How I treat sinusoidal obstruction syndrome

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Sinusoidal obstruction syndrome (SOS), previously called veno-occlusive disease (VOD) can be a difficult problem after hematopoietic cell transplantation (HCT). The overall incidence has changed since the early days of allogeneic HCT. Prophylaxis and treatment remain important components of supportive care. As the indication and the comorbidities for HCT continue to change, especially with older and more infirm patients, SOS remains an important area for clinicians. I discuss how SOS could be addressed, from prophylaxis to diagnosis and potential therapy. (*Blood*. 2014;123(26):4023-4026)

Introduction

Sinusoidal obstruction syndrome (SOS), previously called veno-occlusive disease (VOD), can be a devastating complication after hematopoietic cell transplantation (HCT). Although the overall incidence and severity has fallen significantly, severe SOS remains a formidable problem. As the name implies, the hepatic vascular endothelial cells are damaged by the preparatory regimen, initiating the clinical syndrome.[1-4] The damaged endothelium can be seen in the sinusoidal endothelial cells and in the hepatocytes, with deposition of fibrinogen, factor VIII, and erythrocyte congestion resulting in enlarged sinusoids. Sloughed sinusoidal endothelial cells, red cells, and stellate cells embolize downstream, leading to venous occlusion that can progress to disruption of the normal liver architecture and centrilobular necrosis.[5,6] In the late phases of the disease, fibrosis and occlusion of the terminal venules develop, leading to hepatic failure and possibly death. Parallel to the physical damage, there is a procoagulant state with low levels of antithrombin, protein C (which may be a useful marker) and factor VII, and increased levels of plasminogen activator inhibitor 1.[7-11] The severity of the syndrome is proportional to the extent of injury to the liver.

The old adage "an ounce of prevention is worth a pound of cure" is appropriate to ascribe to this disease because therapeutic options are limited. Yet the data on prevention is not very solid. The first randomized studies used low-dose heparin and demonstrated that this approach was effective in preventing SOS in adults and children, although other larger prospective studies did not show an effect on prevention of death from SOS.[12-15] A meta-analysis demonstrated that there was a significant decrease in the incidence of SOS using ursodeoxycholic acid for prophylaxis, but 2 randomized studies showed conflicting results.[16-18] Other observational or historical controlled studies suggest that use of defibrotide (discussed in detail later), glutamine supplementation, peripheral blood progenitors, and T-cell depletion as graft-versus-host disease (GVHD) prophylaxis have been associated with a lower incidence of SOS.[19-24] In one pediatric study, the use of defibrotide for prevention of SOS was also associated with a lower incidence of acute GVHD.[22] A recent publication by the British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation nicely reviews the current data.[25] The treatment of SOS can be problematic and will be illustrated in the 2 cases that follow. This study was conducted in accordance with the Declaration of Helsinki.

Clinical cases

Case 1

J.S. is a 49-year-old woman with FLT3-ITD$^+$ acute myeloid leukemia who achieved complete remission after induction chemotherapy with daunorubicin and cytarabine. She subsequently underwent an allogeneic stem cell transplant using busulfan and cyclophosphamide as the conditioning regimen and tacrolimus and methotrexate for GVHD prophylaxis, as well as low-dose heparin for SOS prophylaxis. She was noted to have an increase in her bilirubin on day 12, which increased steadily over the next week to a level of 8 mg/dL. During this time, she developed ascites and gained ~12 pounds. She had a palpable liver edge on examination but no complaints of pain in the right upper quadrant. She also excreted 1 to 1.5 L of diarrhea per day. Endoscopy of the upper and lower gastrointestinal tracts demonstrated erythema and edema, but the biopsy results were equivocal for GVHD with no evidence for cytomegalovirus. Liver ultrasonography did not show any abnormalities. Because of increased bilirubin and ascites and a question of whether this was SOS or GVHD, a transjugular liver biopsy was performed. The portal-hepatic wedge pressure was 12 mm Hg. The biopsy demonstrated changes consistent with SOS without any evidence of GVHD. Because there were no medications available for the treatment of SOS, she was treated with supportive care consisting of light diuresis for fluid management, tapping and removing the ascitic fluid to improve her respiratory status, and "watchful waiting." Her bilirubin level peaked at 11 mg/dL and gradually decreased to normal over the ensuing 3 weeks. The ascites mobilized spontaneously and her weight gain resolved.

