TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (2): Hepatitis C virus

Hepatitis C virus and diffuse large B-cell lymphoma: Pathogenesis, behavior and treatment

Carlo Visco, Silvia Finotto

Carlo Visco, Silvia Finotto, Department of Hematology and Cell Therapy, San Bortolo Hospital, 36100 Vicenza, Italy
Author contributions: Visco C and Finotto S contributed equally to this work.
Correspondence to: Carlo Visco, MD, Department of Hematology and Cell Therapy, San Bortolo Hospital, Ospedale San Bortolo, Via Rodolfi 37, 36100 Vicenza,
Italy. carlovisco@hotmail.com
Telephone: +39-4-44753626   Fax: +39-4-44753922

Abstract

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.

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.

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 chemo-immunotherapy 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[2] 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[4,31]. Its role in Northern America[21] seems to be emergent, while other countries like England and Scotland[32], India[33], France[22] 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[34]. 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[35]. 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[36]. 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[36]. 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[37].

Based on these and others experiments, several hypothetical models of B-cell transformation by HCV have been formulated[38,39]. 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[40,41].

In addition to its being hepatotrophic, HCV is also a lymphotrophic 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[42]. Furthermore, the disappearance of the t(14;18) translocation following antiviral treatment was strongly associated with virologic response[5]. Altogether, these findings again suggest a possible pathogenetic link between HCV and aggressive lymphomas, which are known to be charac-

terized by BCL2 translocation in around 20% of *de-novo* DLBCL[43].

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[43]. 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[44].

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[45]. 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[46,47] or mantle cell lymphoma[48] 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[49,50], 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[16,51]. 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[52,53]. 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[54], 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
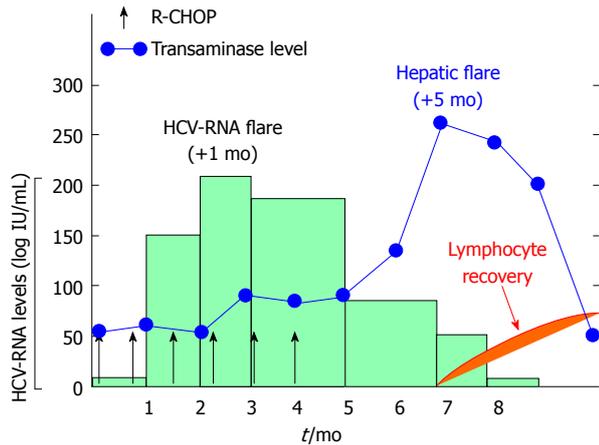
Figure 1 Speculative illustration. Speculative illustration of expected hepatitis C virus (HCV)-RNA load and transaminase flare during and after rituximab cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone (R-CHOP) immmunochemotherapy for a diffuse large B-cell lymphoma ideal patient (not 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[56]. 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%)[14,56-60]. 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[59]. 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[57]. 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[62]. 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[63]. Viral genotype might also condition chemotherapy induced hepatotoxicity[51,64].

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[65].

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].

Table 1 Clinical outcome of hepatitis C virus-positive diffuse large B-cell lymphoma patients according to retrospective studies

Ref.	DLBCL-HCV positive patients (*n*)	Treatment	PFS/EFS (3 yr)	OS (3 yr)
Besson *et al*[16]	26	Intensive protocols	53%	56%
Visco *et al*[14]	156	CHOP and CHOP-like/R-CHOP	60%	80%
Park *et al*[15]	32	CHOP(18)/R-CHOP(11)	54.7% at 5 yr	59.2% at 5 yr
Tomita *et al*[17]	25	CHOP/CHOP-like	NA	46%
Ennishi *et al*[60]	131	R-CHOP	69%	75%
Merli *et al*[59]	535	CHOP(214)/+R-CHOP (252)	53% (58% for R-CHOP)	68% (71% for R-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[12-18], 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[14,16,59,60].

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[18]. Persistent human hepatitis virus infections, especially HCV, have been also claimed to play an important role in the tumorigenesis of splenic DLBCL in Japan[68].

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 DLBCL 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[59]. 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[59]. Concomitant HBV infection or HBV related hepatocarcinoma has been reported to confer an extremely negative influence on outcome of these patients[14,60].

