

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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