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REVIEW

Non-Hodgkin Lymphoma and Hepatitis C: Where We are and What Next?

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Abstract The association between hepatitis C virus and certain B-cell non-Hodgkin lymphomas, such as marginal zone lymphomas, is supported by epidemiological studies. The exact pathogenetic mechanism is still unknown but both chronic antigenic stimulation and viral lymphotropism may contribute to the evolution of the malignant clone. Furthermore, the hematologic response following hepatitis C antiviral treatment suggests that the virus may have an etiologic role. Interferon and ribavirin based treatment proved to be successful in small case series of hepatitis C virus associated splenic lymphoma with villous lymphocytes, therefore, it is suggested that antiviral treatment could be an alternative to chemo-immunotherapy. In the near future new more potent direct acting antivirals will make interferon free treatments possible. It is still an open question whether these new short-course regimens are also effective in the treatment of associated lymphomas and what is the importance of the lymphoid reservoir in eliminating HCV.

Keywords Hepatitis C · Cryoglobulinemia · Non-Hodgkin lymphoma · Direct acting antivirals · Interferon

Introduction

Hepatitis C virus (HCV) is a hepato- and lymphotropic flavivirus with the capability to cause chronic infection. The global prevalence of HCV infection is about 3 % creating an increasing public health problem for both industrialized and developing countries [1]. Chronic HCV infection is estimated to be responsible for 25 % of liver cirrhosis and hepatocellular carcinoma (HCC) [2]. Among the numerous extrahepatic manifestations of chronic infection lymphoproliferative disorders are very important. Type II "mixed" cryoglobulinemia (MC) is detectable in nearly 50 % of chronically HCV infected individuals although it causes symptoms only in 10–20 % of patients. Cryglobulinemia increases the risk of B-cell non-Hodgkin lymphoma (B-NHL) by 35-fold [3]. Epidemiological and biologic studies from the last decade strengthened the evidence for the link between the development of certain B-NHL types and chronic HCV infection. In this review, we try to summarize the main evidences and theoretic models for the association between B-NHL and HCV infection and the possible effect of antiviral therapy (AVT) on B-NHL.

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NHL Subtypes Associated with HCV

Bacterial pathogens play an important role in the development of marginal zone lymphoma (MZL). There is a well established association between *Helicobacter pylori* infection and gastric mucosa associated lymphatic tissue (MALT) lymphoma and *Chlamydophila psittaci* is a putative causative agent in the rare lymphomas of the ocular adnexa [4]. Pathogen induced immune activation plays an important role in MZ lymphomagenesis. It is also well known that elimination of the infective agent may result in the regression of the lymphoid proliferation.

MZL is the most common HCV associated B-NHL subtype. According to the WHO classification of lymphomas there are 3 types of MZL: splenic marginal zone lymphoma (SMLZ), nodal marginal zone lymphoma (NMZL), and mucosa associated lymphoid tissue (MALT) lymphoma. In

SMLZ, villous lymphocytes can frequently be detected in the peripheral blood (splenic lymphoma with villous lymphocytes-SLVL). According to a large case series of 255 SLVL patients 49 (19 %) individuals had positive serology for HCV and 25 % of the tested 56 patients had detectable HCV-RNA [5]. SLVL is typically associated with MC. In another case series type II MC was detectable in all of the 18 SLVL patients. In 13 cases MC also caused symptoms of vasculitis [6] which preceded the development of lymphoma in 7 cases (mean 3.5 years). The authors concluded that HCV associated SLVL with type II MC may be a separate clinical entity. The less frequent primary NMZL is also associated with HCV. A study showed that the HCV serology was positive in 9 of 38 NMZL patients [7].

