Thrombocytopenia in Chronic Liver Disease

New Management Strategies

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KEYWORDS

• Thrombocytopenia • Thrombopoietin • TPO receptor agonists • Cirrhosis
• Advanced liver disease • Invasive procedures • Low platelets

KEY POINTS

- Thrombocytopenia is common in advanced liver disease and can pose management difficulties in patients who require invasive procedures.
- One mechanism of thrombocytopenia in advanced liver disease is decreased hepatocyte production of thrombopoietin.
- Although platelet transfusions are the current standard of care to address preprocedure thrombocytopenia, disadvantages include patient risks, costs, and logistical difficulties.
- Two novel thrombopoietin receptor agonists, avatrombopag and lusutrombopag, were approved in the United States to augment platelet counts before elective procedures in patients with thrombocytopenia caused by advanced liver disease.
- These agents are effective and generally safe in carefully selected patient populations, including those with lower Model for End-stage Liver Disease and Child-Turcotte-Pugh scores.

INTRODUCTION

Chronic liver disease caused by cirrhosis is frequently complicated by thrombocytopenia, particularly when portal hypertension is present. Coagulopathy manifested by increases in prothrombin time (PT) and International Normalized Ratio (INR), in the absence of vitamin K deficiency, are other laboratory signs indicating hepatic synthetic dysfunction. Many patients show both thrombocytopenia and coagulopathy. Consequently, these patients are often assumed to be at higher risk of bleeding complications from invasive procedures, including gastrointestinal endoscopy. Moreover,

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Clin Liver Dis 24 (2020) 437–451
https://doi.org/10.1016/j.cld.2020.04.009
liver.theclinics.com

this patient population is more ill than the general population, and thus more likely to need invasive procedures in general. Invasive procedures are especially common in patients with cirrhosis and complications of portal hypertension, including those undergoing liver transplant evaluation.

Thrombocytopenia may be the first laboratory sign heralding the presence of liver dysfunction. The severity of thrombocytopenia correlates to both severity of liver disease as well as to long-term outcomes.[1] Thrombocytopenia is categorized as mild (platelet count >75,000/μL), moderate (50,000–75,000/μL), and severe (<50,000/μL).[2] It is also common. As many as 76% of patients with cirrhosis have mild thrombocytopenia, and an additional 13% may have more significant degrees of thrombocytopenia.[1]

MECHANISMS OF THROMBOCYTOPENIA IN LIVER DISEASE

The thrombocytopenia observed in liver disease is often multifactorial.[2,3] The most commonly taught mechanism is the sequestration of platelets by the spleen as a result of portal hypertension. Thrombocytopenia in patients with liver disease is such a specific marker of portal hypertension that it is an indication for screening endoscopy for gastroesophageal varices according to the Baveno VI guidelines.[4] However, other causes of thrombocytopenia exist (**Box 1**).

In the setting of hepatic dysfunction, platelets are also underproduced. The growth factor thrombopoietin (TPO), discovered in 1994, is the main regulator of platelet production.[3] TPO acts to prevent platelet apoptosis and increases both the size and number of platelets, as well as their differentiation via binding to its receptor on platelet and megakaryocyte membranes.[2,5] TPO is primarily produced by hepatocytes, and its production is reduced in patients with hepatic dysfunction.[6] In addition, attenuation in platelet response to TPO has been observed in liver disease,[7] and restoration of functioning hepatocytes via liver transplant has been shown to increase both TPO levels and circulating platelets levels.[8] In addition to reduction of TPO, platelets may also be underproduced in liver disease because of concurrent bone marrow suppression from alcohol abuse, untreated hepatitis C virus (HCV), other infections, medications, and nutritional deficiencies.

Increased destruction of existing platelets is a third mechanism of thrombocytopenia in liver disease. These mechanisms include immune-mediated destruction by autoantibodies as well as direct splenic destruction. In addition, dilutional thrombocytopenia is a less common phenomenon in patients with liver disease but can occur with massive blood transfusions or large amounts of crystalloid or colloid for volume resuscitation.

Box 1
Mechanisms of thrombocytopenia in liver disease

Decreased platelet production
- Reduction in thrombopoietin production in hepatic dysfunction
- Marrow suppression (alcohol, hepatitis C virus, nutritional deficiencies, medications)

Removal of circulating platelets
- Hypersplenism/sequestration caused by portal hypertension
- Immune-mediated destruction (autoantibodies)
- Direct splenic destruction

Dilutional
- Intravascular volume resuscitation with crystalloid or colloid
- Massive blood transfusions

The platelet counts measured on routine blood counts are a quantitative measure only, and the numerical value provides no information about platelet function. Platelet dysfunction, even with normal platelet counts, may occur in the setting of chronic kidney disease with uremia, and use of medications that inhibit platelets, such as aspirin, clopidogrel, nonsteroidal antiinflammatory drugs, and serotonin agents. Infections, and sepsis in particular, as well as nutritional deficiencies can also impair platelet function. In addition, in liver disease, bile salts, apolipoprotein E, and fibrinogen degradation products also can inhibit platelet function.[9] The impairment in platelet function directly correlates with the degree of liver dysfunction as measured by the Child-Turcotte-Pugh (CTP) score.[10]

Despite the thrombocytopenia and coagulopathy, patients with liver disease show an increased risk of thromboembolism, particularly in the mesenteric and portal venous circulations. Decreased hepatic synthesis of the anticoagulants antithrombin III and protein C, increases in the procoagulant factor VIII, and decreased fibrinolysis all contribute to a prothrombotic state.[11] When these are combined with reduced velocity of blood flow through the portal circulation from cirrhosis and portal hypertension, portal and/or mesenteric vein thrombosis may occur.

