HEMATOLOGICAL SIDE EFFECTS OF ANTI-VIRAL THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C

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ABSTRACT

Background: This study was carried out to determine the frequency of hematological side effects of anti viral therapy in patients with chronic hepatitis C.

Methods: This cross sectional descriptive study was carried out in the department of gastroenterology, Hayatabad Medical Complex, Peshawar from March to December 2010. A total of 107 patients were included in the study. Non-probability convenience sampling technique was used. Patients with chronic hepatitis C with baseline hemoglobin (Hb), total leukocyte count (ANC) and platelet count (PLT) within the normal reference ranges, treated by interferon Alfa 2a and oral Ribavirin were included. All patients were assessed for Hemoglobin, Neutrophil count and platelet count fortnightly in the first month. Thereafter, a monthly follow up was instituted till the completion of therapy i.e. 6 months. Data was analyzed using statistical software SPSS version 10.0.

Results: 107 patients, 51(47.70%) male and 56(52.30%) females were included in the study. There was a drop of about 2 gm/dL of mean Hb, 2310.64/mm3 of mean TLC and 29719.63/mm3 of mean platelet count from baseline at 6 months of therapy, Anemia (i.e. Hb <12g/dl in men and < 11g/dl in women) were observed in 74.77% patients. Clinically significant anemia (i.e. Hb <10 gm/dL) developed in 26.2%, Neutropenia (i.e. ANC < 1500/mm3) in 18.7% and thrombocytopenia (i.e. platelet <150000/mm3) in 48.6% of patients at 6 months 0f therapy.

Conclusion: Interferon and ribavirin has significant adverse effects on hematological parameters.

Key Words: Chronic hepatitis C, Antiviral therapy, Anemia, Neutropenia, Thrombocytopenia.

INTRODUCTION

Hepatitis C Virus (HCV) infection is a global health problem. It is a leading cause of chronic liver disease world wide especially in developing countries[1]. The World Health Organization (WHO) estimates that approximately 3 % of the world population has been infected with HCV thus far. There are about 170 million patients with HCV in the world and 3-4 million individuals are diagnosed as new cases every year. Approximately 10 million patients (6 % of the population) are infected with HCV in Pakistan[2].

Currently the combination of Interferon (conventional or pegylated) and Ribavirin is the treatment of choice for hepatitis C Virus[3-5]. One of the barriers to adherence in combination therapy for hepatitis C is the incidence of treatment related side effects that can lead to dose reduction and sometimes premature discontinuation. Side effects are observed in almost 80-90 % of patients receiving Interferon and Ribavirin therapy for chronic hepatitis C infection[6,7]. There are no significant difference in the side effects of pegylated and conventional Interferon. Hematological adverse effects are the most common lab abnormalities associated with anti viral therapy leading to dose reduction and discontinuation[8]. Anemia is extremely common among patients taking anti viral therapy. 39 to 56 % of patients experience a decrease in Hemoglobin of > 3 g/dl. Anemia may be due to Interferon induced bone marrow suppression or Ribavirin induced hemolytic anemia[9-11]. Interferon may also cause decrease in Neutrophils and Platelets secondary to bone marrow suppression[12]. Interferon may also cause auto immune thrombocytopenia[13]. Neutropenia is observed in 34% while thrombocytopenia in up to 50% of patients taking antiviral therapy[14,15].

Care of patients on antiviral therapy for chronic hepatitis C depends upon recognition of those at increased risk of side effects and appropriate response when they occur. The ability to achieve SVR (Sustained Virological Response) depends in part on degree of compliance with the therapy. Reduction of the dose in these patients or discontinuation due to side effects can potentially compromise the outcome, depending upon when dose reduction occurs. Overall side effects result in 10 to 20% premature withdrawal from therapy and additional 20 to 30% require dose modification[6,15].

The rationale of the study was to determine the frequency and spectrum of hematological side effects related to anti viral therapy for chronic hepatitis C

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infection in our population. The purpose is to create awareness among the practicing physicians about the side effects of antiviral therapy for chronic HCV infection. So that while treating such patients, they should follow them properly for the hematological side effects and when encountered, should address them in time. This will improve adherence to the treatment leading to the achievement of optimal outcomes, especially the SVR (Sustained Virological Response).

MATERIALS AND METHODS

This Cross Sectional Descriptive study was carried out in the department of gastroenterology and Medical OPDs (Out Patient Departments), Post Graduate Medical Institute Hayat Abad Medical Complex Peshawar from March to December 2010 after taking proper approval from the hospital ethical committee. Sample size was 107 using 34% prevalence of side effects (Neutropenia), 95% confidence level and 9% margin of error, under WHO formula for sample size collection. Non-probability Convenience sampling technique was used.

