Original article

Good prognosis of adult immune thrombocytopenia in a provincial hospital

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Abstract

Objective: *This study aimed to assess the clinical course and identify factors related to sustained responses to treatment among patients with immune thrombocytopenia (ITP).* ***Methods:*** *This observational retrospective cohort study of patients with ITP was conducted from January 2013 to December 2022 at Trang Hospital.* ***Results:*** *A total of 125 newly diagnosed patients with ITP were enrolled. The characteristics of the patients were as follows: age below 60 years (78.4%), female (75.2%), secondary ITP (32.8%), bleeding symptoms (54.4%), lost to follow-up (10.4%) and death (4%). The median platelet count at baseline was 6 x10^9/L (range, 1-96 x10^9/L) with 64% had platelet < 10 x10^9/L. Platelet recovery time after treatment was 28 days (range, 0-730 days). The median response duration after the first line treatment especially corticosteroids was 14 months (range, 0-131 months). The clinical courses were as follows: recovery within 3 months in 68.8%, persistence in 13.6% and chronic ITP in 17.6%. The responses to corticosteroid treatment included early response (32.8%), initial response (47.5%) and durable response (69.6%). The responses to second-line treatments were early response (46.4%), initial response (42.9%) and durable response (92.8%). Only female sex (Adjusted Odds ratio, 3.5; 95%CI: 1.40-8.72) was significantly associated with the durable response to corticosteroids.* ***Conclusion:*** *This study reveals a favorable prognosis for ITP with the majority of patients showing a durable response. Female patients were more likely to respond.*

Keywords : ● *Immune thrombocytopenia* ● *Durable response* ● *Natural history* ● *Prognosis*

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นิพนธ์ต้นฉบับ

การพยากรณ์โรคที่ดีของผู้ป่วยเกล็ดเลือดต่ำจากการทำลายโดยกลไกทางอิมมูนในโรงพยาบาลจังหวัด

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บทคัดย่อ

วัตถุประสงค์ *ประเมินลักษณะทางคลินิกและปัจจัยที่มีผลต่อการตอบสนองต่อการรักษาของโรคเกล็ดเลือดต่ำจากถูกทำลายโดยกลไกทางอิมมูน (Immune thrombocytopenia, ITP)* ***วิธีการศึกษา*** *ศึกษาข้อมูลย้อนหลังของผู้ป่วยที่วินิจฉัย ITP ในโรงพยาบาลตรัง ช่วงมกราคม 2556 ถึงธันวาคม 2565* ***ผลการศึกษา*** *ผู้ป่วยทั้งหมด 125 คน คุณลักษณะของผู้ป่วย: อายุ < 60ปี (78.4%) เพศหญิง (75.2%) ITP จากเหตุทุติยภูมิ (32.8%) มีเลือดออก (54.4%) ไม่มาตามนัด (10.4%) และเสียชีวิต (4%) มัธยฐานพื้นฐานของเกล็ดเลือดคือ 6 x10^9/L (ช่วง 1-96 x10^9/L) ร่วมกับมีเกล็ดเลือด < 10 x10^9/L (64%) ระยะเวลาฟื้นตัวเกล็ดเลือดหลังรักษาคือ 28วัน (ช่วง 0-730 วัน) ค่ามัธยฐานระยะเวลาตอบสนองหลังรักษาด้วยยาทางเลือกแรกคือ 14 เดือน (ช่วง 0-131 เดือน) การดำเนินโรค: เกล็ดเลือดฟื้นตัวภายใน 3 เดือน (68.8%) เกล็ดเลือดฟื้นตัวใน 3-12 เดือน (13.6%) และเกล็ดเลือดต่ำมากกว่า 12 เดือน (17.6%) ตอบสนองด้วยคอร์ติโคสเตียรอยด์ คือ ตอบสนองช่วงต้น (32.8%) ตอบสนองเบื้องต้น (47.5%) และตอบสนองอย่างคงทน (69.6%) ตอบสนองด้วยยาทางเลือกที่สอง คือ ตอบสนองช่วงต้น (46.4%) ตอบสนองเบื้องต้น (42.9%) และตอบสนองอย่างคงทน (92.8%) ปัจจัยที่มีความสัมพันธ์อย่างมีนัยสำคัญต่อการตอบสนองอย่างคงทนด้วยคอร์ติโคสเตียรอยด์ คือ เพศหญิง (adjusted odds ratio 3.5 ค่าขอบเขตความเชื่อมั่นร้อยละ 95 (95%CI) 1.40-8.72)* ***สรุป*** *ผู้ป่วยส่วนใหญ่ตอบสนองอย่างคงทน เพศหญิง ตอบสนองดีต่อการรักษา*

