ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Updated Recommendations for the Treatment of Immune Thrombocytopenia

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H&O Briefly, what is immune thrombocytopenia?

JC Immune thrombocytopenia (ITP) is an immunologically mediated bleeding disorder in which autoantibodies against platelet antigens cause premature platelet destruction that leads to thrombocytopenia.

H&O How can physicians determine whether a patient has primary or secondary ITP?

JC ITP is a diagnosis of exclusion and clinical acumen. No sensitive or specific diagnostic test is available. Physicians must suspect ITP and rule out other potential causes of thrombocytopenia. The history, physical examination, complete blood cell count with leukocyte differential, and examination of the peripheral smear are the pillars of the workup. The results of these assessments direct further testing. The clinical history should include questions about recent infectious symptoms, potentially causative medications, and stigmata of other systemic conditions, such as liver disease, lymphoproliferative disorders, and rheumatologic disorders. Screening for HIV and hepatitis C is recommended as part of the initial workup in at-risk populations. Additional testing, based on clinical judgment, may include viral serologies, antiphospholipid antibodies, antinuclear acid antibodies, thyroid function tests, a Coombs test, *Helicobacter pylori* testing, a disseminated intravascular coagulation panel, tests for bleeding disorders such as type 2B von Willebrand disease, and quantitative immunoglobulins.

Routine bone marrow biopsies are no longer recommended, although some physicians will choose to perform this procedure in patients older than age 60, when the risk for myelodysplastic syndromes increases. Bone marrow biopsies are indicated if the patient has other cytopenias, suspicious findings on the peripheral smear, or isolated thrombocytopenia with other clinical features associated with bone marrow failure syndromes.

Although antiplatelet antibody testing is available, it is not recommended in the evaluation of ITP because it has not been shown to be sensitive or specific. Antiplatelet antibody testing neither confirms nor excludes the diagnosis. Approximately 50% of patients with ITP have antiplatelet antibodies, and they may also be detected in individuals with other causes of thrombocytopenia. The presence or absence of antiplatelet antibodies does not correlate with outcomes.

H&O When is treatment required for ITP?

JC The decision to start treatment in adults with ITP is guided by the platelet count and symptoms of bleeding. ITP is a chronic condition. Treatment is not curative, so even when remission is achieved, relapses may occur, sometimes years later. The goal of therapy is to reduce the risk for bleeding so patients can live effectively normal lives. Interestingly, the risk for bleeding is generally lower in ITP than in other disorders causing thrombocytopenia. Even when patients have severely low platelet counts, they most often present with only minor symptoms of bleeding, such as acute petechiae or purpura. The bleeding is generally not life-threatening. The reason for this is still something we are trying to understand. That said, great heterogeneity is found among adults with ITP. Death from hemorrhage is rare in this disease, but it does happen.

A platelet count of 20,000/µL to 30,000/µL is the commonly accepted threshold below which major bleeding may occur. The risk is greatest when the platelet count falls even further, below 10,000/µL. Other patient factors, such as age, medications, and comorbidities, contribute to the risk for bleeding. The current 2019 guidelines from the American Society of Hematology (ASH) recommend treatment in adults with newly diagnosed disease who are having clinically important bleeding. Per the ASH guidelines, treatment is also recommended for patients with severe thrombocytopenia (platelet count <30,000/µL) even if they are not bleeding or have only minor symptoms of bleeding. Individual treatment decisions for patients with higher platelet counts are made on the basis of patient-specific factors and history of bleeding. For example, if a patient is undergoing a procedure that requires a higher platelet count for safety, then that patient needs to be treated. Similarly, because of the low certainty of the evidence, some individuals with platelet counts between 20,000/µL and 30,000/µL may be simply observed closely.

H&O How effective is treatment?

JC ITP is a treatable chronic disease. Because treatment is generally not curative and relapses can occur years later, the goal of therapy is to stabilize the platelet count in a safe range, not necessarily to normalize the count. A response is achieved in the majority of patients, although some may require multiple rounds of therapy over time. Patients whose platelet counts are greater than 30,000/µL to 50,000/µL may be regularly monitored, and because drops in platelet counts can be precipitous, they should also receive counseling about signs and symptoms that require urgent evaluation.

