

## MANAGEMENT OF NON-HODGKIN LYMPHOMAS ASSOCIATED WITH CHRONIC VIRAL INFECTIONS

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### Abstract

*The number of viruses known to have pathogenetic and therapeutic implications in non-Hodgkin lymphomas (NHL) has increased significantly during the last years. Some of these viruses have direct oncogenic effect, for exemple Epstein-Barr virus, Human T-cell lymphotropic virus-1 or human herpesvirus-8, while others cause lymphoma due to chronic antigenic stimulation (like hepatitis C virus) or due to immunosuppression associated with the virus, which is the case of human immunodeficiency virus. Beside their role in pathogenesis, lymphoma-associated viral infections have major therapeutic implications. Treatment of these lymphomas is difficult because of the risk of reactivation after immunosuppressive treatment which could cause severe organ-damage (like severe hepatitis in case of hepatitis virus B or C reactivation), resulting sometimes in the reduction of the scheduled doses or even treatment discontinuation. These patients should be monitored carefully and antiviral therapy should be associated to chemotherapy. In other cases, especially in indolent NHL (for example splenic marginal zone lymphoma associated with hepatitis C virus), antiviral therapy alone could lead to regression of lymphoma. Recognizing this category of NHL is important because correct management of them could improve survival of the patients.*

**Keywords:** non-Hodgkin lymphoma, viruses, reactivation, chemotherapy.

## TRATAMENTUL LIMFOAMELOR NON-HODGKIN ASOCIATE CU INFECȚII VIRALE

### Rezumat

*Numărul virusurilor cunoscute ca având implicații patogenetice și terapeutice în limfoame a crescut considerabil în ultimii ani. Unele dintre aceste virusuri au efect oncogenic direct, ca de exemplu virusul Epstein-Barr, virusul limfotropic uman-1 sau herpesvirusul-8, în timp ce alte virusuri cauzează limfoame datorită stimulării antigenice cronice (de exemplu virusul hepatitic C) sau datorită imunodeficienței asociate infecției virale, cum este cazul virusului imunodeficienței umane. Pe lângă rolul patogenic, aceste infecții virale au și implicații terapeutice majore. Tratamentul limfoamelor asociate cu infecții virale este dificil, datorită riscului de reactivare în urma tratamentului imunosupresiv, putând conduce la afectare organică severă (de exemplu hepatită fatală în urma reactivării virusului hepatitic B sau C), cauzând de multe ori reducerea dozelor de chimioterapie sau chiar întreruperea tratamentului. Acești pacienți trebuie monitorizați atent și tratamentul antiviral trebuie asociat chimioterapiei. În unele limfoame indolente, cum este cazul limfomului splenic de zonă marginală asociat cu hepatită cronică C, tratamentul antiviral singur poate conduce la regresia limfomului. Recunoașterea acestor categorii de limfoame este importantă, deoarece managementul corect al lor poate îmbunătăți supraviețuirea pacienților.*

**Cuvinte cheie:** limfom non-Hodgkin, virusuri, reactivare, chimioterapie.

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## Introduction

The number of viruses associated with non-Hodgkin lymphomas (NHL) has increased during the last years. The following viruses are known to have pathogenetic and therapeutic implications in lymphoma: hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein-Barr virus (EBV), cytomegalic virus (CMV), human immunodeficiency virus (HIV), human T-cell lymphotropic virus (HTLV 1) and human herpesvirus-8 (HHV-8). Some of them cause lymphoma by direct oncogenesis (e.g. EBV associated with Burkitt lymphoma, HHV-8, HTLV-1), while others cause lymphoma due to chronic stimulation of the immune system (for example HCV) or due to immunosuppression (HIV). Successful treatment of these virus-associated NHL is often difficult due to the risk of reactivation of infection during chemotherapy or immunosuppressive treatment, requiring sometimes interruption of treatment or dose reduction to prevent a fatal hepatitis. In other cases, like in low-grade lymphomas, antiviral treatment alone can lead to THE remission of lymphoma (for example in HCV-associated splenic lymphoma).

