Review Series

blood

CLINICAL PLATELET DISORDERS

Clinical updates in adult immune thrombocytopenia

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Immune thrombocytopenia (ITP) occurs in 2 to 4/100 000 adults and results in variable bleeding symptoms and thrombocytopenia. In the last decade, changes in our understanding of the pathophysiology of the disorder have led to the publication of new guidelines for the diagnosis and management of ITP and standards for terminology. Current evidence supports alternatives to splenectomy for second-line management of patients with persistently low platelet counts and bleeding. Long-term follow-up data suggest both efficacy and safety, in particular, for the thrombopoietin receptor agonists and the occurrence of late remissions. Follow-up of patients who have undergone splenectomy for ITP reveals significant potential risks that should be discussed with patients and may influence clinician and patient choice of second-line therapy. Novel therapeutics are in development to address ongoing treatment gaps. (*Blood*. 2017;129(21):2829-2835)

Introduction

Immune thrombocytopenia (ITP) is an acquired thrombocytopenia, defined as a platelet count $<100 \times 10^9$/L, and caused by immune destruction of platelets.[1] It occurs in both adults and children, with a multimodal incidence with 1 peak in childhood and second and third peaks in young adults and the elderly. The underlying disease process in childhood ITP and adult ITP may be fundamentally different, as evidenced by the rate of chronic ITP in these patient populations.[2] Although the majority of children have self-limited disease, in adults, ITP is more often a chronic disorder.

In 2010 to 2011, the American Society of Hematology (ASH)[3] and an international consensus report[4] both published guidelines for the diagnosis and management of ITP. In 2009, an International ITP Working Group (IWG) also published recommendations for standardization of definitions and terminology to allow for alignment of research studies and eventually aid in management of patients with ITP.[1] The IWG defined the abbreviation in common use (ITP) to be Immune Thrombocytopenia (neither Idiopathic nor Purpura) because the pathophysiology is better understood and the majority of both adult and pediatric patients do not present with purpura,[5] even if they have petechiae and bruising.[1] The IWG also removed the term "acute" ITP, as this diagnosis can only be made in retrospect, after the patient has recovered from the thrombocytopenia. Instead, they proposed standardized terminology, which is outlined in Table 1.

Since the publication of these seminal papers to help define and guide the diagnosis and management of ITP, research has continued into optimal therapy, diagnostic evaluation, and prognostic indicators for adults with ITP. New evidence suggests that some populations of patients may be safely observed, and the development of the thrombopoietin receptor agonists (TPO-RA) have changed the landscape of management of chronic disease. The purpose of this review is to summarize the recent clinical development in diagnosis and management of adults with ITP.

Epidemiology of ITP

The incidence of primary ITP in adults is 3.3/100 000 adults per year with a prevalence of 9.5 per 100 000 adults. There is a predilection for female patients in younger adults, but the prevalence of ITP in men and women is fairly even in the elderly (>65 years).[6-8] A recent meta-analysis looked at risk of thrombosis in adult patients with ITP and concluded that patients with ITP have a higher risk of thromboembolism (TE) after ITP diagnosis of 1.6 (1.34, 1.86) based primarily on 2 large cohort studies.[9] Interestingly, this same analysis showed a risk of TE prior to the ITP diagnosis in these patients with a prevalence of ~8%.[9] Secondary ITP (ITP associated with other disorders) makes up ~20% of ITP diagnoses[10] and is part of the reason that some patients undergo extensive diagnostic evaluations at the time of diagnosis. However, the prevalence of autoimmune disease in the ITP population without additional signs/symptoms was quite low in the largest population-based study examining ITP by using the United Kingdom General Practice Research Database, where it was 8.7%.[7] In a French epidemiological study, the incidence of secondary ITP was 18%.[8] Population studies also suggest an increased mortality for patients with ITP compared with the general population, with risk of mortality likely related to severity of disease. A Danish study reported a 1.5-fold higher mortality in ITP patients compared with the general population, with significant increased risk of bleeding and infection (relative risk [RR], 2.4 and 6.2, respectively) as well as hematologic malignancy (RR, 5.7).[11] Subsequent studies have not confirmed the increased risk of malignancy.[12]

