



EDUCATIONAL OBJECTIVE: Readers will review the pathophysiology, diagnosis, and management of immune thrombocytopenia in adults

SWAPNA THOTA, MD

Department of Internal Medicine,
Fairview Hospital, Cleveland Clinic
Hospitals

GAURAV KISTANGARI, MD

Department of Hospital Medicine,
Cleveland Clinic

HAMED DAW, MD

Assistant Professor, Cleveland
Clinic Lerner College of Medicine;
Department of Regional Oncology,
Taussig Cancer Institute,
Cleveland Clinic

TIMOTHY SPIRO, MD

Assistant Professor, Cleveland Clinic
Lerner College of Medicine; Chair,
Department of Regional Oncology,
Taussig Cancer Institute,
Cleveland Clinic

Immune thrombocytopenia in adults: An update

ABSTRACT

Immune thrombocytopenia (ITP) in adults is a chronic disease resulting from increased platelet destruction and impaired platelet production. Splenectomy remains the most effective and durable treatment in cases that are refractory to first-line therapy, but its use has declined because of the availability of alternate medical therapy, the associated risk of infection, and concern for surgery-related complications. Rituximab (Rituxan) may be an effective alternative but carries the risk of immunosuppression.

KEY POINTS

Secondary ITP can be drug-induced or be a manifestation of human immunodeficiency virus (HIV), hepatitis C virus (HCV), a lymphoproliferative disorder, or systemic lupus erythematosus.

Nonautoimmune conditions should also be considered, including pseudothrombocytopenia (a laboratory artifact induced by EDTA), thrombotic thrombocytopenic purpura, thrombocytopenia in pregnancy, and myelodysplastic syndrome (common in the elderly).

Treatment is indicated to keep the platelet count above $30 \times 10^9/L$ or to control bleeding.

Initial treatment usually begins with glucocorticoids, with the duration limited by side effects.

Patients for whom glucocorticoids fail generally require splenectomy, rituximab, or thrombopoietin receptor agonists.

doi:10.3949/ccjm.79a.11027

IMMUNE THROMBOCYTOPENIA (ITP), formerly known as idiopathic thrombocytopenic purpura, is an autoimmune disorder characterized by a low platelet count and increased risk of mucocutaneous bleeding. During the last decade its management has changed, with the advent of new medications and with increased awareness of treatment side effects. This article will focus on the pathophysiology, diagnosis, and management of ITP in adults.

A SLIGHT FEMALE PREDOMINANCE UNTIL AGE 65

The estimated age-adjusted prevalence of ITP in the United States is 9.5 to 23.6 cases per 100,000.¹ In a recent study in the United Kingdom, the incidence was 4.4 per 100,000 patient-years among women and 3.4 among men.² A slight female predominance was seen until age 65; thereafter, the incidence rates in men and women were about equal.

INCREASED PLATELET DESTRUCTION AND DECREASED PRODUCTION

ITP is a complex immune process in which cellular and humoral immunity are involved in the destruction of platelets³ as well as impaired platelet production. Several theories have emerged in the last decade to explain this autoimmune process.

Autoantibodies form against platelets

The triggering event for antibody initiation in ITP is unknown.³ Autoantibodies (mostly immunoglobulin G [IgG] but sometimes IgM and IgA) are produced against the platelet membrane glycoprotein GPIIb-IIIa. The antibody-

TABLE 1

Basic evaluation for immune thrombocytopenia in adults

Patient history
Family history
Physical examination
Complete blood cell and reticulocyte counts
Peripheral blood smear
Blood group (Rh)
Direct antiglobulin test
Human immunodeficiency virus screen
Hepatitis C virus screen

coated platelets are rapidly cleared by the reticuloendothelial system in the spleen and liver, in a process mediated by Fc-receptor expression on macrophages and dendritic cells. Autoantibodies may also affect platelet production by inhibiting megakaryocyte maturation and inducing apoptosis.^{4,5}

Patients with ITP also have CD4+ T cells that are autoreactive to GPIIb-IIIa and that stimulate B-cell clones to produce antiplatelet antibodies. Although autoreactive T cells are present in healthy individuals, they appear to be activated in patients with ITP by exposure to fragments of GPIIb-IIIa rather than native GPIIb-IIIa proteins.⁶ Activated macrophages internalize antibody-coated platelets and degrade GPIIb-IIIa and other glycoproteins to form “cryptic” epitopes that are expressed on the macrophage surface as novel peptides that induce further proliferation of CD4+ T-cell clones. Epitope spread thereby sustains a continuous loop that amplifies the production of GPIIb-IIIa antibodies.⁷

Defective T-regulatory cells appear to be critical to the pathogenesis of ITP by breaking self-tolerance, allowing the autoimmune process to progress.⁸ This, together with several other immune mechanisms such as molecular mimicry, abnormal cytokine profile, and B-cell abnormalities, may lead to enhanced platelet clearance.⁹

In addition to destroying platelets, antibodies may impair platelet production.¹⁰ Good

evidence for platelets being underproduced in patients with ITP is that treating with thrombopoietin agonists results in increased platelet counts.