### 1. HBV and non-Hodgkin lymphomas

In case of HBV there is no direct pathogenetic correlation between the virus and lymphoma but the presence of HBV has major therapeutic implications. Chemotherapy or immunosuppressive drugs could lead to reactivation or acceleration of a pre-existing chronic hepatitis. Reactivation could have several clinical manifestations, ranging from self-limiting anicteric to fulminant forms or to chronic hepatitis with an accelerated clinical course towards liver failure. Hepatitis reactivation may influence the continuation of treatment and survival of patients.

There are 2 forms of persistent HBV infection:

1. HBV carriers, when the hepatitis B surface antigen (HBsAg) is positive-active carriers in presence of hepatitis B envelope antigen (HBeAg) or of anti-HBe antibodies and of a viral load  $> 20.000$  IU/ml or inactive carriers, in case of subjects HBeAg negative and anti-HBe positive, HBV DNA  $< 20.000$  IU/ml.

2. Occult HBV carriers (HBsAg negative) with positive anti-HBc (hepatitis B core antigen) antibodies [1].

### Pathogenesis of HBV-related liver dysfunction

Reactivation means the return of the active necrotic-inflammatory liver disease in a known inactive HBsAg carrier or in a person with cured HBV acute infection. Reactivation might take place during immunosuppressive treatment or immediately after. In most cases, reactivation is followed by an asymptomatic increase of aminotransferase levels, sometimes by hepatitis with jaundice, hepatic failure or death [1,2].

The natural history of HBV infection consists of 4 phases: immune tolerance phase, immune clearance phase,

inactive HBsAg carrier state and reactivation phase.

HBV is a DNA virus which integrates in the host's cell genome. It remains within the liver for decades. The notion of "cure" does not imply viral clearance, only immunological control of the disease. Reactivation requires the alteration of balance between the host's immune response and viral replication. Liver injury is a 2-step process:

1. First, during chemotherapy, the viral replication amplifies with an increase of serum HBV DNA and anti-HBe antibodies level, the reappearance of HBsAg and decrease of anti-HBs antibodies level, resulting in spreading the liver infection.

2. During the immunological reconstruction at the end of chemotherapy, there is a massive and rapid destruction of infected hepatocytes, manifested by increase of aminotransferase level, hepatitis, liver failure and, sometimes, death [2].

### Risk factors for reactivation of HBV infection:

- increased HBV DNA level ( $> 1$  million copies/ml)
- positive HBsAg and HBeAg
- highly active immunosuppressive chemotherapy regimens, therapy including glucocorticoids and Rituximab (monoclonal anti-CD20 antibodies)
- male gender
- young age
- pre-core or core promoter HBV mutations [2]

### Management of patients with lymphoma and HBV infection

All patients with lymphoma who are going to receive chemotherapy or immunotherapy with Rituximab should be tested for HBsAg and anti-HBe antibodies. If HBsAg is detectable, HBeAg, anti-HBe antibodies and viral load should be determined and prophylactic antiviral treatment should be initiated.

The aim of antiviral treatment is to prevent cytolysis and symptomatic liver disease. It decreases the risk of severe hepatitis, increases the adherence to chemotherapy and prevents dose-reductions or therapy discontinuation. The following antiviral agents are used in prophylactic treatment: Lamivudine, Adefovir, Entecavir and Telbivudine. Lamivudine often induces the selection of resistant mutants in locus YMDD, while Entecavir induces it at a lower rate. Interferon alpha is contraindicated due to its myelosuppressive effect. It is recommended to start antiviral therapy 7 days before chemotherapy and to continue it for 6 month after the end of therapy. In patients with high viral load, treatment should be continued for one year. Patients who are negative for HbsAg but with positive anti-HBe antibodies should be monitored frequently (HBV DNA every four weeks) to detect an increase of viral replication as soon as possible and antiviral treatment should be started in case of increase of viral load.

Monitoring of patients should be extended for 6-8 month after the end of therapy, especially in patients who received Rituximab [2].

