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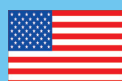
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**BRIEF ARTICLE****278 Hepatitis C virus-related B cell subtypes in non Hodgkin's lymphoma**

Pellicelli AM, Marignani M, Zoli V, Romano M, Morrone A, Nosotti L, Barbaro G, Picardi A, Vespasiani Gentilucci U, Remotti D, D'Ambrosio C, Furlan C, Mecenate F, Mazzoni E, Majolino I, Villani R, Andreoli A, Barbarini G

Contents

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APPENDIX I Meetings
I-V Instructions to authors

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Hepatitis C virus-related B cell subtypes in non Hodgkin's lymphoma

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Abstract

AIM: To evaluate if indolent B cell-non Hodgkin's lymphoma (B-NHL) and diffuse large B-cell lymphoma (DLBCL) in hepatitis C virus (HCV) positive patients could have different biological and clinical characteristics requiring different management strategies.

METHODS: A group of 24 HCV related B-NHL patients (11 indolent, 13 DLBCL) in whom the biological and clinical characteristics were described and confronted. Patients with DLBCL were managed with the standard of care of treatment. Patients with indolent HCV-related B-NHL were managed with antiviral treatment pegylated interferon plus ribavirin and their course observed. The outcomes of the different approaches were compared.

RESULTS: Patients with DLBCL had a shorter duration of HCV infection and a higher prevalence of HCV genotype 1 compared to patients with indolent B-NHL in which HCV genotype 2 was the more frequent genotype. Five of the 9 patients with indolent HCV-related

B-NHL treated with only antiviral therapy, achieved a complete response of their onco-haematological disease (55%). Seven of the 13 DLBCL patients treated with immunochemotherapy obtained a complete response (54%).

CONCLUSION: HCV genotypes and duration of HCV infection differed between B-NHL subtypes. Indolent lymphomas can be managed with antiviral treatment, while DLBCL is not affected by the HCV infection.

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Key words: Hepatitis C virus infection; Diffuse large B cell lymphoma; Indolent lymphoma; Pegylated interferon; Lymphomagenesis

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INTRODUCTION

The relationship between lymphoproliferative disorders and infectious agents has been studied for many decades. Epidemiological studies have linked hepatitis C virus (HCV) infection to B-cell non Hodgkin's Lymphomas (B-NHL)^[1,2]. The majority of these studies were conducted in Italy, where the prevalence of HCV infection is particularly high^[3-5]. However, studies conducted in countries with a lower prevalence of HCV infection also found a possible positive association between HCV and risk of developing B-NHL^[6]. In a large pooled analysis of combined data from several countries, de Sanjose *et al*^[7] demonstrated that presence of HCV infection was linked not only to marginal zone lymphoma, considered an indolent course B-NHL, but also to diffuse large B-cell lymphoma (DLBCL), a high-grade B-NHL. However, the strongest argument for a causative role of HCV infection in lymphoproliferative disease derives from interventional studies where antiviral regimen directed to HCV were successful in achieving the cure of HCV-related B-NHL^[8-11].

In our study, the authors have analyzed and compared the biological and clinical features of HCV-related indolent B-NHL versus DLBCL. Furthermore, the authors have evaluated the outcomes of the different treatment approaches used in the management of these two types of B-NHL, and evaluated the influence of HCV infection on disease course.

MATERIALS AND METHODS

Patients

One hundred and twenty-five consecutive patients with B-NHL referred to our institution between January 2008 and January 2009 were included in the study and analyzed retrospectively. The diagnosis of lymphoma was established according to the 2008 World Health Organization (WHO) classification of tumours of haematopoietic and lymphoid tissues^[12]. Total body computed tomography (CT) scan, bone marrow biopsy (BOM), lesion biopsies and physical examination were used to assess the stage and extranodal involvement according to Costwolds modification of the Ann Arbor classification^[13]. Indolent B-NHL was defined by the 2008 WHO classification of Tumours of haematopoietic and lymphoid tissue^[12] and included: marginal zone lymphoma (nodal, splenic and extranodal), lymphoplasmacytoid lymphoma and follicular lymphoma. Clinically, indolent course lymphoma was also defined as having a lesion doubling time greater than 1 year, no B symptoms and no masses > 10 cm (bulky disease). The study was approved by the local institutional review board.