Few studies evaluated the clinical outcome of HCV-positive DLBCL (Table 1). In the pre-rituximab era, Besson *et al*[16] reported a worse overall survival (OS) in HCV-positive DLBCL patients treated with intense chemotherapeutic protocols. On the contrary, the study by Ennishi *et al*[60] 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*[59] (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 hepatologists 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.

REFERENCES

1   **Pioltelli P**, Zehender G, Monti G, Monteverde A, Galli M. HCV and non-Hodgkin lymphoma. *Lancet* 1996; **347**: 624-625 [PMID: 8596360 DOI: 10.1016/S0140-6736(96)91328-8]

2   **Mele A**, Pulsoni A, Bianco E, Musto P, Szklo A, Sanpaolo MG, Iannitto E, De Renzo A, Martino B, Liso V, Andrizzi C, Pusterla S, Dore F, Maresca M, Rapicetta M, Marcucci F, Mandelli F, Franceschi S. Hepatitis C virus and B-cell non-Hodgkin lymphomas: an Italian multicenter case-control study. *Blood* 2003; **102**: 996-999 [PMID: 12714514 DOI: 10.1182/blood-2002-10-3230]

3   **Zuckerman E**, Zuckerman T, Levine AM, Douer D, Gutekunst K, Mizokami M, Qian DG, Velankar M, Nathwani BN, Fong TL. Hepatitis C virus infection in patients with B-cell non-Hodgkin lymphoma. *Ann Intern Med* 1997; **127**: 423-428 [PMID: 9312998 DOI: 10.7326/0003-4819-127-6-199709150-00002]

4   **Stach RW**, Wagner BJ, Stach BM. A more rapid method for the isolation of the 7S nerve growth factor complex. *Anal Biochem* 1977; **83**: 26-32 [PMID: 920944]

5   **Zuckerman E**, Zuckerman T, Sahar D, Streichman S, Attias D, Sabo E, Yeshurun D, Rowe JM. The effect of antiviral therapy on t(14; 18) translocation and immunoglobulin gene rearrangement in patients with chronic hepatitis C virus infection. *Blood* 2001; **97**: 1555-1559 [PMID: 11238090 DOI: 10.1182/blood.V97.6.1555]

6   **Hermine O**, Lefrère F, Bronowicki JP, Mariette X, Jondeau K, Eclache-Saudreau V, Delmas B, Valensi F, Cacoub P, Brechot C, Varet B, Troussard X. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. *N Engl J Med* 2002; **347**: 89-94 [PMID: 12110736]

7   **Vallisa D**, Bernuzzi P, Arcaini L, Sacchi S, Callea V, Marasca R, Lazzaro A, Trabacchi E, Anselmi E, Arcari AL, Moroni C, Bertè R, Lazzarino M, Cavanna L. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. *J Clin Oncol* 2005; **23**: 468-473 [PMID: 15659492 DOI: 10.1200/JCO.2005.06.008]

8   **Giannelli F**, Moscarella S, Giannini C, Caini P, Monti M, Gragnani L, Romanelli RG, Solazzo V, Laffi G, La Villa G, Gentilini P, Zignego AL. Effect of antiviral treatment in patients with chronic HCV infection and t(14; 18) translocation. *Blood* 2003; **102**: 1196-1201 [PMID: 12689948 DOI: 10.1182/blood-2002-05-1537]

9   **Quinn ER**, Chan CH, Hadlock KG, Foung SK, Flint M, Levy S. The B-cell receptor of a hepatitis C virus (HCV)-associated non-Hodgkin lymphoma binds the viral E2 envelope protein, implicating HCV in lymphomagenesis. *Blood* 2001; **98**: 3745-3749 [PMID: 11739181 DOI: 10.1182/blood.V98.13.3745]

10 **Sung VM**, Shimodaira S, Doughty AL, Picchio GR, Can H, Yen TS, Lindsay KL, Levine AM, Lai MM. Establishment of B-cell lymphoma cell lines persistently infected with hepatitis C virus in vivo and in vitro: the apoptotic effects of virus infection. *J Virol* 2003; **77**: 2134-2146 [PMID: 12525648 DOI: 10.1128/JVI.77.3.2134-2146.2003]

