatitis C virus (HCV) infection have documented a significant epidemiological association between HCV infection and development of B-cell non Hodgkin’s lymphoma[1-4]. A direct role of the virus in lymphomagenesis is primarily suggested by the prominent curative potential of antiviral therapy on HCV-related B-cell proliferation or low-grade B-cell lymphomas[5-8]. Such an effect implies a specific role for the virus in maintaining B-cell proliferation, although the exact mechanism remains unknown[9,10].

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype in the western countries and is characterized by aggressive clinical behavior. Despite its pathological heterogeneity[11], it is commonly managed with the combination of chimeric monoclonal antibody against the protein CD20 (rituximab) and polichemotherapy (immuno-chemotherapy) in the front-line setting. The available literature regarding the pathobiology and management of patients with DLBCL in the setting of HCV is quite limited compared to low-grade B-cell lymphomas. Indeed, several recent retrospective studies[12-18] have reported that patients with HCV related DLBCL have peculiar characteristics compared to their HCV-negative counterparts, suggesting a possible influence of the virus since the very early steps of lymphomagenesis. HCV-positive patients are usually older, have more frequent spleen/liver or extranodal involvement and elevated lactate dehydrogenase. However, epidemiological data are among the strongest argument in favor of a role of the viral infection in the development of DLBCL. Due to the lack of prospective studies, tolerance to chemoinmunotherapy and outcome of HCV-positive patients with DLBCL are controversial. Several issues like clinical management of patients with transaminases elevation, criteria for discontinuing or starting immuno-chemotherapy in the event of escalation in HCV replication in an asymptomatic patient, as well as the exact role of monoclonal antibodies, remain unclear.

**Epidemiology**

Over the past two decades considerable evidence has accumulated on the association between HCV and hematologic malignancies, most notably B-cell pre-malignant and malignant proliferations. Early results[19] reported a strong association of HCV with lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia that were possibly related to the association existing between HCV-infected patients and type II mixed cryoglobulinemia[20], which may sometimes represent a pre-malignant disorder. Later on, a strong association emerged also in regard to marginal zone lymphomas and DLBCL[21]. Epidemiological works demonstrated that the relative risk of lymphoma was significantly higher in geographical areas with high rather than with low HCV prevalence. In fact, several studies[22-24] from countries with low HCV prevalence did not observe such association, although relying on small numbers of patients. A recent larger report from Sweden[25] where the HCV prevalence among healthy population is low, reported an increased risk of lymphoma occurrence among HCV infected patients also in this northern country. Another large-base survey on 4784 adult cases of non-Hodgkin’s lymphoma and 6269 age- and sex-matched controls from an International Lymphoma Epidemiology Consortium including centers from Spain, North America and Australia[21] reported a significantly increased risk in HCV infected patients for development of marginal zone lymphoma (OR = 2.47; 95% CI: 1.44-4.23), DLBCL (OR = 2.24; 95% CI: 1.68-2.99), and lymphoplasmacytic lymphoma (OR = 2.57; 95% CI: 1.14-5.79). An Italian case-control study[26] reported an even higher association of HCV infection with DLBCL (OR = 3.5) with respect to indolent/low-grade B-cell lymphomas (OR = 2.3), suggesting that approximately 1 out of 20 cases of incidental DLBCL in Italy may be attributable to HCV. Interestingly, development of DLBCL in these patients was not reported to be preceded by cryoglobulinemia or indolent lymphomas, which pointed to the association of HCV with de-novo DLBCL not transformed from a previous low-grade entity.

Overall, partly due to the worldwide distribution of HCV infection, the association of HCV infection with lymphomas appears more relevant in Southern Europe, Turkey, Egypt, other Mediterranean countries[26], Taiwan[27-30] and Japan[31]. Its role in Northern America[21] seems to be emergent, while other countries like England and Scotland[32, India[33], France[24] or Thailand[23] have reported much lower incidence and impact of this association in the clinical practice. Large scale studies including higher numbers of patients are warranted from regions with low HCV prevalence before driving conclusions on the association between virus and lymphomas in these areas.

