Management of Hepatic Sinusoidal Obstruction Syndrome Following Treatment with Gemtuzumab Ozogamicin (Mylotarg®)

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Abstract

Gemtuzumab ozogamicin (Mylotarg®) therapy may cause sinusoidal obstruction syndrome (SOS), the mechanism of which probably involves targeting of CD33+ cells in the sinusoids of the liver, activation of stellate cells, damage to sinusoidal endothelial cells, sinusoidal vasoconstriction, and ischemic hepatocyte necrosis. The clinical manifestations of this liver injury are hepatomegaly, weight gain, ascites, jaundice, and elevation of serum aminotransferase enzymes. An approach to patient management includes being certain that SOS is the correct diagnosis; ensuring that liver flow is optimized; and managing the accumulation of fluid in the peritoneal cavity, pleural spaces, and pulmonary interstitium. Currently, there is no specific therapy that is directed at the sinusoidal pathology caused by gemtuzumab ozogamicin. There are, however, several rational therapies that might be tried in patients who exhibit adverse prognostic signs early in the course of SOS. There is also considerable ongoing hepatology research dealing with stellate cell and sinusoidal endothelial cell biology and regulation of sinusoidal blood flow that can be brought to bear on this problem in the future.

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Introduction

Liver injury has been reported in patients who have received gemtuzumab ozogamicin (Mylotarg®) for the treatment of acute myeloid leukemia. The initial site of injury appears to be cells residing in the sinusoids of the liver (Kupffer cells, stellate cells, sinusoidal endothelial cells), resulting in a clinical syndrome that is different from hepatocyte injury or cholestatic liver disease common to many hepatic drug reactions. Rather, this sinusoidal obstruction syndrome (SOS) leads to hepatomegaly, portal hypertension, fluid retention by the kidneys, and ascites, followed by the development of jaundice and the elevation of serum aminotransferase enzymes, probably as a result of centilobular ischemia.

Although the term veno-occlusive disease (VOD) has been applied to this clinical presentation, this is a misnomer, as venular obstruction is not a requirement for the diagnosis, and the majority of damage involves hepatic sinusoids, including injury to sinusoidal endothelial cells, deposition of collagen in sinusoids, and pericentral hepatocyte necrosis. This liver toxicity appears to be precipitated by the targeting of CD33+ cells, specifically, Kupffer cells residing in the hepatic sinusoids.

The management of patients who develop liver dysfunction following gemtuzumab ozogamicin therapy can be difficult, as these patients may be very ill with fever, infection, neutropenia, and thrombocytopenia, which limit tissue biopsy for diagnosis. The following approach is recommended for such patients.

Determining the Cause of Liver Dysfunction

Not all liver disease that temporally follows gemtuzumab ozogamicin is caused by the drug. Further, Occam’s razor might be disposable in this situation; that is, sinusoidal obstruction might be accompanied by other types of liver injury in patients with acute myeloid leukemia (AML). For these reasons, clarifying the cause of liver dysfunction is the first step in management.

Applying Bayes’ Theorem

The presence of SOS is more probable in patients who have received gemtuzumab ozogamicin following relapse of AML after a myeloablative hematopoietic cell transplantation (HCT) and in patients who received gemtuzumab ozogamicin along with other chemotherapeutic or biological agents. Other risk factors for SOS following gemtuzumab ozogamicin have not been identified, but it is clear that SOS occurs outside of the transplant and multidrug chemotherapy settings.

Identifying the Cause of Jaundice

Elevations of serum bilirubin in SOS typically follow other manifestations of sinusoidal obstruction and peak bilirubin levels may only be modestly elevated. For example, the median total serum bilirubin levels in 2 series of patients with gemtuzumab ozogamicin–related SOS was 8.5 mg/dL (range, 3.2-33.6 mg/dL; n = 14) and 5.6 mg/dL (range, 1.5-13.2 mg/dL; n = 11), respectively.

The most common cause of jaundice in this setting results from cholestatic liver injury. The most frequent cause of cholestasis in patients with relapsed AML is cholangitis lenta, a result of the effect of inflammatory cytokines on the transport of bilirubin at the level of the bile canaliculus. Usually, the presentation is rising bilirubin levels following an episode of febrile neutropenia. Serum bilirubin levels may rise to 15 mg/dL, with or without elevated alkaline phosphatase elevations. Imaging
tests of the liver are normal. There is no specific treatment other than elimination of the underlying sepsis or infection.

