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Immune Thrombocytopenia: Characteristics of the Population and Treatment Methods—One-Center Experience

Weronika Lebowa[1] Joanna Zdziarska[1] Tomasz Sacha[1,2]

[1] Department of Haematology, University Hospital, Jagiellonian University Medical College, Cracow, Poland
[2] Department of Haematology, Jagiellonian University Medical College, Cracow, Poland

Address for correspondence Joanna Zdziarska, MD, PhD, Department of Haematology, Jagiellonian University Medical College, Kopernika 17, 31-501 Cracow, Poland (e-mail: jzdziarska@su.krakow.pl).

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Abstract

Background Immune thrombocytopenia (ITP) is a disease with variable clinical presentation, requiring different treatment lines.

Aim The study aimed to characterize a group of ITP patients in terms of clinical picture and disease treatment, as well as to present the current standard of care of ITP in Poland, in the context of local and international guidelines.

Materials and Methods The study included adult patients diagnosed with ITP, treated at the Department of Haematology of the Jagiellonian University Hospital in Krakow from January 2006 to January 2021. Patient characteristics, clinical manifestation of ITP, and treatment methods were analyzed.

Results A total of 245 ITP patients were included. 57.1% of them were asymptomatic at diagnosis. Most common symptoms were thrombocytopenic purpura (68.2%), followed by epistaxis (34.7%) and gum bleeds (19.2%). Life-threatening bleedings were noted in three cases (1.2%). 23.2% of patients did not require treatment. Prednisone was the most commonly used first-line therapy (75.5% of patients). Treatment with eltrombopag and romiplostim was used in 40.4 and 8.5% of patients requiring second-line therapy, respectively. 14.3% of all patients ultimately underwent splenectomy, including 51.5% of those who needed second-line treatment. The initial response rate was 74.3%; however, post-splenectomy relapses occurred in 22.9% of patients.

Conclusions ITP is a disease of mild clinical course, often asymptomatic. Chronic disease often requires multiple treatment lines and balancing between bleeding risk and treatment toxicity, based on individual risk–benefit assessment. Local access restrictions to thrombopoietin receptor agonists determined the treatment strategy.

Keywords
- immune thrombocytopenia
- refractory ITP
- splenectomy
- thrombopoietin receptor agonists

Zusammenfassung

Einleitung Immunthrombozytopenie (ITP) ist eine Krankheit mit variabler klinischer Ausprägung, die verschiedene Therapielinien benötigt.

Zielsetzung Ziel der Arbeit ist, eine Gruppe von Patienten mit ITP zu beschreiben, hinsichtlich der klinischen Manifestation und Therapie, als auch den aktuellen Behandlungsstandard von ITP in Polen vorzuführen, im Kontext von lokalen und internationalen Richtlinien.

Material und Methoden Die Analyze beinthaltet Klinik- und Therapiedaten von erwachsenen Patienten mit diagnostizierter ITP, die in der Klinik für Hämatologie der Jagiellonen-Universität in Krakau zwischen Januar 2006 und Januar 2021 betreut waren.

Schlüsselwörter
- Immunthrombozytopenie
- therapieresistente ITP
- Splenektomie
- Thrombopoetin-Rezeptoragonisten

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Georg Thieme Verlag KG,
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Ergebnisse 245 ITP-Patienten wurden identifiziert, von denen 57.1% waren asymptomatisch bei Diagnose. Die am häufigsten gemeldeten Symptome waren thrombozytopenische Purpura (68.2%), Nasenbluten (34.7%) und Zahnfleischbluten (19.2%). Lebensbedrohliche Blutung tritt auf in 3 Patienten (1.2%). In 23.2% der Patienten keine Therapie war notwendig. Prednison war die häufigste Erstlinientherapie (75.7% der Patienten). Eltrombopag und Romiplostim waren in 40.4% und 8.5% der Patienten verabreicht, die eine Zweitlinientherapie benötigten. Splenektomie wurde in 14.3% aller Patienten durchgeführt und in 51.5% deren, in denen Zweitlinientherapie nötig war. Die initiale Ansprechrate auf Splenektomie war 74.3%, jedoch 22.9% der Patienten erlitten ein Rückfall.

Schlussfolgerungen Das klinische Bild von ITP ist mild, oft symptomfrei. Chronische Krankheit benötigt dagegen oft viele Therapielinien. Balancieren zwischen Blutungsrisiko und Toxizität der Therapie ist nonwendig, anhand der individuellen Nutzen/Risiko-Abwägung. Lokale Einschränkungen der Verfügbarkeit der Thrombopoetin-Rezeptoragonisten determinierten die Therapiestrategie.

