ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

Advances in the Management of ITP in Children and Adults

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H&O What is the correct terminology to use when referring to ITP?

PI We used to refer to this disease as *idiopathic thrombocytic purpura*, but now that we have a better understanding of the disease, we know that the pathogenesis involves the immune system. This advance came about through clinical and laboratory research linked to the introduction of intravenous human derived immunoglobulin G (IgG) concentrate as an immunomodulatory treatment for ITP and other disorders related to the immune system. Therefore, the *I* of ITP came to stand for *immune* instead of *idiopathic*.

We have also moved away from using the word *purpura* because the majority of patients do not exhibit hemorrhages in the skin caused by bleeding. Therefore, the preferred terminology has changed from *idiopathic thrombocytic purpura* to *immune thrombocytopenia*.

Another change in terminology came about from a 2006 expert workshop on ITP in Switzerland, where we looked at follow-up data from the Intercontinental Cooperative ITP Study Group (ICIS) registry 1 of 2031 children with newly diagnosed ITP. The patients were prospectively followed over 12 months. We found that between 6 and 12 months after diagnosis, 25% of children recovered from their ITP (Figure 1). Therefore, we proposed changing the definition of *chronic ITP* from disease lasting 6 months or more to that lasting 12 months or more, as discussed in a 2006 article in *Pediatric Blood Cancer.* One of the ICIS participating members, Dr Francesco Rodeghiero, took the initiative for a new nomenclature and built an international working group. The results of this working group were published in the journal *Blood* in 2009. In short, *acute ITP* is a retrospective term. We now say *newly diagnosed ITP* within the first 3 months, *persistent ITP* when recovery occurs during months 3 to 12, and *chronic ITP* when ITP lasts for more than 12 months.

H&O Could you please give a brief overview of ITP?

PI Primary ITP is characterized by isolated thrombocytopenia in an otherwise healthy individual. Bleeding occurs in individuals whose platelet counts fall below 10,000 to 20,000.

The causes of ITP are unknown. Genetic factors may play a role, and infectious or inflammatory disorders often are associated with ITP.

At initial diagnosis, 77% of children have no or mild bleeding, 20% have moderate bleeding, and 3% have severe bleeding. Signs of bleeding diminish during the follow-up period. Severe, life-threatening bleeding (ie, intracranial hemorrhage) is rare, affecting less than 1% of patients.

H&O What are the differences between ITP in adults and children?

PI When we analyzed the Pediatric and Adult Registry on Chronic ITP (PARC-ITP), we found—to our surprise—that the initial presentation of the disease in adults and children was similar, which stood in contrast to the information on ITP in textbooks. For example, the initial platelet counts were similar in adults and children (Figure 2).