■ A DIAGNOSIS OF EXCLUSION

ITP is defined as isolated thrombocytopenia with no clinically apparent associated conditions or other causes of thrombocytopenia.¹¹ No diagnostic criteria currently exist, and the diagnosis is established only after excluding other causes of thrombocytopenia.

A recent report¹² from an international working group established a platelet count threshold of less than $100 \times 10^9/L$ for diagnosing ITP, down from the previous threshold of $150 \times 10^9/L$. The panel also recommended using the term “immune” rather than “idiopathic” thrombocytopenia, emphasizing the role of underlying immune mechanisms. The term “purpura” was removed, because many patients have no or minimal signs of bleeding at the time of diagnosis.¹²

The 2011 American Society of Hematology’s evidenced-based guidelines for the treatment of ITP present the most recent authoritative diagnostic and therapeutic recommendations.¹³

ITP is considered to be primary if it occurs in isolation, and secondary if it is associated with an underlying disorder. It is further classified according to its duration since diagnosis: newly diagnosed (< 3 months), persistent (3–12 months), and chronic (> 12 months).

In adults, ITP tends to be chronic, presenting with a more indolent course than in childhood, and unlike childhood ITP, infrequently following a viral infection.

Clinical features associated with ITP are related to thrombocytopenia: petechiae (pinpoint microvascular hemorrhages that do not blanch with pressure), purpura (appearing like large bruises), epistaxis (nosebleeds), menorrhagia, gum bleeding, and other types of mucocutaneous bleeding. Other common clinical features include fatigue, impaired quality of life, and treatment-related side effects (eg, infection).¹⁴

A low platelet count may be the sole initial manifestation. The patient’s history, physical examination, blood counts, and findings on

Current platelet threshold for ITP: $< 100 \times 10^9/L$ (down from $< 150 \times 10^9/L$ in previous criteria)

blood smear are essential to rule out other diagnoses. Few diagnostic tests are useful in the initial evaluation (TABLE 1). Abnormalities in the blood count or blood smear may be further investigated with bone marrow biopsy but is not required if the patient has typical features of ITP, regardless of age.

Because there are no specific criteria for diagnosing ITP, other causes of thrombocytopenia must be excluded. The differential diagnosis can be further classified as ITP due to other underlying disease (ie, secondary ITP) vs nonautoimmune causes that are frequently encountered in clinical practice.

■ SECONDARY ITP

The differential diagnosis of thrombocytopenia due to known underlying immune disease includes the following:

Drug-induced ITP

Recurrent episodes of acute thrombocytopenia not explained by other causes should trigger consideration of drug-induced thrombocytopenia.¹¹ Patients should be questioned about drug use, especially of sulfonamides, antiepileptics, and quinine. Thrombocytopenia usually occurs 5 to 7 days after beginning the inciting drug for the first time and more quickly when the drug is given intermittently. Heparin is the most common cause of drug-related thrombocytopenia among hospitalized patients; the mechanism is unique and involves formation of a heparin-PF4 immune complex.

Human immunodeficiency virus infection

Approximately 40% of patients with human immunodeficiency virus (HIV) infection develop thrombocytopenia at some time.¹⁵ HIV infection can initially manifest as isolated thrombocytopenia and is sometimes clinically indistinguishable from chronic ITP, making it an important consideration in a newly diagnosed case of thrombocytopenia.

The mechanism of thrombocytopenia in early HIV is similar to that in primary ITP: as the disease progresses, low platelet counts can result from ineffective hematopoiesis due to megakaryocyte infection and marrow infiltration.¹⁶

Hepatitis C virus infection

Hepatitis C virus (HCV) infection can also cause immune thrombocytopenia. A recent study demonstrated the potential of the HCV core envelope protein 1 to induce antiplatelet antibodies (to platelet surface integrin GPII-Ia49-66) by molecular mimicry.¹⁷ Other causes of thrombocytopenia in HCV infection may be related to chronic liver disease, such as portal hypertension-related hypersplenism, as well as decreased thrombopoietin production.¹⁸ Antiviral treatment with pegylated interferon may also cause mild thrombocytopenia.¹⁹

Helicobacter pylori

The association between *H pylori* infection and ITP remains uncertain. Eradication of infection appears to completely correct ITP in some places where the prevalence of *H pylori* is high (eg, Italy and Japan) but not in the United States and Canada, where the prevalence is low.²⁰ The different response may be due not only to the differences in prevalence, but to different *H pylori* genotypes: most *H pylori* strains in Japan express CagA, whereas the frequency of CagA-positive strains is much lower in western countries.²⁰

In areas where eradication therapy may be useful, the presence of *H pylori* infection should be determined by either a urea breath test or stool antigen testing.