MALT lymphoma is the most frequent type of MZL, responsible for 8 % of all NHLs [8]. An Italian study showed HCV infection in 60 (35 %) of 172 patients with non-gastric MALT lymphoma [9]. The most frequently involved sites were the skin (35 %), salivary glands (25 %), and orbit (15 %). Other studies also found a link between HCV infection and salivary gland, orbit and skin MALT lymphoma [10, 11]. A relatively uncommon presentation associated with HCV is subcutaneous 'lipoma' like MALT lymphoma. A study performed by Paulli et al. [12] found HCV RNA positivity in all tested 10 patients.

Lymphoplasmacytic lymphoma (LPL) is another HCV related lymphoma subtype. In Waldeström macroglobulinemia (WM) IgM type immunoglobulin (macroglobulin) can be detected from the sera of patients with LPL. The relationship WM and HCV is still under debate as the association of the viral infection with the disease shows big geographical differences. A study from the USA did not find any HCV infection in 100 patients with WM [13].

MZL and LPL are indolent lymphomas but HCV might also be associated with high grade lymphoid malignancies [14]. The most common HCV related aggressive lymphoma type is high-grade diffuse large B-cell lymphoma (DLBCL). Interestingly, in DLBCL genotype 1 virus is more frequent while in indolent lymphomas the dominant virus subtype is genotype 2 [15]. There is far less evidence for the association of DLBCL and HCV than for MZL. A French study on HCV related DLBCL patients found higher rates of splenic involvement, higher LDH levels, more frequent chemotherapy related hepatotoxicity and lower overall survival compared to the HCV negative DLBCLs. The 0.5 % HCV prevalence in 5586 DLBCL patients was lower than the 1 % overall HCV prevalence in the French population. Most of the HCV associated DLBCLs carried molecular and morphological characteristics of transformation from indolent low grade lymphomas [16]. An Italian study of 156 HCV-DLBCL patients showed similar results: the most frequent site of extranodal involvement was the spleen, followed by the liver and the stomach [17].

Epidemiology

Several epidemiological studies investigated the association between HCV infection and B-NHLs but there are still much more questions than answers. Earlier studies with lower case numbers revealed a strong association in some geographical regions with high HCV infection prevalence [18]. Most of these were Italian or Japanese studies emphasizing the fact is that in some areas of Southern Italy the infection prevalence reaches 12.6 % [19]. Other studies from low prevalence countries found no association between hematologic malignancies and HCV [20]. A systematic review of 48 studies (5542 patients with NHL) published in 2003 by Gisbert et al. [21] found that HCV prevalence is 15 % higher in NHL patients than in the normal population. A meta-analysis of 23 studies (4049 patients with NHL) performed by Matsuo et al. [22] in 2004 also found an elevated risk for NHL ([OR] 5.7, 95 % [CI]: 4.09–7.96) in HCV positive individuals. Dal Maso et al. also found an association ([RR] 2.5; p5 % [CI] 2.1–3) in their meta-analysis of 18 studies (4678 patients) [23].

The multicenter European EPILYMPH study also showed a slightly elevated risk for NHL in HCV infected patients compared to the HCV negatives. HCV infection was detected in 2.9 % of lymphoma cases and in 41 (2.3 %) of control subjects ([OR] 1.42; 95 % [CI]: 0.93–2.15) [24]. Data presented by the InterLymph Epidemiology Consortium, involving 4784 patients and 6269 controls showed an association between HCV and MZL ([OR], 2.47; 95 % [CI]: 1.44–4.23), DLBCL ([OR] 2.24; 95 % [CI]: 1.68–2.99) and LPL ([OR], 2.57; 95 % [CI]: 1.14–5.79). There was no association with follicular lymphoma (FL) ([OR] 1.02; 95 % [CI]: 0.65–1.60) [25].

Overall, large epidemiologic studies and meta-analyses show that HCV infection is an important factor in the development of certain types of B-NHL. Local HCV prevalence and genetic and environmental factors may be responsible for the geographically diverging results. The most common HCV related NHL is MZL (usually of splenic origin with or without villous lymphocytes). The association with DLBCL is still under debate. The common feature of HCV related B-NHL is long-standing infection (15 years) and the frequent involvement of extranodal sites like the spleen, the liver, and the salivary glands.

