Hematological abnormalities during treatment of chronic hepatitis C –Albanian experience

Stela Taci[1], Sonela Xinxo[2], Edite Sadiku[1], Floreta Kurti[1,3], Adriana Babameto[1], Jovan Basho[1]

[1]Department of Gastrohepatology, UHC "Mother Teresa", Tirana, Albania;
[2]Institute of Public Health, Tirana, Albania;
[3]Faculty of Technical Medical Science, University of Medicine, Tirana, Albania.

Corresponding author: Stela Taci
Address: Str. Kodra e Diellit, Lgj. Nr. 5, Tirana, Albania;
Telephone: +355682152433; E-mail: stelataci@yahoo.com

Abstract

Aim: This study aims to identify the occurrence of hematological side effects of treatment of chronic hepatitis C in Albanian patients and to describe the distribution of side effects by sex, genotypes of HCV and age.
Methods: In this prospective study, there were included all patients who met the criteria for treatment of hepatitis C (peg interferon and ribavirin). It was conducted from 2006-2015 at the Gastrohepatology Department of University Hospital Centre "Mother Teresa" in Albania. The demographic data (age, sex), the results of blood test (level of Hg, number of white blood cell and platelets) and genotype of the hepatitis C were collected at the beginning, after three and after six months of treatment.
Results: In total, 265 patients were included in the study. One hundred and forty patients (52.8%) were male. The most prevalent genotype was 1b with 55% of cases. After six months of treatment, anemia was the most prevalent hematological abnormality (67.6%), followed by thrombocytopenia (50.6%), whereas leucopenia was the least prevalent (4.5%) hematological abnormality during treatment. Anemia was significantly more frequent among females, whereas leucopenia was more frequent among the younger patients. Genotype of HCV did not affect the occurrence of hematological abnormalities.
Conclusion: Hematologic abnormalities such as anemia, leucopenia and thrombocytopenia are common during the combined therapy with peg- interferon and ribavirin for chronic hepatitis C among Albanian patients. Anemia is more frequent among females and leucopenia among the younger patients.

Keywords: hematological abnormalities, hepatitis C, treatment.

Introduction

Hepatitis C is a relatively common disease. Hepatitis C is a global public health problem where about 130 to 150 million people suffer from chronic HCV. HCV is the leading cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC). About 55-85% of HCV infected cases become chronic active cases and progress to fibrosis, cirrhosis or further more can progress till to decompensate cirrhosis and hepatocellular carcinoma (1).

Chronic hepatitis C is also generally asymptomatic, resulting in unexpected diagnosis in vast majority of cases, which may be made at an end stage of disease. The severity of HCV related liver disease is extremely variable but may, in some cases, induce progressive liver fibrosis which evolves to cirrhosis and then to hepatocellular carcinoma in a delay ranging from a few years to many decades (2).

The treatment of hepatitis C has dramatically improved over the past decade and unlike any other chronic viral infection, a significant proportion of patients with chronic hepatitis C can be cured. One of the best treatments currently available for HCV infection is combination therapy with pegylated interferon and ribavirin.

The goal of treatment is to achieve the sustained virological response which means the elimination of HCV viral ribonucleic acid (RNA) from the serum at 24 months post-treatment. Successful treatment rates range from 45% to 85% and it depends on the HCV genotype. Patients with genotype 2 or 3 infection are more sensitive to interferon and may only require 24 weeks of treatment. Patients with genotype 2 or 3 infection, achieve sustained virological response rates of approximately 75-80%. Patients with genotypes 1 or 4 require 48 weeks of treatment to achieve sustained virological response rates of 45-56% (3,4).

The combined therapy of pegylated interferon and ribavirin is associated with a number of side effects, particularly hematological abnormality (anemia, thrombocytopenia and leucopenia). Anemia is the most frequently reported hematologic abnormality associated with the combination antiviral therapy and is related to both hemolytic anemias due to ribavirin and marrow depression form interferon. Anemia is often a limited factor during treatment, raising the consideration of either dose reduction of ribavirin or supportive therapy with epoetin or darbepoetin alfa. Neutropenia is also very often common with the combination therapy. However, it is not found any clear association with the occurrence of infections during therapy and thus the dose reduction or support with granulocyte colony stimulating factors is less required. Thrombocytopenia is less troublesome side effect and seldom requires therapy (4-7).

