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ORIGINAL ARTICLE

# Hepatitis B and C Virus Reactivation Patterns in a Romanian Cohort of Patients with Chronic Lymphoproliferative Disorders

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**Abstract** Hepatitis B and C virus (HBV and HCV) reactivations have become more common following the intensive use of biological therapies for the treatment of chronic lymphoproliferative disorders (CLD). We evaluate risk factors for virus reactivation and exitus in patients diagnosed with CLD and HBV or HCV infection, undergoing rituximab-chemotherapy (R-chemo). A prospective, observational study in two tertiary-care Romanian hospitals, between December 2007 and May 2010, of patients diagnosed with CLD undergoing R-chemo. HBV and HCV serological markers, viral load, fibrosis and necroinflammation were assessed at baseline and every 3–6 months. We screened 502 patients diagnosed with CLDs (77.2% non-Hodgkin lymphomas) and enrolled 57 patients with HBV and/or HCV infection with a mean age of 61.35 ± 11.1 years. The replicative virus was HBV in 23 patients (40.3%), HCV in 33 patients (57.9%). HCV reactivation rate (15.6%) was lower than for HBV (45.5%) ($p = 0.02$). In univariate analysis, viral reactivation was associated with aggressive CLD ($p = 0.01$), HBV ($p = 0.01$) and lymphopenia ($p = 0.02$). Death was associated with aggressive CLD ($p = 0.01$), viral reactivation ($p = 0.001$) and high baseline viremia ($p = 0.05$). In multivariate analysis, viral reactivation was associated with lymphopenia (OR 0.05, 95% CI 0.003–0.85, $p = 0.03$). Risk of death was 10 times higher for patients with viral reactivation (95% CI 1.54–65.5, $p = 0.01$). A quarter of the infected patients were diagnosed with viral reactivation. While hepatitis C was more prevalent than hepatitis B in patients with CLD, viral reactivation was found 3 times more frequently in patients with hepatitis B than C.

**Keywords** Lymphoproliferative disorders · Hepatitis B virus reactivation · Hepatitis C virus reactivation · Biological therapies

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**Abbreviations**

| | |
|---|---|
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| CLD | Chronic lymphoproliferative disorder |
| NHL | Non-Hodgkin lymphoma |
| CHB | Chronic hepatitis B |
| CHC | Chronic hepatitis C |
| R-chemo | Rituximab-chemotherapy |

## Introduction

Apart from liver tropism, hepatitis B and hepatitis C viruses (HBV, HCV) express lymphotropism, replicating in peripheral blood mononuclear cells, lymph nodes and bone marrow. Romania still has an intermediate prevalence of chronic hepatitis B (CHB) (4.2%) and a high prevalence of HCV (5.6%) [1]. The predominant genotype is 1b. HCV infection can be associated with extra-hepatic involvement, especially with type II and III cryoglobulinemia (a benign chronic lymphoproliferative disorder—CLD) and B cell non-Hodgkin lymphoma (NHL).

Several studies have reported that CHB and chronic hepatitis C (CHC) are independent risk factors for B-cell NHL, increasing their associated mortality and morbidity [2, 3]. The prevalence of HBV or HCV infection in patients with NHLs is 2–3 times higher than in general population [4]. Patients with CHB or CHC receiving rituximab and chemotherapy (R-chemo) for CLDs have a high risk of viral reactivation and of developing a severe form of hepatitis and exitus because of fulminant hepatic failure. Viral reactivation is a frequent cause of R-chemo discontinuation [4]. Our objective was to evaluate the patterns of viral reactivation and death in patients with CLDs diagnosed with CHB and/or CHC, undergoing R-chemo, which consisted of rituximab + either of CVP (cyclophosphamide, vincristine, prednisone)/CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)/CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone).

## Materials and Methods

We performed a prospective observational study that enrolled patients with CLDs (chronic lymphocytic leukemia—CLL, Hodgkin lymphoma—HL, non Hodgkin lymphoma-NHL) undergoing R-chemo and who had associated HBV or HCV infection. Study participants were enrolled between December 2007 and May 2010 and were monitored in a Hematology Department and an Infectious Diseases Department, both tertiary-care hospitals.

