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REVIEW ARTICLE

REVIEW OF LITERATURE WITH CURRENT TREATMENT GUIDELINES FOR IDIOPATHIC THROMBOCYTOPENIC (ITP)

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ABSTRACT

Idiopathic Thrombocytopenic Purpura (ITP) is an autoimmune disorder involving antibody and cell mediated destruction of platelets and suppression of platelet production that may predispose to bleeding. Over the past few decades, the rising awareness of treatment and it side effects and newer medications have led to newer recommendations. Treatment is mainly directed at achieving a safe platelet count to prevent a major bleeding event rather than correcting the platelet count to normal levels. Splenectomy is now a second line treatment. Corticosteroids with IVIG or anti –Rh(D), danazol, alone or in combination with azathioprine, and dapsone have been used as first line drugs. Rituximab and Thrombopoietin receptor agonists are also approved for treating adults with chronic ITP. This paper deals with all aspects of treatment modalities and their safety with latest recommendation.

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INTRODUCTION

Immune thrombocytopenic (ITP; formerly known as Idiopathic thrombocytopenia, Idiopathic thrombocytopenic purpura) (Ruggeri *et al*., 2008) is an autoimmune disorder that is characterized by isolated thrombocytopenic (platelet count < 100x 10^9/l) and increased risk of muco-cutaneous bleeding, secondary to immune-mediated destruction of platelets and possibly inhibition of platelet release from the megakaryocytes. (Rodeghiero *et al*., 2006) In 1735, Paul Gottlieb Werlhofwrotean initial report on purpura of ITP. A complete workup on ITP was first done in 1916, when Paul Kaznelson had described a female patient's response who underwent splenectomy. Splenectomy remained mainstay treatment until 1950s. Adult-onset and childhood onset ITP is strikingly different. Children affected with ITP are usually previously healthy but typically can present with sudden onset of petechial or purpura few days or weeks post an infectious illness which resolves in six months without any intervention; while those in adults usually are of insidious onset following a chronic course with slight predominance seen in females. During the last decade its management has changed, with the advent of new medications and with increased awareness of treatment related side effects. The disorder is primary and idiopathic in most adult patients, although it can be associated with connective tissue disorders such as Systemic lupus Erythematosis (SLE), Lymph proliferative disorders, medications, and infections like hepatitis C virus, HIV infection, H.Pylori).

The International Working Group (IWG) consensus panel has recently provided specific guidelines for ITP.[2]Hence,Primary ITP is defined as a platelet count less than 100 x 10^9/L when there are no signs of other disorders that may be associated with thrombocytopenic. The IWG based their recommendations for the use of an upper threshold platelet count of 100 x 10^9/L on three considerations:

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i) A study demonstrating that patients presenting with a platelet count between 100 and 150 x 10^9/L have only a 6.9% chance of developing a persistent platelet count of less than 100 x 10^9/L over 10 years of follow-up (Stasi *et al*., 2006),
ii) In non-Western ethnicities normal values in healthy individuals may be between 100 and 150 x 10^9/L,
iii) The hypothesis that a cut-off value of 100 x 10^9/L would reduce concern over the mild "physiological" thrombocytopenic associated with pregnancy.

It also defines acute ITP as newly diagnosed if the diagnosis is upto 3 months, persistent when it is 4 to 12 months from diagnosis or chronic lasting for more than 12 months (Rodeghiero *et al*., 2006). (Table 1)

Table 1. Diagnosis of acute ITP

Newly Diagnosed	• Upto 3 months
Persistent	• 4 to 12 months
Chronic	• Lasting more than 12 months

Specific recommendations have been put forth to assess the response to ITP treatments. As per IWG complete response (CR) is considered to have a new diagnostic threshold of ≥ 100 x 10^9/L. Response (R) is defined as a platelet count ≥30 but <100 x 10^9/L and a doubling from baseline. The duration of response is measured from the achievement of a first measured CR or R until the loss of CR or R. When there is a continuous need for administration of corticosteroids to maintain a platelet count in excess of 30 x 10^9/L to avoid bleeding then it is called as corticosteroid dependence. Severe ITP is reserved for patients who have clinically relevant bleeding, such that the bleeding is so severe that an increase in drug dose or a new intervention treatment have to enacted upon to control the new bleeding symptom. Refractory ITP is an ITP that occurs even after splenectomy. Non-splenectomized patients are defined as responders and non-responders to various drug therapies, but should not be considered refractory. (Table 2)