คำสำคัญ : ● *โรคเกล็ดเลือดต่ำเนื่องจากถูกทำลายโดยกลไกทางอิมมูน* ● *การตอบสนองคงทน* ● *การดำเนินโรค* ● *การพยากรณ์โรค*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2566;33:287-93.

Background

Immune thrombocytopenia (ITP) is an autoimmune disease resulting from platelet destruction and impaired platelet production. The annual incidence rate of ITP is 2 to 4 new cases per 100,000 adults and the prevalence is 9 to -26 per 100,000 in related studies.[1] ITP is classified based on duration as newly diagnosed < 3 months, persistent 3 to 12 months, and chronic > 12 months.[2] The ITP guidelines of the American Society of Hematology (ASH) 2019 suggests that patients with platelets lower than 30 $x10^9$/L require corticosteroids for initial treatment.[2] However, some experience refractory ITP, relapses after steroid tapering (steroid dependence) or intolerance to steroid side effects. The standard options for second line treatments include thrombopoietin receptor agonists (TPO-RAs), rituximab and splenectomy. These are not accessible to most patients in Thailand. The aim of this study was to assess the clinical course and identify factors related to sustained responses to corticosteroids and second line treatments among patients with ITP in a provincial hospital setting in a low to middle income country.

Materials and methods

This observational retrospective cohort study was conducted from January 2013 to December 2022 at Trang Hospital, Trang Provincial, Thailand.

Patients

We enrolled patients with newly diagnosed ITP by the International Statistical Classification of Diseases and Related Health Problems, 10^{th} Revision Thai Modification (ICD-10-TM) codes. This study was presented and approved by the hospital ethics committee. The inclusion criteria were patients aged ≥ 15 years and platelet count less than 100 $x10^9$/L with either primary ITP as diagnosed by excluding other causes by a hematologist, or secondary ITP as associated with various medical conditions (systemic lupus erythematosus, human immunodeficiency virus (HIV), Hepatitis C virus (HCV), and lymphoproliferative disorder) or precipitating factors (vaccination or drugs). The clinical outcomes comprised clinical bleeding and death. Clinical bleeding included petechia or ecchymosis, bleeding per gums, heavy menstrual bleeding, gastrointestinal bleeding, epistaxis and hematuria.

Definition of terms in ITP[2,3]

Newly diagnosed ITP definition was ITP duration of < 3 months, persistent ITP definition was ITP duration of 3 to 12 months and chronic ITP definition was ITP duration of > 12 months. Refractory ITP definition was treatment failure to achieve at least a response or loss of response after splenectomy.

Treatments

The first line treatments included corticosteroids (dexamethasone, prednisolone) and intravenous immunoglobulin (IVIg). The dose of initial corticosteroid treatments in this study were dexamethasone 40 mg/day for 4 days and prednisolone 1 mg/kg/day for 1 to 2 weeks.

The second line treatments included azathioprine, colchicine, cyclosporine, cyclophosphamide, dapsone, mycophenolate mofetil and elthrombopag.

Criteria for treatment response[2,3]

Early response definition was a platelet count ≥ 30 $x10^9$/L and at least doubling baseline at one week. Initial response definition was a platelet count ≥ 30 $x10^9$/L and at least doubling baseline at one month. Durable response definition was a platelet count ≥ 30 $x10^9$/L and at least doubling of the baseline count at six months. Nonresponse definition was a platelet count < 30 $x10^9$/L or less than a two fold increase of baseline platelet count or bleeding.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics 28 (Statistical Packages for Social Sciences) Software. We used descriptive analysis to calculate the percentage of data. Variable factors of treatment response to corticosteroids and second line treatment were calculated using the Chi-square test and binary logistic regression test. The significance *p*-value was < 0.05.

