

# SOS Prophylaxis and Treatment

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# Sinusoidal obstruction syndrome (SOS)

- ✓ A potentially fatal complication after stem cell transplantation
- ✓ The pathophysiology of SOS/VOD is characterized by endothelial injury caused by the conditioning regimen as well as pre-transplant damage ➡ post-sinusoidal portal hypertension leads to the clinical syndrome
- ✓ Usually resolves within weeks in most patients, an estimated 30-60% of affected children may progress to multi-organ dysfunction/failure (mortality rate > 80%)
- ✓ SOS/VOD is essentially a clinical diagnosis in the absence of sensitive and specific biologic markers or imaging tools
- ✓ Conditioning regimens:
  - Autologous HCT: 5-30%
  - Allogeneic HCT: Myeloablative (10-60%) (10-15%), Reduced-intensity (less often) (<5%)

# Current incidence, severity, and management of veno-occlusive disease/sinusoidal obstruction syndrome in adult allogeneic HSCT recipients: an EBMT Transplant Complications Working Party study

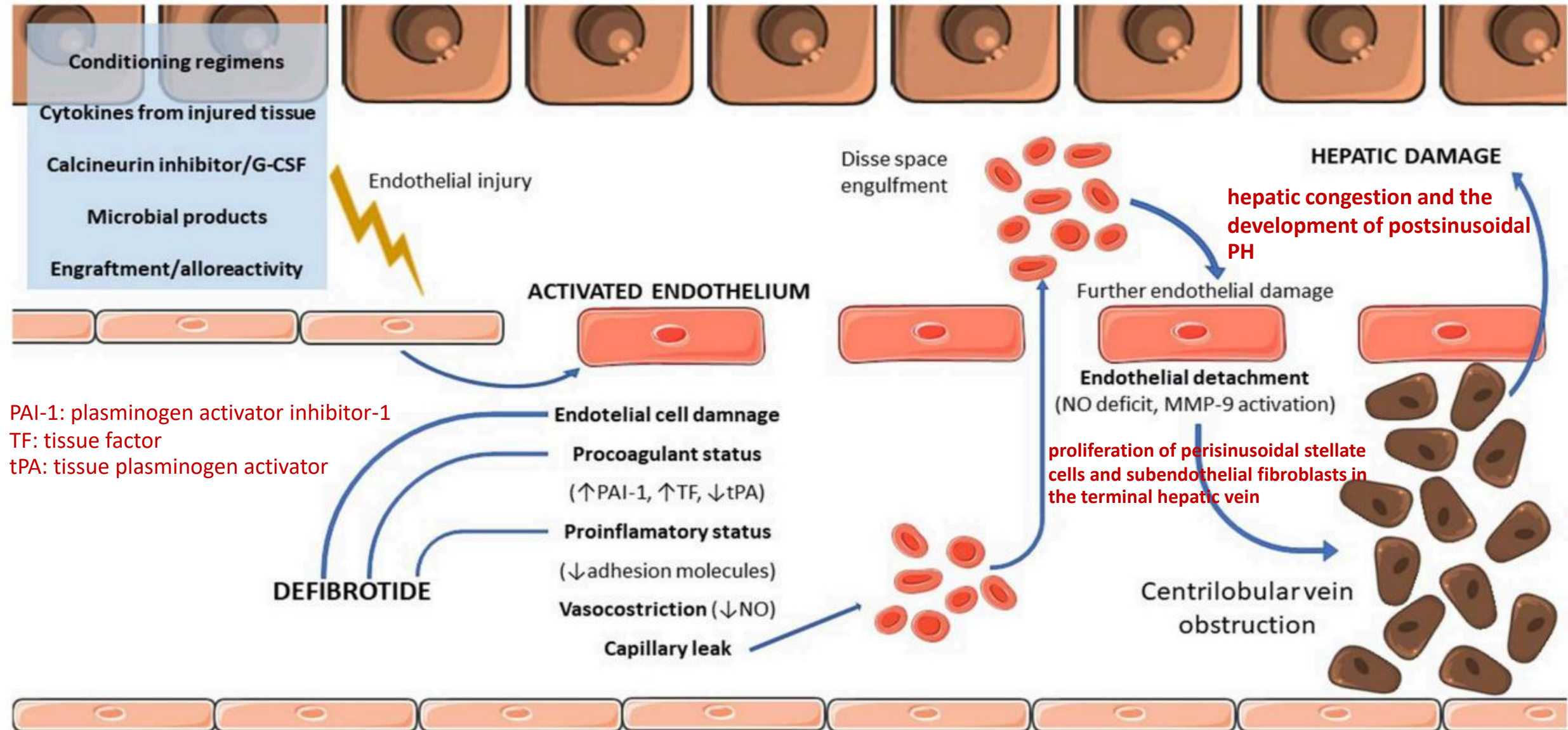
A total of 2886 allogeneic transplantations and 93 cases of VOD/SOS in 2018

- ✓ MAC= 51.5%, RIC =48.5%
- ✓ The cumulative incidence of VOD/ SOS
  - at day 21= 1.8%
  - at day 100= 2.4%
- ✓ 52 (78%)were classical and 15 (22%) late onset (>day 21)
- ✓ Forty patients (60%) had received VOD/SOS prophylaxis
  - ✓ Defibrotide : 7 patients
  - ✓ Heparin : 15 patients (alone: 9, plus UDCA: 5, plus defibrotide: 1)
  - ✓ Ursodeoxycholic acid : 22 patients

Defibrotide treatment: resolved in 58% of the cases, and 57% of the patients were alive at day 100

|                                                     |                        |
|-----------------------------------------------------|------------------------|
| Participating centers                               | 71                     |
| Total number of allogeneic transplantations in 2018 | 2886                   |
| Number of patients with VOD/SOS diagnosis in 2018   | 93                     |
| Cumulative VOD/SOS incidence at 21 days             | 1.8 (95% CI 1.4–2.4) % |
| Cumulative VOD/SOS incidence at 100 days            | 2.4 (95% CI 1.9–3.0) % |
| Patients with VOD/SOS data for detailed analysis    | 67                     |
| VOD/SOS prophylaxis given                           | 40/67 (60%)            |
| Severity of VOD/SOS according to EBMT criteria      |                        |
| Moderate                                            | 3                      |
| Severe                                              | 29                     |
| Very severe                                         | 35                     |
| Late onset of VOD/SOS ( > 21 days)                  | 15/67 (22%)            |
| VOD/SOS-targeted treatment given                    | 60/67 (90%)            |
| Defibrotide                                         | 54                     |
| Resolution of VOD/SOS                               | 37/64 (58%)            |
| Severe grade                                        | 22/28 (79%)            |
| Very severe grade                                   | 12/33 (36%)            |
| Survival at 100 days post transplant                | 38/67 (57%)            |
| Severe grade                                        | 22/29 (76%)            |
| Very severe grade                                   | 13/35 (37%)            |

