

Hepatic Sinusoidal Obstruction Syndrome Following Hematopoietic Stem Cell Transplantation

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J.M., a 43-year-old man with acute myelogenous leukemia with a monosomy 7 cytogenetic abnormality, received an allogeneic hematopoietic stem cell transplantation (HSCT) from his human leukocyte antigen-matched brother. Past treatments included idarubicin and cytarabine induction therapy followed by a cycle of high-dose cytarabine. J.M. was in complete remission prior to the HSCT. The conditioning regimen for the HSCT was busulfan and cyclophosphamide. Eighteen days after his HSCT, J.M.'s total bilirubin had risen from 1.0 mg/dl the previous day to 3.6 mg/dl. His alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase were normal. J.M. complained of mild right upper-quadrant abdominal pain (3 on a 0–10 scale). J.M. had been gaining one to two pounds per day over the past few days, for a total of 10 pounds in the past week. He was slightly jaundiced. The transplantation team suspected that J.M. was developing hepatic sinusoidal obstruction syndrome (SOS).

What is hepatic sinusoidal obstruction syndrome?

Hepatic SOS is a serious complication that occurs following allogeneic and autologous HSCT (Goldberg et al., 1996; Levy et al., 1996; Pegram & Kennedy, 2001; Wadleigh, Ho, Momtaz, & Richardson, 2003). Hepatic SOS is a toxic injury to sinusoidal endothelial cells causing a cascade of events, including compromised blood flow to centrilobular hepatocytes, fibrosis, and obstruction of

hepatic blood flow (DeLeve, Shulman, & McDonald, 2002). DeLeve et al. suggested that hepatic SOS is a more suitable term for the syndrome than veno-occlusive disease of the liver.

Hepatic SOS develops early in the transplantation process, usually by day 35, and, in its severe form, can have a mortality rate as high as 67% (Pegram & Kennedy, 2001). The incidence of hepatic SOS can be as high as 70% depending on factors such as the conditioning regimen used and hepatic function prior to transplantation (DeLeve et al., 2002; Helmy, 2006).

The clinical symptoms of hepatic SOS include unexplained weight gain, painful hepatomegaly, and jaundice (Chalandon et al., 2004; DeLeve et al., 2002; Pegram & Kennedy, 2001). Diagnostic criteria developed by Jones et al. (1987) include jaundice (total bilirubin > 2.0 mg/dl) and at least two of the following: hepatomegaly, acites, or a gain of more than 5% of the patient's total body weight. Hepatic SOS remains difficult to diagnose because of the many causes of hepatic toxicity in patients undergoing HSCT.

What is the pathogenesis of hepatic sinusoidal obstruction syndrome?

The liver is comprised of hepatocytes, the functional cells of the liver that are supported by reticuloendothelial cells. Sinusoids are the vascular spaces that separate individual plates of hepatocytes. Blood from the hepatic and portal veins combine in the sinusoids and drain into the central

venules (Lingappa, 2003; Wadleigh, Ho, et al., 2003). Although the pathogenesis of hepatic SOS is not understood, it is believed to begin with injury to the hepatic venules. This vascular inflammatory process leads to the deposits of fibrin in the portal vessels, causing obstruction (Harper, 2006). The sinusoids become dilated and hepatocytes become necrotic when collagen accumulates in the sinusoids and venules. Injury to the sinusoidal endothelial cells and the hepatocytes in zone 3 of the liver, located around the central veins, is an important initial event in hepatic SOS. Hepatocytes in zone 3 contain high concentrations of cytochrome P450, an enzyme that metabolizes many chemotherapeutic agents, including busulfan and metabolites of cyclophosphamide. Inability to effectively metabolize those chemotherapeutic agents increases liver damage (Wadleigh, Ho, et al.). The events lead to widespread disruption of liver function (Chalandon et al., 2004).

What are risk factors of hepatic sinusoidal obstruction syndrome?

Certain cytotoxic agents are implicated in the development of hepatic SOS. Busulfan, a common conditioning agent used in HSCT, may contribute to the incidence of hepatic SOS (Pegram & Kennedy, 2001; Wadleigh, Ho, et al., 2003). Significantly higher rates of hepatic SOS have been found in patients receiving busulfan and cyclophosphamide than those receiving cyclophosphamide and total body irradiation in preparation for HSCT (Ringden et al., 1994; Rozman et al., 1996). Gemtuzumab, an anti-CD33

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monoclonal antibody linked to the potent toxin calicheamicin, has been suspected in cases of hepatic SOS. Gemtuzumab targets the bone marrow cells because they express CD33. Endothelial cells of the liver also express CD33 and, thus, also are potential targets for gemtuzumab (Wadleigh, Ho, et al.). Patients receiving gemtuzumab 3.5 months prior to or after HSCT are at increased risk of developing hepatic SOS (Rajvanshi, Shulman, Sievers, & McDonald, 2002; Wadleigh, Richardson, et al., 2003).