Lymphoproliferative disorders

Secondary forms of ITP can occur in association with chronic lymphocytic leukemia, non-Hodgkin lymphoma, and Hodgkin lymphoma. These diagnoses should especially be considered in patients presenting with thrombocytopenia accompanied by systemic illness. ITP occurs in at least 2% of patients with chronic lymphocytic leukemia and is usually difficult to distinguish from thrombocytopenia secondary to marrow infiltration or from fludarabine (Fludara) therapy.²¹

It is especially important to determine if a lymphoproliferative disorder is present because it changes the treatment of ITP. Treatment of ITP complicating chronic lymphocytic leukemia is challenging and includes corticosteroids and steroid-sparing agents such as cyclosporine (Gengraf, Neoral, Sandimmune), rituximab (Rituxan), and intravenous immunoglobulin.²²

Heparin is the most common cause of drug-related thrombocytopenia in hospitalized patients

Systemic lupus erythematosus and other autoimmune diseases

Thrombocytopenia is a frequent clinical manifestation of systemic lupus erythematosus, occurring in 7% to 30% of patients,²³ and is an independent risk factor for death.²⁴ Lupus should be suspected in patients with ITP who have multiorgan involvement and other clinical and laboratory abnormalities. A small percentage of patients with ITP (about 2%–5%) develop lupus after several years.²¹

Thrombocytopenia can also result from other autoimmune disorders such as antiphospholipid antibody syndrome²⁵ and autoimmune thyroid diseases as well as immunodeficient states such as IgA deficiency and common variable immunodeficiency with low IgG levels.

■ NONAUTOIMMUNE THROMBOCYTOPENIA

Thrombocytopenia can also be caused by a number of nonautoimmune conditions.

Pseudothrombocytopenia

Pseudothrombocytopenia can occur if ex-vivo agglutination of platelets is induced by anti-platelet antibodies to EDTA, a standard blood anticoagulant. Automated counters cannot differentiate the agglutinated platelet clumps from individual cells such as red cells. This can frequently be overcome by running the counts in a citrate or ACD reagent tube. A peripheral blood smear can demonstrate whether platelet clumps are present.

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura presents with thrombocytopenia, purpura, and anemia. Associated clinical abnormalities (fever, neurologic symptoms, and renal failure) and the presence of fragmented red cells on blood smear help to distinguish it from ITP. Plasma exchange is the treatment of choice.

Gestational thrombocytopenia

Five percent of pregnant women develop mild thrombocytopenia (platelet counts typically $> 70 \times 10^9/L$) near the end of gestation.²⁶ It requires no treatment and resolves after delivery. The fetus' platelet count remains unaffected.

Gestational thrombocytopenia should be

differentiated from the severe thrombocytopenia of preeclampsia and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), which requires immediate attention.

Myelodysplastic syndrome

Myelodysplastic syndrome is common among elderly patients and should be considered in cases of unexplained cytopenia and abnormalities in the peripheral blood smear suggestive of dysplastic cytologic features. It can be diagnosed by bone marrow biopsy. Thrombocytopenia occurs in about 40% to 65% of cases of myelodysplastic syndrome.²⁷

■ MANAGE ITP TO KEEP PLATELET COUNT ABOVE $30 \times 10^9/L$

ITP does not necessarily require treatment, and the initial challenge is to determine whether treatment or observation is indicated. Treatment is based on two major factors: the platelet count and degree of bleeding. The goals of management are to achieve a safe platelet count to prevent serious bleeding while minimizing treatment-related toxicity.⁷

Adults with platelet counts of less than $30 \times 10^9/L$ are usually treated. In multiple large cohort studies, patients with platelet counts above that level have been safely observed without treatment.^{11,28}

TABLE 2 outlines a comprehensive approach to therapy.

■ INITIAL TREATMENT: STEROIDS AND IMMUNOGLOBULINS

Oral corticosteroids are the initial agents of choice

Oral prednisone 1 mg/kg/day in tapering doses for 4 to 6 weeks is the most common initial regimen. Other regimens, such as high-dose dexamethasone (Decadron) (40 mg daily for 4 days per month) for several cycles, have been reported to be more effective²⁹ but have not been studied in head-to-head trials with oral prednisone.

