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Strategies for the Management of Hepatic Veno-Occlusive Disease in Patients Undergoing Bone Marrow Transplant

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Abstract: Hepatic veno-occlusive disease (VOD) is a common complication of the chemotherapeutic and radiotherapeutic conditioning used in preparation for blood and marrow transplant (BMT). Also known as sinusoidal obstruction syndrome, the disease results from damage to the endothelial cells of the hepatic sinusoids. VOD affects approximately 14% of patients who undergo stem cell transplant. In severe cases, VOD can cause multiorgan failure, leading to death in up to 80% of patients. VOD has an unpredictable course that makes early diagnosis and treatment crucial. However, currently accepted therapies are inadequate, and many approaches have demonstrated unacceptable levels of toxicity. Defibrotide is a derivative of single-stranded deoxyribonucleotides that has been shown to restore the thrombofibrinolytic balance and heal the endothelium through multiple mechanisms of action. It was recently approved by the European Medicines Agency for the treatment of severe VOD. In September 2015, the New Drug Application for defibrotide was accepted for priority review by the US Food and Drug Administration for the treatment of VOD with evidence of multiorgan dysfunction following hematopoietic stem cell transplant. The drug has demonstrated promising efficacy and safety in phase 2 and 3 trials examining treatment and prophylaxis of VOD in adults and children.

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Target Audience

This activity has been designed to meet the educational needs of oncologists, hematologists, and nurses involved in the management of patients undergoing transplant.

Statement of Need/Program Overview

Hematopoietic stem cell transplant is a standard-of-care treatment for several hematologic malignancies. Unfortunately, successful outcomes following transplant are limited by several life-threatening complications associated with the intense chemotherapy conditioning regimens that are administered before the procedure. Damage to endothelial cells has been implicated as a direct contributor to many of these complications. Hepatic veno-occlusive disease (VOD) is a common complication of the chemotherapeutic conditioning used in preparation for bone marrow transplant. In severe cases, VOD can cause multiorgan failure, leading to death in approximately 80% of patients. VOD has an unpredictable course that makes early diagnosis and treatment crucial. Patient-related risk factors include antecedent liver toxicity and active viral hepatitis. Throughout the past several decades, the primary treatment for veno-occlusive disease has been limited to supportive care with systemic anticoagulants and thrombolytics, but these therapies have limited efficacy and excessive toxicity. The novel agent defibrotide, a derivative of single-stranded deoxyribonucleotides, has been shown to restore the thrombofibrinolytic balance and heal the endothelium through multiple mechanisms of action. In phase 2 and 3 trials, defibrotide has demonstrated efficacy and safety in the treatment and prophylaxis of VOD in adults and children.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the characteristic symptom onset and underlying pathology of hepatic veno-occlusive disease
- Monitor patients for early signs of veno-occlusive disease by identifying patient-related, disease-related, and transplant-related factors that increase the risk of developing hepatic veno-occlusive disease following stem cell transplant
- Assess the efficacy and safety outcomes associated with the use of traditional and novel therapies for the management of hepatic veno-occlusive disease
- Describe how novel agents for the prevention and treatment of hepatic veno-occlusive disease can be effectively incorporated into clinical practice

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Hepatic Veno-Occlusive Disease: The Importance of Early Detection

Kenneth R. Cooke, MD

Throughout the past several decades, blood and marrow transplant (BMT) has emerged as a critical therapeutic option for patients with cancer and other disorders of the blood and immune systems. Unfortunately, successful outcomes following BMT are limited by several life-threatening complications associated, in part, with the chemotherapeutic and radiotherapeutic conditioning regimens that are administered prior to transplant. Damage to endothelial cells has been implicated as a direct contributor to many of these complications. Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a nonhematologic toxicity associated with BMT. It is potentially life-threatening and contributes significantly to transplant-related toxicity, morbidity, and mortality.

In clinical studies, the incidence of VOD varies widely. In a recent comprehensive analysis of 135 studies, VOD was reported in a mean of 13.7% patients who underwent BMT with myeloablative conditioning.[1] In one study, VOD was observed in 62% of patients. This variation in incidence reflects differences in conditioning regimen intensity and the type of transplant, along with several patient-related factors. Additionally, the incidence may be underreported as a result of poor understanding of risk factors, disease pathogenesis, and the clinical criteria needed to make the diagnosis.

Pathogenesis

VOD is believed to primarily involve injury to hepatic sinusoidal endothelial cells.[2,3] Responses to the endothelial injury include venular microthrombosis, fibrin deposition, ischemia, and fibrogenesis. The endothelial surface is normally smooth and forms a selectively permeable vascular barrier. Endothelial barrier integrity is established by a balance between the contractile forces within endothelial cells that create intercellular gaps and the adhesive forces between endothelial cells that restrict such gaps. When endothelial cells are injured, they become swollen, activated, and more adhesive. Moreover, endothelial cells become rounded, creating gaps that allow fluid and blood cells to exit the vasculature and enter the space of Disse. Fibrin and cellular debris can also combine within the endothelial pores. These changes lead to the congestion of the hepatic sinusoids, which in turn causes liver swelling and pain. Left untreated, VOD can ultimately progress and cause reversal of portal flow, portal hypertension, and, in the worst-case scenario, hepatorenal syndrome, multiorgan failure, and death.

The pace of progression of VOD can be somewhat unpredictable, underscoring the need for early diagnosis and monitoring of patients, particularly those who are deemed to be at high risk of developing this complication. Although symptoms may resolve in patients with mild or moderate VOD, the disease can progress despite supportive care measures. Severe VOD is associated with multiorgan dysfunction that typically affects the lungs and/or kidneys, and mortality for this subset of patients can exceed 80%.[1]

Risk Factors

Several risk factors have been identified for the development of VOD (Table 1).[4,5] Patient-related risk factors include antecedent liver toxicity and viral hepatitis. Another factor, iron overload, can develop in patients with thalassemia or sickle cell disease who require chronic, and possibly life-long, transfusions and patients receiving multiple blood transfusions for treatment of an underlying malignancy or bone marrow failure syndrome. Pediatric patients treated for neuroblastoma, hemophagocytic lymphohistiocytosis, or osteopetrosis are at higher risk, as are patients with lower performance scores. The risk of VOD is increased among patients previously treated with gemtuzumab ozogamicin or radiation to the liver. Allogeneic BMTs are associated with a higher risk of VOD compared with autologous transplants. The more intense chemotherapy conditioning regimens, particularly those that combine busulfan with cyclophosphamide, are also associated with increased risk of developing VOD.

