The 4 T's of ITP: Tailoring Therapies to Treat Thrombocytopenia

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Abstract

Immune thrombocytopenia (ITP) is an acquired autoimmune bleeding disorder characterized by the destruction of platelets and megakaryocytes. Its management has changed significantly in recent years, and at JADPRO Live Virtual 2021, David Hughes, PharmD, BCOP, reviewed the background and pathophysiology of ITP and clinical practice guidelines with an emphasis on patient preference when selecting first and subsequent lines of therapies in the chronic ITP setting.

The treatment of chronic immune thrombocytopenia (cITP) has changed significantly in recent years with the approval of several new drugs, but patient preference still plays an important role in the management of this disease. During JADPRO Live Virtual 2021, David Hughes, PharmD, BCOP, of Boston University School of Medicine, evaluated clinical practice guidelines when selecting first and subsequent lines of therapy and shared clinical pearls within each of the drug classes used to treat cITP.

OVERVIEW OF ITP

Immune thrombocytopenia is an acquired autoimmune bleeding disorder characterized by the destruction of platelets and megakaryocytes (large bone marrow cells that produce platelets, which are necessary for normal blood clotting).

There are two types of ITP: primary ITP and secondary ITP. Primary ITP, which accounts for 80% of all cases, is an isolated thrombocytopenia (not caused by or associated with another disorder) and is characterized by a platelet count < 100,000/μL. Secondary ITP comprises all other immune-mediated thrombocytopenias, including autoimmune disorders (e.g., systemic lupus erythematosus), lymphoproliferative disorders (e.g., CLL), drug-induced (e.g., linezolid), and infections (e.g., HIV).

Although presenting symptoms vary among patients, minor bleeding, bruising, and small petechiae tend to be the most common, said Dr. Hughes, who emphasized the role of the advanced practitioner (AP) in diagnosis.

"Mucosal bleeding or mucosal petechiae are very commonly detected in an oral exam," he said. "Petechiae may also show up bilaterally on the lower legs, and it's important

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to check their backs when patients with ITP are admitted as they may be bedridden for prolonged periods of time."

"Females can get heavier bleeding of presenting symptoms when they're in their menstrual cycle," he added.

PATIENT PREFERENCES

As Dr. Hughes explained, there are clinical practice guidelines that dictate treatment, but patient preferences also inform the management of cITP. While some patients may fear low platelet counts, others may be more accepting. In addition, some patients may want to avoid chronic therapy, while others may want to avoid major surgery. Younger females who are looking to have children and raise a family may also have pregnancy concerns.

According to Dr. Hughes, it's important to prioritize patient goals and place weight on patient-dependent factors, as ITP can be associated with impairments in emotional, functional, and reproductive quality of life. It can affect the activities of daily living, he said, and up to 72% of patients may experience depression (Provan et al., 2019).

FIRST-LINE TREATMENT

According to most guidelines and most practitioners, corticosteroids are the first step in managing ITP. American Society of Hematology (ASH) guidelines suggest either prednisone (0.5–2.0 mg/kg/day) or dexamethasone (40 mg/day for 4 days) in adults with newly diagnosed ITP.

When these steroids were compared head-to-head, dexamethasone demonstrated faster initial response (82% vs. 67%), faster complete response (51% vs. 27%), and faster time to response, but there was no increase in sustained level of activity (Wei et al., 2016). The faster responses may be helpful in severely thrombocytopenic patients, said Dr. Hughes.

Given that 50% of patients relapse after corticosteroids in the first 6 months, efforts have been made to improve sustained responses in the upfront setting. The phase III FLIGHT trial randomized patients over 16 years with a diagnosis of ITP to receive either mycophenolate plus corticosteroid vs. corticosteroid alone in the first-line setting (Bradbury et al., 2021). Although findings demonstrated the same levels of toxicity between treatment arms, said Dr. Hughes, patient-reported outcomes were worse with the addition of mycophenolate (Figure 1).

SECOND-LINE TREATMENT

For adults with ITP who are dependent or unresponsive to corticosteroids, there are numerous treatment options available. For those with ITP lasting longer than 12 months, splenectomy is an option, said Dr. Hughes, but it's rarely needed.

