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TOPIC HIGHLIGHT

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HCV infection, B-cell non-Hodgkin's lymphoma and immunochemotherapy: Evidence and open questions

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Abstract

There is plenty of data confirming that hepatitis C virus (HCV) infection is a predisposing factor for a B-cell non-Hodgkin's lymphoma (B-NHL) outbreak, while relatively few reports have addressed the role of HCV in affecting B-NHL patients' outcome. HCV infection may influence the short-term outcome of B-NHL because of the emergence of severe hepatic toxicity (HT) during immunochemotherapy. Furthermore, the long term outcome of HCV-related liver disease and patients' quality of life will possibly be affected by Rituximab maintenance, multiple-lines of toxicity during chemotherapy and hematopoietic stem cell transplantation. In this review, data dealing with aggressive and low-grade B-NHL were separately analyzed. The few retrospective papers reporting on aggressive B-NHL patients showed that HCV infection is a risk factor for the outbreak of severe HT during treatment. This adverse event not infrequently leads to the reduction of treatment density and intensity. Existing papers report that low-grade B-NHL patients with HCV infection may have a more widespread disease, more frequent relapses or a lower ORR compared to HCV-negative patients. Notwithstanding, there is no statistical evidence that the prognosis of HCV-positive patients is inferior to that of HCV-negative subjects. HCV-positive prospective studies and longer follow-up are necessary to ascertain if HCV-positive B-NHL patients have inferior outcomes and if there are long term sequels of immunochemotherapies on the progression of liver disease.

Key words: Marginal zone lymphoma; Diffuse large B cell lymphoma; Hepatitis C virus; Non-Hodgkin's lymphomas; Hepatotoxicity; Chemotherapy; Immunochemotherapy; Prognosis; Rituximab

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INTRODUCTION

Non-Hodgkin's lymphomas (NHL) are a vast group of lympho-proliferative diseases, with heterogeneous clinical characteristics, biological behavior and outcome[1].

Patients within different NHL sub groups require differentiated treatment modalities. Prevalence of hepatitis C virus (HCV) infection is higher in B-cell NHL (B-NHL) patients and HCV is presently considered a predisposing factor for the development of B-NHL[2]. Despite the prevalence of HCV infection in B-NHL, the number of papers addressing the potential role of HCV in affecting treatment outcome in B-NHL patients is scanty[3-13]. It has been suggested that HCV infection could influence outcome, determining a higher than expected incidence of hepatic toxicity (HT) during chemotherapy (CHT) and causing patients to receive modified CHT protocols, in terms of duration, dosages and composition, thus providing treatments below the standard of care[9,11,13]. In fact, HCV-positive status has been increasingly reported to be a risk factor for HT in B-NHL patients receiving Rituximab-based CHT[10,11]. Furthermore, the immunological stimulus determined by the presence of HCV infection[14] could induce biologically more aggressive lymphoma diagnosed in advanced stage and HCV persistence may also predispose patients to subsequent relapses[15]. In addition, the present availability of prolonged maintenance Rituximab, CHT treatments and autologous and allogeneic hematopoietic stem cell transplantation (HSCT) will probably affect the long-term course of HCV-related liver disease[16] and patients' quality of life.

In addition, the definition of HCV-positive patients as a "difficult-to-treat" NHL population has contributed to making it an exclusion criterion in recent clinical CHT trials. This has several important implications: (1) HCV-positive/B-NHL patients have probably less therapeutical chances of being treated with the most effective therapy; (2) There are no consistent prospective data regarding the prognostic impact of bearing HCV infection in B-NHL patients; and (3) We are currently unaware of which parameters are more predictive for the emergence of severe HT. Thus, since newer CHT or immuno-CHT protocols will not be tested in this group, it can be expected that side effects will only be reported in phase four, post-marketing studies.

In this paper, we will review the current literature on this issue and provide a global comment on the available data. We focused on existing reports dealing with the outcome of HCV-positive/B-NHL patients treated with radiotherapy, chemotherapy and Rituximab alone or in combination with other treatments. Since B-NHLs are heterogeneous entities that require specific treatments, we considered only those studies dealing with homogeneous diagnostic sub-groups and containing detailed information as regards therapy.