**Pathogenesis**

Some important arguments in the literature describe a possible pathogenetic role of HCV infection in the development of aggressive B-cell lymphomas. Cumulative evidence have suggested an HCV-related antigen driven process in lymphoma development, similarly to what ob-
served with Helicobacter pylori and lymphoid proliferation in mucosa-associated lymphoid tissue. However, even if recent progress in better understanding HCV-related lymphoproliferations has been made, the precise relationship between HCV and lymphoma development remains to be clarified.

Some recent observations are in favor of an active role of the virus in lymphomagenesis. HCV transgenic mice expressing the full HCV genome in B-cells have been shown to develop DLBCL in 25% of cases. Moreover, HCV has been shown to protect human B lymphocytes from Fas-mediated apoptosis via E2-CD81 engagement, even in the absence of viral entrance into the human B-cell. Finally, the viral core and NS3 proteins were responsible for the inhibition of DNA repair, mediated by nitric oxide and reactive oxygen species in another study. Stable expression of core protein induced frequent chromosome translocations in cultured cells and in transgenic mice, describing an HCV mediated inhibition of DNA damage-repair and enhancement of chromosomal breaks. It must be noted that B-cell associated virus can readily infect hepatoma cells, harboring an enhanced infectivity compared to extracellular virus. According to this theory, the virus can modify the normal tropism of B-cells, escape natural immunity and survive in the infected liver.

Based on these and others experiments, several hypothetical models of B-cell transformation by HCV have been formulated. A direct transformation model, where HCV would directly infect B cells, possibly through CD81-E2 interaction, expressing its oncogenic potential through cellular nitric oxide-synthase and NS3/4 mediated mutations of proliferation genes. On the other, an indirect transformation model would rely on the interaction between E2 and CD81 on the cell surface, which would induce expression of activation-induced deaminase and somatic hypermutation of immunoglobulin genes and potential proto-oncogenes, inducing a sustained B cell stimulation. Finally, the so called “hit and run” theory, which relies on virus-induced genetic damage of B-cells caused by a transiently intracellular virus [e.g., mutation of tumor suppressor genes (p53, BCL-6, beta-catenin)]. All theories may imply a role for microRNA dysregulation, since recently a key role of miR-26b downregulation has been suggested in undermining tumor suppression.

In addition to its being hepatotrophic, HCV is also a lymphotropic virus that is able to infect and replicate within peripheral blood mononuclear cells, as witnessed by its association with mixed cryoglobulinemia type II, which is characterized by clonal expansion of B cells. An increased expression of the BCL2 oncogene, mediated by a high prevalence of t(14;18) translocation has been detected in peripheral blood mononuclear cells of HCV infected patients by polymerase chain reaction. Furthermore, the disappearance of the t(14;18) translocation following antiviral treatment was strongly associated with virologic response. Altogether, these findings again suggest a possible pathogenetic link between HCV and aggressive lymphomas, which are known to be characterized by BCL2 translocation in around 20% of de-novo DLBCL.

Lymphomas that develop in HCV-infected patients seem to combine disease-specific signatures and different sets of genes whose expression is associated with B-cell receptor activation and specific nuclear factor kappa-light-chain-enhancer of activated B cells transcription factors, including BCL2 translocations. Identification of molecular signatures in lymphomas occurring in the HCV-infected population could facilitate a more rational approach to the diagnosis as well as more tailored treatments, also in DLBCL.

CLINICAL MANAGEMENT AND TOLERANCE TO TREATMENT

In the management of HCV-associated DLBCL, anthracycline-based chemotherapy [usually cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone (CHOP)] associated with rituximab (immuno-chemotherapy) is the standard of care. Differently from indolent B-cell lymphomas, antiviral treatment yet does not play a significant role in HCV-positive DLBCL.

