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Current Management of Thrombocytopenia in Chronic Liver Disease

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G&H How common is thrombocytopenia in patients who have chronic liver disease?

RB Thrombocytopenia, defined as a platelet count under 150,000/µL, is probably the most common complication of advanced liver disease or cirrhosis. This condition tends to occur prior to the clinical manifestations associated with decompensation (ie, ascites or encephalopathy), and is often the first presenting sign of chronic liver disease. In fact, a low platelet count is used as a clinical diagnostic tool for the presence of cirrhosis and is included in the Aspartate Aminotransferase to Platelet Ratio Index and Fibrosis-4 scores, as well as in all of the noninvasive blood testing methods of diagnosing advanced liver disease.

G&H What is the pathophysiology of thrombocytopenia in chronic liver disease?

RB The pathophysiology is multifactorial. Portal hypertension leads to splenomegaly and then splenic sequestration of platelets. In addition, thrombopoietin levels in patients with chronic liver disease are low, leading to decreased production of platelets. The combination of increased sequestration and decreased production leads to low platelet counts, which tend to correlate with both the degree of portal hypertension as well as with the degree of liver dysfunction. In other words, the more liver dysfunction, the lower the thrombopoietin levels, and also the more portal hypertension patients tend to have, which leads to progressive thrombocytopenia.

G&H Should prophylactic measures always be used in patients with thrombocytopenia and chronic liver disease who are undergoing a procedure with a risk of bleeding?

RB This is a controversial issue. The recommendations for using prophylactic measures should depend on both the degree of thrombocytopenia and the inherent bleeding risks associated with the procedure planned. However, most of the guidelines have been made with an absence of concrete data or are based on extrapolation from patients who have hematologic disorders and thrombocytopenia—in whom the risk of bleeding is higher due to absent platelets from bone marrow failure. For higher-risk (eg, operative) procedures, generally a platelet count threshold of 100,000/µL is used. For less-invasive procedures, a platelet count threshold of

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50,000/μL is used. For procedures with intermediate risk (eg, liver biopsy), some physicians use an in-between platelet count threshold, such as 75,000/μL. However, these thresholds are not based on high-quality data, and there is no clear consensus on the optimal approach to periprocedural bleeding risk, leading to inconsistent practices. Nevertheless, we do know that patients with lower platelet counts have an increased risk of bleeding and that the corollary is also likely true, that if the platelet count can be effectively and safely increased, the risk of bleeding will be reduced to some extent.

G&H What are the current management options for chronic liver disease patients who have thrombocytopenia and are undergoing an invasive procedure?

RB The gold standard has traditionally been platelet transfusion, but there are several disadvantages with this approach. It involves transfusion of blood products, which can be associated with transfusion reactions, are costly, and become less effective over time due to allosensitization. In addition, exogenous platelets often do not last for the duration of the procedure, never mind for the entire risk period for bleeding, which could extend up to 1 week postprocedure. Thus, platelet transfusions are often avoided due to their lack of clear beneficial effect and their potential for side effects, leading to a need for alternative management options, such as thrombopoietin analogues.

The advantages of thrombopoietin analogues are that they are long-lasting (with durations of increased platelet counts of 3+ weeks) and are more predictable in terms of their increase in platelet counts. The US Food and Drug Administration (FDA) approved the second-generation thrombopoietin analogues avatrombopag (Doptelet, Dova Pharmaceuticals) and lusutrombopag (Mulpleta, Shionogi) in May and July 2018, respectively, for thrombocytopenia in patients with chronic liver disease who are undergoing invasive procedures. These agents have structural differences, but their mechanisms of action are similar. Both bind to the thrombopoietin receptor in a noncompetitive manner. The first-generation thrombopoietin analogues eltrombopag (Promacta, Novartis) and romiplostim (Nplate, Amgen) were not approved by the FDA for the management of thrombocytopenia in patients with chronic liver disease, and prior clinical trials of eltrombopag in chronic liver disease patients had safety issues related to portal vein thrombosis. However, despite carrying the same FDA warning, the second-generation agents did not have excess clotting events in their clinical trials and were shown to be safe and efficacious at avoiding platelet transfusions for invasive procedures in chronic liver disease patients. In my opinion, avatrombopag and lusutrombopag will evolve to be the new standard of care for managing thrombocytopenia in this patient population.

G&H What were the key study findings that led to the recent FDA approval of avatrombopag and lusutrombopag?

RB Both of these agents were approved based on results from 2 randomized, double-blind, placebo-controlled, phase 3 studies (ADAPT-1 and -2 for avatrombopag and L-PLUS 1 and 2 for lusutrombopag, with 300-400 patients enrolled in each set of studies). The studies had a similar design in that they consisted of patients with thrombocytopenia (defined as a platelet count under 50,000/μL) who were undergoing invasive procedures in which a platelet transfusion was planned, and patients were randomized to the agent vs placebo. Both agents were shown to decrease the percentage of patients requiring platelet transfusion and increase the platelet count in a statistically significant manner compared to placebo, with a large number of patients having a consistent increase to above 50,000/μL. The relative proportion of patients receiving a platelet transfusion was approximately the same, and both agents decreased the likelihood of receiving a platelet transfusion by approximately 50%.