Table 2. Assessing the response to ITP patients

Severe ITP is reserved for patients who have clinically relevant bleeding. ***Refractory ITP*** is defined as the presence of severe ITP occurring after splenectomy	***Complete response (CR)*** : New diagnostic threshold of ≥ 100 x 10^9/L.
Assessing the response to ITP treatments	
Corticosteroid dependence: The need for repeated administration of corticosteroids to maintain a platelet count in excess of 30 x 10^9/L and/or to avoid bleeding	***Response (R)*** : Platelet count ≥30 but <100 x 10^9/L and a doubling from baseline.

Epidemiology

The annual incidence of ITP is expected to be 5 cases per 100,000 children and 2 cases per 100,000 adults but the major drawback of the study was limited population and hence this data is insufficient to conclude. (Fogarty and Segal, 2007) ITP in children don't need specific medical attention as they are self-limiting. This makes it difficult to understand the disease and usually remains understated. The age-adjusted prevalence of immune thrombocytopenic purpura (ITP) was reported as 9.5 per 100,000 persons in Maryland by Segal and Powe. (Segal and Powe, 2006) Recent epidemiologic data suggest that the incidence in adults is approximately equal for both sexes except in the mid adult years (30-60 years), when the disease is more prevalent in women. (Segal and Powe, 2006)

The estimated age adjusted prevalence of ITP in a study carried out in United States is 9.5 to 23.6 cases per 100,000 (KUhne *et al.,* 2001) while that in the United Kingdom, was 4.4 per 100,000 patients per year among women and 3.4 among men. (Michel *et al.,* 2011) A recent report from Italy puts it at 2.6 cases per 100,000 patient per year. (Gernsheimer *et al.,* 1989) Middle age women (30 to 40years) are known to be frequently diagnosed with ITP though it can occur in adults at any given age. Patient above 60 years of age may rarely present with ITP and hence other factors of thrombocytopenic must be considered. Some of the most common diseases that present with thrombocytopenic aremyelodysplastic syndromes, acute leukemia, and marrow infiltration (myelophthisis). Spontaneous bleeding and treatment related side effects are more often seen in patients above 70 years of age. (Michel *et al*., 2011)

In children, immune thrombocytopenic purpura (ITP) is more common among boys compared with girls with the incidence being 1.9-6.4 per 100,000 children per year [Stasi *et al*., 2008]. Children may be affected at any age with immune thrombocytopenicpurpura (ITP), but is frequently seen in age group 1 to 6 years.

Pathogenesis

The exact etiology remains unknown; though there is immune dysregulation, due to increase in destruction and impaired production of Platelets.[9]Tolerance against platelet antigens is lost, and formation of self-reacting antibodies takes place. Initial pathogenic mechanisms leading to primary ITP have not been identified. In ITP, immunoglobulin G (IgG), binds to circulating platelets. [Stasi *et al*., 2008; McMillan, 2007] Plateletsare coated with auto antibodies that induce Fc receptor-mediated phagocytosis with the help of mononuclear macrophages which doesn't necessarily take place in spleen always. [Crow and Lazarus, 2003] Spleen plays an important role in ITP, with the white pulp producing platelet auto antibodies and mononuclear macrophages in the red pulp. (Sandler, 2000) Patients with ITP also have CD4+ T cells that are auto reactive to GPIIb-IIIa and that stimulate B-cell clones to produce antiplatelet antibodies. Although auto reactive 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. (Kuwana

et al., 2001) Activated macrophages degrade GPIIb-IIIa and other glycoproteins forming cryptic epitopes that are expressed on the macrophage surface which in turn induce proliferation of CD4+ T-cell clones. Epitope spread creates a continuous reaction and hence amplifies the production of GPIIb-IIIa antibodies (Cines and Blanchette, 2002).