LITERATURE SCREENING: SEARCH STRATEGY, STUDY SELECTION CRITERIA AND DATA EXTRACTION

A computerized literature search of MEDLINE was performed, considering English-written literature only, using the following search terms: (HCV) AND (Rituximab) AND (chemotherapy) AND (lymphoma). To identify additional studies, the bibliographies of the identified papers were searched for further relevant articles. All those studies in which it was not possible to extrapolate data on homogeneous diagnostic sub-groups or detailed information on treatment protocols were excluded from the review process, as well as data reported only in abstract form.

LITERATURE REPORT

The prevalence of HCV infected individuals within NHL published series varied, ranging from 0.5%[13] up to 25%[11]. The International Lymphoma Epidemiology Consortium (InterLymph), based in Europe, North America and Australia, performed a pooled case-control study data including the analysis of 7 previous surveys[17]. 4784 cases of NHL and 6269 controls were matched by sex, age and study center. HCV infection was detected in 172 NHL cases (3.6%) and in 169 (2.7%) controls. In subtype-specific analyses, HCV prevalence was associated with marginal zone lymphoma (MZL) (OR = 2.47), DLBCL (OR = 2.24) and lymphoplasmacytic lymphoma (OR = 2.57). In a recent meta-analysis that selected 15 studies[18], the pooled relative risk (RR) of all NHL among HCV-positive persons was found to be 2.5 (95% CI: 2.1-3.1) in case-control studies and 2.0 (95% CI: 1.8-2.2) in cohort studies. RRs were similarly increased for all major B-NHL subtypes and primary sites of presentation. Notably, this study disproved previous suggestions that the RRs for HCV differed by NHL subtype[12,19].

Aggressive lymphomas

In 2006, Visco *et al*[6] described the clinical features and outcome of 156 previously untreated consecutive HCV-positive patients with DLBCL in northern Italy between 1994 and 2004 (Table 1).

The median age was 63 years. Overall, 43% had a primary extranodal DLBCL: spleen (34%), liver (11%) and stomach (10%) were the most frequently involved extranodal sites. Among other extranodal sites, skin was involved in 9 of 156 (6%), mouth (including tongue, palate, gingiva and salivary glands) in 7 of 156 (4%), tonsils in 7 of 156 (4%) and bone in 5 of 156 (3%). Six patients could be classified as primary cutaneous DLBCL. Fourteen patients (8%) had DLBCL transformed from a low-grade lymphoma (t-DLBCL). Liver function tests at diagnosis revealed that 116 patients (75%) had mild or no signs or symptoms (grade 0-1) of HCV infection except for a positive serological test, 27 (17%) had hepatitis, while 13 (8%) had cirrhosis. Notably, the liver was more frequently involved by DLBCL in patients with hepatitis or cirrhosis (26%).

One hundred and thirty-two patients received poly-chemotherapy with curative intent and 112 (84.8%) patients completed their treatment program without interruption or reduction. Twenty patients (15.3%) had modifications in the scheduled treatments: 15 patients (11.3%) had cycle reduction or prolongation of intervals mainly because of

Table 1 Features and outcome of hepatitis C virus + patients with aggressive B-cell non-Hodgkin's lymphoma treated with chemotherapy and immunochemotherapy

Author	Year	HCV + patients[1]	Histology	Study	Therapy	Severe HT (%)	Poor prognostic factors	ORR (%)	PFS	OS
Visco *et al*[6]	2006	132	DLBCL	Multicenter, retrospective	CHOP-like (85%) R-CHOP-like (26%)	15	Hepatic dysfunction HBV co-infection High IPI Advanced stage Nodal origin	93	51% (5 yr)	72% (5 yr)
Besson *et al*[13]	2006	26	DLBCL	Case control, retrospective	Intensified CHT, no Rituximab	45	Advanced stage High IPI	72	-	56% (5 yr)
Arcaini *et al*[9]	2010	101	DLBCL	Retrospective series	CHOP-like R-CHOP-like (23%)	15	HCV genotype 1 HT during CHT	77	43% (5 yr)	68% (5 yr)
Marignani *et al*[10]	2011	8	DLBCL = 7 BL = 1	Retrospective series	R-CHOP-like	28	NE	80	70% (4 yr)	80% (4 yr)
Ennishi *et al*[11]	2010	131	DLBCL	Retrospective series	R-CHOP-like	27	Hepatic dysfunction Age High IPI Advanced stage	-	69% (3 yr)	75% (3 yr)

[1]Number of hepatitis C virus (HCV) + patients treated with curative intent. NE: Not evaluable; PFS: Progression-free survival; OS: Overall survival; HT: Hepatic toxicity; CHT: Chemotherapy; IPI: International Prognostic Index.

elevated liver enzymes and chemotherapy had to be discontinued due to severe HT only in 5 patients (4%).