Pathophysiology

In the last several years, our understanding of the pathophysiology of ITP has significantly improved. It is now clear that Primary ITP is an acquired immune disorder where the thrombocytopenia results from

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pathologic antiplatelet antibodies,[13] impaired megakaryocytopoiesis,[14] and T-cell–mediated destruction of platelets,[15] with each pathologic mechanism playing varying roles in each patient. Secondary ITP is associated with other underlying disorders, such as autoimmune disease (systemic lupus erythematosus or rheumatoid arthritis), HIV, *Helicobacter pylori*, or underlying immune dysregulation syndromes, such as common variable immunodeficiency.[10] The majority of adults with ITP (~80%) have primary ITP. Treatment and pathophysiology of secondary ITP are generally based on the underlying disorder and are not the subject of this review, although some patients with secondary ITP and severe disease may require ITP-like therapy to stabilize the platelet count while other treatment is initiated.

As many as 60% to 70% of patients with ITP have platelet-specific immunoglobulin G antibodies.[16] These are generally directed at the most abundant platelet surface glycoproteins, GPIIb/IIIa and GP1b/IX/V.[17] The type of epitope targeted by these autoreactive antibodies may influence the course of the disease, and some research has suggested that these different types of antibodies may differentially alter clearance,[18] inhibit megakaryopoiesis,[19] or induce platelet apoptosis.[20] In addition, the presence of antiplatelet antibodies has been associated with increased risk of thrombosis.[21,22]

Some patients who do not have antiplatelet antibodies will have abnormal T cells that result in platelet destruction,[23] whereas in other patients it is T-cell dysregulation that results in autoantibody production.[24] Cytotoxic $CD8^+$ T cells have been found in some patients with ITP,[25,26] which are able to directly lyse platelets and accumulate in bone marrow, potentially impairing platelet production.[27] In addition, data suggest that patients with active ITP have decreased regulatory T-cell populations (which may help explain loss of tolerance), abnormal cytokine profiles,[28-30] and an altered T helper 1/T helper 2 balance,[31] all of which suggest underlying immune dysregulation and present possible targets for novel therapies.

Finally, evidence suggests that platelet production is impaired in many ITP patients. The megakaryocytes of patients with ITP are not normal, with electron microscopic changes showing abnormal apoptosis and impaired megakaryocyte growth in cell culture with ITP plasma.[32,33] Furthermore, serum thrombopoietin levels in patients with ITP are minimally elevated, if at all. The success of the TPO receptor agonists validates these observations to some degree.[34]

Several recent studies have also focused on the role of the Ashwell-Morrell receptor (AMR) system in the liver as an additional mechanism by which platelet number is regulated, driven by platelet clearance.[35] Under nonpathologic conditions, platelets that have been in the circulation longer (have senesced) will lose sialic acid on their surface.[36] These platelets are then recognized by the AMR and cleared from circulation. This clearance by the AMR drives TPO messenger RNA production.[37] Surface expression of sialic acid is regulated by intrinsic sialidases,[38] and these molecules have been targeted in other settings to treat viral infections. A single small study and 2 case reports have looked at oseltamivir phosphate (a sialidase inhibitor developed to treat influenza) as a potential therapeutic option in ITP, further examining the role of this platelet clearance mechanism in ITP.[39-41]

