ORIGINAL ARTICLE

Cytopenias with Traditional Therapy of Hepatitis C in Pakistani Population

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ABSTRACT

Objective: To find out the frequency of blood cytopenias among the relapsers, non-responders and responders to traditional therapy of Hepatitis C in a tertiary care hospital of Rawalpindi, Pakistan

Study Design: Cross sectional descriptive study.

Place and Duration of Study: Hematology and Gastroenterology departments of Military Hospital, Rawalpindi, for a period of one year, from August 2014 to July 2015.

Methodology: After six months of treatment with conventional interferons and ribavirin 5mL blood was obtained in EDTA bottles from responders, relapsers and non-responders in laboratory, and was analyzed using Hematology Analyzer sysmex KX-21. The hemoglobin levels, total leukocyte counts and platelet counts were measured. The results were entered into SPSS 16 and the analysis for descriptive statistics was applied for finding out the frequencies.

Results: A total of 380 patients were studied, out of which 204 were non-responders, 52 were responders and 121 were relapsers. Ninety eight patients [25.9%] had anemia, 12 [3.2%] had leukopenia and 48 [12.7%] had thrombocytopenia. Among non-responders, 56 [27.5%] had anemia, 7 [3.4%] had leukopoenia and 31 [15.2%] had thrombocytopenia. Among responders, 16 [30.8%] had anemia, 2 [3.8%] had leukopoenia and 4 [7.7%] had thrombocytopenia. Among relapsers, 26 [21.5%] had anemia, 3[2.5%] had leukopoenia and 13 [10.7%] had thrombocytopenia.

Conclusions: Anemia is most common among relapsers, non-responders and responders, while leukopenia is least commonly seen. Thrombocytopoenia occurs more commonly among non-responders and least commonly among responders.

Key Words: hepatitis C, interferons, ribavirin, anemia, thrombocytopenia, leukopenia

Introduction

Cytopenia is the reduction in the number of blood cells.[1] Low red blood cell count or less than the normal quantity of hemoglobin in the blood is called anemia. Low white blood cell count is called leukopenia, while low platelet count is known as thrombocytopenia. [1] Relapsers are patients in whom Hepatitis C Virus (HCV) RNA reappears in serum after completion of therapy. Non- responders are patients in whom there is inability of the body to clear HCV RNA from serum after completion of therapy and responders are the ones in which HCV RNA is cleared from the serum after therapy. [1]

HCV infection is usually associated with peripheral blood cytopenias. [2] Thrombocytopenia and anemia are associated with HCV infected patients undergoing therapy. After the therapy, in responders, the platelet counts and the hemoglobin level comes to normal with time. The relapsers and non-responders usually have cytopenias. [2] Cytopenias are a major challenge during treatment and may present as a problem. Hematologic abnormalities, including anemia,

neutropenia and thrombocytopenia, are among the side effects of combination therapy, which have been found to result in dose reduction and discontinuation of therapy in up to 25% and 3% of patients, respectively. [3] Nearly 10% of the patients undergo reversible hemolytic anemia with ribavirin therapy, while interferon or peg-interferon therapy may also result in anemia and neutropenia. [4]

Numerous studies have found interferons and ribavirin as causative agents of hematologic toxicity, including anemia, neutropenia and thrombocytopenia. [5] This hinders adherence with treatment and maintenance of adequate dose. Timely identification of such patients helps plan additional treatment options, including growth factors. [5]

Although Hepatitis C is on the rise, there is little data available in our country on this topic. The serious side effect of HCV treatment, led us to our objective to find out the frequency of cytopenias among responders, relapsers and non-responders to traditional therapy of Hepatitis C.

Methodology

A cross sectional descriptive study was conducted in Hematology and Gastroenterology departments of Military Hospital & Army Medical College Rawalpindi, for a period of one year, from August 2014 to July 2015. Our Study sample included 380 HCV infected patients, either relapsers, responders or non-responders. Hospital ethical committee approval was taken before starting the study.

Patients included in our study were responders, non-responders and relapsers to traditional anti-HCV therapy with ribavirin and conventional interferons. Patients excluded from our study were those having splenomegaly and decompensated portal hypertension. Other diseases like renal failure, organ transplant, and IHD were also excluded.