Risk factors for hepatic SOS include a Karnofsky score less than 90%, being older than age 20, a history of liver disease, an intensive conditioning regimen, fungal infection (Pegram & Kennedy, 2001), an elevated aspartate aminotransferase at the start of HSCT, previous abdominal radiation, female gender, advanced malignancy, prior exposure to amphotericin B, increased number of days on broad-spectrum antibiotics, and increased number of days with fever before HSCT (Carreras et al., 1998; Wadleigh, Ho, et al., 2003). Reiss, Cowan, McMillan, and Horn (2002) found that having an unrelated donor and advanced-stage malignancy also were substantial risk factors for hepatic SOS in pediatric patients.

What are other causes of hepatic toxicity during hematopoietic stem cell transplantation?

Hepatic toxicity may be caused by graft-versus-host disease of the liver, drug toxicity, use of total parenteral nutrition, sepsis, or viral hepatitis (Wadleigh, Ho, et al., 2003). In addition, hemolysis and gallbladder disease have signs and symptoms similar to hepatic SOS.

Graft-versus-host disease of the liver can be confused with hepatic SOS. The signs of liver graft-versus-host disease include elevations in total bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. The clinical symptoms of liver graft-versus-host disease can be very similar to those of hepatic SOS, including right upper-quadrant discomfort, jaundice, and an enlarged liver (Anderson-Reitz & Baumert, 2004). A liver biopsy can differentiate between graft-versus-host disease and hepatic SOS.

Hepatotoxic drugs, such as cyclosporine, tacrolimus, voriconazole, and fluconazole, all of which inhibit bile transport, can produce a drug-induced cholestasis and elevate the bilirubin level. If hepatotoxic drugs are the suspected cause of hyperbilirubinemia, stopping one offending drug at a time until the bilirubin level returns to normal range is recommended (Vinayek, Demetris, & Rakela, 2000). Drugs used in the conditioning regimen, such as busulfan, can cause chemical hepatitis and transient elevations in liver enzymes within the first two weeks after HSCT. Elevated liver enzymes, in the

absence of other sources of liver dysfunction, should return to normal in approximately 14 days (Ozdogan et al., 2003).

Total parenteral nutrition can cause chemical hepatitis with a rise in the serum transaminases and alkaline phosphatase. The elevation in liver function enzymes usually is transient and resolves when the patient begins eating. If the patient cannot tolerate oral nutrition, alterations in the schedule or composition of the total parenteral nutrition can decrease the liver function enzymes (Anderson-Reitz & Baumert, 2004).

Infection is another complication of HSCT that can cause elevations in liver function enzymes. Chemotherapy and immunosuppressive drugs make patients undergoing an allogeneic HSCT at high risk for infection. Sepsis can cause deterioration of liver function. When that happens, elevated bilirubin and alkaline phosphatase levels often are accompanied by fevers (Ozdogan et al., 2003). Finally, patients undergoing HSCT can develop active viral hepatitis because of progression of a pre-HSCT infection, activation of a latent virus, or transmission from an infected donor resulting in elevations in total bilirubin and aminotransferase levels, hepatomegaly, and flulike symptoms (Ozdogan et al.).

How is hepatic sinusoidal obstruction syndrome diagnosed?

Because of the danger of bleeding or infection from invasive procedures during HSCT, diagnosis of hepatic SOS often is made clinically (Wadleigh, Ho, et al., 2003) based on the classic signs of weight gain, painful hepatomegaly, hyperbilirubinemia, and ascites (Jones et al., 1987). A clinical diagnosis of hepatic SOS is difficult to make with certainty because the diagnostic criteria overlap with many other complications that can occur following HSCT (Wadleigh, Ho, et al.). Transfemoral or transjugular liver biopsy and wedged hepatic venous pressure gradient measurement are the preferred methods of pathologic diagnosis of hepatic SOS. Percutaneous liver biopsy is not recommended.

Doppler ultrasound of the liver, computer tomography of the abdomen, magnetic resonance imaging of the liver, and a hepatitis panel can assist in the clinical diagnosis. Ultrasound and computer tomography are helpful in identifying hepatomegaly and ascites. Doppler measurements can identify attenuation, reversal of venous flow in the liver, and portal vein thrombosis associated with SOS. Although the direct utility of magnetic resonance imaging in the diagnosis of hepatic SOS has not yet been established, the scan can be useful in identifying fungal infections (Wadleigh, Ho, et al., 2003). A hepatitis blood panel can exclude active viral hepatitis as a cause of liver dysfunction.

Can hepatic sinusoidal obstruction syndrome be prevented?

Several medications to prevent hepatic SOS have been studied, including low-dose heparin, low-molecular-weight heparin, and ursodiol. Pegram and Kennedy (2001) reported that evidence for the use of low-dose heparin to prevent hepatic SOS is inconclusive. Low-molecular-weight heparin was studied as prophylaxis for hepatic SOS in a randomized pilot study with 24 patients undergoing allogeneic HSCT and 37 patients undergoing autologous HSCT (Or et al., 1996).

Clinical symptoms of SOS were fewer in patients randomized to low-molecular-weight heparin; however, 13 patients were withdrawn from the study because of bleeding.