Defective T-regulatory cells appear to be critical to the pathogenesis of ITP by breaking self-tolerance, allowing the autoimmune process to progress. (Littman and Rudensky, 2010) This, together with several other immune mechanisms such as molecular mimicry, abnormal cytokine profile, and B-cellabnormalities, may lead to enhanced platelet clearance.[17] Molecular mimicry has proven useful and plays an important role in the development of self-reactive platelet antibodies after vaccination and certain viral infections. For example, antibodies to viral and bacterial antigens that cross-react with platelets antigens, often lead to formation of epitope within glycoprotein IIIa, and as such have associations with HIV hepatitis C virus, and Helicobacter pylori infection (Littman and Rudensky, 2010; Semple *et al.,* 2010). The mechanisms leading to autoantibody production may differ in secondary forms of ITP associated with immunosuppression or immune dysregulation. Platelet life span is reduced as a consequence of antibody mediated clearance by tissue macrophages in essentially all patients. Meta-analysis on studies of platelet kinetics points us out to the contribution of immune mediated suppression of megakaryocyte and megakaryocyte apoptosis (Ballem *et al.,* 1987).

Platelet reactive antibodies are not detected in all individuals with ITP, and few patients do not respond to pharmacologic or surgical inhibition of antibody mediated platelet clearance or B-cell suppression, which prove that other pathogenic mechanisms exist such as antibody mediated apoptosis, antigen shedding, and T-cell mediated platelet destruction or marrow suppression. (Newton *et al.,* 2011) Not only are platelets beingdestroyed but antibodies impair platelet production. In addition to destroying platelets, anti-bodies may impair platelet production.

Clinical features

There is marked inter-patient variability. Onset may be acute and abrupt, but more often insidious.

Characteristics of ITP

i) Muco-cutaneous bleeding is noted in patients which can originate from oral mucosa, GI tract or due to heavy menstrual bleeding. The mucocutaneous bleeding is in the form of petechiae (pin point hemorrhages that do not blanch on pressure) which is usually asymmetrical and more prominent over lower limbs
ii) Low platelet count or thrombocytopenic with otherwise normal peripheral smear.
iii) Patients present either with ecchymosis and petechiae, purpura (appearing like large bruises), epistaxis (nose bleed), menorrhagia, gum bleeding.
iv) Rarely, life-threatening, including central nervous system, bleeding can occur but are rare.

Other common clinical features include fatigue, impaired quality of life, and treatment related side effects like infections (Newton *et al*., 2011).

Diagnosis

ITP is an isolated thrombocytopenic with no clinically apparent associated conditions or other causes of thrombocytopenic. (George, 2009) No diagnostic criteria currently exist, and the diagnosis is established only after excluding other causes of thrombocytopenic. (Table 3) If during the course of treatment or monitoring atypical features develop, e.g. abnormalities in the white blood cell count, lymphadenopathy, multiple cytopeniasthen the diagnosis of ITP should be reassessed. Abnormalities in the blood count or blood smear (other than thrombocytopenic, and perhaps iron deficiency anemia secondary to chronic blood loss) may be further investigated with bone marrow biopsy but is not required if the patient has typical features of ITP, regardless of age.

Table 3. Diagnosis of ITP

General physical examination	•Identify evidence of bleeding and exclude other causes of thrombocytopenic or secondary ITP.
Secondary causes of ITP	•HIV, HCV, H.Pylori), lymphoproliferative disorders, autoimmune disorders (SLE, thyroid disorders, APLA, Evans syndrome), drugs (heparin), post vaccination and common variable immune deficiency.
Laboratory investigations	•complete blood count, a peripheral blood smear, blood group, direct antiglobulin tests, HIV serology and hepatitis C virus screen.
Peripheral blood smear	• Normal Red blood cells (RBCs) and leukocytes. • Platelets are typically normal, with varying numbers of large cells.
Bone Marrow Evaluation	• Normal cellularity and morphology of erythroid and myeloid precursors. • Increased megakaryocytes,with morphology but may present with large size.
Test for antiplatelet antibodies	• Platelet antigen–specific antibodies, • Platelet-associated immunoglobulin, • Other antiplatelet antibodies

Peripheral blood smear the morphology of red blood cells (RBCs) and leukocytes is normal. Platelets are typically normal, with varying numbers of large cells. Some patients with acute immune thrombocytopenic purpura (ITP) may have mega thrombocytes or stress platelets, reflecting the early release of megakaryocytic fragments into the circulation. If most of the platelets are large, approximating the diameter of RBCs, or if they lack granules orhave an abnormal color, it's considered as an inherited platelet disorder. Clumps of platelets on a peripheral smear prepared from EDTA–anticoagulated blood are evidence of pseudo thrombocytopenic. (Nilsson and Norberg, 1986) The diagnosis of this type of pseudo thrombocytopenic is established if the platelet count is normal

when repeated on a sample from heparin-anticoagulated or citrate-anticoagulatedblood.