Laboratory analysis

Enzyme-linked immunosorbent assays were used to determine anti-HCV antibodies in the 125 patients. All patients anti-HCV antibodies positive, underwent HCV-RNA testing [reverse transcription polymerase chain reaction (RT-PCR); detection limit <15 UI/mL]. HCV-RNA determination was performed at disease diagnosis and subsequently at one, three, six and twelve months during antiviral treatment, and at six and twelve month after the its completion. HCV genotyping was performed in all viremic HCV patients (Immunogenetics Line Probe Assay, INNO-lipa HCV, Innogenetics, Ghent, Belgium). All HCV patients were tested for the presence of cryoglobulins. In all HCV-positive patients alanine aminotransferase (ALT) plasma levels were determined and expresses as UI/L. All HCV positive patients were tested for hepatitis B virus (HBV) antibodies and HBsAg (AxSYM, Abbott Laboratories, North Chicago, IL, United States), and for antibodies to human immunodeficiency virus (HIV) using an HIV-1 third-generation assay (AxSYM HIV 1/2, Abbott Laboratories). Presence of Bcl2 and Bcl6 were evaluated in biopsy samples or peripheral and medullary blood mononuclear cells using immunohistochemistry in all cases of HCV related B-NHL. The presence of HBV, HIV infection or concomitant neoplastic diseases excluded patients from the study. In HCV positive patients, demographic information such as periods of first and last exposure to injecting drug use or blood transfusion, tattoos and occupational exposure, needlestick injuries were recorded and considered as valid surrogate timepoints to define duration of HCV infection, expressed as mean \pm SD.

Liver Biopsy

Fifteen of the 24 patients with HCV-related B-NHL gave informed consent to perform liver biopsy. Histologic

evaluation was carried out according to the Ishak score^[14].

Antiviral treatment

Patients with indolent HCV-related B-NHL were offered treatment with antiviral therapy on the basis that previous interventional studies had demonstrated the efficacy of this approach in inducing a complete response of onco-hematological diseases (CR)^[8-11]. In detail, pegylated interferon alpha 2a (180 µg) was administered subcutaneously once a week. It was combined with oral ribavirin: 800 mg/d when the patient weighed < 65 kg, 1000 mg/d when the weight was between 65 and 85 kg and 1200 mg/d when the patient was > 85 kg. Treatment was scheduled for 1 year if the patient had HCV genotype 1 or 4, and for 6 mo if the genotype was 2 or 3. Epoetin alfa was given at the dosage of 40 000 IU/week subcutaneously if haemoglobin levels (Hb) decreased by more than 2 g/100mL as compared to baseline in the first 4 wk of treatment, or when Hb was below 10 g/100 mL during treatment. Toxicity of antiviral treatment was evaluated according National Cancer Institute Common Terminology Criteria for Adverse Events; treatment dose was reduced in the case of grade 2 development, or withheld in the case of grade 3 toxicity (until toxicity had resolved to grade 2). Treatment was stopped in the case of grade 4 toxicity. Sustained virologic response (SVR) was defined as HCV-RNA negativity (< 12 IU/mL) 24 wk after stopping antiviral treatment. Patients were categorized as non-responders if HCV-RNA was positive after three months from the beginning of antiviral treatment. Relapser status was defined as the reappearance of HCV-RNA after antiviral treatment stoppage.

Haematologic Response

Antiviral treatment: In lymphoma patients managed with the antiviral treatment, haematological response was evaluated at the end of antiviral therapy, and every 3 mo thereafter.