Results

A total of 125 newly diagnosed patients with ITP were enrolled. The median duration of follow-up was 38 months (range, 1 to 131 months). The median platelet count at baseline was 6 $x10^9$/L (range, 1 to 96 $x10^9$/L) and platelet recovery time after treatment was 28 days (range, 0 to 730 days). The median response duration after the first line treatment was 14 months (range, 0 to 131 months). The majority of patients were aged below 60 years (75.2%), female (75.2%), newly diagnosed ITP (68.8%), primary ITP (67.2%), platelet count < 10 $x10^9$/L (64%) and bleeding presentation (54.4%) as shown in Table 1.

Table 1 Baseline characteristics and clinical courses of patients with ITP

Characteristic	Number (%)
Age (Mean±SD)	42.34±18.44 years
≥ 60 years	27 (21.6%)
Female	94 (75.2%)
Pregnant	2 (1.6%)
Newly diagnosed ITP	86 (68.8%)
Persistent ITP	17 (13.6%)
Chronic ITP	22 (17.6%)
Primary ITP	84 (67.2%)
Secondary ITP	41 (32.8%)
- Systemic lupus erythematosus	26 (63%)
- HIV	3 (7.3%)
- Antiphospholipid syndrome	3 (7.3%)
- Evans syndrome	3 (7.3%)
- Lymphoma	2 (4.8%)
- HCV	1 (2.4%)
- Helicobacter pylori	1 (2.4%)
- Vaccination	1 (2.4%)
- Rifampicin	1 (2.4%)
Bleeding	68 (54.4%)
- Petechia or ecchymosis	35 (51.4%)
- Bleeding gums	21 (30.8%)
- Heavy menstrual bleeding	11 (16.1%)
- Gastrointestinal bleeding	6 (8.8%)
- Epistaxis	3 (4.4%)
- Hematuria	2 (2.9%
No bleeding	57 (45.6%)
Platelet count [Median; Interquartile Range (IQR)]	6 $x10^9$/L; 13.5 $x10^9$/L
- Platelet count < 10 $x10^9$/L	80 (64%)
- Platelet count 10-30 $x10^9$/L	36 (28.8%)
- Platelet count 30-50 $x10^9$/L	7 (5.6%)
- Platelet count > 50 $x10^9$/L	2 (1.6%)
Splenectomy	5 (4%)
Observation only	3 (2.4%)
Second line treatment requirement	28 (22.4%)
Lost to follow-up	13 (10.4%)
Death	5 (4%)

The most common cause of secondary ITP was systemic lupus erythematosus (63%). We encountered only one patient with thrombocytopenic from COVID-19 (Sinovac®) vaccination (2.4%), as shown in Table 1.

Among the 68 patients present with bleeding symptoms, the most common were petechiae and ecchymosis (51.4%) (Table 1).

Causes of death in 4% of patients with ITP were infections including bacterial pneumonia, COVID-19 pneumonia, cellulitis and septicemia with septic shock.

Totally, 93.6% of patients with ITP received initial treatment with corticosteroids consisting of dexamethasone (70.4%) and prednisolone (23.2%) (Table 2). Severely thrombocytopenic patients with ITP, who were close to giving birth or had life-threatening bleeding, received IVIg.

Of the 28 patients (22.4%) with ITP not responding to initial treatment and requiring second-line treatments, more than one half received colchicine treatment (60.7%) and prednisolone combined. Only one patient received eltrombopag treatment (3.5%), as shown in Table 3.

The treatment response to corticosteroids included early response, 32.8%, initial response, 47.5% and durable response, 69.7%. The treatment response to second line treatments included early response, 46.4%, initial response, 42.9% and durable response, 92.8% (Table 4). The majority of patients (71.2%) with durable responses maintained their platelet count using low dose prednisolone. On the other hand, 28.8% of patients achieved a durable response without the use of any drugs. Only female sex (*p*-value 0.007) was significantly associated with the durable response, as shown in Table 5.