Antiviral Therapy and Regression of Lymphomas

According to several clinical observations, antiviral therapy of HCV may result in the regression of HCV related lymphomas. This phenomenon points at the key role of the virus in the etiology and pathogenesis of certain lymphoproliferative diseases.

In one study, 7 out of 9 patients with SLVL and HCV infection achieved a total hematologic remission as the virus had bocome undetectable in the peripheral blood following interferon alfa-2b monotherapy or dual combination treatment with ribavirin [26]. Later, two other patients who also showed response after ribavirin were added to the therapy. None of the HCV negative 6 cases with SLVL responded to interferon. This underlines the fact that the favorable outcome in HCV positive SLVL individuals was not primarily due to the effect of interferon on lymphoma.

In a retrospective study by Kelaidi et al. HCV infected patients with MZL (1 ileac, 1 duodenal, 3 SLVL, 1 SMZL, 1 disseminated MZL and 1 leukemic MZL) showed a favorable hematologic outcome after AVT with peginterferon (PIFN) with or without ribavirin (RBV) [27]. Six patients achieved complete remission and later one relapsed. In this cohort, there was a patient with MZL and γ/δ large granular cell leukemia (LGL) which also disappeared after the virological response.

AVT of 16 patients with gastric MALT lymphoma also resulted in an impressive outcome. All 16 and 11 patients achieved a complete hematologic and virologic remission, respectively [28]. PIFN was found to be more effective than interferon (IFN) in achieving hematologic remission in LPL patients [29]. Peveling-Oberhag et al. summarized 18 studies and case reports evaluating the effect of AVT on low-grade lymphomas [30]. Out of the 106 patients (22 LPL, 28 SLVL, 16 SMZL, 34 other MZL /mainly MALT/, 1 Hodgkin disease, 4 follicular lymphoma, 1 liver B-NHL) 75 achieved complete and 14 partial hematologic response and 31 reached sustained virologic response (SVR) [12, 15, 26–29, 31–41].

Despite the substantial heterogeneity in lymphoma subtypes, AVTs and other factors, in all studies complete hematologic response was closely correlated with virological response. Again, in this light, the hematologic response to antiviral therapy in low-grade lymphomas underlines the role of HCV in lymphomagenesis.

In aggressive high grade lymphomas the situation seems to be different. The exact role of antiviral treatment is not known and its usefulness is not established. This may be because the antitumoral effect (clinical remission) follows the antiviral treatment with some lag and the duration of AVT is just too long (6–12 months) to be used in aggressive malignancies. In addition, it seems likely that the HCV antigen dependency is much lower as compared to low-grade lymphomas, therefore, viral eradication may not control and eliminate all tumorigenic mechanisms. Nevertheless, there are some sporadic case reports for DLBCL patients who achieved complete remission (CR) following PIFN/RBV therapy [42].

As outlined above, virus eradication can stop and reverse the lymphoproliferative process. According to this logic, achieving SVR using AVT after chemotherapy may also prevent relapses. The usefulness of this combined approach was shown in a study of La Mura et al. but randomized controlled trials are missing [43]. Simultaneous administration of AVT with chemotherapeutic agents is not recommended because of additvive toxicities, adverse effects and unfavorable drug interactions. Newer anti-HCV drugs (telaprevir, boceprevir) proved to be effective in combination with PIFN/RBV in achieving virologic response, but there are not enough data on their use in the setting of HCV associated malignant hematologic disease. Their numerous interactions and hematologic adverse events associated with PIFN/RBV raises concerns about the safety in these patient population. However, interferon sparing combinations of direct acting antivirals (DAA) are a promising alternative. Most of these combination therapies last for shorter time intervals (generally 12 weeks) and there are less hematologic adverse events than with PIFN/RBV treatment. There are high expectations towards using them in combination or even instead of standard immune-chemotherapy.

Pathogenesis of HCV-Driven NHL

Despite numerous studies, the exact role of HCV in B-cell lymphomagenesis is still unknown. Three, non mutually-exclusive theories exist (Table 1).

