Review Article

Hepatitis C Associated B-cell Non-Hodgkin Lymphoma: Clinical Features and the Role of Antiviral Therapy

Syed Tasleem[1] and Gagan K Sood*[1,2]

[1]Department of Surgery, St. Luke's Center for Liver Disease, Baylor College of Medicine, Houston, Texas, USA; [2]Department of Gastroenterology and Hepatology, Baylor College of Medicine, Houston, Texas, USA

Abstract

The link between chronic hepatitis C virus (HCV) infection and a subset of B-cell non-Hodgkin lymphomas (B-NHL) is strongly supported by epidemiological studies. Evidence demonstrating complete regression of lymphoma after antiviral treatments suggests possible chronic antigenic stimulation for the origin of B-NHL and provides evidence for a virus-mediated lymphomagenesis. B-NHL is a heterogeneous group of lymphomas with varied clinical presentation and may be indolent or aggressive. The optimal management of HCV related B-NHL is not clear. Antiviral treatment may be sufficient for low-grade lymphomas, but chemotherapy is necessary in patients with high grade lymphomas. Interferon (IFN)-based antiviral treatment regimens for HCV infection are limited by poor tolerance and suboptimal antiviral response. Recently approved novel direct acting antiviral (DAA) drugs are highly effective and safe. This has opened a new era for the treatment of HCV related B-NHL alone or in conjunction with chemotherapy. Treatment of HCV associated B-NHL should be performed in an interdisciplinary approach in close consultation with hematologist and hepatologist. In this review, we summarize data regarding clinical features and epidemiology of B-NHL and discuss novel therapeutic approaches, including DAAs, that may prove to be effective in the treatment of HCV associated lymphomas.

Introduction

Chronic hepatitis C is a worldwide problem affecting nearly 180 million people. Hepatitis C virus (HCV) infection leads to chronic hepatitis and is a major cause of liver cirrhosis and hepatocellular carcinoma.[1] HCV is also a lymphotropic virus that triggers B-cells and promotes favorable conditions for B lymphocyte proliferation. As a consequence, several lymphoproliferative disorders have been associated with the virus, including mixed cryoglobulinemia (MC) and B-cell non-Hodgkin lymphoma (B-NHL).[2,3] Recently, many experimental studies have increased our understanding of the molecular mechanisms of HCV-mediated B-cell proliferation and transformation to NHL.[4] HCV eradication with antiviral therapy (AVT) achieves complete regression of a subset of indolent lymphomas.[5] Immune-chemotherapy followed by AVT is the mainstay of treatment for aggressive lymphomas. Recently approved direct acting antiviral (DAA) agents have significantly changed the treatment of HCV infection.[6] This raises the hope that high sustained virologic response (SVR) rates achieved with these DAAs will significantly improve the outcome of HCV associated B-NHL.

HCV infection, mixed cryoglobulinemia (MC), and B-NHL

The initial finding that lead to extensive investigation of association between HCV and B-NHL was high prevalence of HCV infection in patients with type II MC.[7] Type II MC is characterized by a combination of monoclonal and polyclonal immunoglobulins, with monoclonal component directed against immunoglobulin G (IgG). The production of IgG is sustained by the clonal expansion of B-cells. Overt symptoms of cryoglobulinemic vasculitis develop in only approximately 5% of chronic HCV infection cases, but circulating mixed cryoglobulin complexes are much more common and detected in 40–50% of chronic HCV-infected patients.[8] Although clinically benign, MC is a lymphoproliferative disorder that predisposes patients to B-NHL in about 5–10% of cases.[9] The overall risk of NHL in patients with MC is about 35 times higher than that in the general population.[10] The risk of lymphoma decreases after viral eradication with AVT. In one recent study, clearance of HCV RNA was achieved in nearly 50% of patients with MC. HCV RNA clearance led to persistent resolution or improvement of symptoms related to MC. No case of lymphoma was observed during a long follow-up period, ranging from 35–124 months.[11] Since HCV infects about 180 million individuals worldwide; the number of patients at risk for MC and its complications is substantial. HCV-MC patients are at higher risk for developing B-NHL and should be considered for AVT even at an early stage of liver disease.

