THE INVOLVEMENT OF HEPATITIS VIRUSES IN THE PATHOGENESIS OF HODGKIN MALIGNANT LYMPHOMAS. EPIDEMIOLOGICAL DATA AND PATHOGENETIC MECHANISMS

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Abstract: *Viral infections proved to have an important role in oncogenesis, particularly in developing countries. The infection with hepatitis B or C was identified to be an important pathogenetic factor in the pathogenesis of chronic lymphoproliferative malignancies, especially malignant Hodgkin lymphoma (NHL) cell B. The most common types of NHL identified in the HCV seropositive patients were: NHL diffuse large B cell marginal zone NHL. HBV infection is associated with a higher incidence of clinically aggressive NHL, although HBV infection was less identified in patients with NHL than HCV infection. Recently, it was shown the possible association between the risk of NHL and hepatitis G infection, infected carriers of this virus having an increased risk of being diagnosed with NHL diffuse large cell B. In literature, there are three mechanisms of the involvement of hepatitis virus infection in the NHL pathogenesis. 1. Immunosuppression due to chronic lymphoproliferative neoplasia that could cause reactivation of viral B or C infection. 2. Transmitting and unknown virus with a pathogenic mechanism similar to the hepatitis virus and which might act as an oncogenic stimulus. 3. The existence of a causal relationship between the infection with the hepatitis virus and NHL, the hepatitis playing an oncogenic role. More recently, it is taken into consideration the involvement in lymphomagenesis, a multi cause mechanism involving the convergent action of at least two factors.*

Cuvinte cheie: *virusuri hepatitice, limfoame maligne nonhodgkin, epidemiologie, mecanisme patogenetice*

Rezumat: *Infecţiile virale s-au dovedit a avea un rol important în oncogeneză, mai ales în ţările în curs de dezvoltare. Infecţia cu virus hepatitic B sau C a fost identificată a fi un factor patogenetic important în patogeneza neoplaziilor limfoproliferative cronice, în special a limfoamelor maligne nonhodgkin (NHL) cu celulă B. Cele mai frecvente tipuri de NHL identificate la pacienţii seropozitivi pentru VHC au fost: NHL difuz cu celulă mare B şi NHL de zonă marginală. Infecţia cu VHB se asociază cu o incidenţă mai mare a NHL agresiv clinic, deşi infecţia VHB a fost mai puţin identificată comparativ cu infecţia VHC la pacienţii cu NHL. Recent s-a demonstrat posibila asociere între riscul apariţiei NHL şi infecţii, virusul hepatitic tip G, purtătorii infectaţi cu acest tip de virus având risc crescut de a fi diagnosticaţi cu NHL difuz celulă mare B. În literatură sunt menţionate trei mecanisme ale implicării infecţiei cu virus hepatitic în patogeneza NHL. 1. Imunosupresia datorată existenţei neoplaziei limfoproliferative cronice care ar putea determina reactivarea unei infecţii virale B sau C sau apariţia infecţiei. 2. Transmiterea unui virus necunoscut cu mecanism patogen similar virusului hepatic şi care ar avea rol de stimul oncogen. 3. Existenţa unei relaţii cauzale între infecţia cu virus hepatitic şi NHL, virusul hepatitic jucând rol oncogen. Mai recent se consideră implicarea în limfomageneză a unui mecanism multicauzal care implică acţiunea convergentă a cel puţin doi factori.*