This thrombotic tendency is not measured on routine laboratory testing and this makes it difficult to accurately estimate the bleeding risks in patients with liver disease. Measures of platelet count, PT, and partial thromboplastin time (PTT) are only a partial reflection of the overall hemostatic balance in liver disease.[11,12] Discrepancies exist in perception of bleeding risk, with some data suggesting thrombin generation is adequate for clotting as long as platelets are at least 56,000/μL,[13] whereas other studies have shown higher procedure bleeding risk caused by thrombocytopenia.[14,15] To obviate this issue, some centers use thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to help characterize specific degradations in clot formation and dissolution and thus clarify whether a patient has tendencies toward bleeding versus clotting. TEG is commonly used during liver transplant[16] and increasingly used in inpatient settings to help guide transfusions.

AVAILABLE THROMBOPOIETIN AGONISTS

The cloning of TPO in 1994 generated interest in the use of TPO receptor agonists to treat thrombocytopenia.[3] The original agents mimicked the structure of TPO but caused severe cross reactivity and subsequent inhibition of endogenous TPO, resulting in a paradoxic reduction in platelet counts.[2,3] Newer agents are structurally dissimilar to TPO and thus avoid this cross reactivity.

The original TPO receptor agonist was romiplastin (Nplate, Romiplate). Only small studies exist in patients with liver disease, and currently it is limited to use for hematological disorders.[17–19] A second agent, eltrombopag (Promacta, Revolade), was used to address thrombocytopenia in patients with liver disease. However, both romiplastin and eltrombopag carry significant safety concerns, including formation of portal venous thrombosis (PVT),[20–22] and additionally, eltrombopag has risks of hepatotoxicity. Thus, neither agent is currently recommended for use in patients with thrombocytopenia caused by liver disease.

The interest in platelet count augmentation with TPO receptor agonists increased once again with the development of newer oral agents with high efficacy and fewer safety concerns. In 2018, 2 oral agents, avatrombopag (Doptelet), and lusutrombopag (Mulpleta), were both approved by the US Food and Drug Administration (FDA) for use in patients with thrombocytopenia caused by liver disease undergoing elective procedures.

Avatrombopag was studied in the ADAPT-1 and ADAPT-2 studies.[23,24] These studies were randomized, double-blind, placebo-controlled, multicenter, global phase III clinical trials. In both trials, avatrombopag at dosages of 40 or 60 mg/d (based on initial platelet counts <40,000/μL or ≥40,000/μL but <50,000/μL) for 5 days, or placebo, was administered to 231 (ADAPT-1) and 204 (ADAPT-2) patients with thrombocytopenia caused by advanced liver disease who were undergoing scheduled outpatient procedures. The study drug was taken orally once daily for a total of 5 days. The platelet counts were measured again at the procedure date, as well as 1 week and 5 weeks after the procedure.

The procedures varied in bleeding risk but were deemed lower risk in 61% of the patients, and no higher-risk (intracranial/intraspinal) procedures were included. In addition, because of the potential PVT risk observed with earlier TPO receptor agonists, patients were carefully selected to reduce this risk. Patients with known prior PVT or advanced hepatocellular carcinoma (HCC), prior thrombosis, current mesenteric or PVT, or decreased portal vein velocities were excluded.

Avatrombopag increased the platelet count by a mean of 31,000 to 32,000/μL at the higher dosage of 60 mg/d, versus a change of 800 to 3000/μL for placebo groups. At the lower dosage of 40 mg/d, for patients with slightly higher baseline counts, the mean platelet count increased by 37,000 to 45,000/μL in both trials, compared with 1000 to 6000/μL in the placebo group. Overall, 65% of patients in the lower platelet count group, and 87% in the higher baseline platelet group, reached the primary end point of platelet count greater than 50,000/μL and no bleeding events before the procedure, compared with placebo rates of 22% to 23%. Platelet counts began to increase by day 4, peaked between 10 and 13 days, and gradually returned to baseline over the next month.

The drug showed an excellent safety profile. With the exclusion criteria listed earlier, PVT risks were overall low, occurring in 1 patient on 40 mg, discovered on day 18 and not thought to be related to the study drug. The overall thromboembolic rate was not different than placebo.[23,24]

Lusutrombopag had been used in the correction of thrombocytopenia caused by liver disease in patients in Asia for a few years before approval in the United States, mostly in procedures done by interventional radiology.[25–30] However, the FDA approval for lusutrombopag use in the United States came after the completion of the phase III L-PLUS-1 and L-PLUS-2 trials.[31,32]

In these randomized, double-blind, placebo-controlled studies, patients with liver disease and thrombocytopenia undergoing procedures necessitating platelet correction were administered 3 mg/d of oral lusutrombopag or placebo before their elective procedures. These procedures were performed 9 to 14 days after the first dose. The L-PLUS-1 trial included 97 patients and the L-PLUS-2 included 215 patients. Unlike the ADAPT trials, the L-PLUS-1 and L-PLUS-2 trials included platelet monitoring at days 5 to 8, and, if the platelet count surpassed the 50,000/μL target by days 5 to 7, the drug could be stopped early. In addition, screening ultrasonography scans were used to detect PVT before and after study drug dosing.