Case 2

T.R. is a 58-year-old man with myelodysplastic syndrome. He had become red cell transfusion–dependent and proceeded to a matched unrelated donor peripheral blood transplant. He was conditioned with busulfan and cyclophosphamide and received tacrolimus and methotrexate for GVHD prophylaxis. He received ursodeoxycholic acid for SOS prophylaxis. By day 6, there was an increase in his bilirubin, which continued to increase to >20 mg/dL by day 20. During this time, he had rapid weight gain and an

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increase in his abdominal girth from the development of ascites. He also developed severe right upper quadrant pain requiring narcotic analgesia. Abdominal ultrasonography done on day 14 demonstrated reversal of portal venous flow. He was started on defibrotide through a compassionate-use program. His bilirubin gradually decreased to a normal range within the next 2 weeks and his ascites also resolved.

Evaluation

These 2 cases illustrate some of the complexities of SOS. As mentioned before, the best treatment would be to try and prevent the development of this disease; however, the prophylactic strategies are suboptimal. Heightened awareness for SOS includes patients with known liver injury such as prior irradiation to the liver, hepatitis, iron overload, use of sirolimus for GVHD prophylaxis, busulfan in the conditioning regimen, use of gemtuzumab ozogamicin, and a poor performance status.[24-43] Despite equivocal data, these patients should have prophylaxis with ursodeoxycholic acid or low-dose heparin. The triad of weight gain (usually from ascites), elevated bilirubin, and right upper quadrant pain or hepatomegaly is common in severe SOS but may be variable in less fulminant courses. The "20 by 20" rule—that is, a bilirubin of 20 by day 20—predicts a poor outcome.

What should be done for a patient with an elevated bilirubin level? When a patient has a rapid rise in bilirubin level, ascites causing weight gain, and right upper quadrant pain, the diagnosis of SOS should be high on the list of differential diagnoses. Other etiologies such as GVHD or an infectious process can present in a similar manner. Moreover, most patients are receiving multiple drugs that can cause cholestasis. Ultrasonography of the liver with Doppler studies is usually performed to look specifically for ascites and reversal of flow in the portal veins, hepatic artery resistance index >0.75, or an abnormal portal vein waveform.[44-47] This test is not diagnostic, but these findings, especially reversal of flow, would suggest the presence of SOS. If the patient has no other confounding findings suggestive of other reasons for the triad of symptoms and laboratory abnormalities, then treatment of SOS should begin (discussed later). It is important to stress that the diagnosis of SOS is an iterative process; therefore, if these diagnostic study results are initially negative, they may need to be repeated because the clinical scenario changes with time.

The more difficult patient is one who has a more insidious onset of clinical findings. In some cases, the occurrence of SOS may be late or recognized at a later time.[47] The bilirubin level rises more gradually, usually staying under 10 mg/dL. This change occurs around the time of methotrexate administration, which can cause a rise in the bilirubin, or at time when the calcineurin inhibitor levels are high, which again are other potential reasons for an elevated bilirubin level. Another confounder around this early time before engraftment would be a new fever, suggesting an infection, which could also increase the bilirubin. Because mild-to-moderate SOS has a good outcome, there is less of an urgency to document SOS. However, if the suspicion is high but there are clinical confounders that could explain the rise in bilirubin, fluid retention, right upper quadrant pain, or hepatomegaly, and liver ultrasonography is not helpful, then a transjugular liver biopsy could be performed. In addition to obtaining a pathology specimen, portal hepatic wedge pressure can be measured. This wedge pressure partially reflects the sinusoidal pressure.[48-50] A pressure gradient of $\geq$10 mm Hg is highly sensitive and specific for the presence of SOS. Most patients do not need a liver biopsy because the morbidity of a percutaneous biopsy in immunosuppressed thrombocytopenic patients is prohibitive. If a biopsy is needed, the transjugular approach is preferable and should be done by an experienced interventional radiologist. Although this approach is safer, it is not without significant risk for complications. Because the biopsy is done through fluoroscopy and the image is two-dimensional, the guided catheter can lodge close to the capsule of the liver, and the biopsy may cause a perforation through the capsule, which would result in significant bleeding potentially requiring surgical repair. Moreover, the biopsy specimens are quite small and sometimes lack sufficient portal areas for a clear diagnosis.

