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New Strategies for the Treatment of Immune Thrombocytopenia

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H&O Which guidelines should physicians refer to when taking care of patients with immune thrombocytopenia (ITP)?

CK The American Society of Hematology (ASH) published updated guidelines for ITP in 2019, and Provan and colleagues published an updated International Consensus Report on primary ITP the same year. Important goals of these guidelines were to modernize the treatment of ITP, factoring in the most recent data provided by clinical trials; to standardize how we describe the phases of ITP, so that all physicians can use the same terminology in designing and discussing clinical trials; and to minimize the duration of the use of corticosteroids, which have been demonstrated in repeated studies to increase the morbidity of ITP. As for the definition of its phases, ITP is now designated as follows: (1) newly diagnosed, meaning ITP that has been diagnosed within the past 3 months; (2) persistent, meaning ITP that has lasted between 3 and 12 months; or (3) chronic, meaning ITP that has lasted longer than 12 months.

H&O What is now considered to be standard treatment in ITP?

CK The initial treatment of adults with newly diagnosed ITP typically consists of the early administration of a corticosteroid (dexamethasone or prednisone), with anti-D concentrate or intravenous gamma globulin used for rapid hemostasis to prevent or reverse bleeding in the context of marked thrombocytopenia. Corticosteroids can achieve an initial platelet count response in approximately 70% of patients within the first 6 months of treatment. For the remaining 30% of patients, in whom this regimen is ineffective or inadequate, we move to agents that the US Food and Drug Administration (FDA) has approved for use in persistent or chronic ITP. Second-line agents include the monoclonal anti-CD20 antibody rituximab; the thrombopoietin (TPO) receptor agonists eltrombopag (Promacta, Novartis), avatrombopag (Doptolet, Dova), and romiplostim (Nplate, Amgen); and the spleen tyrosine kinase (SYK) inhibitor fostamatinib (Tavalisse, Rigel). Additional second-line agents for which evidence is more limited are azathioprine, cyclosporin A, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, and vinca alkaloids. Another option for second-line treatment is splenectomy.

Whatever the treatment used, the goal is to increase and maintain the patient's platelet count above 30,000/μL, preferably above 50,000/μL, to prevent serious bleeding complications.

H&O What are we learning from the most recent research on ITP?

CK Data on many new approaches to the treatment of ITP have been presented over the last couple of years, and several trends are emerging. First, researchers are trying to reduce the duration of high-dose corticosteroid management to minimize the complications that occur with long-term use. Second, researchers are moving treatment with the medications that have been licensed by the FDA

for chronic ITP into earlier phases. Third, researchers are working to identify approaches that will lead to a more rapid platelet count response in patients with ITP, hoping to reduce the use of corticosteroids and increase the durability of the response.

One example is the FLIGHT trial, which was presented at the 2020 ASH annual meeting by Dr Charlotte Bradbury and published in the *New England Journal of Medicine* in 2021. In this trial, researchers randomly assigned 120 patients with ITP to receive corticosteroids alone or a corticosteroid plus mycophenolate mofetil as first-line treatment. The increment in platelet rise was significantly greater and the risk for refractory or relapsed ITP was lower in the patients who received the combination treatment than in those who received corticosteroids alone, a finding that was notable in a population that included patients ranging in age from 17 to 87 years. One caveat is that the quality of life of patients in the combination group was somewhat decreased; physical function was worse and fatigue was more pronounced in this group than in the corticosteroid-alone group. Still, the ability to reduce the use of corticosteroids by adding mycophenolate mofetil is an important finding. Limiting the use of corticosteroids is especially important in the current era because immunosuppression makes people more vulnerable to COVID and less likely to benefit from vaccination.

We also have been seeing some very interesting ITP research from China in the past couple of years. For example, at the most recent ASH annual meeting, Dr Zhuo-Yu An and colleagues presented the results of an open-label, phase 2 study that randomly assigned 140 patients with ITP to first-line treatment with either high-dose dexamethasone plus tacrolimus—which has not been widely used in the treatment of ITP—or high-dose dexamethasone alone. The study used high-dose dexamethasone rather than standard-dose prednisone because clinical trials have established that high-dose dexamethasone produces a more rapid increase in platelet counts and reduces the duration of corticosteroid use. The researchers found that the complete response rate at 14 days in patients who had ITP was significantly higher with combination treatment than with high-dose dexamethasone alone, at 77% vs 56%, respectively. In addition, the relapse rate at 24 weeks was significantly lower with combination treatment than with high-dose dexamethasone alone, at 19% vs 29%, respectively. The combination of agents used in this study was extremely efficient and very safe, with a durable response at 6 months after the beginning of treatment.

Another interesting open-label, phase 2 study from China, which was published by Dr Qiu-Sha Huang and colleagues in *Lancet Hematology* in 2021, randomly assigned 132 patients with newly diagnosed ITP to first-line treatment with either all-trans retinoic acid (ATRA; 10 mg orally twice daily for 12 weeks) plus high-dose dexamethasone (40 mg intravenously daily for 4 days) or high-dose dexamethasone alone. The 4-day course of dexamethasone was repeated if the patient did not respond by day 14. At 6 months, a sustained response was significantly more likely in the combination group than in the dexamethasone-alone group, at 68% vs 41%, respectively. Both treatments were well tolerated, and no grade 4 adverse events occurred; ATRA is a relatively benign drug.

