Identifying the characteristics, natural behavioral pattern, and response to therapy in ITP in a multi-center population in Sri Lanka

Gunawardena Dammika1, Senadheera Nipunika2, Costa Yasintha3, Senanayake Sameera Jayan4, Wijesiriwardena Indira1

1Department of Pathology, Faculty of Medicine, University of Sri Jayawardenapura, Sri Lanka, 2Department of Hematology, General Hospital, Ratnapura, Sri Lanka, 3Department of Haematology, General Hospital, Chilaw, Sri Lanka, 4Ministry of Health, Sri Lanka

Objective: To describe some selected characteristics of immune thrombocytopenia (ITP) such as presentation, the disease pattern, treatment options, and response to therapy and side effects to common therapeutic options.

Methods: A group of 72 patients diagnosed as ITP were studied over a period of 5 years in two main centers in Sri Lanka. Characteristics of the disease such as presentation, the disease pattern, treatment options, and response to therapy and side effects to common therapeutic options were studied.

Results: The ages of the patients ranged from 12 to 71 years but the majority (64.2%) were between 20 and 45 years. In 47 (65.3%) the average platelet count at presentation was below $30 \times 10^9/l$ and in these patients there was a significant increase in bleeding manifestations. Sixty-nine patients were given steroids as the initial treatment and all had responded initially. Time to respond ranged from 3 to 30 days with an average of 11 days. Twenty-four patients developed steroid-related side effects. In 24 patients second-line treatment options such as dapsone, azathioprine, and danazol were given but a satisfactory response to them could not be demonstrated.

Discussion: The heterogeneous behavioral patterns of the disease with patients who are having the same platelet count ($<30 \times 10^9/l$) were observed and this revealed that ITP needs an individualized approach regardless of the platelet count of the patient. A close follow-up of the patients revealed that the patient’s understanding of the disease and ability to identify the warning signs resulted in less intervention with drugs which lead to many harmful long-term side effects.

Keywords: Immune thrombocytopenia, Steroids, Remissions, Platelets, Sri Lanka

Introduction

Primary immune thrombocytopenia (ITP) is an acquired immune-mediated disorder which results in persistent lowering of the platelet count causing bleeding into various sites leading to a chronic illness. It is an autoimmune disorder resulting in increased platelet destruction as well as decreased platelet production. Now it is believed that this is a complex process of both impaired platelet production due to T-cell-mediated effects, in addition to the antibody-mediated peripheral destruction of platelets. This illness brings a lot of anxiety to the patient although clinical problems anticipated even in severe thrombocytopenia (counts $<10 \times 10^9/l$) are not encountered often. However, this anxiety can lead to the practice of unnecessary treatment in order to improve the platelet counts rather than treating the clinical symptoms of the disorder.

This study was aimed at evaluating the relationship between the severity of the thrombocytopenia and the incidence of bleeding manifestations. Due to the restricted financial resources in Sri Lanka, currently used drugs such as thrombopoietin receptor inhibitors and rituximab are not a commonly available option. Thus we wanted to study the option of ‘NO drug therapy’ vs. ‘drug therapy’ for counts $<30 \times 10^9/l$.

Further this paper discusses the types of therapy which are commonly practiced in Sri Lanka and the response rate to commonly used therapeutic options in ITP.

Material and methods

A retrospective analysis was performed among 72 ITP patients attending the ITP clinics in two major
hospitals in the country, Colombo South Teaching Hospital and Ratnapura General Hospital. The data were analyzed through a questionnaire which had a descriptive evaluation on various aspects of the disease. The questionnaire was completed by trained medical officers and it contained information about the demographic factors, nature of symptoms, and information on investigations.

Chronic ITP was diagnosed under the following criteria. It is a clinical diagnosis based on the exclusion of other disorders causing thrombocytopenia, and anti-platelet antibodies do not play a major role in the diagnosis due to its lack of specificity and sensitivity.2

1. Asymptomatic presentation (absence of any symptoms which could indicate the presence of an underline secondary cause).
2. Platelets count <100 × 10^9/l at the time of presentation lasting for >6 months.
3. Other blood counts are normal.
4. No organomegaly or lymphadenopathy.
5. No significant causes for a secondary thrombocytopenia (drugs, SLE, DIC, etc.).
6. Normal or increased number of megakaryocytes in the bone marrow.

