A physiopathological approach to diagnosis and management of adult primary immune thrombocytopenia

Răzvan Stoia, Ana-Maria Moldovianu
Department of Hematology and Bone Marrow Transplantation - Fundeni Clinical Institute, Bucharest

Terminology

Although it was described more than two centuries ago, progress in our understanding of the main aspects of ITP has only become significant in the last few years. New guidelines and expert recommendations were developed based on diagnostic and treatment advances. Searching for an international consensus, an international working group has provided new standardized terminology and outcome criteria in immune thrombocytopenia (Rodeghiero F, 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).
Members of the same group with additional experts have also provided a new consensus guideline on the investigation and management of ITP (Provan D, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2009).

According to the international consensus report, immune thrombocytopenia is characterized by isolated thrombocytopenia, defined as a platelet count < 100 x 109/L, with otherwise normal CBC and peripheral smear and is defined in 3 stages: newly diagnosed (< 3 months), persistent (3-12 months) and chronic (> 12 months). Defining patients as acute vs chronic is a retrospective determination; the new stage definitions will allow for better selection of patients for clinical trials.

Immune thrombocytopenia can be separated into a primary and a secondary form. In ITP no other disorder can be identified. Secondary forms are associated with various diseases such as infections (eg, hepatitis C, HIV or Helicobacter pylori), autoimmune disorders (eg, lupus erythematosus or antiphospholipid syndrome), and last but not least, malignancies (eg, chronic lymphocytic leukemia or lymphomas). It is estimated that in 20% of patients with ITP, the disease develops in the background of other disorders and these patients may require a different approach to treatment.

New definitions and recommendations were provided for assessing the quality of response to ITP treatments. Only patients who fail or relapse after splenectomy are considered as having refractory ITP. Complete response (CR) is consistent with platelet count ≥ 100 x 109/L and absence of bleeding, Response (R) means platelet count ≥ 30 x 109/L and at least 2-fold increase the baseline count and absence of bleeding and No response (NR) is defined as a platelet count < 30 x 109/L or less than 2-fold increase of baseline platelet count or bleeding. Timing of assessment of response to ITP treatments is variable, it depends on the type of treatment. Corticosteroid-dependence is defined as the need for ongoing or repeated doses administration of corticosteroids for at least 2 months to maintain a platelet count at or > 30 x 109/L and/or to avoid bleeding (patients with corticosteroid dependence are considered nonresponders).

Diagnosis

According to the new recommendations for ITP evaluation, the diagnosis of ITP is made by exclusion of secondary causes of thrombocytopenia as there are no diagnostic tests to confirm ITP. A careful history, physical examination and review of the CBC and peripheral smear are the key components of the diagnosis of ITP. In patients presenting with suspected ITP, abnormalities in the CBC and peripheral blood smear other than thrombocytopenia, should be further investigated before the diagnosis of ITP is made.

Bone marrow examination is recommended for patients older than 60 years of age, for those with systemic symptoms or abnormal signs, or for some cases in which splenectomy is considered. In addition to excluding underlying myelodysplasia, flow studies may be helpful in identifying patients with an ITP secondary to chronic lymphocytic leukemia (CLL).

Screening for HIV and HCV antibodies and assessing H. pylori infection by urea breath or stool antigen test should be considered as 4% to 30% of patients, depending on the background infection rates in the local population, may have ITP secondary to HIV, HCV, or H. pylori; treatment of the primary chronic infection can result in an increase in the platelet count.

Quantitative immunoglobulins test should be done before patients receive intravenous immunoglobulins; this will reveal patients with CVID or IgA deficiency. Direct antiglobulin test (DAT) is appropriate if patient has anemia and/or a high reticulocyte count. Blood group Rh(D) typing is important if treatment with anti-RhD immunoglobulin is being considered; should be

done in conjunction with DAT, since a positive DAT may modify a decision to use anti-D therapy.