# Physiopathology of SOS



# Risk factors



- Transplant- related factors
  - ✓ Pre-transplant: antibodies tagged with calicheamicin derivatives (**gemtuzumab ozogamicin (GO) and inotuzumab ozogamicin**), ursodeoxycholic acid are recommended for previously treated with InO
  - ✓ Conditioning regimen: **oral high-dose BU, high-dose fractionated ( $\geq 12$  G) TBI-based conventional MAC, GO, combination of BU and Cy and/or Mel, mismatched/MUD/haploidentical transplant, T-replete transplants, second SCT**
  - ✓ Targeted IV BU: a predictable pharmacokinetic profile, but the measurement of BU serum levels is complicated by differences in methodology and lack of a reliable target range for safety. Therefore, **targeted IV BU cannot guarantee a reduced incidence of SOS/VOD**
    - MAC : a regimen containing either TBI with a dose  $\geq 8$  Gy**  
**a total dose of oral busulfan  $\geq 8$  mg/kg, or a total dose of I.V. busulfan  $\geq 6.4$  mg/kg**
- Patient and disease related factors
  - ✓ **Older age, Karnofsky score below 90%, metabolic syndrome, female receiving norethisterone, R/R disease**
  - ✓ Patient-specific factors including genetic predisposition: infantile osteopetrosis (60%), familial HLH or Griscelli syndrome and X-linked lymphoproliferative disease (30%), Thalassemia patients with hepatomegaly and high iron overload (30-40%), High-risk neuroblastoma (high-dose chemotherapy and autologous HCT: conditioning with BU/Mel (15-30%), Wilm's tumor (30%), rhabdomyosarcoma (30%) and brain tumors given conventional chemotherapy with actinomycin D based regimen (30%) , Sickle cell
  - ✓ **Disease with iron overload** **thalassemia, genetic factors (GSTM1 polymorphism, C282Y allele, MTHFR 677CC/1298CC haplotype)**
- Hepatic related factors
  - ✓ **Preexisting liver disease, active viral hepatitis, transaminases  $>2.5 \times$  ULN, serum bilirubin  $>1.5 \times$  ULN, cirrhosis and hepatotoxic drug**

# Clinical presentation



- Generally occurs within 21 days after transplant
- Rapid weight gain, tendentially unresponsive to diuretics
- Hyperbilirubinemia
- Painful hepatomegaly
- Ascites
- Multiorgan failure: lung: pleural effusion, pulmonary infiltrates, hypoxia  
kidney: renal insufficiency/failure  
central nervous system: confusion, encephalopathy
- Consumptive thrombocytopenia and refractoriness to platelet transfusions, most probably due to uncontrolled endothelial activation

## Late-onset VOD/SOS

- Distinct VOD/SOS feature by recent diagnostic criteria elaborated by the EBMT
- Mild forms spontaneously resolving within a few weeks to severe forms with organ damage and MOD

# Daily monitoring



- ✓ Fluid overload with weight gain
- ✓ RUQ pain
- ✓ Jaundice
- ✓ Hepatomegaly
- ✓ Ascites

| Modified Seattle criteria                                                                                          | Baltimore criteria                                                                                                | EBMT criteria                                                                                                     |                                                                                                                                                                          |
|--------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Onset: within 20 days                                                                                              | Onset: within 21 days                                                                                             | Classical VOD/SOS (onset: within 21d)                                                                             | Late-onset VOD/SOS                                                                                                                                                       |
| 2 symptoms of the following<br>- Bilirubin >2 mg/dL<br>- Hepatomegaly, RUQ pain<br>- Weight gain >2% over baseline | bilirubin 2 mg/dL<br>and at least 2 of the following:<br>– Painful hepatomegaly<br>– Weight gain >5%<br>– Ascites | bilirubin 2 mg/dL<br>and at least 2 of the following:<br>– Painful hepatomegaly<br>– Weight gain >5%<br>– Ascites | - Classical SOS beyond day 21<br>OR<br>- Histologically proven SOS<br>OR<br>- 2 of the classical criteria <b>and</b> ultrasound<br><b>or</b> hemodynamic evidence of SOS |

**Children :** **No time onset limitation** for SOS/VOD occurrence and presence of 2 of the following parameters:

- Unexplained refractoriness to platelets transfusions defined as 1 weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines
- Otherwise unexplained weight gain on 3 consecutive days despite the use of diuretics or a weight gain >5% above baseline value
- Hepatomegaly (best if confirmed by imaging such as US, CT or MRI) above baseline value measured pre-HSCT
- Ascites (best if confirmed by imaging such as US, CT or MRI) above baseline value measured pre-HSCT
- Increase of bilirubin above baseline value on 3 consecutive days or bilirubin 2 mg/dL within 72 h

**daily measurements of weight and abdominal circumference**



# Major differences in hepatic SOS/VOD between adults and children

| Criteria                                               | Children                                                                                                                                                                                                                                                                                               | Adults                                                                                                    |
|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Incidence                                              | <ul style="list-style-type: none"> <li>- Approximately 20%</li> <li>- Up to 60% in high-risk patients</li> </ul>                                                                                                                                                                                       | - Approximately 10%                                                                                       |
| Risk factors                                           | <ul style="list-style-type: none"> <li>- Additional pediatric risk factors: <ul style="list-style-type: none"> <li>- Infants</li> <li>- Diseases with incidences above average</li> </ul> </li> </ul>                                                                                                  | - Established risk factors                                                                                |
| Clinical presentation                                  | <ul style="list-style-type: none"> <li>- Late-onset SOS: 20%</li> <li>- Anicteric SOS: 30%</li> <li>- Hyperbilirubinemia, if present: <ul style="list-style-type: none"> <li>- Is frequently pre-existent</li> <li>- Occurs late during SOS</li> <li>- Is typical of severe SOS</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>- Late-onset SOS (rare)</li> <li>- Anicteric SOS (rare)</li> </ul> |
| Need for proper assessment of ascites and hepatomegaly | High incidence of disease-related hepatomegaly and ascites pre-HCT                                                                                                                                                                                                                                     |                                                                                                           |
| Treatment                                              | Defibrotide for severe SOS with multi-organ failure was associated with better results in children compared with adults                                                                                                                                                                                |                                                                                                           |
| Prevention                                             | Defibrotide demonstrated efficacy for prevention of SOS in children in a randomized prospective trial                                                                                                                                                                                                  |                                                                                                           |

# Differential diagnosis

- Fluid overload and hypoalbuminemia
- Drug-induced cholestasis, drug-induced liver injury (DILI)
- Sepsis, infectious hepatitis
- Hepatic graft-versus-host disease (GvHD)
- Parenteral nutrition associated liver disease (PNALD), used long term (> 14 days): inflammation causing cholestasis, steatosis
- Ascites of different origin (pancreatic, chylous)
- Cholangitis

## Biomarkers : **absence of sensitive and specific biologic markers**

- Plasminogen activator inhibitor 1 (increased PAI-1 level)
- Other markers of endothelial injury: elevated levels of
  - ✓ Von Willebrand factor
  - ✓ Thrombomodulin
  - ✓ Soluble intercellular adhesion molecule 1
  - ✓ Suppressor of tumorigenicity2
  - ✓ Angiopoietin 2
  - ✓ Hyaluronic acid
- Inflammation markers: IL-6, IL-10, CD97