11 **Visco C**, Li Y, Xu-Monette ZY, Miranda RN, Green TM, Li Y, Tzankov A, Wen W, Liu WM, Kahl BS, d'Amore ES, Montes-Moreno S, Dybkær K, Chiu A, Tam W, Orazi A, Zu Y, Bhagat

G, Winter JN, Wang HY, O'Neill S, Dunphy CH, Hsi ED, Zhao XF, Go RS, Choi WW, Zhou F, Czader M, Tong J, Zhao X, van Krieken JH, Huang Q, Ai W, Etzell J, Ponzoni M, Ferreri AJ, Piris MA, Møller MB, Bueso-Ramos CE, Medeiros LJ, Wu L, Young KH. Comprehensive gene expression profiling and immunohistochemical studies support application of immunophenotypic algorithm for molecular subtype classification in diffuse large B-cell lymphoma: a report from the International DLBCL Rituximab-CHOP Consortium Program Study. *Leukemia* 2012; **26**: 2103-2113 [PMID: 22437443 DOI: 10.1038/leu.2012.83]

12 **Luppi M**, Longo G, Ferrari MG, Barozzi P, Marasca R, Morselli M, Valenti C, Mascia T, Vandelli L, Vallisa D, Cavanna L, Torelli G. Clinico-pathological characterization of hepatitis C virus-related B-cell non-Hodgkin's lymphomas without symptomatic cryoglobulinemia. *Ann Oncol* 1998; **9**: 495-498 [PMID: 9653489 DOI: 10.1023/A:1008255830453]

13 **De Vita S**, Sacco C, Sansonno D, Gloghini A, Dammacco F, Crovatto M, Santini G, Dolcetti R, Boiocchi M, Carbone A, Zagonel V. Characterization of overt B-cell lymphomas in patients with hepatitis C virus infection. *Blood* 1997; **90**: 776-782 [PMID: 9226178]

14 **Visco C**, Arcaini L, Brusamolino E, Burcheri S, Ambrosetti A, Merli M, Bonoldi E, Chilosi M, Viglio A, Lazzarino M, Pizzolo G, Rodeghiero F. Distinctive natural history in hepatitis C virus positive diffuse large B-cell lymphoma: analysis of 156 patients from northern Italy. *Ann Oncol* 2006; **17**: 1434-1440 [PMID: 16766591 DOI: 10.1093/annonc/mdl131]

15 **Park BB**, Kim JS, Lee YY, Kang HJ, Ryoo BY, Kang JH, Kim HY, Kim BS, Oh SY, Kwon HC, Won JH, Kim K, Park K, Suh C, Kim WS. Clinical characteristics and outcome for hepatitis C virus-positive diffuse large B-cell lymphoma. *Leuk Lymphoma* 2008; **49**: 88-94 [PMID: 18203017 DOI: 10.1080/10428190701732861]

16 **Besson C**, Canioni D, Lepage E, Pol S, Morel P, Lederlin P, Van Hoof A, Tilly H, Gaulard P, Coiffier B, Gisselbrecht C, Brousse N, Reyes F, Hermine O. Characteristics and outcome of diffuse large B-cell lymphoma in hepatitis C virus-positive patients in LNH 93 and LNH 98 Groupe d'Etude des Lymphomes de l'Adulte programs. *J Clin Oncol* 2006; **24**: 953-960 [PMID: 16418500 DOI: 10.1200/JCO.2005.01.5016]

17 **Tomita N**, Kodama F, Takabayashi M, Kawano T, Yamaji S, Fujimaki K, Fujisawa S, Kanamori H, Motomura S, Ishigatsubo Y. Clinical features and outcome in HCV-positive aggressive non-Hodgkin's lymphoma. *Leuk Lymphoma* 2003; **44**: 1159-1164 [PMID: 12916868 DOI: 10.1080/1042819031000083055]

18 **De Renzo A**, Perna F, Persico M, Notaro R, Mainolfi C, de Sio I, Ciancia G, Picardi M, Del Vecchio L, Pane F, Rotoli B. Excellent prognosis and prevalence of HCV infection of primary hepatic and splenic non-Hodgkin's lymphoma. *Eur J Haematol* 2008; **81**: 51-57 [PMID: 18397390 DOI: 10.1111/j.1600-0609.2008.01081.x]