**Patient selection**

All the participants in the study had an isolated thrombocytopenia at the outset and most patients presented as an incidental finding during an episode of severe menorrhagia or skin bleeding. A detailed history was taken with regard to the past medical history, drug history, and any history to exclude symptoms of systemic lupus erythematosus (SLE) such as alopecia, hair loss, skin rashes, and joint pain, also to exclude a liver pathology. All the patients were examined to rule out hepatosplenomegaly and lymphadenopathy. None of the patients had clinical features related to connective tissue disorder or liver disease. Ultrasound scan was performed to check for the state of the liver and spleen. dsDNA, antinuclear factor, and ESR were performed. In all the patients, in addition to the automated platelet count, a manual platelet count was also performed in the modified Neubauer chamber to confirm the platelet count. A blood film was performed in all patients who demonstrated an isolated thrombocytopenia with large platelets. This was also used to some extent to exclude the presence of viral infection, underlying marrow pathology (leukemia, aplastic anemia, etc.). In patients who had a low hemoglobin, a direct antiglobulin test was undertaken. In some of the patients, a bone marrow was requested by the physician which demonstrated increased megakaryocytes as the only abnormal feature in the marrow. None of the patients had positivity for any other test. They were followed up for a period of 5 years.

All statistical analysis was computed with SPSS statistical software. Data were presented as mean values and percentages. Several variables were studied such as age at presentations, gender, platelet count at presentation, symptoms at presentation, and response to corticosteroids. A *P* value of less than 0.05 was considered statistically significant.

**Results**

A total of 72 patients from the two hospitals were included in the study. The ages of the patients ranged from 12 to 71 years but the majority (64.2%) were between 20 and 45 years. There was a significant female predominance in this study population with 63 (87.5%) being females. Six patients had presented in their pregnancies.

Severe bleeding such as hematuria, intracranial bleeds, and GI bleeding occurred in 5.6% during the study period but the majority of (70.8%) patients had only mucocutaneous bleeding while in 17 (23.6%) the thrombocytopenia was asymptomatic.

In 47 (65.3%) the average platelet count at presentation was below 30 × 10^9/l. In 40 (55.5%) it was 10 × 10^9/l or less. In 11 it was above 50 × 10^9/l. Occurrence of bleeding manifestations was significantly different (*χ^2^ = 8.827; *P* < 0.05) between those who had the average platelet count at presentation below 30 × 10^9/l (*n*= 41; 87.2%), compared to those who had the average platelet count at presentation above 30 × 10^9/l (*n*= 14; 56.0%). A bone marrow biopsy had been performed in 53 (73.6%) patients and out of them, in 36 (67.9%) the megakaryocytes were reported as increased.

**Table 1** Distribution of the study participants according to the time taken to respond to steroid

| Time taken to respond | Frequency | Percentage |
|-----------------------|-----------|------------|
| In 1 week             | 21        | 29.2       |
| In 2 weeks            | 36        | 50.0       |
| In 3 weeks            | 9         | 12.5       |
| >3 weeks              | 2         | 2.8        |
| Steroids not given    | 4         | 5.6        |
| Total                 | 72        | 100.0      |

**Table 2** Distribution of the study participants according to development of steroid-related side effects

| Side effect                          | Frequency (n = 24) | Percentage |
|--------------------------------------|--------------------|------------|
| Cushingoid features                  | 13                 | 54.2       |
| Gastritis                            | 11                 | 45.8       |
| Diabetes mellitus                    | 04                 | 16.7       |
| Acne                                 | 01                 | 4.2        |
| Avascular necrosis of the hip         | 01                 | 4.2        |
| Depression                           | 01                 | 4.2        |
| Other                                | 04                 | 16.7       |
When considering the management, all these patients except for three were given steroids as the initial treatment. The platelet counts in those who were not treated were $62 \times 10^9/l$, $88 \times 10^9/l$, and $108 \times 10^9/l$ at the time of making the decision.

All those who were given steroids had responded initially. There were no steroid-resistant patients in this group. The time to respond ranged from 3 to 30 days with an average of 11 days (Table 1).

Twenty-four patients developed steroid-related side effects (Table 2). Of the 24, 6 (25.0%) developed long-term complications while in 18 (75.0%) the complications were short term. Commonest symptoms were gastritis ($n = 11$) and Cushingoid features ($n = 13$). Four developed diabetes and one had avascular necrosis of the hip.

Splenectomy was performed only in six of these patients and it was successful in three, leading to sustained increase of platelets.

In 24 patients second-line treatment options such as azathioprine and danazole were given but a significant response to them could not be demonstrated. However, the use of dapsone led to a persistent remission for more than 6 months in 10 patients. Out of six patients who were given rituximab, two demonstrated a response in terms of clinical symptoms. Two patients were post-splenectomy patients.

Twenty-five achieved a stable platelet count after tapering off steroids. In 11 the platelet count normalized. The others maintained a low count but without bleeding and were followed up without treatment. Thirty-two were maintained on a low dose of steroids (Table 3).