H&O What changed in last year's guidelines from ASH?

JC Corticosteroids remain the frontline therapy of choice in adults with newly diagnosed ITP, but now a shorter duration of therapy—6 weeks or fewer—is recommended in place of the previously recommended longer courses plus taper. This new recommendation is based on the desire to minimize exposure to and the side effects of long-term steroid use, with the opinion that patients who do not respond by 6 weeks may be less likely to achieve a significant response beyond that time.

Intravenous immunoglobulin (IVIG) and anti-D therapy are still frontline options for patients in whom corticosteroids are contraindicated. IVIG also can be used in combination with corticosteroids should a faster response time be important.

The recent ASH guidelines also moved thrombopoietin receptor agonists into a more up-front setting according to the response rates at 1 month and the durability of the responses. Other second-line treatment options are rituximab and splenectomy.

H&O When should physicians use rituximab as second-line treatment?

JC Rituximab is a chimeric monoclonal anti-CD20 antibody that eliminates B cells by triggering apoptosis, antibody-dependent cell-mediated cytotoxicity, and complement-mediated lysis. Approximately two-thirds of patients with ITP show a response at 1 month of second-line rituximab, although that does not always last—the rate of durable responses is about 20% to 39%. The remission rate is 23%. Compared with other second-line therapies, splenectomy offers a high response rate of 86% at 1 month, and 53% of the responses are durable. Thrombopoietin receptor agonists have a 65% response rate at 1 month, with 63% of the responses durable. However, rituximab has a favorable safety profile compared with surgery, and some patients and their physicians put a premium on avoiding surgery. Additionally, rituximab is a time-limited therapy, as opposed to the thrombopoietin receptor agonists.

As a side note, frontline rituximab has also been studied in combination with dexamethasone. In a phase 3 study published in *Blood* in 2013 by Gudbrandsdottir and colleagues, patients who were randomly assigned to receive rituximab in combination with dexamethasone had a better response rate than did those who received dexamethasone alone (58% vs 37%, respectively; P=.02). Patients in the rituximab/dexamethasone group also experienced a longer time to relapse and a longer time to next rescue therapy. Grade 3/4 toxicity was more frequent in the combination arm than in the dexamethasone-alone arm, however. The use of rituximab in first-line treatment also increases costs and requires more health care resources. For these reasons, the routine use of rituximab in frontline treatment is not recommended.

H&O What should hematologists know about splenectomy in ITP?

JC Splenectomy is the surgical removal of the site where antibody-coated platelets undergo phagocytosis by the reticuloendothelial system. Furthermore, the spleen may also be the location of the lymphocytes responsible for producing these aberrant autoantibodies, explaining the procedure's efficacy.

Splenectomy can be either a laparoscopic procedure or open surgery; the 2 techniques are equally effective. It

is best done at a center of excellence, particularly when the laparoscopic technique is used.

In accordance with the current ASH guidelines, splenectomy is used in second-line treatment when ITP persists and is corticosteroid-refractory or -dependent for at least 3 months. Before surgery, patients need to have their platelet counts optimized; they may be ineligible for splenectomy if their platelet count is too low or if they have significant comorbidities. They also must be vaccinated against pneumococcus, *Haemophilus influenzae*, and meningococcus at least 2 weeks but preferably at least 10 to 12 weeks before surgery.

Splenectomy is highly effective as second-line treatment. The response rate is as high as 88%, and up to 68% of individuals experience remission according to a 2004 article by Kojouri and colleagues in *Blood*. Even when the surgery is effective, however, relapses can still occur.