In the L-PLUS-1 trial, 79% of patients receiving lusutrombopag achieved platelet counts of greater than 50,000/μL, compared with 12.5% in the placebo group. In the L-PLUS-2 trial, 70% of patients who received lusutrombopag achieved the target platelet count and showed an increase greater than 20,000/μL, compared with 14% in the placebo group. The mean increase in platelet count was approximately 45,000/μL compared with 11,000/μL in the placebo group. Similar to avatrombopag, lusutrombopag did not have an increased risk of PVT. One patient receiving lusutrombopag developed a PVT not thought to be related to the study

drug, but the overall thrombosis rates between the study drug and placebo were similar.

These studies showed the safety and efficacy of oral TPO receptor agonists to augment platelet counts with sustained duration, allowing completion of procedures, in patients who were not at increased risk of PVT formation.

INDIVIDUALIZED APPROACHES TO THROMBOCYTOPENIA

In the elective procedure setting, significant variation is observed in the approach to thrombocytopenia management. Although society guidelines are available, these reflect recommendations in the general population and are not specific to thrombocytopenia or coagulopathy in patients with advanced liver disease. As discussed earlier, bleeding and thrombosis in liver disease are not accurately reflected in the routine laboratory abnormalities observed in advanced liver disease, making estimation of bleeding risk in these patients less straightforward than in those with thrombocytopenia from a hematological abnormality.

Many components contribute to the variation in the approach to thrombocytopenia,[33] summarized in **Table 1**. Factors that are specific to each patient include the degree of thrombocytopenia, in conjunction with coexistent coagulopathy (PT/INR or PTT increases), as well as use of medications that could increase bleeding risks (such as aspirin, nonsteroidal antiinflammatory drugs, clopidogrel, low-molecular-weight heparin, warfarin, and newer oral anticoagulants). The presence and degree of uremia in patients with kidney disease may also affect platelet function. Thus, severe thrombocytopenia in a patient with coexistent kidney disease with uremia is likely clinically different than the same platelet count in a patient without kidney disease.

In addition, a prior history of bleeding (particularly procedurally related), the severity of prior bleeding, the precise platelet count, the procedure, and other circumstances in which the bleeding occurred are also relevant. Spontaneous or unprovoked bleeding, such as severe bleeding from routine polypectomy, may be viewed with more concern than bleeding from higher-risk procedures, such as severe bleeding from biliary sphincterotomy. Prior response to platelet transfusions may also be relevant. Attempts to transfuse platelets preprocedure may be inadvisable in patients who

Table 1
Factors influencing platelet count preferences

Patient Specific	Provider Specific	Procedure Specific
• Severity of thrombocytopenia • Concurrent coagulopathy • Medications (antiplatelet agents, anticoagulants) • Prior bleeding history and degree of thrombocytopenia at prior bleeding • Known platelet refractoriness	• Institutional protocols • Local practice patterns • Population socioeconomics and medical-legal culture • Degree of risk aversion, including concerns about litigation or recent poor outcome • Prior training methods • Degree of experience and comfort with the procedure	• Procedure bleeding risk in general population • Severity of bleeding outcomes (likelihood of catastrophic outcome vs minor manageable outcome) • Location/facility type: stand-alone endoscopy center or tertiary center with emergency room, interventional radiology, and surgery readily available

have historically responded poorly, and procedure-specific modifications may be undertaken in patients with known platelet transfusion refractoriness.

Provider-specific factors also occur. The clinical experience of the provider, training patterns, personality, and degree of risk aversion all contribute to stylistic differences in baseline platelet count preferences before a particular procedure.

Practice locale and patient population may also affect practice patterns. Providers who frequently perform procedures for patients with advanced liver disease may have less aversion to procedures and have lower thresholds for concern with lower platelet counts in these patients, compared with those who rarely care for such patients. Institutional culture and formally designed protocols, patient socioeconomic status, and associated regional medicolegal culture may also influence practice patterns. Facility factors are relevant; some practitioners, particularly in stand-alone procedure facilities, may prefer to avoid higher-risk procedures in patients with severe thrombocytopenia and instead perform them at hospital-based facilities, where emergency department, interventional radiology, laboratory and blood bank services, and surgical backup are immediately available. In such centers, that same provider may tolerate a greater degree of bleeding risk (including lower platelet counts) than in an isolated facility requiring ambulance transport if a complication occurred.

In addition, another consideration is the severity of bleeding; consequences may be vastly different depending on the location within the body, as well as available methods to treat the bleeding. For example, intracranial bleeding could be catastrophic with long-term sequelae, whereas biliary sphincterotomy bleeding is often self-limited and overall less likely to have long-term consequences. Treatment options are also a factor. For example, a severe polypectomy bleed where interventional radiology is not readily available for embolization may result in emergent partial colectomy to control bleeding. Thus, all of these considerations are important in any specific provider's approach to an elective procedure in patients with advanced liver disease and severe thrombocytopenia.