Bone Marrow Evaluation

It is recommended in patients older than 60 years, to exclude Myelodysplastic syndrome or leukemia and not in patients with classical features of ITP. Examination on aspiration shows, normal cellularity and morphology of erythroid and myeloid precursors, increased megakaryocytes, megakaryocyte morphology is normal but may be large size. Trephine biopsy reveals normal marrow cellularity, without evidence of hypoplasia or increased fibrosis, increased number of megakaryocytes, consistent with peripheral destruction of platelets. (Raife *et al.,* 1997)

Test for antinuclear antibodies

In selected women, the medical history may suggest a chronic, recurrent, multisystem illness with vague, generalized signs or symptoms, such as recurrent, multiple, painful, tender, or swollen joints. In such cases, a negative antinuclear antibody result is useful in diagnosing immune thrombocytopenic purpura (ITP) if the patient's thrombocytopenic becomes chronic and resistant to treatment.

Test for antiplatelet antibodies

Assays for platelet antigen–specific antibodies, platelet-associated immunoglobulin, or other antiplatelet antibodies are available in some medical centers and certain reference laboratories. The reliability of the results of a platelet antibody test is highly specific to the laboratory used. A negative antiplatelet antibody assay result does not exclude the diagnosis of immune thrombocytopenic purpura (ITP). (Raife *et al.,* 1997) Generally this test is not required to diagnose immune thrombocytopenic purpura (ITP).

Helicobacter pyloritesting

Studies from Italy and Japanindicate that many patients who present with ITP have a strong association with H.Pylorigastric infections and their eradication helps in increased platelet counts. But it is not the case in the United States and Spain, therefore, routine testing for H. pylori infections in adults and children with ITP is not recommended. (Sundell and Koka, 2006; Inaba *et al*., 2005; Sato *et al*., 2004)

Direct antiglobulin test

If anemia and thrombocytopenic are present, a positive direct antiglobulin (Coombs) test result may help establish a diagnosis of Evans syndrome

Test for HCV screen

Thrombocytopenic is a recognized complication of HCV and according to American society of hematology (2011).All adult patients with newly diagnosed ITP should undergo screening for HCV, since the treatment of underlying etiology may alter the course of disease.

Differential diagnosis

Differential diagnosis of ITP includes both immune and non-immune causes of thrombocytopenic.

A)Drug-induced ITP

Recurrent episodes of acute thrombocytopenic not explained by other causes should trigger consideration of drug-induced thrombocytopenic. Patients should be questioned about drug use, especially of sulfonamides, antiepileptic's, and quinine. Thrombocytopenic 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 another most common cause of drug relatedthrombocytopenic among hospitalized patients.The mechanism is unique and involves formation of a heparin-PF4 immune complex (Jubelirer and Harpold, 2002; George, 2009).

B) Infectious association

i) Human immunodeficiency virus infection

Approximately 40% of patients with human immunodeficiency virus (HIV) infection develop thrombocytopenic at some time. (Stasi *et al*., 2009) HIV infection can initially manifest as isolated thrombocytopenic and is sometimes clinically indistinguishable from chronic ITP, making it an important consideration in a newly diagnosed case of thrombocytopenic. The mechanism of thrombocytopenic 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. (Moses *et al*., 1998)

ii) Hepatitis C virus infection

Hepatitis C virus (HCV) infectioncan alsocause immune thrombocytopenic. A recentstudydemonstrated the potential of the HCVcore envelope protein 1 to induce antiplateletantibodies (to platelet surface integrin GPIIIa49-66) by molecular mimicry. (Zhang *et al*., 2009) Other causesof thrombocytopenic in HCV infection may berelated to chronic liver disease, such as portalhypertension-related hypersplenism, as well as decreased thrombopoietin production. Antiviraltreatment with pegylated interferon mayalso cause mild thrombocytopenic. (Roomer *et al*., 2010)

iii) Helicobacter pylori
iv)