19 **Ferri C**, Caracciolo F, Zignego AL, La Civita L, Monti M, Longombardo G, Lombardini F, Greco F, Capochiani E, Mazzoni A. Hepatitis C virus infection in patients with non-Hodgkin's lymphoma. *Br J Haematol* 1994; **88**: 392-394 [PMID: 7803287 DOI: 10.1111/j.1365-2141.1994.tb05036.x]

20 **Mussini C**, Ghini M, Mascia MT, Giovanardi P, Zanni G, Lattuada I, Moreali S, Longo G, Ferrari MG, Torelli G. Monoclonal gammopathies and hepatitis C virus infection. *Blood* 1995; **85**: 1144-1145 [PMID: 7849303]

21 **de Sanjose S**, Benavente Y, Vajdic CM, Engels EA, Morton LM, Bracci PM, Spinelli JJ, Zheng T, Zhang Y, Franceschi S, Talamini R, Holly EA, Grulich AE, Cerhan JR, Hartge P, Cozen W, Boffetta P, Brennan P, Maynadié M, Cocco P, Bosch R, Foretova L, Staines A, Becker N, Nieters A. Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. *Clin Gastroenterol Hepatol* 2008; **6**: 451-458 [PMID:

18387498 DOI: 10.1016/j.cgh.2008.02.011]

22 **Hausfater P**, Cacoub P, Sterkers Y, Thibault V, Amoura Z, Nguyen L, Ghillani P, Leblond V, Piette JC. Hepatitis C virus infection and lymphoproliferative diseases: prospective study on 1,576 patients in France. *Am J Hematol* 2001; **67**: 168-171 [PMID: 11391713 DOI: 10.1002/ajh.1101]

23 **Udomsakdi-Auewarakul C**, Auewarakul P, Sukpanich-nant S, Muangsup W. Hepatitis C virus infection in patients with non-Hodgkin lymphoma in Thailand. *Blood* 2000; **95**: 3640-3641 [PMID: 10877553]

24 **Collier JD**, Zanke B, Moore M, Kessler G, Krajden M, Shepherd F, Heathcote J. No association between hepatitis C and B-cell lymphoma. *Hepatology* 1999; **29**: 1259-1261 [PMID: 10094973 DOI: 10.1002/hep.510290422]

25 **Duberg AS**, Nordström M, Törner A, Reichard O, Strauss R, Janzon R, Bäck E, Ekdahl K. Non-Hodgkin's lymphoma and other nonhepatic malignancies in Swedish patients with hepatitis C virus infection. *Hepatology* 2005; **41**: 652-659 [PMID: 15723449 DOI: 10.1002/hep.20608]

26 **Bellentani S**, Tiribelli C, Saccoccio G, Sodde M, Fratti N, De Martin C, Cristianini G. Prevalence of chronic liver disease in the general population of northern Italy: the Dionysos Study. *Hepatology* 1994; **20**: 1442-1449 [PMID: 7982643 DOI: 10.1002/hep.1840200611]

27 **Franceschi S**, Lise M, Trépo C, Berthillon P, Chuang SC, Nieters A, Travis RC, Vermeulen R, Overvad K, Tjønneland A, Olsen A, Bergmann MM, Boeing H, Kaaks R, Becker N, Trichopoulou A, Lagiou P, Bamia C, Palli D, Sieri S, Panico S, Tumino R, Sacerdote C, Bueno-de-Mesquita B, Peeters PH, Rodríguez L, Barroso LL, Dorronsoro M, Sánchez MJ, Navarro C, Barricarte A, Regnér S, Borgquist S, Melin B, Hallmans G, Khaw KT, Wareham N, Rinaldi S, Hainaut P, Riboli E, Vineis P. Infection with hepatitis B and C viruses and risk of lymphoid malignancies in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Cancer Epidemiol Biomarkers Prev* 2011; **20**: 208-214 [PMID: 21098651 DOI: 10.1158/1055-9965.EPI-10-0889]

28 **Paydas S**, Kiliç B, Sahin B, Buğdayci R. Prevalence of hepatitis C virus infection in patients with lymphoproliferative disorders in Southern Turkey. *Br J Cancer* 1999; **80**: 1303-1305 [PMID: 10424729 DOI: 10.1038/sj.bjc.6690522]