Thirty-five patients (26.5%) were treated with Rituximab combined with chemotherapy (R-CHT) and only 5 (14.2%) of these experienced mild HT (grade 1), not requiring discontinuation of treatment. Worthy of note, the authors reported that there was no association between the initial severity of hepatic disease and subsequent liver drug toxicity, regardless of the regimen administered. Overall, 88 of these 132 patients achieved CR (67%), 32 had a PR (24%) and 12 had PD (9%). The median follow-up was 42 mo. Patients with no hepatic dysfunction at diagnosis shared a better 5-year overall survival (OS) compared to patients with hepatitis or cirrhosis at baseline (80% *vs* 70% *vs* 50%, respectively), but these differences did not reach statistical significance (0.33). Survival was instead significantly conditioned by the presence of hepatitis B virus (HBV) co-infection, with 5 of 9 HBV-positive patients who died within 2 years from diagnosis (2-year OS of 42% *vs* 87% for HBV-seronegative, 0.004). Primary extranodal DLBCL was a good prognostic factor. Thus, the most important poor prognostic factors were: hepatitis B co-infection, advanced stage, nodal origin and a high International Prognostic Index (IPI) value. LDH was not of prognostic significance. Unfortunately, in this paper, there was no HCV-seronegative control group; however, it was compared to the largest published series of HCV-seronegative/DLBCL. Its results were that HCV-positive/DLBCL patients reported by Visco *et al*[6] had a higher incidence of primary extranodal DLBCL, more frequent intra-abdominal extranodal localizations, older age and increased LDH. HCV-positive/DLBCL compared favorably in terms of ORR, progression-free survival (PFS) and OS to the data reported in the literature for age-matched DLBCL HCV-seronegative patients[20]. The authors stated in the conclusions that HCV-positive/DLBCL have distinctive clinical features, good response to CHOP-like or R-CHOP-like treatments and an acceptable liver tolerance to chemotherapy. They also suggested that the intrinsic prognostic power of LDH, which affects IPI score, could be hampered in these patients by hepatic LDH isoforms, which are normally released by the infected liver, creating a confounding effect.

In 2006, Besson *et al*[13] reported a high incidence of HT and poor clinical outcomes in HCV-positive/DLBCL enrolled in the GELA first-line intensified programs LNH 93 and LNH 98. The prevalence of HCV infection was low (0.5%) but patients with an abnormal liver test (WHO grade > 2) were excluded from the trials. The median follow-up time was 47 mo. The data of 26 HCV-positive/DLBCL patients were compared to matched HCV-seronegative DLBCL patients who were enrolled in the same protocols (3 matched controls for every one HCV-patients). Four patients were co-infected with HBV and 2 of these had chronic hepatitis B infection. Serum transaminase levels (AST and ALT) at inclusion were normal in 17 cases, grade 1 in 6 cases, grade 2 in two cases with hepatic NHL and grade 3 in one case.

The HCV-infected patients were significantly younger than other patients and more frequently presented with a DLBCL transformed from low-grade disease. In agreement with the data reported by Visco *et al*[6], it was found that HCV-positive/DLBCL more frequently had involvement of the spleen, an elevated LDH and a higher proportion of high and high-intermediate IPI score. Worthy of note, in the series described by Besson *et al*[13], patients were given non standard intensified treatments without Rituximab (GELA LNH 93 and LNH 98 trials).

Short term HT after CHT was strongly increased among the HCV-positive/DLBCL (65%). Fifteen HCV-positive patients experienced HT that was grade 3-4 in 45% of them. OS at 2 years was different in the 2 groups ($P = 0.02$), respectively 56% in HCV-positive and 80% in HCV- seronegative. Event free survival (EFS) was respec-

tively 53% in HCV-positive *vs* 73% in HCV seronegative, but the difference did not reach statistical significance. LDH and IPI did not appear to be related to the poor prognosis of HCV-positive patients.