Since the treatment of DLBCL is usually based on rapidly active drugs due to the aggressive clinical behavior of the disease, antiviral regimens have not been tested so far on large series, especially due to their slow effect on lymphoid proliferation, if any. Nevertheless, few anecdotal reports that show successful antiviral treatment in patients with DLBCL or mantle cell lymphoma suggest that these lymphomas might also be sensitive to a drop in the viral load, as is the case of low-grade lymphomas. Sequential immune-chemotherapy followed by antiviral therapy has been claimed in two preliminary reports with promising results, but more mature and prospective data are eagerly awaited.

Due to the lack of prospective studies, tolerance to chemo-immunotherapy and outcome of HCV-positive patients with DLBCL are controversial. Moreover, the literature existing on HCV-positive DLBCL is unbalanced on the side of hematologists, with scanty detailed reports on the hepatic side. It has been reported that the addition of rituximab in the R-CHOP regimen may add hepatotoxicity, favor HCV reactivation or acceleration of viral liver inflammation. In a benign disorder like HCV-associated mixed cryoglobulinemia, rituximab therapy have demonstrated an excellent safety and tolerability profile, including lack of viral or hepatic flares. Patients with aggressive B-cell lymphoma that undergo anthracycline-based chemotherapy coupled with rituximab (R-CHOP) usually have good tolerance to the combination of drugs, but a less beneficial safety profile than rituximab monotherapy in benign diseases. Most frequent complications are represented by hepatic flares. Immunochemotherapy can enhance viral replication, especially in the presence of hepatitis B virus (HBV) or human immunodeficiency virus co-infections or when older or particularly immunocompromised
Speculative illustration of expected hepatitis C virus (HCV)-RNA load and transaminase flare during and after rituximab cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone (R-CHOP) immunochemotherapy for a diffuse large B-cell lymphoma ideal patient (not cirrhotic, no other risk factors) experiencing transient toxicity. Curves and histograms reflect the average behavior of patients reported so far in the literature. 

Patients are treated\[55\]. Indeed, hepatic complications of grade 3 or more (according to the Common Terminology Criteria for Adverse Events v4.0) are quite unusual, but symptomatic liver dysfunction, elevation of aspartate aminotransferase/alanine aminotransferase levels, fibrosis, decompensated cirrhosis, and reactivation of chronic hepatitis may occur\[31\]. One study reported poor tolerance to intensive chemotherapy including autologous stem cell transplant\[16\], but most studies have described acceptable liver toxicity\[14,15,17,18\]. Whether rituximab causes an additive negative effect on hepatotoxicity is still a matter of debate as only few systematic comparative data exist\[60\]. After CHOP without rituximab hepatitis flares have been described in some cases, occurring 2 to 3 wk after the end of the cycle, grade 3-4 liver toxicity was in the range of 10% to 28%, and fatal complications were rare. It must be noted that prednisone therapy alone can increase HCV-RNA levels in chronic hepatitis patients (but decrease transaminase levels). With the addition of rituximab, hepatitis flares have been described in 26% to 33%, being significantly more frequent than in control series of patients with HCV-negative DLBCL (2%-3%)\[14,15,17,18\]. In all studies major toxicities were rare. Treatment discontinuation due to liver function impairment has been described in 0% to 11% of patients, while death due to liver failure in 0% to 5%\[57,59,60\]. Severe hepatotoxicity was observed in 14% of patients in a recent large Italian multicenter survey\[60\]. The use of rituximab was not associated with increased rate of hepatotoxicity (P = 0.5) compared to patients receiving chemotherapy only or localized approaches. Furthermore, severe hepatic toxicity was not associated with poor progression-free survival or overall survival in patients who were HCV-positive\[60\]. Clinical and serological behaviour of HCV viral load and transaminase level after an ideal immunochemotherapy with 6 courses of R-CHOP, based on available literature, in a patient without known risk factors, is summarized in Figure 1. Median time from start of treatment to development of severe hepatic failure is expected around the 100th day, but the range is wide, with cases reported since the first 10 d after R-CHOP up to 320 d after. Importantly, no relation was described between pre-treatment HCV-RNA levels and hepatic toxicity afterwards, with two patients that developed severe hepatic toxicity but had low HCV-RNA levels before treatment. This finding was substantiated by other studies\[57,59,60\]. However, patients presenting with cirrhosis or compromised liver function usually experience earlier toxicity. HCV-RNA levels dramatically falls at the time of increase of the transaminases, suggesting that the cause of liver damage is an immune reaction against hepatocytes, again supporting the notion that HCV viral load is not necessarily directly associated with liver damage\[60\]. B-cell recovery is also implied, with progressive restoration of immune homeostasis that seems to contribute to liver function recovery\[61\].