Viral infections have proven to play an important role in the pathogenesis of cancer, the results of recent studies indicating an incidence of 18%, a more frequent association in developing countries (22%) vs. developed countries (7%).(1) The most frequently involved are: human papilloma viruses (5.2%), hepatitis B and C (4.9%), Epstein-Barr virus (1%), human immunodeficiency virus (HIV) and human herpes virus 8 (0.9%).(2) The published epidemiological data from some studies indicate a higher prevalence of neoplasia at uterus level, stomach, liver level.(3) The infection with hepatitis B or C was identified to be an important pathogenetic factor in the pathogenesis of chronic lymphoproliferative malignancies, especially malignant Hodgkin lymphoma (NHL) cell B. According to the study conducted by the European Prospective Investigation into Cancer and Nutrition (EPIC) the incidence of HCV seropositivity was 5.3% in patients with chronic lymphoproliferative malignancies in Spain and 3.9% for those in Italy. For the batch of chronic lymphoproliferative malignancies patients from Germany and Greece, the prevalence of HCV infection association was 0%. HBV infection was higher in patients with chronic lymphoproliferative malignancies from Greece (2.7%), Spain (2.6%) and Italy (2.4%).(4) According to the EPIC study, HCV infection is not a risk factor for chronic lymphoproliferative malignancies. Still other studies conducted in the U.S. and Korea have identified an association of the prevalence of HCV infection in patients with chronic lymphoproliferative malignancies, particularly NHL.(5,6) SMARTH U.S. study, based on SEER-Medicare data, reported for the elderly population diagnosed with NHL presented the HCV infection as a risk factor. The most common types of NHL identified were: diffuse large cell NHL (OR 1.52, 95% CI 1.05-2.18), Burkitt (OR 5.21, 95% CI 1.62-16.8), follicular (OR 1.88, 95% CI 1.17-3.02), and marginal zone NHL (OR 2.20, 95% CI 1.22-3.95).(6) Data from another study indicate a higher

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likelihood of developing diffuse large B-cell NHL (OR, 2.24, 95% CI, 1.68-2.99), NHL marginal zone especially splenic type (OR, 2.47, 95% CI, 1.44-4.23) and lymphoplasmocytic NHL (OR, 2.57, 95% CI,1.14-5 .79). It was not proven in this study an increased incidence of follicular NHL patients HCV seropositive.(7)

HBV infection plays an important part in the pathogenesis of chronic lymphoproliferative malignancies according to the study from Korea, the result being confirmed by the EPIC study only on the pathogenesis of multiple myeloma (OR = 4.00, 95% CI: 1.00-16.0).(4,5) The SMARTH study did not identify a significant association between HBV infection and the risk of chronic lymphoproliferation.(6) However, a recent study identified HBV as a risk factor in the development of NHL, obtaining results of statistic significance (OR 2.24, 95% CI 1.80-2.78, $p \leq 0.001$), the most common types being diffuse large B cell NHL, follicular NHL T-cell NHL.(8) Engels confirmed the role of HBV as a risk factor in a cohort study conducted on a group of NHL patients in South Korea. In this study but the most common form was diffuse large B-cell NHL.(9) HBV infection is associated with a higher incidence of clinically aggressive NHL, although HBV infection were less frequently identified than HCV infection on patients with chronic lymphoproliferative malignancies studied in the LIMFOVIR study in Romania.(10)

Recently, it was shown a possible association between the risk of NHL and hepatitis G infection, infected carriers of this virus having an increased risk of being diagnosed with NHL.(11) The high level of HGV viremia is associated with an increased risk of diffuse large B-cell NHL.(12) The association of HGV and HCV infection does not cause a rise in the risk of NHL.(13) Renzo et al showed in a study conducted in Italy that the coinfection mechanism is not involved in the increased prevalence of HCV and HGV in the group of patients with NHL. In this study, it was demonstrated the existence of a higher risk of Hodgkin's disease breakthrough on patients with NHL that HGV infection in patients with chronic HCV infection; suggesting that the mechanism of oncogenesis is not identical.(14)

