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CLINICO-IMMUNOLOGICAL PROFILE AND TREATMENT RESPONSE OF IMMUNE THROMBOCYTOPENIA (ITP) PATIENTS IN A TERTIARY CARE CENTRE: A RETROSPECTIVE REAL WORLD STUDY

Medicine

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ABSTRACT

Introduction: Immune thrombocytopenia (ITP) is a benign bleeding disorder affecting 1 in 10,000 population and presenting with prominent muco-cutaneous bleeds. It is treated with steroids and other immunomodulatory drugs, but due to frequent and unpredictable relapses multiple lines of therapy may be needed.

Methods: This was a retrospective real world analysis of 98 ITP patients who were treated at a single centre between 2010 to 2018. Age, sex distribution, clinical presenting feature, platelet counts and treatments taken were analysed.

Results: 98 patients (40 males & 58 females) with a median age of 31 years (2-81 yrs) presented with various muco-cutaneous bleeding manifestations. The median platelet count on presentation was 21,200/ µL (2000 – 70,000). Patients were treated with one or more agents, and followed up periodically to monitor remission status. 82% patients showed response to therapy, and out of the 18% non responders, one patient died of dapsone induced neutropenic sepsis. No platelet transfusions were used.

KEYWORDS

INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired bleeding disorder that is caused by antibody mediated destruction of normal platelets by the immune system resulting in thrombocytopenia and bleeding. It is characterized by isolated thrombocytopenia often occurring in the absence of identifiable and specific precipitants [1]. The low peripheral blood platelet count is caused by premature platelet destruction by self-reacting antibodies in addition to an impairment of platelet production [2]. The estimated incidence of ITP is 100 cases out of a million people per year; and in the pediatric age group, it represents the most frequent blood disorder[1]. The disease is heterogeneous in its pathophysiology, clinical features and responses to treatment[2]. In the American Society for Haematology guidelines ITP is defined as 'isolated thrombocytopenia with no clinically apparent associated conditions or other causes of thrombocytopenia. The diagnosis of ITP requires decreased platelets on the blood film and the exclusion of other causes of thrombocytopenia. Normal or increased numbers of marrow megakaryocytes are found in the majority of patients. ITP can be classified based on the absence or presence of other diseases (primary or secondary), patient age (adult or childhood ITP), and duration of thrombocytopenia (acute or chronic). Antibody-mediated platelet destruction may develop in several infectious diseases, lymphoproliferative diseases, and autoimmune diseases, and in association with drug therapy .Clinical observation and experience indicate a spectrum of manifestations ranging from trivial bruising to catastrophic haemorrhage. In 2009,an International Working Group (IWG) consensus panel of both adult and pediatric experts in ITP provided guidance on terminology, definitions and outcome criteria for this disorder. Primary ITP was defined by the IWG as a platelet count less than 100 x 10^9/L in the absence of other causes or disorders that may be associated with thrombocytopenia. The IWG also gave terminology for ITP based on the duration of the disease. The new terms for ITP are: 'newly diagnosed' (from diagnosis until 3 months), 'persistent ITP' (3-12 months) and 'chronic ITP' (ITP lasting for more than 12 months). This terminology was provided by the International Working Group (IWG). They also described the response to treatment; "complete response" (CR) was defined as platelet count greater than 100x109/L. "Response" was defined as platelet count between 30x109/L and 100x109/L or doubling of the baseline count. Any platelet count lower than 30x109/L or less than doubling of the baseline count was described as "no response" [3]. ITP is usually benign and, in most patients, resolves spontaneously 6- 18 months after diagnosis. Since available treatment for ITP does not affect the natural evolution of the disease, but is used in order to alleviate clinical symptoms, it is indicated in only a minority of patients who have a low platelet count associated with active bleeding [4]. The main aim of treatment is to achieve a safe platelet count for each patient on a case-by-case basis [5]. Approximately 80% of pediatric patients and 40% adult patients will respond to a single treatment or combination of first line therapies, which include watchful waiting, corticosteroids, IVIG, or anti-D [6]. However, management is not fully standardized, and treatment decisions incorporate multiple considerations including the patient's presenting characteristics, patient values and preferences, and the provider's experience with the various pharmacologic options [7]. The current study sought to undertake retrospective analysis of clinical profile & response to treatment in patients of ITP reporting to a tertiary care centre of armed forces medical services in India.

AIMS & OBJECTIVES

Primary Objectives

1) To study the clinical profile of patients of ITP.
2) To analyse the outcomes of the various treatments administered in the first 12 months of diagnosis.

Secondary Objectives

1) To compare treatment outcomes with different agents used to treat acute and chronic ITP.