Immunotherapy: Immunotherapy was reserved for patients with DLBCL, an aggressive form of lymphoma. The multi-drug regimen used in all patients was Cyclophosphamide, Doxorubicin, Vincristine and Prednisone associated with Rituximab (CHOP-R).

The haematological response was evaluated by means of physical examination, biochemical evaluation, CT scan and BOM when indicated according to standard response criteria^[13]. CR was defined as no evidence of lymphoma. In patients with marginal splenic lymphoma, CR was defined as resolution of splenomegaly, absence of peripheral circulating villous lymphocytes, and normalization of platelet and white blood cells counts. When the BOM was initially positive, a negative BOM evaluation was an additional required criterion for confirming CR. Partial haematological response (PR) was defined as a $\geq 50\%$ decrease in the size of all measurable lesions. The criteria for progressive haematological disease (PD) was a > 25% size increase in a previously documented lesion or the ap-

pearance of new lesions^[15].

Statistical analysis

Continuous data were expressed as mean and standard deviation, and analysed using the *t*-test for independent samples with 95% confidence intervals. Categorical data were analysed using the χ^2 test, with Yates's correction and the Fisher's exact test. The significance level was set at a two-tailed *P* value < 0.05.

RESULTS

Of 125 consecutive patients presenting with B-NHL, 24 patients were HCV antibody positive, and all were viremic. The prevalence of HCV-related B-NHL in our population was 19.2%. Of these patients, 13 (54%) had DLBCL, while 11 (46%) had an indolent, HCV-related B-NHL (Table 1).

As compared to the indolent HCV-related B-NHL group, the DLBCL group had significantly more male patients, had a short duration of HCV infection, and a preponderance of patients with HCV genotype 1 infection. No differences in HCV-RNA titres, ALT levels, and histologic grading and staging between the two group of B-NHL were detected (Table 2). All DLBCL patients were treated with immunochemotherapy. Antiviral treatment was proposed to all 11 patients with indolent HCV related B-NHL. Nine out of 11 (81%) agreed to be treated with the antiviral treatment.

Antiviral treatment outcome

During antiviral treatment, 4 patients experienced grade 2 anaemia and were treated with epoetin alfa. One patient developed depression, and treatment with sertraline (50 mg/d) was started. However, all nine indolent, HCV-related B-NHL patients treated with antiviral treatment completed the scheduled course. All the patients had an end treatment response. Six months after antiviral treatment completion, 7 patients had a SVR, while 2 patients had a relapse of HCV infection (Table 3).

Haematologic outcome in patients treated with antiviral treatment

Complete response of onco-hematological diseases was obtained in 5 of the 7 patients with SVR (71%), while the remaining 2 patients with SVR had a PR. The two patients not responding to antiviral treatment developed PD. After a median of (14.2 \pm 2) mo, the 5 patients originally obtaining SVR were still in CR (Table 3).

Haematological outcome in patients treated with immunochemotherapy

Thirteen patients with DLBCL were treated with immunochemotherapy as first line therapy. A CR was observed in 7 patients. In 2 of the 13 DLBCL patients treated with chemotherapy, there was an increase in ALT value (> 1.5 normal value) during treatment. None of the HCV-positive DLBCL patients had to stop treatment because of liver related events.

Table 1 Clinical and biological characteristics of 24 hepatitis C virus patients with low and high grade B cell-non Hodgkin's lymphoma