G&H How safe are these agents? What side effects were found in the studies?

RB Safety was similar for both agents, with no increases in thrombotic events compared to placebo. Their overall side-effect profiles were not very different from placebo, and the side effects that were seen were quite mild. In addition, the number of patients with adverse events was equivalent between the agent and placebo. In both sets of clinical trials, patients experienced adverse effects because they had cirrhosis and were undergoing procedures, but the adverse events were fairly balanced between the treatment and placebo arms, demonstrating the importance of having a placebo arm.

G&H How were avatrombopag and lusutrombopag dosed?

RB Avatrombopag was given for 5 days, and the dose varied based on whether the patient's platelet count was below 40,000/μL or from 40,000/μL to 50,000/μL (with the latter group receiving a lower dose). Lusutrombopag was given for 7 days with the same dose administered to all patients.

G&H In the studies, how long did the effects of the agents last?

RB For avatrombopag, the peak effect was between days 10 and 13, and platelet counts tended to return to their baseline by day 35. Lusutrombopag had similar findings, with the peak effect occurring between days 9 and 14, and platelet counts tending to return to baseline in approximately a month.

G&H Prior to administering these agents, is a patient evaluation needed?

RB Because of the risk of thrombotic events, portal vein flow was assessed in most of the clinical trials. However, the labels do not require the assessment of portal vein patency prior to the use of the agents. In my clinical practice, I make sure that the patient's hepatocellular carcinoma screening is up-to-date because that is indicated in all patients with cirrhosis, and the imaging required for the screening includes the ability to evaluate portal vein patency. Other than routine blood testing, that is the extent of our standard evaluation before using avatrombopag or lusutrombopag.

When thrombotic events were seen with the first-generation thrombopoietin analogues, most of these events occurred when the platelet count was too high. Thus, if there is concern because a patient's platelet count is close to 50,000/μL, the platelet count can be measured at the time of the procedure or shortly before, which many physicians will do to ensure an adequate platelet response as part of their clinical practice. However, in the absence of a high platelet count, I would not feel the need to monitor for the presence of portal vein thrombosis postprocedure.

G&H Are there any contraindications associated with these treatments?

RB Thrombopoietin analogues should not be used, or should be used with great caution, in patients who have a history of thrombotic events, and I would not recommend the use of these treatments in patients who have portal vein thrombosis.

G&H Are avatrombopag and lusutrombopag currently being used commonly in clinical practice, or is platelet transfusion still the standard of care?

RB In my clinical practice, we are using these agents instead of platelet transfusions in elective situations where we have the time to wait for the agents to work. (In an emergency situation, platelet transfusion is the only choice.) Given the superior efficacy of these agents, and as education about them increases, we will likely see more and more of their use and a corresponding decrease in the use of platelet transfusions. As we are becoming more comfortable with the use of thrombopoietin analogues, we are now allowing patients to undergo elective procedures that they could not previously undergo because of their thrombocytopenia. We are also seeing fewer repeat procedures due to the inability to perform a therapeutic maneuver because of thrombocytopenia. For example, in the past, a patient with thrombocytopenia who underwent colonoscopy might not have been able to undergo polypectomy if the physician was not ready to provide a platelet transfusion, which meant that the colonoscopy had to be repeated. In addition to allowing therapy to be administered at the time of the initial procedure, increased use of the second-generation thrombopoietin analogues will hopefully reduce the risk of invasive interventions and allow access to elective procedures that will improve the length and quality of patients' lives.

G&H What are the next steps in research?

RB Avatrombopag and lusutrombopag should be studied in patients with more advanced liver disease and in patients with very low platelet counts. In the aforementioned clinical trials, some patients did not exceed platelet counts of 50,000/μL even with these agents, so it may be necessary to use higher doses or a longer duration of treatment to achieve platelet increase in patients with very low counts, particularly 20,000/μL and below. In addition, we need to define which procedures benefit the most from treatment with thrombopoietin analogues and which procedures can be performed safely with a lower platelet count.

Dr Brown has received research support from and has consulted for both Dova Pharmaceuticals and Shionogi. In the past, he served as a clinical investigator for trials on eltrombopag.

Suggested Reading

Afdhal N, Duggal A, Ochiai T, et al. Platelet response to lusutrombopag, a thrombopoietin receptor agonist, in patients with chronic liver disease and thrombocytopenia undergoing non-emergency invasive procedures: results from a phase 3 randomized, double-blind, placebo-controlled study. *Blood*. 2017;130(suppl 1):291.

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