Introduction

Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by reduction in the peripheral platelet (PLT) count below 100×10^9/L, in the absence of known factors or disorders inducing thrombocytopenia.[1,2] In Poland, ITP occurs with an incidence rate of 3.5 per 100,000 people per year.[3] The pathomechanism of primary ITP includes PLT destruction in the reticuloendothelial system mediated by autoantibodies, complex autoimmune processes involving T lymphocytes, and impaired megakaryocytopoiesis.[1,2,4–6] Secondary ITP can be associated with other autoimmune diseases (e.g., systemic lupus erythematosus or rheumatoid arthritis), infections (e.g., HIV, HBV, HCV, *Helicobacter pylori*), or underlying immune dysregulation syndromes, such as common variable immunodeficiency.[2] According to its duration, ITP is divided into acute (<3 months), persistent (3–12 months), and chronic (>12 months).[7] ITP typically manifests with mucocutaneous bleeds, but may also be asymptomatic. Severe bleeding manifestations such as intracranial hemorrhage and gastrointestinal or genitourinary bleeds are relatively uncommon.[8] The primary purpose of ITP treatment is to protect patients from life-threatening bleeding by keeping the PLT count at the hemostatic level ($>$ 20–30 $\times 10^9$/L in most cases). First-line treatment includes corticosteroids and intravenous immunoglobulins, whereas second-line therapy usually consists of thrombopoietin receptor agonists (TPO-RAs), rituximab, immunosuppressants, and splenectomy.[9]

Aim of the Study

The aim of the study was to characterize a group of adult ITP patients in terms of clinical manifestation and treatment, as well as to present the current standard of care of ITP in Poland, in the context of local and international guidelines.

Materials and Methods

The study population was identified in the tertiary reference center in Krakow, Poland (Haematology Clinic, Jagiellonian University). We enrolled into the study consecutive patients with ITP diagnosis, treated in our clinic between January 2006 and January 2021, identified from the patient registry. The initial number of patients was 249. We excluded four patients with incomplete medical records. Data were obtained retrospectively from medical documentation (both inpatient and outpatient files). At presentation, 85.7% of patients ($n = 210$) had already been diagnosed with ITP and had previously been treated or observed in other centers (mean duration of previous care was 5.8 ± 7.6 years, median: 2 years, range: 0.1–49). The assessment of secondary ITP in our center included abdominal ultrasound; peripheral blood smear; testing for HBV, HCV, HIV, *H. pylori*, and immunoglobulin levels; basic coagulation screen; and antinuclear antibody, antineutrophil cytoplasmic antibody, antiphospholipid antibodies, and/or bone marrow examination.

Results

Patient Characteristics

A total of 245 patients diagnosed with ITP were identified: 81 men (33.1%) and 164 women (66.9%). The mean follow-up of the whole population was 17.8 months (range: 1 week–138 months). The overall survival of the population was 99.6% ($n = 244$) during the follow-up. There was one death (0.4%) due to endometrial cancer. The mean age at diagnosis was 41.3 (median: 40, range: 4–87). In 12.7% of patients ($n = 31$), the disease was diagnosed in younger than 18 years. The mean PLT count at ITP diagnosis was 35.8×10^9/L (median: 30×10^9/L, range: 0–100×10^9/L; see ►Table 1).

Among all patients, 90.6% ($n = 222$) were diagnosed as having primary ITP and 9.4% ($n = 23$) were diagnosed with

Table 1 Patient characteristics and clinical manifestation of ITP

	Overall		Male		Female	
	$n = 245$	(%)	$n = 81$	(%) (33.1)	$n = 164$	(%) (66.9)
Age at ITP diagnosis (years)						
Mean ± SD	41.3 ± 20.6	–	48.7 ± 20.3	–	38 ± 20	–
Median (range)	40 (4–87)	–	52.5 (4–83)	–	33 (4–87)	–
PLT count at ITP diagnosis ($\times 10^9$/L) Mean ± SD Median (range)	35.8 ± 32.9 30 (0–100)	–				
Duration of ITP						
• Newly diagnosed (<3 mo after diagnosis)	18	(7.4)				
• Persistent (3–12 mo after diagnosis)	38	(15.5)				
• Chronic (>12 mo after diagnosis)	189	(77.1)				
Primary ITP	222	(90.6)				
Secondary ITP	23	(9.4)				
The circumstances of primary ITP diagnosis						
• Infection	27	(11.1)				
• Pregnancy					16	(9.8)
The circumstances of ITP diagnosis						
Accidentally	140	(57.1)	45	(55.6)	95	(57.9)
Symptoms present at diagnosis	105	(42.9)	36	(44.4)	69	(42.1)
Bleeding symptoms						
Present	196	(80.0)	61	(75.3)	135	(82.3)
Absent	49	(20.0)	20	(24.7)	29	(21.5)
• Thrombocytopenic purpura	167	(68.2)	51	(63.0)	116	(70.7)
• Epistaxis	85	(34.7)	23	(28.4)	62	(37.8)
• Gum bleeds	47	(19.2)	15	(18.5)	32	(19.5)
• Bleeding from the genital tract	44	(18.0)	–	–	44	(26.8)
• Lower gastrointestinal bleeding	15	(6.1)	8	(9.9)	7	(4.3)
• Hematuria	11	(4.5)	6	(7.4)	5	(3.0)
• Prolonged bleeding from wounds/ subcutaneous hematomas	11	(4.5)	2	(2.5)	9	(5.5)
• Prolonged bleeding after tooth extraction	10	(4.1)	1	(1.2)	9	(5.5)
• Postpartum/post-cesarean hemorrhage	6	(2.4)	–	–	6	(3.7)
• Subconjunctival hemorrhage	6	(2.4)	2	(2.5)	4	(2.4)
Life-threatening bleeding	3	(1.2)	1	(0.4)	2	(0.8)
• Intracranial hematoma	1	(0.4)	1	(1.2)	–	–
• Genital tract bleeding	1	(0.4)	–	–	1	(0.6)
• Retroperitoneal hemorrhage	1	(0.4)	–	–	1	(0.6)