Due to their effectiveness, low cost, and convenience of use, corticosteroids have been the backbone of initial treatment in ITP. However, in most patients the platelet count

Oral prednisone 1 mg/kg/day in tapering doses for 4 to 6 weeks is the most common initial regimen

decreases once the dose is tapered or stopped; remission is sustained in only 10% to 30% of cases.³⁰ Continuation of corticosteroids is limited by long-term complications such as opportunistic infections, osteoporosis, and emotional lability.³¹

Intravenous immunoglobulin and anti-D immunoglobulin are alternatives

Intravenous immunoglobulin is recommended for patients who have not responded to corticosteroids and is often used in pregnancy. It is thought to act by blocking Fc receptors in the reticuloendothelial system. Intravenous immunoglobulin rapidly increases platelet counts in 65% to 80% of patients,³² but the effect is transient and the drug requires frequent administration. It is usually well tolerated, although about 5% of patients experience headache, chills, myalgias, arthralgias, and back pain. Rare, serious complications include thrombotic events, anaphylaxis (in IgA-deficient patients), and renal failure.

Anti-D immunoglobulin, a pooled IgG product, is derived from the plasma of Rh(D)-negative donors and can be given only to patients who are Rh(D)-positive. Response rates as high as 70% have been reported, with platelet effects lasting for more than 21 days.³³ Studies have shown better results at a high dose (75 µg/kg) than with the approved dose of 50 µg/kg.³⁴

Anti-D immunoglobulin can also be given intermittently whenever the platelet count falls below a specific level (ie, $30 \times 10^9/L$). This allows some patients to avoid splenectomy and may even trigger long-term remission.³²

Common side effects of anti-D immunoglobulin include fever and chills; these can be prevented by premedication with acetaminophen or corticosteroids. Rare but fatal cases of intravascular hemolysis, renal failure, and disseminated intravascular coagulation have been reported, precluding its use for ITP in some countries, including those of the European Union.

Emergency treatment: Combination therapy

Evidence-based guidelines are limited for treating patients with active bleeding or who are at high risk of bleeding. For uncontrolled

TABLE 2

Treatment of immune thrombocytopenia

First-line

Prednisone (1 mg/kg/day in tapering doses \times 4–6 weeks)

High-dose dexamethasone (Decadron) (40 mg daily \times 4 days/month for several cycles)

Intravenous immunoglobulin (0.8–1 g/kg)

Intravenous anti-D immunoglobulin (50–75 µg/kg)

Second-line

Rituximab (Rituxan) (375 mg/m^2 weekly \times 4 weeks)^a

Splenectomy^a

Thrombopoietin receptor agonists^a

Romiplostim (Nplate) (1–10 µg/kg subcutaneously weekly)

Eltrombopag (Promacta) (25–75 mg orally daily)

Azathioprine (Imuran)

Cyclosporine A (Gengraf, Neoral, Sandimmune)

Cyclophosphamide (Cytoxan)

Danazol (Danocrine)

Dapsone

Mycophenolate mofetil (CellCept)

Vinca alkaloids

Third-line

Combination chemotherapy

Hematopoietic stem cell transplantation^b

^a Commonly used

^b Warranted only for severe refractory immune thrombocytopenia with bleeding complications unresponsive to other agents

bleeding, a combination of first-line therapies is recommended, using prednisone and intravenous immunoglobulin.³⁵ Other options include high-dose methylprednisolone and platelet transfusions, alone or in combination with intravenous immunoglobulin.³⁶

SECOND-LINE TREATMENTS

Splenectomy produces complete remission in most patients

Patients who relapse and have a platelet count of less than $20 \times 10^9/L$ are traditionally con-

sidered for splenectomy. More than two-thirds of patients respond with no need for further treatment.³⁷

Although splenectomy has the highest rate of durable platelet response, the risks associated with surgery are an important concern. Even with a laparoscopic splenectomy, complications occur in 10% of patients and death in 0.2%. Long-term risks include the rare occurrence of sepsis with an estimated mortality rate of 0.73 per 1,000 patient-years, and possible increased risk of thrombosis.^{38,39}

Adherence to recommended vaccination protocols and early administration of antibiotics for systemic febrile illness reduce the risk of sepsis.⁴⁰ Patients are advised to receive immunization against encapsulated bacteria with pneumococcal, *Haemophilus influenzae* type b, and meningococcal vaccines. These vaccines should be given at least 2 weeks before elective splenectomy.⁴¹

Treatment of patients refractory to splenectomy is challenging and requires further immunosuppressive therapy, which is associated with an increased risk of infections and infection-related deaths.⁴²

Rituximab in addition to or possibly instead of splenectomy

Rituximab (Rituxan) is a chimeric anti-CD20 monoclonal antibody that targets B cells. Although initially approved for treatment of lymphomas, rituximab has gained popularity in treating ITP due to its safety profile and ability to deplete CD20+ B cells responsible for antiplatelet antibody production by Fc-mediated cell lysis.

In the largest systematic review of published reports of rituximab use in ITP (19 studies, 313 patients), Arnold and colleagues⁴³ reported an overall platelet response (defined as platelet count $> 50 \times 10^9/L$) in 62.5% (95% confidence interval [CI] 52.6%–72.5%) of patients. The median duration of response was 10.5 months (range 3–20), and median follow-up was 9.5 months (range 2–25). Nearly all patients had received corticosteroid treatment and half of them had undergone splenectomy.