Tests of potential utility include Thyroglobulin antibodies and/or TSH - the presence of hyperthyroidism or hypothyroidism can result in resistance to standard ITP therapy, antiphospholipid antibodies in patients with a history of either fetal loss or thrombosis, antiplatelet antibody assay - not routinely recommended because platelet-associated IgG is elevated in both immune and non-immune thrombocytopenia, other acute and persistent infections – acute viral infections and some vaccinations (with live attenuated virus) have been associated with transient thrombocytopenia and some chronic infections, for example, parvovirus and CMV, can also produce thrombocytopenia.

TPO, reticulated platelets, platelet survival study, platelet-associated IgG, bleeding time, serum complement have uncertain or no proven benefit in the differential diagnosis of ITP.

Pathogenesis

Once regarded as idiopathic, primary immune thrombocytopenia is now understood to have a complex pathogenesis.

In 1951, William Harrington, a fellow at Washington University, infused blood from a patient with ITP into himself and, subsequently, into normal volunteers. The majority of recipients demonstrated significant reductions in the platelet count, sometimes severe. This experiment provided the first demonstration that ITP was caused by a factor that circulates in blood. However, some recipients did not develop thrombocytopenia, suggesting an alternative mechanism. Later, Luiken et al and Hirschman demonstrated that the transmissible agent in the blood was immunoglobulin, primarily IgG.

We now understand that an important part of the pathogenesis of ITP is caused by antibodies against platelet glycoproteins, most commonly platelet glycoprotein IIb/IIIa, the platelet fibrinogen receptor. Some patients, especially those with chronic ITP, also have antibodies against other platelet glycoproteins, including Ib/IX (the receptor for von Willebrand factor) and Ia/IIa (a collagen receptor). It is believed that ITP may begin with antibodies against a single glycoprotein, which leads to accelerated clearance of antibody-coated platelets in the spleen. Degradation of cleared platelets by splenic macrophages leads to the release and subsequent presentation of antigenic peptides from proteolyzed platelet components, including glycoproteins, on the macrophage or dendritic cell. This may lead to recruitment and activation of specific T cells that in turn interact with and stimulate B cells to produce new antibodies against the platelet-derived peptides. This phenomenon is known as epitope spreading.

The autoantibody-producing cells are a limited number of B-cell derived clones with somatic mutations and antigen-driven affinity. These clones require costimulatory signals from activated T-helper cells. Also a decreased number of T regulatory cells is observed in ITP patients.

In addition to accelerated platelet destruction, ineffective thrombopoiesis has been recognized as another important underlying mechanism. Obviously, the same autoantibodies directed against platelet glycoproteins are also capable of inhibiting megakaryocyte production. Thrombopoietin levels in patients with ITP are minimally increased compared to other thrombocytopenic disorders like aplastic anemia. TPO bound to the platelets is destroyed in the platelet phagocytosis process in the spleen. Thus there is less TPO available to stimulate platelet production by the megakaryocytes in the bone marrow.

Treatment of ITP

Reduced platelet survival and decreased platelet production, the two main mechanisms leading to thrombocytopenia, are likely two ends of a spectrum of ITP, and most patients likely have some degree of both processes.

There are 3 different strategies for treatment of chronic ITP deriving from the pathophysiological mechanisms: 1. stimulating thrombopoiesis and increasing platelet production, 2. reducing phagocytosis by macrophagocytes and increasing platelet survival, and 3. immunosuppression and decreasing autoantibody production.

· Stimulating thrombopoiesis and platelet formation: steroids, TPO agonists

The main mechanism by which steroids increase platelet counts is thought to be their immunosuppressive action; however recent data support the role in increasing platelet production. Steroids are still the first line of treatment. Either prednison 1mg/kg daily for three weeks with a response rate of approximately 60% or pulsed dexamethasone 40mg for four days per month may be used. Dexamethasone results in a more rapid response (2-4 days) but has more side effects such as hyperglycemia and oedema. Despite high initial response rates the long term remissions with steroids alone is only 10-30% for patients with chronic ITP.