We included patients aged $\geq$ 18 years, able to provide a written informed consent. The patients were divided into two groups according to the replicative virus (HBV and/or HCV). The study was approved by the local ethics committee.

Bone-marrow and extra-medullary biopsies followed by flow cytometric immunophenotyping (BD FACSCalibur desktop flow cytometer, Becton–Dickinson, Franklin Lakes, NJ, USA) and immunohistochemistry techniques (the two-step Envision$^{TM}$ + Dual Link System-HRP IHC staining technique, Dako North America, Carpinteria, CA, USA) were performed in all patients. Baseline viral hepatitis assessment included viral load, FibroMax, and abdominal ultrasound. DNA and RNA levels were determined every 3–6 months and a hematological evaluation was performed before every round of R-chemo. HBV-DNA levels were performed for patients tested positive for at least one serological marker of HBV infection and HCV RNA level was determined in all patients positive for anti-HCV antibodies. Serological tests were repeated 3 and 6 months after the initiation of immunosuppressive therapy. HBsAg, anti-HBs, HBeAg, anti-HBe, IgM anti-HBc, IgG anti-HBc, anti-HCV were determined using the MEIA method (ARCHITECT i2000SR Immunoassay Analyzer, Abbott Laboratories, Libertyville, IL, USA).

Real time PCR quantification assays were performed to evaluate HBV DNA and HCV-RNA levels (COBAS TaqMan 48 analyzer, Roche Molecular Diagnostics, Pleasanton, CA, USA).

### Definitions [5]

HBV reactivation was defined as an increase in HBV DNA level $\geq$ 2 $\log_{10}$ versus the baseline value or the detection of a HBV DNA level $\geq$ 100 IU/ml in a patient who previously had an undetectable/stable viral load. HCV reactivation was defined as an increase in HCV RNA level $\geq$ 1 $\log_{10}$ versus the baseline value.

CLL was diagnosed by evaluation of the blood count, blood smear, and the immune phenotype of the circulating lymphoid cells. A value of at least $5 \times 10^9$ B lymphocytes/L (5000/μL) in the peripheral blood is required for diagnosis. NHLs were defined by assessing the immunophenotype of the malignant lymphoid population by immunohistochemistry using modified REAL and WHO classifications [6–8]. Lymphopenia was defined as an absolute lymphocyte count less than 1.2 cells/μL $\times 10^3$, which is the lower limit of normal in our clinic and according to the definition of the Merk Manual of Diagnosis and Therapy 19th Ed [9].

### Statistical Analysis

Data were processed using IBM® SPSS® Statistics version 22 software (New York, USA). In descriptive analysis, normally-distributed variables were expressed as mean ± standard deviation (SD) and non-Gaussian variables as median with interquartile range. In univariate analysis we used Chi square test for the association of dependable variables and possible risk factors. Statistical significance was defined as two-tailed $p < 0.05$.

## Results

### Patient Characteristics

We screened 502 patients diagnosed with CLDs and enrolled 57 patients with HBV and/or HCV infection. The mean age at baseline was 61.3 ± 11.1 years. The most common age group was 60–70 years (36.8% of participants) and the female/male ratio was 1.2. The prevalence of hepatic viruses in our study was 11.35%.

In patients co-infected with two hepatitis viruses, we took into consideration the replicative virus only, so the study group was separated as follows (Table 1): 23 cases with CLD and HBV as the replicative virus (40.3%)—HBV group, 33 patients with CLD and HCV as the replicative virus (57.9%)—HCV group. One patient had no replicative virus. Women were more frequent than men in the HCV group (75.8%) versus the HBV group which had consisted predominantly of men (60.9%) ($p = 0.01$).

