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HEPATITIS C;
FREQUENCY OF THROMBOCYTOPENIA PATIENTS TREATED WITH INTERFERON

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ABSTRACT... Objectives: To determine the frequency of thrombocytopenia and its manifestations in patients with Chronic Hepatitis C Virus infection treated with interferon and ribavirin. **Data Source:** In door and out door patients. **Design of Study:** Case series. **Setting and Period of Study:** Department of Medicine PNS Shifa Hospital Karachi, from 1st August 2006 to 1st July 2007. **Materials and Methods:** A Proforma was designed to enter the data of 100 patients fulfilling the inclusion criteria included in the study. Adult patients between the ages of 18 and 50 years of both gender were selected. Presence of anti HCV antibodies, elevated serum alanine transaminase, a positive polymerase chain reaction for hepatitis C ribonucleic acid and compensated liver disease were prerequisites. All patients were treated with combination of interferon and ribavirin. Blood counts, alanine transaminase and prothrombin time were done at baseline and at 2, 4 & 8 weeks intervals after starting interferon. A drop in platelets count below 100,000/cmm was taken as interferon induced thrombocytopenia. **Results:** In our study thrombocytopenia occurred in 11% patients. Grade 3 thrombocytopenia (platelet counts < 50,000) occurred in 01 patient out of hundred in which there was severe gum bleeding and purpura so antiviral treatment was discontinued. Grade 2 thrombocytopenia (platelet counts between 50,000 - 75,000) was observed in 03% patients but there were no bleeding episodes, 50% reduction dose was done in these patients. Grade 1 thrombocytopenia (platelet counts between 75,000– 100,000) was noticed in 07% patients but there were no bleeding manifestations and dose reduction was not done. **Conclusion:** Combination therapy is well tolerated, however, it can cause life threatening complications like bleeding episodes in a few patients. Bleeding complications and manifestations as a result of thrombocytopenia are uncommon.

Key words: Chronic Hepatitis C, Interferon and Ribavirin Therapy, Thrombocytopenia

INTRODUCTION

Hepatitis C virus (HCV) infects an estimated 170 million persons worldwide and thus represents a viral pandemic[1]. It is estimated that 4.8% - 14% people in our country are suffering from hepatitis C[2]. Routine reuse of syringes in Pakistan's back-street health centers has caused a surge in blood-borne infections of hepatitis B and C, which experts have dubbed "the AIDS of Pakistan"[3].

The prevention of HCV infection can be achieved by blood screening for HCV before donation, avoiding sharing needles or any injecting equipment and following safe sexual practices[4]. Combination therapy with interferon alfa and ribavirin is the standard treatment,

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however, a new formulation of interferon alfa, called peginterferon alfa-2a, offers significantly better results than the standard formulation[5]. Hematologic abnormalities such as anemia, neutropenia, and thrombocytopenia are common during combination therapy with standard or pegylated interferon and ribavirin[6]. Treatment of chronic hepatitis C with interferon alfa (IFN-a) often induces thrombocytopenia. About 10 percent of the patients discontinue therapy because of adverse effects and 3 percent discontinue it because of thrombocytopenia[5]. Timely intervention requires early detection of its clinical manifestation like gum bleeding, epistaxis, menorrhagia, purpura and petechial haemorrhages.

MATERIALS & METHODS

This case series study was conducted in Department of Medicine PNS Shifa Hospital, Karachi from 1st August 2006 to 1st Jul 2007. A Proforma was designed to enter patients data. A total of 100 consecutive patients meeting the diagnostic criteria of Hepatitis C infection were included in the study. Inclusion criteria was anti HCV antibody positive patients, age between 18-50 years, persistently raised alanine transaminase for three months and Hepatitis C virus RNA detected by PCR. Patients with ultrasound or clinical evidence of cirrhosis, comorbid medical conditions, psychiatric disorders, alcoholism, haemotological diseases malignancy and pregnant ladies were excluded.

Individuals were treated with interferon alfa 2b 3 millions units thrice weekly subcutaneously and ribavirin 1000 mg to 1200 mg per day as per body weight orally.

Hematological alterations particularly thrombocytopenia secondary to therapy was noted at 2, 4 & 8 weeks following commencement of therapy. Patients were observed for manifestations of thrombocytopenia like gum bleeding, epistaxis, purpura, menorrhagia and subconjunctival hemorrhages.

Data analysis was performed through SPSS version 10. Descriptive analysis was done for demographic and clinical features. Results were presented as X (mean) ± SD (Standard deviation) for quantitative variables. Age was presented by X (mean) ± SD. Frequencies and percentages were computed to present all categorical variables. Platelet counts and manifestations of thrombocytopenia were compared with fisher's exact test.

RESULTS

In this study 100 patients fulfilling the inclusion criteria were enrolled. Out of these 81 were male and 19 were female. The mean age of the patients was 34-25 years & standard deviation was ±7.47.

In our study thrombocytopenia occurred in 11 patients (Table-I). At 2nd week four patients suffered grade I thrombocytopenia. At 4th week 11 patients had thrombocytopenia out of them one had grade III thrombocytopenia alongwith gum bleeding and purpura so interferon treatment was discontinued. Grade II thrombocytopenia was observed in three patients, though there were no bleeding episodes in these patients but reduction of dose was done till the counts raised to baseline. Grade I thrombocytopenia was seen in 7 patients which were monitored closely but dose reduction was not done. The maximum number of patient suffered from thrombocytopenia at 4th week of interferon therapy.