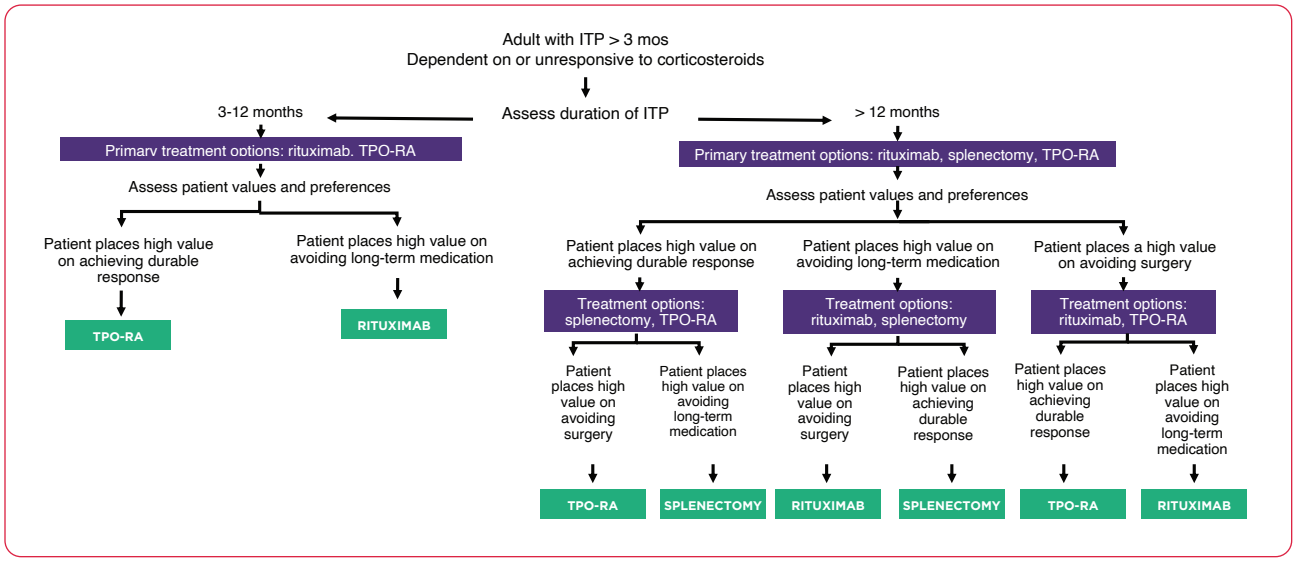

Figure 1. ASH Clinical Guidelines. ITP = immune thrombocytopenia; TPO-RA = thrombopoietin receptor agonists. Information from Neunert et al. (2019).

"If possible, we try to delay splenectomy 12 to 24 months to allow disease to recover or remit, but this option has fallen out of favor," said Dr. Hughes, who noted that splenectomy is not synonymous with cure. "Early response rate is approximately 80%, and a small percentage of patients are cured with this procedure, but it carries additional risks, including infections."

For patients who do undergo splenectomy, Dr. Hughes underscored the importance of vaccination because of the higher risk of infection and reported a higher incidence of coronary artery disease and stroke (Cooper & Ghanima, 2019). Splenectomy is also associated with higher rates of venous thromboembolism.

RITUXIMAB IN ITP

Rituximab (Rituxan), an anti-CD20 monoclonal antibody, can lead to rapid B-cell depletion and results in a decreased platelet production of antibodies. According to Dr. Hughes, rituximab may be preferred for patients who want to avoid surgery or cannot afford an oral drug because of insurance (Lucchini et al., 2019).

Several studies have looked at different doses, but the dose will vary depending on the preferences of the patient, said Dr. Hughes, who noted several safety concerns.

"The first dose of rituximab is a prolonged infusion that requires the patient to be in clinic for hours," he said. "Patients may have an infusion reaction, so APs should have the corticosteroid, Tylenol, famotidine, and Benadryl ready."

Patients receiving rituximab are also at an increased risk of hepatitis B, so routine screening is essential, he added.

THROMBOPOIETIN RECEPTOR AGONISTS

Thrombopoietin receptor agonists (TPO-RAs) are drugs that stimulate the megakaryocytes to increase production of platelets. There are currently three TPO-RAs available on the market (romiplostim [Nplate], eltrombopag [Promacta], and avatrombopag [Doptelet]), but several others are currently under investigation.

According to Dr. Hughes, selecting the right TPO-RA depends on patient preferences, as each drug has its own set of tradeoffs. While romiplostim is a subcutaneous injection administered once per week, eltrombopag is an orally available drug taken daily, but it must be taken on an empty stomach in a fasting state. Avatrombopag is a once daily option for patients who typically have a faster onset.

"It really comes down to which drug we want to use and the conversation between the provider and the patient," said Dr. Hughes. "Response times can vary slightly, and all three drugs carry a risk of thromboembolism."

"If a patient comes in with unilateral leg swelling or shortness of breath, that should prompt quick discussions about monitoring and perhaps an ultrasound should be ordered," he continued. "Eltrombopag also has an additional black box warning for hepatotoxicity and hepatic decompensation in patients with hepatitis C."

With respect to romiplostim, the FDA recommended starting dose is 1 µg/kg/week. However, Dr. Hughes noted that initial doses have been higher in clinical practice (DasGupta et al., 2019).

"There is a lot of rationale to start with a higher dose of romiplostim," he said. "In my practice at Boston Medical Center, we typically start patients at 3 µg/kg/week and then titrate up or down as needed."

According to Dr. Hughes, avatrombopag is a reasonable option as time to onset appears quicker than other commercially available TPO-RAs. A recent study evaluating avatrombopag vs. placebo in patients with previously treated chronic ITP reported an increase in response rates (Jurczak et al., 2018). Median platelet counts of patients on avatrombopag quickly peaked, said Dr. Hughes, but these tend to "die off over time."

"Avatrombopag is an effective option and has tended to work much faster than some of the other agents in my practice, but you still need to weigh the pros and cons with your individual patient," said Dr. Hughes.

FOSTAMATINIB

Fostamatinib (Tavalisse), a spleen tyrosine kinase inhibitor, is a reasonable option for earlier-line treatment in patients with previous venous thromboembolism. Results of the FIT2 and FIT3 trials, multicenter, randomized, double-blind, placebo-controlled trials, demonstrated a higher level of response in fostamatinib vs. placebo (Bus-

sel et al., 2018). Findings also showed lower use of rescue medication, and the platelet count over 24 weeks was higher in the fostamatinib group.

Importantly, more recent post-hoc analysis of fostamatinib administered as a second- or third-line option showed "higher response rates numberically" than the 40% rate seen in earlier trials (Boccia et al., 2020).

"When fostamatinib is used as a second- or third-line agent, we see a 78% increase in platelet responses," said Dr. Hughes.

Key toxicities of fostamatinib include diarrhea, hypertension, and a small risk of hepatotoxicity.

Disclosure

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