In addition, and most importantly, the risk stratification of the procedure is critical in influencing whether platelet counts must be augmented in patients with severe thrombocytopenia. Patients with advanced liver disease often require many different types of procedure (**Table 2**). Within gastroenterology, the American Society of Gastrointestinal Endoscopy (ASGE) guidelines designate procedures as higher or lower risk.[34] Procedures in which bleeding is lower risk include paracentesis and routine esophagogastroduodenoscopy (EGD) or colonoscopy with biopsy, as well as polypectomy of smaller polyps, endoscopic variceal ligation, push or balloon enteroscopy, and capsule endoscopy. More advanced procedures at lower risk of bleeding include Barrett esophageal ablation, argon plasma coagulation, endoscopic ultrasonography (EUS) without fine-needle aspiration (FNA), and endoscopic retrograde cholangiopancreatography (ERCP) without sphincterotomy. Transjugular liver biopsy is also considered by some clinicians to be low risk, but opinions on this vary widely.

Moderate-risk procedures in terms of bleeding include percutaneous liver biopsy, colonoscopy with polypectomy of larger polyps, ERCP with sphincterotomy, placement of percutaneous gastrostomy or jejunostomy tubes, cystogastrostomy, ampullectomy, endoscopic mucosal resection or submucosal dissection, and pneumatic dilation of esophageal or other strictures. Many other procedures outside gastroenterology and hepatology are low or moderate risk, such as bronchoscopy, cardiac catheterization, bone marrow biopsy, and lumbar puncture. Those procedures deemed at the highest bleeding risk are generally intracranial or intraspinal procedures.

In general, the provider who is performing a procedure determines the specific platelet threshold for a specific procedure. This decision is individualized but may

Table 2
Commonly performed procedures in patients with liver disease

Bleeding Risk Suggested Platelet Target	Gastroenterology/Hepatology	Other Procedures/Specialists
Low >20,000/μL	Paracentesis Small polypectomy Diagnostic EGD or colonoscopy Mucosal biopsies Push enteroscopy Capsule endoscopy EUS without FNA Enteral stent deployment Argon plasma coagulation Barrett esophagus ablation ERCP without balloon dilation ERCP without stent Prophylactic variceal banding	Transjugular liver biopsy Bone marrow biopsy Central line placement Bronchoscopy, without biopsy Thoracentesis Percutaneous biliary interventions TIPS placement
Moderate >50,000/μL	Percutaneous liver biopsy Large polypectomy CystogastrostomyAmpullectomy Endoscopic mucosal resection or submucosal dissection Pneumatic or bougie dilation ERCP with sphincterotomy Endoscopic tumor ablation Percutaneous gastrostomy/jejunostomy tube EUS with FNA Endoscopic hemostasis	Cardiac catheterization Percutaneous organ biopsy Lumbar puncture Locoregional therapy for HCC Surgery (noncranial, nonspine)
High >100,000/μL	—	Intracranial Intraspinal

Abbreviations: EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; TIPS, transvenous intrahepatic portosystemic shunt.

be made in collaboration with the referring provider. Providers in specialties outside of gastroenterology and hepatology who perform procedures on patients with advanced liver disease and severe thrombocytopenia determine the thrombocytopenia management strategy.

PROCEDURE-SPECIFIC PLATELET RECOMMENDATIONS

Despite the aforementioned variations in practice, certain procedures have established recommendations for platelet goals. Guidelines from the ASGE for gastrointestinal endoscopy procedures[35] suggest routine laboratory monitoring before procedures in patients who may have a higher risk of bleeding, which generally includes patients with advanced liver disease.[34] Although higher-risk procedures may be safest if platelets are augmented to at least 50,000/μL, lower-risk procedures such as diagnostic upper endoscopy may be safely performed at platelet counts of 20,000/μL.[36]

The American Association for the Study of Liver Disease (AASLD) guidelines for paracentesis[37] do not recommend augmenting platelets before performing this procedure because of low bleeding risks even in patients with severe thrombocytopenia.[38] In contrast, liver biopsy is considered a higher-risk procedure, with nonsevere bleeding occurring in 1 in 500 cases.[39] Most hepatologists and interventional radiologists performing percutaneous liver biopsies prefer to correct thrombocytopenia to levels of at least 50,000/μL before the procedure.

Providers outside of gastroenterology and hepatology performing procedures in patients with advanced liver disease often prefer platelet counts of at least 50,000/μL. This level is supported by guidelines,[40–43] even if not directly studied in advanced liver disease. However, in 2019, the Society of Interventional Radiology released updated guidelines on this topic.[44,45] Procedures are now categorized as low or high risk. Recommendations for low-risk procedures include a platelet threshold of 20,000/μL, and, for higher-risk procedures, at least 50,000/μL. Lower-risk procedures relevant to patients with advanced liver disease include paracentesis, thoracentesis, lumbar puncture, and transvenous liver biopsy. Higher-risk procedures performed by interventional radiologists include biliary and portal vein interventions, percutaneous liver and other solid organ biopsies, arterial interventions (including locoregional therapy for HCC), and placement of transvenous intrahepatic portosystemic shunt (TIPS). These updated guidelines will likely result in the evolution of practice patterns of correction of thrombocytopenia in the future.