Diagnosis of ITP

Significant progress has been made in recent years in harmonizing definitions and terminology for ITP to provide recommendations that are applicable to many patients with ITP. However, significant gaps in available data (including lack of data and/or consensus on second-line therapies and optimal management of chronic ITP) still exist and lead to uncertainty in optimal management of patients. Diagnosis of ITP is generally made by review of peripheral smear and evaluation of history and examination of the patient. The IWG recommended a few additional tests for all patients with ITP (Table 2), including *H pylori* testing, HIV, and hepatitis C testing as well as a direct antiglobulin test and blood type.[4] The ASH guidelines recommend similar testing for adults with ITP except for *H pylori* testing (only recommended for some geographic areas and if treatment of eradication is possible). The recommendations from the IWG is to do bone marrow examinations in patients >60 years old with newly diagnosed ITP, whereas the ASH guidelines suggest that bone marrow may not be necessary in any patient population, as supported in some population studies.[42] Therefore, the majority of patients may have the diagnosis of ITP established with careful history and physical examination as well as review of the peripheral smear and minimal further testing. Additional "screening" testing for immunodeficiency (with immunoglobulin levels) and other autoimmune disease is rarely helpful in the absence of symptoms in adults with uncomplicated newly diagnosed ITP and, in fact, a positive antinuclear antibody in the absence of other features of autoimmune disease is rarely predictive of development of other disease.[43] Although some studies in children have suggested that a positive antinuclear antibody may be associated with increased risk of chronic or refractory disease, studies in adults are limited and do not demonstrate a clear association with response to treatment or chronicity.[43-45]

Antiplatelet antibody testing is not indicated for the diagnosis of ITP in the majority of patients, and both the ASH and the IWG guidelines do not recommend routine testing of antiplatelet antibodies for the diagnosis of ITP.[3,4]

Table 1. Descriptive terminology for ITP according to the IWG

Term	ITP description
Newly diagnosed	<3-mo duration
Persistent	3-12-mo duration
Chronic	>12-mo duration
Severe	Clinically relevant bleeding of sufficient magnitude to mandate treatment or requiring additional interventions or increase in drug dose
Refractory	Presence of severe ITP after splenectomy
Response	Platelet count $\geq 100 \times 10^9$/L measured on 2 occasions >7 d apart
Response	Platelet count $\geq 30 \times 10^9$/L and a greater than twofold increase in platelet count from baseline measured on 2 occasions >7 d apart

Bleeding risk

Understanding bleeding risk and underlying determinants of bleeding is important in order to help recognize patients that will require pharmacologic therapy even at higher platelet counts. Previous studies have suggested that low platelet counts, increased patient age, use of concurrent medications, and male sex are associated with increased bleeding risk. Melboucy-Belkhir and colleagues examined risk factors in a cohort of patients with ITP and intracranial hemorrhage (ICH) and found that, in their patients, 37% presented with ICH during the first 3 months after diagnosis.[46] They noted that those patients with ICH had more bleeding symptoms, including more hematuria and more visceral hemorrhage compared with control ITP patients, and were more likely

Table 2. Utility of various evaluations in the diagnosis of ITP

Basic evaluation	Tests of potential utility	Tests of unproven benefit
Patient/family history	Glycoprotein-specific antibody	Thrombopoietin
Physical examination	Antiphospholipid antibodies (including anticardiolipin and lupus anticoagulant)	Reticulated platelets
Complete blood count and reticulocyte count	Antithyroid antibodies and thyroid function	Platelet-associated immunoglobulin G
Peripheral blood film	Pregnancy test in women of childbearing potential	Bleeding time
Quantitative immunoglobulin level measurement*	Antinuclear antibodies	Platelet survival study
Bone marrow examination (in selected patients)	Viral PCR for parvovirus and CMV	Serum complement
Blood group (Rh)		
Direct antiglobulin test		
H pylori†		
HIV†		
HCV†		

Adapted from Provan et al.[4]

CMV, cytomegalovirus; HCV, hepatitis C virus; PCR, polymerase chain reaction; Rh, rhesus.

*Quantitative immunoglobulin level measurement should be considered in children with ITP and is recommended in those children with persistent or chronic ITP as part of reassessment evaluation.