Epidemiology

Several epidemiological studies have been performed in the last 20 years to investigate the link between HCV and B-NHL. Early studies based on relatively low case numbers revealed a high risk of B-NHL in HCV positive patients, especially from geographical regions with high HCV infection prevalence;[12] while studies from areas with low prevalence did not show any significant association.[13]

The link between HCV and B-NHL has been strengthened by large epidemiological studies and meta-analyses published in recent years. Gisbert *et al*. performed a systematic review of studies evaluating the prevalence of HCV infection in B-NHL.[14] In total, 48 studies (5,542 patients) were identified. Mean HCV infection prevalence in this study was 13%. In 10 case-control studies in which the control group was comprised of healthy donors, HCV prevalence in B-NHL was 17% compared to 1.5% in healthy controls (odds ratio (OR)=10.8). Therefore, it was concluded that HCV prevalence in patients with B-NHL is higher than the general population, suggesting a role for HCV in the etiology of B-NHL. Subsequently, in 2006, a meta-analysis of 15 case-control studies on the association between HCV infection and NHL demonstrated a pooled relative risk of lymphoma of 2.5 (95% confidence interval (CI), 2.1–3.1) among HCV-positive subjects.[15]

The International Lymphoma Epidemiology Consortium (InterLymph) study reported pooled results of HCV related B-NHL from a large international multicenter data source. The study included 11,053 participants, 4,784 cases, and 6,269 controls from seven case-control studies conducted in the United States, Europe, and Australia with information on HCV infection. HCV infection was detected in 172 NHL cases (3.6%) and in 169 (2.7%) controls (OR=1.8; CI, 1.4–2.3).[16]

Overall, large epidemiologic studies and meta-analyses have shown that HCV infection is an important factor in the development of certain types of B-NHL.[12,14,15,17,18] Local HCV prevalence and genetic and environmental factors may be responsible for the geographically diverging results.

Common features of HCV related B-NHL are long duration of infection (15 years) and frequent involvement of extranodal sites. The B-NHL subtypes associated with HCV vary between different studies. The B-NHL subtype commonly reported in European and Japanese studies were marginal zone lymphoma (MZL), particularly splenic zone lymphoma (SMZL), lymphoplasmacytic lymphoma (LPL), and diffuse large B-cell lymphoma (DLBCL).[14,19] In contrast, a recent study from the United States reported that the most common HCV related B-NHLs was DLBCL (62%), followed by follicular lymphoma (13%) and MZL (11%).[20]

NHL subtypes associated with HCV

Chronic HCV infection has been associated with both B-cell indolent lymphomas, especially MZL, and aggressive lymphomas, mainly DLBCL. Indolent lymphomas are defined clinically as minimally symptomatic lymphomas that grow and spread slowly. According to the World Health Organization (WHO) classification system, HCV associated lymphomas include the following histologic subtypes:

(a) Marginal zone lymphoma (MZL)

Marginal zone lymphomas (MZL) is the most common HCV associated B-NHL subtype and accounts for approximately 12% of all B-cell lymphomas.[21,22] It has a very indolent course and is often diagnosed among patients 65 years and or older patients.

MZL is categorized into three different sub-types: (i) Extranodal MZLmarginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type; (ii) Nodal marginal zone lymphoma (NMZL); and (iii) Splenic marginal zone lymphoma (SMZL).[23]

MALT lymphoma is the most frequent type of MZL, responsible for 8% of all NHL. Gastric MALT and nongastric MALT are two subtypes of MALT lymphomas. There is a well-established link between *Helicobacter pylori* (*H. pylori*) infection and gastric MALT lymphoma. HCV infection has also been associated with gastric MALT lymphoma,[24] but HCV infection was more often associated with nongastric lymphoma.[25] An Italian study showed HCV infection in 60 of 172 (35%) patients with nongastric MALT lymphoma.[21] The most frequent nongastric sites of MALT lymphoma were the skin (35%), salivary glands (25%), and orbit (15%).[21] Other studies have also found a link between HCV infection and salivary gland, orbit, and skin MALT lymphoma.[4,26,27] HCV-positive nongastric MALT lymphomas have an indolent course similar to HCV-negative patients.[26]

The second type of MZL is Nodal Marginal cell Lymohoma (NMZL) also called monocytoid B-cell lymphoma. NMZL is characterized by exclusive primary lymph node localization in absence of prior or concurrent extranodal site involvement. Primary NMZL is a rare disease, accounting for nearly 2% of lymphoid neoplasms, and is frequently associated with HCV infections.[26,28,29] In a large series of NMZL reported from Italy, HCV serology was positive in 9 out of 38 patients (24%).[21]

The third type of MZL is splenic marginal zone lymphoma (SMZL). It is a rare indolent lymphoma subtype, which accounts for less than 2% of all NHL. The clinical course is indolent, but symptomatic splenomegaly is the presenting feature in some patients. In a large series of splenic MZL, HCV serology was positive in 49 out of 255 available patients (19%).[30] Among 56 patients tested for HCV-RNA, 25 (45%) were positive. Cryoglobulins were detected in 13 out of 130 patients tested (10%). SMZL was reported to be associated with MC; few studies reported detectable type-II MC in all patients with SMZL.[31] This observation suggested that HCV associated SMZL with MC may be a separate clinical entity.