Less common causes of cholestasis in patients with relapsed AML include drug-liver injury (eg, fluconazole, trimethoprim-sulfamethoxazole, prochlorperazine) and biliary sludge syndrome (obstruction of the common bile duct by microcrystalline bile). Rarer causes of cholestasis in patients with AML include a chlorma impinging on the common hepatic or common bile ducts, ascending cholangitis, acute cholecystitis with Mirizzi's syndrome, and biliary fungal infection. In one special circumstance of treatment with gemtuzumab ozogamicin for relapsed AML following HCT, two additional causes of cholestasis must be considered: graft-versus-host disease and cyclosporine-related impairment of bilirubin transport.

**Evaluation of Painful Hepatomegaly**

In SOS, the liver enlarges because of obstruction to hepatic blood flow, a process that may be painful due to the stretching of Glisson's capsule (parietal peritoneum that encapsulates the liver). It may be difficult to tell whether right upper-quadrant pain is of liver or gallbladder origin, but in a patient with SOS, pain can often be elicited by tapping over the left lobe of the liver in the epigastrium or over Riedel's lobe on the right, away from the gallbladder fossa. Similar information can be derived from a gentle McKnight punch (a flattened hand is placed over the liver and struck gently by the opposite hand).

Ultrasonography can also determine if pressure is painful to the gallbladder. There are other processes that can lead to a congested, tender liver in this setting, such as constrictive pericarditis, right heart failure, and Budd-Chiari syndrome, but these diagnoses would be rare in a patient with AML unless there was a fungal obstruction in the hepatic vein, cardiomyopathy, or the patient had a history of chest irradiation that might have led to constrictive pericarditis. The most common cause of liver tenderness in a patient with AML is fungal abscesses, usually caused by *Candida* species.

While a liver imaging study that shows multiple liver defects strongly suggests fungal infection, there is a false-negative rate of 50%-70%, explained by the low sensitivity for small miliary abscesses in neutropenic patients.

**Evaluation of Ascites**

Unless a patient has a past history of fibrotic liver disease, development of ascites 1-3 weeks following gemtuzumab ozogamicin is almost pathognomonic of SOS, as fluid drips off the surface of the liver when there is obstruction to sinusoidal blood flow. The differential diagnosis includes Budd-Chiari syndrome, cardiac conditions leading to increased caval pressure, and rarely, pancreatic ascites. Ultrasound examination of the liver and paracentesis should readily resolve any confusion about the cause of ascites. Ultrasound findings in SOS are nonspecific in the early stages of the disease, showing attenuation of hepatic venous flow, hepatomegaly, ascites, and possibly gallbladder wall edema. Late changes that are more specific for SOS include reversal of portal venous flow, portal vein thrombosis, and possibly an increased resistive index to hepatic artery flow, the latter being quite variable from patient to patient.

**Evaluation of Elevations of Serum Aspartate/Alanine Aminotransferase**

In a cohort of patients with AML treated with gemtuzumab ozogamicin, sometimes in concert with other chemotherapy drugs, elevation of aspartate aminotransferase (AST) peaked at a median of 17 days after infusion (range, 2-30 days), with peak values ranging from 43-1789 U/L (median, 201 U/L). In a cohort of patients who developed SOS after gemtuzumab ozogamicin therapy for relapsed AML following HCT, elevations of serum AST peaked at a median of 8 days after infusion (range, 3-37 days), with peak values of AST ranging from 86-3091 U/L (median, 242 U/L). Histological findings of necrosis and dropout of pericentral hepatocytes in association with sinusoidal fibrosis suggest that the cause of hepatocyte necrosis is ischemic injury.

Other causes of hepatocyte injury in this setting include injury from other drugs and acute viral hepatitis. The viruses that should be considered in this time frame are herpes simplex virus, varicella-zoster virus, and adenovirus. Hepatitis viruses B and C are unlikely causes of hepatitis in a leukopenic patient because liver injury is related to T-cell recognition of viral antigens and there are too few T cells to mount an immune response. Starting empiric therapy with acyclovir, performing a liver biopsy, and collecting blood for viral DNA testing by polymerase chain reaction should be considered, particularly if AST and alanine aminotransferase are rising rapidly above 750-1000 U/L. As there is no specific treatment for gemtuzumab ozogamicin-related liver injury, identification of a treatable cause of hepatocyte necrosis, whether drug-related or viral, should be a priority.