Splenectomy carries significant perioperative risks. Complication rates are approximately 9% to 10% with the laparoscopic technique and 12% to 13% with the open technique. The risk for infection immediately after surgery is approximately 10%, and the lifetime risk for infection and sepsis from encapsulated organisms is also increased. In addition, splenectomy carries a risk for thrombosis, cardiovascular morbidity, and pulmonary hypertension. Meanwhile, we have reasonably good medical alternatives to this surgery. For all of these reasons, and because spontaneous remission can occur within 6 to 12 months after the diagnosis, the guidelines suggest delaying splenectomy for 6 months to a year. In fact, the guidelines recommend rituximab over splenectomy as second-line treatment.

H&O Is dexamethasone considered preferable to prednisone?

JC High-dose dexamethasone is an excellent choice for the treatment of ITP and may be preferable to prednisone in many instances, especially when severe thrombocytopenia is present. Data from randomized trials (including a 2016 study by Wei and colleagues and a 2016 meta-analysis by Mithoowani and colleagues) comparing pulse dexamethasone and prednisone found that high-dose dexamethasone, 40 mg/d for 4 days, produces a better time to response, response rate, and remission rate than standard-dose prednisone within the first 1 to 2 weeks. However, no clear benefit of dexamethasone over prednisone exists in regard to durability or to responses at 1 and 6 months. Repeated pulses of dexamethasone may be needed. Data from these trials have suggested that patients experience less bleeding with dexamethasone than with prednisone, but other trials have found no difference. The safety profile of dexamethasone is at least comparable if not favorable, and the lower number of days on corticosteroid therapy is valued because of the cumulative toxicity.

However, heterogeneity is found among clinical trials in regard to the specific corticosteroid doses and schedules, and to the number of cycles of high-dose dexamethasone used as well as the definition of remission. As a result, the ASH guidelines express a low level of confidence that high-dose dexamethasone improves the rate of remission. In addition, standard prednisone treatment with a subsequent taper has been associated with greater platelet stability than has treatment with dexamethasone pulses.

> Refractory, nonresponsive disease should always cue physicians to reconsider and reassess the diagnosis of ITP, to make sure alternative causes of thrombocytopenia are not present.

H&O What is the recommended treatment for acute catastrophic bleeding in ITP?

JC Patients with thrombocytopenia who are admitted to the hospital with acute catastrophic bleeding are treated emergently with therapies to (1) control the rate of platelet destruction and (2) supplement the platelet count. Acute medical therapy is initiated immediately, with concomitant corticosteroids in combination with IVIG. Dexamethasone is frequently selected over prednisone because it improves the time to response. These patients should receive platelet transfusions as needed for acute bleeding or bleeding at a critical site, such as intracranial hemorrhage, with the goal of bringing the counts up to the target range. If the patient is on long-term ITP therapy, such as a thrombopoietin receptor agonist, this is generally continued and adjusted. Meanwhile, standard critical care and supportive care procedures are performed, such as erythrocyte transfusions, and control of the source of bleeding should be sought through endoscopy, interventional radiology, or surgery, as needed. Adjunct hemostatic therapies—for example, antifibrinolytic agents—may also

be employed for bleeding that continues despite the aforementioned ITP therapies and platelet transfusions.

H&O How is refractory ITP defined, and what is the best way to treat it?

JC Refractory ITP, as defined by Rodeghiero and colleagues, is disease that does not respond to or relapses following splenectomy, and that requires treatment to reduce the risk for clinically significant bleeding. Refractory, nonresponsive disease should always cue physicians to reconsider and reassess the diagnosis of ITP, to make sure alternative causes of thrombocytopenia are not present. Observation may be considered if the platelet counts are higher than the threshold of 20,000/µL to 30,000/µL, but the choice of treatment should be individualized for those patients with low platelet counts. No head-to-head clinical trials have compared different third-line agents in refractory ITP. Following splenectomy, either rituximab, corticosteroids, or thrombopoietin receptor agonists may be used. Other third-line treatments include azathioprine, cyclophosphamide, danazol, the spleen tyrosine kinase (SYK) inhibitor fostamatinib (Tavalisse, Rigel), and other immunosuppressive regimens. Interim results presented at ASH 2019 by Dr Catherine Broome and colleagues demonstrated promising results with the monoclonal C1s inhibitor sutimlimab in patients with chronic ITP; the drug is a novel treatment that may benefit at least a subset of these patients. Clinical trial enrollment is always encouraged when available.