In 2010, Arcaini *et al*[9] reported a single institution series of 160 HCV- positive/NHL Italian patients treated from 1995-2007. Ninety-nine were DLBCL, 59 were low-grade lymphomas, 3 Mantle cell lymphomas and 2 T-cell lymphomas. Part of the 99 DLBCL was also reported previously in the paper by Visco *et al*[6]. The data regarding HCV status and liver parameters were pooled together for patients with DLBCL and other NHL: 146 out of 149 were HCV-RNA positive, genotypes were 1b in 23, 2a/2c in 34 and 3a in 3. One hundred and twenty patients received an anthracycline-based therapy and 28 received chemotherapy plus Rituximab. Cytotoxic drug doses were reduced in 63 patients. Among 93 patients with normal ALT at presentation, 16 patients developed WHO grade II-III HT. Among 67 patients with abnormal ALT, eight patients had a 3.5-fold elevation during treatment. Among 28 patients treated with Rituximab and chemotherapy, 5 patients (18%) developed HT. Thirty-four patients (21%) did not complete treatment (8 for HT). Median PFS for patients who experienced HT was significantly shorter than median PFS of patients without HT (respectively, 2 years and 3.7 years, $P = 0.03$). After a median follow-up of 2 years, 32 patients died (three for hepatic failure). Within the DLBCL group, CR was 60%, PR 17% and ORR 77%. Low-grade B-NHL had a CR of 52%, a PR of 29% and an ORR of 79%. Twenty-four patients developed significant HT (15%), 5 of these patients were in the R-CHT treated group (18%). Median OS in DLBCL was 8.9 years and it was not reached in low-grade NHL. HT developed more frequently in patients with genotype 1 (26%) than among genotype 2 (3%): 85% of significant HT happened in genotype 1 and similarly maximum HCV-RNA increases occurred in genotype 1. HCV RNA levels and ALT levels seemed to behave irrespectively and were not useful to predict HT. The authors suggested that HCV1 lymphomas represent a distinct clinical subset of NHL that deserves a specific clinical approach to limit HT and ameliorate survival.

In 2010, we published[10] a retrospective study on a group of Italian patients with CD20-positive, B-cell NHL treated with R-CHT. Nine patients (8.6%) were HCV-positive and viremic at baseline. Two were also HBsAg-positive but HBVDNA-negative at baseline and received appropriate prophylaxis, remaining HBVDNA negative thereafter. Three (33%) of the 9 HCV-positive patients and none (0%) of the 95 negative developed HT ($P < 0.001$). All had normal ALT before treatment. In two, the ALT peak developed approximately 5 mo after the end of treatment. Fifty-six patients had DLBCL and 7 (2.9%) were HCV-positive. All patients were treated with R-CHOP-like therapy. HCV-positive/DLBCL in our series more frequently had multiple extranodal involvement and LDH above the normal value. Severe HT developed in 2 out of these 7 patients (28%); this event required postponement of chemotherapy. After a median follow-up of 36 mo EFS, PFS and OS were not significantly different in HCV-positive compared to HCV-seronegative patients. No significant correlation were detected between ALT and HCVRNA levels before, during and 12 mo after HT development.