MATERIALS & METHODS

Patients

This retrospective study was conducted at a tertiary care teaching hospital in southern India, in the department of clinical hematology. Clinical & laboratory data of 98 diagnosed patients of ITP registered in the period between 2010 to 2018, who were eligible for receiving treatment, and took treatment, was retrospectively analysed. ITP diagnosis was based on physical examination, complete blood cell count, and analysis of bone marrow aspiration. We excluded cases with isolated thrombocytopenia induced by drugs, infectious agents, or related to other diseases like systemic lupus erythematosus, antiphospholipid syndrome, lymphoma, or myelodysplasia. All patients who had a platelet count <70 x 10^3 /µL for at least two consecutive blood counts were subjected to bone marrow examination, and on confirmation of diagnosis of ITP were considered eligible for treatment. While all patients with baseline counts below 30 x 10^3 /µL opted for some pharmacological treatment, some patients with platelet counts in the range of 30 to 70 x 10^3 /µL did not consent for any therapy. They were not included in the analysis. Patients with isolated thrombocytopenia - platelet counts between 70 to 100 x 10^3 /µL on two occasions more than 2 weeks apart, were counselled and all secondary causes including viral infections, drugs, autoimmune conditions, gestation, liver disease etc were excluded. They were subjected to bone

marrow examination only if age was > 40 years, or the patient desired so. On confirmation of diagnosis they were put on observation alone, and not offered any treatment.

Baseline data

For each case, the following information was collected: age, gender, and clinical characteristics; complete blood count and bone marrow aspiration analysis; drugs administered, including dose, administration method, start and withdrawal date, and observed side-effects.

Outcomes

All patients (n=98) with platelet counts below 70 x 10^3 /µL who were put on some treatment regime, were followed up at least monthly for the first 3 months with CBC, and thereafter at least three monthly till 12 months of diagnosis. We analysed patient responses to the following different therapies given alone or in combination : corticosteroids, intravenous immunoglobulin, splenectomy, dapsone, cyclosporine, azathioprine, rituximab, and thrombopoietin analogues (Eltrombopag).

Response to treatment were characterised according to the descriptive terminology recommended by the international working group consensus panel:

1) Complete Response (CR)- platelet count ≥ 100 x 10^3/µL measured on 2 occasions > 7 days apart.
2) Response®- Platelet count ≥30 x 10^3/µL and a greater than twofold increase in platelet count from baseline measured on 2 occasions >7 days apart.
3) Non- Response (NR) - Platelet count ≤30 x 10^3/µL and / or persistence of bleeding manifestation
4) Refractory ITP- presence of severe ITP even after splenectomy.

Non-splenectomized patients are defined as responders and non-responders to various drug therapies, but should not be considered refractory.

RESULTS

A total of 98 patients registered over a period of 08 yrs (2010-2018) were analysed. 40 patients (40.81%) were males & 58(59.19%) females, with male : female ratio of 1:1.58. Mean age of presentation was 31.2 yrs (range 2-81) with distribution across various age groups as in table 1. Platelet count on presentation is as per fig-1, with mean of 21,200/ µL. The most common clinical presentation was ecchymosis, epistaxis & petechiae. Menorrhagia was the most common symptom in female patients(34.48%). Various clinical symptoms at presentation are tabulated in fig-2. 16 patients(16.32%) were asymptomatic on presentation and were detected incidentally either during evaluation for febrile illness(13.26%) or during periodic health screening related medical examination(3.06%).

Table -1 Age distribution of patients (n=98)

Age group	Number of patients(n)	Percentage (%)
Less than 15 yrs	24	24.5%
16-30 yrs	29	29.6%
31-50 yrs	23	23.5%
More than 50 yrs	22	22.4%

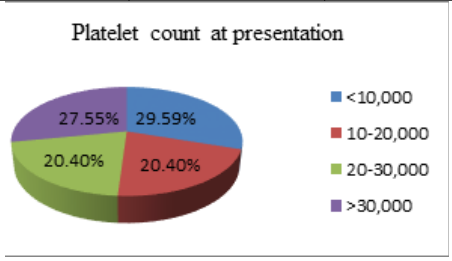

Fig-1

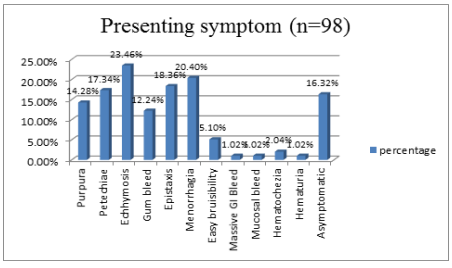

Fig-2

Peripheral blood smear in all patients showed thrombocytopenia & bone marrow aspiration was suggestive of megakaryocytic thrombocytopenia. Other investigations which were done included ANA, HBsAg, Anti HCV, HIV, G-6-PD levels & direct Coombs test. 07 patients (7.14%) had ANA positiity.