# Recommendations for Imaging in the Diagnosis of VOD/SOS



- Ultrasound and Doppler US can easily detect the typical signs of PH such as ascites, hepatomegaly, splenomegaly, and dilatation

| Ultrasound Variables and Criteria Measurements |                                                                                                                                                                                                                                             |                                                                                                                          |
|------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| Variable                                       | Lassau's criteria                                                                                                                                                                                                                           | HokUS-10 scoring                                                                                                         |
| <b>Gray-scale ultrasound</b>                   |                                                                                                                                                                                                                                             |                                                                                                                          |
| Hepatomegaly                                   | Liver enlargement: increase in 2 of 3 measurements of >2 cm in adults and >1 cm in children relative to baseline                                                                                                                            | Hepatic left lobe vertical diameter $\geq 70$ mm (1 point); hepatic right lobe vertical diameter $\geq 110$ mm (1 point) |
| Splenomegaly                                   | Spleen enlargement: increase >1 cm relative to baseline measurement of the greatest axis                                                                                                                                                    | Long axis increase                                                                                                       |
| Gall bladder wall thickening                   | >6 mm                                                                                                                                                                                                                                       | $\geq 6$ mm (1 point)                                                                                                    |
| Portal vein diameter                           | >8 mm in children; >12 mm in adults                                                                                                                                                                                                         | $\geq 12$ mm (1 point)                                                                                                   |
| Hepatic vein diameter                          | <3 mm                                                                                                                                                                                                                                       |                                                                                                                          |
| Ascites                                        | Presence                                                                                                                                                                                                                                    | Mild (1 point); moderate/severe (2 points)                                                                               |
| Paraumbilical vein                             | Visualization                                                                                                                                                                                                                               | Diameter $\geq 2$ mm (2 points)                                                                                          |
| <b>Color Doppler ultrasound</b>                |                                                                                                                                                                                                                                             |                                                                                                                          |
| Absence/presence of flow                       | Flow recorded in paraumbilical vein                                                                                                                                                                                                         | Appearance of paraumbilical vein blood flow signal (2 points)                                                            |
| Flow direction                                 | Reversed flow in the main portal vein                                                                                                                                                                                                       | Congestion or hepatofugal flow in the portal vein (1 point)                                                              |
| <b>Spectral Doppler ultrasound</b>             |                                                                                                                                                                                                                                             |                                                                                                                          |
| Portal vein velocity/density/congestion        | Flow demodulation (disappearance of velocity variations with breathing); decreased spectral density in portal vein; maximal flow in the main portal vein <10 cm/s; portal vein congestion index $\geq 1$ ; monophasic flow in hepatic veins | Velocity <10 cm/s (1 point)                                                                                              |
| Hepatic artery resistive index                 | $\geq .75$                                                                                                                                                                                                                                  | $\geq .75$ (1 point)                                                                                                     |

- CT/MRI (logistic issues: critical patients)
- Hepatic venous gradient pressure by cannulation of the jugular vein was demonstrated in adults to be a very accurate, but invasive **X**
- Transjugular liver biopsy provides histologic evidence of SOS/VOD **X**

# EBMT criteria for severity grading of suspected VOD in adults and children

|                                                    | Mild     | Moderate     | Severe                                          | Very severe                                                          |
|----------------------------------------------------|----------|--------------|-------------------------------------------------|----------------------------------------------------------------------|
| <b>(A) ADULTS</b>                                  |          |              |                                                 |                                                                      |
| Time since first symptoms                          | >7 d     | 5–7 d        | ≤4 d                                            | Any time                                                             |
| Bilirubin (mg/dL)                                  | ≥2 to <3 | ≥3 to <5     | ≥5 to <8                                        | ≥8                                                                   |
| Kinetics of bilirubin increase                     |          |              | Doubling in 48 h                                |                                                                      |
| AST, ALT (× UNV)                                   | ≤2       | >2 to ≤5     | >5 to ≤8                                        | >8                                                                   |
| Weight gain (%)                                    | <5       | ≥5 to <10    | ≥5 to <10                                       | ≥10                                                                  |
| Creatinine (× baseline pre-HSCT)                   | <1.2     | ≥1.2 to <1.5 | ≥1.5 to <2                                      | ≥2 or other data of MOD                                              |
| <b>(B) CHILDREN</b>                                |          |              |                                                 |                                                                      |
| Liver function tests (AST, ALT, GLDH) <sup>a</sup> | ≤2×      | >2 and ≤5×   |                                                 | >5×                                                                  |
| Persistent platelets refractoriness <sup>a</sup>   | <3 d     | 3–7 d        |                                                 | >7 d                                                                 |
| Bilirubin (mg/dL) <sup>a,b</sup>                   |          | <2           |                                                 | >2                                                                   |
| Ascites <sup>a</sup>                               | Minimal  | Moderate     |                                                 | Need of paracentesis                                                 |
| Kinetics of bilirubin increase                     |          |              |                                                 | Doubling within 48h                                                  |
| Coagulation                                        |          | Normal       | Impaired                                        | Impaired coagulation with need of replacement of coagulation factors |
| Renal function GFR (mL/min)                        | 89–60    | 59–30        | 29–15                                           | <15                                                                  |
| Pulmonary function (oxygen requirement)            | <2 L/min | >2 L/min     | Invasive pulmonary ventilation (including CPAP) |                                                                      |
| CNS impairment                                     |          | Absent       |                                                 | New onset cognitive impairment                                       |

# Treatment

- Supportive care : diuretics, dialysis, oxygen
- **Defibrotide (FDA approval: March 2016)**
- A mixture of polydeoxyribonucleotide, mainly single-stranded, derived from the porcine intestinal mucosa
- Its mechanism of action is not yet fully understood:
  - ✓ Oligonucleotides interact with heparin-binding proteins such as fibroblast growth factors



Exert fibrogenetic, angiogenetic effects with endothelial stabilization

- ✓ Acts as an antithrombotic and profibrinolytic drug



Reduces platelet adhesion and activation (without systemic anticoagulant effects)

- ✓ Inhibition of P-selectin expression



Inhibition of PAI-1, thrombin, and leukocyte adhesion process

- ✓ Decreases vascular permeability and apoptosis (calcineurin inhibitors and chemotherapy)

# Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure

- Historically controlled, multicenter, open-label, phase 3 study where defibrotide-treated patients (July 2006 to June 2008)
- Included pediatric ( $\leq 16$  years), adult patients with severe hepatic SOS with MOF post-HSCT
- Hepatic SOS: Baltimore diagnostic criteria (bilirubin  $\geq 2$  mg/dL by day +21 , and  $\geq 2$  of: ascites, weight gain  $\geq 5\%$ , or new onset or worsening hepatomegaly)
- Severe SOS: SOS with advanced MOF (renal and/or pulmonary dysfunction by day+ 28)
- Renal function: (1) serum Cr  $\geq 3 \times$  the value at admission to the HSCT unit for conditioning or  $\geq 3 \times$  the lowest value during conditioning before HSCT (whichever was lower), or
  - (2) Cr clearance or glomerular filtration rate  $\leq 40\%$  of admission value, or
  - (3) Dialysis dependence
- Pulmonary dysfunction: oxygen saturation  $\leq 90\%$  on room air or requirement for oxygen supplementation/ventilator dependence

## Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure

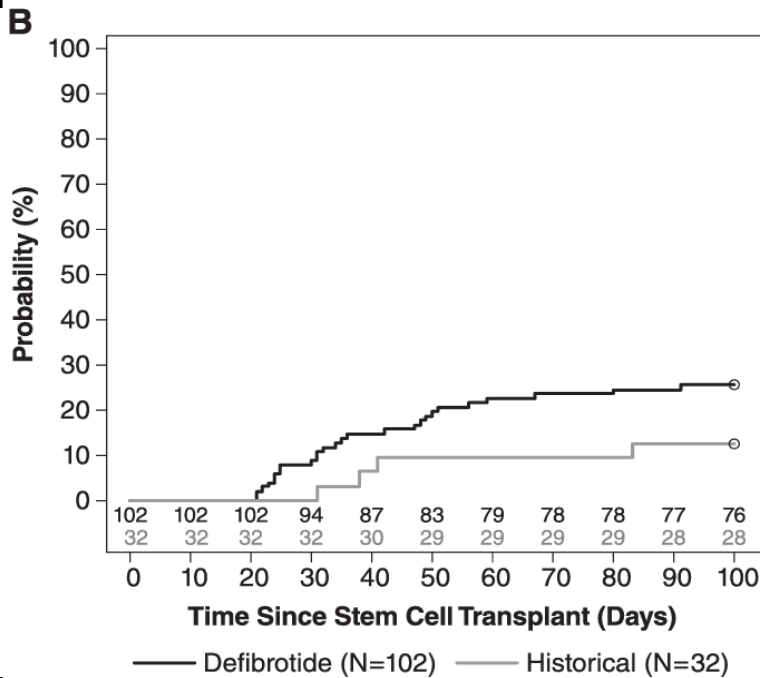
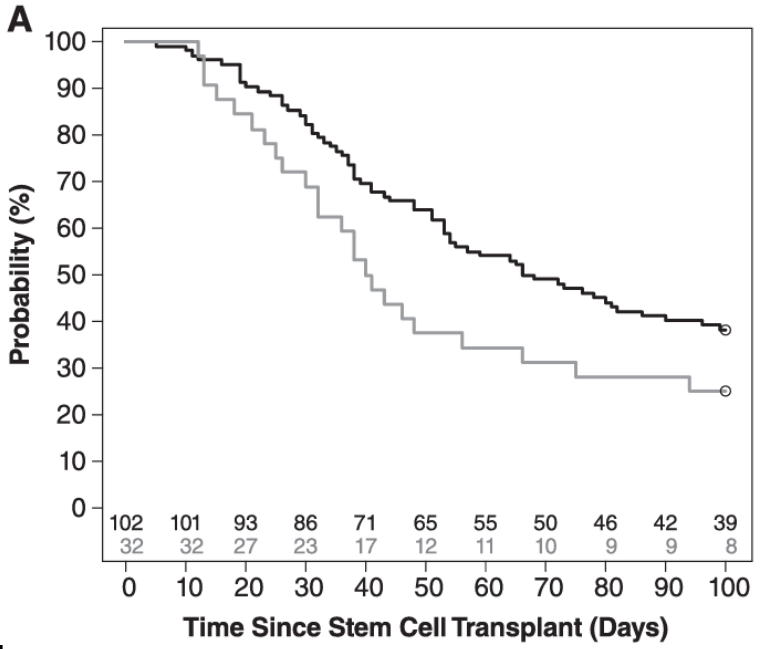
- The primary objective: to demonstrate the efficacy of defibrotide in patients with hepatic SOS with MOF (difference of survival at day +100 **in the defibrotide group vs the historical-control group**)
- The secondary efficacy objectives: the difference of CR rate by day +100 and survival at day +180 (compared between the arms)
- Incidence of adverse events (compared between the arms)

Defibrotide: 25mg/kg/day in 4 divided doses, each infused over 2 hours, for a minimum of 21 days

Treatment was to continue beyond 21 days until resolution of SOS or until the patient's discharge from the hospital

|                                                 | Defibrotide<br>treatment<br>group* (n = 102) | Historical-control<br>cohort (n = 32) | P† |
|-------------------------------------------------|----------------------------------------------|---------------------------------------|----|
| <b>Age at HSCT (y)</b>                          |                                              |                                       |    |
| Mean (SD)                                       | 26 (21.37)                                   | 25.1 (20.23)                          | —  |
| Median (range)                                  | 21 (0-72)                                    | 18 (1-57)                             | —  |
| <b>Age category (y), n (%)</b>                  |                                              |                                       |    |
| ≤16                                             | 44 (43.1)                                    | 14 (43.8)                             | —  |
| >16                                             | 58 (56.9)                                    | 18 (56.3)                             | —  |
| <b>Gender (n [%])</b>                           |                                              |                                       |    |
| Male                                            | 64 (62.7)                                    | 18 (56.3)                             | —  |
| Female                                          | 38 (37.3)                                    | 14 (43.8)                             | —  |
| <b>Weight at baseline (kg)</b>                  |                                              |                                       |    |
| Mean (SD)                                       | 53.7 (33.7)                                  | 52.6 (30.6)                           | —  |
| Median (range)                                  | 60.4 (4-135)                                 | 58.4 (6-111)                          | —  |
| <b>Height (cm)‡</b>                             |                                              |                                       |    |
| Mean (SD)                                       | 140.1 (42.8)                                 | 141.7 (41)                            | —  |
| <b>Race (n [%])</b>                             |                                              |                                       |    |
| White                                           | 77 (75.5)                                    | 23 (71.9)                             | —  |
| Black or African American                       | 6 (5.9)                                      | 2 (6.3)                               | —  |
| Hispanic or Latino                              | 10 (9.8)                                     | 1 (3.1)                               | —  |
| Asian                                           | 4 (3.9)                                      | 2 (6.3)                               | —  |
| Native Hawaiian/other<br>Pacific Islander       | 1 (1.0)                                      | 0                                     | —  |
| Other§                                          | 4 (3.9)                                      | 4 (12.5)                              | —  |
| Use of ursodeoxycholic acid                     | 71 (69.6%)                                   | 21 (65.6%)                            | —  |
| Use of low-dose dopamine/<br>dopamine HCl       | 34 (33.3%)                                   | 18 (56.3%)                            | —  |
| <b>Stratification factors,   n (%)</b>          |                                              |                                       |    |
| ≤16-years-old                                   | 44 (43.1)                                    | 14 (43.8)                             | —  |
| Allogeneic transplant                           | 90 (88.2)                                    | 27 (84.4)                             | —  |
| Prior HSCT                                      | 13 (12.7)                                    | 3 (9.4)                               | —  |
| Ventilator/dialysis-dependent<br>at study entry | 34 (33.3)                                    | 7 (21.9)                              | —  |