Rituximab has also been investigated as an alternative to splenectomy. In a prospective, single-arm, phase 2 trial, 60 patients

with chronic ITP (platelet counts $< 30 \times 10^9/L$) for whom one or more previous treatments had failed received rituximab infusions and were followed for up to 2 years. A good response (defined as a platelet count $\geq 50 \times 10^9/L$, with at least a doubling from baseline) was obtained in 24 (40%) of 60 patients (95% CI 28%–52%) at 1 year and 33.3% at 2 years. The authors concluded that rituximab could be used as a presplenectomy therapeutic option, particularly in patients with chronic ITP who are at increased surgical risk or who are reluctant to undergo surgery.⁴⁴ Based on these results, rituximab may spare some patients from splenectomy, or at least delay it. However, it has never been tested in randomized controlled trials to establish its role as a splenectomy-sparing agent in ITP.

Side effects include infusion reactions, which are usually mild but in rare cases can be severe. Recently, progressive multifocal leukoencephalopathy has been recognized as a complication of rituximab treatment in patients with lymphoproliferative and autoimmune disorders.⁴⁵ Although this complication is rare in patients with ITP, careful monitoring is required until additional long-term safety data are available.

Thrombopoietic receptor agonists require continuous treatment

In the early 1990s, recombinant thrombopoietin was tested in clinical studies. These were halted when antibodies developed to recombinant thrombopoietin that cross-reacted with endogenous thrombopoietin, resulting in severe thrombocytopenia.⁴⁶

This led to the development of nonimmunogenic thrombopoietin receptor agonists that mimic the effect of thrombopoietin and stimulate the production of platelets. In 2008, the US Food and Drug Administration approved two drugs of this class for treating ITP: romiplostim (Nplate) and eltrombopag (Promacta). They are mainly used to treat patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Although well tolerated and effective in increasing platelet counts, these agents share common drawbacks. They do not modify the course of the disease, they are used only to sus-

Patients who relapse and have a platelet count of less than $20 \times 10^9/L$ are traditionally considered for splenectomy

TABLE 3

Newer therapies for immune thrombocytopenia refractory to first-line treatment in adults

	RITUXIMAB (RITUXAN)	ROMIPLOSTIM (NPLATE)	ELTROMBOPAG (PROMACTA)
Drug class	Anti-CD20 monoclonal antibody	Thrombopoietin receptor agonist	Thrombopoietin receptor agonist
Route	Intravenous	Subcutaneous	Oral
Dosing	375 mg/m ² weekly × 4	1–10 mg/kg weekly	25–75 mg daily
Approximate platelet count response rate*	60% ⁴¹	79% (splenectomized patients) ⁴⁷ 88% (nonsplenectomized patients) ⁴⁷	70% (receiving 50-mg dose) 80% (receiving 75-mg dose) ⁵¹
Approximate time to response	1–8 weeks ³⁵	1–4 weeks	2 weeks
Duration of response	Up to 2 years (median 10.5 months) ⁴³	Platelet count returns to baseline 2 weeks after discontinuing treatment	Platelet count returns to baseline 2 weeks after discontinuing treatment
Safety concerns	Mild infusion reaction Rare: infections, serum sickness, bronchospasm	Bone marrow reticulin formation, thrombosis	Elevated liver enzymes, bone marrow reticulin formation, thrombosis

*Platelet count > 50 × 10⁹/L

tain the platelet count, they require repeated administration, and they must be given for about 7 days to achieve an adequate platelet response, so they cannot be used in emergencies. Long-term adverse effects include bone marrow fibrosis and thrombosis.

Romiplostim is a synthetic peptide capable of binding to the thrombopoietin receptor c-Mpl. It has no sequence homology with endogenous thrombopoietin,⁴⁷ so does not induce cross-reacting antibodies. It has a half-life of 120 to 160 hours and is usually given subcutaneously 1 to 10 µg/kg weekly.

Phase III clinical trials have shown the effectiveness of romiplostim in attaining a durable platelet response (platelet count > 50 × 10⁹/L) in splenectomized and nonsplenectomized populations. It is well tolerated, and only two uncommon serious adverse effects have been reported: bone marrow reticulin formation and thromboembolism.⁴⁸

A long-term open-label extension study of 142 patients treated with romiplostim for up

to 156 weeks showed that 124 (87%) achieved a platelet count of more than 50 × 10⁹/L at some point, and 84% of patients were able to reduce or discontinue concurrent medications for ITP.⁴⁹

Kuter et al,⁵⁰ in a randomized controlled trial, confirmed the efficacy of romiplostim in attaining durable increased platelet counts. Patients treated with romiplostim at a mean weekly dose of 3.9 µg/kg ± 2.1 µg/kg demonstrated a higher rate of platelet response, lower incidence of treatment failure, and improved quality of life vs patients treated with standard care.