MANAGEMENT OF THROMBOCYTOPENIA

Two major strategies exist to address periprocedure thrombocytopenia. These strategies include modification of the procedure technique, setting, or personnel, or augmentation of the patient's platelet count via platelet transfusion or use of the TPO receptor agonists.

Procedural Modifications

Rather than correcting thrombocytopenia, postponement of the intended procedure may be justified in some cases. For example, biopsies are generally considered low risk, but they may be forsaken in patients who have salmon-colored esophageal mucosa suggestive of Barrett esophagus with no visible lesion, in the setting of esophageal varices. Deferral of elective procedures until after liver transplant is also an option for some patients.

In addition, if a procedure is necessary, providers who are less comfortable can refer the patient to another provider. Further, a provider may choose to perform a procedure in a hospital-based setting instead of an outpatient facility if there is increased risk.

In cases where the procedure must be performed (such as ERCP for choledocholithiasis and cholangitis), the endoscopist may alter the procedure technique to minimize bleeding risks, such as avoiding sphincterotomy. Even hemostatic techniques are influenced by thrombocytopenia and coagulopathy; electrocautery methods may be avoided in favor or mechanical options, such as hemostatic clips.

Platelet Transfusions

Frequently, elective procedures must be performed in patients with advanced liver disease and severe thrombocytopenia. In these settings, transfusion of platelets is the standard of care and the most rapid method to correct thrombocytopenia.

In the general patient population, 1 unit of platelets increases the total platelet count by approximately 30,000/μL, within the first few minutes of completion. One unit of platelets can be administered in 20 to 30 minutes.[40] However, in patients with advanced liver disease, platelet transfusions are less effective in increasing the platelet count; the average increase in platelet count is only 12,000/μL. Despite this, studies of rotational thromboelastometry in patients with liver disease have shown that, even though the increase in platelet counts may be blunted, clot firmness is still augmented.[46]

Issues with platelet transfusions are summarized in **Box 2**. Although platelet transfusion is generally considered safe and efficacious, adverse events are common.[40] Febrile, allergic, or hypersensitivity reactions are observed, and, in some cases, patients must be pretreated with diphenhydramine, acetaminophen, and/or prednisone. Transfusion-related acute lung injury and transfusion-associated circulatory overload can also occur; however, this is likely more common in the inpatient setting when patients require a large number of transfusions, and less likely in an outpatient setting when fewer units are transfused.

Additional medical risks of platelet transfusions include transfusion-related graft-versus-host disease; bacterial, viral, or parasitic infections; and hemolysis.[40] In addition, in patients who have required multiple blood product transfusions, alloimmunization can occur, whereby recipients form antibodies against donor platelets. Alloimmunization is difficult to prevent in the setting of frequent transfusions. It may contribute to the refractoriness seen in some patients who fail to achieve an adequate increase in platelet counts after platelet transfusion. For patients with significant alloimmunization, matched platelets can be sought. Although effective, the strategy of matching platelets can cause significant delays related to availability. In patients who are liver transplant candidates, alloimmunity can create significant difficulty

Box 2
Platelet transfusion issues

Medical safety issues
- Febrile reactions
- Allergic or hypersensitivity reactions
- Transfusion-related lung injury or cardiac overload
- Graft-versus-host disease
- Hemolysis (minor ABO incompatibilities)
- Infections (viral, bacterial, and parasitic)
- Alloimmunization/platelet refractoriness

Failure of platelet counts to increase to desired target
- Additional units must be ordered/administered
- Procedure is canceled, delayed, or modified to address thrombocytopenia

Cost issues
- Actual platelet doses
- Pretreatment of patients with prior sensitivity
- Monitoring during/after transfusion
- Any necessary treatment of reactions
- Lost productivity for patient/caregiver, transportation, and parking costs

Logistical issues
- Patients must come to a transfusion center or hospital setting for monitoring
- Availability of platelets must be timed, including matched platelets
- Scheduling issues (holidays/center closures, patient scheduling)
- Storage and shelf life of platelets (doses may be discarded, and so forth)

with appropriate response to platelets intraoperatively. Thus, particularly in patients who are liver transplant candidates or undergoing other major surgeries in which large amounts of blood products may be required, repeated platelet transfusions are best avoided when possible.

In addition, transfusion of platelets is associated with high costs and logistical issues. One study estimated that the cost of platelet transfusion in patients undergoing percutaneous liver biopsy was more than $7000.[47] In addition, platelet transfusions are usually administered in either a transfusion center or hospital center to allow for adequate monitoring; this may pose logistical difficulties if patients must travel to the center. Logistical issues may result in missed days of work or school for the patient or caregivers, as well as nonadherence to transfusion strategies if transportation is burdensome. Additional logistical issues include availability of platelets (particularly if matched platelets are necessary), scheduling of transfusions in coordination with the scheduled procedure, and the storage and shelf life of platelets. However, despite these issues, platelet transfusion remains the mainstay of managing thrombocytopenia before invasive procedures in the inpatient and outpatient settings.

