Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/thrombocytopenia-and-new-pathways-forward/10462/

Released: 10/31/2018
Valid until: 10/31/2019
Time needed to complete: 15 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Thrombocytopenia & New Pathways Forward

Announcer: This is CME on ReachMD! The following activity *Thrombocytopenia and New Pathways Forward* is provided in partnership with Prova Education and supported by an independent educational grant from Shionogi.

Before beginning this activity, please review the disclosures and learning objectives.

Here's your host, Dr. Matt Birnholz.

Dr. Birnholz: Thrombocytopenia, or low platelet count, is the most frequent hematologic complication of chronic liver disease, and its impact can be devastating on patient care. Due to the risk of bleeding, patients with thrombocytopenia are blocked from receiving crucial invasive therapeutic and diagnostic procedures which affects those with severe disease the most. This leads to questions on how to best manage thrombocytopenic patients with chronic liver disease – questions that we'll address now.

This is CME on Reach MD, and I'm Dr. Matt Birnholz. Joining me is Dr. Robert Brown, Clinical Chief of the Division of Gastroenterology and Hepatology at Weill Cornell Medicine's Center for Liver Disease in New York, New York. Today, we'll discuss recent advances in therapeutic options for patients with severe thrombocytopenia caused by chronic liver disease. Dr. Brown, welcome to the program.

Dr. Brown: It's great to be here. Thank you.

Dr. Birnholz: So, to start off our discussion, can you just give some background on why coagulation disorders occur so frequently in chronic liver disease?

Dr. Brown: Well, the liver is central in the production of both clotting factors and platelets. And, additionally, in the presence of significant liver disease or portal hypertension, we get splenomegaly and then splenic sequestration of platelets. So, in addition to having low clotting factors and an elevated INR, we have low platelet counts, due to both splenic sequestration and low levels of thrombopoietin, which stimulates platelet production. We define this as mild – 100,000 to 150,000, moderate – which some people divide at 100,000, others at 75,000, and severe – which is usually defined as a platelet count of less than 50,000. Patients with severe thrombocytopenia do have an increased risk of bleeding, but paradoxically, perhaps because these platelets are more active, and also because the reduction in anticoagulant and procoagulant factors occur in chronic liver disease, patients are at risk of both bleeding and thrombosis. This thrombocytopenia, bleeding risk, poses an increase in healthcare costs, due to monitoring and complications, as well as decreased access to medical procedures, as you highlighted in the introduction.

Dr. Birnholz: Right, a vicious cycle, if you will, of the liver disease, cascading towards thrombocytopenia, which leads to more consequences downstream. Maybe you can talk to us about the consequences for patients effected with this condition.

Dr. Brown: Well, patients with liver disease and thrombocytopenia, 1) have an increased risk of bleeding when they undergo procedures. Thus, they're less likely to actually have needed procedures, and that is really a difficult number to get your hands around because we don't know how many patients miss necessary procedures, whether that be screening colonoscopies or interventions like cardiac catheterizations that may be lifesaving, as well as orthopedic procedures, et cetera, which greatly impact their quality of life. And, finally, when they do have procedures, they are not only at increased risk, they have increased cost because we often need to do more monitoring, there may be platelet transfusions, other therapies that they need to receive to minimize that risk.

Dr. Birnholz: So given that significant burden of this condition, which, as you're talking about, creates a number of limitations on standard management strategies, it's clear that we, as clinicians, need to find new options for our patients. So, can you just give us an overview of the new agents out there and their mechanisms of action?

Dr. Brown: The gold standard, prior to these new agents being approved, was platelet transfusion. Now, it seems so easy and simple, but platelet transfusion in patients that have large spleens, those new platelets suffer the same consequence as the patient's own platelets – they get sequestered in the spleen, so they're generally poorly effective and have short duration. Other therapies, like splenic artery embolization, where we try to knock out part of the spleen or even, more drastically, splenectomy, have much more morbidity and mortality and haven't been worth the intervention. And that's really where we stood until really the understanding of thrombopoietin or TPO analogs, and we've had thrombopoietin or TPO analogs around for a while, but the first generation never were approved by the FDA for use in chronic liver disease, and until recently, when we had two new agents approved, we didn't have FDA-approved options that were safe and effective.

Dr. Birnholz: For those just tuning in, you're listening to CME on Reach MD. I'm Dr. Matt Brinholz, and I'm joined by Dr. Robert Brown to discuss current and emerging agents for the management of patients with thrombocytopenia due to chronic liver disease.

So, Dr. Brown, you just touched upon that there are some FDA-approved agents for managing these patients. Maybe we can dig a little bit deeper into their properties and indications, respectively. Can you just talk to us about each of these agents and how they compare to each other?