Seven were resistant to first- and second-line treatment which included steroids, intravenous immunoglobulin (IVIG), danazole, splenectomy, and azathioprine. Rituximab was tried in three patients. These patients continued to have bleeding manifestations and one died during the study period following an intracranial hemorrhage.

Eleven patients were not on any form of treatment (watch and wait) in spite of having a platelet count of less than $30 \times 10^9/l$ with no bleeding manifestations. All were educated about the risk of bleeding and were followed up closely. In this group, only one patient (9.1%) developed significant bleeding. Compared to the above group, patients who had a platelet count of less than $30 \times 10^9/l$ and who were on steroids ($n = 24$) had significantly ($\chi^2 = 4.659; P < 0.05$) more bleeding manifestations ($n = 12$).

In 15 patients the disease led to loss of job. One patient was separated from her husband as a result of the disease.

**Discussion**

This retrospective study of ITP patients demonstrated a significant female preponderance in keeping with previously reported data. A majority of patients presented at the ages of 20–40 years with a few younger people. We identified a category of patients who had persistently low platelet counts ($<30 \times 10^9/l$) and who did not have any bleeding manifestations when they were off steroid or any other therapy. However, in usual practice this category of patients is continued on steroids despite lack of symptoms. However current study revealed that it would be best to leave them on a watch and wait policy, if they could be closely followed up. A smaller number of patients were totally resistant to any other therapy and this category demonstrated a clinically aggressive pattern of disease which needed close follow-up and patient education. Most of those patients ended up with rituximab therapy or splenectomy.

In our study two had intracranial hemorrhage out of whom one died 3 years after diagnosis and the other patient survived with no residual neurological effects. They both had counts less than $10 \times 10^9/l$ with a past history of significant bleeding episodes which did not respond to any therapy. Out of the patients who had splenectomy, only three responded which is slightly lower than the western figures of 80–85%. It could be that in some patients, the antibody-coated platelets get destroyed mainly in the liver and the other reticuloendothelial tissues. They demonstrate only a partial response to splenectomy. Two patients needed a small boosting dose of steroids to remain asymptomatic. Development of diabetes in a number of patients was a disturbing finding. One 28-year-old patient who was taking long-term intermittent courses of steroids developed avascular necrosis of the femoral head which led to residual joint deformities with impaired leg movements. Several others were detected as having osteoporosis and were put on bisphosphonates subsequently. Depression, increased weight were common problems.

Several patients were responsive but steroid dependent. However, the good category of ITP patient who had $<30 \times 10^9/l$ platelet counts could manage either with watch and wait policy or a very small every other day dose of steroids to be asymptomatic regardless of the platelet counts. Often the sudden

### Table 3 Distribution of the study participants according the outcome of treatment

| Outcome of treatment   | Frequency | Percentage |
|------------------------|-----------|------------|
| Resistant              | 7         | 9.7        |
| Watch and wait         | 15        | 20.8       |
| Remission              | 15        | 20.8       |
| Dependent low dose     | 32        | 44.4       |
| Never treated          | 3         | 4.2        |
| Total                  | 72        | 100.0      |
drops of platelet counts in patients who had otherwise stable platelet counts were due to subclinical or symptomatic infection which ultimately recovered without increasing the dose of steroids. A policy of using therapy only when absolutely required is suggested by some guidelines.\textsuperscript{5} It was very important to tabulate the platelet count over the years and study the pattern of bleeding and the platelet count and give each patient an individual approach to the management of their disease.

In our study, usage of azathioprine alone or in combination with steroids have demonstrated poor results probably due to the long period needed for its action. Dapsone demonstrates promising response especially in patient with chronic refractory ITP.\textsuperscript{5,6} Often the only therapy which worked in sudden severe thrombocytopenia with life-threatening bleeding was IVIG. Platelet transfusion is found to be ineffective and exposed the patient to risks of transfusion.\textsuperscript{7} This could lead to harmful adverse effects for the patient.\textsuperscript{8} One child who had evidence of intracranial hemorrhage in the past succumbed due to severe intracranial hemorrhage followed by trauma. She was lost for follow-up and had counts $<30 \times 10^9$/l on admission.

In conclusion, our study shows some of the characteristics of the disease and the pattern of response to common therapeutic options. To avoid unwanted treatment-related side effects and reduce anxiety of the patient, the ideal management of ITP is an individual approach where the goal will be to achieve a symptom-free patient irrespective of the platelet count.

Disclaimer statements

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ORCID

Gunawardena Dammika \( \text{http://orcid.org/0000-0002-4512-7553} \)

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