Correction of Thrombocytopenia via Thrombopoietin Receptor Agonists

TPO receptor agonists are a useful alternative to outpatient platelet transfusions in appropriate settings. With these agents, platelet counts remain increased for a longer duration than platelet transfusions, and thus allow a longer window to complete, reschedule, or even repeat the procedure. After 5 doses of avatrombopag, platelet counts increase, and return to baseline over the next month.[23] With lusutrombopag, platelet counts may remain more than 50,000/μL for up to 3 weeks.[31,48,49]

TPO receptor agonists are inappropriate in certain populations. The products were not studied in pediatric populations or in pregnant and lactating women. There are also few data in patients with significant kidney disease. However, in patients with creatinine clearance more than 30 mL/min, no dose adjustments are needed. Both approved drugs undergo hepatic metabolism. Lusutrombopag was only studied in cirrhotic patients with CTP class A and B, whereas avatrombopag was studied in CTP A, B, and C, but only in patients with Model for End-stage Liver Disease (MELD) scores less than 23. In these specific populations, neither drug needs to be dose reduced. However, in patients with more severe liver disease, dosing is not specified, and caution or complete avoidance is suggested.

No antidotes are available in the setting of overdose of TPO receptor agonists and neither drug can be removed by hemodialysis. Furthermore, rapid increases in platelet count with older TPO receptor agonists were associated with the formation of PVT.[49,50] Patients at higher risk of PVT have a relative, but not necessarily absolute, contraindication, to use of the newer agents. These patients include those with advanced hepatocellular carcinoma, Budd-Chiari syndrome, sinusoidal obstructive syndrome, and those with inherited hypercoagulable states. The presence of slow portal vein flow (<10 cm/s) and/or prior platelet transfusions within 7 days were also exclusion criteria in the pivotal studies, and thus patients meeting these conditions should ideally avoid these agents. Absolute contraindications to use of TPO receptor agonists include patients with prior PVT or current thrombosis of the portal or mesenteric vessels.

Usage of TPO receptor agonists must be timed correctly before the planned date of the elective procedure. Because of potential delays related to insurance, it is recommended to prescribe the medication several weeks in advance of the procedure.

The dosing of TPO receptor agonists is based on baseline platelet count, and timing is based on the date of the procedure. Avatrombopag comes in 20-mg tablets. The dosage of 60 mg/d is used for patients with platelet counts less than 40,000/μL, whereas the 40 mg dose is used if platelet counts are greater than or equal to 40,000 to 49,000/μL. Both regimens are dosed once daily for 5 days. After the last dose, the procedure is recommended to be performed 5 to 8 days later. Thus, if day 1 is designated as the first dose, the procedure can be performed on day 10 to 13. Lusutrombopag has 1 dosing schedule of 3 mg/d for 7 days for patients with any platelet count less than 50,000/μL. The procedure should be performed in a 7-day window beginning 1 day after the drug is finished. Assuming day 1 represents the first dose of lusutrombopag, the procedure is ideally performed on day 9 to 15.

Platelet counts should be obtained on the day of the procedure or the day preceding to ensure they are at or greater than the desired target range[49,50]; if they are not, platelet transfusion may still be necessary. There are no recommendations on checking the platelet count during the course of therapy.

Ideally, the procedure should not be deferred after the patient has started the medication, and, if the procedure is delayed outside the recommended window, platelet counts must be rechecked. Prescribing a second course or extending the course of the dose to accommodate procedure schedule delays was not studied. Thus, it is ideal to confirm the procedure date with the patient, the proceduralist, and the location earlier than usual to ensure that rescheduling is unnecessary, that the patient obtained the medication, and that the patients is completely clear on when to start the medication.

FUTURE STUDIES

Avatrombopag and lusutrombopag are still new, and postmarketing data will be important to help clinicians refine the use of these agents. At present, none of the American gastroenterology and hepatology societies have incorporated these agents into their guidelines. Many questions remain unanswered. These questions include the appropriate dosing for patients with thrombocytopenia who have platelet goals lower or higher than 50,000/μL. Furthermore, monitoring of the platelet count during the course of therapy is not delineated by current prescribing guidelines. It is also unclear whether additional doses are safe and result in longer duration of increased platelets counts, or whether repeated courses of the drugs are safe and effective. Although small studies suggest overall safety with repeated dosing,[25,27] the appropriate safety period between a first and second course has yet to be determined.

In addition, whether or not patients should be monitored for PVT is unclear. It may be prudent to obtain baseline portal vein imaging with MRI or Doppler ultrasonography to avoid prescribing these agents in patients with unidentified PVT.

In addition, use of TPO receptor agonists in patients with platelet counts 50,000/μL or higher in need of neurosurgical procedures that require platelet counts of greater than 100,000/μL is also unstudied.

Another potential area of study is the effect of TPO receptor agonists on the clotting and dissolution parameters measured by TEG and ROTEM. If thrombocytopenia is corrected but the TEG parameters suggest that the patient remains at increased risk for bleeding based on platelet dysfunction, platelet transfusion may still be necessary. In the clinical trials, the absence of bleeding was used as a surrogate marker for adequate platelet function.

Although these novel agents are exciting, caution must be exercised. These issues will be important to revisit in the next few years as more experience with the TPO receptor agonists is gained.