Stimulating megakaryopoiesis via the TPO receptor is based on finding of suboptimal thrombopoietin levels in patients with chronic ITP. At this moment there are two TPO receptor agonists that are licensed for the treatment of chronic ITP: romiplostim and eltrombopag.

Romiplostim consists of two identical peptide sequences targeting the TPO receptor. By binding to TPO receptor with high affinity induces megakaryocyte differentiation. Romiplostim induces a dose dependent rise in platelet counts peaking 12-16 days after onset of treatment, but the platelet counts revert close to the baseline by day 28. The efficacy was the same either by subcutaneous or intravenous administration. In a phase III study the overall response rate including transient response was obtained in 88% of non-splenectomized and 79% of splenectomized patients. Platelet counts of 50,000/μL where achieved by 25% of patients after one week and by 50% within 2 to 3 weeks. A durable response was obtained in 49% of patients. The baseline TPO levels did not correlate with the rate of response.

Eltrombopag is a small non-peptide molecule that stimulates proliferation and differentiation of megakaryocytes by interacting with a transmembrane part of the TPO receptor. Eltrombopag is taken orally once daily and its absorption is significantly affected by food. The pharmacodynamics and pharmacokinetics are comparable with those of romiplostim. In a phase III study the response rate was 59% at 6 weeks. There was no correlation of response rate with concomitant use of other ITP drugs, splenectomy or number of previous ITP treatments. Platelet counts returned to baseline within 2 weeks after cessation of treatment.

There are still considerable drawbacks to the treatment with TPO receptor agonists: (1) cessation of drug results in rapid decline of platelet counts and thus continuous treatment is required, (2) time to response is 1 to 4 weeks and in emergency situations treatment with TPO agonists alone is not adequate, (3) the long-term effects of these drugs are still unknown - it is possible that these agents induce reticuline deposition in bone marrow and may also contribute to carcinogenesis, as the neoplastic cells in many hematopoietic malignancies express TPO receptors.

· Increasing platelet survival: splenectomy, immunoglobulins and vinca alkaloids

As the spleen is considered the main site for removal of autoantibody-coated platelets from the circulation splenectomy or suppression of macrophages by immunoglobulins or vinca-loaded platelets seems a rationale approach.

Splenectomy as the only surgical treatment option for ITP is effective in approximately 85% of patients and durable response are seen in two thirds of patients with ITP. Refractory disease, advanced age, dominant hepatic platelet sequestration and secondary forms of ITP are risk factors associated with an inferior response to splenectomy. In recent years laparoscopic procedures proved to be as safe as open surgery and it is the preferred technique. The decision of splenectomy requires consideration or risk factors and anesthesia related risk. To minimize surgical related complications a preoperative rise of platelet count is mandatory and may be achieved by intravenous immunoglobulins.

Intravenous immunoglobulins act by blocking Fc-gamma receptors on macrophages. They remain the mainstay of therapy in emergency settings resulting in a reliable increase in platelet counts within a few days and lasting sometimes for weeks or even months. Immunoglobulins are mainly used preoperative before splenectomy, in case of an acute major bleeding complication associated with platelet transfusions or even activated factor VII or in pregnancy.

The transfusion of vinca-loaded platelets is an attractive theoretical means to target chemotherapy to effecter phagocytes. The results seem promising in heavily pretreated ITP patients. The substitute for ex-vivo vinca-loaded platelets is intravenous vincristine given over 6 to 8 hours but with inferior outcome.

· Reducing autoantibodies production by immunosuppression

Patients failing to respond to the treatments described above are candidates for monoclonal antibodies or immunosuppressive therapy.

The use of anti-CD20 antibody Rituximab results in response rates up to 50% within 1 to 2 months by depleting the B lymphocytes. It might be a valuable option for patients requiring splenectomy in a non-emergency setting.