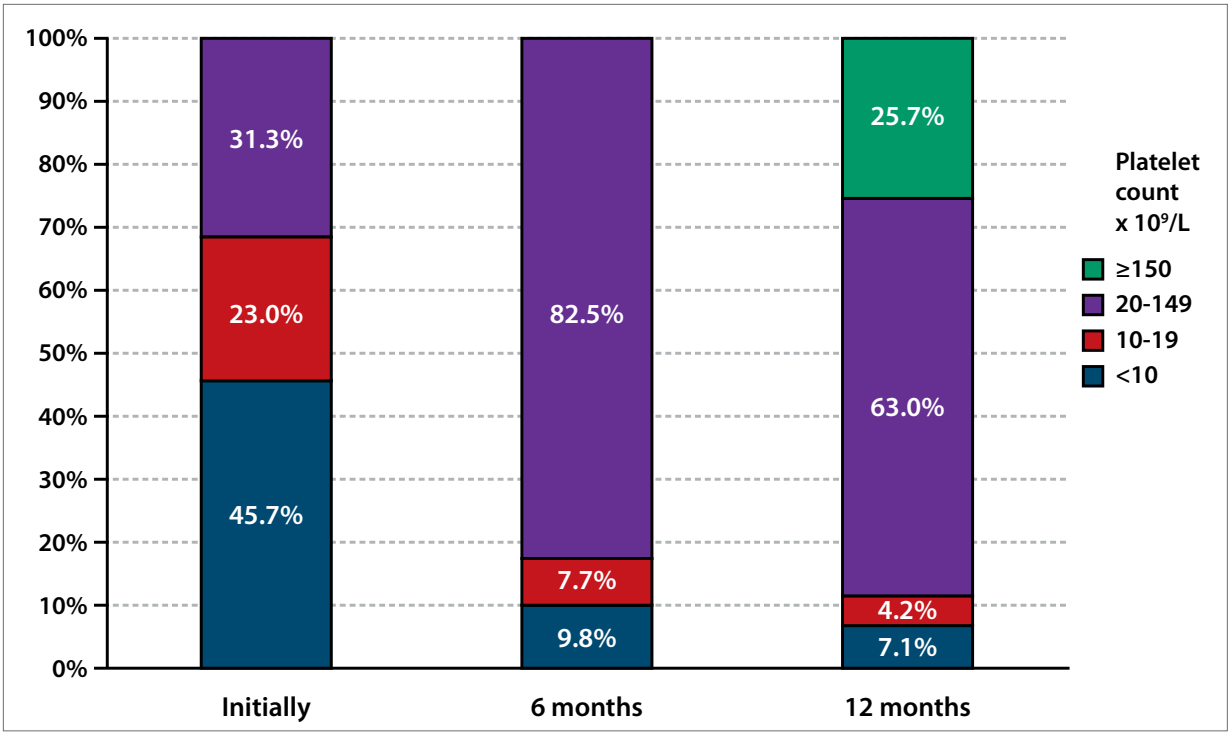

Figure 1. Percentage of platelet counts less than 10×10^9/L, 10-19 $\times 10^9$/L, 20-149 $\times 10^9$/L, and at least 150×10^9/L in children with immune thrombocytopenia (N=308) at the time of diagnosis (initially), and at 6 and 12 months after diagnosis. The platelet counts reflect the platelet number prior to treatment in those patients with persistent immune thrombocytopenia.

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H&O What is the procedure for diagnosing ITP?

PI For the initial diagnosis of isolated thrombocytopenia, the patient history, clinical presentation, and results of a blood smear may be sufficient for making the diagnosis. If uncertainty exists or if the patient has ongoing, severe ITP, further analyses are necessary to exclude secondary ITP.

H&O What are the most recent recommendations on when to treat ITP?

PI The most recent recommendations state that active treatment should begin in patients who have ongoing mucosal bleeding; who are at risk of severe bleeding; or who have recurrent bleeding and secondary symptoms, including fatigue syndrome and other symptoms that affect quality of life.

H&O What first-line treatments are available, and what are the advantages and disadvantages of the various options?

PI The first-line treatment options that are supported by some evidence are intravenous immunoglobulin (IVIG), short-term corticosteroids, and anti-D immunoglobulin.

Patients with ITP who take IVIG have a high rate of rapid and sufficient response, and the agent has been shown to have a biologic effect on the disturbed immune response, as discussed in a 2012 article in *Vox Sanguinis* that I coauthored. The disadvantages of IVIG are the high cost of treatment, the need to administer treatment over 2 to 4 hours, and the fact that response can be transient—lasting just 2 to 4 weeks—in patients with persistent or chronic ITP.

The use of oral corticosteroids for less than 10 days at a high dose—4 mg per kg of body weight per day for 4 days—is an inexpensive, easily administered treatment that has fewer side effects than long-term corticosteroid use. The disadvantages are that it is a symptomatic treatment, and that the mechanism of action is unclear.

Anti-D immunoglobulin increases platelet counts, but as a side effect demonstrates slight hemolysis, and rarely, severe hemolysis. Anti-D immunoglobulin is unavailable in most countries, including the United States.

H&O What second-line treatments are available?

PI Guidelines from an international panel and those from the American Society of Hematology guideline panel provide detailed information on numerous options for second-line treatment of ITP (both published in *Blood* with Provan and

