

Antiviral Treatment in Patients with HCV-Associated Lymphoproliferative Disorders

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Abstract

Clinical course of HCV infection may be connected with extra-hepatic manifestations associated with lymphoproliferative disorders as mixed cryoglobulinemia (MC) and non-Hodkin B cell lymphoma (B-NHL). The incidence of HCV infection in MC patients exceeds 80%, and among patients with B cell non-Hodgkin's lymphoma 10-17%, whereas this frequency is correlated with the prevalence of HCV in different geographic regions.

2015 European Association for the Study of the Liver (EASL) recommendations on Treatment of Hepatitis C prioritizes therapy of patients with extra-hepatic manifestations of HCV infection regardless of liver fibrosis. Antiviral treatment resulted in HCV RNA serum disappearance and tumor regression in the majority of patients with indolent B-NHL. It was revealed the high percentage of 5-year overall survival (OS), and 5-year progression-free survival (PFS) for the treated patients. Antiviral therapy improved the prognosis of lymphoproliferative disease, independent of its histological form.

Due to the higher than in the general population, incidence of HCV infections in patients with haematological malignancies, it is desirable to test towards the infection all patients with B-NHL. Antiviral therapy should be considered as a therapeutic option for patients with indolent B-NHL who do not require intensive cytoreduction, because effective anti-HCV treatment induces lasting B-NHL clinical remission. It is also recommended to test towards the HCV infection and carry out an examination evaluating the anti HCV treatment in patients with acute and chronic lymphocytic leukemia (ALL and CLL).

Keywords: HCV-infection; Non-hodkin B-cell lymphoma; Pegylated interferon; D ribavirin

Introduction

HCV infection has always been a problem of public health due to adverse clinical outcome in the form of liver cirrhosis, liver failure and hepatocellular carcinoma (HCC). In the clinical course of HCV infection, in addition to the main hepatic location, we often observe extra-hepatic manifestations associated with lymphoproliferative disorders. There are primarily mixed cryoglobulinemia (MC) and non-Hodkin B cell lymphoma (B-NHL), including especially marginal zone lymphoma-(MZL). HCV replication in the cells of the bone marrow is associated with the occurrence of pancytopenia, myelodysplastic syndromes and acute myeloid leukemia. One should not forget that there are cases of extra-hepatic manifestations existing next to hepatic, and liver cirrhosis, in the course of infection, may further worsen the functioning of haematological system through intensification of cytopenia [1].

The first reports describing compounds of HCV infection, MC and B-NHL appeared a few years after the discovery of HCV. It has been proved that the incidence of HCV infection in MC patients exceeds 80%, and among patients with B cell non-Hodgkin's lymphoma 10-17%, whereas this frequency is correlated with the prevalence of HCV in different geographic regions. The greatest percentage of HCV-associated non-Hodkin B cell lymphoma was recorded in Italy, Egypt, Japan and Southern USA. HCV infection was associated with indolent B-cell lymphomas, especially MZL as well as with aggressive lymphomas mainly diffuse large B-cell lymphomas (DLBCL) [2].

As shown in 2003 meta-analysis of 48 studies and of 5542 patients, HCV infection was detected in 15% of patients with B-NHL and in 2.9% of patients with other lymphoproliferative syndromes as compared with 1.5% in the general population. It was revealed that the risk of developing of B-NHL is 35 times higher in HCV- infected with symptomatic MC, and 8-10% of patients with HCV-MC showed progressions to B-NHL [3].

Among the 41 patients with chronic lymphoproliferative disorders (CLD) associated with B, C and / or D hepatitis infection, diagnosed and monitored in 2007-2009 in the Hematology Department of the University Hospital in Bucharest predominated women (60%) and patients over 50 years of age (85%). Analysis of histological types CLD was in favor of non-Hodgkin B-cell lymphoma in 68% and chronic lymphocytic leukemia in 17%. Among 34% of patients HBV infection was confirmed, in 59% - HCV infection. Analysis of CLD malignancy depending on HBV and HCV infections demonstrated that among HBV infected dominated (64%) aggressive type of CLD. In the group of HCV infected non-aggressive type of CLD, most often in extra-nodular location, was confirmed in 63% of patients. Clinically, in most patients hepatomegaly and lymphocytosis were observed [4].

Italian researchers in observations of 1313 patients with chronic hepatitis C in 2006-2013, compared a group of 121 HCV infected with lymphoproliferative disorders (LPD) to a group of 130 infected with HCV without LPD. In 41 patients with LPD the presence of B-NHL lymphoma was observed. In multivariate analysis, the presence of cirrhosis was an additional factor in the development of lymphoproliferative disease in the HCV infected [5].

2015 European Association for the Study of the Liver (EASL) recommendations on Treatment of Hepatitis C prioritize therapy of patients with extra-hepatic manifestations of HCV infection, regardless

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of liver fibrosis, including patients with non-Hodgkin B cell lymphoma [6]. The legitimacy of this recommendation was pointed out, among others, by Torres et al., who described a small severity of histological changes in the liver in patients with HCV combined with B-NHL [7].