†Recommended by the majority of the panel for adult patients regardless of geographic location.

to have head trauma, and 74% of patients had received treatment prior to the ICH event.[46] These results are consistent with other studies that have shown that prior significant hemorrhage is a risk for subsequent ICH.[47] They did not find an increased risk in men. Overall, studies report a risk of ~1.5% to 1.8% for ICH in adult patients[48,49] (higher than the reported rate of ICH in children, <1% in most studies),[48] with the most recent prospective cohort study from France demonstrating that 4.9% of patients had visceral bleeding (although the incidence of ICH was not reported).[50]

Altomare and colleagues examined a large administrative database to try to determine the rate of bleeding in adults with primary ITP.[51] In this study, the investigators defined bleeding-related events (BREs) as actual bleeding or use of rescue therapy, which may overestimate the risk of bleeding because physicians often treat for indications other than bleeding symptoms. The investigators, nonetheless, described a cohort of 6651 patients followed for 13 046 patient-years. In this cohort, the rate of BRE was highest in newly diagnosed ITP and lowest in chronic ITP with an overall rate of 1.08 (95% confidence interval [CI], 1.06-1.10) BRE per patient-year (2.67 per patient-year in newly diagnosed; 0.73 per patient-year in chronic). Fifty-eight percent of the BRE were defined only by the use of rescue medication, and only 2% of the BRE contained a diagnostic code for bleeding and use of rescue medication,[51] consistent with other recent studies examining physician practice/guideline concordance. This database review was unable to give good information about ICH, but suggested a remission rate of ~25%, consistent with previously reported remission rates of ~30%.[8,52]

It seems reasonable to assume that those patients who have significant bleeding symptoms may have different platelets than those who do not have bleeding. This question was addressed in a study that examined platelet function in adult ITP patients to try to determine whether this correlated with bleeding risk.[53] Previous studies have suggested that measuring platelet function may help define patients at highest risk of bleeding.[54] In this new study, Middelburg and colleagues corrected platelet function for quartile of platelet count, using $<32 \times 10^9$/L as the lowest cohort and $>132 \times 10^9$/L as the top quartile. They demonstrated that increased platelet reactivity (as measured by flow cytometry) was associated with decreased risk of bleeding but particularly for those patients with the lowest platelet counts.[53] Further studies in a larger cohort are needed to confirm this association.

First-line management

Prednisone 1 mg/kg/d for 2 to 4 weeks has been the standard first-line treatment for many years.[55,56] However, recent work has investigated whether intensification of treatment, in adults with ITP, by using high-dose dexamethasone (HDD), rituximab, or the TPO-RA may result in increased remission rates. A recent randomized clinical trial compared HDD as a pulse (40 mg/d for 4 days) with standard prednisone therapy. In this randomized trial, patients received 6 treatment cycles of 21 days of HDD (dosed at 0.6 mg/kg/d) vs standard prednisone therapy of 1 mg/kg/d for 2 weeks and then tapered.[56] In an intention-to-treat analysis of the 26 enrolled patients, the complete response rate (platelet count $\geq 150 \times 10^9$/L) was higher in the HDD arm with 77% of patients achieving a "long-term" remission (median follow-up was 46 months with a range of 17-148).[56] Data from other studies suggest that repeated dosing of HDD (as was done in the study by Matschke et al) may be better at inducing long-term remission than a single cycle.[57,58] Another randomized trial of HDD every 14 days for 3 cycles vs prednisone 1 mg/kg/d × 4 weeks is currently underway (ClinicalTrials.gov identifier NCT00657410).

Two clinical trials have examined rituximab in combination with HDD in newly diagnosed patients with ITP vs HDD alone showing that the remission rate was higher in patients treated with the combination at 6 months (63 vs 36%[59] and 58 vs 37%[60]) and at 1 year (53 vs 33%).[60] However, at 3 months, there was no demonstrable difference in remission rates between HDD alone or in combination with rituximab.[47] Improved remission rates occurred at the cost of increased grade 3 and 4 toxicity.[59,60] Subsequently, some investigators have combined HDD with lower-dose rituximab (100 mg × 4 doses) and additional immunosuppressive medications (cyclosporine) to try to improve long-term remission rates. One study treated 20 patients with 12-month treatment-free survival of adults with chronic ITP of 75% (95% CI, 49% to 88%), with 30% of patients demonstrating complete response (platelet count $>100 \times 10^9$/L) at 6 months.[61] More data with longer follow-up to determine the efficacy of this approach are needed.