A recent retrospective study published by Chinese authors analyzed the prevalence and mortality of HBV reactivation in HBsAg-positive patients with NHL undergoing rituximab based-therapy. From the 50 patients enrolled in this study, 30 received prophylactic treatment with Lamivudine, while 20 patients didn't receive Lamivudine prophylaxis. They've found a higher prevalence of HBV reactivation (60% vs. 13,3%), severe hepatitis (45% vs. 6,7%), and mortality (25% vs. 3,3%) in the group without Lamivudine prophylaxis [3].

## 2. HCV and non-Hodgkin lymphoma

The prevalence of HCV infection is higher in patients with B-cell NHL (approximately 15%) than in general population (approximately 1,5%), suggesting a role of HCV in the etiology of B-cell non-Hodgkin lymphoma, while T-cell and Hodgkin lymphoma show no association with HCV. The most frequent association is with lymphoplasmacytoid lymphoma, up to 30% of patients with this type of lymphoma presenting HCV infection. Other histological types associated with HCV are: follicular, lymphocytic, marginal zone and diffuse large B-cell NHL. Lymphoma associated with HCV often present as primary extranodal lymphoma (especially in liver, spleen, salivary glands) [4].

HCV is an RNA virus, unable to integrate into the host's genome and does not encode any oncogenes. HCV can infect the B lymphocytes, leading to malignant lymphoma by a multistep pathonegetic pathway: first, HCV induces an oligoclonal proliferation of B-cells carrying the virus chronically, then the presence of HCV in lymphocytes could initiate growth disturbances and predispose the lymphocyte to the development of further molecular changes, leading eventually to malignant lymphoma. The HCV E2 envelope protein has been identified as a potential antigen that may drive the development of lymphoma [5].

## Pathogenesis of HCV-related liver dysfunction

HCV-related liver dysfunction usually occurs 2-4 weeks after the termination of chemotherapy. In the early phase, due to immunosuppression caused by chemo- or immunotherapy, the balance between the host's immune system and viral replication is disrupted, with a consequent increase in the number of infected hepatocytes. Withdrawal of immunosuppressive therapy leads to the restoration of the immune function resulting in rapid destruction of the infected cells and hepatic injury, the so called „immune reconstitution hepatitis” [4,5].

## Risk factors associated with liver injury:

- HBV co-infection
- High viral load and evidence of active hepatitis or

cirrhosis

- Steroid treatment, especially if abruptly terminated, combined use of chemotherapy and immunotherapy with Rituximab.

In addition to acute complication, chemoimmunotherapy may also accelerate progression to cirrhosis [6].

## Management of HCV-associated lymphoma

In all patients with positive HCV antibodies the viral load should be determined by PCR and liver biopsy should be performed to assess the liver damage before initiation of treatment. Patients with high risk should be monitored closely for serum transaminase, bilirubin and HCV RNA levels. In cases of low-grade lymphoma (for example splenic lymphoma with villous lymphocytes) antiviral treatment alone could result in regression of lymphoma, but in high grade lymphomas chemotherapy is mandatory. In contrast to HBV-associated lymphomas, where prophylactic antiviral treatment is indicated to prevent reactivation, in case of HCV-associated lymphoma there is no consensus in administration of such treatment. There are studies with concomitant administration of chemoimmunotherapy plus antiviral treatment with pegylated interferon and ribavirin which resulted in extensive hematological toxicity, thus antiviral treatment should probably only be started after chemotherapy for 3 month [6].

In a large study conducted by Visco et al., among 132 patients with NHL and HCV infection, five patients (4%) had to discontinue treatment due to severe hepatic toxicity while 15 patients (11%) required prolongation of treatment intervals or dose reduction. One patient died secondary to grade 4 hepatotoxicity. In another study, among 104 HCV-positive NHL patients, Cavanna et al. reported seven cases (6,7%) with hepatic toxicity that had modified the planned treatment and one patient died due to severe hepatotoxicity [6]. A Japanese multicenter analysis made on 553 patients with NHL, of whom 131 were HCV-positive and 422 HCV-negative, treated with rituximab containing regimens, revealed that HCV infection wasn't a significant risk factor for prognosis but it was a significant risk factor for severe hepatic toxicity [7].