The association between H pylori infection and ITP remains uncertain. The prevelance of H.Pylori is varied with it being low in U.S.A and Spain while in Japan and Italy higher prevelance is seen. (Stasi *et al*., 2009) The different response may be due different H pylori genotypes: most H pyloristrains in Japan express CagA, whereas the frequency of CagA-positive strains is much lower in western countries. 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.

C)Auto-immune and other disorders

i) Lymph proliferative disorders

Secondary forms of ITP can occur in association with chronic lymphocytic leukemia, non-Hodgkin lymphoma, and Hodgkin lymphoma. These diagnoses should be considered in patients presenting with thrombocytopenic accompanied by systemic illness. ITPoccurs in at least 2% of patients with chroniclymphocytic leukemia (CLL) and is usually difficultto distinguish from thrombocytopenia secondaryto marrow infiltration or from fludarabinetherapy. (Cines *et al*., 2009) Evidence of presence of lymphoproliferative disease is necessary as the course of treatment for ITP changes. Treatment of ITP complicating CLL includes corticosteroidsand steroid-sparing agents such as cyclosporine, rituximab, and intravenous immunoglobulin. (Zent and Kay, 2010)

ii) Systemic lupus erythematosis and other autoimmune diseases

Thrombocytopenic is a frequent clinical manifestation of systemic lupus erythematosis, occurring in 7% to 30% of patients, and is an independent risk factor for death. (Hepburn *et al*., 2010) 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 over several years. Thrombocytopenic can also result from other autoimmune disorders such as antiphospholipid antibody syndromeand autoimmune thyroid diseases as well as immunodeficient states such as IgA deficiency and common variable immunodeficiency with low IgG levels.

iii) Myelodysplastic syndrome

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

D) Variants of Thrombocytopenic

i) Pseudo thrombocytopenic

Pseudo thrombocytopenic can occur if ex-vivo agglutination of platelets is induced by antiplatelet 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.

ii) Thrombotic thrombocytopenic purpura(TTP)

Thrombotic thrombocytopenic purpura presentswith thrombocytopenic, purpura, andanemia. Associated clinical abnormalities (fever, neurologicsymptoms, renal failure and the presence of fragmented red cells onblood smear help to distinguish it from ITP. Plasma exchange is the treatment of choice for TTP.

Gestational thrombocytopenic

Five percent of pregnant women develop mildthrombocytopenic (platelet counts typically> 70×10^9/L) near the end of gestation. (Burrows and Kelton, 1993) It requires no treatment and resolves after delivery. The fetus' platelet count remains unaffected. Gestational thrombocytopenic should be differentiated from the severe thrombocytopenic of preeclampsia and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), which requires immediate attention.

Treatment

The main approach towards an ITP patient solely rests on achieving adequate hemostasis rather than a normal or near normal cell count. Initial management depends upon the disease status, including, extent of bleeding, comorbidities predisposing to bleeding and complications of specific therapies. Treatment is indicated in patients with platelet counts $< 30 \times 10^9$/L or clinically significant bleeding. ITP has no cure, and relapses may occur years after seemingly successful medical or surgical management. (Sandler and Tutuncuoglu, 2004)

1. First line Drugs

A) Corticosteroids

They are considered as backbone for initial treatment if ITP. 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 40 mg daily for 4 days per month) for several cycles, have been reported to be more effective but have not been studied in head-to-head trials with oral prednisone. (Cheng *et al*., 2003)

Due to their effectiveness, low cost, and convenience of use, corticosteroids have been used in treatment of ITP. However, in most patients the platelet count decreases once the dose is tapered or stopped; remission is sustained in only 10% to 30% of cases. (Bromberg, 2006) Continuation of corticosteroids is limited by long-term complications such as opportunistic infections, osteoporosis, and emotional liability. (Guidry *et al*., 2009)

B) Intravenous Immunoglobulin's

When patients don't respond to corticosteroid therapy, intravenous immunoglobulin in a dose of (0.8-1 g/kg) is recommended 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, (Cooper, 2009) but the effect is transient and the drug requires frequent administration. It is usually well tolerated, although about 5% of patients

experience headache, chills, myalgia's, arthralgia's and back pain. Rare, serious complications include thrombotic events, anaphylaxis (in IgA-deficient patients), and renal failure.