Two small studies have examined TPO-RA in newly diagnosed patients with ITP. The first study was a 12-month study of romiplostim in 75 patients with ITP for <6 months where the romiplostim was tapered if the platelet count was $\geq 50 \times 10^9$/L after the 12 months.[62] In this study, 32% of patients met the primary endpoint: platelet count $\geq 50 \times 10^9$/L off therapy for 24 consecutive weeks after

discontinuation.[62] A second study looked at the combination of HDD × 4 days followed by eltrombopag 50 mg/d for days 5 to 32. There were 12 adults in this study, and 9/12 patients (75%) had a platelet count ≥30×10^9/L at 6 months and 8/12 (67%) at 12 months.[63] These preliminary data are interesting, but additional studies with more patients are needed to evaluate the long-term outcomes and better characterize toxicities with these alternative regimens.

Second-line therapy

At the time of the publication of the guidelines (2010-2011), there were little data available on the long-term safety and efficacy of many second-line therapies for ITP, in particular, for the TPO-RA. In part because of this, splenectomy was recommended in the ASH guidelines as second-line therapy for ITP with the recommendation to try to delay splenectomy to 6 months to 1 year after diagnosis.[3] The International Consensus group on ITP listed additional alternatives to splenectomy as acceptable second-line therapies, however.[4] For decades, surgical splenectomy was the treatment of choice; however, recent data suggest that <25% of patients with ITP undergo splenectomy,[64] despite 5-year response rates of 60% to 70%.[65,66] Risk of infection (5- to 30-fold increase in the first 90 days and 1- to 3-fold life-long increased risk of invasive bacterial infection and sepsis), risk of thrombosis (>30-fold compared with the general population), as well as reports of pulmonary hypertension and immediate postoperative complications may have contributed to decreased splenectomy rates. Thai and colleagues examined the long-term complications of splenectomy in ITP patients in particular.[12] In that study of 93 patients with ITP, 17% of patients had early postoperative complications, including hemorrhage, infection, and venous thromboembolism (VTE). After a median follow-up of 192 months (range, 0.5-528), 52% had a sustained response and 80% were alive. The rate of VTE in this study was 16% in the splenectomy group vs 2% in the control group.[12] A second recent long-term follow-up study of 174 adult patients who underwent splenectomy had a 2.9% rate of VTE in their cohort.[67] The smaller study also suggested an increased risk of cardiovascular events compared with control patients (12% vs 5%), although this did not reach statistical significance ($P = .143$).[12] The rates of infection were not significantly different between splenectomy and control; however, the rate of bacterial infection was higher in the postsplenectomy group and were more likely to result in hospitalization (all of the postsplenectomy patients) with an increased risk of sepsis (19%), with 3 fatalities (vs 0 for the control group).[12] Other studies have suggested an overall risk of mortality from overwhelming postsplenectomy infection of 0.73 per 1000 patient-years.[66] These data support the overall assessment that splenectomy is relatively safe, but not without risk or potential long-term complications.

Several studies have examined the efficacy of rituximab as an alternative to splenectomy in patients with ITP. Using the standard dosing of 375 mg/m^2 per dose × 4 doses results in initial response rates of 40% to 60%.[55] Unfortunately, the long-term response rates with rituximab are not as good as splenectomy with sustained response of ~20% at 5 years post initial rituximab treatment.[68] A recent trial in 112 adult patients comparing standard dosing of rituximab and placebo showed no difference in complete remission at 1.5 years.[69] Many patients who initially respond to rituximab can respond to subsequent doses; however, the safety and efficacy of repeated dosing of rituximab have not been systematically evaluated.

The most recent clinical development that has changed the landscape of second-line ITP therapy is the TPO-RA (romiplostim and eltrombopag are both US Food and Drug Administration approved for adults with chronic ITP, and eltrombopag is approved for use in children as well). A recent meta-analysis of eltrombopag in ITP examined the 6 randomized controlled trials demonstrating that eltrombopag significantly improved platelet counts (RR, 3.42; 95% CI, 2.51-4.65) and decreased incidence of bleeding (RR, 0.74; 95% CI, 0.66-0.83).[70] In the reported clinical trials of both TPO-RA, >80% of patients had at least 1 platelet count >50×10^9/L, even among highly refractory and multiply treated patients.[71] In clinical practice, the response rate is somewhat lower (74% to 94%), reflecting perhaps the increased heterogeneity of a nonclinical trial population.[72-74] The literature also suggests that patients who are intolerant of 1 TPO-RA can successfully switch to the other.[75]