Five ml of blood was sampled in EDTA in lab after six months of treatment with conventional interferons and ribavirin, which was analyzed by using Hematology Analyzer sysmex KX-21. Hemoglobin levels, total leukocyte counts and platelet counts were measured. Parameters were defined in accordance with WHO criteria. Hb < 12 g/ dL was considered as anemia for females. Hb < 13 g/ dL was viewed as anemia for males. TLC < 4 × 10^9 / L was labelled as leucopenia. Platelet < 150 x 10^9 / L was taken as thrombocytopenia. The data was entered into data editor window of SPSS-16. The variables of Hb, TLC and platelets were recorded as anemia, leucopenia and thrombocytopenia. Cut off points for variables were defined as per WHO criteria mentioned above. Mean and standard deviation were found for quantitative variables (age, BMI) and frequencies with percentages were found for qualitative variables (anemia, leucopenia and thrombocytopenia).

Results

A total of 380 patients were studied, in which male individuals constituted 38.3 % (n=146) of the patients while 61.7% (n=234) were females. Mean age was 41.26 ± 7.32 years. Mean BMI was 26.56 ± 6.4 kg/ m^2.

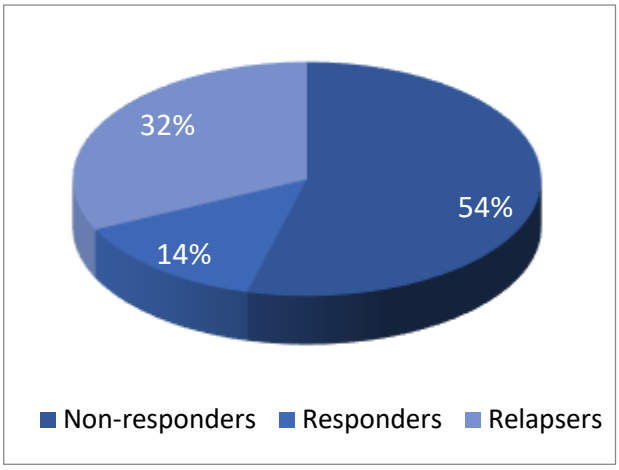

Figure 1: Percentage of Responders, Non Responders and Relapsers (n=380)

204 patients were non-responders, 52 were responders and 121 were relapsers [Figure 1].

Ninety eight patients had anemia, 12 had leukopenia and 48 had thrombocytopenia (12.7%). [Figure 2].

The frequency of cytopenias among responders, relapsers and non-responders is shown in Table I.

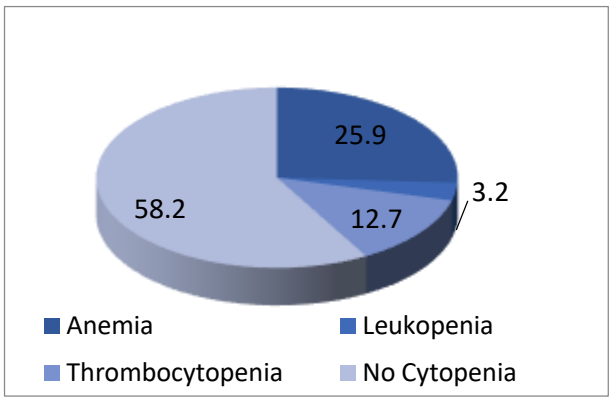

Figure 2: Frequency of cytopenias (n=380)

Discussion

It is estimated that 180 million people are infected worldwide with HCV, which is a major cause of chronic liver disease. [6] Chronic HCV infection treatment has advanced since the discovery of the HCV in 1989 and the introduction of interferon [IFN] monotherapy or peg interferon alfa combined with ribavirin has provided a breakthrough in treatment, which produces sustained virologic response [SVR] in up to 56% of patients. [7]

Hematologic abnormalities, including anemia, neutropenia, and thrombocytopenia, are common during combination therapy with standard interferon and ribavirin for chronic hepatitis C. [3] Hence, there is a need to exercise caution in treatment and maintain very close supervision of patients during therapy.

In our study, 53.7% patients were non-responders. In non-responders, the approach of treatment depends on the nature of the initial response, strength of initial treatment and host–viral factors. Twenty to fifty percent of patients treated with interferons and ribavirin do not attain required Serum Virologic Response. It can be due to non-response, virological breakthrough, or relapse. Poor observance of the prescribed treatment and incorrect dose reductions can add to poor response rates. [8] Relapsers in our set-up were up to 31.8%. Mostly virological relapse arises within the first three months and late relapse, after six months, is very unusual. Relapsers more likely respond to the same regimen, when administered second time, but experience a high relapse rate. [8]

Anemia among the relapsers and non-responders may be due to different reasons. Major reasons include anemia of chronic disorder, coagulopathies and nutritional anemia due to folate deficiency. [9] Anemia was most prevalent of all cytopenias in our study. These results are consistent with another study claiming that one third of patients were found to be anemic. [8] Anemia is a major reason of premature discontinuation of combination therapy, comprising for about 36% of all discontinuations, which is almost 8.8% of all

Table I: The frequency of cytopenias among responders, relapsers and non-responders.