Diagnosis

VOD is a clinical syndrome. The diagnosis includes the development of hyperbilirubinemia, weight gain (ranging from 2% to 5%), ascites, and hepatomegaly, which is often painful.[4,6] Other findings that support the diagnosis of VOD include thrombocytopenia, hypernatremia, increasing abdominal girth, and respiratory or renal dysfunction. Symptoms are generally observed within the first 3 to 4 weeks after BMT. Published criteria specify that symptoms should manifest within 21 days after

Table 1. Risk Factors for Veno-Occlusive Disease

Transplant-Related
Allogeneic BMT > autologous BMT
Unrelated donor
HLA-mismatched donor
Myeloablative conditioning regimen
Busulfan-based conditioning regimen
TBI-based conditioning regimen
Non–T-cell–depleted graft
Second BMT
Patient- and Disease-Related
Increased age (in adult patients)
Norethisterone (in women or girls)
Karnofsky score less than 90%
Gene polymorphism (GSTM1, GSMTT1, heparanase)
Advanced disease (beyond second CR or relapse)
Metabolic syndrome
Deficit of antithrombin III and tPA
Resistance to activated protein C
Thalassemia
Hepatic
Transaminase >2.5 ULN
Serum bilirubin >1.5 ULN
Cirrhosis
Hepatic fibrosis
Active viral hepatitis
Hepatic irradiation
Previous use of gemtuzumab ozogamicin
Use of hepatotoxic drugs
Iron overload
Pediatric
Hemophagocytic lymphohistiocytosis
Adrenoleukodystrophy
Osteopetrosis
High-dose autologous BMT in neuroblastoma
Young age (under 1-2 years)
Low weight
Juvenile myelomonocytic chronic leukemia

CR, complete response; BMT, blood and marrow transplant; TBI, total body irradiation; tPA, tissue plasminogen activator; ULN, upper limit of normal.
Adapted from Mohty M et al. *Bone Marrow Transplant*. 2015;50(6):781-789.[4]

transplant. The differential diagnosis for VOD includes several other transplant-related complications, including graft-vs-host disease (GVHD) of the liver and various types of infection, such as hepatitis, systemic sepsis, and cholangitis. Cholestasis that occurs following total parenteral nutrition can also masquerade as VOD, as can drug toxicity, right heart failure, and iatrogenic fluid overload.

Ultrasound of the liver should be included as part of the diagnostic workup, particularly if the diagnosis is uncertain. It can be particularly important to help exclude other diagnoses.[4,6] In the presence of VOD, ultrasound can confirm the presence of ascites or hepatomegaly and demonstrate

Table 2. Modified Seattle Criteria and Baltimore Criteria

Modified Seattle Criteria
Two of the following symptoms must be present within 20 days of transplant: • Bilirubin >34.2 µmol/L (2 mg/dL) • Hepatomegaly or right upper quadrant pain • Weight gain (>2% from pretransplant weight)
Baltimore Criteria
Bilirubin >34.2 µmol/L (2 mg/dL) within 21 days of transplant and 2 of the following symptoms: • Hepatomegaly • Ascites • Weight gain (>5% from pretransplant weight)

Adapted from Dignan FL et al. *Br J Haematol*. 2013;163(4):444-457.[6]

alterations in, and ultimate reversal of, blood flow in the portal venous system. Liver biopsy is usually reserved for patients in whom the diagnosis of VOD remains unresolved after consideration of the available clinical and radiographic data. Evidence for sinusoidal obstruction, tissue injury, scarring, fibrosis, or necrosis can often be observed histopathologically, particularly when VOD is severe.

Baltimore and Seattle Criteria

Scoring criteria have been developed to facilitate the clinical diagnosis of patients with VOD (Table 2). The modified Seattle criteria stipulate that, within 20 days of transplant, at least 2 or more clinical features must develop, including a bilirubin level of at least 2 mg/dL, hepatomegaly or right upper quadrant pain, and/or unexplained weight gain of more than 2%.[7,8] The Baltimore criteria specify an elevated bilirubin level of at least 2.0 mg/dL plus at least 2 of the following characteristics developing within 21 days of transplant: hepatomegaly, ascites, and/or at least 5% weight gain.[9] To summarize, the Baltimore criteria require the presence of hyperbilirubinemia, whereas the modified Seattle criteria do not.

Biomarkers for VOD Onset and Severity

Predicting the onset and overall severity of hepatic VOD remains challenging. Several molecules that are expressed as a result of endothelial injury have been investigated as biomarkers for VOD. Plasminogen activator inhibitor type 1 (PAI-1) inhibits fibrinolysis and was shown to increase significantly in patients with VOD.[10] In a study of 115 patients conditioned with busulfan and cyclophosphamide followed by allogeneic BMT, 44% of patients developed VOD, and PAI-1 was identified as both a prognostic and diagnostic biomarker for the syndrome.[11] VOD was characterized as mild, moderate, or severe, and PAI-1 and bilirubin were identified as independent variables associated with the occurrence of severe VOD.