Abbreviations: ITP, immune thrombocytopenia; PLT, platelet.

secondary ITP. The causes of secondary ITP included the following: viral hepatitis C ($n = 5$), cytomegalovirus (CMV) infection ($n = 2$), *H. pylori* infection ($n = 2$), systemic lupus erythematosus ($n = 2$), rheumatoid arthritis ($n = 2$), chronic lymphocytic leukemia ($n = 2$), Evans syndrome ($n = 2$), primary biliary cholangitis ($n = 1$), antiphospholipid syndrome ($n = 1$), human immunodeficiency virus ($n = 1$), viral hepatitis B ($n = 1$), coexisting CMV and Epstein–Barr virus infection ($n = 1$), and alcoholic liver cirrhosis ($n = 1$). The diagnosis of primary ITP was related to previous infection in 11.1% ($n = 27$), in particular an infection of the upper respiratory tract.

In 9.8% ($n = 16$) of female patients, primary ITP was revealed during pregnancy. ITP exacerbations during

pregnancy were reported in 15% of females ($n = 26$). In all cases, pregnancy-associated thrombocytopenia was excluded (based on the clinical picture) as well as pregnancy-associated syndromes causing low PLT count. Twenty-three women (43.4%) required treatment during pregnancy (prednisone: 78.3%, methylprednisolone: 13.0%, intravenous immunoglobulin [IVIg]: 13.0%, dexamethasone: 4.3%), but only 15 (28.3%) in the postpartum period. No bleeding complications were noted in the perinatal period. Medical records of 10 newborns were available: 4 presented with normal PLT count; 2 presented with mild thrombocytopenia, requiring no treatment; 3 were transfused with IVIg; and 1 was transfused with PLT concentrate due to PLT count $< 30.0 \times 10^9$/L. None manifested with bleeds.

Patient characteristics and clinical manifestation of ITP according to sex are presented in ►Table 1.

In 42.9% ($n = 105$) of patients, the diagnosis was preceded by clinical symptoms, whereas the remaining 57.1% ($n = 140$) were asymptomatic and diagnosed accidentally during routine follow-up. The mean PLT count in asymptomatic patients at diagnosis was 45.3×10^9/L (median: 40.0×10^9/L, range: 0–100×10^9/L). The mean PLT count in patients with bleeding at diagnosis was 23.10^9/L (median: 11.0×10^9/L, range: 0–100×10^9/L). In the course of the disease, symptoms appeared in another 91 patients. Altogether, 80% of patients had bleeding symptoms and 20% remained asymptomatic throughout the course of the disease. The most common symptom was thrombocytopenic purpura (68.2%; see ►Table 1). The incidence of life-threatening bleedings was 1.2% ($n = 3$): intracranial hematoma without previous trauma, retroperitoneal hemorrhage (postovulatory ovarian hemorrhage), and genital tract bleeding. In the first two cases, major bleeding was the first symptom of ITP. All three patients had no identifiable bleeding risk factors besides thrombocytopenia. In the first case, prednisone and intravenous methylprednisolone were administered which resulted in a rapid, but transient, increase in the PLT count to a hemostatic level (45.0×10^9/L). Further workup revealed systemic lupus erythematosus and the diagnosis of secondary ITP was established. Prednisone and chloroquine were ordered with good effect and the patient remains in outpatient control. The second patient was treated with prednisone for a total of 5 months after the major bleed. The subsequent splenectomy led to disease remission with several episodes of thrombocytopenia below 10.0×10^9/L with mild hemorrhagic symptoms during follow-up, treated successfully with short courses of prednisone. In the third case, major bleeding was observed 15 years after ITP diagnosis. The patient was treated with prednisone with periodic fluctuations in the PLT count (20.0–70.0×10^9/L), but treatment tolerance was poor. Currently, she remains untreated in outpatient control, with PLT count $> 10.0 \times 10^9$/L and no bleeding.

In 14 patients, minor isolated bleeding symptoms occured despite PLT count $> 50.0 \times 10^9$/L (easy bruising, mild mucosal bleeds). They could be explained by prolonged steroid treatment, local pathologies, or concomitant diseases (e.g., hemorrhoids or arterial hypertension).

Treatment

►Table 2 presents data on ITP treatment. Among all patients, 23.2% ($n = 57$) did not require therapy (stable asymptomatic disease or spontaneous remission). The mean value of PLT count at treatment implementation was 12.4×10^9/L (median: 13.0×10^9/L, range: 0–56×10^9/L, number of patients: 188). The median number of therapy lines for the whole cohort was 1 (range: 0–3). Prednisone was the most commonly used first-line treatment (in 75.5% of the patients; see ►Table 2). An intravenous steroid was administered to 22.9% of the patients. The mean time of steroid therapy in our clinic was 3.2 months (median: 1.7 months, range: 0.1–37.7 months). In case of using steroids in doses above 20 mg/d of prednisone, the median time was 1.0 month (median: 0.5, range: 0.1–11 months). A total of 115 patients (61.2%) who were treated with steroids in our clinic were also treated with steroids before being admitted to our center. As many as 63.8% of treated patients (120/188) did not require second-line treatment at all; 38.3% of them ($n = 46$) achieved complete response (CR) after first-line treatment. Partial response (PR) was reported in 54.2% ($n = 65$). The remaining 7.5% ($n = 9$) were treated by first-line therapy with no effects, but they dropped out of follow-up. Steroids were used repetitively in the treatment of 84.9% of relapses after first-time steroid treatment.