Ursodiol, a nonhepatotoxic bile salt, may be beneficial in the prevention of hepatic SOS because it replaces toxic bile salts and prevents cholestasis.

A randomized, double-blind, placebo-controlled trial with 67 patients undergoing allogeneic HSCT showed a statistically significant decrease in hepatic SOS with ursodiol (Essell et al., 1998). A second prospective, unblinded, randomized, multicenter trial of 132 patients undergoing allogeneic HSCT showed a significant decrease in hepatic SOS in those receiving ursodiol (Ohashi et al., 2000). A randomized study that compared continuous infusion heparin to continuous infusion heparin plus ursodiol in 165 patients receiving allogeneic and autologous HSCT found no significant difference in the occurrence of hepatic SOS between the groups (Park et al., 2002). Some common side effects of ursodiol are bladder pain, cloudy urine, painful urination, dizziness, palpitations, indigestion, nausea, vomiting, weakness, shortness of breath, itching, rashes, and wheezing (Mayo Clinic, 2007).

What does the management of hepatic sinusoidal obstruction syndrome include?

No definitive treatment exists for hepatic SOS, and recommendations center around supportive care measures. Approximately 70% of cases of hepatic SOS following HSCT will resolve spontaneously with supportive care (Helmy, 2006). Supportive care involves maintaining adequate intake and output, adjusting medication doses if hepatic and renal impairment is present, and protecting the patient's kidney function. Nursing assessments should include monitoring mental status changes to detect the development of hepatic encephopathy, daily measurement of abdominal girth for ascites, and daily weight measurement to assess fluid retention (O'Connell, 2000). Supportive care should continue until the hepatic SOS resolves and the liver cells regenerate.

Defibrotide, a drug that modulates endothelial injury without causing bleeding, is being studied as a possible prevention and treatment for SOS. Early studies have shown some promising results. Using historical control cohorts, Chalandon et al. (2004) compared heparin to defibrotide for SOS prophylaxis. None of the patients who received defibrotide developed SOS. Wadleigh, Ho, et al. (2003) have reported that defibrotide prevented the fibrin deposit responsible for collagen formation and fibrosis of the liver. In Richardson et al.'s (1998) study, a 42% response rate to defibrotide was shown in 19 patients with severe hepatic SOS.

Since that time, in large, multicenter international trials of patients with severe hepatic SOS, treatment with defibrotide has produced response rates of 36%–60% with few significant side effects (Richardson et al.).

Because of the promising results of those trials, a prospective, multinational trial of defibrotide currently is being conducted in patients diagnosed with severe hepatic SOS (Ho, Linden, Revta, & Richardson, 2007). Defibrotide has great potential in not only the treatment of hepatic SOS but also its prevention (Chalandon et al., 2004; Pegram & Kennedy, 2001).

Hepatic SOS is a serious toxicity-related complication of HSCT. It has high morbidity and mortality rates and requires specialized nursing care. Oncology nurses are in a unique position to recognize the signs and symptoms of hepatic SOS and to assist in the research, treatment, and prevention.

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Clinical Highlights: Hepatic Sinusoidal Obstruction Syndrome

Definition

Hepatic sinusoidal obstruction syndrome (SOS) is a common toxicity that occurs early in the course of a hematopoietic stem cell transplantation. The clinical triad of hepatic SOS includes unexplained weight gain, painful hepatomegaly, and jaundice (Pegram & Kennedy, 2001).

Pathophysiology

Hepatic SOS is believed to begin with damage to the hepatic venules, sinusoidal endothelial cells, and hepatocytes (Wadleigh, Ho, Momtaz, & Richardson, 2003). Several events occur in hepatic SOS, including deposits of fibrin within the venular walls followed by venular occlusion (Harper, 2006) that lead to widespread liver disruption (Chalandon et al., 2004).

Risk Factors

Factors that can affect hepatic SOS include chemotherapy agents such as busulfan, cyclophosphamide, and gemtuzumab (Reiss, Cowan, McMillan, & Horn, 2002). Age, Karnofsky score, female gender, advanced disease, fever prior to transplantation, exposure to amphotericin B, and history of abdominal radiation also influence the occurrence of hepatic SOS (Carreras et al., 1998).

Prevention

Medications used to treat hepatic SOS include heparin, low-molecular-weight heparin, and ursodiol (Pegram & Kennedy, 2001).

Clinical Findings

The clinical findings of hepatic SOS include unexplained weight gain, painful hepatomegaly, and jaundice. For a syndrome to be considered hepatic SOS, jaundice (bilirubin level, > 2.0 mg/dl) must be present along with any two of the following features: hepatomegaly, ascites, or a gain of more than 5% of total body weight (Jones et al., 1987).

Differential Diagnosis

Differential diagnosis of SOS includes drug hepatotoxicity, viral hepatitis, infection, and graft-versus-host disease (Ozdogan et al., 2003).

Treatment

The treatment of hepatic SOS is supportive care measures such as maintaining fluid and electrolyte balance, protecting kidney function, and monitoring respiratory function (O'Connell, 2000). Defibrotide is showing promise in the treatment of SOS with response rates of 42% (Chalandon et al., 2004).

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