Other immunosuppressive drugs such as azathioprine, mycophenolat mophetil, cyclosporin A, cyclophsophamide, dapsone, mainly target T lymphocytes. Remission rates are very variable and time to response can be months. Their use is limited by potentially severe adverse events such as neutropenia, renal failure or hepatitis.

Who should be treated?

In making the treatment decision one should consider the extent of bleeding, comorbidities predisposing to bleeding, complications of specific therapies, lifestyle, potential side effects, potential interventions that may cause bleeding, accessibility of care, patient expectations and the need of other medications that may increase the bleeding risk. The rate of fatal hemorrhage is very low (0,04 cases per adult patient-year at risk). A high risk is seen in patients older than 60 years and those with a hemorrhage history. Bleeding and infection contribute equally to mortality. Treatment is rarely indicated in patients with platelet counts > 50,000/μL in the absence of the risk factors mentioned above.

In our opinion patients with platelet counts above 30,000/μL and without risk factors and bleeding history should not be treated whenever it is possible; patients

expectations and worries might be a limiting factor to that approach.

According to the international consensus report on the investigation and management of primary immune thrombocytopenia, the treatment for ITP patients should be different for those newly diagnosed (first-line treatment) vs. relapsed/refractory disease (second-line treatment). The treatment options are detailed in tables 1 and 2 (reproduced from Blood volume 115, no.2).

Although significant progress in understanding the physiopathological mechanisms in adult chronic ITP was made in the past decade, and new drugs were developed targeting specific mechanisms (TPO agonists), at this moment there is no standard approach to the management of the patient with chronic ITP. There are also very few validated risk factors to predict response to therapies and there was no progress in identifying specific criteria for diagnosis to substitute the "exclusion diagnosis". The treatment must be tailored considering the individual risk factors and the patient preferences and cost effectiveness. Very limited evidence has been obtained from the randomized and controlled clinical trials and the management of relapsed/refractory adult ITP remains a challenging and often frustrating issue.

Table 1 First-line treatment options for adult patients with ITP

Recommended treatment strategy	Approximate response rate	Approximate time to response	Toxicities	Duration of sustained response
Corticosteroids				
Dexamethasone 40 mg daily for 4 d every 2-4 wk for 1-4 cycles	Up to 90% of patients respond initially	Several days to several weeks	Vary with length of administration: mood swings, weight gain, anger, anxiety, insomnia, Cushingoid faces, dorsal fat, diabetes, fluid retention, osteoporosis, skin changes including thinning, alopecia, hypertension, GI distress and ulcers, avascular necrosis, immunosuppression, psychosis, cataracts, opportunistic infections, adrenal insufficiency; hypertension, anxiety. Tolerability decreases with repeated dosing. Possibly lower rate of adverse events when used as short-term bolus therapy	As high as 50%-80% reported, the latter with 3-6 cycles (during 2-5 y of follow-up)
Methylprednisolone 30 mg/kg/d for 7 d	As high as 95%	4.7 d vs 8.4 d (high-dose methylprednisolone [HDMP] vs prednisone)		23% of patients have sustained platelet count ($> 50 \times 10^9$/L) at 39 mo
Prednis(ol)one 0.5-2 mg/kg/d for 2-4 wk	70%-80% of patients respond initially	Several days to several weeks		Remains uncertain; estimated 10-y disease-free survival 13%-15%
IV anti-D				
50-75 μg/kg	Initial response rate similar to IVIg (dose dependent)	4-5 d	Common: hemolytic anemia (dose-limiting toxicity), fever/chills Rare: intravascular hemolysis, disseminated intravascular coagulation, renal failure, rare death	Typically last 3-4 wk but may persist for months in some patients
IVIg*				
0.4 g/kg/d for 5 d or infusions of 1 g/kg/d for 1-2 d	Up to 80% of patients respond initially; half achieve normal platelet counts	Rapid; many respond in 24 h; typically 2-4 d	Headaches common: often moderate but sometimes severe Transient neutropenia, renal insufficiency, aseptic meningitis, thrombosis, flushing, fever, chills, fatigue, nausea, diarrhea, blood pressure changes and tachycardia IVIg preparations may contain small quantities of IgA, which occasionally causes anaphylactoid reactions in patients with IgA deficiency; in these cases use IgA-depleted IVIg	Usually transient; platelet counts returning to pretreatment levels 2-4 wk after treatment; persists for months in a few patients