**Table 1** The correlation of HBV and HCV viral replication with various clinical and biological parameters

| Variable, n (%) | HBV replicative group (n = 23) | HCV replicative group (n = 33) | *p* value |
|---|---|---|---|
| Female gender—n (%) | 9 (39) | 25 (76) | 0.01 |
| Aggressive histologic types—n (%) | 13 (57) | 14 (42) | 0.41 |
| Non-Hodgkin lymphomas—n (%) | 15 (65) | 28 (85) | 0.08 |
| Splenomegaly—n (%) | 10 (44) | 20 (61) | 0.28 |
| Hepatomegaly—n (%) | 16 (70) | 24 (73) | 0.8 |
| Cryoglobulinemia—n (%) | 0 (0) | 8 (24) | 0.01 |
| Viral reactivation—n (%) | 10 (45.5) | 5 (15.6) | 0.02 |
| Fibrosis F4 (cirrhosis)—n (%) | 4 (17) | 9 (27) | 0.52 |
| Deaths—n (%) | 6 (26) | 4 (12) | 0.17 |

*HBV* hepatitis B virus, *HCV* hepatitis C virus

The most common CLD was NHL (40 cases were B-cell NHLs and 4 patients had T-cell NHLs) followed by CLL (10 cases), HL (2 cases) and Waldenström's macroglobulinemia (1 patient). The histologic types of CLD were evenly distributed amongst the two study groups, so that NHLs and CLL were the main CLDs affecting the HBV and HCV groups ($p = 0.08$).

### Evaluation of the Severity of CLD

An aggressive histological type of CLD was discovered in almost half of all patients (47.4%) In the HBV group, the aggressive type was more common (56.5%) versus HCV group (36.4%), ($p = 0.42$). Considering all the patients, the lymphocyte absolute count was normal in 72.2% of the cases, lymphopenia was present in 9.3% of cases and lymphocytosis in 18.5%.

### Evaluation of the Viral Infection

Hepatomegaly and splenomegaly were present respectively in 69.6% and 43.5% in HBV group, versus 72.7% and 60.6% in HCV group ($p = 0.28$). HBV DNA levels $> 10^6$ copies/ml and HCV RNA > 600.000 IU/ml were considered high levels; these were detected in 50% of patients from the HBV group and 48.5% from the HCV group.

A FibroMax test was used for 41 of the 57 study participants (72%). 52.5% of them had severe fibrosis (F3 and F4), 38.5% had severe necroinflammatory activity (A2 and A3) and 32.3% had an S2–S3 steatosis score. Eight cases (14%) of cryoglobulinemia were discovered amongst patients from the HCV group ($p = 0.016$).

### Characteristics of Patients with Viral Reactivation

Viral reactivation occurred overall in 15 patients (28.1%). This was correlated with the aggressive histological type of CLD, with 12 cases of reactivation being discovered amid aggressive CLD versus 4 cases amid indolent CLD ($p = 0.019$). Also, HBV-reactivation was significantly more common (45.5%) than HCV-reactivation (15.6%) ($p = 0.02$).

The HBV-reactivation group had a sex ratio M:F = 1.75, a mean age of 52.9 ± 11.6 years and a predominance of aggressive B-cell NHLs. Patients were treated with Lamivudine and had a favorable outcome. No deaths caused by hepatic failure were registered.

The HCV-reactivation group had a mean age of 61.8 ± 8.7 years, a sex ratio F:M = 1.5 and B-cell NHL was the most common CLD (4 times more frequent than other CLD). Alanine aminotransferase (ALAT) was increased in 2 out of 5 cases. One death occurred secondary

**Table 2** Multivariate analysis for significant factors of patients with viral hepatitis reactivation and death

| Independent variables in multivariate analysis | Viral hepatitis reactivation | | Death | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | *p* value | Odds ratio (95% CI) | *p* value |
| Age | 1.03 (0.96–1.11) | 0.33 | 1.01 (0.94–1.1) | 0.65 |
| Type of CLD (aggressive vs. indolent) | 0.227 (0.048–1.07) | 0.06 | 4.63 (0.66–32.3) | 0.12 |
| Main/single replicative virus (HBV vs. HCV) | 0.279 (0.06–1.32) | 0.1 | NA | NA |
| Lymphopenia versus normal/high lymphocyte count | 0.049 (0.003–0.85) | 0.03 | NA | NA |
| Viral reactivation versus no reactivation | NA | NA | 10.1 (1.54–65.5) | 0.01 |
| High versus low viral load at baseline | NA | NA | 5.2 (0.88–30.3) | 0.06 |

*HBV* hepatitis B virus, *HCV* hepatitis C virus, *CLD* chronic lymphoproliferative disorder

to acute liver failure in a patient with an aggressive type of NHL treated with rituximab-CHOP.