(b) Lymphoplasmacytic lymphoma (LPL)

LPL is a rare type of HCV related B-cell NHL. It is composed of a mixture of malignant clonal lymphocytes, plasmacytoid lymphocytes, and plasma cells. It usually involves bone marrow and sometimes the lymph node and spleen. In some patients, LPL is associated with Waldenström's macroglobulinemia (WM).[32] Patients typically present at an advanced age, and substantial proportions are asymptomatic at diagnosis.

(c) Diffuse large B-cell lymphoma (DLBCL)

In Western countries, DLBCL is the most common lymphoma subtype associated with HCV infection.[33] DLBCL frequently develops from low-grade lymphomas. In the ANRS HC-13 lympho-C study, 16/45 (36%) were transformed from underlying indolent lymphomas, mainly MZL.[34] The clinical

presentation of HCV-associated DLBCL has been consistently reported to differ from HCV negative lymphoma.[27,35] DLBCL is characterized by aggressive clinical behavior, and HCV related DLBCL has peculiar characteristics. HCV-positive DLBCL patients are usually older and are more likely to have spleen/liver or extranodal involvement and elevated lactate dehydrogenase.[35,36]

Pathogenesis

HCV is a positive, single-strand RNA virus without a DNA intermediate in its replicative cycle; and integration of HCV nucleic-acid sequences into the host genome seems unlikely.[2] Therefore, HCV is not considered an oncogenic virus. It has been suggested that HCV infection exerts a chronic antigenic stimulus on the immune system, very similar to *H. pylori* in gastric MALT lymphoma.

According to a multistep theory of lymphomagenesis, the first step in antigenic stimulation is replication of HCV, which leads to proliferation of B-lymphocytes and subsequent development of MC. This causes generation of low grade NHL, and this occurs in some patients as a second step. The pathologic process can be reversed at this stage with eradication of the virus. In the final step, due to subsequent accumulation of additional mutations and genetic alterations, antigen dependency is lost and viral elimination by itself is insufficient for the treatment of HCV associated high grade NHL.[33,37] Biological processes and molecular mechanisms involved in development of NHL have been investigated[4,38] but are beyond the scope of this review.

Antiviral therapy for HCV associated B-NHL

AVT is effective in low-grade lymphomas. Numerous studies have reported regression of lymphoma after AVT, but these studies were limited by their retrospective design, small number of patients, and variable AVT protocols.[39–45] Early studies used IFN-α, but later studies used pegylated IFN with and without ribavirin. These studies are summarized in Table 1; studies containing single case reports or a small number of patients were excluded.[5,27,39–42,44,46]

Recently, Arcaini *et al.* reported updated results from the Italian lymphoma consortium.[5] They followed 704 HCV positive patients with indolent B-NHL between 1993 and 2009 at 39 centers. Among these, 100 patients received as the first line of treatment AVT with either IFN-α or pegylated IFN alone or with ribavirin. Virological and hematological remission was achieved in a large number of patients. HCV RNA clearance was achieved in 80% patients, 44% patients achieved complete remission, and 33% achieved partial remission of B-NHL.[5] The use of AVT at any time during the life of these patients seemed to be associated with improved outcome and, based on this, investigators recommended that AVT must be considered as a first line approach for patients with indolent lymphoma. The high rate of HCV clearance achieved in this study was probably related to a preponderance of HCV genotype 2 infection (55%), which is more responsive to AVT.