|                                                                                                         | Defibrotide<br>treatment<br>group (n = 102) | Historical-control<br>cohort (n = 32) |
|---------------------------------------------------------------------------------------------------------|---------------------------------------------|---------------------------------------|
| <b>VOD/SOS eligibility</b>                                                                              |                                             |                                       |
| Elevated total bilirubin                                                                                | 102 (100)                                   | 32 (100)                              |
| Hepatomegaly                                                                                            | 84 (82.4)                                   | 27 (84.4)                             |
| Ascites                                                                                                 | 95 (93.1)                                   | 27 (84.4)                             |
| Weight gain                                                                                             | 98 (96.1)                                   | 29 (90.6)                             |
| <b>Total bilirubin (mg/dL)</b>                                                                          |                                             |                                       |
| Mean (SD)                                                                                               | 7.3 (7.4)                                   | 7.8 (10)                              |
| Median (min, max)                                                                                       | 4.9 (1, 41.4)                               | 4.9 (2.1, 57)                         |
| <b>AST (U/L)</b>                                                                                        |                                             |                                       |
| N                                                                                                       | 101                                         | 30                                    |
| Mean (SD)                                                                                               | 458.3 (964.6)                               | 299.5 (742.3)                         |
| Median (min, max)                                                                                       | 90 (8, 5397)                                | 38 (11, 3790)                         |
| <b>ALT (U/L)</b>                                                                                        |                                             |                                       |
| N                                                                                                       | —                                           | 26                                    |
| Mean (SD)                                                                                               | 100.240 (403.3)                             | 304.8 (746.7)                         |
| Median (min, max)                                                                                       | 62 (5, 2130)                                | 33 (6, 3596)                          |
| <b>Underlying disease, n (%)</b>                                                                        |                                             |                                       |
| Acute myelogenous leukemia                                                                              | 29 (28.4)                                   | 8 (25)                                |
| Acute lymphocytic leukemia                                                                              | 17 (16.7)                                   | 7 (21.9)                              |
| Myelodysplastic syndrome                                                                                | 7 (6.9)                                     | 3 (9.4)                               |
| Non-Hodgkin lymphoma                                                                                    | 5 (4.9)                                     | 2 (6.3)                               |
| Neuroblastoma                                                                                           | 6 (5.9)                                     | 0                                     |
| Chronic myelogenous leukemia                                                                            | 4 (3.9)                                     | 1 (3.1)                               |
| Multiple myeloma                                                                                        | 3 (2.9)                                     | 1 (3.1)                               |
| Aplastic anemia                                                                                         | 1 (1)                                       | 1 (3.1)                               |
| Hodgkin lymphoma                                                                                        | 1 (1)                                       | 2 (6.3)                               |
| Immunodeficiency                                                                                        | 1 (1)                                       | 0                                     |
| Chronic lymphocytic leukemia                                                                            | 1 (1)                                       | 0                                     |
| <b>Other</b>                                                                                            |                                             |                                       |
| Myelofibrosis                                                                                           | 4 (3.9)                                     | 0                                     |
| Hemophagocytic lymphohistiocytosis                                                                      | 3 (2.9)                                     | 1 (3.1)                               |
| Medulloblastoma                                                                                         | 2 (2)                                       | 1 (3.1)                               |
| Osteopetrosis                                                                                           | 2 (2)                                       | 0                                     |
| Juvenile myelomonocytic leukemia                                                                        | 2 (2)                                       | 0                                     |
| β-thalassemia major                                                                                     | 1 (1)                                       | 1 (3.1)                               |
| Chronic granulomatous disease                                                                           | 1 (1)                                       | 0                                     |
| Fanconi anemia                                                                                          | 1 (1)                                       | 0                                     |
| Tay-Sachs disease                                                                                       | 1 (1)                                       | 0                                     |
| Sickle cell disease                                                                                     | 1 (1)                                       | 0                                     |
| Severe combined immunodeficiency                                                                        | 1 (1)                                       | 0                                     |
| Retinoblastoma                                                                                          | 1 (1)                                       | 0                                     |
| Omenn syndrome                                                                                          | 1 (1)                                       | 0                                     |
| Krabbe disease                                                                                          | 1 (1)                                       | 1 (3.1)                               |
| Hurler syndrome                                                                                         | 2 (2)                                       | 0                                     |
| Acute undifferentiated leukemia                                                                         | 1 (1)                                       | 0                                     |
| Myeloproliferative disease                                                                              | 0                                           | 1 (3.1)                               |
| Congenital amegakaryocytic<br>thrombocytopenia                                                          | 0                                           | 1 (3.1)                               |
| Thalassemia major                                                                                       | 1 (1)                                       | 0                                     |
| Hepatosplenic T-cell lymphoma                                                                           | 0                                           | 1 (3.1)                               |
| Waldenstrom macroglobulinemia                                                                           | 1 (1)                                       | 0                                     |
| <b>HSCT graft type, n (%)</b>                                                                           |                                             |                                       |
| Allogeneic                                                                                              | 90 (88.2)                                   | 27 (84.4)                             |
| Related matched donor                                                                                   | 33 (36.7)                                   | 11 (40.7)                             |
| Related mismatched donor                                                                                | 2 (2.2)                                     | 1 (3.7)                               |
| Unrelated matched donor                                                                                 | 29 (32.2)                                   | 10 (37)                               |
| Unrelated mismatched donor<br>(including cord blood, donor bone<br>marrow, peripheral blood stem cells) | 26 (28.9)                                   | 5 (18.5)                              |
| Myeloablative conditioning regimen                                                                      | 89 (87.3)                                   | 30 (93.8)                             |



# Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure

| System organ class/abnormality preferred term               | Defibrotide treatment group (n = 102), n (%) | Historical-control cohort (n = 32), n (%) |
|-------------------------------------------------------------|----------------------------------------------|-------------------------------------------|
| <b>Blood and lymphatic system disorders</b>                 |                                              |                                           |
| Coagulopathy                                                | 2 (2)                                        | 5 (15.6)                                  |
| <b>Cardiac disorders</b>                                    |                                              |                                           |
| Bradycardia                                                 | 10 (9.8)                                     | 6 (18.8)                                  |
| Tachycardia                                                 | 10 (9.8)                                     | 14 (43.8)                                 |
| <b>GI disorders</b>                                         |                                              |                                           |
| Diarrhea                                                    | 24 (23.5)                                    | 12 (37.5)                                 |
| Nausea                                                      | 13 (12.7)                                    | 10 (31.3)                                 |
| Vomiting                                                    | 20 (19.6)                                    | 8 (25)                                    |
| Abdominal pain                                              | 4 (3.9)                                      | 7 (21.9)                                  |
| Constipation                                                | 6 (5.9)                                      | 5 (15.6)                                  |
| Lip hemorrhage                                              | 2 (2)                                        | 4 (12.5)                                  |
| <b>General disorders and administration site conditions</b> |                                              |                                           |
| MOF*                                                        | 15 (14.7)                                    | 3 (9.4)                                   |
| Pyrexia                                                     | 14 (13.7)                                    | 9 (28.1)                                  |
| Peripheral edema                                            | 13 (12.7)                                    | 4 (12.5)                                  |
| Hypothermia                                                 | 5 (4.9)                                      | 5 (15.6)                                  |
| Generalized edema                                           | 8 (7.8)                                      | 8 (25)                                    |
| Edema                                                       | 3 (2.9)                                      | 7 (21.9)                                  |
| <b>Immune system disorders</b>                              |                                              |                                           |
| GVHD in skin                                                | 5 (4.9)                                      | 5 (15.6)                                  |

## Metabolism and nutrition disorders

|                    |         |          |
|--------------------|---------|----------|
| Hyperglycemia      | 5 (4.9) | 4 (12.5) |
| Fluid overload     | 0       | 5 (15.6) |
| Metabolic acidosis | 1 (1)   | 4 (12.5) |

## Nervous system disorders

|        |       |          |
|--------|-------|----------|
| Tremor | 2 (2) | 4 (12.5) |
|--------|-------|----------|

## Psychiatric disorders

|                   |           |          |
|-------------------|-----------|----------|
| Agitation         | 11 (10.8) | 9 (28.1) |
| Confusional state | 4 (3.9)   | 5 (15.6) |
| Anxiety           | 4 (3.9)   | 4 (12.5) |
| Insomnia          | 1 (1)     | 4 (12.5) |
| Disorientation    | 0         | 4 (12.5) |

## Renal and urinary disorders

|           |          |          |
|-----------|----------|----------|
| Hematuria | 10 (9.8) | 5 (15.6) |
|-----------|----------|----------|

## Respiratory, thoracic, and mediastinal disorders

|                               |           |          |
|-------------------------------|-----------|----------|
| Epistaxis                     | 13 (12.7) | 5 (15.6) |
| Respiratory failure           | 12 (11.8) | 4 (12.5) |
| Pulmonary alveolar hemorrhage | 12 (11.8) | 5 (15.6) |
| Pleural effusion              | 5 (4.9)   | 6 (18.8) |
| Rales                         | 1 (1)     | 6 (18.8) |
| Dyspnea                       | 0         | 5 (15.6) |