The percentage of patients suffering from steroid adverse events was 29.0% (51 patients). They included the following: mental disorders from depression to psychosis, steroid-induced diabetes, osteoporosis with compression fractures, severe bone and muscle pain, headache, dizziness, cataract, edema, weight gain, and impaired concentration. In 8.5% of cases (15 patients), they led to therapy change, despite a good PLT response. The median time between initiation of therapy and adverse event onset was 2 months, ranging from 4 days (blood pressure fluctuations and edema of the lower limbs during a dexamethasone pulse) to 10 years (edema, bone pain, and steroid-induced osteoporosis). In 27.8% ($n = 68$), the second-line treatment was introduced: pharmacological or splenectomy. The most common second-line therapy was danazol (53.2% of patients). 28% of patients treated with danazol ($n = 7$) responded well to treatment (achieved CR or response), whereas in 44% ($n = 11$) this therapy failed (PLT count $< 30 \times 10^9$/L). 20% ($n = 5$) of patients discontinued danazol due to intolerance. Splenectomy was performed in 51.5% ($n = 35$) of patients. The percentage of laparoscopic procedures was 88.6% ($n = 31$), while that of open splenectomies was 11.4% ($n = 4$). The mean time from ITP diagnosis to splenectomy was 31.9 months (median: 12.0 months, range: 0.5–204 months). The mean value of PLT count at the day of splenectomy was 57.4×10^9/L (median: 90.0×10^9/L, range: 33–245×10^9/L). Prednisone was the drug that in most cases (34.4%) raised the PLT count to a level at which splenectomy could be safely performed (see ►Table 2). The mean time of post-splenectomy follow-up was 4.5 years (median: 2 years, range: 2 weeks to 22 years). Nine patients (25.7%) failed to respond to splenectomy at all, and a further 22.9% (eight patients) relapsed. The mean time from splenectomy to relapse was 11.3 months (median: 3.5

Table 2 ITP treatment

Treatment	Number of patients	
	n	(%)
Without treatment	57	(23.2)
First-line treatment	188	(76.7)
• Prednisone	142	(75.5)
• Methylprednisolone	38	(20.2)
• Dexamethasone	20	(10.6)
• IVIg	12	(6.4)
Steroid IV	56	(22.9)
Steroid complications	51	(29.0)
First-line treatment only	120	(63.8)
Second-line treatment	68	(27.8)
Pharmacological treatment	47	(69.1)
• Danazol	25	(53.2)
• Cyclophosphamide	22	(46.8)
• Eltrombopag Before splenectomy	19 10	(40.4) (21.3)
• Azathioprine	14	(29.8)
• Rituximab	7	(14.9)
• Romiplostim Before splenectomy	4 1	(8.5) (2.1)
Splenectomy	35	(51.5)
• As second-line treatment	21	(60.0)
• As third-line treatment	14	(40.0)
Treatment immediately before splenectomy		
Prednisone	11	(34.4)
IVIg	8	(25.0)
Methylprednisolone	5	(15.6)
Methylprednisolone + IVIg	3	(9.4)
Eltrombopag	2	(6.3)
Azathioprine	1	(3.1)
Romiplostim + prednisone	1	(3.1)
Prednisone + azathioprine	1	(3.1)
Splenectomy outcome		
No response to splenectomy	9	(25.7)
Relapse after splenectomy	8	(22.9)
Treatment after relapse		
Eltrombopag	6	(75.0)
Prednisone	4	(50.0)
Cyclophosphamide	4	(50.0)
Methylprednisolone	3	(37.5)
Danazol	3	(37.5)
Romiplostim	2	(25.0)
Dexamethasone	1	(12.5)
IVIg	1	(12.5)

Abbreviations: ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin.

months, range: 1–60 months). After relapse, the most common treatment was eltrombopag (in 75% of the patients; see ►Table 2).

Elderly patients (≥ 65 years; $n = 37$) and pediatric patients (<18 years; $n = 31$) were analyzed separately (see ►Tables 3 and 4). Among all elderly patients, 18.9% ($n = 7$) did not require therapy. The mean value of PLT count at treatment implementation was 19.6×10^9/L (median: 20.0×10^9/L, range: 0–50×10^9/L, number of patients: 30). Twenty-three patients (76.7% of patients who started treatment) required only first-line therapy. Of those, more than half (52.2%) achieved CR (PLT count ≥ 100×10^9/L and resolution of bleeding symptoms). In 18.9% ($n = 7$) of patients, the second-line treatment was introduced: cyclophosphamide (in 4 patients), danazol (in 3 patients), and azathioprine (in 1 patient). Splenectomy was performed in two patients (5.4%). In response to splenectomy, one patient achieved complete remission of ITP and did not require further treatment, while the other relapsed after 1 year and was thereafter ineffectively treated with eltrombopag and finally achieved complete remission after implementation of prednisone with cyclophosphamide.