Patients with chronic hepatitis C (proven by positive Anti HCV and HCV RNA) with baseline hemoglobin (Hb), total leukocyte count (ANC) and platelet count (PLT) within the normal reference ranges, treated by interferon Alfa 2a (3million units subcutaneously three times / week) and oral Ribavirin (1200 mg per day) were included. Cirrhotic patients and pregnant ladies in whom antiviral therapy is contraindicated were excluded as were patients with bleeding disorder because it may be a confounding factor and may introduce bias.

Patients from Gastroenterology and Medical OPDs were enrolled according to the inclusion criteria with base line HCV Ab, HCV RNA PCR, CBC, LFTs, PT, Albumin and Ultrasound abdomen performed. Risks, benefits and alternatives about the treatment and no treatment for chronic hepatitis C were explained to the patients. The patients were counseled about the side effects of antiviral therapy. Informed written consent was taken from each patient before starting antiviral therapy. The patients were followed up fortnightly after the commencement of antiviral therapy for the first month. Thereafter, a monthly follow up was instituted till the completion of therapy. On each visit, CBC with platelets and reticulocytes were done and were documented on a standard proforma. Appropriate remedial measures were taken for relevant adverse events. Exclusion criteria were strictly followed to overcome confounders and bias in the study.

Information thus collected was analyzed using statistical software SPSS version 10. Results were presented in tabulated form. Means were calculated for numerical variables like Hb, neutrophil count and platelet count. Frequency and percentages were calculated for categorical variables like gender, anemia, neutropenia and thrombocytopenia.

RESULTS

A total number of 107 patients diagnosed as chronic hepatitis C and receiving antiviral therapy were included in this study. Out of 107 cases 51 (47.7%) were males and 56 (52.3%) were females with male to female ratio of 0.91:1. The age of the patients ranged from 18-55 years with a mean of 40.7383 ± 9.051 years. Majority of patients 50 (46.7%) were in the age range of 41-50 years, followed by 25 (23.47%) patients in the age groups of 31-40 years and 16 (15%) patients in the age group of 18-30 and 51-55 years.

Mean Hb level before the start of therapy was 13.518 +1.34 gm/dl, at 2nd week 12.66 + 1.22 gm/dl, at 4th week 11.80 +1.33gm/dl, at 2nd month 11.53 + 1.36gm/dl, at 3rd month 11.42 +1.46gm/dl, at 4th month 11.36+1.46 gm/dl, at 5th month 11.43+1.46 gm/dl, at 6th month 11.61 +1.35gm/dl. There was a drop of 2gm/dl of mean Hb from base line at 6 months of therapy.

Mean Neutrophil count before the start of therapy was 5429.78 + 1583.79/mm^3, at 2nd week 4354.43 + 1216.46 / mm^3, at 4th week 3847.26 + 1633.80/ mm^3, at 2nd month 3456.99 + 1537.05/ mm^3, at 3rd month 4688.33 + 8255.46/mm^3, at 4th month 3328.15+ 1189.34/mm^3, at 5th month 3217.58 + 1163.67/ mm^3, at

Table No 01: Mean Drop of Hb, anc & Platelets

Mean drop at 6 months of therapy			
	Hb	**ANC**	**Platelets**
Males	2.04 gm/dl	2321.98/mm3	30020/mm3
Females	1.62 gm/dl	29357.14/ mm3	29357.14/ mm3

Table No 02: Frequency of Anemia, Neutropenia and Thrombocytopenia

Anemia			
	Yes	**No**	**Total**
Male	37(46.25%)	14(51.85%)	51(47.66%)
Female	43(53.75%)	13(48.15%)	56(52.34%)
Total	80(100%)	27(100%)	107(100%)
Neutropenia			
	Yes	No	Total
Male	9(45%)	42(48.28%)	51(47.66%)
Female	11(55%)	45(51.72%)	56(52.34%)
Total	20(100%)	87(100.00%)	107(100.00%)
Thrombocytopenia			
	Yes	No	Total
Male	29(56.86%)	22(43.14%)	51(100%)
Female	23(41.07%)	33(58.93%)	56(100%)
Total	52	55	107(100%)

6th month 3119.14 + 1155.22/ mm^3 Decrease in mean Neutrophil count from base line was 2310.64/mm^3 at 6 months of therapy.

Mean platelet count before the start of therapy was 210495.33 + 51444.85/ mm^3. At 2 weeks platelet count was 200140.19 + 51049.88/ mm^3, at 4 weeks 201084 + 69089.38/ mm^3, at 2 months 199149.51 + 72696.42/ mm^3, at 3 months 200635.51 + 86541.99/ mm^3, at 4 months 192981.31 + 82508.88/ mm^3, at 5 months 176514.02 + 59308.17/ mm^3 and 180775.70 +44263.64/ mm^3 at 6 months follow up. Total drop of 29719.63/mm^3 in platelet count was observed at 6 months of therapy.

At 6 months of therapy there was a drop of 2.04 gm/dl of mean Hb in male and 1.62 gm/dl in females, mean ANC drop of 2321.98/mm^3 in males and 2406.91/ mm^3 in females and mean drop in platelet count of 30020/mm^3 in males and 29357.14/mm^3 in females (Table No 01).