## Skin and subcutaneous tissue disorders

|               |         |          |
|---------------|---------|----------|
| Blister       | 6 (5.9) | 8 (25)   |
| Petechiae     | 6 (5.9) | 9 (28.1) |
| Rash          | 8 (7.8) | 7 (21.9) |
| Skin disorder | 3 (2.9) | 5 (15.6) |
| Alopecia      | 2 (2)   | 5 (15.6) |

## Vascular disorders

|             |           |         |
|-------------|-----------|---------|
| Hypotension | 40 (39.2) | 16 (50) |
|-------------|-----------|---------|

# CUP study: open-label multicenter program provided defibrotide on a compassionate-use

- Patients were required to meet the Baltimore criteria or modified Seattle criteria for hepatic SOS
- For this study, the Seattle criteria were further modified to use a >5%, rather than >2% weight gain threshold
- Patients were also eligible if they did not meet 2 of the Seattle criteria but, per the report of the treating physician, had hemodynamic (eg, hepatic venous pressure gradient), ultrasound, or histologic evidence of hepatic VOD/SOS
- Severe SOS was defined as SOS with MOF or by ≥30% predicted risk of retrospectively assessed severe hepatic SOS using the Bearman model
- MOF was defined by
  - renal dysfunction (at least a doubling of Cr levels from baseline or reduced creatinine clearance from baseline with or without need for dialysis)
  - respiratory dysfunction (the need for oxygen supplementation with or without assisted ventilation)
  - CNS dysfunction (cerebral failure)
- Recommended starting dose: 10mg/kg/day, administered I.V. in 4 divided doses over 2 hr. each, **with titration up** to a recommended maximum of 60mg/kg/day based on tolerability and response
- Recommended dose of defibrotide **was amended to a fixed 25mg/kg/ day, in 4 divided doses**, each administered over 2hr
- 
- Recommended treatment duration: a minimum of 14 days

# CUP study: open-label multicenter program provided defibrotide on a compassionate-use

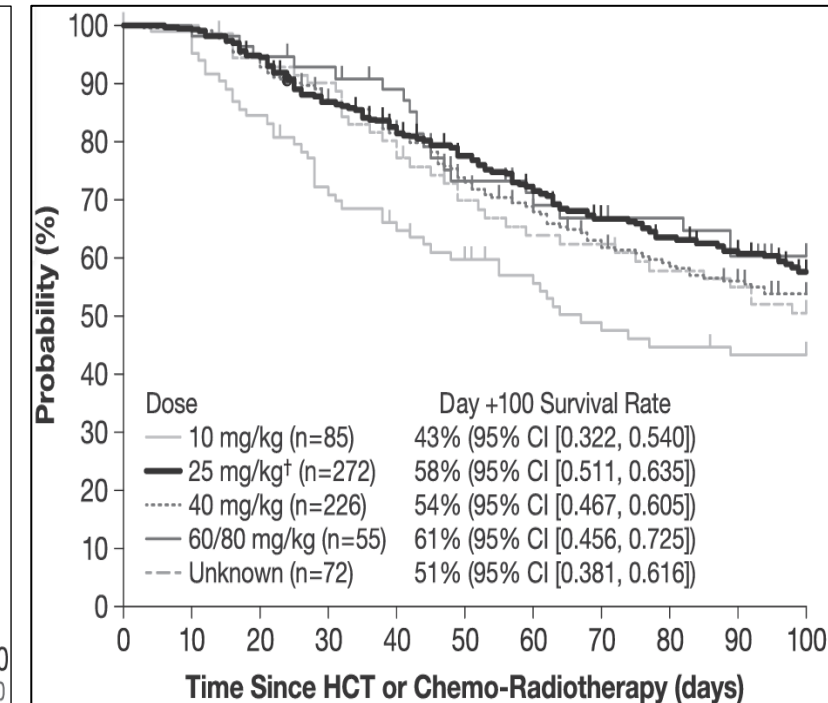
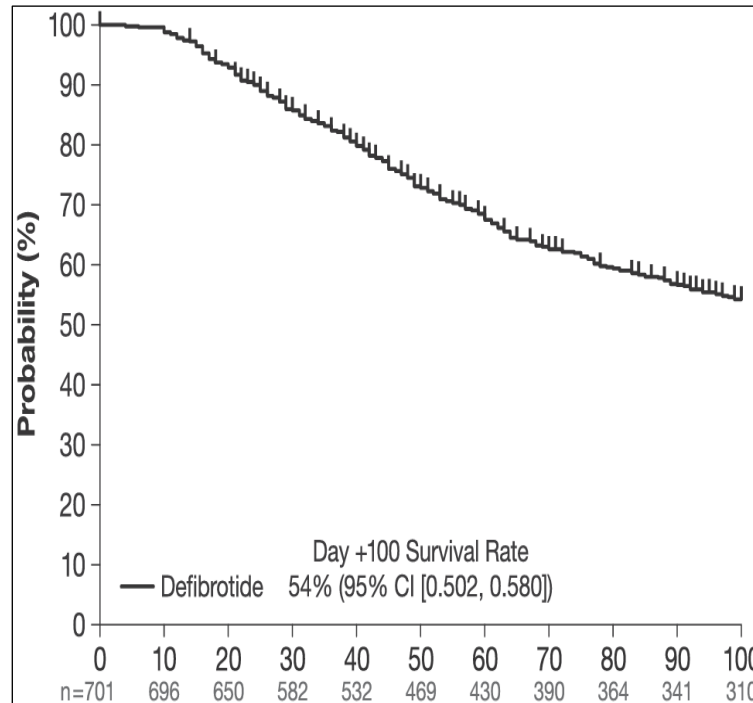
| Characteristic                                                     | Analysis Population (N = 710) |
|--------------------------------------------------------------------|-------------------------------|
| Transplantation*                                                   | 628 (89)                      |
| Allograft                                                          | 499 (71)                      |
| Autograft                                                          | 112 (16)                      |
| Other/not specified                                                | 17 (2)                        |
| Nontransplantation*: chemotherapy/radiotherapy treatment†          | 79 (11)                       |
| Conditioning regimen (>10% of patients)                            |                               |
| Cyclophosphamide                                                   | 369 (52.0)                    |
| Busulfan                                                           | 300 (42.3)                    |
| Total body irradiation                                             | 209 (29.4)                    |
| Antithymocyte globulin                                             | 141 (19.9)                    |
| Melphalan                                                          | 134 (18.9)                    |
| Fludarabine                                                        | 124 (17.5)                    |
| GVHD prophylaxis                                                   |                               |
| Cyclosporine                                                       | 403 (57)                      |
| Methotrexate                                                       | 287 (40)                      |
| Antithymocyte globulin‡                                            | 105 (15)                      |
| Tacrolimus                                                         | 71 (10)                       |
| Mycophenolate mofetil                                              | 61 (9)                        |
| Prednisone                                                         | 58 (8)                        |
| Other§                                                             | 22 (3)                        |
| Median time to hepatic VOD/SOS onset,   d                          | 13                            |
| Hepatic VOD/SOS criteria met                                       |                               |
| Bilirubin >2 mg/dL                                                 | 623 (88)                      |
| Weight gain >5%                                                    | 584 (82)                      |
| Hepatomegaly                                                       | 548 (77)                      |
| Ascites                                                            | 477 (67)                      |
| Right upper quadrant pain                                          | 455 (64)                      |
| Liver histology                                                    | 22 (3)                        |
| Bearman criteria [26]¶                                             |                               |
| Severe                                                             | 337 (48)                      |
| Not severe                                                         | 217 (31)                      |
| Not assessed                                                       | 147 (21)                      |
| Missing                                                            | 9                             |
| MOF                                                                | 292 (41)                      |
| Renal#                                                             | 229 (32)                      |
| Dialysis#                                                          | 41 (6)                        |
| Respiratory#                                                       | 162 (23)                      |
| Assisted/mechanical ventilation (associated with hepatic VOD/SOS)# | 37 (5)                        |
| Cerebral#                                                          | 37 (5)                        |
| Other**                                                            | 4 (<1)                        |
| No MOF                                                             | 418 (59)                      |