In 2010, Ennishi *et al*[11] published the largest series dealing with HCV-positive/DLBCL treated with R-CHOP-like chemotherapy. This retrospective analysis described 533 previously untreated DLBCL: 131 patients were HCV-positive (25%) and 422 (75%) HCV-seronegative. The study analyzed HT and prognosis during and after R-CHOP-like treatments. HBsAg and HIV-positive patients were excluded. HCV positivity was defined by the detection of anti-HCV antibodies. No data on HCV-serotypes were provided[10]. HCVRNA titer was determined in 79 patients before therapy, in 47 patients during therapy and in 44 after therapy, but for all 3 time points, only 34 patients were assessed. There was a trend towards an increase of HCV-RNA during therapy and a reduction after therapy (from 1000 up to 3187 down to 1986 kIU\mL). In 3 patients in whom pretreatment levels were under the detection limit, HCV-RNA increased over 100-fold and 2 of these developed severe HT. The median follow-up time was 31 and 32 mo, respectively for HCV-positive and HCV-seronegative patients. The PFS was 69% *vs* 77% respectively in HCV-positive and in HCV-seronegative patients ($P = 0.22$) and the OS 75% *vs* 84% respectively in HCV-positive and HCV-seronegative patients ($P = 0.07$). Severe HT was significantly more frequent in HCV-positive patients (27%) compared to HCV-seronegative patients (3%). The transaminase levels before starting the chemotherapy were predictive of HT. In 16 patients, HT determined a reduction of the scheduled dose (12.2%) and in 6 patients, therapy was withdrawn (4.5%). A progression from hepatitis to cirrhosis was described in 2 and in another 2, from cirrhosis to hepatocarcinoma (HCC). However, it was not entirely clear what was intended for progression to cirrhosis and how this was diagnosed. In addition, it should be noted that progression to HCC is part of the natural history of HCV-related cirrhosis, occurring at a reported annual rate of 3%-5% year[21], and thus, we believe that it should not be considered as a complication of treatment. Overall, 24 HCV-positive patients died: 14 from lymphoma progression and 6 from hepatic failure. HCV-positive patients were older, more frequently had elevated LDH, more than 2 extranodal sites, spleen involvement and a higher IPI. In this study, HCV infection was not a poor prognostic factor. However, the incidence of severe HT was higher in HCV-positive patients and, accordingly, HCV infection was determined to be a strong risk factor for the development of this adverse event. The authors recommended that a well-designed study should be carried out in order to determine if prevention of HCV replication would improve disease management during immune-chemotherapy[22].

Low-grade lymphomas

Despite the above mentioned papers[17,18] which have dis-

proved the prevalence of HCV infected subjects within a specific B-NHL subtype, the bulk of papers analyzing the outcome of low-grade lymphoma patients who are HCV-positive derive mainly from MZL series[12,19,23,24]. Several authors, especially from Italy, have recently described a very high prevalence of HCV-positive patients in MZLs[12,19,23,24] in papers dealing with features and outcomes of this subgroup.

Since the focus of this review was to compare the outcome of HCV- positive/B-NHL to HCV-seronegative/B-NHL following standard treatment, we omitted reporting on studies dealing with the activity of anti-viral therapy in B-NHL[25-28]. This is a new and exciting field of research and recent trials[29] have shown that antiviral therapy in low-grade B-NHL resulted in remissions of HCV-positive/NHL but not of HCV-seronegative NHL patients[25,26]. These results represent the most straightforward demonstration of an oncogenic role of HCV in B-NHL.

In 2006, the Italian Lymphoma Intergroup, in order to identify relevant prognostic factors, retrospectively analyzed a series of 309 patients[19] with a diagnosis of splenic MZL (SMZL). HCV infection was also investigated in 255 patients (83%) and in 49 (19%), HCV infection was documented. HCV-positive/SMZL patients differed significantly from HCV seronegative because of a female prevalence, more frequent B symptoms, more frequent abdominal lymph nodes involvement and the presence of villous lymphocytes and cryoglobulins. Patients were not homogenously treated: 80 received no treatment, 124 underwent splenectomy, followed by chemotherapy in 47 patients, 88 received chemotherapy only (single or combined agents), 5 immuno-chemotherapy, 3 received only Rituximab, 4 spleen radiation and 4 only Interferon. No details regarding therapy in HCV-positive/SMZL are given. The median follow-up time was 3.1 years, 5-year OS of the entire cohort was 72%, 5-year cause-specific survival (CSS) was 76% and 5-year EFS was 46%. In multivariate analysis anemia, above normal LDH and albumin below 3.5 g/dL were identified as poor prognostic factors. The authors reported that HCV-positive patients achieved complete remission in 42% of cases compared to 62% of HCV-seronegative, but in univariate analysis, the HCV status was not predictive of OS or CSS.