29 **Goldman L**, Ezzat S, Mokhtar N, Abdel-Hamid A, Fowler N, Gouda I, Eissa SA, Abdel-Hamid M, Loffredo CA. Viral and non-viral risk factors for non-Hodgkin's lymphoma in Egypt: heterogeneity by histological and immunological subtypes. *Cancer Causes Control* 2009; **20**: 981-987 [PMID: 19263231 DOI: 10.1007/s10552-009-9316-0]

30 **Chuang SS**, Liao YL, Chang ST, Hsieh YC, Kuo SY, Lu CL, Hwang WS, Lin IH, Tsao CJ, Huang WT. Hepatitis C virus infection is significantly associated with malignant lymphoma in Taiwan, particularly with nodal and splenic marginal zone lymphomas. *J Clin Pathol* 2010; **63**: 595-598 [PMID: 20530156 DOI: 10.1136/jcp.2010.076810]

31 **Takai S**, Tsurumi H, Ando K, Kasahara S, Sawada M, Yamada T, Hara T, Fukuno K, Takahashi T, Oyama M, Onishi H, Tomita E, Takami T, Imawari M, Moriwaki H. Prevalence of hepatitis B and C virus infection in haematological malignancies and liver injury following chemotherapy. *Eur J Haematol* 2005; **74**: 158-165 [PMID: 15654908 DOI: 10.1111/j.1600-0609.2004.00376.x]

32 **Nicolosi Guidicelli S**, Lopez-Guillermo A, Falcone U, Conconi A, Christinat A, Rodriguez-Abreu D, Grisanti S, Lobetti-Bodoni C, Piffaretti JC, Johnson PW, Mombelli G, Cerny A, Montserrat E, Cavalli F, Zucca E. Hepatitis C virus and GBV-C virus prevalence among patients with B-cell lymphoma in different European regions: a case-control study of the International Extranodal Lymphoma Study Group. *Hematol Oncol* 2012; **30**: 137-142 [PMID: 22105737 DOI: 10.1002/hon.1015]

33 **Varma S**, Menon MC, Garg A, Malhotra P, Sharma A, Chawla YK, Dhiman RK. Hepatitis C virus infection among patients with non-Hodgkin's lymphoma in northern India. *Hepatol Int* 2011; **5**: 688-692 [PMID: 21484139 DOI: 10.1007/s12072-010-9244-9]

34 **Kasama Y**, Sekiguchi S, Saito M, Tanaka K, Satoh M, Kuwahara K, Sakaguchi N, Takeya M, Hiasa Y, Kohara M, Tsukiyama-Kohara K. Persistent expression of the full genome of hepatitis C virus in B cells induces spontaneous development of B-cell lymphomas in vivo. *Blood* 2010; **116**: 4926-4933 [PMID: 20733156 DOI: 10.1182/blood-2010-05-283358]

35 **Chen Z**, Zhu Y, Ren Y, Tong Y, Hua X, Zhu F, Huang L, Liu Y, Luo Y, Lu W, Zhao P, Qi Z. Hepatitis C virus protects human B lymphocytes from Fas-mediated apoptosis via E2-CD81 engagement. *PLoS One* 2011; **6**: e18933 [PMID: 21526201 DOI: 10.1371/journal.pone.0018933]

36 **Machida K**, McNamara G, Cheng KT, Huang J, Wang CH, Comai L, Ou JH, Lai MM. Hepatitis C virus inhibits DNA damage repair through reactive oxygen and nitrogen species and by interfering with the ATM-NBS1/Mre11/Rad50 DNA repair pathway in monocytes and hepatocytes. *J Immunol* 2010; **185**: 6985-6998 [PMID: 20974981 DOI: 10.4049/jimmunol.1000618]

37 **Stamataki Z**, Shannon-Lowe C, Shaw J, Mutimer D, Rickinson AB, Gordon J, Adams DH, Balfe P, McKeating JA. Hepatitis C virus association with peripheral blood B lymphocytes potentiates viral infection of liver-derived hepatoma cells. *Blood* 2009; **113**: 585-593 [PMID: 18838615 DOI: 10.1182/blood-2008-05-158824]

38 **Bachy E**, Besson C, Suarez F, Hermine O. Hepatitis C virus infection and lymphoma. *Mediterr J Hematol Infect Dis* 2010; **2**: e2010004 [PMID: 21415946 DOI: 10.4084/MJHID.2010.004]