In literature, there are three mechanisms of involvement of the infection with hepatitis in the NHL pathogenesis. Immunosuppression due to chronic lymphoproliferative neoplasia existence could cause the reactivation of viral B or C infection or the infection. This first possibility does not explain the existence of hepatitis infection for new diagnosed cases or who did not receive treatment as well as for patients who do not have a significant immunosuppression status. Another possibility is purely theoretical and refers to transmitting an unknown virus with similar pathogenic mechanism to the hepatitis virus which might act as oncogenic stimulus. This hypothesis is supported by a recent study which refers to the chronic infections, clinical unobvious, with Epstein Barr virus, HPV. Chronic viral infection is necessary but not sufficient for the initiation or progression of cancer, requiring the presence of coinfections. This can cause an imbalance of the immune system causing an increase in the occurrence of cancer susceptibility; coinfections were reported more frequent in developing countries.(15)

The most widely accepted mechanism is the one that refers to a causal relationship between hepatitis virus infection and NHL, hepatitis playing an oncogenic role. Oncogenic role of HCV in NHL has been demonstrated by many studies which shown the therapeutic role of the antiviral medications: Peginterferon and Ribavirin in achieving partial remission / total HCV in patients positive with NHL.(16) It proved by a group of Japanese researchers that the annual incidence of diagnosis with NHL on HCV-carrier patients was 0.23% cumulative rate of newly diagnosed NHL, after 15 years being 2.6% in the HCV-positive patients untreated or non-responding. The group of patients responding to antiviral therapy had a cumulative rate 0 suggesting the prophylactic role of antiviral therapy.(17)

The chronic antigenic stimulation achieved by HCV-E2 protein is the first mechanism and it demonstrated histological appearance existing in most NHL B cell from the impaired germ centres (GC) or post-GC B cells. HCV-E2 protein shows the binding site for CD81, HCV receptor found on the surface of hepatocytes and B lymphocytes. The interaction between HCV-E2 - CD81 represents the second possible mechanism of oncogenesis. As a result of this interaction, it results a decrease in the production of interleukin-2 leading to a proliferation of T lymphocytes. The consequence of this mechanism will result in the chronic activation and possibly the chronic proliferation of B lymphocytes. The chronic proliferation of B lymphocytes can determine the excess synthesis of the protein Bcl-2 (protein more commonly found in follicular NHL). HCV infection and replication in B cells represent a third possible mechanism of oncogenesis.(10) It was demonstrated a high level of HCV viral replication in B lymphocytes but not in T lymphocytes and in other cells involved in the immune response (3.35 + / - 3.85 vs. 1.75 + / - 2.52, 2.15 + / - 2.94 or 2.10 + / - Log copies/100 2.90 ng, $p < 0.01$ for the B-cells as compared to CD4 + T lymphocytes (+), CD8 (+) and other cells).(15)

HCV cells infection requires the expression of a co-receiver Claudina-1. B cells can be infected with hepatitis C virus, but liver lymphocytes cannot replicate. However CD5 lymphocytes can be hosts of HCV viral replication, this subset of lymphocytes expressing high levels of CD81, the receiver for HCV-E2 viral protein.

EBV virus coinfection may increase the viral replication of HCV. HCV infection of B lymphocytes causes mutations in the DNA polymerase and activation of cytidine deaminase which contributes to a 5 to 10 times increase in the frequency of mutations in immunoglobulin heavy chain genes, BCL6, p53 and catenin. Mutant proto-oncogenes were amplified in patients HCV-positive with NHL. Marcucci and Mele proposed a multi cause mechanism of lymphomagenesis being required at least two oncogenic stimuli. These two stimuli could be the simultaneous stimulation of CD81 and the specific receiver HCV-E2 leading to the activation of c-jun N-terminal protein kinase or the co-infection with EBV. The multi cause mechanism could explain such differences between the incidence rates of NHL and prevalence rates of HBV or HCV viral infection in different geographic areas.(16)

REFERENCES

1. Vedham V, Divi RL, Starks VL, Verma M. Multiple Infections and Cancer: Implications in Epidemiology, Technol Cancer Res Treat 2013 Aug 2. [Epub ahead of print].
2. Parkin DM. The global health burden of infection-associated cancers in the year 2002, Int J Cancer 2006 Jun 15;118(12):3030-44.
3. De Martel C, Ferlay J, Franceschi S, Vignat J, Bray F et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis, Lancet Oncol 2012 Jun;13(6):607-15.
4. Franceschi S, Lise M, Trépo C et al, Infection with Hepatitis B and C Viruses and Risk of Lymphoid Malignancies in the European Prospective Investigation into Cancer and Nutrition (EPIC), Cancer Epidemiol Biomarkers Prev 2011;20:208-214.