Table 2 Second-line treatment options for adult ITP patients

Recommended treatment strategy	Approximate response rate	Approximate time to response	Toxicities	Duration of sustained response
Azathioprine 1-2 mg/kg (maximum: 150 mg/d)	Up to two-thirds of patients; 40% in anecdotal reports	Slow; may need to be continued for 3-6 mo	Low incidence and generally mild: weakness, sweating, transaminase elevations, severe neutropenia with infection, pancreatitis	Up to a quarter of patients off therapy maintain response
Cyclosporin A 5 mg/kg/d for 6 d then 2.5-3 mg/kg/d (titration to blood levels of 100-200 ng/mL)	Dose-dependent. High response rate (~50%-80%) in small series	3-4 wk	In most patients, the following are seen to some degree; moderate but transient: increase in serum creatinine, hypertension, fatigue, paresthesias, gingival hyperplasia, myalgia, dyspepsia, hypertrichosis, tremor	More than half of responders receiving low doses sustain remission (at least 2 y)
Cyclophosphamide (1-2 mg/kg orally daily for at least 16 wk) or IV (0.3-1 g/m^2 for 1-3 doses every 2-4 wk)	24%-85% of patients	1-16 wk	Most are mild to moderate: neutropenia, acute deep venous thrombosis, nausea, vomiting	Up to 50% show a sustained response
Danazol 200 mg 2-4 times daily	67% complete or partial response; 40% in anecdotal reports	3-6 mo	Frequent side effects: acne, increased facial hair, increased cholesterol, amenorrhea, transaminitis	46% remained in remission at a median of 119 ± 45 mo and mean duration of danazol therapy was 37 mo
Dapsone 75-100 mg	Response in up to 50% of patients	3 wk	Infrequent and treatable/reversible: abdominal distension, anorexia, nausea, methemoglobinuria, hemolytic anemia in those with G6PD deficiency. Severe: skin rash may require drug to be stopped	Sustained response in up to two-thirds of responders off therapy
Mycophenolate mofetil 1000 mg twice daily for at least 3-4 wk	Up to 75% of patients; complete response in up to 45%	4-6 wk	Mild and infrequent: headache (most common and dose-limiting), backache, abdominal distension, anorexia, nausea	Sustained for short time after treatment discontinuation
Rituximab 375 mg/m^2 weekly ×4 (lower doses may also be effective)	60% of patients; complete response in 40% of patients	1-8 wk	Low rate, usually mild-to-moderate first-infusion fever/chills, rash, or scratchiness in throat. More severe reactions include serum sickness and (very rarely) bronchospasm, anaphylaxis, pulmonary embolism, retinal artery thrombosis, infection, and development of fulminant hepatitis via reactivation of hepatitis B. Rare cases of progressive multifocal leukoencephalopathy.	Sustained response > 3-5 y in 15%-20% of responders. Responders may require retreatment months to years later
Splenectomy	80% of patients respond; approximately two-thirds achieve a lasting response	1-24 d	Hemorrhage, peripancreatic hematoma, subphrenic abscess, wound infection, death, pneumococcal infection, fever, overwhelming sepsis syndrome, thrombosis	Response sustained with no additional therapy in approximately two-thirds of patients over 5-10 y
TPO receptor agonist: eltrombopag 25-75 mg orally daily	Platelet responses (platelet count > 50 × 10^9/L on d 43 of study): 70% receiving 50-mg dose, 81% receiving 75-mg dose	By d 15, more than 80% of patients receiving 50 or 75 mg of eltrombopag daily increased platelet count	Adverse events in at least 20% of patients: headache Treatment-related serious adverse events: increased bone marrow reticulin, worsening thrombocytopenia upon discontinuation, thrombosis, liver function abnormalities in 13%	Up to 1.5 y with continual administration of the drug
TPO receptor agonist: romiplostim Doses 1-10 μg/kg subcutaneously weekly	Overall platelet response rate: non-splenectomized, 88%; splenectomized, 79%	1-4 wk (in patients with platelet count < 30 × 10^9/L to achieve > 50 × 10^9/L)	Adverse events in at least 20% of patients: headache, fatigue, epistaxis, arthralgia and contusion (similar incidence in placebo groups) Treatment-related serious adverse events: increased bone marrow reticulin, worsening thrombocytopenia upon discontinuation, thrombosis	Up to 4 y with continual administration of the drug
Vinca alkaloid regimens: vincristine total dose of 6 mg (1-2 mg per infusion weekly); vinblastine total dose of 30 mg (10 mg per infusion weekly), and some patients, vincristine and vinblastine infusions administered alternatively	Highly variable transient response in 10%-75% of patients	5-7 d	Neuropathy especially with repeated dose and in the elderly; neutropenia, fever, inflammation/thrombophlebitis at the infusion site	A normal platelet count was observed in 6 of 9 (9/12 had response) patients under long-term 3-36 mo monitoring; average, 10 mo