In our group of patients, we identified 31 children (age <18 at the time of ITP diagnosis). Among all children, 41.9% ($n = 13$) did not require therapy. The mean value of PLT count at treatment implementation was 12.10^9/L (median: 8.5×10^9/L, range: 1–40×10^9/L, number of patients: 18). Sixteen patients (88.9% of patients who started treatment) required only first-line therapy. The second-line treatment (eltrombopag) was implemented in two pediatric patients (6.5%): one achieved partial response, and the other did not respond to therapy. One patient (3.2%) underwent splenectomy, but the disease relapsed after a month and TPO-RA therapy was initiated. The patient did not respond either to eltrombopag or to romiplostim (the last measured PLT count was 7×10^9/L, without bleeding symptoms). Of the 13 patients with spontaneous remission observed in the pediatric period, 6 relapsed in adulthood (46.2%).

Patients requiring anticoagulation were treated based on individual stratification of bleeding risk (PLT count, bleeding symptoms, and concomitant diseases). We generally continued full doses of new oral anticoagulants (NOACs) in patients with PLT count in the range of 50 to 100×10^9/L. In the range of 20 to 50×10^9/L, we individually decided to reduce the NOAC dose by half or discontinue it. In the PLT range of 0 to 20×10^9/L, NOAC therapy and other oral anticoagulation were avoided because of the high risk of spontaneous bleeding. Close clinical observation and monitoring of PLT levels were implemented at each stage of anticoagulant therapy.

Discussion

The studied population consists mainly of chronic ITP patients, referred to our center for consultation or further treatment. It does not reflect the true distribution of clinical forms of ITP in the general population. According to literature, 30 to 66.7% of adults with ITP become chronic

Table 3 Elderly patients with ITP (≥ 65 y)

Category	*n*	(%)
Number of patients ≥ 65 y	37	(100)
Age at ITP diagnosis (years; mean ± SD)	73.8 ± 5.9	–
Age at ITP diagnosis (years; median (range))	74 (65–87)	–
PLT count at ITP diagnosis ($\times 10^9$/L): mean ± SD	37.0 ± 30.3	–
PLT count at ITP diagnosis ($\times 10^9$/L): median (range)	30 (0–100)	–
Symptoms present at diagnosis	14	(37.8)
Bleeding symptoms in the course of ITP	26	(70.3)
Without treatment	7	(18.9)
First-line treatment	30	(81.1)
First-line treatment only	23	(76.7)
Complete response after first-line treatment	12	(52.2)
Second-line treatment	7	(18.9)
Splenectomy	2	(5.4)

Abbreviations: ITP, immune thrombocytopenia; PLT, platelet.

Table 4 Pediatric patients with ITP (<18 y)

Category	*n*	(%)
Number of patients < 18 y	31	(100)
Age at ITP diagnosis (years; mean ± SD)	11.1 ± 4.5	–
Age at ITP diagnosis (years; median (range))	10 (4–17)	–
PLT count at ITP diagnosis ($\times 10^9$/L): mean ± SD	31.3 ± 30.0	–
PLT count at ITP diagnosis ($\times 10^9$/L): median (range)	19.5 (1–100)	–
Symptoms present at diagnosis	16	(51.6)
Bleeding symptoms in the course of ITP	17	(54.8)
Without treatment	13	(41.9)
First-line treatment	18	(58.1)
First-line treatment only	16	(88.9)
Second-line treatment	2	(6.5)
Splenectomy	1	(3.2)

Abbreviations: ITP, immune thrombocytopenia; PLT, platelet.

(significantly more than in children: 21–25%) and the rate of spontaneous remissions is 20 to 45%.[10–15]

ITP occurs with an incidence rate of 1.6 to 3.9 per 100,000 person-years, increasing with age, and has a slight female propensity.[16] In our study, the percentage of males with ITP was 33.1% and that of females was 66.9%. The reported rate of secondary ITP is up to 20%,[2,11] whereas in our group 9.4% of patients were diagnosed with an underlying condition. This observation may indicate that only the minority of secondary cases become chronic and are therefore underrepresented in our group, or may reflect the selection bias (secondary ITP patients are less likely to be referred to our center). It may also suggest that more stress should be put on differential diagnostics and search for possible causes of secondary ITP.

ITP is asymptomatic in some patients; however, up to two-thirds may experience bleeding manifestations.[8] Hammond et al described the asymptomatic diagnosis of ITP in 49% of cases.[17] In our study, 80% of patients presented symptoms in the disease course, although at the moment of diagnosis bleeds were present in only 42.9% of patients.

The risk of bleeding is most significant at PLT counts less than 20 to 30 $\times 10^9$/L. Bleeding typically occurs in the skin or mucous membranes, with petechiae, bruising, epistaxis, and gum bleeding being common.[18] ICH occurs in 1.1 to 1.8% of adult ITP patients and usually presents during the first 3 months after ITP diagnosis.[10,19,20] In our study, severe life-threatening bleeding was noted in three cases (1.2%), of which ICH occurred in one patient.