| | Sex | Age (yr) | HCV RNA log ₁₀ (UI/mL) | HCV genotype | Duration of HCV-infection (mo) | Ishak (grading) | Ishak (staging) | Type of lymphoma | Stage | Extranodal | Cryoglobulin | Bcl2/Bcl6 |
|----|-----|----------|-----------------------------------|--------------|--------------------------------|-----------------|-----------------|-----------------------------|-------|--------------------|--------------|-----------|
| 1 | F | 70 | 5.90 | 2a/2c | 21 | 4 | 0 | Marginal extranodal (MALT) | IV | Orbit/BM | Positive | +/- |
| 2 | F | 69 | 5.40 | 2a | 19 | 12 | 6 | Marginal extranodal (MALT) | IV | Parotid/BM | Positive | -/- |
| 3 | F | 64 | nd | 2 | 25 | nd | nd | Marginal extranodal (MALT) | IV | Orbit/BM | Positive | na |
| 4 | M | 36 | nd | 2 | 7 | 6 | 1 | Splenic marginal | IV | Spleen/BM | Negative | -/- |
| 5 | F | 72 | 6.00 | 1b | 22 | 8 | 2 | Splenic marginal | III | Spleen | Negative | -/- |
| 6 | F | 65 | nd | 2a/2c | nd | nd | nd | Splenic marginal | IV | Spleen/BM | Negative | -/- |
| 7 | F | 70 | 5.90 | 2 | nd | 8 | 1 | Marginal nodal | IV | BM | Positive | -/- |
| 8 | F | 55 | 5.07 | 2a/2c | 31 | 17 | 6 | Follicular lymphoma | III | None | na | +/+ |
| 9 | M | 67 | 6.80 | 2a | 30 | 6 | 0 | Follicular lymphoma | IV | Liver/BM | Negative | +/- |
| 10 | F | 59 | nd | 2 | 20 | 16 | 6 | Follicular lymphoma | III | None | Negative | +/+ |
| 11 | F | 78 | nd | 2a | 30 | nd | nd | Lymphoplasmacytoid lymphoma | IV | BM | Positive | na |
| 12 | M | 61 | nd | 1b | 18 | 5 | 2 | DLBCL | IV | BM | na | na |
| 13 | M | 29 | 7.80 | 1a | 4 | 6 | 0 | DLBCL | II | None | Negative | +/+ |
| 14 | M | 66 | 6.70 | 1b | nd | 12 | 6 | DLBCL | | Liver, Lung | na | na |
| 15 | M | 62 | 6.90 | 1a | 10 | nd | nd | DLBCL | IV | BM | na | na |
| 16 | M | 56 | 5.1 | 1b | nd | nd | nd | DLBCL | IV | BM | na | na |
| 17 | F | 55 | 5.4 | 1b | nd | nd | nd | DLBCL | IV | Liver | na | na |
| 18 | F | 59 | 6.4 | 1a/1b | nd | nd | nd | DLBCL | IV | Lung/BM | na | +/+ |
| 19 | M | 65 | 5.8 | 1b | 11 | 10 | 2 | DLBCL | IV | Lung | Negative | +/+ |
| 20 | M | 46 | nd | 1b | 6 | 8 | 1 | DLBCL | IV | Liver | Negative | +/+ |
| 21 | M | 51 | 6.3 | 1b | 15 | 10 | 2 | DLBCL | IV | Lung/BM | Negative | -/- |
| 22 | M | 49 | 5.9 | 3 | 15 | nd | nd | DLBCL | IV | Gastric | Negative | -/- |
| 23 | M | 78 | 6.2 | 2a/2c | 19 | 10 | 1 | DLBCL | III | None | Negative | +/+ |
| 24 | F | 74 | 5.0 | 1 | 16 | 10 | 4 | DLBCL | IV | Palatine Tonsil/BM | Negative | -/- |

DLBCL: Diffuse large B cells lymphoma; nd: Not determined; Extranodal: Extranodal involvement; BM: Bone marrow; na: Not available; MALT: Mucosal associated lymphoid tissue; HCV: Hepatitis C virus.