**Evaluation of Nonhepatic Conditions that Contribute to Jaundice**

The level of jaundice in patients with SOS may be greatly influenced by hemolysis, recent transfusions, and renal insufficiency. If one or more of these conditions are present in addition to SOS, the level of serum bilirubin may not accurately presage a fatal outcome.

**Liver Biopsy and Measurement of Sinusoidal Pressure**

In circumstances where a clinical diagnosis is in doubt and the patient is worsening clinically, transvenous liver biopsy and measurement of the wedged hepatic venous pressure gradient can be done safely, even in a thrombocytopenic patient. A transfemoral approach, using a forceps device for obtaining tissue and a small Swan-Ganz balloon for measuring the wedged and free hepatic venous pressures is effective. Others approach the liver via the jugular vein, using a needle device to obtain liver tissue. Liver tissue should be fixed in B5, Carnoy's solution, Bouin's fixative, or Hollande's fixative and stained with hematoxylin and eosin, a trichrome stain, and a reticulin stain to identify collagen deposition in sinusoids. Also, tissue should be sent for viral
Medical Care of Patients with Sinusoidal Obstruction Syndrome

Care of patients with relapsed AML and pancytopenia who then present with liver dysfunction can be challenging. There is no specific treatment that has been shown to reverse sinusoidal injury and hepatocyte necrosis in patients with gemtuzumab ozogamicin–related SOS. However, the following strategies are suggested, based on a large experience in treating patients with VOD of the liver following myeloablative conditioning therapy for HCT, a similar, but not identical, disease process.

Maintain Liver Blood Flow

There is reason to believe that prognosis in patients with SOS is related to the extent of pericentral hepatocyte necrosis and that the extent of hepatocyte necrosis is related to centrilobular ischemia, based on an animal model of sinusoidal injury. One should avoid jeopardizing hepatic blood flow and causing further hepatocyte ischemia by the prevention and early treatment of sepsis and sepsis-related hypotension, and by avoiding hypovolemia and low-cardiac output states, for example. General anesthesia, with its attendant fall in splanchnic blood flow, should be avoided unless absolutely necessary, as this may precipitate hepatic failure.

Minimize Extravascular Fluid Accumulation

Sinusoidal obstruction syndrome leads to portal hypertension, which leads to renal sodium retention. Renal sodium retention leads to accumulation of fluid as ascites, peripheral edema, and interstitial pulmonary edema. Large-volume ascites can also lead to restrictive lung disease and pleural effusions. Thus, the fluid-retentive aspects of SOS can be a source of morbidity above and beyond the level of liver dysfunction.

The goal of therapy is to minimize the deleterious effects of fluid excess on cardiopulmonary function, without jeopardizing effective renal plasma flow. The ability to mobilize excess salt and water can often be gauged by measuring urinary sodium concentration, the fractional excretion of sodium, and by the amount of diuresis achieved by a test dose of furosemide. The sodium and water content of intravenous fluid and the salt content of food should be reduced to balance urinary outputs plus insensible losses, as one would manage a patient with end-stage cirrhosis. Fortunately, many patients with SOS following gemtuzumab ozogamicin have preserved renal and cardiopulmonary function, in contrast to patients with VOD of the liver following myeloablative conditioning regimens for HCT, where there is substantial renal and pulmonary damage from the conditioning regimen.

The goal of fluid balance in SOS then is not complete diuresis, but minimization of interstitial pulmonary fluid and ascites, while maintaining euvolemia. Avoidance of renal toxins, eg, in the form of amphotericin and aminoglycosides, will allow renal compensation for the effects of portal hypertension when ascites is painful or causes respiratory compromise. Large-volume paracentesis can be done safely even in the face of thrombocytopenia. A midline, linea-alba approach is recommended, with protection of the intravascular compartment by infusion of crystalloid or albumin. When there is progressive fluid accumulation and renal insufficiency, management of excess fluid may require hemofiltration or hemodialysis.

Avoidance of Further Hepatic Injury

Obvious hepatic toxins such as ethanol should be avoided. Acetaminophen should not be used to treat fever, as low doses of this drug can cause additional liver injury in the face of liver compromise. Acetaminophen also depletes hepatocyte and sinusoidal endothelial cell glutathione content.