In Italy the majority of patients with B-NHL are diagnosed for HCV. The largest study published to date concerning the effectiveness of antiviral therapy for HCV infected with lymphoproliferative disease was led by Fondazione Italiana Linfomi. It described antiviral therapy carried out in the years 1993-2009 in 134 patients with B-NHL from 39 Italian centers. 47 of them were treated with interferon and ribavirin and 87 received pegylated interferon and ribavirin. Among the 100 patients who received antiviral treatment in line I there were 60 with HCV-associated marginal zone lymphoma. In 52 patients HCV genotype 2 and in 37 genotype 1 HCV were confirmed. The mean treatment duration was 7 months, 87/100 patients completed treatment; 6 discontinued due to adverse effects, 7 due to progression of lymphoma and lack of virologic response. Loss of HCV RNA was observed in 80% of patients. Complete remission of cancer was obtained in 44 (44%) and partial in 33 (33%) patients. Response to treatment was significantly statistically correlated with HCV RNA serum disappearance ($p < 0.003$). Antiviral treatment resulted in HCV RNA serum disappearance and tumor regression in the majority of patients with indolent B-NHL. Percentage of 5-year overall survival (OS), and 5-year progression-free survival (PFS) for the treated patients were 78% and 48%, respectively. According to the authors, antiviral treatment should be considered as a therapeutic option for patients with indolent B-NHL who do not require intensive cytoreductive treatment [8].

In observations of many authors the regression of lymphoma was closely associated with obtaining sustained virologic response (SVR) also the limitations of these studies were the small numbers of treated patients [9].

The impact of antiviral therapy for HCV-associated B-NHL was evaluated in the ANRS HC-13 lympho-C study, which was attended by patients treated in the years 2006 to 2012 in 26 centers in France. SVR following treatment with pegylated interferon and ribavirin was achieved in 43/70 (61%) treated patients, more often in those infected with HCV genotype 2 or 3 HCV than in infected with genotype 1 or 4 HCV, (SVR -75% and 55% respectively). After 3 years of follow-up survival rates and progression-free survival in patients who were administered antiviral therapy was 78% and 64% respectively and they were statistically significantly higher in comparison to untreated, $p < 0.02$ and $p < 0.04$, respectively. Antiviral therapy improved the prognosis of lymphoproliferative disease, independent of its histological form: MZL or DLBCL [10].

Coskun et al. reported a case HCV-associated lacrimal gland marginal zone lymphoma in 43-year-old woman, who achieved complete regression after treatment with pegylated interferon and ribavirin [11].

Rossotti et al. presented a regression HCV-associated splenic marginal zone lymphoma (SMZL), after treatment with faldaprevir, deleobuvir and ribavirin. SMZL regression was correlated with HCV serum viral load disappearance [12].

These studies emphasize the need for testing towards HCV in patients with lymphoproliferative diseases and legitimacy of antiviral therapy in patients with HCV-related indolent B-NHL, especially MZL.

Antiviral therapy applied after effective chemotherapy was the subject of a study published by La Mura et al. They observed 343 patients

who underwent chemotherapy for NHL, among whom 69 (20%) were infected with HCV. In the group of HCV-infected patients dominated female sex, elderly persons and indolent forms of NHL. There were no statistically significant differences in clinical classification (Ann Arbor stage) and predictive scale (International Prognostic Index-IPI) between patients from both groups. After ending chemotherapy and achieving remission 25/69 patients were treated with interferon and ribavirin. Sustained virological response was received in 8/25 patients and in none of them NHL relapse was observed. Such relapses occurred in 5/17 treated who did not respond to therapy. In the multivariate analysis indolent histology at the onset of lymphoma and antiviral therapy were found as independent and the only factors related to better clinical outcome of NHL. Authors suggested that antiviral treatment may represent a therapeutic option for HCV-positive NHLs after chemotherapy in order to reinforce remission of the neoplastic disease [13].

The data presented clearly affirms the legitimacy of antiviral treatment with pegylated interferon and ribavirin in patients with HCV-associated B-NHL. In the literature, there are also reports of the effective antiviral therapy of HCV-infected patients with chronic or acute leukemia.

Christensen et al. presented the first report of the outcome in women with chronic lymphocytic leukemia (CLL) and chronic HCV infection, treated with Peg-IFN and ribavirin and subsequent retreated with telaprevir-based therapy. The patient showed a haematological response after anti-HCV therapy with Peg-IFN and ribavirin with normalization of leukocyte and lymphocyte counts. She showed a late virological relapse and was successfully retreated with telaprevir-based therapy with no evidence of progression of CLL status. Therapy was not associated with any unexpected adverse events and did not affect CLL status. The authors suggest that patients with CLL may show haematological response after successful antiviral therapy [14].

On the other hand Ayyub et al. reported the case of a young man who was treated with combined therapy with peginterferon and ribavirin for HCV while he was on maintenance anti-leukemic treatment. During the therapy the patient required reduction in the dose of peginterferon and the addition of filgrastim due to neutropenia. The patient maintained a sustained viral response two years after the end of treatment and developed complete remission of leukemia, whereupon his anti-leukemic therapy was also discontinued [15].

Conclusion

Due to the higher than in the general population, incidence of HCV infections in patients with haematological malignancies it is desirable to test towards the infection all patients with B-NHL, especially MZL. Antiviral therapy should be considered as a therapeutic option for patients with indolent B-NHL who do not require intensive cytoreduction, because effective anti-HCV treatment induces lasting B-NHL clinical remission. It is also recommended to test towards the HCV infection and carry out an examination evaluating the anti HCV treatment in patients with acute and chronic lymphocytic leukemia (ALL and CLL).

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