References

1. 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(11):2386–2393.
2. Schoonen WM, Kucera G, Coalson J, et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. Br J Haematol. 2009;145(2):235–244.
3. CinesDB,BusselJB,LiebmanHA,etal.TheITPsyndrome:pathogenic and clinical diversity. Blood. 2009;13(26):6511–6521.
4. Cortelazzo S, Finazzi G, Buelli M, et al. High risk of severe bleeding in aged patients with chronic idiopathic thrombocytopenic purpura. Blood. 1991;77(1):31–33.
5. Raife TJ, Olson JD, Lentz SR. Platelet antibody testing in idiopathic thrombocytopenic purpura. Blood. 1997;89(3):1112–1114.
6. Brighton TA, Evans S, Castaldi PA, et al. Prospective evaluation of the clinical usefulness of an antigen-specific assay (MAIPA) in idiopathic thrombocytopenic purpura and other immune thrombocytopenias. Blood. 1996;88(1):194–201.
7. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115(2):168–186.
8.McMillanR,WangL,TaniP.Prospectiveevaluationoftheimmunobead assay for the diagnosis of adult chronic immune thrombocytopenic purpura (ITP). J Thromb Haemost. 2003;1(3):485–491.
9. Van Leeuwen EF, van der Ven JT, Engelfriet CP, et al. Specificity of autoantibodies in autoimmune thrombocytopenia. Blood. 1982;59(1): 23–26.
10. He R, Reid DM, Jones CE, et al. Spectrum of Ig classes, specificities, and titers of serum antiglycoproteins in chronic idiopathic thrombocytopenic