Response to therapy was documented as Complete response (CR), Response(R), Non- responders (NR) & Refractory as per the criteria recommended by the IWG consensus panel. 19(19.38%) patients were treated with steroids alone, of which 17(17.34%) had complete Response & 02(2.04%) had Response to steroids. 03(3.06%) patients had CR to intravenous immunoglobulin (IvIg). Rest of the patients were given multiple drug therapy in view of poor response to a single agent. 16(16.32%) patients received steroids plus Dapsone, of which 13(13.26%) had Complete Response & 02(2.04%) had Response. 05(5.10%) patients were given steroids plus IvIg, of which 04(4.08%) had CR & 01(1.02) had Response. Splenectomy was done in 15(15.3%) patients, out of which 11(11.22%) achieved a complete response, 01(1.02%) Response & 03(3.06%) patients were refractory to splenectomy. 36 patients were given three or more drugs. Eltrombopag was used in 10 patients & Rituximab was used in 08 patients. Of this group 18(18.36%) patients achieved Complete Response, 06(6.12%) achieved Response, and 14(14.28%) patients were declared non- responders as the platelet count in them failed to increase above 30000 despite use of four or more drugs. Spontaneous remission was seen in 02 children with platelet counts between 30 to 70 x 10^3/µL without any drugs, when they were advised oral prednisolone but they did not take the medication. 01 patient died in study due to severe sepsis. This patient had developed the rarely seen but well documented – Dapsone induced myelosuppression. The nadir platelet count in our patients was 2 x 10^3/µL, but no patient after the confirmation of diagnosis of ITP was given any platelet transfusions, even if they presented with mucosal bleeds to the emergency department during follow up.

Table-2 Response to therapy at 12 months of diagnosis (n=98)

Treatment given	Complete Response	Response	Refractory/ Nonresponders	Death
Spontaneous remission(no drugs)	2.04%	-	-	-
Steroids alone	17.34%	2.04%	-	-
IvIg alone	3.06%	-	-	-
Steroids plus Dapsone	14.28%	2.04%	-	1.02%
Steroids plus IvIg	4.10%	1.02%	-	-
Splenectomy	11.22%	1.02%	3.06%	-
Three or more drugs	18.36%	6.12%	14.28%	-
TOTAL	69.4%	12.2%	17.4%	1%

Table -3 Comparison between responders & non responders/ refractory ITP

Parameter	Responders	Non Responders
Mean age	32.1 yrs	28.75 yrs
Mean platlet count (at presentation)	22100	16800
Male:female ratio	1:1.34	1:2.2
ANA positive	9.75%	6.25%

DISCUSSION

ITP is an autoimmune disorder caused by one or more antiplatelet autoantibodies usually directed to the platelet glycoprotein IIb/IIIa complex, GPIb/ IX complex or both that cause platelet destruction by the reticuloendothelial system. The demographics, clinical presentation and the response to treatment can be very varied. Neylon et al studied 245 patients with ITP. The mean age in their study was 56 years. The mean age in our study was 31.2 years (range 02 years – 81 years). Most of the published studies have shown a female preponderance. Our study had male to female ratio of 1:1.58. the commonest presenting symptom was ecchymosis in males & menorrhagia in females. 16.32 % of the patients were asymptomatic on presentation. Steroids as a first line therapy were offered to majority of patients except 3.06% of patients who received IvIg. Depending on the clinical response, further therapeutic agents were added sequentially. Splenectomy was offered to patients who had shown no response to at least three different drugs in adequate doses. Clinical response to different therapies are tabulated in table-2. In our study, 16.32% of the patients were labelled as non responders/refractory, as they continued to have thrombocytopenia below 30,000 despite being on adequate treatment. Comparison between the two groups ie responders vs non

responders revealed a lower mean age & platelet count at presentation (table-3). Also the male to female ratio was 1:2.2 in non responder group as compared to 1:1.34 in responder group. 8.16% patients in the study developed dapsone induced hemolysis, though all patients were screened for G6PD deficiency prior to starting Dapsone. The cause for this intravascular hemolysis, which remitted on stopping Dapsone, remains unclear and requires further studies.

While prospective studies have the advantage of standardising statistical analysis, they suffer from the fact that due to strict inclusion – exclusion criteria, they do not represent completely the real world patients. Retrospective data analyses are not suitable for comparing treatment outcomes between two or more groups of patients, or for analysing survival data. These retrospective studies however have the advantage of putting forward the patient outcomes as such- as it happened in the real world. Our analysis therefore demonstrates the heterogenous nature of initial treatments offered to ITP patients over 8 years by different treating physicians. We observed that while a particular treatment did not have a statically superior response to any other treatment, but using sequential treatments, more than 80% patients showed some response to therapy. Though we had 18.5% patients not showing any response to therapy, there were no bleeding related fatalities or any major bleeding episode causing ICU admission. The lone fatality was due to Dapsone induced neutropenic sepsis. We did not do a subgroup response to therapy analysis in paediatric or adult populations, as the numbers in each sub-group was small. ITP is a benign disorder, and in a diagnosed case of ITP, mere drop in platelet counts to any value, or some muco-cutaneous bleeding should not be treated with platelet transfusions.

CONCLUSION

ITP is a benign disorder with a high rate of treatment response to one or more lines of therapy given over a period of time. It may have frequent relapses and remissions, but major bleeding is rare. No one line of therapy is superior to another, and the physician has to optimise the therapy that most suits his patient. Platelet transfusions should not be given for any level of thrombocytopenia or minor muco-cutaneous bleeds.

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