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Challenges and priorities for patients with immune thrombocytopenic purpura and their physicians

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1. Immune thrombocytopenic purpura: Definition and clinical features

Immune thrombocytopenic purpura (ITP) is a disorder of too few platelets (termed thrombocytopenia), the smallest of the circulating blood cells. ITP is defined as isolated thrombocytopenia with no clinically apparent associated conditions or other causes of thrombocytopenia, such as congenital/hereditary thrombocytopenias, drug-induced thrombocytopenia, or autoimmune disorders such as systemic lupus erythematosus [1,2]. "Isolated" thrombocytopenia implies that the red blood cells and white blood cells are normal in number and appearance.

The function of blood platelets is to provide initial hemostasis in response to vessel injury, creating a plug to prevent bleeding. Hemostasis is a term to describe prevention of bleeding. If blood vessel injury is small and superficial, the platelet plug is sufficient to stop bleeding. If the vessel injury is extensive, platelets can provide only an initial, temporary seal; permanent hemostasis of larger wounds requires plasma coagulation factors (such as antihemophilic factor and fibrinogen) to provide a strong fibrous matrix to strengthen the platelet plug [3]. Therefore the health problem of patients with ITP, and perhaps their only problem, is a risk for excessive bleeding.

The normal platelet concentration in blood is 150,000–350,000 $\times$ 10^6/L. Like many body functions, the normal number of platelets far exceeds the minimum requirement to provide effective hemostasis. A platelet count of 50,000 $\times$ 10^6/L is sufficient to stop excessive bleeding following major trauma, surgery, or childbirth. A platelet count of 10,000–20,000 $\times$ 10^6/L is sufficient to prevent spontaneous bleeding

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such as minor bruises, termed purpura or ecchymoses, or the tiny pinpoint bleeding spots, described as petechiae, caused by blood leaking of small lesions of superficial vessels. Petechiae and purpura are the characteristic signs of a low platelet count. Dangerous bleeding is not a risk until the platelet count approaches zero.

2. Pathogenesis

For many years, ITP was described as a disorder of excessive platelet destruction, exceeding the ability of the bone marrow to compensate by increased platelet production. Normally, platelets circulate for 10 days following their production in the bone marrow. In patients with ITP, platelets are destroyed by autoantibodies and their survival in the circulation may be less than one day [4]. The presence of plasma autoantibodies directed against platelets was apparent from two observations made over 50 years ago. First, infants born to mothers with ITP occasionally had transient thrombocytopenia, caused by maternal autoantibodies that had crossed the placenta. Second, in heroic experiments, plasma from patients with ITP was infused into healthy physician volunteers causing prompt, severe, and symptomatic thrombocytopenia [5]. Bone marrow examinations in patients with ITP are characteristically normal, with normal numbers of the large platelet producing cells, megakaryocytes. However more recent data have documented that marrow production of platelets is also impaired in patients with ITP, limiting the ability to compensate for accelerated platelet destruction [4].

3. Diagnosis

No specific criteria establish the diagnosis of ITP; the diagnosis relies on the exclusion of other causes of thrombocytopenia. Therefore the initial diagnostic evaluation requires careful exclusion of other disorders. Careful examination of the patient, laboratory data, and the appearance of the blood cells through the microscope must reveal no indication for other diseases that may be associated with thrombocytopenia. This diagnostic process may be inaccurate and patients with an initial diagnosis of ITP may be subsequently discovered to have another reason for their low platelet count [6].

4. Clinical course

ITP is distinct in children and adults. In children, ITP is typically an acute disorder with the sudden appearance of petechiae, purpura, and excessive bleeding. The peak age for childhood ITP is 3–5 years; the occurrence is equal among girls and boys [7]. The natural history of ITP in most children is self-limited, with spontaneous

remissions occurring within several months. Treatments to increase the platelet count and minimize risk for bleeding do not alter the natural history of the disease and are often not required [1,2,4].

In adults, ITP is almost always a chronic disorder. For patients with severe and symptomatic thrombocytopenia, treatment is required to induce remissions. Among younger adults, ITP is more common in women, similar to other autoimmune disorders. In older adults, men and women are equally affected.

The goal of management for both children and adults is only to provide a safe platelet count in order to prevent critical bleeding, not to achieve a normal platelet count. Critical, life-threatening bleeding is extremely rare, occurring in far less than 1% of patients [7,8]. Death from bleeding is much rarer [9]. However a few patients, less than 5% of adults with ITP and even fewer children, have persistent severe thrombocytopenia, refractory to current treatments and causing repeated bleeding episodes [10].

5. Incidence and prevalence

Accurate incidence and prevalence data are difficult to estimate because of the imprecise diagnostic criteria. Incidence estimates of ITP among children are perhaps more accurate because of the abrupt onset of overt purpura and the uncommon occurrence of other causes of thrombocytopenia. The incidence of ITP in children is estimated to be 5 per 100,000 children per year [11,12]. Consistent with the typical self-limited clinical course, the prevalence of childhood ITP is only slightly greater than the annual incidence, approximately 8 per 100,000 children [13,14]. The incidence estimate of ITP in adults is 2 per 100,000 adults per year [6,15]. Consistent with the persistent clinical course, the prevalence of ITP in adults is approximately six-fold the annual incidence, 12 per 100,000 adults [14]. These prevalence data are consistent with the designation by the US FDA of ITP as an orphan disorder, defined by a US prevalence of less than 200,000 patients.