Table 2 Comparison of biological, virological and clinical characteristics of hepatitis C virus-related low vs high grade B cell-non Hodgkin's lymphoma

| | DLBCL (n = 13) | Indolent B-NHL (n = 11) | 95% CI | P value |
|--|----------------|-------------------------|---------------|---------|
| Age (yr) ¹ | 57 ± 12 | 64 ± 11 | -16.8 to 2.8 | 0.153 |
| Sex (M/F) | 10/3 | 2/9 | - | 0.014 |
| Duration of HCV infection (yr) ¹ | 12 ± 5 | 22 ± 7 | -15.1 to -4.9 | < 0.001 |
| ALT value (UI/L) ¹ | 58 ± 40 | 40 ± 27 | -11.5 to 47.5 | 0.219 |
| Genotype 1/not 1 | 10/3 | 2/9 | - | 0.014 |
| HCV RNA log ₁₀ (UI/mL) ¹ | 6.1 ± 0.6 | 5.8 ± 0.3 | -0.11 to 0.71 | 0.147 |
| Ishak (grading) ¹ | 8.4 ± 2.1 | 9.3 ± 5.0 | -4.05 to 2.25 | 0.560 |
| Ishak (staging) ¹ | 1.5 ± 1.2 | 2.75 ± 2.7 | -2.97 to 0.47 | 0.146 |

¹Means ± SD; HCV: Hepatitis C virus; B-NHL: B cell-Non Hodgkin's lymphoma; DLBCL: Diffuse large B cells lymphoma; CI: Confidence interval.

DISCUSSION

In accordance with de Sanjose *et al*^[7], we found a high prevalence of HCV-positives (19%) among DLBCL and indolent lymphoma patients. We observed that DLBCL patients had a history suggestive of a short duration of HCV infection, and a higher prevalence of genotype 1, as compared to patients with indolent, low-grade B-NHL, who had a higher prevalence of genotype 2. Various clinical studies failed to demonstrate an association between

B-NLH and specific HCV genotypes, although the possible association between specific HCV genotypes and particular subtypes of B-NHL was not considered in these studies^[3,9,16].

Several studies have demonstrated differences between infection due to HCV genotypes 1 and 2^[17,18]. In HCV genotype 2 infection, HCV-RNA titre was lower, there were more patients with normal ALT values, and the patients had a longer duration of HCV infection as compared to genotype 1 patients. Conversely, chronic HCV hepatitis progression appears to have a more rapid and severe course in genotype 1 as compared to genotype 2^[17]. Because HCV genotype 2 is associated with a longer duration of viral infection, it can be speculated that over time it might induce a persistent immunostimulation of B cells. Zignego *et al*^[19,20] have found that type II mixed cryoglobulinemia and *bcl-2* expression in HCV genotype 2 patients was the more frequent cause of a prolonged immunostimulation of the B cell exerted by HCV over time. In our study HCV genotype 2 was detected in 5 out of 8 patients who had *bcl-2* positivity and in all the patients where a long duration of HCV infection was found. We believe that *bcl-2* expression in indolent lymphoma, such as, follicular lymphoma and marginal zone lymphoma, is the expression of a chronic B cell proliferation in response to antigenic stimulation or polyclonal activation in genotype 2 patients with and without cryoglobulins.

It has been demonstrated that the HCV envelope

Table 3 Results of antiviral treatment in patients with low grade B cell-non Hodgkin's lymphoma