Michot *et al.* reported the effect of AVT on HCV associated B-NHL in a multicenter ANRS HC-13 Lympho-C study. This French study enrolled 116 HCV-positive patients with B-NHL between 2006 and 2012. Fourteen patients with MZL were given AVT only as first line of therapy. Of those, 11 achieved SVR and hematological remission. Nonresponders to AVT

Table 1. Studies of antiviral treatment in patients with HCV-associated lymphoma

	N° Pts*	Antiviral treatment	Diagnosis	Virologic response	NHL response
Hermine *et al.*, 2002[39]	9	IFNα	SLVL	7	7 CR
Kelaidi *et al.*, 2004[41]	8	IFNα + RBV	SMZL (*n*=4), MZL/MALT (*n*=4)	5 SVR, 2 NSVR	5 CR
Tursi *et al.*, 2002[42]	16	IFNα + RBV	MZL/MALT	11	16 CR
Saadoun *et al.*, 2005[43]	18	IFNα IFNα + RBV	SLVL	14 CR, 4 NSVR	14 CR, 4 PR
Mazzaro *et al.*, 2009[44]	18	IFNα + RBV PegIFNα + RBV	SLVL (*n*=1), FL (*n*=1), LPL (*n*=16)	3 SVR, 4 NR, 1 NSVR 6 SVR, 2 NR, 2 NSVR	3 CR, 2 PR 6 CR, 2 PR
Pellicelli *et al.*, 2011[45]	9	PegIFNα + RBV	SMZL (*n*=3), MZL (*n*=4), FL (*n*=2)	7 SVR, 2 NSVR	5 CR, 2 PR
Vallisa *et al.*, 2005[40]	13	PegIFNα + RBV	SMZL (*n*=4), MZL/MALT (*n*=4), FL (*n*=1), LPL (*n*=4)	7 SVR, 1 NSVR	7 CR, 2 PR
Arcaini *et al.*, 2014[5]	100	IFNα + RBV PegIFNα + RBV	SMZL (*n*=36), MZL/MALT (*n*=29), FL (*n*=12), LPL (*n*=10)	80 SVR	44 CR, 33 PR
Michot, JM *et al.*, 2015[67]	116	IFNα + RBV PegIFNα + RBV	MZL (*n*=45) (AVT only first line *N*=14)	11 SVR, 3 NSVR	8 CR, 3 PR

MALT, mucosa associated lymphoid tissue; MZL, marginal zone lymphoma; SMZL, splenic marginal zone lymphoma; AVT, antiviral therapy; IFN, interferon; CR, complete response; PR, partial response; SVR, sustained virologic response; NSVR, nonsustained virologic response; n.a, not available.

were treated with a combination of AVT and rituximab.[46] Patients who received AVT at the time of diagnosis of NHL or during follow-up had significantly better overall survival.

Recently, DAA has significantly increased the SVR in patients with chronic HCV.[6,47] A few highly encouraging reports demonstrated lymphoma regression after HCV clearance with DAAs. Rossotti *et al.* reported a rapid virologic and hematologic response with an all-oral, IFN-free regimen, based on the combination of a NS3/NS4A inhibitor (faldaprevir) and a non-nucleoside NS5B inhibitor (deleobuvir) in a patient with HCV associated SMZL. The viral load decreased to undetectable levels within 4 weeks of treatment, and hematologic response was achieved within 8 weeks.[48] This is a typical feature in the DAA era, where virologic response is significantly enhanced compared to the classic IFN- and ribavirin-based treatment.[6,49] In another report, Sultanik *et al.* showed complete regression of MZL after 12 weeks of therapy with sofosbuvir and ribavirin.[50]

A regimen including DAAs may be considered when treating HCV-related extra-hepatic disease. Until 2011, the combination of pegylated IFN-α and ribavirin for 24 or 48 weeks was the approved treatment for chronic hepatitis C. With this regimen, patients infected with HCV genotype 1 had SVR rates of approximately 40% in North America and 50% in Western Europe. Higher SVR rates were achieved in patients infected with HCV genotypes 2 and 3. In 2011, telaprevir and boceprevir were licensed for use in HCV genotype 1 infection. These two drugs were first-wave, first-generation DAAs. However, the side effect profiles of these triple combination therapies were not favorable and are no longer used in patients infected with HCV.[51] Currently, in addition to pegylated IFN-α and ribavirin, three new HCV DAAs are available in Europe and the United States for use as part of combination therapies for HCV infection. Sofosbuvir (nucleotide analogue inhibitor of HCV RNA-dependent RNA polymerase), ledispavir, and daclatasvir (NS5A inhibitors) have been approved in Europe.[6,47] In the United States sofosbuvir alone or in combination with ledispavir is available. In addition, high SVR rates have been achieved by combining paritaprevir with ritonavir, ombitasvir, and dasabuvir. These combinations of DAA are highly effective, safe, well-tolerated, and with limited drug interactions.[52–57] In patients with HCV related indolent B-NHL, the first line of therapy may be offered, using combination of these highly active antiviral agents. These regimens, however, need to be studied in clinical trials, for determination of optimal dose and duration for treatment of HCV associated B-NHL.