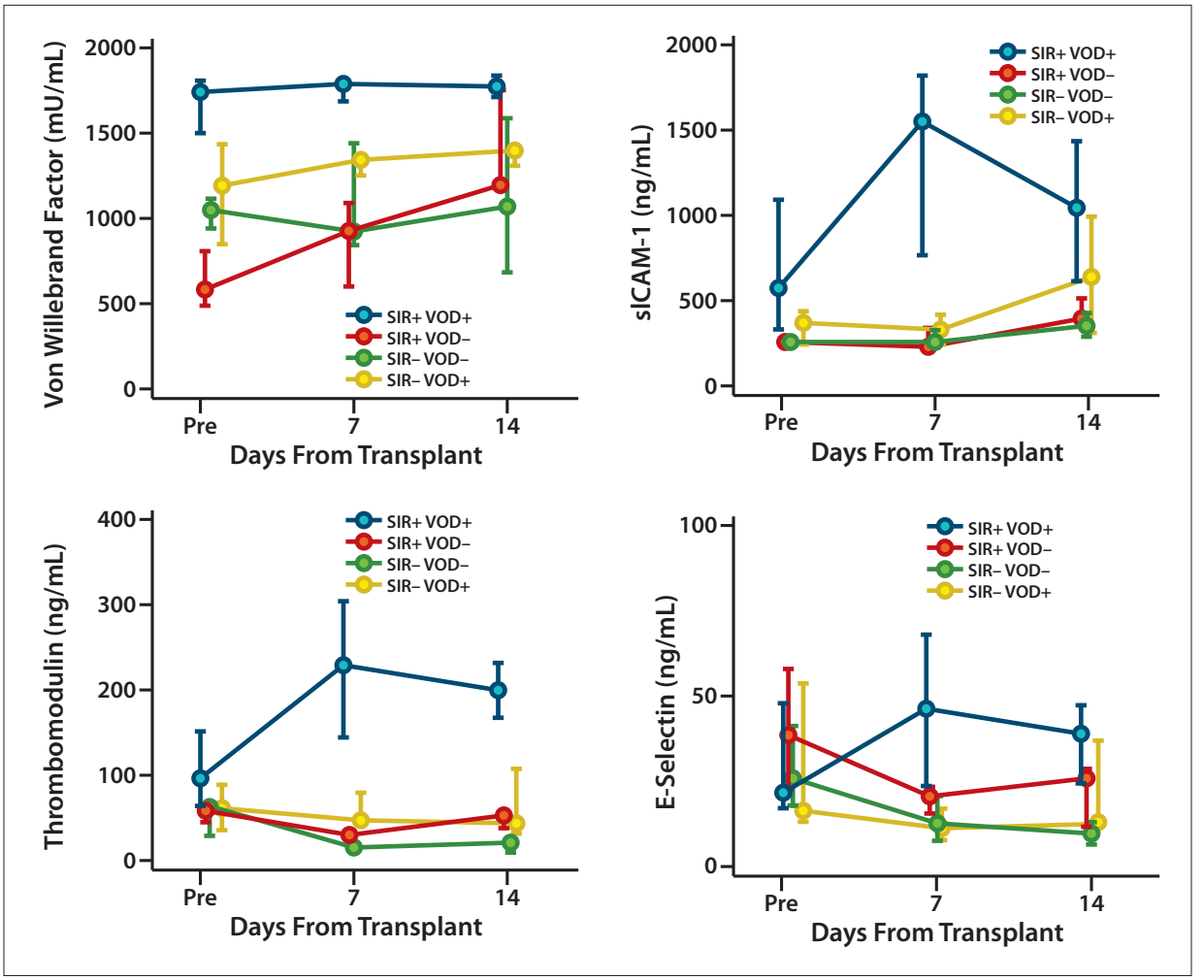

Figure 1. A study of patients who received cyclophosphamide conditioning and total body irradiation plus tacrolimus and sirolimus showed a correlation between the development of VOD and increasing levels of von Willebrand factor, sICAM-1, thrombomodulin, and E-selectin. sICAM-1, soluble intercellular adhesion molecule-1; SIR, sirolimus exposure level; VOD, veno-occlusive disease outcome. The confidence intervals, as indicated by the bars, represent the interquartile ranges. Adapted from Cutler C et al. *Biol Blood Marrow Transplant*. 2010;16(8):1180-1185.[13]

Sirolimus is commonly administered to prevent GVHD in patients undergoing allogeneic BMT. However, sirolimus is associated with an increased risk of VOD, particularly when given in combination with tacrolimus.[12] A retrospective analysis was performed to identify markers of endothelial injury to predict the onset of VOD in patients treated with sirolimus.[13] Among the 61 patients who received cyclophosphamide conditioning and total body irradiation plus tacrolimus and sirolimus, 21 (34%) developed VOD. The study showed a correlation between the development of VOD and increasing levels of von Willebrand factor, soluble intercellular adhesion molecule (ICAM-)1, thrombomodulin, and E-selectin (Figure 1).

A proteomics approach has also been investigated to identify biomarkers for the diagnosis and prognosis of VOD. In a recent study of plasma samples from 80 patients, the combination of suppression of tumorigenicity-2, angiopoietin-2, L-ficolin, hyaluronic acid, and vascular cell adhesion molecule-1, ultimately assessed by enzyme-linked immunosorbent assays (ELISAs), was used as a biomarker panel for the diagnosis of VOD.[14] By invoking a subset of these markers combined with clinical characteristics, Bayesian modeling correctly predicted VOD onset in more than 80% of cases. Although PAI-1 has been established as a valid biomarker for VOD, more recently identified markers are still experimental and warrant continued validation.

Importance of Early Diagnosis and Treatment

The unpredictable progression of VOD and the high mortality rate associated with severe VOD make early

diagnosis, vigilant monitoring, and institution of appropriate treatment crucial for posttransplant patients.[4,15] In particular, high-risk patients must be closely watched for the development of early symptoms. Fluid intake and output should be monitored carefully, and patients should be assessed at least once daily for symptoms such as weight gain, fluid retention, overt edema and ascites, hepatomegaly, and jaundice. Patients with signs and symptoms of fluid overload require supportive care with sodium restriction in concert with avoidance of free water and maintenance of intravascular volume. In more advanced cases, consultation with a renal specialist may be considered for assistance with optimizing fluid management, which may include the judicious use of diuretics (via intermittent or continuous infusion) or continuous renal replacement therapy. Measures should always be taken to prevent and manage hepatorenal syndrome.

Patients should be observed for signs and symptoms of potential multiorgan failure. Signs and symptoms of pulmonary dysfunction may include shortness of breath, increased respiratory rate, and increased work of breathing along with decreased oxygen saturation and the need for supplemental oxygen or mechanical ventilation. Renal dysfunction as measured by increased creatinine level or decreased creatinine clearance must be recorded, and the need for continuous renal replacement therapy or hemodialysis assessed. Factors that may predict the development of severe VOD include a rapid increase in weight and increased serum levels of bilirubin.[16] In addition, the rate of change in parameters such as bilirubin levels, weight gain, and liver and renal function may also be useful.[15]

VOD severity can be determined retrospectively based on the therapeutic intervention that was required. VOD that did not require intervention is considered mild. Moderate VOD is characterized by changes in laboratory parameters; the need for pain medications, diuretics, or sodium restriction; and reversible symptoms. Severe VOD is indicated by multiorgan failure and/or irreversible changes in laboratory parameters resulting in death.

Disclosure

Dr Cooke is a consultant for Jazz Pharmaceuticals and also a member of the company's advisory board.

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Review of Data Supporting Use of Novel Therapies in Veno-Occlusive Disease

Amrita Y. Krishnan, MD

Patients with an increased risk of developing VOD should be considered for prophylactic treatment.[1] Agents such as ursodiol, heparin, and glutamine have been used since the 1990s. Studies of these agents, however, have yielded conflicting outcomes regarding their efficacy, as well as safety concerns.[2] In clinical trials from the 1990s, low–molecular-weight heparin appeared to prevent VOD with no significant adverse events.[3,4] In a trial from 2006, low-dose heparin or prostaglandin E1 reduced the incidence, though not the severity, of VOD.[5] In recent guidelines, prostaglandin E1 is not recommended for the prophylaxis of VOD based on lack of efficacy and toxicity.[6] Data suggest that preemptive administration of antithrombin III does not alter the incidence of VOD.[7]

Patients with advanced leukemia often undergo multiple salvage chemotherapy regimens in an attempt to induce remission. Moreover, these treatments may include antibody-drug conjugates, which are known to increase VOD. For example, in the case of relapsed acute lymphoblastic leukemia, the use of inotuzumab ozogamicin as a bridge to transplant is becoming more common. Inotuzumab ozogamicin was designated by the US Food and Drug Administration (FDA) as a Breakthrough Therapy in October 2015. Data suggest that inotuzumab ozogamicin may increase rates of VOD.[8] This risk is not surprising given the prior known experience with the antibody-drug conjugate gemtuzumab ozogamicin, which has been associated with an increase in VOD, especially when given within 3 months of transplant.[9,10] Further adding to the risk of VOD in advanced leukemia patients is the use of more intensive transplant conditioning regimens, including total marrow irradiation.