The aims for the future should be to develop a treatment beyond peg interferon and ribavirin with less side effects and higher efficacy. Knowledge of the molecular structure of the hepatitis C proteins has allowed the design of new drugs that directly target the sites of HCV encoded enzymes that are important for the replication of the virus (6).

Actually in Albania, the treatment of hepatitis C consists on using the combined therapy (pegylated interferon and ribavirin). Thus, the study aims to identify the occurrence of hematological side effects during the treatment of chronic hepatitis C in Albanian patients during the last years, and to describe the effect of sex, age, and genotypes of HCV on the occurrence of side effects.

Methods

A prospective study was conducted from 2006-2015 at the Department of Gastrohepatology of the University Hospital Centre “Mother Teresa” in Albania. All patients who met the criteria for treatment of chronic Hepatitis C were included in the study. The treatment regime consisted of peg interferon and ribavirin.

The demographic data (age, gender), the results of blood test (level of Hg, number of white blood cell and platelets) and the genotype of the hepatitis C were collected at the beginning and after three months and six months of treatment.

Anemia was defined as a level low than 12 g/dl;

leucopenia was defined as a number of white blood cells less than 4000 per field; and thrombocytopenia as a number of platelets less than 150000 per field. The categorical variables were presented by frequency distributions, whereas the continuous variables as means and standard deviations. Chi-square test was used to analyze differences on the occurrence of side effects by sex, age of the patients and genotype of hepatitis C. $P \leq 0.05$ was considered as statistically significant.

Results

In total, 265 patients were included in the study. One hundred and forty patients (52.8%) were male. The most prevalent genotype was type 1b with 55% of cases, followed by genotype 2a/2c with 18.5% and genotype 2 with 13.2%. The other genotypes of HCV were encountered in about 15% of the patients.

The mean age was 43.4 years (95% CI=41.2-45.7) and the vast majority of the patients belonged to the age group >45 years old (56.6%).

As it is presented on the Table 1, after three months of treatment, only 259 patients had continued the treatment and after six months only 244 patients had continued the treatment.

Prior to treatment, none of the patients had hematological abnormality such as leucopenia and thrombocytopenia and about 6.8% had developed anemia (Table 1).

Table 1. Occurrence of hematological abnormalities after three months and six months of treatment

Hematological abnormalities	At the beginning of treatment *N=265*	After three months of treatment *N=259*	After six months of treatment *N=244*
	Percent	Percent	Percent
Anemia	6.8	61.8	67.6
Leucopenia	0	2.6	4.5
Thrombocytopenia	0	5.7	50.6

After three months of treatment, about 62% of patients had developed anemia, 2.6% leucopenia and 5.7% had developed thrombocytopenia. Meanwhile, after six months of treatment, the occurrence of anemia is 67.5%, leucopenia 4.5% and thrombocytopenia 50.6%.

Table 2. Occurrence of hematological abnormalities after three months and six months of treatment by group age

Hematological abnormalities	Age-group (in years)			Sex		
	<45	≥45	P value	Male	Female	P value
After three months	%	%		%	%	
Anemia	62.3	61.4	0.675	46.4	79.3	0.001
Thrombocytopenia	8.8	3.4	0.061	5.1	6.6	0.526
Leucopenia	5.3	0.7	0.024	3.6	1.7	0.345
After six months						
Anemia	63.8	70.5	0.269	50.4	80.7	0.001
Thrombocytopenia	55.8	46.8	0.165	47.7	54	0.328
Leucopenia	8.7	1.4	0.007	3.1	6.2	0.244

Table 2 presents the occurrence of hematological abnormalities over the time (after three and six months of treatment) by age groups and sex.