The main goal of ITP treatment is achieving a PLT count that protects against severe bleeding, rather than keeping it within the normal range. The International Working Group (IWG) defines CR as PLT count $\geq 100 \times 10^9$/L. Response is defined as PLT count ≥ 30 but $< 100 \times 10^9$/L and a doubling from baseline. The majority of clinicians use a PLT count of 30×10^9/L as the target threshold of treatment.[21] However, in selected asymptomatic patients, lower thresholds may be kept as a balance between bleeding risk and treatment toxicity. In our patient group, 6.5% ($n = 16$) had a chronic history of PLT count below 30×10^9/L. Four of them were left untreated, chronically or temporarily, despite PLT count of less than 10×10^9/L (due to treatment intolerance or inefficiency). None of these patients presented with significant bleeds.

Initial treatment of newly diagnosed adults includes several options: corticosteroids (usually oral prednisone, intravenous methylprednisolone, or oral dexamethasone), IVIg, and intravenous anti-D immunoglobulins (not available in Poland).[22,23] The recommended drug of the first choice is prednisone, administered orally at an initial dose of 1 mg/kg for 2 to 3 weeks, or dexamethasone 40 mg/d for 4 days, repeated up to three times.[22] Some studies suggest a higher CR rate with high doses of dexamethasone than with standard dose of prednisone.[24–26] First-line treatment is effective in 70 to 90% of patients.[23] In most cases, initial treatment will not lead to a sustained increase in PLT count, however, and as many as 80% of these patients will eventually relapse.[27] Only 10 to 20% of patients achieve sustained response to corticosteroids.[16] Moreover, this group of drugs may cause significant side effects, directly proportional to the dose and duration of treatment.[16] Steroid dose should therefore be gradually reduced and, in most cases, discontinued.

In the presented group of patients, the most common first-line treatment was oral prednisone (75.5% of patients) which is in line with Polish and international ITP treatment guidelines. Dexamethasone was used in 10.6% of patients only, because it entered the clinical practice only after evidence of its efficacy was published. In our group, 73.6% of patients could eventually cease steroid therapy. Comparing with data from the literature, Chang et al described CR to steroids in 65.2% and PR in 23.3% of patients.[28]

Second-line treatment of ITP includes pharmacotherapy and splenectomy. Drugs with proven effectiveness include eltrombopag, avatrombopag, romiplostim, fostamatinib, and rituximab, whereas potentially useful agents are azathioprine, cyclosporine A, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, and vinca alkaloids.[22] Avatrombopag, fostamatinib, and dapsone are not available in Poland.

TPO-RAs: eltrombopag, avatrombopag, and romiplostim increase the number of PLTs by stimulating their production in the bone marrow. With their excellent efficacy of 60% (regardless of splenectomy status), eltrombopag and romiplostim have transformed the care of patients with chronic ITP.[29–31] After treatment cessation, durable responses are observed in 10 to 30% of patients.[13] Both agents were licensed for chronic refractory ITP in adults and children since 1 year of age. Recently, the registration of romiplostim was extended to include adults with newly diagnosed and persistent ITP. Eltrombopag is reimbursed in Poland since 2018 and romiplostim since 2020, in splenectomized patients only. Unfortunately, high cost limits their broader use in clinical practice (see ►Table 2).

Rituximab is a chimeric humanized antibody directed against the CD20 surface antigen of B lymphocytes. Rituximab is useful in patients who have not responded to steroids or require high doses of steroids to maintain target PLT count.[32,33] The literature shows that approximately 60% of ITP patients respond to treatment, and 20 to 40% achieve complete remission.[14,34–36] In some studies, the initial effectiveness of rituximab was as high as 80%.[28] Rituximab is used in ITP treatment off-label, it requires hospitalization in Poland (due to reimbursement strategy), and its cost was until recently high; this is why it was rarely administered in the studied group (see ►Table 2).

Immunosuppressants are characterized by variable efficacy, significant side effects, and delayed onset of action (up to several months). Their use should be limited to patients failing other therapies, those in whom splenectomy is contraindicated, or if other agents are unavailable.[22]

Eltrombopag and romiplostim were used in 40.4% ($n = 19$) and 8.5% ($n = 4$) of patients, respectively. In 21.3% ($n = 10$) and 2.1% ($n = 1$) of patients, respectively, TPO-RAs were used before splenectomy. Due to the reimbursement policy of TPO-RAs in Poland, nonsplenectomized patients had the chance to benefit from this therapy only through donations or self-funding. The relatively common use of eltrombopag in our group results from its availability since 2019 within a compassionate-managed access program held by Novartis.

►Fig. 1 presents the evolution of pharmacological ITP treatment in our center over the years. The increase in the use of eltrombopag from 2018 in the second and third lines of ITP treatment was due to the introduction of TPO-RAs reimbursement in Poland. Single cases of TPO-RAs treatment before 2018 were short-term therapies in which drugs were donated by pharmaceutical companies. The increase in cyclophosphamide and danazol in 2019 can be attributed to the need for preoperative PLT rise (TPO-RAs became at that time available for splenectomized patients only).