Eltrombopag is a nonpeptide thrombopoietin agonist that binds to the transmembrane domain of the thrombopoietin receptor and stimulates the proliferation and differentiation of megakaryocytes in bone marrow. It is given orally in doses of 25 to 75 mg daily.

Eltrombopag has been shown to be effective in increasing platelet counts in chronic ITP.⁵¹ In a phase III trial conducted by Cheng

and colleagues, 197 patients were randomized to eltrombopag or placebo.⁵² Patients treated with eltrombopag were eight times more likely to achieve platelet counts of more than $50 \times 10^9/L$ during the 6-month treatment period (odds ratio 8.2, 95% CI 4.32–15.38, $P < .001$) vs placebo. Patients treated with eltrombopag had fewer bleeding episodes and were more likely to reduce or discontinue the dose of concurrent ITP medications. The only significant side effect seen was a rise in aminotransferases (seen in 7% of eltrombopag recipients vs 2% with placebo).⁵²

Additional thrombopoietin agonists under investigation include ARK-501, totrombopag, and LGD-4665. MDX-33, a monoclonal antibody against the Fc-receptor, is also being studied; it acts by preventing opsonization of autoantibody-coated platelets.⁵³

THIRD-LINE TREATMENTS FOR REFRACTORY CASES

Patients with ITP that is resistant to standard therapies have an increased risk of death, disease, and treatment-related complications.^{28,42}

Combination chemotherapy

Immunosuppressants such as azathioprine (Imuran), cyclosporine (Neoral, Sandimmune), cyclophosphamide (Cytosan), and mycophenolate (CellCept) were used in the past in single-agent regimens with some efficacy, but their use was limited due to drug-related toxicity and a low safety profile.³ However, there is increasing evidence for a role of combination chemotherapy to treat chronic refractory ITP to achieve greater efficacy and fewer adverse effects.⁵⁴

Arnold and colleagues⁵⁵ reported that combined azathioprine, mycophenolate, and cyclosporine achieved an overall response (platelet count $> 30 \times 10^9/L$ and doubling of the baseline) in 14 (73.7%) of 19 patients with chronic refractory ITP, lasting a median of 24 months.

REFERENCES

1. Feudjo-Tepie MA, Robinson NJ, Bennett D. Prevalence of diagnosed chronic immune thrombocytopenic purpura in the US: analysis of a large US claim database: a rebuttal. *J Thromb Haemost* 2008; 6:711–712.
2. Abrahamson PE, Hall SA, Feudjo-Tepie M, Mitrani-Gold FS, Logie

Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation has provided remission in a limited number of patients. However, it is associated with fatal toxicities such as graft-vs-host disease and septicemia, and therefore it is reserved for severe refractory ITP with bleeding complications unresponsive to other therapies.^{56,57}

THERAPY FOR SECONDARY ITP DEPENDS ON THE CAUSE

Treatments for secondary ITP vary depending on the cause of thrombocytopenia and are often more complex than therapy for primary disease. Optimal management involves treating the underlying condition (eg, chronic lymphocytic leukemia or systemic lupus erythematosus).

Drug-induced thrombocytopenia requires prompt recognition and withdrawal of the inciting agent.

Treating ITP due to HCV infection primarily involves antiviral agents to suppress viral replication. If treating ITP is required, then intravenous immunoglobulin is preferable to glucocorticoids because of the risk of increasing viral load with the latter.⁵⁸ Eltrombopag may effectively increase platelet counts, allowing patients to receive interferon therapy for HCV.⁵⁹ However, a recent study was halted due to increased incidence of portal vein thrombosis, raising concerns about the safety of eltrombopag for patients with chronic liver disease.⁶⁰

Secondary ITP due to HIV infection should always be treated first with antivirals targeting HIV unless thrombocytopenia-related bleeding complications warrant treatment. If treatment for ITP is necessary, it should include corticosteroids, intravenous immunoglobulin, or anti-D immunoglobulin as first-line therapy.

Eradication therapy for *H pylori* is recommended for patients who are positive for the organism based on urea breath testing, stool antigen testing, or endoscopic biopsies. ■

J. The incidence of idiopathic thrombocytopenic purpura among adults: a population-based study and literature review. *Eur J Haematol* 2009; 83:83–89.