| | Sex | Age (yr) | Histology | Stage | HCV RNA log ₁₀ (UI/mL) | Genotype | Staging (Ishak) | Treatment | Treatment duration (mo) | Response to treatment | Remission lymphoma |
|---|-----|----------|---------------------|-------|-----------------------------------|----------|-----------------|-------------------------------|-------------------------|-----------------------|---------------------------------|
| 1 | F | 70 | Marginal extranodal | IV | 5.9 | 2a/2c | 0 | Peg 180 µg/wk + RBV 800 mg/d | 6 | SVR | Complete hematological response |
| 2 | F | 69 | Marginal extranodal | IV | 5.4 | 2a | 6 | Peg 180 µg/wk + RBV 800 mg/d | 6 | SVR | Complete hematological response |
| 3 | F | 64 | Marginal extranodal | IV | 5.6 | 1b | nd | Peg 180 µg/wk + RBV 1000 mg/d | 12 | Relapser | Progressive disease |
| 4 | M | 36 | Marginal splenic | IV | 5.5 | 2 | 1 | Peg 180 µg/wk + RBV 800 mg/d | 6 | SVR | Partial response |
| 5 | F | 72 | Marginal splenic | III | 6.0 | 1b | 2 | Peg 180 µg/wk + RBV 1000 mg/d | 12 | SVR | Partial response |
| 6 | F | 65 | Marginal splenic | IV | 5.6 | 2a/2c | nd | Peg 180 µg/wk + RBV 1200 mg/d | 6 | SVR | Complete hematological response |
| 7 | F | 70 | Marginal nodal | IV | 5.9 | 2 | 2 | Peg 180 µg/wk + RBV 800 mg/d | 6 | SVR | Complete hematological response |
| 8 | F | 55 | Follicular lymphoma | III | 5.0 | 2a/2c | 6 | Peg 180 µg/wk + RBV 800 mg/d | 6 | Relapser | Progressive disease |
| 9 | M | 67 | Follicular lymphoma | IV | 6.8 | 2a | 0 | Peg 180 µg/wk + RBV 800 mg/d | 6 | SVR | Complete hematological response |

MU: Million of units; RBV: Ribavirin; SVR: Sustained virological response.

glycoprotein E2 interacts with a specific B cell receptor associated with the CD19/CD21/CD81 complex. This interaction lowers the threshold for B cell activation and induces the proliferation of benign B cells. However, this prolonged exposure to stimuli may render B cells at risk for additional events leading to malignant transformation^[21]. This mechanism may offer a clue to interpreting lymphomagenesis in genotype 2 patients affected by indolent HCV-related B-NHL in whom a prolonged exposure to immunostimulation of the B-cell compartment seems to be a characteristic.

On the contrary, in our study direct lymphocyte transformation could be hypothesized in HCV genotype 2 patients on the basis of the shorter duration of HCV infection. Furthermore we found positivity of *bcl-6* in five DLBCL patients, while *bcl-6* negativity was found in only three patients. Positivity of *bcl-6* in DLBCL is found in typical DLBCL and not in DLBCL transformed from indolent lymphoma. We believe that this data reinforces the hypothesis of a direct lymphomagenesis of HCV in DLBCL^[22]. B cell receptors can bind HCV and efficiently internalize the virus, possibly causing genomic instability^[21,23-25]. This mechanism might be involved in a possible scenario of direct lymphomagenesis. Direct lymphocyte transformation has been demonstrated for Epstein-Barr virus, human herpes virus 8, and human T lymphotropic virus 1. However this mechanism, even if intriguing, has not been conclusively demonstrated for HCV^[26].

Because the etiopathogenetic mechanisms underlying HCV-related low and high-grade B-NHL may differ, the optimal management approach also differs. Indolent, HCV-related B-NHL is a subset of neoplasms characterized by an unrelenting course that requires chemotherapy only if an aggressive behaviour develops. In this subset of lymphomas, antiviral treatment alone may eradicate

the HCV infection and stop the chronic antigen-driven lymphoproliferation. Clinical studies have demonstrated the efficacy of antiviral treatment in these patients^[9-11]. A systematic review of Gisbert *et al*^[8] has shown that in 65 HCV infected patients with lymphoproliferative disorders treated with antiviral regimen, CR was achieved in 75% of cases. In contrast, HCV negative patients did not respond to interferon, indicating that CR in HCV positive patients was not merely due to the antiproliferative action of interferon.

Our study confirms that combined antiviral therapy is effective in inducing CR in indolent, HCV-related B-NHL, and that reaching SVR seems to be crucial in maintaining it. In our studies most patients reaching SVR achieved a CR, while 2 patients relapsing after treatment had a progression of haematologic disease. However, two of the HCV positive, indolent B-NHL reaching SVR had a PR, suggesting that other mechanisms may intervene in determining CR. Obviously, the high percentage of SVR obtained in this group is also associated to the elevated prevalence of genotype 2, a well known easier-to-treat genotype. However, antiviral therapy of HCV-positive indolent B-NHL is an attractive therapeutic option, even if SVR is the objective.