Management of DLBCL associated with HCV

For the management of HCV-associated DLBCL, anthracycline-based chemotherapy [cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone (CHOP)] combined with rituximab is the standard of care. AVT to eradicate HCV is the logical step after successful chemotherapy. The use of sequential immunochemotherapy followed by AVT has promising results in some studies.[58,59] La Mura *et al.* reported improved disease free survival (DFS) and clinical outcome with AVT after immunochemotherapy.[60] In a French multicenter ANRS Lympho-C study, most DLBCL patients received front-line immunochemotherapy with a standard anthracycline regimen (R-CHOP). Seventeen of 45 (38%) with DLBCL also received antiviral treatment. Patients who received AVT at the time of diagnosis of NHL or during follow-up had significantly

better OS (*p*=0.029) and PFS (*p*=0.049) than those who did not receive antiviral treatment.[34]

The addition of rituximab to chemotherapy is considered the greatest advance in the treatment of B-NHL. Addition of rituximab enhances viral replication, but the probability of severe hepatic complications remain variable in different studies.[5,61–63] Ennishi *et al.* reported hepatotoxicity was more likely to occur if pretreatment aminotransferase levels were high.[64] Besson *et al.* reported hepatotoxicity increased with each cycle of chemotherapy and proposed that this may be related to increased viral replication or immune reactivation after stopping chemotherapy.[61] A recent study from Egypt reported 53/200 (26%) patients with HCV-B-NHL on rituximab experienced significant hepatotoxicity compared to those on rituximab free regimens, 11/80 (14%). There was no information about HCV RNA replication in this study.[65] Zaki *et al.* reported severe hepatotoxicity (aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >5 upper limit of normal (ULN)) in 28% and vs. 14% of patients treated with R-CHOP and compared to rituximab free regimen, respectively.[66] Hepatic toxicity led to the modification and the discontinuation of immune-chemotherapy in nearly 25% of patients, resulting in progression of lymphoma. They also demonstrated increased HCV RNA replication during chemotherapy.[66] In another study, Arcaini *et al.* also reported significant hepatotoxicity in HCV-positive DLBCL treated by rituximab but found no correlation with HCV RNA levels.[5] Monitoring of serum HCV-RNA levels and transaminases may be helpful to understand the cause of liver dysfunction in patients receiving chemotherapy. Several issues, like clinical management of patients with advanced liver disease or baseline transaminases elevation, and risk of HCV replication during immunotherapy, remain unclear. Further studies will be necessary to investigate fully the relationship between changes in HCV viral load and liver function during chemotherapy in order to prevent unnecessary dose modifications or stopping chemotherapy due to hepatotoxicity.

In earlier studies, antiviral prophylaxis was not protective against HCV replication in patients receiving chemotherapy. However, these prior studies used IFN-based regimens, which were less efficacious and had higher hematological side effects. With the availability of the new potent DAAs sofosobuvir, ledispavir, and daclatasvir, new approaches for HCV eradication, before or concomitant with chemotherapy, should be evaluated in controlled clinical trials. Newer antiviral agents are well-tolerated with very high efficacy, have a strong safety profile,[6,54] and may be used in conjunction with chemotherapeutic agents. HCV eradication also reduces the risk of lymphoma relapse. In one study, none of the patients with eradicated HCV infection had relapse, while one-third of cases that did not respond to antiviral treatment showed relapse.[60]

Well-designed multicenter studies will be necessary to determine whether early detection and prevention of HCV replication will provide improved disease management for HCV-infected patients receiving immunochemotherapy.

Conclusions

The spectrum of HCV infection include hematological manifestations such as MC and B-NHL. The most common B-NHL subtypes associated with HCV infection are MZL and DLBCL. Antiviral treatment achieves virological and hematological

remission in HCV associated indolent lymphoma. More aggressive lymphoma requires combination of AVT and chemotherapy. New generation HCV antiviral drugs are safe and highly efficacious. Regimens including DAAs appear promising and should be investigated in clinical trials for treatment of HCV-related extrahepatic disease. HCV associated B-NHL should be treated in close association with hepatologist and hematologist.

Conflict of interest

None

Author contributions

Review of literature and drafting article (ST), drafting the article and revising the article for important intellectual content (GKS).

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