Parameter	Responders (n=52)		Relapsers (n=121)		Non-Responders (n=204)	
	Frequency of patients	Percentage of total	Frequency of patients	Percentage of total	Frequency of patients	Percentage of total
Anemia	16	30.8%	26	21.5%	56	27.5%
Thrombocytopenia	4	7.7%	13	10.7%	31	15.2%
Leucopenia	2	3.8%	3	2.5%	7	3.4%

patients. [10] Treating with corticosteroids is an effective method to control blood cell counts, without increasing viral load and worsening of liver disease. Growth factors (erythropoietin / darbepoietin) have been employed to pawn the anemia linked with interferon and ribavirin. Growth factors improve patient's sense of comfort and decrease the need for ribavirin dose reduction, but their use has not been demonstrated to increase SVR rates. [11] They also double the cost of treatment and cause cardiovascular and thromboembolic effects. Anti-viral drugs like ribavirin induce haemolytic anaemia by a process involving the oxidation-induced aggregation of band 3, resulting in binding of autologous anti-band 3 antibodies [natural antibody]. These antibodies, when activated by complement, induce intra- or extra-capillary haemolysis. [12]

It is also postulated that depletion of adenosine triphosphate occurs when ribavirin is phosphorylated into its active form, after entering red blood cells. [12] This leads to reduced antioxidant mechanisms, leading to membrane oxidative damage and successive extravascular red blood cell removal by the reticuloendothelial system. Interferons also result in anemia, mainly through bone marrow suppression. [13]

The package insert for ribavirin mentions reducing the ribavirin dose at hemoglobin levels less than 10 g/dL and permanently discontinuing the drug at levels less than 8.5 g/dL. [14] Reduction of dose can have adverse implications for Serum Virologic Response [SVR], as studies indicate that, in order to achieve greater SVR rates, high doses of ribavirin are required. [15] Neutropenia in such patients is believed to result from bone marrow suppression or deficiency in release of neutrophils and lymphocytes. [13] Once treatment is discontinued, the levels rapidly return to base line. Filgastrim may be used to treat neutropenia.

Patients in our study having thrombocytopenia were 12.7%. In another study carried out on non-alcoholics having chronic liver disease, 64% cirrhotic patients were found to have platelet counts below 150,000, whereas only 5.5% of non-cirrhotic patients had thrombocytopenia. Similar to ours, leukopenia was quite rare in even in that study. [16] Thrombocytopenia is common in chronic liver disease. It arises as a result of portal hypertension, hypersplenism, decreased thrombopoietin production and virus-induced bone marrow suppression. [17] Various autoantibodies, including ANA, anti-phospholipid antibodies, cryoglobulins and rheumatoid factor, are formed as a result of HCV infection. [18] Thrombocytopenia may signify extrahepatic immunologic manifestation of HCV infection due to development of anti-platelet glycoprotein antibodies. [19]

Systematic review proves that, in patients with chronic hepatitis C, the prevalence of thrombocytopenia may vary from 0.16 to 45.4%. [20] If thrombocytopenia occurs during antiviral therapy, interferons may need to be reduced or stopped. In relapsers, thrombopenia is believed to improve progressively during antiviral therapy, but worsens after the end of treatment. Neutropenia also improves during antiviral therapy.

There is a dire need to continuously check the blood cell counts during treatment of HCV infections, as they are quite common among these patients. Dose reduction is not an appropriate remedy for this problem; many new drugs are now available to treat cytopenias. HCV infection must be deliberated in differential diagnosis of reasons of cytopenias, especially in immunosuppressed patients. [21]

Conclusion

Anemia is most common among relapsers, non-responders and responders, while leukopenia is least commonly seen. Thrombocytopoenia occurs more commonly among non-responders and least commonly among responders. Sometimes due to minimum viral load the

diagnostic tests for HCV including PCR is negative but the patient is harboring HCV infection. Such patients can be diagnosed by identifying persistent cytopenias among them.

Foot note : The paper was read as student original research paper at 8th Annual Amcolians Alumni Association Symposium and won 3rd prize in category of student oral presentation.

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