For HCV-positive DLBCL, immunochemotherapy is necessary. A recently published paper observed that HCV-positive status is a risk factor for the development of hepatitis flare in patients treated with rituximab-containing regimens. In this retrospective study none of the HCV-negative lymphoma patients receiving rituximab-containing therapy developed hepatitis flares as compared with a significant percentage in the HCV positive group. However, even if no liver-related deaths deriving from the hepatitis flare were observed in this paper, it was impossible to define the exact mechanism of toxicity^[27]. In our

study we treated all HCV-positive DLBCL patients with CHOP-R regimen, and CR was obtained and maintained over the period in 7 of 13 patients despite the persistence of HCV infection. Hepatotoxicity, expressed by an increase in transaminases and bilirubin, was noted in 2 patients, with liver biopsy showing cirrhosis in both (patients 14 and 24). However, in our study none of the patients had to stop or modify treatment because of liver-related complications.

In conclusion, indolent HCV-related B-NHL and DLBCL have different biological and clinical features: the former is associated with a higher prevalence of HCV genotype 2 and a longer exposure to HCV infection, whereas the latter more frequently shows infection with genotype 1 and a shorter duration of HCV exposure. These characteristics and the differential response of indolent HCV-related lymphomas to antiviral treatment suggest that these two groups might follow different pathways of lymphomagenesis. Thus, we strongly believe that antiviral treatment should be the first line of treatment to be offered in these patients. As far as the treatment of DLBCL patients is concerned, we observed that liver-related complications can develop in HCV-positive cases, but these are marginal and do not require modifications to the onco-hematological treatment schedule, thus not affecting the opportunity of obtaining CR. Further studies are needed to determine the utility of antiviral treatment as consolidation therapy after cytostatic treatment for high-grade B-NHL.

COMMENTS

Background

Non Hodgkin's Lymphoma (NHL) is the hematologic malignancy with the highest prevalence worldwide. Among the risk factor for NHL are primary and acquired immune deficiency as well as several infectious agents such as hepatitis C virus (HCV). A positive association between HCV and NHL has been confirmed in a large number of studies. It has been reported that clearance of HCV infection by antiviral treatment led to regression of the tumor burden in indolent HCV-related NHL, while the therapeutic approach for HCV-related high grade NHL could be different. In this study the authors have analyzed and compared the biological and clinical features of HCV-related indolent B cell-non Hodgkin's lymphoma (B-NHL) *vs* HCV-related high grade lymphomas, such as diffuse large B cell lymphoma. Furthermore, the authors have evaluated the outcomes of the different treatment approaches used in the management of these two types of B-NHL, and evaluated the influence of HCV infection on disease course.

Research frontiers

HCV-related lymphomagenesis could be due to different immunopathologic mechanisms. While in indolent HCV-related lymphoma an indirect role of HCV in lymphomagenesis is hypothesized, in HCV-related high grade lymphoma a direct mechanism could be possible. A deep understanding of the mechanism of HCV lymphomagenesis is essential for the development of further therapeutic approaches.

Innovations and breakthroughs

This is the first study that has analyzed and compared the biological and clinical features of two subtypes of HCV-related B cell NHL. Characteristics of HCV infection such as viral genotype, duration of HCV infection, and histopathology could be of fundamental importance to understand the different treatment approaches used in the management of these two subtypes of HCV-related B cell NHL.

Applications

The observations could have clinical importance for future therapeutic approaches in HCV-related B cell NHL.

Terminology

HCV-related B cell NHL is a lymphoma that is linked to HCV infection

Peer review

This is a study that analyzes the mechanism of HCV-related lymphomagenesis and then the rationale of therapeutic approaches.