6. Challenges faced by patients with ITP and their physicians

As with other rare diseases, perhaps the greatest challenge faced by patients with ITP is their initial sense of isolation. A new diagnosis of ITP, accompanied by the fear of uncontrolled bleeding, is a difficult time for patients since the patient and her family have typically never heard of ITP. Their primary care physician may also be unfamiliar with ITP, causing even greater concern.

A second cause of apprehension among patients is the frequent uncertainty about the diagnosis of ITP. Because there are no tests that specifically document ITP and exclude other causes of thrombocytopenia, the initial diagnosis of ITP is often uncertain. For patients, uncertainty may be the greatest source of apprehension

with any illness. These causes of concern can be effectively managed with proper physician support.

Perhaps the greatest challenge for both patients and physicians is to balance the risks of treatment with the risks for serious bleeding [9,10]. The patient's perspective concerning the need for treatment may conflict with the physician's perspective. Since patients with ITP are typically young and otherwise in excellent health, the physician feels great responsibility for preventing severe hemorrhage. Physicians may therefore treat patients who have a low platelet count and a potential risk for bleeding even through they may have had only minimal bleeding symptoms. From the patient's perspective, this can be a difficult dilemma. Many patients report that their treatment has been worse than the disease itself. They may have only rarely experienced problems with bleeding, but they have experienced substantial side effects of medications. The initial treatment of ITP is with corticosteroids, which are inexpensive, almost always effective for increasing the platelet count, but rarely effective for establishing a durable remission when treatment is discontinued. The side effects of corticosteroids can be profound, though most experience is anecdotal [16]. Many patients report severe emotional changes, but these may be underestimated by physicians. This discrepancy of perceptions is a major challenge. Patients view the side effects of treatment as more serious than their physicians; physicians view the potential risk for bleeding as more serious than their patients. These divergent views can only be resolved by shared decision making [17]. A long-term cohort study of patients with ITP has reported that more deaths were caused by infections associated with treatment-related immunosuppression than from bleeding [9], providing objective documentation of the potential critical risks of treatment.

7. Opportunities for patients with ITP and their physicians

Recognition that management of patients with ITP should be based on more than the platelet count may provide a more sound basis for treatment. Since the platelet count is easily measured and since it correlates with bleeding risk, traditional patient management has focused solely on increasing the platelet count to a safe level, such as greater than $30{,}000 \times 10^6$/L. However, the correlation of the platelet counts and bleeding risks is not consistent, particularly at very low platelet levels. Many patients may have platelet counts less than $10{,}000 \times 10^6$/L, levels that are alarming to physicians, but have no or minimal bleeding symptoms. Therefore objective measures of actual bleeding are being developed to provide more direct guidance for appropriate treatment [18].

Questionnaires to quantitatively assess health-related quality of life (HRQoL) may also help to guide treatment [19–21]. Even the process of development of these HRQoL measures has had an important impact on the care of patients with ITP. Focus groups to develop HRQoL questionnaires have revealed previously unappreciated problems faced by these patients [20].

Together with the platelet count, objective measures of bleeding occurrence and HRQoL will provide more comprehensive patient assessments, more effective use of therapies, and more consistent perspectives between patients and physicians. However more research is required to understand how these three parameters of ITP, platelet count, bleeding severity, and HRQoL, are related to each other and to the morbidity of ITP [21].

Finally, new interest of the pharmaceutical industry for development of treatments for ITP has created valuable opportunities for patients with refractory ITP. Multiple pharmaceutical/biotechnology companies have developed new agents that stimulate platelet production by mimicking the effect of the natural hormone, thrombopoietin [22]. The first two agents, approved by the US FDA in 2008, have been documented to be effective in most patients refractory to all standard treatments, without risks of immunosuppression [23,24]. Although the number of ITP patients who have refractory and symptomatic ITP is small [10], the benefit for these patients is great.

8. Physician initiatives for the benefit of patients with ITP

The development of the new thrombopoietin mimetic agents for ITP has provided the resources for many randomized controlled clinical trials in many countries throughout the world [22–24]. These clinical research initiatives have yielded many dividends, in addition to documenting the effectiveness and safety of the new treatments. Previous treatments were accepted as effective based only on anecdotal or small observational studies. No large randomized controlled trials had been carried out in patients with ITP comparing one treatment to another or treatment to placebo prior to the development of the new thrombopoietin mimetic agents. The recent large clinical trials of the thrombopoietin mimetic agents have provided an opportunity for establishing measures of HRQoL as an integral part of patient management [25]. Finally, new knowledge concerning evaluation and management of patients with ITP must be interpreted and disseminated as guidelines for clinical practice. In 1996, the American Society of Hematology developed a comprehensive practice guideline for evaluation and management of patients with ITP [1]. This effort was updated by the British Committee for Standard in Hematology Task Force in 2003 [2]. Currently, because of the surge of new information, another updated guideline for evaluation and management of ITP is being prepared by the American Society of Hematology. Development of guidelines is essential, but audit of practice to assess adherence to published guidelines is required to insure that patients with ITP are receiving proper care [26]. Ensuring optimal management of patients with ITP is facilitated by the establishment of international registries, such as the Intercontinental Childhood ITP Study Group. [27] and by dissemination of information by national agencies [28].

9. Summary

Patients with ITP face problems of limited information and a sense of isolation, common to many patients who have rare diseases. Greater understanding of the biology of ITP has lead to new initiatives for development of effective treatments. These initiatives have, in turn, resulted in greater understanding of the challenges faced by patients with ITP. These new initiatives have also created important new opportunities for effective patient management.

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