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Sinusoidal Obstruction Syndrome

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Introduction

Sinusoidal Obstruction Syndrome (SOS), formerly veno-occlusive disease of liver, is a distinct clinical syndrome consisting of fluid retention and liver dysfunction first described in cases of accidental poisoning with pyrrolizidine alkaloids. When severe, it results in renal dysfunction, encephalopathy and multiorgan failure and is associated with high mortality. SOS is seen in only a limited number of situations, the most common of which is high-dose chemotherapy with stem cell transplantation (SCT). The incidence of SOS varies with patient- and transplant-related factors, and is reported to complicate between 5% and 55% of myeloablative transplants.^{1,2} The incidence of SOS appears to be decreasing over time with the earlier application of high-dose therapy in patients with hematological malignancy and the lower incidence of hepatitis C virus infection among transplant recipients. The use of intravenous busulfan, which may be targeted pharmacokinetically to ensure consistent dosing,³ and the greater use of non-myeloablative conditioning regimens among at-risk patients⁴ will likely result in lower rates of SOS in future.

Risk Factors for SOS

Risk factors for SOS include the use of stem cell transplantation to treat patients with advanced disease. This is especially the case among recipients of prior high-dose therapy with autologous or allogeneic stem cell transplantation: SOS was the leading cause of early death among second transplant recipients reported by the EBMT.⁵ A case-control study of 146 transplant recipients demonstrated a significantly lower incidence of non-relapse mortality among recipients of non-myeloablative transplant, compared to recipients of ablative transplants, despite a higher co-morbidity score among the recipients of reduced intensity transplants. In this report 18% of myeloablative transplant recipients developed SOS, in comparison to 0% in recipients of non-myeloablative transplants.⁶ Prior treatment with carboplatin and etoposide⁷ or abdominal radiotherapy⁸ has also been implicated. Other risk factors are shown in Table 1.

Diagnosis of SOS

Two sets of diagnostic criteria for SOS after SCT are in common use (see Table 2). Both sets of criteria emphasize the presence of hepatic dysfunction (hyperbilirubinemia), tender hepatomegaly and weight gain due to fluid retention

(2% in the modified Seattle criteria, 5% in the Baltimore criteria). Recognition of this syndrome within the first three weeks after SCT should prompt investigations to rule out other syndromes that may mimic this disorder, including congestive heart failure, fungal or viral infection of the liver, sepsis- or drug-induced cholestasis and tumor infiltration of liver.

Non-invasive diagnostic methods for SOS are preferred over liver biopsy due to the increased rate of bleeding complications seen in patients post-SCT. Several criteria on grey-scale and Doppler ultrasound have been described in association with SOS, including increased gallbladder thickness, elevated hepatic artery resistive index (hepatic artery systolic velocity-diastolic velocity/systolic velocity)²⁰ and decreased portal venous flow velocity.²¹ Individually these criteria show low sensitivity and specificity for SOS, especially in early disease. In more advanced disease the sensitivity and specificity of ultrasound detection of ascites and paraumbilical vein flow in diagnosis of SOS, are 72% and 99%, and 52% and 99%, respectively.²² Ultrasound has been shown to be helpful in monitoring response to therapy for patients with SOS.^{23, 24}

Transvenous liver biopsy has become the preferred route to obtain samples of liver tissue for histological diagnosis of SOS. Despite the relative safety of this approach bleeding is a common complication (11 of 60 biopsies) with a 5% incidence of procedure-related mortality.²⁵ In the setting of early post-SCT liver dysfunction, however, liver biopsy may either confirm a clinical diagnosis or provide an additional diagnosis in the majority of cases. Measurement of the hepatic venous pressure gradient may also allow earlier confirmation of a diagnosis of SOS: A pressure gradient of ≥ 10 mmHg has 91% specificity and 86% positive predictive value in predicting histological SOS.

Management of SOS

Efforts to prevent the development of SOS are of paramount importance given its high mortality. Patients at very high risk of mortality following stem cell transplantation, such as those with established cirrhosis clinically or on liver biopsy, should be considered for non-transplant treatments if these are available. Other at-risk patients may be considered for transplants using reduced-intensity or non-Busulfan based conditioning regimens. Pharmacological prophylaxis of SOS has been described. A randomized, double blind, placebo controlled study has demonstrated the superiority of ursodeoxycholic acid (Urso) over placebo for prevention of SOS following allogeneic matched sibling transplantation using busulfan-cyclophosphamide conditioning.²⁶ A larger and more recent study was unable to detect a difference in the incidence of SOS between Urso- and placebo-treated patients. In this study the rate of SOS was very low among placebo-treated patients (12%, modified Seattle criteria), and there were fewer

hepatic complications overall in the group randomized to Urso than to placebo.²⁷ Prophylactic low-dose heparin (100 U/kg by continuous IV infusion daily) or liposomal PGE₂ (1 mcg/kg by continuous IV infusion daily) was shown to reduce the incidence of severe SOS among children undergoing SCT following busulfan-based conditioning.²⁸