In 2006, Ferreri *et al*[12] reported a retrospective series of 55 Italian patients diagnosed between 1990 and 2004 with ocular adnexal lymphoma (OAL) of the MALT type. In 7 patients (13%), antibody titers against HCV were detected and all of them had a positive determination of HCV RNA. HCV-positive/OAL patients more frequently had advanced extra-orbital disease (57% *vs* 6%, $P = 0.003$), lymph node dissemination (43% *vs* 10%, $P = 0.05$) and involvement of other extranodal organs (43% *vs* 6%). First-line treatment consisted of 45 Gy orbit irradiation ($n = 22$), alkylating-based chemotherapy ($n = 16$) and Doxycycline ($n = 8$); nine patients with stage I disease did not receive any treatment after complete surgical resection of the lesion. Fifty-one patients (93%) achieved an objective response after first-line treatment. Sixteen patients experienced failure: five (71%) patients were HCV-positive and 11 (23%) were HCV-seronegative ($P = 0.01$), with a median TTP of 31 and more than 50 mo ($P = 0.01$) and a 5-year PFS of 43% ± 18% and 77% ± 7% ($P = 0.005$), respectively. HCV-positive patients experienced frequent relapses despite further lines of therapy. After a median follow-up of more than 5 years for both subgroups, 4 (57%) of the 7 HCV-positive patients experienced two failures or more, which was observed in 5 (10%) of the 48 HCV-seronegative patients ($P = 0.01$). Relapses in HCV-positive patients were systemic in all cases but one. The authors pinpointed that, as the risk of systemic dissemination associated with HCV infection may be important, the use of radiation therapy as exclusive treatment might be inappropriate in HCV-positive/OAL, even in the presence of limited stage disease.

In 2007, Arcaini *et al*[23] published a clinical series of 47 patients from Italy diagnosed with primary nodal MZL, which is a rare disease, accounting for only 2% of all lymphomas. The diagnosis was carried out between 1994 and 2004 (Table 2). HCV infection was tested in 38 patients and 9 (24%) were found to be seropositive. Patients were treated with heterogeneous modalities: 21 with polychemotherapy and 11 with monochemotherapy (Fludarabine and Chlorambucil). Five patients received only radiotherapy and 3 Rituximab only. Details of treatment in HCV-positive patients are not given. In univariate and multivariate analysis, the FLIPI score was associated with shorter OS, while HCV-positive status was of borderline significance. In multivariate analysis for EFS, anemia and use of chemotherapy (advanced disease) were poor prognostic factors.

In 2007, Arcaini *et al*[30] described another retrospective series of 172 patients from Italy diagnosed with non gastric marginal zone B-cell lymphoma of MALT. The authors investigated the prevalence of HCV infection, disease features and outcome, comparing HCV-positive and seronegative patients. Sixty patients (35%) were HCV-positive and two patients were HBV co-infected. HCV-positive patients more frequently had a single MALT site, with a preferential localization to the orbits (35%), the salivary glands (47%) and the skin (43%). Statistically significant differences for HCV-positive patients were older age, female prevalence, mild splenomegaly, less frequent involvement of the bone marrow and a higher IPI. The percentage of patients requiring treatment was similar in the 2 groups. Treatment modalities were chemotherapy in 59% of HCV-positive and in 53% of HCV-seronegative (the use of anthracycline and alkylators was similar in the 2 groups), radiotherapy in 29% of HCV-positive and in 20% of HCV seronegative, and surgery in 12% of HCV-positive and 27% of HCV seronegative patients. The ORR did not differ in the HCV-positive (93%) and in the HCV-seronegative group (87%). OS and EFS were also not different in the 2 groups. The response rate within different treatment modalities did not differ, either in HCV-positive or HCV-seronegative patients. In multivariate analysis, advanced disease was associated with poorer OS while HCV infection and need for treatment were not significant for OS.

Table 2 Clinical features and prevalence of hepatitis C virus-positive patients in low grade B-lymphoma series

Author	Year	HCV-positive patients number	Histology	Study type	Clinical features of HCV-positive[1]
Arcaini *et al*[19]	2006	49 (15%) out of 309	SMZL	Retrospective series analysis	B-symptoms Female prevalence Abdominal lymph nodes Villous lymphocytes Monoclonal component Cryoglobulin
Ferreri *et al*[12]	2006	7 (12%) out of 55	OAL of the MALT type	Retrospective series analysis	Advanced extra-orbital disease Lymph node dissemination Involvement of other extranodal organs Worse progression free survival
Arcaini *et al*[23]	2007	9 (19%) out of 47	Nodal MZL	Retrospective series analysis	Advanced stage B-symptoms Cryoglobulin
Arcaini *et al*[30]	2006	60 (35%) out of 172	Non-gastric MALT	Retrospective series analysis	Single MALT site Older age Female prevalence Less frequent marrow involvement
Strianese *et al*[24]	2010	23 (18%) out of 129	OAL	Retrospective series analysis	More widespread disease at the onset