Antigen-Driven Lymphomagenesis The presence of HCV proteins present a potent trigger for lymphoproliferation and clonal expansion of B-cells. This is supported by the fact that most of the HCV associated lymphomas are of germinal center or post-germinal center origin [44]. Analysis of the V(D)J region of B-cells derived from MC and NHL patients supports the hypothesis that HCV proteins cause lymphoma through chronic antigenic stimulation. Based on the work of Quinn et al. antibodies generated against the viral E2 protein cross-react with the anti-IgG IgM (rheumatic factor, RF) isolated from MC patients [45]. Immunoglobulin-E2 complexes may further stimulate RF producing B-cell clones. An important role of E2 is the binding to CD81 which serves as a receptor for HCV binding on the surface of B-lymphocytes. Furthermore, E2 facilitates the assembly of the CD81/CD19/CD21 complex that, in turn, lowers the cellular activation threshold [46]. Another interesting finding is the decreased level of micro-RNA-26b (miRNA-26B) in HCV positive SMZL compared to HCV negative controls. The low levels of this miRNA species is associated with unfavorable phenotype in hepatocellular carcinomas [47, 30]. Moreover, HCV replication induces the release of different cytokines and growth factors acting as lymphoproliferative signals. B-cell activating factor of the TNF family (BAFF) plays an important role in B-cell maturation and can support the survival of autoreactive B-cell clones and HCV infection itself can cause elevated BAFF levels [48, 49]. An interesting study showed

Table 1 Factors participating in HCV-associated lymphomagenesis clustered according to the main three, non-mutually exclusive theories [30]

	Direct infection of B-cells	Chronic antigenic stimulation, interaction of E2 and CD81	"Hit and run" theory
Decreased activity	caspase 3/7,9	miR-26b	p53, BCL-6, β-catenin
Increased activity	BAFF, BCL-2, s-IL2R, IL-2,IL-10, IL-17, NOS	IL-6, SHM	

elevated BAFF levels in patients with HCV associated MC and NHL as compared in HCV negative individuals [50, 51]. There are other cytokines and cytokine receptors responsible for B-cell proliferation in HCV infection such as IL-17, IL-2, IL-10 and sIL2R [52, 53]. Additionally, decreased activity of caspase 3/7 and 9 in lymphocytes can also be associated with HCV infection [30]. The t(14;18) translocation involving the Bcl-2 gene is frequently detectable in HCV-associated NHL, especially when MC is also present [54]. Sometimes the translocation can be detected in a clonal B-cell population without the evidence of frank lymphoma. These presence of this population can be reversed with AVT [55].

Direct Oncogenic Potential HCV is a lymphotropic virus and it uses CD81 for entering B-cells. By binding to this receptor the virus activates the CD81/CD19/CD21 complex which is a strong proliferative signal to lymphocytes [46]. Similar to the Epstein-Barr virus (EBV) and the human T-cell leukemia-lymphoma virus (HTLV), using its oncogenic proteins HCV may be able to directly immortalize and transform B-lymphocytes.

Both HCV core and NS3 proteins can induce NO (nitrogen oxid) and ROS (reactive oxygen species) production which—by causing DNA breaks—may lead to genetic instability and can be an additive mechanism in the transformation of B-cells [56]. HCV RNA (a sign of active viral replication) is often detectable from B-cells of MC and less frequently of those of NHL patients [57]. Nevertheless, in the majority of HCV related lymphomas HCV RNA is not present in the malignant clone making the direct transformation theory less probable, although the so called "hit and run" tumorigenic mechanism (see below) can not be excluded in these cases.

"Hit and Run" Theory According to this theory, B-cell transformation occurs without direct replicative HCV infection. HCV can cause mutations in the immunoglobulin heavy chain, Bcl-6, p53 and beta-catenin in vitro and can induce DNA double strand breaks [58]. In addition, it activates AID (activation induced deaminase) [59]. In these mutator phenotype B-cells the balance in the function of cellular protooncogenes and tumor suppressors is deteriorated. If the DNA repair system is not able to eliminate the errors of the genetic material genetic instability and malignant transformation may occur, even if the virus has already left the cell.