The Kaplan-Meier plots showed significant incremental rises in the platelet counts of individuals who received combination therapy with ATRA. Significant durable responses were similar regardless of whether the platelet counts exceeded 50,000/μL. Patients who received combination treatment also were less likely than those who received dexamethasone alone to require rescue therapy for bleeding complications, at a rate of 12% vs 30%, respectively. This study provides another example of how drugs that were not traditionally used for ITP can be integrated into novel regimens for patients with newly diagnosed disease.

H&O Can patients who receive a TPO receptor agonist for ITP ever stop taking the drug?

CK This is a question that has recently gained prominence. In a study from France, Dr Mathieu Mahevas and colleagues identified 49 patients with persistent or chronic ITP as part of a nationwide, prospective, multicenter interventional study. Participants were required to have had a stable platelet count of more than 100,000/μL for more than 2 months while on a TPO receptor agonist, and to have been on treatment with one of these agents for at least 3 months. For the tapering protocol, eltrombopag was tapered by 25 mg every 2 weeks, and romiplostim was tapered by 1 μg/kg every week. All TPO receptor agonists were stopped at 10 weeks. The researchers found that at week 24 after discontinuation of their TPO receptor agonist, 55% of the patients remained in complete remission. At week 52 after discontinuation of their TPO receptor agonist, 52% of the patients remained in complete remission. These results are remarkable and important because they show that we may be able to limit the use of TPO receptor agonists after at least 3 months of treatment. TPO receptor agonists not only carry a possible risk for complications but also are quite expensive. Among the patients who had a relapse, the median time until relapse was 8 weeks after the initiation of tapering. More than half of these patients restarted the same TPO receptor agonist, and all of them had a complete response after a median of 2 weeks. None of the patients had severe bleeding. These results show that if patients have a relapse,

they can be rescued without difficulty. The results of this study need to be reproduced in other large clinical trials.

H&O What other agents are being examined for earlier use in ITP?

CK Although fostamatinib is one of the agents that is recommended as a second-line treatment, I think that it has been inadequately explored as a first-line treatment. Fostamatinib is unique in ITP treatment because it is the only treatment based on a SYK inhibitor approach. Unlike other agents, which predominantly involve immunosuppression by interfering with the lymphocyte production of antibody (eg, corticosteroids), by reducing the lymphocyte burden (eg, rituximab or cytotoxic drugs), or by increasing thrombopoiesis, SYK inhibitors are believed to work by interfering with the phagocytosis of antibody-coded platelets in the process of ITP. Older studies looked at the use of fostamatinib in patients with chronic phase ITP who had failed to respond to at least 2 prior treatment strategies, but some of the newer studies are showing that an earlier introduction of fostamatinib in ITP may lead to a higher response rate. In addition, according to updated results from a phase 3 trial that Dr Caroline Piatek presented at the 2021 annual meeting of ASH, fostamatinib is also a useful agent for patients with warm antibody autoimmune hemolytic anemia. These results support the use of fostamatinib in antibody-mediated cytopenias.

ITP guidelines recommend the use of rituximab in chronic phase ITP; however, many hematologists are also using monoclonal anti-CD 20 antibody in the persistent or newly diagnosed phase of ITP despite the lack of availability of randomized controlled study data. The early use of rituximab in ITP may be associated with a significant rate of late recurrent disease, and its potential benefits are further tempered in this era of highly contagious COVID and the need to respond to vaccination strategies.

H&O Are any other agents being explored in ITP?

CK At the most recent ASH annual meeting, Dr David Kuter gave an interesting presentation on the use of the experimental Bruton tyrosine kinase inhibitor rilzabrutinib in ITP. In a phase 3 study, 194 adults and 30 adolescents with persistent or chronic ITP were randomly assigned in a 2:1 ratio to rilzabrutinib or placebo. Preliminary results showed a robust response, although not as clear as the responses with other treatments.

Dr Catherine Broome gave a notable presentation at the 2020 ASH annual meeting on the use of sutimlimab (Enjayvo, Bioverativ), a specific blocker of C1S in the complement pathway, in adults with chronic ITP and an inadequate response to 2 or more prior therapies. This open-label, phase 1 trial supported the use of sutimlimab in individuals whose ITP has failed to respond to agents from other drug classes. The study also revealed that activation of the complement pathway may contribute to the heterogeneity of immune platelet destruction.

In a phase 2 study that was published in *Blood Advances* in 2020, Dr Tadeusz Robak and colleagues investigated the use of the neonatal Fc receptor inhibitor rozanolixizumab in patients with persistent or chronic ITP. The study found that rozanolixizumab effectively increased platelet counts and appeared to be tolerable and safe. A phase 3 trial of this agent is currently recruiting patients (NCT04200456).

Disclosures

Dr Kessler has served as a consultant to and on the advisory board for Rigel, Novartis, and Sobi.

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