Treatment of VOD has traditionally focused on supportive care. However, these agents have limited efficacy and substantial toxicity.[11] Prostaglandin E1 has been associated with a suboptimal response rate and a high risk of bleeding.[11] Tissue-plasminogen activator (tPA) has been used to treat severe cases of VOD, but it is associated with a significant risk of life-threatening hemorrhage.[12] In a chart review study of 42 patients with VOD who had received tPA and heparin, the response rate was 29%, and 24% of patients experienced severe bleeding.

Defibrotide

Defibrotide is a polydisperse mixture of single-stranded oligonucleotides derived from porcine intestinal mucosa.[13] Its mechanism of action has not been fully characterized, but it is clearly complex and includes antithrombotic, anti-ischemic, and anti-inflammatory effects. Many of these effects are consistent with an ability to reverse some of the endothelial cell damage that is incurred with chemotherapeutic conditioning. The antithrombotic activity of defibrotide is mediated by increasing levels of plasmin and tPA and decreasing levels of PAI-1, which induce an endothelial milieu that favors fibrinolysis and discourages coagulation.[14,15] Defibrotide has also been shown to decrease the adhesion of leukocytes to endothelial cells.[16] The drug has demonstrated efficacy with acceptable safety in several clinical trials of VOD.[1] In October 2013, defibrotide was approved by the European Medicines Agency for treatment of severe VOD in patients older than 1 month of age. An investigational new drug (IND) application has been accepted for priority review by the FDA.

A large pediatric study examined the safety and efficacy of defibrotide (25 mg/kg daily) for the prevention of VOD at 28 European treatment centers.[17] This open-label, phase 3 trial randomly assigned 356 patients to defibrotide or a control. VOD was assessed within 30 days after BMT. Patients had at least 1 risk factor for VOD. Patients in the control group who developed VOD were permitted to receive defibrotide. The incidence of VOD of any severity was reduced in the treatment arm (12% vs 20%; Z test for competing risk analysis P=.0488; log-rank test P=.0507). In addition, defibrotide treatment appeared to provide protection against the development of acute GVHD.[18] At day +100, the incidence of acute GVHD was 47% in the defibrotide arm and 65% in the control arm (P=.0046). The severity of GVHD was also reduced with defibrotide (P=.0130). Endothelial cell damage may be part of the pathogenesis of GVHD, and hence the endothelial protective effects of defibrotide may account for the lower incidence in the treatment group.

Treatment

Therapies for patients with VOD vary with severity. Mild disease can often be self-limited, with treatment consisting of fluid management and transfusional support. These patients generally do quite well. Patients with moderate VOD present a challenge. It is important to prevent the progression to severe VOD, with can lead to multiorgan failure and death. Biomarkers for early detection hold promise for enabling earlier treatment.

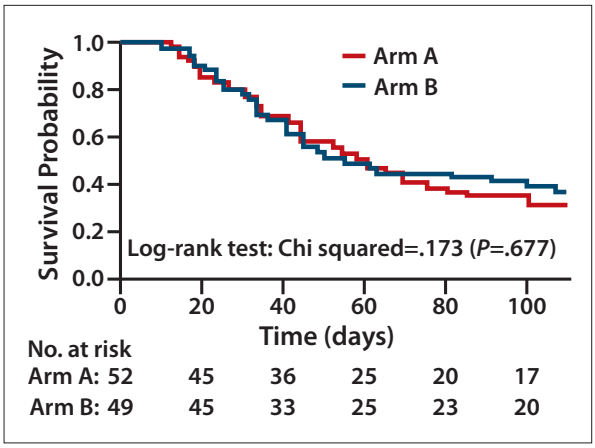

Figure 2. Survival probability among adults in a phase 2 dose-finding study of defibrotide. Patients in Arm A received 25 mg/kg/day. Patients in Arm B received 40 mg/kg/day. Adapted from Richardson PG et al. *Biol Blood Marrow Transplant*. 2010;16(7):1005-1017.[24]

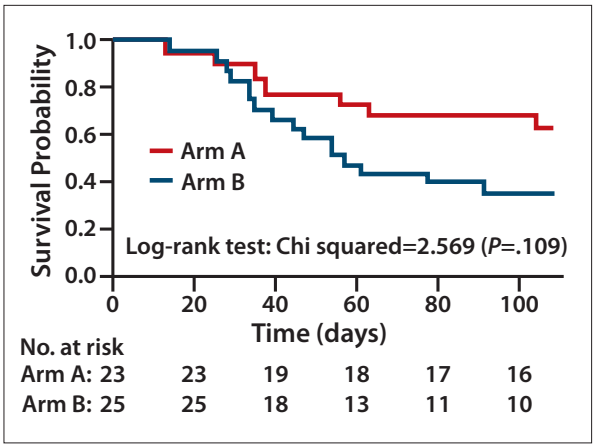

Figure 3. Survival probability among children in a phase 2 dose-finding study of defibrotide. Patients in Arm A received 25 mg/kg/day. Patients in Arm B received 40 mg/kg/day. Adapted from Richardson PG et al. *Biol Blood Marrow Transplant*. 2010;16(7):1005-1017.[24]

Several clinical trials are of great interest in understanding how defibrotide may be used to treat patients who have already developed VOD. An early phase 1 compassionate use trial assessed the efficacy and safety of defibrotide in 19 patients with severe VOD with risk of progression after BMT.[19] In addition to demonstrating efficacy, the study showed a promising safety profile relative to other options. Patients received intravenous defibrotide in doses ranging from 5 mg/kg to 60 mg/kg daily for at least 14 days. No patients discontinued treatment based on toxicity, and no severe hemorrhages were observed in the treatment group. Among the 8 patients (42%) who demonstrated resolution of VOD, 6 survived beyond day 100 posttransplant.

Defibrotide was investigated further in a phase 1/2 trial of 88 patients with severe VOD following BMT.[20] Eligible patients had symptoms including jaundice, hepatomegaly and/or right upper quadrant pain, and at least 5% weight gain. In addition, when applicable, patients were required to have a risk of severe VOD assessed at 30% or higher.[21] Risk was based on the Bearman model and included onset of VOD by day 16 posttransplant, plus use of conditioning treatment with one of several regimens: cyclophosphamide and total body irradiation; busulfan and cyclophosphamide; or cyclophosphamide, carmustine, and etoposide. Alternatively, patients were eligible if VOD was considered their major clinical problem, and at least one other organ system was failing.

At diagnosis, patients had a median bilirubin level of 4.5 mg/dL and a median weight gain of 7%. Ascites was reported in 84%, and 35% had abnormal portal venous flow. At the time of initiating treatment with defibrotide, median bilirubin had escalated to 12.6 mg/dL, and 97% of patients had multiorgan failure. Patients received daily defibrotide doses ranging from 5 mg/kg to 60 mg/kg for a median of 15 days. VOD symptoms resolved completely in 36% of patients, and survival at day 100 posttransplant was 35%. No serious treatment-related toxicities, including severe hemorrhage, were observed.