39 **Peveling-Oberhag J**, Arcaini L, Hansmann ML, Zeuzem S. Hepatitis C-associated B-cell non-Hodgkin lymphomas. Epidemiology, molecular signature and clinical management. *J Hepatol* 2013; **59**: 169-177 [PMID: 23542089 DOI: 10.1016/j.jhep.2013.03.018]

40 **Fognani E**, Giannini C, Piluso A, Gragnani L, Monti M, Caini P, Ranieri J, Urraro T, Triboli E, Laffi G, Zignego AL. Role of microRNA profile modifications in hepatitis C virus-related mixed cryoglobulinemia. *PLoS One* 2013; **8**: e62965 [PMID: 23650540 DOI: 10.1371/journal.pone.0062965]

41 **Peveling-Oberhag J**, Crisman G, Schmidt A, Döring C, Lucioni M, Arcaini L, Rattotti S, Hartmann S, Piiper A, Hofmann WP, Paulli M, Küppers R, Zeuzem S, Hansmann ML. Dysregulation of global microRNA expression in splenic marginal zone lymphoma and influence of chronic hepatitis C virus infection. *Leukemia* 2012; **26**: 1654-1662 [PMID: 22307176 DOI: 10.1038/leu.2012.29]

42 **Zignego AL**, Giannelli F, Marrocchi ME, Mazzocca A, Ferri C, Giannini C, Monti M, Caini P, Villa GL, Laffi G, Gentilini P. T(14; 18) translocation in chronic hepatitis C virus infection. *Hepatology* 2000; **31**: 474-479 [PMID: 10655273 DOI: 10.1002/hep.510310230]

43 **Visco C**, Tzankov A, Xu-Monette ZY, Miranda RN, Tai YC, Li Y, Liu WM, d'Amore ES, Li Y, Montes-Moreno S, Dybkær K, Chiu A, Orazi A, Zu Y, Bhagat G, Wang HY, Dunphy CH, His ED, Zhao XF, Choi WW, Zhao X, van Krieken JH, Huang Q, Ai W, O'Neill S, Ponzoni M, Ferreri AJ, Kahl BS, Winter JN, Go RS, Dirnhofer S, Piris MA, Møller MB, Wu L, Medeiros LJ, Young KH. Patients with diffuse large B-cell lymphoma of germinal center origin with BCL2 translocations have poor outcome, irrespective of MYC status: a report from an International DLBCL rituximab-CHOP Consortium Program Study. *Haematologica* 2013; **98**: 255-263 [PMID: 22929980 DOI: 10.3324/haematol.2012.066209]

44 **De Re V**, Caggiari L, Garziera M, De Zorzi M, Repetto O. Molecular signature in HCV-positive lymphomas. *Clin Dev Immunol* 2012; **2012**: 623465 [PMID: 22952554 DOI: 10.1155/2012/623465]

45 **Coiffier B**. Standard treatment of advanced-stage diffuse large B-cell lymphoma. *Semin Hematol* 2006; **43**: 213-220 [PMID: 17027655 DOI: 10.1053/j.seminhematol.2006.07.004]

46   **Iannitto E**, Ammatuna E, Tripodo C, Marino C, Calvaruso G, Florena AM, Montalto G, Franco V. Long-lasting remission of primary hepatic lymphoma and hepatitis C virus infection achieved by the alpha-interferon treatment. *Hematol J* 2004; **5**: 530-533 [PMID: 15570298 DOI: 10.1038/sj.thj.6200408]

47   **Pellicelli AM**, Marignani M, Zoli V, Romano M, Morrone A, Nosotti L, Barbaro G, Picardi A, Gentilucci UV, Remotti D, D'Ambrosio C, Furlan C, Mecenate F, Mazzoni E, Majolino I, Villani R, Andreoli A, Barbarini G. Hepatitis C virus-related B cell subtypes in non Hodgkin's lymphoma. *World J Hepatol* 2011; **3**: 278-284 [PMID: 22125661 DOI: 10.4254/wjh.v3.i11.278]

48   **Levine AM**, Shimodaira S, Lai MM. Treatment of HCV-related mantle-cell lymphoma with ribavirin and pegylated interferon Alfa. *N Engl J Med* 2003; **349**: 2078-2079 [PMID: 14627800]