SUMMARY

Patients with underlying advanced liver disease develop thrombocytopenia from a variety of mechanisms, and may or may not be at higher risk of bleeding from invasive procedures than those with normal platelet counts. In patients who need procedures for which target platelet counts more than 50,000/μL are recommended, the TPO receptor agonists, avatrombopag and lusutrombopag, are a convenient alternative method to platelet transfusion to augment platelet counts. These oral agents can be taken at home before the planned, elective procedure and thus may avoid the routine use of platelet transfusions normally administered for this purpose. In addition, unlike the rapid decline in platelet counts observed after platelet transfusion, these agents provide a more sustained increase in platelet counts, thus allowing a longer window of opportunity to safely perform the procedure. Avatrombopag and lusutrombopag are overall safe, without the increased risks of PVT concerns of first-generation agents, at least in the setting of selection of patients at lowest risk for this complication. In specific populations of patients with advanced liver disease and severe thrombocytopenia for whom an elective procedure is planned, a TPO agonist may be optimal. However, for certain patients, these agents may be inappropriate, so judicious use is indicated.

DISCLOSURE

K.M. Nilles has nothing to disclose. S.L. Flamm is a consultant for Shionogi.

REFERENCES

1. Giannini EG. Review article: thrombocytopenia in chronic liver disease and pharmacologic treatment options. Aliment Pharmacol Ther 2006;23(8):1055–65.
2. Afdhal N, McHutchison J, Brown R, et al. Thrombocytopenia associated with chronic liver disease. J Hepatol 2008;48(6):1000–7.
3. Maan R, de Knegt RJ, Veldt BJ. Management of thrombocytopenia in chronic liver disease: focus on pharmacotherapeutic strategies. Drugs 2015;75(17):1981–92.
4. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63(3):743–52.
5. Kaushansky K. Thrombopoietin. N Engl J Med 1998;339(11):746–54.
6. Peck-Radosavljevic M, Zacherl J, Meng YG, et al. Is inadequate thrombopoietin production a major cause of thrombocytopenia in cirrhosis of the liver? J Hepatol 1997;27(1):127–31.
7. Peck-Radosavljevic M, Wichlas M, Pidlich J, et al. Blunted thrombopoietin response to interferon alfa-induced thrombocytopenia during treatment for hepatitis C. Hepatology 1998;28(5):1424–9.
8. Peck-Radosavljevic M, Wichlas M, Zacherl J, et al. Thrombopoietin induces rapid resolution of thrombocytopenia after orthotopic liver transplantation through increased platelet production. Blood 2000;95(3):795–801.
9. Witters P, Freson K, Verslype C, et al. Review article: blood platelet number and function in chronic liver disease and cirrhosis. Aliment Pharmacol Ther 2008;27(11):1017–29.
10. Tapper EB, Robson SC, Malik R. Coagulopathy in cirrhosis - the role of the platelet in hemostasis. J Hepatol 2013;59(4):889–90.
11. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med 2011;365(2):147–56.

12. Intagliata NM, Argo CK, Stine JG, et al. Concepts and controversies in haemostasis and thrombosis associated with liver disease: proceedings of the 7th international coagulation in liver disease conference. Thromb Haemost 2018;118(8):1491–506.
13. Tripodi A, Primignani M, Chantarangkul V, et al. Thrombin generation in patients with cirrhosis: the role of platelets. Hepatology 2006;44(2):440–5.
14. Sharma M, Yong C, Majure D, et al. Safety of cardiac catheterization in patients with end-stage liver disease awaiting liver transplantation. Am J Cardiol 2009;103(5):742–6.
15. Giannini EG, Greco A, Marenco S, et al. Incidence of bleeding following invasive procedures in patients with thrombocytopenia and advanced liver disease. Clin Gastroenterol Hepatol 2010;8(10):899–902 [quiz: e109].
16. Stravitz RT. Potential applications of thromboelastography in patients with acute and chronic liver disease. Gastroenterol Hepatol (N Y) 2012;8(8):513–20.
17. Moussa MM, Mowafy N. Preoperative use of romiplostim in thrombocytopenic patients with chronic hepatitis C and liver cirrhosis. J Gastroenterol Hepatol 2013;28(2):335–41.
18. Voican CS, Naveau S, Perlemuter G. Successful antiviral therapy for hepatitis C virus-induced cirrhosis after an increase in the platelet count with romiplostim: two case reports. Eur J Gastroenterol Hepatol 2012;24(12):1455–8.
19. Al-Samkari H, Marshall AL, Goodarzi K, et al. Romiplostim for the management of perioperative thrombocytopenia. Br J Haematol 2018;182(1):106–13.
20. Afdhal NH, Giannini EG, Tayyab G, et al. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. N Engl J Med 2012;367(8):716–24.
21. Afdhal NH, Dusheiko GM, Giannini EG, et al. Eltrombopag increases platelet numbers in thrombocytopenic patients with HCV infection and cirrhosis, allowing for effective antiviral therapy. Gastroenterology 2014;146(2):442–452 e441.
22. Dultz G, Kronenberger B, Azizi A, et al. Portal vein thrombosis as complication of romiplostim treatment in a cirrhotic patient with hepatitis C-associated immune thrombocytopenic purpura. J Hepatol 2011;55(1):229–32.
23. Terrault N, Chen YC, Izumi N, et al. Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. Gastroenterology 2018;155(3):705–18.
24. Terrault NA, Hassanein T, Howell CD, et al. Phase II study of avatrombopag in thrombocytopenic patients with cirrhosis undergoing an elective procedure. J Hepatol 2014;61(6):1253–9.
25. Sato S, Miyake T, Kataoka M, et al. Efficacy of repeated lusutrombopag administration for thrombocytopenia in a patient scheduled for invasive hepatocellular carcinoma treatment. Intern Med 2017;56(21):2887–90.
26. Sakamaki A, Watanabe T, Abe S, et al. Lusutrombopag increases hematocytes in a compensated liver cirrhosis patient. Clin J Gastroenterol 2017;10(3):261–4.
27. Kotani S, Kohge N, Tsukano K, et al. Avoidance of platelet transfusion with readministration of lusutrombopag before radiofrequency ablation in hepatocellular carcinoma: a case report. Nihon Shokakibyo Gakkai Zasshi 2017;114(10):1853–9.
28. Fujita M, Abe K, Hayashi M, et al. Two cases of liver cirrhosis treated with lusutrombopag before partial splenic embolization. Fukushima J Med Sci 2017;63(3):165–71.
29. Kim ES. Lusutrombopag: first global approval. Drugs 2016;76(1):155–8.