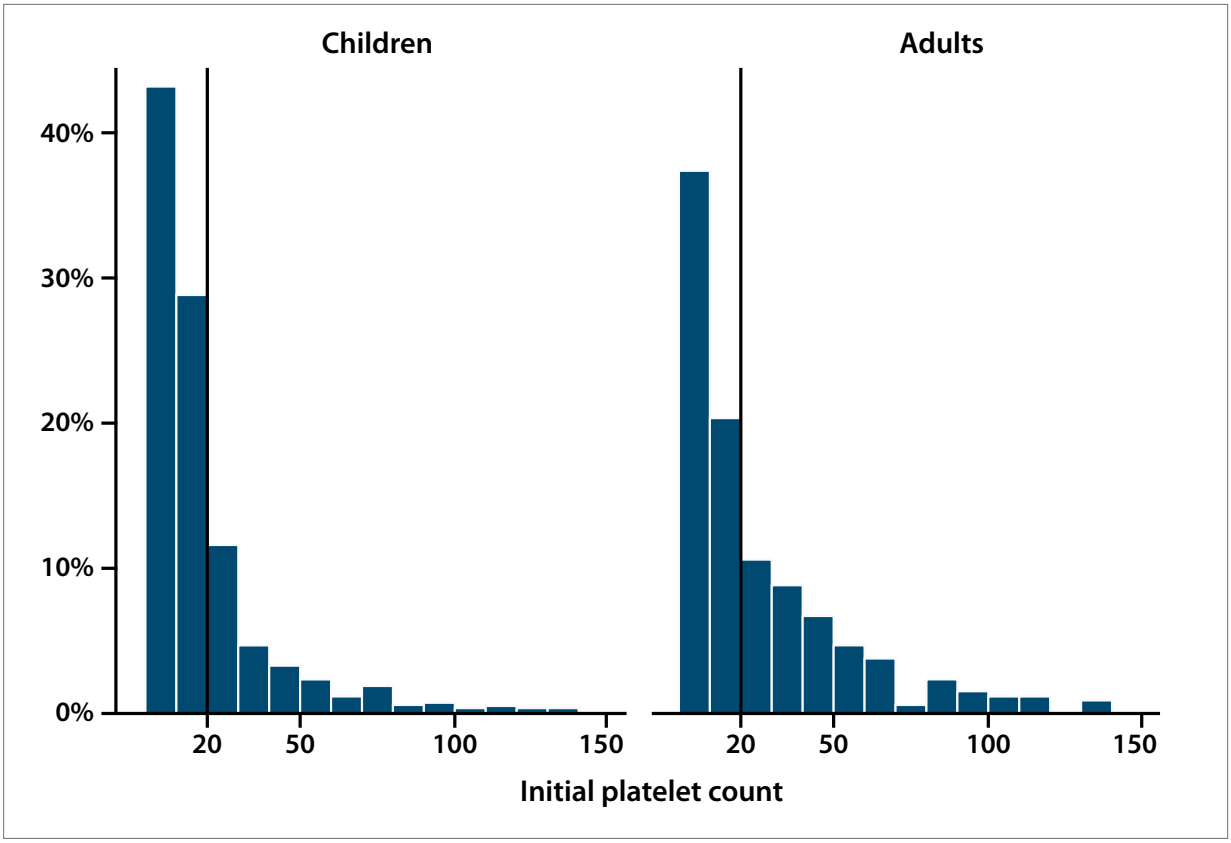

Figure 2. Platelet count of children and adults at the time of immune thrombocytopenia diagnosis. The vertical line indicates a platelet count of 20×10^9/L.

Reprinted with permission from Kühne T et al. *Haematologica.* 2011;96(12):1831-1837.

Neunert as the first authors, respectively). When selecting a second-line treatment, clinicians need to bear in mind the heterogeneous rates of response and the various side effects.

The most commonly used medications for second-line treatment are thrombopoietin receptor agonists (TRAs), anti-CD20 antibodies, and high-dose corticosteroids. TRAs, which include romiplostim (Nplate, Amgen) and eltrombopag (Promacta, GlaxoSmithKline), are expensive agents, but they demonstrate long-term effectiveness as long as they continue to be administered. The efficacy of the anti-CD20 antibody rituximab (Rituxan, Genentech/Biogen Idec) in ITP has been shown in clinical studies. The response rate is 60%, and the duration of response is 9.5 months, as I discussed in a 2011 article in the *New England Journal of Medicine*. Side effects are severe in some patients, and the cost of treatment is high. The drug can be administered repeatedly.

Splenectomy is a second-line option for ITP that has an excellent immediate response rate, but patients continue to remain immunodeficient, which is a problem for patients who relapse after the procedure or who do not respond to it. Therefore, the use of splenectomy is often postponed for as long as possible.

H&O What does the most recent research say about the length of treatment with TRAs?

PI Ongoing studies of TRAs are focused on interval treatment. Some patients with chronic ITP seem to have sufficient improvements in their platelet count after 1 to 6 treatments. This suggests that TRAs are not only a hemostatic vehicle, they probably also act as immunomodulating agents. More research should be focused on the use of these agents.

H&O What combination therapies are in use or being studied?

PI Combination therapies are used in some patients with severe, refractory ITP. No clinical trials of this approach exist, however.

H&O What recent advances have been made in the management of ITP?

PI Recent advances in the management of ITP include individualized treatment, with "wait and see" management as

one possibility; the influence of patient organizations, which has led to a greater emphasis on quality of life in research; the cooperation of many centers to create large patient registries; and the advent of meetings of international experts on ITP, along with the emergence of supplements focusing on ITP in peer-reviewed publications.

H&O What are the key studies that have enhanced our understanding of ITP?

PI More than 20,000 clinical and laboratory studies of IVIG that demonstrate the immunomodulatory effect of administering IVIG and other immunomodulators have been published in peer-reviewed journals. Of these, nearly 500 articles specifically address the mechanisms of action of IVIG. As I mentioned earlier, population-based registries with long-term follow-up in adults and children also have enabled us to distinguish among different groups of patients within this heterogeneous disorder.

H&O What studies are ongoing in ITP?

PI Short-term and long-term clinical studies using TRAs and other new molecules or monoclonal antibodies are ongoing, as well as phase 3 studies of TRAs in children.

H&O Is there anything else you would like to add?

PI It is important to recognize which patients need active treatment for the management of ITP. Management of ITP means agreement of the proposed procedure between the hematologist and the patient, or the parents of a child. Communication is an important factor in management of a patient with ITP.

Suggested Readings

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