49   **La Mura V**, De Renzo A, Perna F, D'Agostino D, Masarone M, Romano M, Bruno S, Torella R, Persico M. Antiviral therapy after complete response to chemotherapy could be efficacious in HCV-positive non-Hodgkin's lymphoma. *J Hepatol* 2008; **49**: 557-563 [PMID: 18678434 DOI: 10.1016/j.jhep.2008.06.025]

50   **Musto P**, Dell'Olio M, La Sala A, Mantuano S, Cascavilla N. Diffuse B-large cell lymphomas (DLBCL) with epatitis-C virus (HCV) infection: clinical outcome and preliminary results of a pilot study combining R-CHOP with antiviral therapy. *Blood* 2005; **106**: 688a

51   **Arcaini L**, Merli M, Passamonti F, Bruno R, Brusamolino E, Sacchi P, Rattotti S, Orlandi E, Rumi E, Ferretti V, Rizzi S, Meli E, Pascutto C, Paulli M, Lazzarino M. Impact of treatment-related liver toxicity on the outcome of HCV-positive non-Hodgkin's lymphomas. *Am J Hematol* 2010; **85**: 46-50 [PMID: 19957347 DOI: 10.1002/ajh.21564]

52   **De Vita S**, Quartuccio L, Isola M, Mazzaro C, Scaini P, Lenzi M, Campanini M, Naclerio C, Tavoni A, Pietrogrande M, Ferri C, Mascia MT, Masolini P, Zabotti A, Maset M, Roccatello D, Zignego AL, Pioltelli P, Gabrielli A, Filippini D, Perrella O, Migliaresi S, Galli M, Bombardieri S, Monti G. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum* 2012; **64**: 843-853 [PMID: 22147661 DOI: 10.1002/art.34331]

53   **Zaja F**, De Vita S, Mazzaro C, Sacco S, Damiani D, De Marchi G, Michelutti A, Baccarani M, Fanin R, Ferraccioli G. Efficacy and safety of rituximab in type II mixed cryoglobulinemia. *Blood* 2003; **101**: 3827-3834 [PMID: 12560225 DOI: 10.1182/blood-2002-09-2856]

54   **Zuckerman E**, Zuckerman T, Douer D, Qian D, Levine AM. Liver dysfunction in patients infected with hepatitis C virus undergoing chemotherapy for hematologic malignancies. *Cancer* 1998; **83**: 1224-1230 [PMID: 9740089 DOI: 10.1002/(SICI)1097-0142(19980915)83:6<1224::AID-CNCR23>3.0.CO;2-6]

55   **Hsieh CY**, Huang HH, Lin CY, Chung LW, Liao YM, Bai LY, Chiu CF. Rituximab-induced hepatitis C virus reactivation after spontaneous remission in diffuse large B-cell lymphoma. *J Clin Oncol* 2008; **26**: 2584-2586 [PMID: 18487576 DOI: 10.1200/JCO.2007.15.4807]

56   **Marignani M**, Mangone M, Cox MC, Angeletti S, Veggia B, Ferrari A, di Fonzo M, Begini P, Gigante E, Laverde G, Aloe-Spiriti A, Monarca B, Delle Fave G. HCV-positive status and hepatitis flares in patients with B-cell non-Hodgkin's lymphoma treated with rituximab-containing regimens. *Dig Liver Dis* 2011; **43**: 139-142 [PMID: 20554488 DOI: 10.1016/j.dld.2010.05.010]

57   **Ennishi D**, Terui Y, Yokoyama M, Mishima Y, Takahashi S, Takeuchi K, Okamoto H, Tanimoto M, Hatake K. Monitoring serum hepatitis C virus (HCV) RNA in patients with HCV-infected CD20-positive B-cell lymphoma undergoing rituximab combination chemotherapy. *Am J Hematol* 2008; **83**: 59-62 [PMID: 17712791 DOI: 10.1002/ajh.21022]

58   **Nosotti L**, D'Andrea M, Pitidis A, Pimpinelli F, Dessanti ML, Pisani F, Vignally P, Petti MC. Hepatitis C virus infection prevalence and liver dysfunction in a cohort of B-cell non-Hodgkin's lymphoma patients treated with immunochemotherapy. *Scand J Infect Dis* 2012; **44**: 70-73 [PMID: 21905952 DOI: 10.3109/00365548.2011.611819]