| Exposure to Defibrotide in Patients with Dosing Data |                     |                     |                           |
|------------------------------------------------------|---------------------|---------------------|---------------------------|
| Dose (mg/kg/day)                                     | Age <18 yr n = 267* | Age ≥18 yr n = 371* | Total Population N = 638† |
| 10                                                   | 22 (8)              | 63 (17)             | 85 (13)                   |
| 25‡                                                  | 131 (49)            | 141 (38)            | 272 (43)                  |
| 40                                                   | 78 (29)             | 148 (40)            | 226 (35)                  |
| 60/80                                                | 36 (13)             | 19 (5)              | 55 (9)                    |

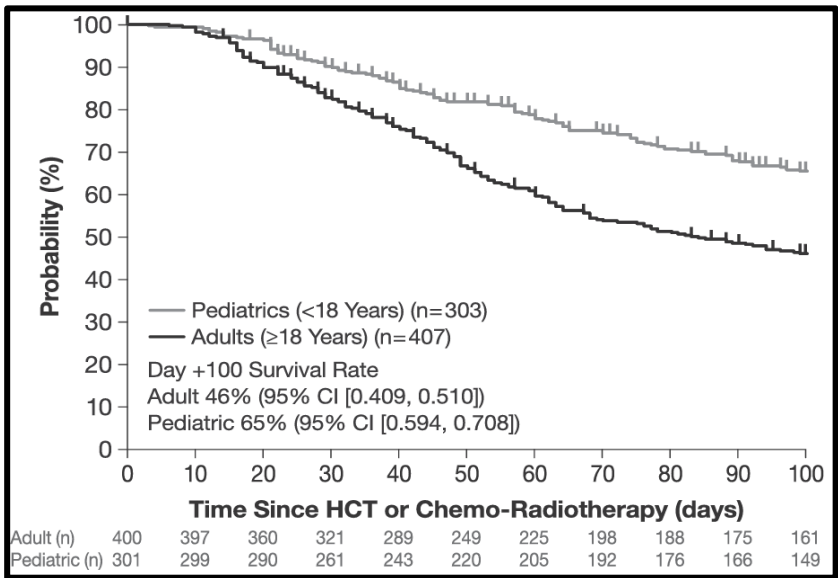
- The median daily dose: 25 (10-80) mg/kg/day

- The median of 15 days (1-119)

- 43% of patients who had available dosing data received 25 mg/kg/day



# CUP study: open-label multicenter program provided defibrotide on a compassionate-use



| Summary of AEs by Dose of Defibrotide |                               |                  |              |              |                |                  |
|---------------------------------------|-------------------------------|------------------|--------------|--------------|----------------|------------------|
| Category of AE                        | Total Population<br>(N = 710) | Dose (mg/kg/day) |              |              |                |                  |
|                                       |                               | 10 (n = 85)      | 25 (n = 272) | 40 (n = 226) | 60/80 (n = 55) | Unknown (n = 72) |
| Any AE (≥1)                           | 378 (53)                      | 59 (69)          | 129 (47)     | 124 (55)     | 27 (49)        | 39 (54)          |
| AE leading to death                   | 350 (49)                      | 56 (66)          | 120 (44)     | 113 (50)     | 24 (44)        | 37 (51)          |
| SAE                                   | 364 (51)                      | 58 (68)          | 123 (45)     | 119 (53)     | 26 (47)        | 38 (53)          |
| AE leading to discontinuation         | 63 (9)                        | 7 (8)            | 23 (8)       | 25 (11)      | 4 (7)          | 4 (6)            |
| AEs of special interest               |                               |                  |              |              |                |                  |
| Hemorrhage event                      | 85 (12)                       | 9 (11)           | 31 (11)      | 31 (14)      | 8 (15)         | 6 (8)            |
| Hypotension event                     | 2 (<1)                        | 1 (1)            | 1 (<1)       | 0            | 0              | 0                |



# FDA Approves Defitelio for Hepatic SOS/VOD

- On March 30, 2016, the FDA approved defibrotide sodium (Defitelio; Jazz Pharmaceuticals) for **the treatment of adults and children with hepatic VOD with renal or pulmonary dysfunction after HSCT**
- Dosing and Administration
  - ✓ Defibrotide sodium is **administered for 2 hours** via a continuous intravenous infusion; defibrotide sodium **should be diluted before infusion**
  - ✓ The recommended **dosage is 6.25 mg/kg every 6 hours**; the dose should be **based on the patient's baseline body weight**
  - ✓ Defibrotide sodium should be **administered for a minimum of 21 days**, and **continued until the signs and symptoms of VOD have resolved, or up to a maximum of 60 days**
  - ✓ Defibrotide sodium is available in a 200mg/2.5 mL (80 mg/mL) single-use vial, containing light yellow to brown, sterile, preservative-free solution
- The most common ( $\geq 10\%$ ) adverse reactions of any grade: hypotension (37%), diarrhea (24%), vomiting (18%), nausea (16%), and epistaxis (14%), alveolar hemorrhage (11%)

SOS/VOD prophylaxis

# Prophylaxis

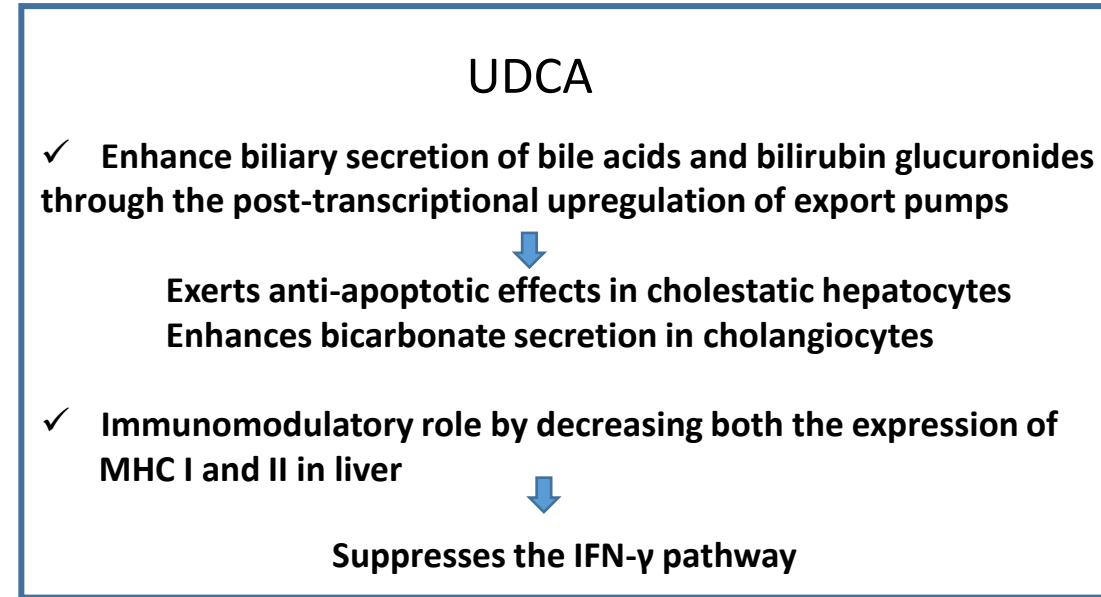
- **Heparin: unfractionated heparin and LMWH** :(extensively studied, including some randomized trials, but with inconclusive results)
- Antithrombin (no efficacy was demonstrated)
- Prostaglandin E1 (inconclusive results and excess of toxicity)
- Pentoxifylline (no efficacy was demonstrated)