Table 1. Grade of SOS

	Mild	Moderate	Severe
Bilirubin, mg/dL	<5	5.1- 8	>8
Liver function	<3× normal	3-8× normal	>8× normal
Weight above baseline	<2%	2-5%	>5%
Renal function	Normal	<2× normal	>2× normal
Rate of change	Slow	Moderate	Rapid

Therapy

Patients with mild SOS can simply be observed, whereas those with moderate disease can be treated expectantly with mild diuretics while carefully preserving renal blood blow so as not to induce prerenal azotemia and possible hepatorenal syndrome. Some patients may require paracentesis if the ascites is causing respiratory compromise or pain. Again, the amount of ascites removed should be modest, around one liter per day so as to not harm renal blood flow. Patients with severe SOS should be treated. Unfortunately, the assignment of these grades can only be done retrospectively because there are no clinical criteria to do this prospectively. An attempt at a model was developed in 1993 (primarily all ablative regimens), where the course of SOS was predicted by the serum bilirubin and the weight gain after cytoreductive therapy.[51] This paper provided a logistic regression model but was helpful only in a minority of patients who ultimately developed severe SOS, and it was also dependent on determining the probability of SOS.

My approach for deciding on therapy is based on the level of bilirubin and liver function tests and their rate of change, the amount and pace of weight gain, the presence of hepatomegaly, and overall symptoms. Table 1 is a possible guide for what could be considered mild, moderate, or severe. It is important to realize that the diagnosis is an iterative process rather than one point in time. Thus a patient's condition may move quickly from moderate to severe or from moderate to mild. For patients with severe SOS defined by a rapid rise in the bilirubin level (eg, doubling or tripling over 24 hours) and rapid weight gain, treatment should be instituted. Defibrotide is probably the drug that has the most promise in SOS. It is a polydeoxyribonucleotide derived from mammalian lung or mucosa and has anticoagulant as well as antiinflammatory activity.[52-56] It also increases levels of prostaglandin I2, E2, and prostacyclin, and increases levels of tissue plasminogen activator (tPA), thus increasing fibrinolysis. It has modest anticoagulation effects, making this drug relatively safe in the setting of thrombocytopenia. A phase 2 trial demonstrated improved survival in patients receiving

defibrotide compared with historical controls.[57-60] This drug has also been shown to be effective in treating SOS in children.[61] I begin the drug dose at 6.25 mg/kg intravenously every 6 hours and continue until the patient's bilirubin levels have normalized. Health care professionals in the United States may be able to obtain defibrotide for the treatment of patients with SOS through a Gentium-sponsored "Expanded Access, Treatment IND Protocol, Protocol 2006-05" (www.gentium.com); the drug is marketed in the EU as Defitelio.

Other drugs have also been tried in SOS but none can confidently be recommended. These include alteplase and heparin, but the bleeding risk was prohibitive. Steroids have also been used in anecdotal reports, but it is my opinion that steroids are more likely to cause significant other problems without a clear benefit. The use of steroids appears to be more common in pediatrics and less common in the adult populations. Antithrombin concentrate can also be used for patients who are deficient, and it appears to be very effective in these patients. PGE1 (alprostadil) has been used in children with some success, although that number is very limited. Other, more extreme approaches include a transjugular intrahepatic portosystemic shunt, which can lead to improvement in hepatic and renal function, although long-term survival is uncommon. Finally, in rare cases, liver transplantation has also been reported but, not surprisingly, these patients are quite fragile at this stage and are not likely to survive such a procedure.

Summary

SOS can be a devastating development after HCT. The important points are that mild SOS does not require any intervention. For patients with moderate disease, efforts are centered around fluid management, with attention to intravascular volume so that kidney perfusion is maintained. Removal of the ascitic fluid can be done judiciously to control pain or difficulty with breathing. It is important to not precipitate renal insufficiency by too-aggressive diuresis or rapid removal of ascitic fluid. Severe SOS should be treated promptly, using the measures described here and with defibrotide. Efforts to prevent SOS should be implemented, especially in patients at higher risk. Although this complication can be devastating, the majority of these patients are expected to improve.

Authorship

Contribution: N.C. wrote the manuscript.

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