C) Anti-D immunoglobulin

Anti-D a pooled IgG product, derived from the plasma of Rh(D)- negative donors and given only to patients who are Rh(D)-positive in a dose of (50-75 microgram/kg), has a response rates as high as 70%, with platelet effects lasting for more than 21 days. (Scaradavou *et al*., 1997) Studies have shown better results at a high dose (75 µg/kg) than with the approved dose of 50 µg/kg. (Newman *et al*., 2001) Anti-D immunoglobulin can also be given intermittently whenever the platelet count falls below a specific level (ie, 30×10^9/L). This allows some patients to avoid splenectomy and may even trigger long-term remission. Common side effects of anti-D immunoglobulin include fever and chills, which 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.

2. 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 bleeding, a combination of first-line therapies is recommended; using prednisone and intravenous immunoglobulin. (Provan *et al*., 2010) Other options include high-dose methylprednisolone and platelet transfusions, alone or in combination with intravenous immunoglobulin. (Spahr and Rodgers, 2008)

3. Second-Line Treatments

Patients who relapse and have a platelet count of less than 20×10^9/L are traditionally considered for splenectomy. More than two-thirds of patients respond with no need for further treatment. (Kojouri *et al*., 2004) 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. (Schilling, 1995)

Adherence to recommended vaccination protocols and early administration of antibiotics for systemic febrile illness reduce the risk of sepsis. (Davies *et al*., 2002) Patients are advised to receive immunization against encapsulated bacteria with pneumococcal, Haemophilus influenza type B,andmeningococci. These vaccines should be given at least 2 weeks before elective splenectomy. (Centers for Disease Control and Prevention, 2011) Treatment of patient's refractory to splenectomy is challenging and requires further immunosuppressive therapy, which is associated with an increased risk of infections and infection-related deaths. (McMillan and Durette, 2004)

4. Rituximab

Rituximab 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 published, use of rituximab in ITP reported an overall platelet response (defined as platelet count > 50 × 109/L) in 62.5% (95% confidence interval [CI] 52.6%−72.5%) carried out by Arnold and colleagues, (Arnold *et al*., 2007) (19 studies, 313 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. 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. Although this complication is rare in patients with ITP, careful monitoring is required until additional long-term safety data are available.

A single course of rituximab (375 $mg.m^2$ weekly for 4 weeks) induces a complete remission (here defined as a platelet count above 150 $x10^9$/L) in approximately 40% of patients at 1 year, one third after 2 years, and 15% to 20% at 5 years. An initial rise in platelet count often occurs within 1 to 2 weeks, suggesting an effect on platelet clearance, but more durable responses may not be observed until several months after treatment. Many patients who achieve an initial complete remission and subsequently relapse respond to retreatment. In a small, uncontrolled study, lower doses (100 mg weekly for 4 weeks) were almost as effective although the time to response was prolonged (Zaja *et al*., ?).

5. Thrombopoietin receptor agonists

In the early 1990s, recombinant thrombopoietin was tested in clinical studies. These were halted when antibodies developed to recombinant thrombopoietin cross-reacted with endogenous thrombopoietin, resulting in severe thrombocytopenic. (Li *et al*., 2001) This led to the development of non-immunogenicthrombopoietin receptor agonists that mimic the effect of thrombopoietin and stimulate the production of platelets (Table 4). In 2008, the US Food and Drug Administration approved two drugs of this class for treating ITP: romiplostim and eltrombopag. They are mainly used to treat patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulin's, 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 sustain 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.