Splenectomy is an effective therapy for steroid-refractory or steroid-dependent ITP. For decades, it was positioned as the second-line ITP treatment of choice. Recent data suggest, however, that nowadays less than 25% of patients with ITP undergo splenectomy,[37] despite an initial response rate of 80% and 5-year response rates of 60 to 70%.[38–41] With the advent of medical alternatives such as rituximab and TPO-RAs, splenectomy has declined and it is generally reserved for patients who fail multiple medical therapies.[38] Splenectomy carries the risk of infection as well as a lifelong risk of septic shock and thrombosis. Fluctuating PLT counts after surgery can be difficult to manage.[13,15] Post-splenectomy relapses most often occur within the first 24 months.[42] Following the Polish ITP treatment guidelines, splenectomy may be considered in patients refractory to corticosteroids for at least 4 to 6 weeks and in patients who require daily prednisone dose ≥ 10 mg to maintain the target PLT

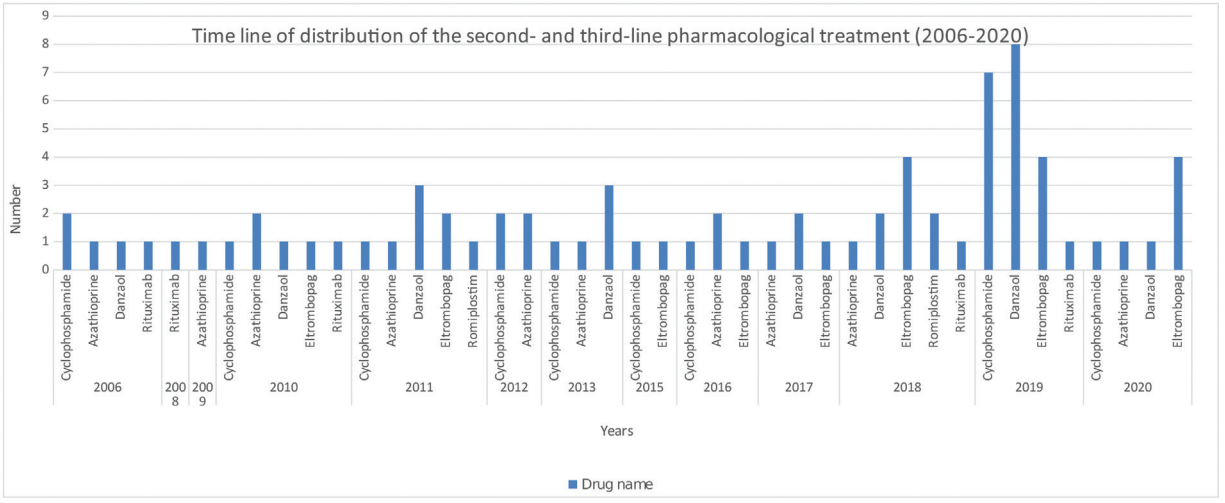

Fig. 1 Time line of distribution of second- and third-line pharmacological treatment (2006–2020)

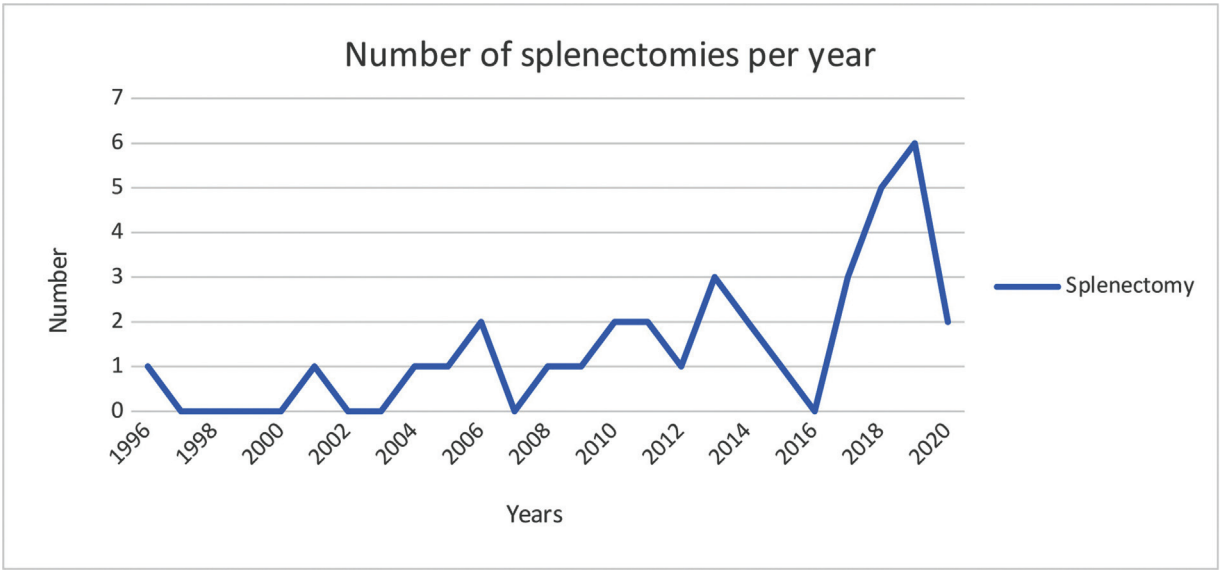

Fig. 2 Number of splenectomies per year

count.[9,23] This recommendation contradicts European guidelines that limit the use of splenectomy in favor of TPO-RAs. Still, it should be noted that Polish guidelines are dated in 2010 and will be updated soon. In clinical practice, more and more physicians point to the need to delay splenectomy, favoring repeated pharmacotherapy lines.[43] For several years, physician-driven efforts are made to extend the availability of TPO-RAs to nonsplenectomized patients with ITP in Poland. ►**Fig. 2** presents the number of splenectomies per year in our study population. The increase in the frequency of splenectomies since 2018 was related to the fact that in 2018 the reimbursement of TPO-RAs in splenectomized patients was started in Poland. Patients with refractory ITP were more readily qualified for splenectomy so that in case of relapse they could be qualified for TPO-RAs therapy.