## 3. EBV and non-Hodgkin lymphoma

EBV is a herpes virus associated with the following types of non-Hodgkin lymphomas: Burkitt lymphoma, post-transplant lymphoproliferative disease, primary effusion lymphoma and T/NK-cell lymphoma (nasal type). EBV is inserted into the nucleus and produces some antigens (EBNA-LP, -1, -2, -3) which are essential for immortalization of the cell and upregulation of other molecules and genes such as latent membrane proteins (LMP-1 and -2). LMPs increase the expression of BCL-2 and drive the cell into a latent state. The EBV-infected cells enter the resting phase avoiding immunosurveillance but more prone to develop secondary oncogenic changes.

EBV encodes a thymidine kinase (TK), enzyme which is the target of antiviral agents. In the latent phase of EBV infection, which is the case of EBV-associated lymphoma, this TK is not expressed, so there is a resistance to antiviral treatment. There are studies that demonstrate the effect of short-chain fatty acids such as butyrate, which induce the expression of TK in latently infected B cells. Therefore, administration of combination therapy with antiviral agents like Gancyclovir and arginine-butirate might be an effective tumor-targeted therapeutic approach. In some cases of post-transplant lymphoproliferative disorders complete remission was observed after antiviral treatment only [8,9].

#### 4. HIV and non-Hodgkin lymphoma

HIV infection increases the risk of lymphoma due to immunosuppression caused by the virus and due to chronic stimulation of B lymphocytes. Other viruses are observed in HIV-associated lymphomas, like EBV and HHV-8. HIV-associated NHLs are predominantly of aggressive histology (such as Burkitt lymphoma, diffuse large B-cell lymphoma, primary effusion lymphoma and plasmablastic lymphoma), often diagnosed at an advanced stage, present constitutional symptoms and often have extranodal onset. The incidence of lymphoma is lower in patients on highly active antiretroviral treatment [10,11].

#### Management of HIV-associated lymphoma

Before the introduction of highly active antiretroviral treatment (HAART), the prognosis of HIV-associated lymphoma was poor, but it is improving in the post-HAART era. Management of HIV-associated lymphoma is challenging due to potential pharmacological interactions and high risk of infectious complications. Antiviral therapy should be associated to chemotherapy and haematopoietic growth factors are used to prevent complications of neutropenia [12].

#### 5. CMV and non-Hodgkin lymphoma

CMV causes mostly asymptomatic infection, but in immunosuppressed patients could cause severe syndromes like interstitial pneumonia, retinitis, hepatitis, encephalitis or disseminated infection [13]. In patients with immunodepression due to the lymphoma (especially in advanced stages) or due to immunosuppressive treatment, reactivation of CMV could occur. Reactivation occurs especially after treatment with Alemtuzumab (monoclonal anti-CD52 antibody), but also after Rituximab, in most cases at 4-6 weeks after treatment initiation [14].

#### Management of CMV reactivation

All immunosuppressed patients who are going to receive monoclonal antibody treatment should be evaluated for CMV-status by PCR. Those with confirmed reactivation should be treated with Gancyclovir or Valgancyclovir for 14-21 days [15].

#### 6. HHV-8 and non-Hodgkin lymphoma

HHV-8 is associated with primary effusion lymphoma, multicentric Castlemann disease and HIV-associated lymphoma. Antiviral treatment has low efficacy due to latent form of infection [16].

#### 7. HTLV-1 and non-Hodgkin lymphoma

HTLV-1 is a retrovirus endemic in Southern Japan and the Caribbean Basin, which causes adult T-cell leukemia/lymphoma (ATLL). All patients with ATLL are seropositive for prior HTLV-1 infection but not all infected patients develop ATLL. During latency, viral products, host epigenetic changes, genetic factors and immunity influence neoplastic transformation. Prognosis of ATLL is poor, the only curative treatment is bone-marrow transplantation and no clinical benefit has been proved for specific antiviral therapy against HTLV-1 infection [17].

#### Conclusions

Management of viral-associated lymphomas is difficult, prognosis being worse than in non-infected patients, due to complications related to viral reactivation and difficulty in respecting the treatment schedules and doses.

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