Despite the lack of productive infection (no replication of the virus inside B-cells), it has been demonstrated that B cells lysed by effector blood cells could release up to four times more infectious virus following rituximab treatment. These data support a role for rituximab lysis of B cells and release of infectious HCV\[60\]. Hepatitis C viremia was shown to increase to approximately twice the baseline level in the responders after rituximab monotherapy, whereas it remained much the same in the non-responders\[60\]. Viral genotype might also condition chemotherapy induced hepatotoxicity\[61,64\].

A recent report described two patients with DLBCL and HCV-related liver cirrhosis experiencing grade > 3 increase in transaminases and ascites while being treated with R-CHOP. Treatment with ribavirin 1000 mg/d was started. Both patients had a rapid decrease in alanine aminotransferase levels and disappearance of the ascitic fluid, suggesting a possible benefit of treating HCV infection when patients experience hepatic flare, also in the course of chemotherapy\[61\].

In conclusion, we suggest to monitor transaminase levels at least twice during the induction cycle, and then once every first day of each R-CHOP cycle in patients with standard risk HCV-positive DLBCL. RNA viral load should be measured at screening and then re-evaluated only in case of transaminase alterations, to rule out different causes of hepatic toxicity. When sudden transaminase increase occurs, subsequent cycles should be postponed before deciding to definitively stop treatment. More frequent controls of transaminase levels and eventually of RNA levels should be reserved to patients with baseline elevated transaminases or with underlying hepatic complications of HCV infection (including cirrhosis, concomitant HBV infection and hepatocarcinoma)\[51,57,66,67\].

Figure 1 Speculative illustration. Speculative illustration of expected hepatitis C virus (HCV)-RNA load and transaminase flare during and after rituximab cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone (R-CHOP) immunochemotherapy for a diffuse large B-cell lymphoma ideal patient (not cirrhotic, no other risk factors) experiencing transient toxicity. Curves and histograms reflect the average behavior of patients reported so far in the literature.
Table 1 Clinical outcome of hepatitis C virus-positive diffuse large B-cell lymphoma patients according to retrospective studies

| Ref.            | DBLCL-HCV positive patients (n) | Treatment                          | PFS/EFS (3 yr) | OS (3 yr) |
|-----------------|---------------------------------|-----------------------------------|----------------|-----------|
| Besson et al.   | 26                              | Intensive protocols               | 53%            | 56%       |
| Visco et al.    | 156                             | CHOP and CHOP-like/R-CHOP         | 60%            | 80%       |
| Park et al.     | 32                              | CHOP(18)/R-CHOP(11)               | 54.7% at 5 yr  | 59.2% at 5 yr |
| Tomita et al.   | 25                              | CHOP/CHOP-like                    | NA             | 46%       |
| Ennishi et al.  | 131                             | R-CHOP                            | 69%            | 75%       |
| Merli et al.    | 535                             | CHOP(214)/+R-CHOP (252)           | 53%            | 68%       |

(58% for R-CHOP) vs (71% for CHOP)

DLBCL: Diffuse large B-cell lymphoma; CHOP: Cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone; PFS/EFS: Progression-free survival/event-free survival; OS: Overall survival; HCV: Hepatitis C virus.