5. Anderson LA, Pfeiffer R, Warren JL, Landgren O, Gadalla S et al. Hematopoietic malignancies associated with viral and alcoholic hepatitis, Cancer Epidemiol Biomarkers Prev 2008 Nov;17(11):3069-75.
6. Kang J, Cho JH, Suh CW, Lee DH, Oh HB et al. High prevalence of hepatitis B and hepatitis C virus infections in Korean patients with hematopoietic malignancies, Ann Hematol 2011 Feb;90(2):159-64.
7. Bachy E, Besson C, Suarez F, Hermine1 O. Hepatitis C Virus Infection and Lymphoma, Medit J Hemat Infect Dis 2010, 2(1): e2010004.
8. Dalia S, Chavez J, Castillo JJ, Sokol L. Hepatitis B infection increases the risk of non-Hodgkin lymphoma: A meta-analysis of observational studies, Leuk Res. 2013 Jun 26. pii: S0145-2126(13)00193-8. [Epub ahead of print].
9. Engels EA, Cho ER, Jee SH. Hepatitis B virus infection and risk of non-Hodgkin lymphoma in South Korea: a cohort study, Lancet Oncol 2010 Sep;11(9):827-34.
10. Vladareanu AV, Ciufu C, Neagu AM, Onisai M, Bumbea H, et al. The impact of hepatitis viruses on chronic lymphoproliferative disorders- preliminary results, Journal of Medicine and Life, 2010 Jul-Sept;3(3):320-329.
11. Wiwanitkit V. Individuals with HGV-RNA are at high risk of B cell non-Hodgkin's lymphoma development Asian Pac J Cancer Prev 2005 Apr-Jun;6(2):215-6.
12. Krajden M, Yu A, Braybrook H, Lai AS, Mak A, Chow R, et al. GBV-C/hepatitis G virus infection and non-Hodgkin lymphoma: a case control study, Int J Cancer 2010 Jun 15;126(12):2885-92.
13. Nicolosi Guidicelli S, Lopez-Guillermo A, Falcone U, Conconi A, Christinat A, et al. Hepatitis C virus and GBV-C virus prevalence among patients with B-cell lymphoma in different European regions: a case-control study of the International Extranodal Lymphoma Study Group, Hematol Oncol. 2012 Sep;30(3):137-42.
14. De Renzo A, Persico E, de Marino F, di Giacomo Russo G, Notaro R, et al. High prevalence of hepatitis G virus infection in Hodgkin's disease and B-cell lymphoproliferative disorders: absence of correlation with hepatitis C virus infection, Haematologica 2002 Jul;87(7):714-8.
15. Marcucci F, Mele A. Hepatitis viruses and non-Hodgkin lymphoma: epidemiology, mechanisms of tumorigenesis, and therapeutic opportunities, Blood 2011 Feb;117(6):1792-98.
16. Inokuchi M, Ito T, Uchikoshi M, Shimozuma Y, Morikawa K, et al. Infection of B cells with hepatitis C virus for the development of lymphoproliferative disorders in patients with chronic hepatitis C, J Med Virol 2009 Apr;81(4):619-27.
17. Kawamura Y, Ikeda K, Arase Y et al. Viral elimination reduces incidence of malignant lymphoma in patients with hepatitis C, American Journal of Medicine, 2007;120(12):1034-41.