[1]Clinical features with statistical relevance compared to hepatitis C virus (HCV)-negative patients. OAL: Ocular adnexal lymphoma; MZL: Marginal zone lymphoma; SMZL: Splenic MZL.

In 2010, Strianese *et al*[24] published a retrospective series of 129 patients from Italy with OAL. All the patients were tested serologically for the presence of HCV infection and the prevalence of HCV-positive/OAL was 17.8%. Patients were divided into 2 groups according to the presence or absence of HCV infection. Seropositivity for HCV infection was significantly associated with extra orbital lymphoma at the onset ($P = 0.006$). High prevalence of MALT lymphoma (79.8%) was registered. Protocol therapy included radiotherapy and chemotherapy, depending on the stage of the disease. Complete remission was achieved in 99 patients (76.7%). A total of 23.6% of patients with HCV-seronegative status and 21.7% with HCV-positive status experienced relapse of the lymphomatous disease. No significant differences in the 5-year OS and disease-free survival between the 2 groups were observed. The authors pinpoint that the prevalence of HCV infection in patients with OAL is a relevant issue, accounting for 17.8% of the examined patients. They suggest that infection with HCV may influence the initial appearance of OAL because HCV-positive/OAL had a more widespread disease at the onset. However, there was no statistically significant difference in OS and DFS in HCV-positive/OAL compared to HCV-seronegative patients.

DISCUSSION

HCV chronic infection is a predisposing condition for a B-NHL outbreak and several mechanisms are probably implicated in lymphomagenesis[2]. Three main pathways supported by evidence or theoretical hypothesis have been suggested: (1) Chronic antigenic stimulation of a B cell that interacts through its surface Ige with the cognate HCV antigen; (2) HCV-E2 protein engaging its high-affinity receptor CD81 expressed on B cells; and (3) Direct infection of a B cell by HCV. Chronic B-cell proliferation, in response to antigenic stimulation or polyclonal activation, may predispose to genetic aberrations such as translocation or overexpression or both of the antiapoptotic protein Bcl-2. Bcl-2 overexpression is especially frequent in follicular lymphomas[2]. It has been found also in B cells of patients with mixed cryoglobulinemia and even in HCV-positive cases without cryoglobulins[2]. Moreover, interaction between HCV-E2 and CD81 on B cells has been shown to trigger the enhanced expression of activation-induced cytidine deaminase and to induce double-strand DNA breaks in the IgVH gene locus, thereby further contributing to a mutator phenotype conducive to malignant transformation[2]. The most straightforward demonstration of an oncogenic role of HCV in NHL comes from trials showing that antiviral therapy, now based mostly on peg-Interferon and Ribavirin, resulted in complete or partial remissions of lymphoma in HCV-positive but not HCV-negative NHL patients[22,25,27,29]. However, it should be pointed out that the association of HCV with B-NHL is not very strong, with a RR of infection in the 2-3 range[2]. This is much less than the enormous increase in risk for the development of HCC brought about by infection with both HBV and HCV[21]. B-NHLs are heterogeneous entities; however, different lymphoma subsets share a high response rate to immunochemo-therapy and to radiotherapy. Presently, most patients with aggressive B-NHL may expect to be cured with intensive immunochemotherapy, while patients affected by low-grade B-NHL may expect to live for many years despite subsequent relapses. Since the clinical history and the treatment strategy of aggressive and low-grade B-NHL differs greatly, it is reasonable to speculate that the impact of HCV infection might affect patients outcome differently. Aggressive B-NHL requires the adminis-