59   **Merli M**, Visco C, Spina M, Luminari S, Ferretti VV, Gotti M, Rattotti S, Fiaccadori V, Rusconi C, Targhetta C, Stelitano C, Levis A, Ambrosetti A, Rossi D, Rigacci L, D'Arco AM, Musto P, Chiappella A, Baldini L, Bonfichi M, Arcaini L. Outcome prediction of diffuse large B-cell lymphomas associated with hepatitis C virus infection: a study on behalf of the Fondazione Italiana Linfomi. *Haematologica* 2014; **99**: 489-496 [PMID: 24270404 DOI: 10.3324/haematol.2013.094318]

60   **Ennishi D**, Maeda Y, Niitsu N, Kojima M, Izutsu K, Takizawa J, Kusumoto S, Okamoto M, Yokoyama M, Takamatsu Y, Sunami K, Miyata A, Murayama K, Sakai A, Matsumoto M, Shinagawa K, Takaki A, Matsuo K, Kinoshita T, Tanimoto M. Hepatic toxicity and prognosis in hepatitis C virus-infected patients with diffuse large B-cell lymphoma treated with rituximab-containing chemotherapy regimens: a Japanese multicenter analysis. *Blood* 2010; **116**: 5119-5125 [PMID: 20823454 DOI: 10.1182/blood-2010-06-289231]

61   **Lake-Bakaar G**, Dustin L, McKeating J, Newton K, Freeman V, Frost SD. Hepatitis C virus and alanine aminotransferase kinetics following B-lymphocyte depletion with rituximab: evidence for a significant role of humoral immunity in the control of viremia in chronic HCV liver disease. *Blood* 2007; **109**: 845-846 [PMID: 17210867 DOI: 10.1182/blood-2006-08-041525]

62   **Harvey DJ**. Lipids from the guinea pig Harderian gland: use of picolinyl and other pyridine-containing derivatives to investigate the structures of novel branched-chain fatty acids and glycerol ethers. *Biol Mass Spectrom* 1991; **20**: 61-69 [PMID: 1883861]

63   **Sansonno D**, De Re V, Lauletta G, Tucci FA, Boiocchi M, Dammacco F. Monoclonal antibody treatment of mixed cryoglobulinemia resistant to interferon alpha with an anti-CD20. *Blood* 2003; **101**: 3818-3826 [PMID: 12506023 DOI: 10.1182/blood-2002-10-3162]

64   **Pitini V**, Sturniolo G, Arrigo C, Leonardi S, Pino S, Altavilla G. HCV genotype 2 as a risk factor for reactivation in patients with B-cell lymphoma undergoing rituximab combination chemotherapy. *Br J Haematol* 2010; **150**: 116-118 [PMID: 20230413 DOI: 10.1111/j.1365-2141.2010.08154.x]

65   **Pellicelli AM**, Zoli V. Role of ribavirin in hepatitis flare in HCV-infected patients with B cell non Hodgkin's lymphoma treated with rituximab-containing regimens. *Dig Liver Dis* 2011; **43**: 501-502 [PMID: 21459059 DOI: 10.1016/j.dld.2010.12.018]

66   **Dizdar O**, Tapan U, Aksoy S, Harputluoglu H, Kilickap S, Barista I. Liver dysfunction after chemotherapy in lymphoma patients infected with hepatitis C. *Eur J Haematol* 2008; **80**: 381-385 [PMID: 18221389 DOI: 10.1111/j.1600-0609.2008.01039.x]

67   **Foran JM**. Hepatitis C in the rituximab era. *Blood* 2010; **116**: 5081-5082 [PMID: 21148335 DOI: 10.1182/blood-2010-09-307827]

68   **Takeshita M**, Sakai H, Okamura S, Oshiro Y, Higaki K, Nakashima O, Uike N, Yamamoto I, Kinjo M, Matsubara F. Splenic large B-cell lymphoma in patients with hepatitis C virus infection. *Hum Pathol* 2005; **36**: 878-885 [PMID: 16112004 DOI: 10.1016/j.humpath.2005.06.005]

Baishideng®