A phase 3 trial underscored the potential of defibrotide for treating patients with VOD and renal and/or pulmonary failure.[22] Because of the risk of death in patients with severe VOD and multiorgan failure, the trial incorporated a historical control instead of a control arm consisting of placebo or best supportive care. The historical control arm included 32 patients with an unequivocal diagnosis of VOD with multiorgan failure secondary to VOD. The treatment arm enrolled 102 patients, with defibrotide administered at 6.25 mg/kg every 6 hours for a recommended duration of at least 21 days. A superior complete response rate at day 100 posttransplant was observed for the patients treated with defibrotide (24% vs 9%; *P*=.015). Mortality at day 100 posttransplant was reduced by defibrotide treatment compared with the historical control (62% vs 75%; *P*=.051). Rates of hemorrhagic adverse events (AEs) of any grade were similar between the 2 groups, and 18% of patients treated with defibrotide discontinued owing to drug-related toxicity. Based on data from the phase 3 trial, a related study calculated the number needed to treat (NNT) to achieve 1 complete response as 7, and the NNT to prevent 1 death at 100 days posttransplant as 8.[23]

A phase 2 study compared the efficacy and safety of 25 mg/kg vs 40 mg/kg defibrotide daily, administered in divided doses every 6 hours for at least 14 days or until complete response in 149 adult and pediatric patients (Figures 2 and 3).[24] All patients had VOD as well as concomitant multiorgan failure or a risk of severe VOD that was 30% or higher.[21] The treatment for the overall study population demonstrated a complete response rate of 46%

and a survival rate at day +100 of 42%, with no significant differences in outcomes observed between the 2 arms. Toxicities were also similar for the 2 dosages, and the recommended dose for future trials was 25 mg/kg daily.

Since 2007, defibrotide has been available in the United States through an expanded access treatment IND (T-IND) protocol. The ongoing study includes patients with severe VOD and multiorgan failure, nonsevere VOD following hematopoietic BMT, and VOD following chemotherapy in the nontransplant setting. The original protocol required patients to have a diagnosis of VOD based on Baltimore criteria, with multiorgan failure following hematopoietic BMT. However, the study was amended to include patients with VOD without multiorgan failure occurring after hematopoietic BMT or chemotherapy. The interim safety analysis included 612 patients with a median age of 12 years (range, <0.1-69 years).[25] AEs considered possibly, probably, or definitely related to study treatment were reported in 454 patients (74.2%). Those occurring in more than 2% of patients included pulmonary hemorrhage (4.7%), gastrointestinal hemorrhage (3.6%), epistaxis (3.1%), and hypotension (2.8%). Serious AEs considered at least possibly related to study treatment occurred in 13.4% of patients and included pulmonary and gastrointestinal hemorrhage (3.9% and 2.9%, respectively). AEs leading to death that were considered possibly related to study medication occurred in 2.8% of patients. Survival rates at day 100 posttransplant for 425 patients were 55% for those who had undergone hematopoietic BMT and 62% for those who had received chemotherapy without transplant.[26]

Subgroup Analysis

Subgroup analysis of the T-IND data has elucidated several important concepts.[26] A key aspect is when to initiate defibrotide therapy. The drug appears most effective when given within the first 48 hours from the initial diagnosis. The complete response rates at day 100 posttransplant were 39% for the patients who received defibrotide within the first 2 days of diagnosis (n=272) vs 25% for those who were treated later (n=134; P=.0052). The survival rates were 61% vs 38%, respectively (P<.0001). These data support the urgency of early intervention. As observed in earlier trials, pediatric patients (n=232) had better outcomes than adults (n=192). At day 100 posttransplant, the complete response rates were 41% for children vs 27% for adults (P<.0038). The survival rates were 60% vs 49% (P<.0203). Defibrotide also demonstrated efficacy in patients with prior BMT, as well as those whose prior treatment had consisted only of chemotherapy. Defibrotide was effective in treating both severe and nonsevere VOD. Complete response rates at day 100 posttransplant ranged from 29% among BMT patients with severe VOD to 47% among BMT patients with nonsevere VOD.

Disclosure

Dr Krishnan has received consulting fees from Jazz Pharmaceuticals and Millennium. She is a member of the speakers bureaus of Celgene, Millennium, and Onyx. She has an ownership interest in Celgene.

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Management of Veno-Occlusive Disease: Best Use of Novel Agents

Paul G. Richardson, MD

VOD presents a major treatment challenge for several reasons during hematopoietic BMT. The time course and symptom onset vary among patients. The tempo of disease can also change within a patient. Endothelial stress can result in mild to moderate VOD escalating to severe VOD, underscoring the importance of early diagnosis and treatment.

Defibrotide has demonstrated efficacy in a wide range of settings of VOD complicating BMT. It can be used to prevent the onset of VOD as well as to treat both moderate and severe disease (Figures 4 and 5).[1,2] Its safety profile and efficacy in the prophylactic setting further supports early administration. Data show that earlier intervention improves outcomes in both adults and children.[1,2] Children have consistently yielded better outcomes than adults, making defibrotide important in the pediatric transplant setting in particular. Fibrinolytic strategies, such as tPA, have a response rate, but are associated with unacceptable toxicity, including prohibitive hemorrhagic risk (Table 3).[3,4] Antithrombin III and prostaglandin E1 also appeared to have promise in terms of mechanism of action, but they showed limited efficacy and also unacceptable toxicity.[4]

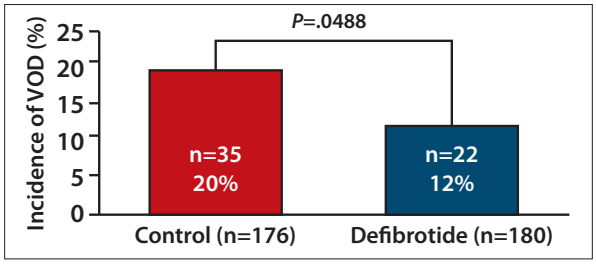

Figure 4. Incidence of veno-occlusive disease in a phase 3 trial evaluating defibrotide. Adapted from Corbacioglu S et al. *Lancet*. 2012;379(9823):1301-1309.[4]

Defibrotide Dose Optimization

Comprehensive work was done with defibrotide to establish the optimal dose range. Evaluation began at 5 mg/kg/day, and patients were then escalated to 10 mg/kg/day, with doses up to 60 mg/kg/day tested initially. Studies have shown that the active daily dose range is between 25 mg/kg and 40 mg/kg. A randomized, phase 2 trial comparing daily dosages of 25 mg/kg vs 40 mg/kg found no significant differences in outcomes.[5] Subgroup analysis, however, showed that the higher dose was associated with more toxicity, with increased hemorrhagic risk observed at the higher dosage in children.

It should be noted that the European label specifies a daily dose of 25 mg/kg, and that dosage is under consideration by the US Food and Drug Administration. The current dose recommendation is 25 mg/kg daily, but doses as low as 10 mg/kg daily are active. Dose reduction in the face of toxicity has been shown to be effective. Conversely, some single-center studies suggest that a higher dose in selected patients, up to 60 mg/kg daily, can be associated with response, especially if treatment failure at a lower dose has been encountered. These data, however, remain preliminary, and further research is required with prospective studies exploring a higher dosage as well as investigating the surrogate markers needed to better understand the effects of defibrotide at higher doses.