In univariate analysis, the viral reactivation was associated with the aggressive type of CLD ($p = 0.01$), HBV infection ($p = 0.01$) and lymphopenia ($p = 0.02$). In multivariate analysis (Table 2), patients with lymphopenia only had a 0.05 times higher risk of developing reactivation versus those with normal lymphocytes/lymphocytosis. There is a correlation of borderline significance between HBV reactivation and the aggressive form of CLD.

### Risk Factors for Death

During the follow-up period 10 patients died (17.5%); 8 cases had an aggressive type of CLD and 2 cases were diagnosed with an indolent CLD. There was a significant correlation between this outcome and baseline viral load ($p = 0.05$), the aggressive type of CLD ($p = 0.01$) and viral reactivation ($p = 0.001$). One death was attributed to acute liver failure secondary to HCV-reactivation.

In multivariate analysis, the risk of death was 10 times higher for patients with viral reactivation ($p = 0.01$) versus cases without HBV or HCV-reactivation and 5 times higher for participants with increased baseline viral load ($p = 0.06$).

### Treatment

All patients underwent immunosuppressive drug therapy (CVP/CHOP/CHOEP + rituximab) for the underlying hematological disorder and 14 cases (24.5%) received antiviral treatment: lamivudine for HBV infection (10 patients—treatment was started after the diagnosis of viral reactivation was made and had a favorable outcome) and ribavirin + PEG interferon for HCV (4 cases—treatment was initiated after remission of the CLD and led to sustained virologic response).

During our research study, no consensus was available in local clinical guidelines regarding the complete screening for hepatitis viruses and the pre-emptive antiviral therapy for selected cases. Presently, all candidates for immunosuppressive therapy are screened for the presence of viral hepatitis infection [10].

## Discussions

Our study is the first prospective study conducted in Romania that evaluated the risk factors for viral hepatitis reactivation in patients diagnosed with CLDs undergoing R-chemo. In univariate analysis, the viral reactivation was associated with the aggressive type of CLD, HBV infection and lymphopenia, while death was linked to aggressive CLD, viral reactivation and high baseline viremia. The histologic type of NHL, hepatomegaly and female gender were risk factors for HCV reactivation. In multivariate analysis, lymphopenia seemed a protective independent factor for viral reactivation. Risk of death was 10 times higher in patients with viral reactivation versus cases without HBV-reactivation or HCV-reactivation and 5 times higher in patients with considerable baseline viral load (the latter result at the edge of statistical significance).

HCV was more common than HBV among our patients with CLDs, a finding supported by other studies [10, 11]. NHL was the most prevalent type of CLD discovered; its presence is associated with HBV and HCV infections, a situation described by similar studies [4]. The incidence of HBV reactivation in NHL patients undergoing R-chemo is 20–55% [12, 13]. In a retrospective cohort study, Yang et al. [13] found that the absence of pre-emptive antiviral treatment led to a 38.7% incidence of HBV-reactivation, viral hepatitis (33% of cases), acute liver failure (13%) and death (5.5%). During the period of our study, 45.5% of patients from the HBV group developed HBV-reactivation, significantly more men than women; similar results were reported by other investigators [14, 15].

Yeo et al. and Lok et al. discovered that younger age was a risk factor for HBV-reactivation, unlike our study

which found no correlation with age [15, 16]. HBV-reactivation occurred mainly in patients with an aggressive type of CLD and in NHLs versus other types of CLD. Baseline lymphopenia, which relates to the degree of immunosuppression, was also associated with HBV-reactivation.

The main HBV genotypes found in Romania are the A (8.1%), D (60.5%) and a recombinant form of A and D genotypes (31.4%). Pre-core (36.4%) and basal core promoter mutations (34.9%) are also frequently encountered [17, 18]. Some authors consider that the presence of HBeAg is a risk factor for viral reactivation, however immunosuppressive drug therapy does not seem to place a preferential selection pressure on wild-type or mutant HBV [18–21]. Two patients from our study were negative for both HBeAg and anti-HBe, probably due to severe immunosuppression.