Long-term follow-up data are now available for both TPO-RAs for adult patients. The EXTEND trial (Eltrombopag eXTENDed dosing) has published data for 3-year follow-up of patients in an open-label extension study for continued dosing of eltrombopag in patients with chronic ITP.[76] They reported on 299 patients, 104 of whom had data available for ≥2 years of follow-up. The overall response was 85%, with median platelet counts increasing to >50×10^9/L by 2 weeks and remaining increased for the duration of the study. Sixty-two percent of patients enrolled had platelet counts ≥50×10^9/L for >50% of weeks on study.[76] The most common adverse events (AE) reported were mild (grade 1 or 2) and consisted of headache, nasopharyngitis, upper respiratory infection, and fatigue. Thrombocytopenia, increased alanine aminotransferase, and fatigue were the most common grade ≥3 AEs. There was a 3% rate of VTEs in the study cohort as well as 10% overall rate of hepatotoxicity and 5% rate of cataracts (13 of the 15 patients with cataracts had previously been on steroids). The rate of thromboembolic events was therefore 3.17 per 100 patient-years. An update to these data was recently presented at the ASH meeting and showed (at 5 years) that 15% of patients had hepatic enzyme elevation and 6.3% of patients had a thromboembolic event.[77] Bone marrow reticulin fiber was assessed in 147 bone marrows and showed 8% of patients to have grade 2 reticulin fiber formation (without collagen fiber formation). Follow-up bone marrows showed 8/11 with no change in grade, 1/11 with an increase (from grade 1 to grade 2), and 2/11 with a decrease in grade at ≥2 years of follow-up.[76]

An integrated analysis of TPO-RAs in ITP by Cines and colleagues reported on 994 patients from 13 clinical trials treated with romiplostim.[78] In this analysis, the median study duration was 75 to 77 weeks (depending on splenectomy status), and the most frequent dose was 5 μg/kg and 4.6 μg/kg (postsplenectomy and unsplenectomized, respectively). The most frequent AEs were headache, contusion, epistaxis, and nasopharyngitis. The rate of TE was 5.5 per 100 patient-years in both romiplostim- and placebo-treated patients (the rate was the same) and occurred over a wide range of platelet counts.[78] The incidence of bone marrow reticulin fiber formation has been reported to be ~3% for romiplostim with higher rates and grades in patients who exceed the currently recommended maximum dose of 10 μg/kg. The incidence of reticulin fiber formation has been calculated to be 1.3/100 patient-years.[78]

Several novel therapies are on the horizon for the management of ITP, and other immunosuppressive medications have been studied in small cohorts of patients.[79] These therapies include antibodies targeting the CD40-CD154 interaction between B and T cells,[80,81] treatments targeting the Fc receptor[82] and the neonatal Fc receptor, targeting downstream signaling after crosslinking of receptors caused by antibody binding (Syk kinase in particular),[83] and novel agents to increase platelet production, including new thrombopoietin receptor agonists and amifostine.[84,85] For patients who fail conventional first- or second-line therapies, there are novel therapies in development and under study based on our improving understanding of the pathophysiology of this complex disease.

ITP in pregnancy

Approximately 7% of pregnancies are complicated by thrombocytopenia (defined as platelet count $<150 \times 10^9$/L), the majority of these due to incidental thrombocytopenia of pregnancy (also called gestational thrombocytopenia).[86] ITP affects 1 to 10 in 10 000 pregnancies[87] and requires treatment in ~30% of cases.[88] As in nonpregnant patients, ITP may be primary or associated with an underlying autoimmune condition.[89] It may present for the first time or be exacerbated during pregnancy and is the most common cause of thrombocytopenia in the first trimester. Severe maternal or neonatal bleeding is rare when these pregnancies are managed by an experienced, multidisciplinary team. However, a survey of women with ITP reported that as many as 28% of women (14/50) were advised not to become pregnant.[90] Despite the rarity of bleeding complications, women with the diagnosis of ITP prior to pregnancy appear to have a higher incidence of fetal loss (11.2% vs 3.9% in women diagnosed during pregnancy) and low birth weight for gestational age (17.9% vs 9.7%).[90] A higher incidence of premature birth has also been reported.[90,91]