Over all anemia (i.e. Hb < 12g/dl in men and < 11 g/dl in women) was observed in 80 (74.77%) patients at 6 months of follow up. Of these patients 37(46.25%) were males and 43(53.75%) were females. Significant anemia (Hb<10gm/dl) was observed in 28(26.2%) patients at 6 months follow up. Of these 28 patients, 7(25%) were males while 21(75%) were females. Neutropenia (i.e. Neutrophils <1500/mm^3) occurred in 20(18.7%) of patients at 6 months follow up. Of these patients, 9(45%) were males, while 11(55%) were female. Thrombocytopenia (i.e. platelet count <150000/ mm^3) occurred in 52(48.6%) of the patients at 6 months follow up. Of these patients 29(56.9%) were males while 23(41.07%) were female. (Table No 02).

DISCUSSION

Gold standard therapy of chronic hepatitis c is interferon alpha and ribavirin. Patients receiving this treatment for hepatitis C may suffer from one or other hematological cell suppression, which cannot be completely counteracted by the endogenous production of hematopoietic growth factors[12]. Direct inhibition of progenitor cell proliferation in the bone marrow seems to be the dominant factor[16,17].

In our study there was a drop of 2gm/dl of Hb from base line at 6 months of therapy. Similar observation was also made by other authors. Shahzad Saeed et al and Turbide et al. also reported a drop of 2gm/dl of Hb from base line at 6 months of therapy.[18,19] Anemia was observed in 74.77% of our patients which is comparable to the study by Khalid Mahmood et al[20] who found anemia in 70% of their patients treated with antiviral therapy. Significant anemia (Hb < 10g/dl) was observed in 26% of patients which was greater in women than men in our study. Sulkowaski et al and Hung et al also found significant anemia (Hb<10gm/dl) which was greater in women than men[9,10].

A common side effect of interferon alpha therapy is bone marrow suppression and particularly a reduction in white cell counts[16]. In our study decrease in mean ANC was 2310/mm^3 at the end of therapy from the baseline. Soza et al found in their study that Absolute neutrophil count typically decreased by 30% to 50% of base line during therapy with the doses of interferon required to treat hepatitis C[14]. Their results were comparable to our study. Chirstial Turbide[19] also noted a significant drop of total leukocyte count of 1.02x10^9/ mm^3. Similarly, Shahzad Saeed et al[18] observed a drop of 1.87 x10^9/cm^3 of total leukocyte count at 6 months of therapy.

In our study significant Neutropenia i.e. ANC < 1500/mm^3 was observed in 18.69%. Antonini MG et al[21] observed neutropenia in 17% of their patients, while Ridruejo E et al, and Shafqut Ali et al[22-23] observed neutropenia in 26-27% of their patients. Their results were comparable to our study.

A drop in platelet count of 29720/mm^3 from base line was observed at 6 months of therapy in our study, whereas no significant difference was noted between male and female. These results are comparable to the study conducted by Shahzad Saeed et al[18]. Significant thrombocytopenia i.e. platelet count < 150000/mm^3 was observed in 48.60% of our patients. Similar results were shown by Porubcin et al[24] who observed thrombocytopenia in 55% of their patients.

There is always a possibility that hematological changes may be the sole manifestation of disease itself rather than any side effects of antiviral therapy. Peck-Radosavljevic M et al[12] noted that thrombocytopenia is common in advanced stage liver disease and may be partly caused by inadequate thrombopoiten production (TPO) in the failing liver. M. Schmid et al.[25] found in his study that hematological toxic effects of combination antiviral therapy with interferon and ribavirin therapy occur in association with a marked increase in endogenous production of erythropoietin and thrombopoietin. Yet these endogenous physiological increases are unable to counteract the adverse effects of interferon and ribavirin. Recent data shows that treatment with super physiological doses of recombinant Erythropoietin can positively impact erythropoiesis, by correcting anemia and thereby permitting maintenance of patients intended ribavirin dose[26].

Overall results of our study were comparable to internationally carried out studies. Our study revealed high ratio of hematological side effects of antiviral therapy but no difference of side effects was observed in male and female patients. So all the chronic Hepatitis C patients, receiving antiviral therapy should be followed throughout the therapy for 24 weeks. Timely intervention such as dose modification or stoppage of treatment should be done to prevent severe complications and save life of patients.

CONCLUSION

Interferon and ribavirin therapy has marked hematological adverse effects on all cell lines. So all the chronic Hepatitis C patients, receiving antiviral therapy

should be followed throughout the therapy for 24 weeks. Timely intervention such as dose modification or stoppage of treatment should be done to prevent severe complications and save life of patients. This will improve adherence to treatment and will help in achieving the final outcome i.e. SVR. More and larger scale studies are needed in our setup to see whether these hematological effects are consequences of disease itself or because of drug therapy.

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