Table 4. Thrombopoietin receptor agonists

	Rituximab	Romiplostim	Eltrombopag
Drug Class	Anti-CD20 monoclonal antibody	Thrombopoietin receptor agonist	Thrombopoietin receptor agonist
Route	I.V	Subcutaneous	Oral
Dosing	375mg/m^2 weekly x 4	1-10 mg/kg weekly	25-75mg daily
Approximate platelet count response	60%	79%	70%
Response time	1-8 weeks	1-4 weeks	2 weeks

6. Newer Agents

Additional thrombopoietin agonistsunderinvestigation include ARK-501, totrombopag, and LGD-4665. MDX-33, a monoclonal antibody against the Fc-receptor, is also being studied and it acts by preventing opsonization of autoantibody-coated platelets. (Li *et al*., 2001)

7. Third line Treatment for Refractory Cases

Patients with ITP that are resistant to standard therapies have an increased risk of death, disease, and treatment-related complications. Refractory cases are usually given combination chemotherapy. Immunosuppressant's such as azathioprine, cyclosporine, cyclophosphamide, and mycophenolatewere 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. 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 colleagues[55]reported that combined azathioprine, mycophenolate, and cyclosporine achieved an overall response (platelet count > 30×10^9/L and doubling of the baseline) in 14 (73.7%) of 19 patients with chronic refractory ITP, lasting a median of 24 months. Vinca alkaloids are also used infrequently although are inexpensive and well tolerated.

8. Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation has provided remission in limited number of patients. However, it is associated with fatal toxicities such as graft-versus-host disease and septicemia, and therefore it is reserved for severe refractory ITP with bleeding complications unresponsive to other therapies. (Arnold, 2010; Passweg and Rabusin, 2008)

Therapy for Secondary ITP

Treatments for secondary ITP vary depending on the cause of thrombocytopenic and are often more complex than therapy for primary disease. Optimal management involves treating the underlying condition (e.g., CLL or SLE). Drug-induced thrombocytopenic requiresprompt recognition andwithdrawal of the incitingagent. ITP secondary to HCV infection primarilyinvolves the use of antiviral agents to suppress viralreplication. If treating ITP is required, thenintravenous immunoglobulin is preferable toglucocorticoids because of the risk of increasingviral load with the latter. (Huhn *et al*., 2003)

Eltrombopagmay effectively increase platelet counts, allowingpatients to receive interferon therapy for HCV. (Magrin *et al*., 1994) However, a recent study raised concerns about the safety of eltrombopag due to increased incidence of portal vein thrombosis in patients with chronic liver disease. (McHutchison *et al*., 2007; US Department of Health & Human Services, 2012) Secondary ITP due to HIV infection should always be treated first with antiviral targeting HIV unless thrombocytopenic-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 pylor is recommended for patients who are positive for the organism based on urea breath testing, stool antigen testing, or endoscopic biopsies.

Pregnant patients requiring treatment should receive either corticosteroids or IVIG. For pregnant women with ITP, the mode of delivery should be based on obstetric indications.

Complications of ITP

Major complication of ITP include hemorrhages (GIT and intra cranial), severe blood loss and medication related side effects. Post splenectomy sepsis is one of the most dreadful complications of ITP therapy.

Conclusion

Primary immune thrombocytopenia (ITP) is an autoimmune disorder involving antibody and cell mediated destruction of platelets and suppression of platelet production that may predispose to bleeding. It is characterized by isolated thrombocytopenia (peripheral blood platelet count< 100x 10^9/L. ITP was initially believed to be a disorder primarily affecting women. Recent epidemiologic data suggest that the incidence in adults is approximately equal for the sexes except in the middle age when the disease is more prevalent in women. While on the other hand, ITP has a good prognosis in children. Treatment is mainly directed at achieving a safe platelet count to prevent a major bleeding event rather than correcting the platelet count to normal levels. Children without bleeding may not require therapy regardless of their platelet count. Corticosteroids, with IVIG or anti –Rh(D) if required are used to stop bleeding and increase the platelet count to safe levels. Danazol, alone or in combination with azathioprine, and dapsone have been used as steroid sparing agents. The guidelines recommended splenectomy as a second line therapy due to extensive study done over the past couple of years.

However, it should not be considered standard first line treatment in children and should be delayed for as long as possible, and should be reserved for children with severe disease that fail other types of conservative management. Rituximab and TRAs are now approved for treating adults with chronic ITP and are under study for pediatric patients. There long term safety profiles need evaluation. Refractory disease has been reported to respond to immune suppressive agents alone or in combination.

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