3. Gernsheimer T. Chronic idiopathic thrombocytopenic purpura: mechanisms of pathogenesis. *Oncologist* 2009; 14:12–21.
4. McMillan R, Wang L, Tomer A, Nichol J, Pistillo J. Suppression of in vitro megakaryocyte production by antiplatelet auto-

Thrombopoietic receptor agonists are mainly used to treat patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy

- antibodies from adult patients with chronic ITP. *Blood* 2004; 103:1364–1369.
5. Houwerzijl EJ, Blom NR, van der Want JJ, et al. Ultrastructural study shows morphologic features of apoptosis and para-apoptosis in megakaryocytes from patients with idiopathic thrombocytopenic purpura. *Blood* 2004; 103:500–506.
 6. Kuwana M, Kaburaki J, Kitasato H, et al. Immunodominant epitopes on glycoprotein IIb-IIIa recognized by autoreactive T cells in patients with immune thrombocytopenic purpura. *Blood* 2001; 98:130–139.
 7. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med* 2002; 346:995–1008.
 8. Littman DR, Rudensky AY. Th17 and regulatory T cells in mediating and restraining inflammation. *Cell* 2010; 140:845–858.
 9. Semple JW, Provan D, Garvey MB, Freedman J. Recent progress in understanding the pathogenesis of immune thrombocytopenia. *Curr Opin Hematol* 2010; 17:590–595.
 10. Ballem PJ, Segal GM, Stratton JR, Gernsheimer T, Adamson JW, Slichter SJ. Mechanisms of thrombocytopenia in chronic autoimmune thrombocytopenic purpura. Evidence of both impaired platelet production and increased platelet clearance. *J Clin Invest* 1987; 80:33–40.
 11. George JN. Definition, diagnosis and treatment of immune thrombocytopenic purpura. *Haematologica* 2009; 94:759–762.
 12. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 2009; 113:2386–2393.
 13. Neuner C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011; 117:4190–4207.
 14. Newton JL, Reese JA, Watson SI, et al. Fatigue in adult patients with primary immune thrombocytopenia. *Eur J Haematol* 2011; 86:420–429.
 15. Stasi R, Willis F, Shannon MS, Gordon-Smith EC. Infectious causes of chronic immune thrombocytopenia. *Hematol Oncol Clin North Am* 2009; 23:1275–1297.
 16. Moses A, Nelson J, Bagby GC Jr. The influence of human immunodeficiency virus-1 on hematopoiesis. *Blood* 1998; 91:1479–1495.
 17. Zhang W, Nardi MA, Borkowsky W, Li Z, Karpatkin S. Role of molecular mimicry of hepatitis C virus protein with platelet GPIIb/IIIa in hepatitis C-related immunologic thrombocytopenia. *Blood* 2009; 113:4086–4093.
 18. Peck-Radosavljevic M. Thrombocytopenia in liver disease. *Can J Gastroenterol* 2000; 14(suppl D):60D–66D.
 19. Roomer R, Hansen BE, Janssen HL, de Knegt RJ. Thrombocytopenia and the risk of bleeding during treatment with peginterferon alfa and ribavirin for chronic hepatitis C. *J Hepatol* 2010; 53:455–459.
 20. Stasi R, Sarpatwari A, Segal JB, et al. Effects of eradication of *Helicobacter pylori* infection in patients with immune thrombocytopenic purpura: a systematic review. *Blood* 2009; 113:1231–1240.
 21. Cines DB, Bussel JB, Liebman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. *Blood* 2009; 113:6511–6521.
 22. Zent CS, Kay NE. Autoimmune complications in chronic lymphocytic leukaemia (CLL). *Best Pract Res Clin Haematol* 2010; 23:47–59.
 23. Hepburn AL, Narat S, Mason JC. The management of peripheral blood cytopenias in systemic lupus erythematosus. *Rheumatology (Oxford)* 2010; 49:2243–2254.
 24. Mok CC, Lee KW, Ho CT, Lau CS, Wong RW. A prospective study of survival and prognostic indicators of systemic lupus erythematosus in a southern Chinese population. *Rheumatology (Oxford)* 2000; 39:399–406.
 25. Cervera R, Piette JC, Font J, et al; Euro-Phospholipid Project Group. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum* 2002; 46:1019–1027.
 26. Burrows RF, Kelton JG. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. *N Engl J Med* 1993; 329:1463–1466.
 27. Kantarjian H, Giles F, List A, et al. The incidence and impact of thrombocytopenia in myelodysplastic syndromes. *Cancer* 2007; 109:1705–1714.
 28. Portielje JE, Westendorp RG, Kluijn-Nelemans HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. *Blood* 2001; 97:2549–2554.
 29. Cheng Y, Wong RS, Soo YO, et al. Initial treatment of immune thrombocytopenic purpura with high-dose dexamethasone. *N Engl J Med* 2003; 349:831–836.
 30. Bromberg ME. Immune thrombocytopenic purpura—the changing therapeutic landscape. *N Engl J Med* 2006; 355:1643–1645.
 31. Guidry JA, George JN, Vesely SK, Kennison SM, Terrell DR. Corticosteroid side-effects and risk for bleeding in immune thrombocytopenic purpura: patient and hematologist perspectives. *Eur J Haematol* 2009; 83:175–182.
 32. Cooper N. Intravenous immunoglobulin and anti-RhD therapy in the management of immune thrombocytopenia. *Hematol Oncol Clin North Am* 2009; 23:1317–1327.
 33. Scaradavou A, Woo B, Woloski BM, et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: experience in 272 patients. *Blood* 1997; 89:2689–2700.
 34. Newman GC, Novoa MV, Fodero EM, Lesser ML, Woloski BM, Bussel JB. A dose of 75 microg/kg/d of i.v. anti-D increases the platelet count more rapidly and for a longer period of time than 50 microg/kg/d in adults with immune thrombocytopenic purpura. *Br J Haematol* 2001; 112:1076–1078.
 35. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010; 115:168–186.
 36. Spahr JE, Rodgers GM. Treatment of immune-mediated thrombocytopenia purpura with concurrent intravenous immunoglobulin and platelet transfusion: a retrospective review of 40 patients. *Am J Hematol* 2008; 83:122–125.
 37. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. *Blood* 2004; 104:2623–2634.
 38. Schilling RF. Estimating the risk for sepsis after splenectomy in hereditary spherocytosis. *Ann Intern Med* 1995; 122:187–188.
 39. Cray SE, Buchanan GR. Vascular complications after splenectomy for hematologic disorders. *Blood* 2009; 114:2861–2868.
 40. Davies JM, Barnes R, Milligan D; British Committee for Standards in Haematology; Working Party of the Haematology/Oncology Task Force. Update of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *Clin Med* 2002; 2:440–443.
 41. Centers for Disease Control and Prevention (CDC). Recommended adult immunization schedule—United States, 2011. *MMWR Morb Mortal Wkly Rep* 2011; 60:1–4.
 42. McMillan R, Durette C. Long-term outcomes in adults with chronic ITP after splenectomy failure. *Blood* 2004; 104:956–960.
 43. Arnold DM, Dentali F, Crowther MA, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. *Ann Intern Med* 2007; 146:25–33.
 44. Godeau B, Porcher R, Fain O, et al. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura: results of a prospective multicenter phase 2 study. *Blood* 2008; 112:999–1004.

45. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood* 2009; 113:4834–4840.
46. Li J, Yang C, Xia Y, et al. Thrombocytopenia caused by the development of antibodies to thrombopoietin. *Blood* 2001; 98:3241–3248.
47. Kuter DJ. New thrombopoietic growth factors. *Blood* 2007; 109:4607–4616.
48. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet* 2008; 371:395–403.
49. Bussel JB, Kuter DJ, Pullarkat V, Lyons RM, Guo M, Nichol JL. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. *Blood* 2009; 113:2161–2171.
50. Kuter DJ, Rummel M, Boccia R, et al. Romiplostim or standard of care in patients with immune thrombocytopenia. *N Engl J Med* 2010; 363:1889–1899.
51. Bussel JB, Provan D, Shamsi T, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 373:641–648.
52. Cheng G, Saleh MN, Marcher C, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet* 2011; 377:393–402.
53. Arnold DM, Nazi I, Kelton JG. New treatments for idiopathic thrombocytopenic purpura: rethinking old hypotheses. *Expert Opin Investig Drugs* 2009; 18:805–819.
54. Boruchov DM, Gururangan S, Driscoll MC, Bussel JB. Multia-gent induction and maintenance therapy for patients with refractory immune thrombocytopenic purpura (ITP). *Blood* 2007; 110:3526–3531.
55. Arnold DM, Nazi I, Santos A, et al. Combination immuno-suppressant therapy for patients with chronic refractory immune thrombocytopenic purpura. *Blood* 2010; 115:29–31.
56. Passweg JR, Rabusin M. Hematopoietic stem cell transplantation for immune thrombocytopenia and other refractory autoimmune cytopenias. *Autoimmunity* 2008; 41:660–665.
57. Huhn RD, Fogarty PF, Nakamura R, et al. High-dose cyclophosphamide with autologous lymphocyte-depleted peripheral blood stem cell (PBSC) support for treatment of refractory chronic autoimmune thrombocytopenia. *Blood* 2003; 101:71–77.
58. Magrin S, Craxi A, Fabiano C, et al. Hepatitis C viremia in chronic liver disease: relationship to interferon-alpha or corticosteroid treatment. *Hepatology* 1994; 19:273–279.
59. McHutchison JG, Dusheiko G, Shiffman ML, et al; TPL102357 Study Group. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med* 2007; 357:2227–2236.
60. US Department of Health & Human Services; US Food and Drug Administration (FDA). Promacta (eltrombopag): Portal Venous System Thromboses in Study of Patients With Chronic Liver Disease <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm211796.htm>. Accessed June 27, 2012.

ADDRESS: Gaurav Kistangari, MD, Department of Hospital Medicine, M2 Annex, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail kistang@ccf.org.