In this context, the phase 2 dose-finding trial comparing 25 mg/kg vs 40 mg/kg included a comprehensive analysis of surrogate markers of endothelial stress.[5] No significant differences were observed between the 2 arms, including for PAI-1. Similarly, pharmacokinetic analysis also showed no differences between the 2 doses. It is reasonable to speculate

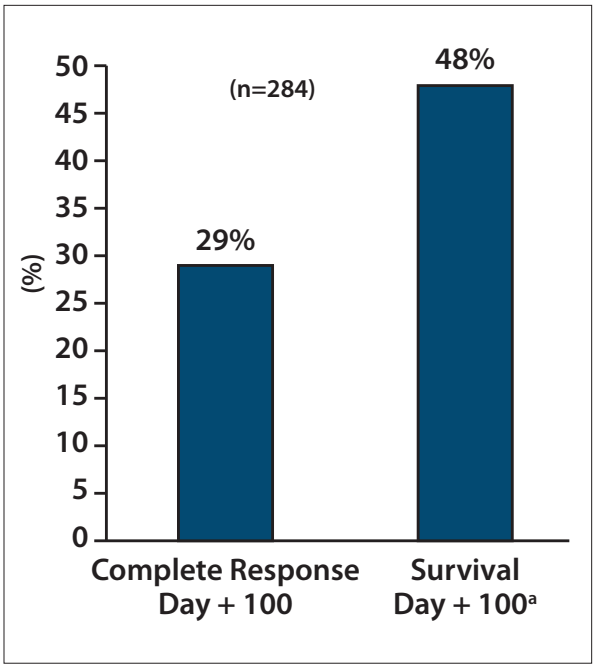

Figure 5. Results from an analysis of the treatment IND expanded access protocol, a large, prospective study of defibrotide for the treatment of severe hepatic veno-occlusive disease. [a]Kaplan-Meier estimates for time to the event. Adapted from Richardson PG et al. ASH abstract 700. *Blood*. 2013;122(21 suppl).[2]

that the difference between the 2 doses may have been insufficiently large, and future trials will hopefully address this issue.

Patient Management

Aggressive supportive care and optimal patient management is essential in treating VOD. Management guidelines are available from organizations such as the joint working group of the British Committee for Standards in Haematology (BCSH), the British Society for Blood and Marrow Transplantation (BSBMT), and the European Blood and Marrow Transplantation (EBMT).[4,6] In addition to addressing any hemorrhagic risk with platelet transfusion, factor support, and management of fluid balance, of particular importance for VOD patients receiving defibrotide is to address any signs of infection as soon as possible. As with GVHD, a frequent source of mortality is infection. In the case of VOD patients, the risk of infection increases due to portal hypertension and the translocation of organisms across the gut barrier. Moreover, patients with liver failure are profoundly immunocompromised, and typically do not mount a febrile response. As mentioned above, crucial components of supportive care include platelet transfusion and correction of coagulation factors. In the context of fluid balance, it is critical to optimize renal perfusion and mitigate hepatorenal syndrome with appropriate measures including

Table 3. Sites of Major Bleeding Among 42 Patients Receiving Recombinant Human Tissue Plasminogen Activator and Heparin for Treatment of Hepatic VOD After Transplant

	Bleeding Caused Death		
Bleeding Site	**Patients (n)**	**Yes**	**Possibly**
Brain	2	2	
GI tract	3	1	2
Lung	3	1	2
Lung, brain	1		1
GI tract, venipuncture, vagina, ETT	1		

ETT, endotracheal tube; GI, gastrointestinal.

Adapted from Bearman SI et al. *Blood*. 1997;89(5):1501-1506.[3]

maintaining adequate intravascular volume and minimizing third spacing. Platelet parameters, hemoglobin levels, and volume status should therefore be monitored carefully, and use of coagulation factor VII can be administered as needed, especially in the face of marked elevation of the international normalized ratio despite fresh frozen plasma support.

Other Therapeutic Agents

Other agents that may be useful in the treatment of VOD include N-acetyl-L-cysteine (NAC) for patients receiving busulfan conditioning. Busulfan is metabolized mainly through glutathione, and NAC is a precursor of glutathione. In a small, preliminary study of 10 patients undergoing allogeneic stem cell transplants who were at risk of VOD because of liver disease or abnormal liver enzymes, NAC was administered during conditioning with busulfan.[7] None of the patients developed VOD or liver failure, suggesting possible benefit.

Methylprednisolone has shown activity in treating VOD. In a retrospective study, 9 pediatric patients received 6 doses of methylprednisolone (500 mg/m^2) intravenously every 12 hours.[8] Corticosteroid therapy was initiated at or before the first ultrasound evidence of reversal of portal venous flow. Four patients also received defibrotide starting 2 to 5 days after initiation of corticosteroid therapy. Eight of the patients had multiorgan failure. While 2 patients died, 7 recovered at a median of 6 days (range, 5-38 days) after diagnosis of VOD. In patients with hematologic cancers who are treated with the checkpoint inhibitors, such as nivolumab and pembrolizumab, in conjunction with BMT, VOD has been seen and may have an inflammatory component. Defibrotide plus methylprednisolone sodium succinate anecdotally has shown impressive results in some of these patients.

In summary, there may well be a strong rationale to combine defibrotide with other agents to further improve outcome, with additional studies in this area anticipated to validate such approaches.

Disclosure

Dr Richardson has served as a member of Jazz Pharmaceutical advisory boards and received research funding.

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Strategies for the Management of Hepatic Veno-Occlusive Disease in Patients Undergoing Bone Marrow Transplant: Discussion

Kenneth R. Cooke, MD, Paul G. Richardson, MD, and Amrita Y. Krishnan, MD

H&O Do you have any recommendations to help health care providers accurately diagnose VOD?

Kenneth R. Cooke, MD It is important to underscore the need to educate transplant physicians and oncologists to be familiar with the diagnostic criteria of VOD and to be on the lookout for them. A true team approach is needed. Everyone who provides care to transplant patients, including nurses, house staff, midlevel practitioners, and bone marrow transplant physicians, must be educated to understand the importance of making an early diagnosis, understanding the diagnostic criteria, and knowing the treatment options, whether or not patients have multiorgan failure.

H&O What are current practices regarding tPA?

Paul G. Richardson, MD The best prospective study was published by Bearman and colleagues in 1997.[1] Forty-two patients with VOD received tPA and heparin. The study demonstrated a response rate of approximately 30%, with response defined as a 50% reduction in bilirubin. A key message from the study was that when patients developed multiorgan compromise, the risk of life-threatening complications from tPA significantly increased, and in fact, no benefit was seen in any of the patients with multiorgan failure. The authors therefore recommended that tPA be used early or not at all, and that it not be used in patients who have already developed multiorgan dysfunction. Subsequent studies have validated this observation, and in the pediatric literature, there are only a small number of experiences that suggest any benefit to tPA/heparin. Dr Cooke, do you know of any other studies?