Table-I. Platelet counts at 2, 4 and 8 weeks of interferon therapy

	02 Weeks	04 Weeks	08 Weeks
Normal=[>100x10^3/dl]	96	89	94
Thrombocytopenia grade 1 [75-100x10^3/dl]	04	07	05
Thrombocytopenia grade 1 [50-75x10^3/dl]	00	03	00
Thrombocytopenia grade 3 [20-50x10^3/dl]	00	01	01
Total	100	100	100

DISCUSSION

Our population showed a good tolerance to the thrombocytopenic effect of combination therapy and it was observed in 11% of patients. In a study carried out at Military

Hospital, Rawalpindi by Siddiq M et al thrombocytopenia occurred in13.72%[7]. Another study carried out at Lahore showed thrombocytopenia in 2.9% of patients[8]. Khan AQ et al found that thrombocytopenia and erythema at the site of injection was common. (2-30%)[9]. In the study by George M Lades and Bruce D Walker thrombocytopenia was very common (>30%)[10].

Moderate to severe thrombocytopenia (4%) in our subjects is comparable to 3% observed by Fried et al[11] and total decline of platelet count of 20% to 25% from the baseline is comparable to 28% subjects as observed by Peck-Radosavljevic and collogues[12]. Moreover treatment discontinuation and dose reduction in 4% cases is also comparable (3% to 6%) to Mc Hutchison et al[13] and Fried MW, Shoffman ML et al[11] .

Thrombocytopenia is a clinical feature that may represent an obstacle to anti-viral treatment in patients with liver disease[14]. Thrombocytopenia can be an important limitation to interferon therapy as it is both an ineligibility criteria and a reason for treatment discontinuation[15]. It represents an important reason for denying or discontinuing treatment in patients who are most often in need of anti-viral therapy. Interferon administration is known to decrease platelet count because of a direct, dose-dependent effect on bone marrow[16].

The use of new pegylated-IFN in patients with chronic viral hepatitis has led to an increase in therapeutic efficacy as well as side effects. Indeed, in one of the largest pegylated-IFN therapeutic trials, 6% of the patients were excluded from treatment because of thrombocytopenia, and in the same study, thrombocytopenia was responsible for dose reduction and therapy discontinuation in approximately 20% and 3% of the patients respectively[17].

These features are likely to be higher in every-day clinical practice. Interestingly, it has been shown that during IFN treatment of chronic viral hepatitis there is a blunted thrombopoietin response to the decreasing platelet count, which is more evident in cirrhotic patients[12]. Noteworthy, successful IFN treatment is associated with restoration of the correct thrombopoietin platelet count feed-back mechanism, probably because of an improvement in liver function[18]. The decrease 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 interferons as a result of reactive thrombocytosis .With peginterferons, the platelet count decreases gradually over 8 weeks, stabilizing thereafter and returning to baseline values within 4 weeks of stopping therapy. Bleeding complications as a result of thrombocytopenia are uncommon[18,13].

In randomized clinical trials of the peginterferons, the rate of dose reduction attributed to thrombocytopenia ranged from 3% to 6%[13, 11].

Peck-Radosavljevic and colleagues[12] demonstrated that the platelet count decreased by nearly 28% in subjects treated with a single dose or multiple doses of interferon and peginterferon. They also found that, despite an increase in serum thrombopoietin levels, the reticulated platelet count did not change or actually decreased among subjects continuously exposed to peginterferon. These data indicate that bone marrow suppression, rather than increased platelet consumption, is the primary mechanism responsible for interferon-related thrombocytopenia.

Similarly, in randomized, controlled trials of peginterferon with or without ribavirin, the median platelet count decreased by approximately 30% during the first 8 weeks of therapy and remained stable until discontinuation of therapy. The decrease in platelet count was smaller among those receiving combination peginterferon/ribavirin therapy compared with those receiving only peginterferon, indicating that ribavirin appears to mitigate thrombocytopenia due to interferon. In randomized, controlled trials of peginterferon/ribavirin, peginterferon dose modification and/or reduction due to thrombocytopenia were relatively rare, occurring in only 3% and < 1% of patients, respectively. Furthermore, no episodes of bleeding were observed in patients with platelet counts < 50,000/mm[19].

During the trial reported by Fried et al., only around 4–6% of patients receiving peginterferon α-2a and ribavirin required dose reductions for thrombocytopenia[11]. This was broadly comparable with patients treated with the peginterferon α-

2b/ribavirin combination (3%) and standard interferon/ribavirin (1%)[13].

Dose reduction is advised when platelet counts fall below 50000/µL. Although discontinuation of therapy is usually unnecessary, it would be recommended if platelet counts fall below 30000/µL. The use of IL-11 (Oprelvekin) has been reported in a small pilot trial for treatment of HCV treatment-related thrombocytopenia[20].

There are limitations of this study as it represents a small proportion of the population. The frequency of thrombocytopenia in our population and its manifestations thus noted must be studied on larger scale. The individual included in the study should be divided into groups on the basis of pretreatment baseline platelet counts and viral load. Our study did not take into account the functional platelet disorders which may manifest as bleeding diasthesis inspite of normal count.

CONCLUSION

Our study concludes that bleeding complications and manifestation as a result of thrombocytopenia are uncommon. Combination therapy is well tolerated in most of the patients but it can cause life threatening complications like bleeding episodes in a few patients.

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