It is recommended to wait for at least 6 months from the diagnosis of ITP to splenectomy because of spontaneous remissions of the disease observed in some patients.[16] Some authors recommend waiting for 12 months after ITP diagnosis.[21,38] In our study, 14.3% ($n = 35$) of all ITP patients ultimately underwent splenectomy. Of the patients who did not respond to first-line treatment, 51.5% ($n = 35$) were enrolled in this procedure. In 60% of them ($n = 21$), splenectomy was used as second-line therapy, while in 40% ($n = 14$) it was used as third-line therapy. Data from the literature widely differ in this respect. In one study, the proportion of ITP patients who underwent splenectomy was 18.7% and it was most commonly used as third-line therapy[37]; in another study, only 3.6% of ITP patients underwent surgery.[10]

The suggested minimum PLT count for a patient with ITP undergoing splenectomy is $\geq$30 to 50 $\times 10^9$/L.[44,45] To achieve a safe PLT count, corticosteroids or IVIgs are used.[22] In our study, the mean PLT count during splenectomy was 57.4 $\times 10^9$/L (median: 90.0 $\times 10^9$/L, range: 33–245 $\times 10^9$/L). Platelet count was risen mainly with prednisone (34.4%, $n = 11$), followed by IVIg (25%, $n = 8$; see ►**Table 2**). The initial response rate was obtained in 74.3% of patients

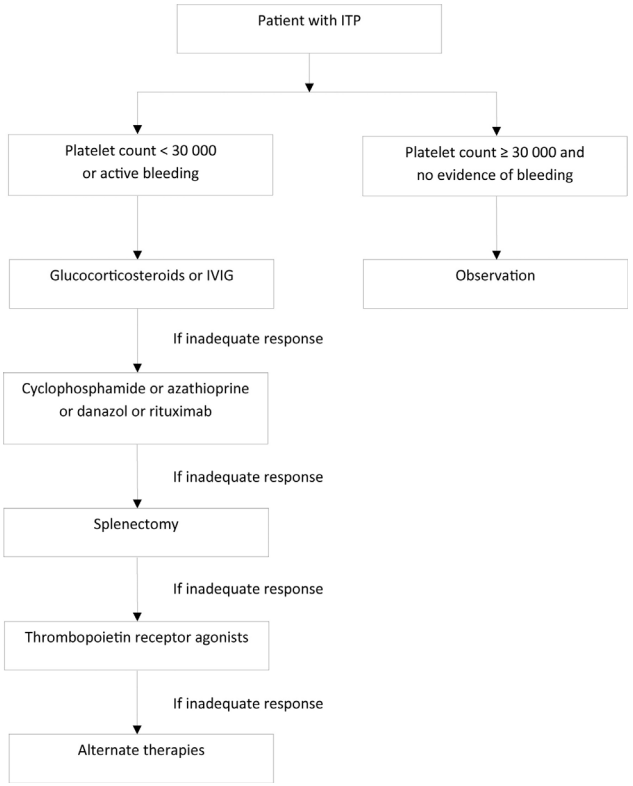

Fig. 3 ITP treatment algorithm in our center

($n = 26$). Post-splenectomy relapses occurred in 22.9% of patients ($n = 8$). The rate of post-splenectomy relapses in our study was similar to data from the literature, reporting a recurrence rate of 20 to 40%.[13,17,42] ►**Fig. 3** presents the current ITP treatment algorithm in our center.

Conclusions

We characterized a large group of Polish patients with ITP in terms of demographics, clinical picture, and treatment policy. Drawbacks of our analysis are its retrospective character and single-center setting. A further limitation of the study is lack of data on fatigue as one of the main symptoms of ITP.

Our results confirm that ITP is a disorder with heterogenous manifestation and variable clinical course. Chronic disease often requires multiple treatment lines and balancing between bleeding risk and treatment toxicity, based on individual risk–benefit assessment.

Drugs with proven efficacy against ITP (TPO-RAs and rituximab) are still not reimbursed in Poland. Eltrombopag and romiplostim are available only for patients resistant to splenectomy. Therefore, in our country, second-line ITP treatment is still based on surgery or immunosuppressants, less effective, and carries higher risk of side effects than TPO-RAs. Steroid therapy also tends to be prolonged, even despite adverse events. Additionally, physicians may sometimes decide to perform splenectomy to be able to qualify refractory patients to effective therapy.[23]

Further efforts should be made to gain access to all approved ITP therapies in Poland. In particular, an important issue is to increase the share of TPO-RAs in the treatment of ITP.

Conflict of Interest

The authors declare that they have no conflict of interest.

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