Kenneth R. Cooke, MD My understanding of the literature is just as you stated. I am not aware of larger trials demonstrating that any of these agents have been efficacious in pediatric patients. From a pediatric care perspective, these agents are not ones that I regularly use to mange even moderate to severe VOD. They have the potential to cause bleeding complications and lack data demonstrating clear efficacy.

Paul G. Richardson, MD I do agree, and in our own BMT group, we have not used this approach for many years.

Amrita Y. Krishnan, MD We do not use it at City of Hope, either. We have used ursodiol plus low-dose heparin for our patients at high risk for VOD. There have been 2 small trials from Europe investigating low-dose heparin, so we use that for high-risk patients when defibrotide is not available.

H&O Can you provide some further insights regarding defibrotide's mechanisms of action?

Amrita Y. Krishnan, MD To me, the biggest effect of defibrotide is its ability to reverse some of the endothelial

cell damage. It also decreases inflammatory cytokines and increases local tissue fibrinolysis. It will increase local tissue tPA, downregulate PAI-1, and change the profiles of some of the cellular adhesion molecules. At a local level, defibrotide can reverse some of the damage done by the conditioning regimen.

Kenneth R. Cooke, MD There are several mechanisms of action. Most importantly, defibrotide can restore thrombofibrinolytic balance and perhaps even have some mild profibrinolytic activity. The bleeding risks have been acceptable, and defibrotide is tolerable even in coagulopathic patients with thrombocytopenia or mild abnormalities in their international normalized ratios or other coagulation studies. It is interesting that defibrotide has a broad mechanism of action, yet still has a reasonable toxicity profile.

Paul G. Richardson, MD I do agree that the mechanism of action of defibrotide as a first-in-class polydeoxyribonucleotide is pleiotropic. What is fascinating is that there is an effect on microvascular endothelium that is not carried across to the macrovasculature, which probably explains why the risk of hemorrhage is less with defibrotide than for other anticoagulants or fibrinolytic drugs. As Dr Krishnan also mentioned, there is a activity across the endothelial surface. It appears to involve adhesion and certain specific soluble markers of endothelial stress, which include thrombomodulin, selectins, vasoactive peptides, and platelet-activating molecules.

Defibrotide also releases tissue factor pathway inhibitor, decreases circulating levels of PAI-1, and upregulates tPA. Another intriguing property of defibrotide is that it downregulates the cell surface expression of heparanase. This effect may explain why defibrotide can also be effective for GVHD both in prophylaxis and perhaps therapeutically, as suggested by various studies to date.

H&O What are the patient eligibility requirements for the T-IND trial?

Amrita Y. Krishnan, MD The T-IND trial has been ongoing since 2007.[2] The trial design has changed as the thinking about VOD has evolved. The initial phase of the trial enrolled posttransplant patients with multiorgan failure. The VOD diagnosis was based on Baltimore criteria, which requires that symptoms occur up to day 21 after transplant. These criteria caused some frustration, as even patients with severe VOD could not be enrolled until they developed multiorgan failure.

This protocol was eventually amended to encompass atypical VOD and later-onset VOD, and it no longer requires multiorgan failure. In addition, the study now allows patients who had not undergone a stem cell transplant because VOD can occur after chemotherapy.

H&O How does the pediatric population respond to defibrotide?

Paul G. Richardson, MD Pediatric subgroups have consistently had higher complete response rates. Specifically, the response rates in children are approximately 10 or 15 percentage points higher in the various studies, and survival has also been more favorable.

An important message is that there is no evidence that children with untreated VOD have a better outcome vs adults. There is a hypothesis that endothelial stress responses in children are more robust, and they are better able to tolerate multiorgan failure, which allows more time for therapeutic efficacy to emerge and might explain why children appear to do better with defibrotide therapy.

Kenneth R. Cooke, MD I agree. The disease process, including pace and severity, whether systemic or at the level of the liver, is probably equally robust for children and adults. Generally speaking, it appears that children are able to shoulder the additional stress that is associated with multiorgan failure, allowing for some additional cushion to initiate defibrotide once the diagnosis is made. This difference may partly explain some of the improved survival data for children.

Disclosures

Dr Cooke is a consultant for Jazz Pharmaceuticals and also a member of the company's advisory board. Dr Richardson has served as a member of Jazz Pharmaceutical advisory boards and has received research funding. Dr Krishnan has received consulting fees from Jazz Pharmaceuticals and Millennium. She is a member of the speakers bureaus of Celgene, Millennium, and Onyx. She has an ownership interest in Celgene.

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Slide Library

Veno-Occlusive Disease

- Hepatic VOD, also known as sinusoidal obstruction syndrome, is a nonhematologic toxicity associated with BMT
- It is potentially life-threatening and contributes significantly to transplant-related toxicity, morbidity, and mortality
- In a recent meta-analysis, VOD was reported in a mean of 13.7% patients who underwent BMT with myeloablative conditioning[1]

BMT, bone and marrow transplant; VOD, veno-occlusive disease.
1. Coppell JA et al. *Biol Blood Marrow Transplant*. 2010;16(2):157-168.

Veno-Occlusive Disease: Prognosis

- The pace of progression of VOD can be somewhat unpredictable, underscoring the need for early diagnosis and monitoring of patients, particularly those who are deemed to be at high risk of developing this complication
- Although symptoms may resolve in patients with mild or moderate VOD, the disease can progress despite supportive care measures
- Severe VOD is associated with multiorgan dysfunction that typically affects the lungs and/or kidneys, and mortality for this subset of patients can exceed 80%

Monitoring for Veno-Occlusive Disease

- High-risk patients must be closely watched for the development of early symptoms
- Fluid intake and output should be monitored carefully
- Patients should be assessed at least once daily for symptoms such as weight gain, fluid retention, overt edema and ascites, hepatomegaly, and jaundice

Veno-Occlusive Disease: Diagnosis

- The modified Seattle criteria stipulate that, within 20 days of transplant, at least 2 or more clinical features must develop, including a bilirubin level of at least 2 mg/dL, hepatomegaly or right upper quadrant pain, and/or unexplained weight gain of more than 2%[1,2]
- The Baltimore criteria specify an elevated bilirubin level of at least 2.0 mg/dL plus at least 2 of the following characteristics developing within 21 days of transplant: hepatomegaly, ascites, and/or at least 5% weight gain[3]

1. McDonald GB et al. *Hepatology*. 1984;4(1):116-122. 2. McDonald GB et al. *Ann Intern Med*. 1993;118(4):255-267. 3. Jones RJ et al. *Transplantation*. 1987;44(6):778-783.