CLINICAL PRESENTATION AND OUTCOME

In some recent retrospective studies, patients with HCV related DLBCL have been described to be usually older, to have more frequent extranodal involvement (especially spleen and liver) and elevated lactate dehydrogenase (LDH) compared to their HCV-negative counterparts. Results regarding the prevalence of transformed DLBCL as compared with de-novo-DLBCL are contradictory. These results suffer of the retrospective selection of patients as well as of the absence of pathology review in largest published series.

Primary hepatic and primary splenic DLBCL are rare entities that have been reported to display an association with HCV infection, with outcomes that were quite favorable. Persistent human hepatitis virus infections, especially HCV, have been also claimed to play an important role in the tumorigenesis of splenic DLBCL in Japan.

The outcome of HCV-positive DLBCL has been shown to be not inferior to that of their HCV-negative counterpart once patients are adequately treated. However, this issue is still a matter of debate. As previously mentioned, HCV-positive DBLCL patients display specific presentation potentially affecting clinical features included in prognostic scores (i.e., age, number of extranodal sites, stage). Furthermore, LDH, which is a mainstay of the international prognostic index (IPI), is potentially biased in HCV-positive patients, as it is influenced not only by lymphoma but also by chronic HCV infection. Notably, the IPI was built and validated in series comprising only HCV-negative patients or with unknown HCV-status, while their predictive significance has never been formally validated in HCV-positive DLBCL.

The Fondazione Italiana Linfomi has recently carried out a large multicenter retrospective study with the aim of constructing a new prognostic system for HCV-associated DLBCL describing an “HCV Prognostic Score” based on performance status, albumin level and HCV-RNA viral load, which appeared extremely reliable. Concomitant HBV infection or HBV related hepatocarcinoma has been reported to confer an extremely negative influence on outcome of these patients.

Few studies evaluated the clinical outcome of HCV-positive DLBCL. In the pre-rituximab era, Besson et al. reported a worse overall survival (OS) in HCV-positive DLBCL patients treated with intense chemotherapy protocols. On the contrary, the study by Ennishi et al. on 131 HCV-positive patients treated with R-CHOP reported a similar outcome in HCV-positive patients compared to HCV-negative (3-year OS 75% vs 84%, P = 0.07). The outcome of patients treated with R-CHOP in the study by Merli et al. (3-year OS 71%) was similar to the latter study reflecting expected figures for a similarly treated DLBCL population of similar age with no HCV infection (i.e., RICOVER-60 study, 3-year OS 72%). Neither HCV infection itself nor the development of severe hepatic toxicity was correlated with survival, suggesting that HCV positive patients derive a similar antilymphoma benefit from the addition of rituximab.

CONCLUSION

Patients with HCV-positive DLBCL should be managed involving different specialists, with the hematologist and the hepatologist both involved from the beginning in the treatment program. Initial evaluation of the liver status and of comorbidities is essential to establish if the patient is candidate to curative approaches including chemotherapy and monoclonal antibodies. Liver biopsy is not mandatory in all cases in our opinion, but its indication should be carefully evaluated with the hepatologist in case a cirrhosis is suspected. Presentations with concomitant HBV infection or liver cirrhosis represent two common clinical issues. Such patients need to be informed before starting chemotherapy that they will have a significantly higher risk of viral reactivation, and serial controls of their liver function are mandatory since the very first weeks of cytotoxic treatment. Unless contraindicated by the hepatologist due to older age or particular comorbidities, we believe that antiviral treatment should be strongly considered after the end of immuno-chemotherapy, when a remission of the lymphoma has been achieved. This might also enhance duration of remission, although still to be demonstrated. Although some favorable reports exist, antiviral therapy should not be routinely associated to chemotherapy outside clinical trials, but eventually administered in the form of ribavirin when symptomatic flares occur.
In conclusion, treatment of HCV associated DLBCL should be performed in an interdisciplinary approach with hematologists and hematologists working hand in hand with close monitoring of liver function. This should ensure a standard curative approach to most HCV-positive DLBCL, not depriving them from the chance of being cured, since severe hepatic complications in patients with no other risk factors are rare.

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