purpura. Blood. 1994;83(4):1024–1032.
11. Fujisawa K, Tani P, O'Toole TE, et al. Different specificities of platelet-associated and plasma autoantibodies to platelet GPIIb-IIIa in patients with chronic immune thrombocytopenic purpura. Blood. 1992;79(6): 1441–1446.
12. Semple JW, Milev Y, Cosgrave D, et al. Differences in serum cytokine levels in acute and chronic autoimmune thrombocytopenic purpura: relationship to platelet phenotype and antiplatelet T-cell reactivity. Blood. 1996;87(10):4245–4254.
13. 17. Ling Y, Cao X, Yu Z, et al. Circulating dendritic cells subsets and CD4+ Foxp3+ regulatory T cells in adult patients with chronic ITP before and after treatment with high-dose dexamethasome. Eur J Haematol. 2007;79(4):310–316.
14.BallemPJ,SegalGM,StrattonJR,etal.Mechanismsoft hrombocytopenia in chronic autoimmune thrombocytopenic purpura. Evidence of both impaired platelet production and increased platelet clearance. J Clin Invest. 1987;80(1):33–40.
15. Kosugi S, Kurata Y, Tomiyama Y, et al. Circulating thrombopoietin level in chronic immune thrombocytopenic purpura. Br J Haematol. 1996;93(3):704–706.
16. Schrezenmeier H, Griesshammer M, Hornkohl A, et al. Thrombopoetin serum levels in patients with aplastic anaemia: correlation with platelet count and persistent elevation in remission. Br J Haematol. 1998; 100(3):571–576.
17. Aledort LM, Hayward CP, Chen MG, et al. Prospective screening of 205 patients with ITP, including diagnosis, serological markers, and the relationship between platelet counts, endogenous thrombopoietin, and circulating antithrombopoietin antibodies. Am J Hematol. 2004; 76(3):205–213.
18. Gernsheimer T, Stratton J, Ballem PJ, et al. Mechanisms of response to treatment in autoimmune thrombocytopenic purpura. N Engl J Med. 1989;320(15):974–980.
19. Houwerzijl EJ, Louwes H, Sluiter WJ, et al. Platelet production rate predicts the response to prednisone therapy in patients with idiopathic thrombocytopenic purpura. Ann Hematol. 2008;87(12):975–983.
20. Rodeghiero F. First-line therapies for immune thrombocytopenic purpura: re-evaluating the need to treat. Eur J Haematol Suppl. 2008;(69):19–26.
21. Stasi R, Stipa E, Masi M, et al. Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. Am J Med. 1995; 98(5):436–442.
22. Wang B, Nichol JL, Sullivan JT. Pharmaco-dynamics and pharmacokinetics of AMG 531, a novel thrombopoietin receptor ligand. Clin Pharmacol Ther. 2004;76(6):628–638.
23. Kuter D, Bussel JB, Lyons B, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet. 2008;371(9610):395–403.
24. Erickson-Miller C, DeLorme E, Tian S, et al. Discovery and characterization of a selective, nonpeptidyl thrombopoietin receptor agonist. Exp Hematol. 2005;33(1):85–93.
25. Jenkins JM, Williams D, Deng, et al. Phase 1 clinical study of eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist. Blood. 2007;109(11):4739–4741.
26. Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med. 2007;357(22):2237–2247.
27. 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(9664):641–648.
28. Columbyova L, Loda M, Scadden DT. Thrombopoietin receptor expression in human cancer cell lines and primary tissues. Cancer Res. 1995;55(16):3509–3512.
29. Kantarjian H, Sekeres MA, et al. Phase 1/2 study of AMG 531 in thrombocytopenic patients with low-risk myelodysplastic syndrome: update including extended treatment [abstract]. Blood. 2007;110: Abstract 250.
30. Schwartz J, Leber MD, Gillis SM, et al. Long term follow-up after splenectomy performed for immune thrombocytopenic purpura (ITP). Am J Hematol. 2003;72(2):94–98.
31. Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). Blood. 2005;106(7):2244–2251.
32. Fabris F, Tassan T, Ramon R, et al. Age as the major predictive factor of long-term response to splenectomy in immune thrombocytopenic purpura. Br J Haematol. 2001;112(3):637–640.
33. Bourgeois E, Caulier MT, Delarozee C, et al. Long-term follow-up of chronic autoimmune thrombocytopenic purpura refractory to splenectomy: a prospective analysis. Br J Haematol. 2003;120(6): 1079–1088.
34. Agnelli G, DeCunto M, Gresele P, et al. Vincristine-loaded platelets for autoimmune thrombocytopenic purpura. Blood. 1982;60(5):1235.
35. Stasi R, Pagano A, Etipa E, et al. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. Blood. 2001;98(4):952–957.