Dr. Brown: Alright. Well, all of them, you know, act through thrombopoietin and the thrombopoietin receptor. Thrombopoietin is made in the liver and responds to low platelet count to increase megakaryocyte activity and platelet production. In patients with chronic liver disease, thrombopoietin levels are too low for the degree of thrombocytopenia. So, increasing the level of thrombopoietin can increase platelet counts. The first agent that was tested from chronic liver disease was eltrombopag. It is a first-generation TPO agonist and it acts on the megakaryocyte through the TPO receptor and was actually tested in patients either undergoing invasive procedures or for interferon-induced thrombocytopenia. Unfortunately, probably due to the dosing, there were thrombotic events, including portal vein thrombosis, likely related to overshooting on the platelet count, and thus, it received a box warning and was never approved for chronic liver disease. Romiplostim is also a first-generation thrombopoietin agonist but was never tested in patients with chronic liver disease. Recently, two agents were specifically approved with the indication of increasing platelet counts in patients with severe thrombocytopenia, defined as a platelet count of less than 50,000, and chronic liver disease in patients undergoing invasive procedures. Precisely the indication that we were looking for. And they designed their study both to look at efficacy but also to maximize safety and minimize the thrombotic risk. Lusutrombopag is a second generation oral TPO receptor agonist and had two registration studies L-Plus 1, L-Plus 2, very similar in design. they compared Lusutrombopag to placebo and showed a statistically lowering in the rate of platelet transfusion, and a statistically higher platelet count compared to placebo. And unlike platelet transfusion, this appeared to have much better duration – over a week – actually over ten days in most patients with a platelet count at the peak. Avatrombopag is another second generation thrombopoietin receptor agonist which is also dosed orally and once daily and, similarly, it had two studies – ADAPT 1 and ADAPT 2. Very similar design. Patients with thrombocytopenia, less than 50,000, with a planned medical or dental procedure where platelet transfusion was going to be given. Drug dosed orally days prior to the procedure – the planned elective procedure – and, once again, compared to placebo, a statistically significant improvement in platelet count and lower platelet transfusion requirements. And, more importantly, both studies did not show that high platelet count, which we define as really above either 150 to 200, and there was no increase in thrombotic events or portal vein thrombosis compared to placebo with either agent.

Dr. Birnholz: A number of the studies focused on procedures that were being prepared for with these agents, so I want to focus then on that perioperative period. Is there any specific perioperative monitoring that you recommend when managing these patients with thrombocytopenia, including those who are taking one of those agents that we just talked about?

Dr. Brown: Well, we don't know really what the optimal platelet count is. But we need to monitor to prevent overshoot with these agents, and so, in general, though if you look into trials, the course of the platelet counts seems to be pretty predictable. In general, what I do is, you know, with enough time before the procedure, that I could arrange for a rescue treatment if I think I need it - for example, platelet transfusion – is to check a platelet count. In patients who start at the high end, close to 50, I may want to check one to look for overshoot. Because of the concern over portal vein thrombosis, I think it's really incumbent on us to document the absence of portal vein thrombosis prior to starting these agents, because portal vein thrombosis can really occur at any time in patients with cirrhosis. And then, whether to do a posttreatment ultrasound is not as clear. Certainly, we did them in the clinical trials to establish safety. Since the rate was so low, I'm not certain that we need to do another ultrasound immediately posttreatment. I'll do an ultrasound prior, and then because all patients with cirrhosis are getting biannual ultrasounds for cancer screening anyway, at the next interval imaging, I

would add on a Doppler of the portal vein to make sure the portal vein is still patent.

Dr. Birnholz: Well, Dr. Brown, before we wrap up, are there any additional takeaway thoughts that you'd like to share with our audience on this subject today?

Dr. Brown: I think the important message is, you know, coagulation disorders and bleeding risks in patients with cirrhosis are complex. They do carry an increased risk of bleeding and, also importantly, an increased risk of clotting. We want to reduce the risk of bleeding in our patients, and these two new drugs provide an addition to our armamentarium to make both ourselves and other doctors, who are performing procedures on our patients, more comfortable with the bleeding risks. We want to prevent overuse because we don't want very high platelet counts. In the ELEVATE study, most of the portal vein thromboses were seen in patients with platelet counts that went over 200,000. I would view as a goal, certainly above 50. in the clinical trials, most patients just had a doubling of their platelet count. These drugs appear to be safe. We are looking forward to future data that really allows us to optimize their use, minimize the monitoring, and, thus, the cost, and does allow our patients to get the procedures that they would benefit from with lower risk and higher comfort, both among surgeons, gastroenterologists, interventional radiologists, and often anesthesiologists, who are reluctant to allow patients to have procedures with substantial thrombocytopenia.

Dr. Birnholz: Well, I have to say it's really encouraging that there are pathways forward for caring for these patients despite the notable challenges posed by thrombocytopenia and chronic liver disease. Dr. Brown, it was great having you on the program. Thanks so much for joining me.

Dr. Brown: Thank you for having me.

Announcer: This CME activity was provided in partnership with Prova Education.

To claim your free CME credits, please complete the post-test and evaluation by visiting ReachMD.com/PROVA.

Thank you for joining us.