Supportive care remains the cornerstone of management of patients with SOS. Careful attention to fluid balance, maintaining intravascular volume and renal perfusion while limiting third space fluid collection, is essential. Judicious use of diuretics to maintain negative sodium balance and use of low-sodium albumin or packed red blood cells to maintain renal blood flow are useful adjuncts. Renal-dose dopamine may help to maintain renal perfusion in the face of reduced effective circulating fluid volume but has not been tested in large controlled studies. Limiting exposure to other hepatotoxic medications, including antifungal antibiotics and methotrexate, and to lipid-based parenteral nutrition is essential.

Early attempts at pharmacotherapy for SOS included the use of thrombolytic agents to relieve thrombotic occlusion of hepatic and central venules. While occasional clinical improvement has been demonstrated with recombinant tissue plasminogen activator (rtPA), its use cannot be recommended due to the unacceptably high rate of fatal bleeding in the post-transplant setting. In the largest series of patients treated with rtPA no patients with multi-organ failure responded.²⁹ The transjugular intrahepatic portosystemic shunt (TIPS) procedure has been described in the setting of severe SOS complicated by portal hypertension. Although fluid balance and hepatocellular dysfunction have been improved in these cases, hyperbilirubinemia responds poorly to this modality and survival is often limited by extrahepatic complications in this extremely ill population.³⁰⁻³²

Defibrotide (DF) is a single-stranded polydeoxyribonucleotide that shows specific binding to endothelial adenosine receptors. Defibrotide shows anti-thrombotic, anti-ischemic and anti-inflammatory properties, likely through modulation of endogenous prostaglandin and thrombomodulin/PAI-1 levels.³³ Early experience with DF in severe SOS with multi-organ failure demonstrated improved survival among treated patients compared to historical experience.³⁴ A larger study, which included 88 patients with severe SOS (multi-organ failure documented in 97%, median peak bilirubin 352 uM) demonstrated complete responses in 36% (95% CI 26% - 47%) and day +100 survival of 35% (95% CI 25% - 46%). Toxicity was mild, with grade 1 – 2 hypotension, fever, abdominal cramping and hot flashes attributed to treatment with DF. No grade 3 – 4 toxicity was attributable directly to DF and there was no worsening of clinical bleeding due to DF in this cohort.³⁵ A phase II study comparing two different dosing schedules of DF (25 mg/kg/d (n=75) vs. 40 mg/kg/d (n=75)) in patients with severe SOS

demonstrated similar response rates (46% CR) and d+100 survival (41%) for the two dosage levels. A trend towards more grade 3 – 4 adverse events, including bleeding, in the group treated at the higher dose led to the adoption of DF 25 mg/kg/d as the standard dose in a pivotal phase III trial currently underway.³⁶

Patient Factors	Disease Factors	Transplant Factors
Prior liver disease ⁹ Age > 20 ¹⁰ Prior fungal infection ¹⁰ Hepatitis C infection ¹¹ Iron overload ¹² HFE C282Y genotype ¹³	Advanced disease Prior SCT ⁵ Malignant disease Abdominal radiotherapy ⁸ Gemtuzumab ozogamicin ¹⁴ Prior chemotherapy ⁷	Myeloablative conditioning ^{4,6} Busulfan-based ¹⁵ High Busulfan AUC ³ Unrelated or MM donor ¹⁶ Sirolimus GVHD prophylaxis ¹⁷ Norethisterone use ¹⁸

Table 1. Selected factors associated with increased risk of Sinusoidal Obstruction Syndrome.

Seattle Criteria	Baltimore Criteria
Development of two of the following within 20 days of transplant: - Hyperbilirubinemia (>34 micromolar) - Tender hepatomegaly - Weight gain (> 2%)	Hyperbilirubinemia (> 34 micromolar) within 21 days of transplant and two of: - Ascites - Hepatomegaly (may be painful) - Weight gain (> 5%)

Table 2. Diagnostic criteria for SOS. Use of the more restrictive Baltimore criteria results in fewer patients being diagnosed with SOS, but higher per-case mortality among those diagnosed.¹⁹

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