- **Defibrotide**

- ✓ **Pediatric patients:** phase III, randomized, open-label, multicenter trial compared defibrotide to placebo as VOD/SOS prophylaxis included 365 patients younger than 18 years: 25mg/kg/d in 4 divided intravenous infusions
- ✓ Incidence of VOD/SOS: 12% (DF) versus 20% (placebo) P = 0.0488
- ✓ **Adult patients:** evidences are far less conclusive

- **Ursodeoxycholic acid (UDCA)**

- ✓ A meta-analysis of 3 trials comparing UDCA with placebo: **the use of UDCA as a possible effective prevention strategy, also because of its safety profile**
- ✓ Another randomized study compared prophylactic use of UDCA with heparin: **revealed no differences in VOD/SOS incidence between the two groups**



# Hepatic Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease (SOS/VOD) Primary Prophylaxis in Patients Undergoing Hematopoietic Stem Cell Transplantation: A Network Meta-Analysis of Randomized Controlled Trials

## Abstract

**Introduction:** Hepatic sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) is a major complication following hematopoietic stem cell transplantation, resulting from immune and chemical toxicity in the sinusoidal endothelium and hepatocellular damage. In the most severe cases, multiorgan dysfunction occurs, so it is essential to promptly identify patients at greater risk of SOS/VOD and to adopt prophylactic strategies. **Objectives:** This study aims to systematize the impact of different approaches as primary prophylaxes against SOS/VOD in patients undergoing hematopoietic stem cell transplantation (HSCT). **Methods:** A systematic review and meta-analysis of randomized clinical trials evaluating different strategies for primary prophylaxis of SOS/VOD was carried out in pairwise fashion and with a consistent network structure. The odds ratio (OR) and corresponding confidence intervals were calculated using the random-effects model. Heterogeneity was assessed by the  $I^2$  method and the efficacy of each approach was estimated by SUCRA (surface under the cumulative ranking curve). **Results:** Considering all patients undergoing HSCT, ursodeoxycholic acid (UDCA) [OR = 0.38, 95%CI 0.14–1.06, SUCRA = 0.720] was associated with a lower incidence of VOD while defibrotide reached a modest reduction in its incidence [OR = 0.64, 95%CI 0.23–1.67; SUCRA = 0.486]. Considering the subgroup of patients undergoing hematopoietic progenitors allotransplantation, defibrotide scored higher [OR = 0.51, 95%CI 0.09–2.85, SUCRA = 0.650] by comparison with UDCA [OR = 0.53, 95%CI 0.14–1.96, SUCRA = 0.639]. **Conclusions:** This is the first meta-analysis comparing primary prophylaxes against SOS/VOD. UDCA yielded more promising results when considering all patients undergoing hematopoietic stem cell transplantation, yet, in a subgroup analysis of the ones exposed to allogeneic grafts, it becomes not significantly overrun by defibrotide.

- ✓ The adoption of primary prophylactic regimens for SOS/VOD in patients undergoing HCT remains a controversial issue
- ✓ Our network meta-analysis revealed that UDCA is an overall promising strategy, considering both patients undergoing autologous or allogeneic HCT
- ✓ A subgroup analysis in allotransplanted patients also supported defibrotide as a promising strategy in this context

# Defibrotide for Sinusoidal Obstruction Syndrome/Veno-Occlusive Disease Prophylaxis in High-Risk Adult Patients: A Single-Center Experience Study

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DF: start on d1 of conditioning regimen to engraftment

UDCA: start on d1 of conditioning regimen until day+ 90

## Defibrotide-Related Bleeding

|                                      | No. of Patients (%) |
|--------------------------------------|---------------------|
| Bleeding site*                       |                     |
| Gastrointestinal                     | 2 (3.2)             |
| Intracerebral                        | 1 (1.6)             |
| Urinary tract (hemorrhagic cystitis) | 11 (17.4)           |
| Severity*                            |                     |
| Grade 2                              | 5 (7.9)             |
| Grade 3                              | 9 (14.3)            |
| Grade 4                              | 0 (0)               |

\* One patient experienced 2 bleeding episodes.



## ABSTRACT

Sinusoidal obstruction syndrome (SOS), also known as hepatic veno-occlusive disease (VOD), is a serious complication after hematopoietic stem cell transplantation (HSCT). SOS/VOD usually occurs within 3 weeks of HSCT, but the 2016 European Society for Blood and Marrow Transplantation diagnosis criteria have been revised to include late forms. Prophylactic use of defibrotide is recommended in the pediatric setting, but its value remains uncertain in the adult population. We report here a single-center series of 63 adult patients considered at high risk for SOS/VOD who received defibrotide prophylaxis in combination with ursodeoxycholic acid between May 2012 and August 2016. The median duration of defibrotide therapy was 23 days. Bleeding occurred in 14 patients (21.5%). Defibrotide prophylaxis was discontinued in 7 patients (10.8%): 4 cases (6.3%) due to bleeding and 3 cases (4.6%) because of the need for antithrombotic therapy. Overall, SOS/VOD occurred in 4 cases (6.3%) within 21 days after HSCT (days 13 and 14) in 2 cases and late-onset SOS/VOD (days 57 and 58) in the other 2 cases. SOS/VOD was moderate in 1 case, very severe in 3 cases, with 2 deaths related to SOS/VOD. Cumulative incidence of grades II to IV acute graft-versus-host disease and transplant-associated thrombotic microangiopathy were 22.2% and 3.2%, respectively. With a median follow-up of 31 months (range, 10.7 to 60.3), the rates of 2-year overall survival, progression-free survival, incidence of relapse, and nonrelapse mortality were 56.5%, 49%, 28.7%, and 22.3%, respectively. In our experience defibrotide prophylaxis is associated with a low incidence of SOS/VOD after allogeneic HSCT in a high-risk adult population with an acceptable safety profile.

# Conclusions

- Diagnosis of VOD/SOS is currently based mainly on clinical criteria, early detection and treatment of SOS can reduce the progression to multi-organ failure
- The most reliable imaging method supporting VOD/SOS diagnosis is US which is now recognized as an essential diagnosis criterion of late-onset VOD/SOS and highly recommended to assess hepatomegaly and ascites in children
- Defibrotide is effective for treatment of adults and children with SOS with renal or pulmonary dysfunction after HSCT
- The recommended dosage of defibrotide is 6.25 mg/kg every 6 hours, the duration of treatment depends on the clinical improvement and the cost of treatment
- No specific medication is used for SOS prophylaxis, UDCA and defibrotide could be used for prevention of SOS