Prevention of Bacterial Translocation

In both experimental animals and patients who have liver dysfunction with portal hypertension, a characteristic hemodynamic picture often develops, ie, high cardiac output, low systemic vascular resistance, and tachycardia. Although the pathogenesis of this clinical picture has not been completely elucidated, it likely involves translocation of bacteria and endotoxin through intestinal mucosa into lymphatic tissues, stimulation of cytokine release, and generation of nitric oxide in the splanchnic circulation. The gut is also the most common source of bacteremia in febrile neutropenia.

Logical, albeit unproven, approaches to the problem of bacterial translocation in patients with liver dysfunction include the use of poorly absorbed antibiotics to eliminate luminal microorganisms, prophylactic systemic antibiotics, and the use of luminal nutrition (with or without probiotics) to maintain intestinal barrier function. Note that antibacterial and probiotic approaches are antithetical and mutually exclusive, yet both approaches are logical. In patients who have developed SOS following gemtuzumab ozogamicin and who have sepsis-like hemodynamics, with or without fever, treatment with both luminal nonabsorbable antibiotics and broad-spectrum systemic antibiotic coverage should be considered.

Prevention of Viral and Fungal Infection

Use of prophylactic fluconazole or itraconazole has largely eliminated candidal infections in the setting of prolonged neutropenia following HCT. Both neutropenia and SOS are risk factors for fungal liver infection after HCT. Thus, fungal prophylaxis is warranted in patients with SOS. Acyclovir prophylaxis against disseminated herpes virus infections (herpes simplex virus, varicella-zoster virus) will cover the possibility that these viruses are involved as a cause of liver dysfunction and will also prevent infection.
Investigational Approaches to Sinusoidal Obstruction Syndrome

Because of the similarity between SOS after gemtuzumab ozogamicin and VOD after myeloablative conditioning therapy, some of the therapies applied to the latter patients might be considered for treatment of SOS. However, there are no controlled trials of any therapy for VOD and no clear evidence of efficacy for any such therapy in patients with severe liver dysfunction caused by either VOD or SOS. Use of thrombolytic agents, such as tissue plasminogen activator, cannot be recommended for treatment of SOS, as there is no evidence for thrombotic process in its pathogenesis and this therapy carries substantial risk of bleeding.

Equally, the use of heparin, antithrombin III, or activated protein C has no rational basis. Uncontrolled studies of defibrotide, a poly-DNA natural product available in Europe, suggest a positive effect in up to 40% of patients with severe VOD after HCT, and the product has few side effects. Use of defibrotide in patients with SOS following gemtuzumab ozogamicin has not yet been reported. When portal hypertension and intractable ascites are the dominant process in a patient with SOS, consideration might be given to placement of a transjugular intrahepatic portosystemic shunt (TIPS) to lower portal pressures. This procedure has been tried in small numbers of patients with severe VOD after HCT, with success in reducing portal pressure, but there is little evidence that this alters outcome, particularly when there is progressive liver dysfunction.

Reports of TIPS for treatment of SOS following gemtuzumab ozogamicin have not yet appeared. Administration of N-acetylcyesteine intravenously or by gavage has been reported to effect improvement in patients with VOD, presumably by increasing glutathione content in hepatocytes and sinusoidal endothelial cells. As this therapy has few serious side effects, it should be considered for patients with SOS who have adverse prognostic signs.

Because an animal model of toxic sinusoidal injury suggests that sinusoidal vasocnstriction may play a role in the pathogenesis of centrilobular ischemia that can be overcome by infusing a nitric oxide donor into the portal vein, there is some rationale for prescribing oral nitrates. For example, isosorbide dinitrate, which will be delivered into the portal circulation, can theoretically improve sinusoidal blood flow. There is little published data on this approach.

One important limitation of this medication is hypotension, as most patients with SOS exhibit the hemodynamic abnormalities of low systemic vascular resistance and high cardiac output. Investigational use of endothelin-1 antagonists and metalloprotease inhibitors to effect improved sinusoidal blood flow is limited by the absence of approved medications with these properties.

An attractive therapeutic target in patients with SOS is the activated stellate cell, which is responsible for production of the extracellular matrix that is a major part of sinusoidal obstruction in SOS. There are no approved drugs for this indication and none that would enhance fibrolysis, a complementary approach.

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