The "Multistep Theory of Lymphomagenesis" The combination of the aforementioned theories have led to the elaboration of the multistep developmental theory of HCV associated lymphomas which is supported by the increased frequency of NHL in MC patients (Table 2.) [60]. According to this model, as a first step the antigenic stimulation caused by the replicating HCV leads to the development of MC. With the consecutive establishment of a fully malignant clone low grade NHL arises in some patients as a second step. In this phase the pathologic process can be reversed with the elimination of the virus. Finally, in few patients, as a result of subsequent accumulation of additional mutations and genetic alterations, antigen dependency is lost and viral elimination by itself seems to be insufficient for the treatment of HCV associated high grade NHL.

Summary

The association between HCV and B-NHL is supported by both epidemiologic studies and response of some low grade

Table 2 According to the multistep model of HCV-associated lymphomagenesis, the development of a HCV-associated diffuse large B-celll lymphoma (DLBCL) is preceded by a low-grade lymphoma (e.g. SLVL-splenic lymphoma with villous lymphocytes) and mixed cryglobulinemia (MC) first. Elimination of the triggering HCV may stop the process until the lymphoma losts its antigenic dependency at the high grade-lymphoma level [60]

	B-cell clonality	Lymphoid disease	Antigendependency of proliferation	Proliferation rate	Effect of anti-HCV treatment on lymphoproliferation
Baseline state	Polyclonal	None	Strong	Normal	Yes
First step	poly/oligoclonal	Mixed cryoglobulinemia	Strong	Normal	Yes
Second step	Oligo/monoclonal	Low-grade malignity (SLVL)	Moderate	Increased	Yes
Third step	Monoclonal	High-grade malignity (DLBCL)	None	Increased	No

NHLs to AVT. Therapeutic successes with antivirals are limited to studies performed on low patient cohorts, most frequently on patients with SLVL. Despite the lymphotropism of HCV, unambigous evidence of its direct oncogenic potential on B-cells is still lacking and the exact role of the virus in the etiology and pathogenesis in B-NHL remains to be established. The major driving force of B-cell lymphomagenesis is most probably the viral protein induced chronic immune activation. The antigen-driven multistep model described by Bachy et al. provides an elegant explanation for the MC-MZL sequence, albeit additional mechanisms to persistent viral infection are likely to play a role in the development of more aggressive entities such as DLBCL.

From a practical point of view viral elimination may be a valuable alternative for immune-chemotherapy in the case of MZLs and it may also be used to prevent relapse in HCV associated DLBCLs subsequent to chemotherapy. Both IFN and RBV have well-known hematologic adverse effect profiles which may contraindicate their use in the tratment of lymphoma patients. Both frequent adverse effects and the fact that SVR is reached only in 55 % of patients may be a limitation for their routine use in the therapy of low grade lymphomas [61]. On the other hand, new IFN free antiviral combinations show superior effectiveness to PIFN/RBV dual therapy. The rate of SVR was 71 % in 98 patients with HCV genotype 2 and 3 following 16 weeks of treatment with sofosbuvir and RBV [62]. In the FISSION study the overall SVR12 was 67 % in 256 treatment naive, genotype 2 or 3 patients treated for 12 weeks with sofosbuvir and RBV [63]. As compared to the conventional PIFN/RBV treatment the duration of IFN-free therapies is also much shorter. Sofosbuvir, simeprevir have already been approved by the FDA. In summation, these DAAs may represent a promising alternative also in the treatment of HCV associated malignant lymphoproliferative disorders, however, to our best knowledge, no studies on such combination therapies were conducted as yet. A close collaboration between hepatologists and hematologists will probably be an important feature in the practice of future treatment of HCV associated lymphomas.

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