30. Tateishi R, Seike M, Kudo M, et al. A randomized controlled trial of lusutrombopag in Japanese patients with chronic liver disease undergoing radiofrequency ablation. J Gastroenterol 2018;54(2):171–81.
31. Hidaka H, Kurosaki M, Tanaka H, et al. Lusutrombopag reduces need for platelet transfusion in patients with thrombocytopenia undergoing invasive procedures. Clin Gastroenterol Hepatol 2018;17(6):1192–200.
32. Peck-Radosavljevic M, Simon K, Iacobellis A, et al. Lusutrombopag for the treatment of thrombocytopenia in patients with chronic liver disease undergoing invasive procedures (L-PLUS 2). Hepatology 2019;70(4):1336–48.
33. Nilles KM, Caldwell SH, Flamm SL. Thrombocytopenia and procedural prophylaxis in the era of thrombopoietin receptor agonists. Hepatol Commun 2019; 3(11):1423–34.
34. Committee ASoP, Pasha SF, Acosta R, et al. Routine laboratory testing before endoscopic procedures. Gastrointest Endosc 2014;80(1):28–33.
35. Committee ASoP, Acosta RD, Abraham NS, et al. The management of antithrombotic agents for patients undergoing GI endoscopy. Gastrointest Endosc 2016; 83(1):3–16.
36. Committee ASoP, Ben-Menachem T, Decker GA, et al. Adverse events of upper GI endoscopy. Gastrointest Endosc 2012;76(4):707–18.
37. Runyon BA, Aasld. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013;57(4):1651–3.
38. Grabau CM, Crago SF, Hoff LK, et al. Performance standards for therapeutic abdominal paracentesis. Hepatology 2004;40(2):484–8.
39. Rockey DC, Caldwell SH, Goodman ZD, et al. American association for the study of liver D. Liver biopsy. Hepatology 2009;49(3):1017–44.
40. Schiffer CA, Bohlke K, Delaney M, et al. Platelet transfusion for patients with cancer: American society of clinical Oncology clinical practice guideline update. J Clin Oncol 2018;36(3):283–99.
41. Patel IJ, Davidson JC, Nikolic B, et al. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. J Vasc Interv Radiol 2012;23(6):727–36.
42. Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med 2015;162(3):205–13.
43. Szczepiorkowski ZM, Dunbar NM. Transfusion guidelines: when to transfuse. Hematology Am Soc Hematol Educ Program 2013;2013:638–44.
44. Davidson JC, Rahim S, Hanks SE, et al. Society of Interventional Radiology Consensus Guidelines for the periprocedural management of thrombotic and bleeding risk in patients undergoing percutaneous image-guided interventions-Part I: review of anticoagulation agents and clinical considerations: endorsed by the Canadian Association for Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe. J Vasc Interv Radiol 2019; 30(8):1155–67.
45. Patel IJ, Rahim S, Davidson JC, et al. Society of interventional radiology consensus guidelines for the periprocedural management of thrombotic and bleeding risk in patients undergoing percutaneous image-guided interventions-part II: recommendations: Endorsed by the Canadian Association for Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe. J Vasc Interv Radiol 2019;30(8):1168–84.e1.

46. Tripodi A, Primignani M, Chantarangkul V, et al. Global hemostasis tests in patients with cirrhosis before and after prophylactic platelet transfusion. Liver Int 2013;33(3):362–7.
47. Basu PNT, Farhat S, Shah NJ, et al. Single use of romiplostim thrombopoietin analogue in severe thrombocytopenia for outpatient percutaneous liver biopsy in patients with chronic liver disease–a randomized double blinded prospective trial. J Hepatol 2012;56(Supplement 2):S38.
48. Afdhal N, Duggal A, Ochiai T, et al. Lusutrombopag for treatment of thrombocytopenia in patients with chronic liver disease who are undergoing non-emergency invasive procedures: results from an international phase 3, randomized, double-blind, placebo-controlled study (L-PLUS-2). Hepatology 2017;66(6):1254A.
49. FDA prescribing information Mulpleta (lusutrombopag). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210923s000lbl.pdf. Accessed November 1, 2018.
50. FDA prescribing information doptelet (avatrombopag). 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210238s000lbl.pdf. Accessed November 1, 2018.