tration of prompt, intensive poly-chemotherapy regimens containing Anthracyclines and Rituximab. The great majority of aggressive lymphomas are DLBCL (60%-70%) and a substantial proportion of DLBCL patients are cured by first line treatment. Patients who are refractory or who relapse after first line immunochemotherapy are treated with high dose therapy and rescued with infusion of HSCT (mainly of autologous origin)[31]. Patients refractory to salvage treatments generally survive for a short time to disease progression. The few retrospective papers dealing with HCV-positive/DLBCL showed that HCV infection is a risk factor for the outbreak of severe HT during treatment but failed to evidence statistically significant differences in the HCV-positive group following standard chemotherapy or immune-chemotherapy. In fact, within these few papers, only Besson *et al*[13] claimed a poorer prognosis for HCV-positive/DLBCL. However, HCV-positive patients reported in the Besson study were a small group (n = 23) and they were not given a standard treatment but an experimental intensive regimen. The majority of data deriving from these retrospective studies argue against a negative role of HCV infection "per-se" in HCV-positive/DLBCL patients.

Nonetheless, different authors reported that the frequent incidence of HT in HCV-positive patients during treatment led to the reduction or even the discontinuation of therapy in a substantial proportion of HCV-positive patients because of severe HT[11,13]. The reduction of dose-density or of dose-intensity due to therapy toxicity has been already recognized as an adverse prognostic factor for aggressive lymphomas[32,33]. It is reasonable to argue that being HCV-positive, patients less compliant to treatment intensity prospective trials would probably disclose a poorer prognostic trend in this group.

Advanced stage low-grade B-NHLs are another story. They are presently considered incurable diseases: treatment is often postponed and a watchful waiting strategy since disease progression might be chosen. There are several therapeutic opportunities and often monochemotherapy plus Rituximab or even Rituximab alone is given. HCV-positive low-grade B-NHL patients may have a more widespread disease[12,24], more frequent relapses[12] or a lower ORR[19], but a negative impact of HCV infection on OS has not yet been shown. Only Ferreri *et al*[12] reported a higher incidence of disease recurrence in HCV-positive/MALT. Notwithstanding the indolent course of this B-NHL subgroup, it would require a very long follow-up in order to establish consistently adverse prognostic factors. In the course of time, patients with low-grade B-NHL undergo multiple lines of therapy and become less responsive to treatment. Given the proven triggering action of HCV on B-cells, it is reasonable to hypothesize that in the long-term clinical history of low-grade B-NHL, HCV infection may predispose to B-NHL recurrence. Furthermore multiple therapies and chronic immunosuppression may also determine the progression of liver damage in HCV-positive patients[16].

Unfortunately, existing reports on HCV infected B-NHL patients generally lack information regarding the specific route of infection[6-19]. Data regarding HCV genotypes, HCV-RNA titer before, during and after treatment and liver biopsy assessment are generally available only for a minority of patients[6-19].

Since HCV and HBV share the same routes of infection and both are retained predisposing factors for lymphomagenesis[2], co-infected B-NHL patients are frequently encountered in clinical practice. Co-infection of HBV and HCV in B-NHL patients is reported with an incidence varying from 7% (Visco) up to 50% (Ennishi). If the prognosis of HCV-positive B-NHL patients is still a matter for debate, the prognostic impact of HCV/HBV co-infection is even more difficult to extrapolate given the very limited number of reported cases and the very low quality of the available data. However, in the papers reported here, some authors (Visco) underline that co-infection is a very poor prognostic factor. In our experience (unpublished data), the incidence of HBV/HCV co-infection was over 30% in B-NHL patients. Most co-infected patients of our series harbored an occult or inactive HBV infection and all of them received Lamivudine prophylaxis during immunochemotherapy. We did not notice a negative outcome in this co-infected subgroup compared to HCV-positive/HBV-negative B-NHL patients.

CONCLUSION

HCV-positive status seems to represent a risk factor for HT emergence in NHL patients but it is not consistently reported to affect patient survival. This may be due to the retrospective nature of available studies that hampers the detection of a poorer outcome in HCV-positive patients due to modifications of CHT. Furthermore, very long follow-up might be necessary to reveal the long term sequels on liver disease of chemotherapy and immunochemotherapy. Data regarding HCV replication or liver damage during and after treatments are even more scanty and incomplete. Prospective clinical and biological studies involving these "difficult-to-treat" B-NHL patients are eagerly needed, especially for those receiving anti-CD20 based CHT.

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