H&O What are the differences between adult and pediatric ITP regarding treatment?

JC Treatment decisions in pediatric ITP have moved away from the use of an absolute platelet count cutoff and are now based on the degree of bleeding. For pediatric patients with no or mild symptoms of bleeding, observation alone is recommended. For those with bleeding that is not life-threatening, a short course of prednisone lasting less than 7 days is recommended over IVIG or anti-D immunoglobulin therapy as frontline treatment. Regarding second-line treatments in children, thrombopoietin receptor agonists are now recommended over rituximab or splenectomy. According to the most recent ASH guidelines, rituximab is recommended over splenectomy in second-line treatment.

H&O What are the latest views on the mechanisms of ITP?

JC We do not completely understand all of the mechanisms underlying platelet destruction and decreased platelet production in ITP. As we discussed earlier, ITP is caused by premature platelet destruction through immunologically mediated mechanisms, which lead to a reduction in the platelet count and production. However, we see a high degree of heterogeneity among people with ITP in terms of presenting symptoms, bleeding, and subsequent responses to available therapies. It is hoped that in the future we will be able to discriminate between subgroups of patients with ITP in a way that will guide therapy.

ITP classically has been explained by the presence of immunoglobulin G autoantibodies produced by B cells. We don't know why this process gets started, although some patients may have had a preceding viral or other infection. Autoantibodies most commonly target glycoprotein IIb/IIIa and glycoprotein Ia/IX, but autoantibodies against multiple platelet antigens are also commonly seen in ITP.

Autoantibodies against multiple platelet antigens arise through the phenomenon of epitope spread, amplifying the immune response against the platelets. Antibody-coated platelets are bound by antigen-presenting cells, taken up through the Fcγ receptor, internalized, and degraded. Novel epitopes are generated, so new peptides are presented with the necessary costimulatory signals to stimulate additional CD4 T-cell clones. In turn, additional B-cell clones recognize the additional platelet antigens, proliferate, and amplify the autoantibody production, leading to more efficient opsonization and phagocytosis. Potentially, autoantibodies may be generated that impair megakaryocyte and platelet production.

Additional potential mechanisms include autoreactive cytotoxic T cells, humoral autoimmunity, and cellular autoimmunity against megakaryocytes. Complement-mediated destruction and increased mononuclear phagocytic activation are areas of exploration, and our understanding of potential additional mechanisms is growing.

H&O How does the treatment of Evans syndrome differ from that of ITP?

JC Evans syndrome is a rare autoimmune disorder characterized by bicytopenias, autoimmune hemolytic anemia, and ITP. In approximately 10% of cases, autoimmune neutropenia occurs as well. Evans syndrome may be resistant to standard therapies, and relapses are common. Overall mortality is higher with Evans syndrome than with standard ITP. As with ITP, first-line treatment consists of corticosteroids with or without IVIG. Rituximab and splenectomy are still second-line options. A variety of immunosuppressive agents may be used for subsequent-line treatment as needed, such as cyclophosphamide or azathioprine.

H&O What do doctors still need to learn to better manage ITP?

JC We have a lot of room for growth in multiple areas to get to where we want to be in managing ITP. Because the diagnosis of ITP is one of exclusion and clinical suspicion, a test that could help us definitively identify the diagnosis would be useful. A better understanding of the underlying pathophysiologic mechanisms and associated predictive markers would help differentiate subgroups of patients with ITP and personalize treatment. We also lack biomarkers of disease severity and risk for bleeding. We need to determine what may be the clinical and pathophysiologic similarities and differences between primary and secondary ITP, and how these should affect treatment protocols. And ultimately, of course, researchers in the field continue to work to develop more efficacious and less toxic therapies.

Disclosure

Dr Cunningham has received honoraria from CTI BioPharma and Bioverativ.

Suggested Readings

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