Therapy does not appear to affect the neonatal risk of thrombocytopenia, and therefore, treatment is directed toward maintaining a safe platelet count in the mother, generally considered 30×10^9/L, until closer to term when delivery must be anticipated. First-line therapy recommended by both ASH[3] and IWG[4] guidelines is with either intravenous immunoglobulin (IVIg) or corticosteroids, and they appear to be similarly efficacious in increasing platelet counts. Toxicity for both the mother and the fetus is relatively mild, but resultant weight gain, hyperglycemia, and hypertension may be problematic for the pregnancy. In 1 study of 235 ITP pregnancies, less than half of the patients required therapy.[91] Of 91 pregnancies requiring treatment, 47 patients were treated with IVIg and 51 with corticosteroids. There were no differences between treatment groups with regard to platelet count at delivery, antepartum or postpartum hemorrhage, or need for predelivery platelet transfusion; women who were treated had higher platelet count at delivery and less need for platelet transfusion compared with untreated women. There was less postpartum hemorrhage in women who were treated for the ITP compared with women who were not treated. There were no differences between the infants born to treated vs untreated women. Maternal therapy and platelet count appear to be poor predictors of the neonate's platelet count, the only reliable predictor the platelet count and course of thrombocytopenia of that of an older sibling.[89]

Patients refractory to first-line treatment may benefit from a combination of IVIg and corticosteroids.[92] Options for second-line therapy are limited by fetal risk. Azathioprine may be used as a steroid-sparing agent. Use of anti-RhD immune globulin, cyclosporine, and rituximab has been reported with good outcomes but cannot be routinely recommended. There are several reports of romiplostim therapy in severe refractory thrombocytopenia in pregnancy, but further evidence of its safety in pregnancy in required.[93] A recent report of the use of a recombinant human thrombopoietin in 60 pregnancies is promising.[94]

The optimal platelet count at delivery has not been established. A platelet count of 75 to 80×10^9/L in the absence of other hemostatic abnormalities is generally recommended by most guidelines.[95] For uncomplicated deliveries, a platelet count of 50×10^9/L is generally adequate and safe for cesarean section, should it become necessary.[96] The risk of complications with the use of neuraxial anesthesia (epidural infusion catheters) in parturients with thrombocytopenia is related to the degree of thrombocytopenia, but a recent study examining risk in 499 thrombocytopenic pregnancies demonstrated safety (risk of 0% to 0.6% of complications) at platelet counts between 75 and 80×10^9/L.[97] In contrast, general anesthesia in the same study was associated with a 6.5% risk of complications.[97] Mode of delivery should be based on obstetrical indication, as the risk of ICH is low, generally <1%. Most reports have found that severe ($<50 \times 10^9$/L) thrombocytopenia in the neonate is uncommon; however, a recent report suggests the incidence may be as high as 30%.[98] Platelet counts generally reach a nadir 2 to 5 days postdelivery, so the neonate should be carefully monitored. Treatment of the thrombocytopenic neonate consists of IVIg, sometimes accompanied by platelet transfusions.

Conclusions

Since the development of guidelines for the diagnosis and management of ITP, emerging data on the use of second-line medical therapies to manage patients requiring pharmacologic intervention have resulted in a decrease in rates of splenectomy. Clinical practice is still lagging behind guidelines in following diagnostic evaluations, but has moved beyond those published guidelines in the use of second-line therapies to minimize risks and side effects while providing treatment options with reasonable chances of success. New guidelines will need to address this emerging body of information, and future clinical trials will examine alternative therapies now in development.

Authorship

Contribution: M.P.L. reviewed the literature and developed the manuscript; T.B.G. reviewed the literature and provided substantial editing of the manuscript.

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