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 AGA Clinical Congress of
 Gastroenterology and Hepatology:
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 Miami, FL 33101, United States

January 20-22, 2011
 Gastrointestinal Cancers Symposium
 2011
 San Francisco, CA 94143, United
 States

January 27-28, 2011
 Falk Workshop, Liver and
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 Franz-Josef-Strauss-Allee 11
 Regensburg 93053, Germany

January 28-29, 2011
 9. Gastro Forum München
 Munich, Germany

February 13-27, 2011
 Gastroenterology: New Zealand
 CME Cruise Conference
 Sydney, NSW, Australia

February 17-20, 2011
 APASL 2011-The 21st Conference of
 the Asian Pacific Association for the
 Study of the Liver
 Bangkok, Thailand

February 22, 2011-March 04, 2011

Canadian Digestive Diseases Week
 2011
 Vancouver, BC, Canada

February 24-26, 2011
 Inflammatory Bowel Diseases
 2011-6th Congress of the European
 Crohn's and Colitis Organisation
 Dublin, Ireland

March 3-5, 2011
 42nd Annual Topics in Internal
 Medicine
 Gainesville, FL 32614, United States

March 7-11, 2011
 Infectious Diseases: Adult Issues in
 the Outpatient and Inpatient Settings
 Sarasota, FL 34234, United States

March 14-17, 2011
 British Society of Gastroenterology
 Annual Meeting 2011
 Birmingham, England, United
 Kingdom

March 17-20, 2011
 Mayo Clinic Gastroenterology &
 Hepatology 2011
 Jacksonville, FL 34234, United States

March 18, 2011
 UC Davis Health Informatics:
 Change Management and Health
 Informatics, The Keys to Health
 Reform

Sacramento, CA 94143, United States

March 25-27, 2011
 MedicReS IC 2011
 Good Medical Research, Istanbul,
 Turkey

March 26-27, 2011
 26th Annual New Treatments in
 Chronic Liver Disease
 San Diego, CA 94143, United States

April 25-27, 2011
 The Second International Conference
 of the Saudi Society of Pediatric
 Gastroenterology, Hepatology &
 Nutrition
 Riyadh, Saudi Arabia

May 7-10, 2011
 Digestive Disease Week
 Chicago, IL 60446, United States

May 19-22, 2011
 1st World Congress on Controversies
 in the Management of Viral Hepatitis
 (C-Hep), Palau de Congressos de
 Catalunya, Av. Diagonal, 661-671
 Barcelona 08028, Spain

May 21-24, 2011
 22nd European Society of
 Gastrointestinal and Abdominal
 Radiology Annual Meeting and
 Postgraduate Course
 Venice, Italy

May 25-28, 2011
 4th Congress of the Gastroenterology
 Association of Bosnia and
 Herzegovina with international
 participation, Hotel Holiday Inn,
 Sarajevo, Bosnia and Herzegovina

June 11-12, 2011
 The International Digestive Disease
 Forum 2011
 Hong Kong, China

June 13-16, 2011
 Surgery and Disillusion XXIV
 SPIGC, II ESYS
 Napoli, Italy

June 22-25, 2011
 ESMO Conference: 13th World
 Congress on Gastrointestinal Cancer
 Barcelona, Spain

October 19-29, 2011
 Cardiology & Gastroenterology
 Tahiti 10 night CME Cruise
 Papeete, French Polynesia

October 22-26, 2011
 19th United European
 Gastroenterology Week
 Stockholm, Sweden

October 28-November 2, 2011
 ACG Annual Scientific Meeting &
 Postgraduate Course
 Washington, DC 20001, United
 States



INSTRUCTIONS TO AUTHORS

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- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ, Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract

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- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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- 12 **Breedlove GK**, Schorheide AM. Adolescent pregnancy. 2nd ed. Wicczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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- 15 Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis* serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

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- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean \pm SD or mean \pm SE.

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