Current Treatment Options for Veno-Occlusive Disease: Defibrotide

- A polydisperse mixture of single-stranded oligonucleotides
- Demonstrated efficacy with acceptable safety in several clinical trials of VOD[1-4]
- Since 2007, defibrotide has been available in the United States through an expanded access treatment IND protocol
- An IND application has been accepted for priority review by the FDA

FDA, US Food and Drug Administration; IND, investigational new drug. 1. Corbacioglu S et al. *Lancet*. 2012;379(9823):1301-1309. 2. Corbacioglu S et al. ASH abstract 4591. *Blood*. 2013;124(21 suppl). 3. Richardson PG et al. *Blood*. 1998;92(3):737-744. 4. Richardson PG et al. *Blood*. 2002;100(13):4337-4343.

Defibrotide: Use in Clinical Practice

- Defibrotide has demonstrated efficacy in a wide range of settings
- It can be used to prevent the onset of VOD as well as to treat both moderate and severe disease[1,2]
- Data show that earlier intervention improves outcomes in both adults and children[1,2]
- Children have consistently yielded better outcomes than adults, making defibrotide particularly important in the pediatric transplant setting

1. Corbacioglu S et al. *Lancet*. 2012;379(9823):1301-1309.
2. Richardson PG et al. ASH abstract 700. *Blood*. 2013;122(21 suppl).

For a free electronic download of these slides, please direct your browser to the following web address:

http://www.hematologyandoncology.net

Strategies for the Management of Hepatic Veno-Occlusive Disease in Patients Undergoing Bone Marrow Transplant

CME Post-Test: *Circle the correct answer for each question below.*

1. In a recent analysis of 135 studies, hepatic veno-occlusive disease (VOD) was reported in a mean of ____ patients who underwent blood and marrow transplant (BMT) with myeloablative conditioning.

   a. 11.2%
   b. 12.8%
   c. 13.7%
   d. 14.1%

2. Severe VOD is associated with multiorgan dysfunction that typically affects the lungs and/or kidneys, and mortality for this subset of patients can exceed:

   a. 80%
   b. 85%
   c. 90%
   d. 95%

3. Which is the most frequent source of mortality among patients with VOD?

   a. Infection
   b. Myocardial infarction
   c. Pulmonary thromboembolism
   d. Stoke

4. Which symptom is NOT associated with VOD?

   a. Epistaxis
   b. Fluid retention
   c. Hepatomegaly
   d. Weight gain

5. Which agents are known to increase the risk of VOD?

   a. Antibody-drug conjugates
   b. BTK inhibitors
   c. HDAC inhibitors
   d. Monoclonal antibodies

6. In a review of patients with VOD who had received tissue-plasminogen activator and heparin, how many patients experienced severe bleeding?

   a. 18%
   b. 24%
   c. 32%
   d. 41%

7. In a study of patients who received cyclophosphamide conditioning and total body irradiation plus tacrolimus and sirolimus, how many developed VOD?

   a. 14%
   b. 23%
   c. 34%
   d. 41%

8. At what point should defibrotide be administered after the initial diagnosis of VOD?

   a. Within the first 48 hours
   b. Within the first 72 hours
   c. Within the first 84 hours
   d. Within the first 5 days

9. In study examining prevention of VOD among pediatric patients, what was the incidence of VOD among those receiving defibrotide?

   a. 12%
   b. 18%
   c. 21%
   d. 26%

10. In a phase 3 trial of patients with VOD and renal and/or pulmonary failure, what was the complete response rate at day 100 posttransplant among patients treated with defibrotide?

    a. 15%
    b. 19%
    c. 22%
    d. 24%

Project ID: 11128

Evaluation Form: Strategies for the Management of Hepatic Veno-Occlusive Disease in Patients Undergoing Bone Marrow Transplant

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 11128**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

1. What degree best describes you?

❒ MD/DO ❒ PA/PA-C ❒ NP ❒ RN ❒ PharmD/RPh ❒ PhD
❒ Other, please specify:

2. What is your area of specialization?

❒ Oncology, Hematology/Oncology ❒ Oncology, Medical ❒ Transplantation

3. Which of the following best describes your *primary* practice setting?

❒ Solo Practice ❒ Group Practice ❒ Government
❒ University/teaching system ❒ Community Hospital
❒ HMO/managed care ❒ Non-profit/community ❒ I do not actively practice
❒ Other, please specify:

4. How long have you been practicing medicine?

❒ More than 20 years ❒ 11-20 years ❒ 5-10 years ❒ 1-5 years
❒ Less than 1 year ❒ I do not directly provide care

5. Approximately how many patients do you see each week?

❒ Less than 50 ❒ 50-99 ❒ 100-149 ❒ 150-199 ❒ 200+
❒ I do not directly provide care

6. How many patients do you currently see each week undergoing transplant?

❒ Fewer than 5 ❒ 6-15 ❒ 16-25 ❒ 26-35 ❒ 36-45 ❒ 46-55
❒ 56 or more ❒ I do not directly provide care

7. Rate how well the activity supported your achievement of these learning objectives:

Describe the characteristic symptom onset and underlying pathology of hepatic veno-occlusive disease

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Monitor patients for early signs of veno-occlusive disease by identifying patient-related, disease-related, and transplant-related factors that increase the risk of developing hepatic veno-occlusive disease following stem cell transplant

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Assess the efficacy and safety outcomes associated with the use of traditional and novel therapies for the management of hepatic veno-occlusive disease

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Describe how novel agents for the prevention and treatment of hepatic veno-occlusive disease can be effectively incorporated into clinical practice

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The content was evidence based

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The educational material provided useful information for my practice

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity enhanced my current knowledge base

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

9. Based upon your participation in this activity, do you intend to change your practice behavior? *(choose only one of the following options)*

❒ I do plan to implement changes in my practice based on the information presented

❒ My current practice has been reinforced by the information presented

❒ I need more information before I will change my practice

10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (for example, 250):

11. If you plan to change your practice behavior, what type of changes do you plan to implement? *(check all that apply)*

❒ Apply latest guidelines ❒ Choice of treatment/management approach
❒ Change in pharmaceutical therapy ❒ Change in current practice for referral
❒ Change in nonpharmaceutical therapy ❒ Change in differential diagnosis
❒ Change in diagnostic testing ❒ Other, please specify:

12. How confident are you that you will be able to make your intended changes?

❒ Very confident ❒ Somewhat confident ❒ Unsure ❒ Not very confident

13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

❒ Formulary restrictions ❒ Insurance/financial issues ❒ Time constraints
❒ Lack of multidisciplinary support ❒ System constraints
❒ Treatment-related adverse events ❒ Patient adherence/compliance
❒ Other, please specify:

14. Was the content of this activity fair, balanced, objective and free of bias?

❒ Yes ❒ No, please explain:

15. Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

Request for Credit (*required fields)

Name* _____

Degree* _____

Organization _____

Specialty* _____

City, State, ZIP* _____

Telephone _____ Fax _____

E-mail* _____

Signature* _____ Date* _____

For Physicians Only:

I certify my actual time spent to complete this educational activity to be:

❒ I participated in the entire activity and claim 1.25 credits.
❒ I participated in only part of the activity and claim _____ credits.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Project ID: **11128**