Without proper pre-emptive antiviral therapy, HBV reactivation can occur in over 85% of patients with NHLs if they are also treated with corticosteroids. The prophylactic use of nucleoside/nucleotide analogues prevents the reactivation of hepatitis B virus and its associated complications. One participant from our study, which went under remission for NHL, also underwent HBs seroconversion, with the appearance of protective levels of anti-HBs after 5 years of antiviral treatment. No cases of death caused by HBV reactivation were registered in our research despite the fact that other studies found a mortality rate of 30–50% correlated with HBV infection [12, 21–25].

A new medical protocol was approved in Romania regarding the prophylaxis of HBV reactivation in candidates for immunosuppressive therapy. It advocates for the screening for HBV, HCV infections, with IgG anti-HBc besides HBsAg and anti-HBs. The use of pre-emptive antiviral therapy for HBsAg-positive patients is justified by the increased risk of HBV reactivation, a situation that can also affect the evolution of the hematological disorder. In our study 10 patients received lamivudine 100 mg/day after the diagnosis of viral reactivation and had a favorable outcome.

HCV reactivation rate obtained from our research is similar to that found by other studies, mainly conducted in high-prevalence areas. Small sample studies found a relatively low risk of HCV reactivation amongst cancer patients [26, 27]. Rituximab therapy can increase the replication of HCV; this is not always followed by increases in ALAT levels. The mortality rate of HCV reactivation is lower than that of HBV reactivation. Fulminant hepatitis was reported to occur following the end of chemotherapy, a situation that is difficult to anticipate. In this case, HCV RNA had a low level due to strong immune reaction so this test would not be helpful in the differential diagnosis [28]. Ideally, complete eradication of HCV should take place prior to immunosuppressive therapy [29].

Screening for HCV infection is mandatory when a lymphoma diagnosis is made, and HCV RNA level should also be determined at baseline and during immunosuppressive treatment in order to detect viral reactivation. Currently there is no prediction method for the individual risk of HCV reactivation. The outcomes of HCV reactivation seem to be less severe than those in HBV reactivation. However, the mortality rates for hepatitis caused by viral reactivation are similar for HBV and HCV reactivation [30].

One patient included in our HCV study group had negative results for anti-HCV and a high level of HCV RNA, probably caused by severe immunodeficiency. Such a case should act as a warning for doctors who monitor oncologic and hematologic patients for the occurrence of HCV infection.

The current international clinical guidelines recommend the screening of all candidates for immunosuppressive therapy, including patients with CLDs for the presence of HBV and HCV infection. The implementation of new therapies for HCV infection and new treatment guidelines provide an option to cure this disease and can also contribute to a reduction in HCV reactivation for patients with CLDs undergoing immunosuppressive drug therapy. It is hoped that HCV eradication will lead to a decrease in the incidence rate of CLDs.

At the time of the study, direct acting antivirals (DAA) for HCV therapy were not yet available. According to a future local protocol, starting with 2018, Romanian patients with HCV infection and malignant lymphoproliferations will have quick priority access to DAA therapy regardless of the degree of fibrosis. Nevertheless, patients can still be diagnosed first with lymphoproliferative diseases and then with hepatitis C. Moreover, sometimes they need to start chemotherapy sooner than the 3 months which would correspond to the DAA treatment. Therefore the risk of viral reactivation may still be a challenge in DAA era.

Our present research evaluated the risk factors for viral hepatitis reactivation in patients diagnosed with CLDs undergoing R-chemo. So far only case series, retrospective and prevalence studies were published on this subject. A multidisciplinary team of doctors took part in the current study, which addresses an important healthcare issue and that finally led to the implementation of a national management protocol which recommends complete serological screening for HBV infection for all candidates requiring immunosuppressive therapy.

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**Authors' Contribution** All authors had equal contributions in writing this paper.

**Conflict of interest** No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

**Ethical Standard** This study was approved by the Ethics Committee of the National Institute for Infectious Diseases "Prof. Dr. Matei Balş" and the University Emergency Hospital Bucharest, Bucharest, Romania.

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