Discussion

Our results showed most patients with ITP were female and mean age was 42 years old (SD 18) which is consistent with the related study.[4] Interestingly, our data showed that the majority of patients (68.8%) had durable responses after steroid treatment alone. On the contrary, related results showed that most adult ITP courses became chronic or relapsing.[5-7]

Table 2 First line treatment among patients with immune thrombocytopenia

First line treatment	Number (%)
Dexamethasone	88 (70.4%)
Prednisolone	29 (23.2%)
Intravenous immunoglobulin	5 (4%)

Table 3 Second line treatments among patients with immune thrombocytopenia

Second line treatment	Number (%)
Colchicine	17 (60.7%)
Azathioprine	10 (35.7%)
Cyclophosphamide	7 (25%)
Dapsone	5 (17.8%)
Vincristine	3 (10.7%)
Mycophenolate mofetil	2 (7.1%)
Cyclosporine	1 (3.5%)
Eltrombopag	1 (3.5%)

Table 4 Treatment response among patients with ITP

Treatment response	Number (%)
Corticosteroids	
- Early response	40 (32.8%)
- Initial response	58 (47.5%)
- Durable response	85 (69.7%)
Second line treatment ± corticosteroids	
- Early response	13 (46.4%)
- Initial response	12 (42.9%)
- Durable response	26 (92.8%)
Second line treatment ± corticosteroids	
- No response	2 (7.1%)

Table 5 Factors associated with durable response to corticosteroids among patients with ITP

Variable factor	Durable response		*p*-value
	Adjusted odds ratio (Adjusted OR)	95%CI of adjusted OR	
Age below 60 years	0.67	0.24 – 1.93	0.462
Female sex	3.5	1.40 – 8.72	0.007
Primary vs. secondary ITP	2.2	0.95 – 4.99	0.067
Bleeding at presentation	0.9	0.39 – 2.01	0.763
Early response	0.6	0.26 – 1.44	0.261

Most patients with ITP had a durable response to corticosteroids (69.7%) as prednisolone was tapered off for more than six weeks. Most were maintained with low dose prednisolone of 10 to 15 mg/week until complications occurred or no response was noted. However, the effects of these low dose steroids were unclear. Approximately 19% of patients had durable responses after stopping corticosteroids.

In the literature, the majority of patients who developed chronic ITP (74%) required splenectomy treatment (N = 63; CR 74.6%).[5] Only 4% of our patients were splenectomized due to no response to second line treatment becoming chronic ITP. Our study showed the majority of patients had newly diagnosed ITP (68.8%) which may explain the more durable response.[8] Most of our patients received an initial treatment with the high dose dexamethasone (40 mg/day) (70.4%) for four days followed by slowly tapering doses of prednisone which may confer rapid responses without changing long term outcomes.[9]

Patients with ITP who failed or depended on high dose corticosteroids needed second line treatments. Only one of our patients received a thrombopoietin receptor agonist (TPO-RA). TPO-RA binds to the TPO receptor and prompts marrow megakaryocytes to produce more platelets. No one received rituximab which is an antiCD20 monoclonal antibody because they could not access these expensive and non-reimbursable medications.

The majority of patients with ITP with second-line treatment (93%) showed a durable response. They were initially used combined with prednisolone which was usually sufficient for our setting in terms of efficacy.

However, the cause of death in our series was severe infections due to long term use of immunosuppressive treatment which was similar to related studies.[7] Therefore, the safety of the treatment is to be considered in clinical practice. Our study found that male sex (17.6%) and secondary ITP (27.1%) were less likely to achieve a durable response after first line steroids. The related results showed that females with ITP duration of less than 12 months revealed continuing responses (78.6%) better than those of males (21.2%), similar to our results.[10] We found systemic lupus erythematosus (63%) was the most common disease among secondary patients with ITP.[11]

The limitation of this study was using a retrospective and single-center study. A prospective cohort study from multiple centers in Thailand is warranted to confirm these findings.

Conclusion

This study, conducted in a provincial hospital, reveals a favorable prognosis for ITP, with a majority of patients showing durable responses, which differs from findings in studies conducted at referral centers. Only female patients were more likely to exhibit persistently durable responses after corticosteroids.

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