After three months of treatment, the occurrence of anemia by age group was quite similar in both age groups. The occurrence of anemia was significantly higher among female. The occurrence of leucopenia is significantly higher among the age group < 45 years old, but no significant difference was observed by sex.

After six months of treatments, the occurrence of anemia by age group was quite similar in both age groups. The occurrence of anemia was significantly higher among female.

The occurrence of leukopenia is significantly higher among the age group < 45 years old, but no significant difference is observed by sex. Even after six months of treatment, leucopenia is more frequent among younger patients. No significant difference was observed between the sexes on the occurrence of leukopenia.

Regarding thrombocytopenia, there was no significant difference by age group and sex after three months and six months of treatment.

Table 3. Occurrence of hematological abnormalities after three months and six months of treatment by HCV genotypes

Hematological abnormalities	Genotype of HCV				
After three months	**1b**	**2a/2c**	**2**	**Other types**	**P value**
	%	%	%	%	
Anemia	58.5	48.6	62.9	72.9	0.139
Thrombocytopenia	4.2	8.8	8.6	6.4	0.622
Leucopenia	3.5	2.9	2.9	0	0.646
After six months					
Anemia	64.2	68.8	74.2	72.3	0.608
Thrombocytopenia	53.3	50	51.6	42.2	0.64
Leucopenia	4.4	6.2	3.2	4.4	0.952

Table 3 shows the occurrence of hematological abnormalities after three and six months of treatment by HCV genotypes. There is not any significant difference of occurrence of hematological abnormalities (anemia, leucopenia and thrombocytopenia) by HCV genotypes after three months or six months of treatment.

Discussion

In our knowledge, this is the first large study that aims to shed light on the hematological abnormalities as side effects of treatment of hepatitis C among patients with chronic hepatitis C.

Hematologic abnormalities such as anemia, leucopenia and thrombocytopenia are common during combination therapy with peg-interferon and ribavirin for chronic hepatitis C among Albanian patients. These finding are consistent with the conclusion of other studies in this field (6-11) which concluded that treatment of hepatitis C with pegylated interferon and ribavirin is associated with hematological abnormalities such as anemia, leucopenia and thrombocytopenia.

Among the hematologic abnormalities associated with combination therapy, anemia is probably the most significant side effect and is related to both hemolytic anemias due to ribavirin and marrow depression form interferon. The occurrence of anemia is presented in high percentage since after three months of treatment and the frequency does not change even after six months of treatment. The occurrence of anemia is not affected by age groups

of the patients or the genotypes of hepatitis C, but is significantly higher among female rather than male. After three months of therapy, thrombocytopenia, as side effect of treatment, is less often than anemia. Meanwhile, the percentage of occurrence of thrombocytopenia increased significantly after six months of treatment (from 5.7 to 50.6%).

Thrombocytopenia is caused primarily by reversible bone marrow suppression, although autoimmune-related thrombocytopenia may also occur. The concurrent use of ribavirin may blunt the thrombocytopenic effect of interferon as a result of reactive thrombocytosis (6,11).

The occurrence of thrombocytopenia is not related to sex and age of the patients or even to the genotypes of HCV.

The occurrence of leucopenia is due to the effect of interferon on bone marrow, which results in decreased granulocytes during treatment (11,12). The findings of our study show that during the treatment of patients with chronic hepatitis leucopenia is not related to sex or genotypes of HCV, but often occurred among younger patients (<45 years old).

Hematologic abnormalities are common side effects during treatment with pegylated interferon and ribavirin among patients with chronic hepatitis C.

Anemia is the most prevalent hematological abnormality and occurs more frequently among women. Leucopenia is a less prevalent hematological abnormality that occurs more frequently among the younger patients. Age and sex of patients do not predict the occurrence of thrombocytopenia during the treatment. Genotypes of HCV do not affect the occurrence of hematological abnormalities during the treatment.

Management of hematologic abnormalities during antiviral therapy with pegylated interferon and ribavirin for HCV infection should be an important strategy for maximizing treatment outcomes.

Conflicts of interest: None declared.

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