Recognizing and Managing VOD in Affected and At-Risk Patient Populations

Faculty

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Disclosures

Dr. Fausel has disclosed no relevant financial relationships with any commercial interest.

Learning Objectives

- Outline the risk factors and diagnostic criteria associated with VOD for the timely identification of at-risk and affected patients
- Distinguish among traditional and newer approaches to VOD management with respect to their clinical rationale for use, efficacy, safety, and tolerability
- Evaluate the available evidence surrounding the clinical and cost benefits of early or preventative VOD treatment in key patient populations
- Integrate the latest clinical evidence and expert recommendations into strategies to overcome barriers to optimal VOD diagnostic and therapeutic practices

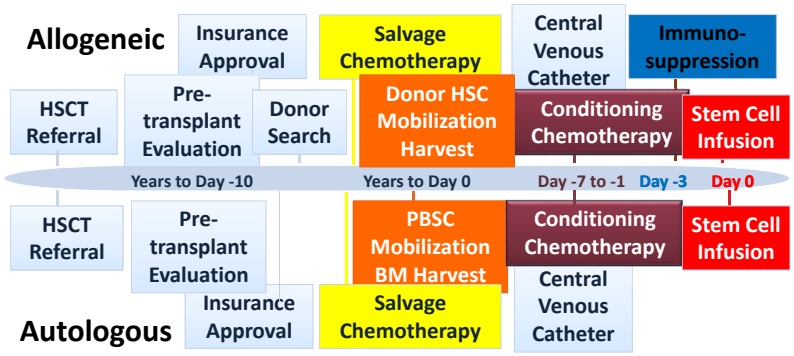
VOD = veno-occlusive disease.

Veno-Occlusive Disease

- Veno-occlusive disease (VOD) is also commonly known as sinusoidal obstructive syndrome (SOS)
- Life-threatening complication that occurs after HSCT
- Incidence is 8% to 14%, depending on the diagnostic criteria used
- Recent literature review of 135 published reports found the mean incidence to be 13.7%
- Incidence and prevalence depend on the portion of patients at high risk and exposure to predisposing agents

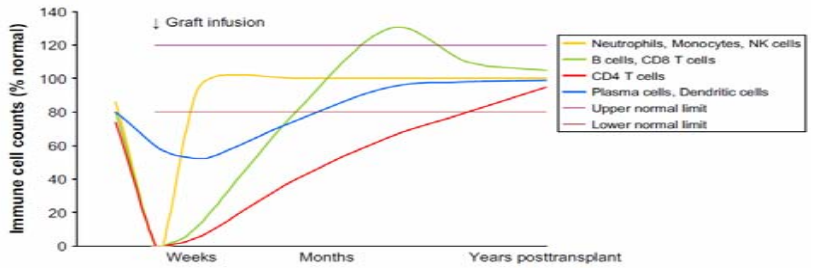
SOS = sinusoidal obstructive syndrome; HSCT = hematopoietic stem cell transplantation.
Dalle JH, et al. *Biol Blood Marrow Transplant.* 2016;22(3):400-409. Coppell JA, et al. *Biol Blood Marrow Transplant.* 2010;16(2):157-168.

HSCT Process



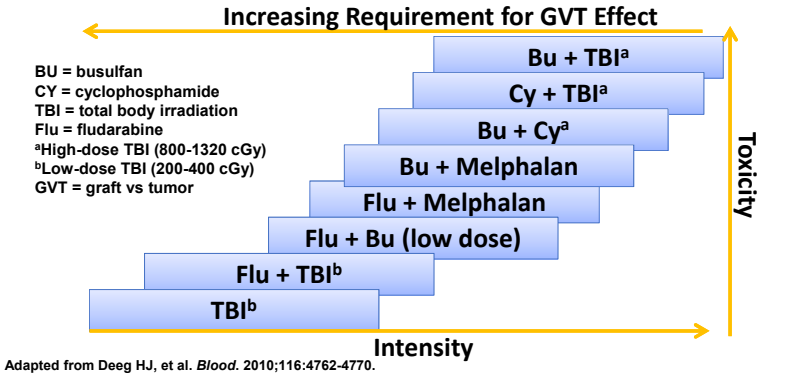
HSC = hematopoietic stem cell; PBSC = peripheral blood stem cell; BM = bone marrow.

Immune Reconstitution after HSCT



NK = natural killer; CD = cluster of differentiation.
Tomblyn M, et al. *Biol Blood Marrow Transplant.* 2009;15:1143-238.

HSCT Conditioning Dose Intensity



Adapted from Deeg HJ, et al. *Blood.* 2010;116:4762-4770.

Commonly Used Preparative Regimens

Preparative Regimen	Days of Treatment	Designation
Fludarabine 25 mg/m^2/d IV TBI 200 cGy	Days -4, -3, -2 Day 0	Non-myeloablative
Fludarabine 30 mg/m^2/d IV Busulfan 10 mg/kg/d IV daily	Days -10 through -6 Days -4 through -1	Reduced-intensity conditioning
Fludarabine 25 mg/m^2/d IV Melphalan 100-180 mg/m^2 IV	Days – 6 to -2 Day -2	Reduced-intensity conditioning
Carmustine 300 mg/m^2 IV Etoposide 200 mg/m^2 IV Q12H Cytarabine 200 mg/m^2 IV Melphalan 140 mg/m^2 IV	Day -6 Days -5 through -2 Days -5 through -2 Day -1	Myeloablative
Cyclophosphamide 60 mg/kg/d TBI 200-200 cGy twice daily	Days -5, -4 Days -3, -2, -1	Myeloablative

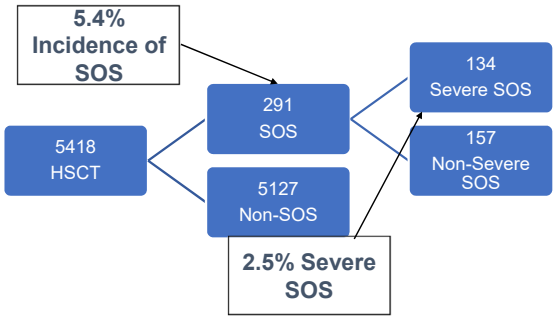
Bensinger WI. In: *Thomas' Hematopoietic Cell Transplantation*. 4th ed. John Wiley and Sons. 2009:316-332. Sandmaier BM and Storb R. In: *Thomas' Hematopoietic Cell Transplantation*. 4th ed. John Wiley and Sons. 2009:1043-1058.

Common Complications of HCST

Autologous	Allogeneic
Nausea/vomiting Myelosuppression/aplasia Mucositis Bleeding Infection (eg, bacterial, fungal, viral) Conditioning-regimen specific end-organ dysfunction • VOD/SOS • IPS • Renal toxicity Late complications (eg, endocrinopathies, cataracts, continued myelosuppression, secondary malignancies)	Nausea/vomiting Myelosuppression/aplasia Mucositis Bleeding Infection (eg, bacterial, fungal, viral) Conditioning-regimen specific end-organ dysfunction • VOD/SOS • IPS • Renal toxicity Late complications (eg, endocrinopathies, cataracts, continued myelosuppression, secondary malignancies) Thrombotic microangiopathy GvHD – acute and chronic

GvHD = graft vs host disease.
Gyurkocza B, et al. *Blood*. 2014;124:344-353.

Burden of VOD



Cao Z, et al. *J Med Econ*. 2017;20(8):871-883.

Hepatic VOD Post-HSCT

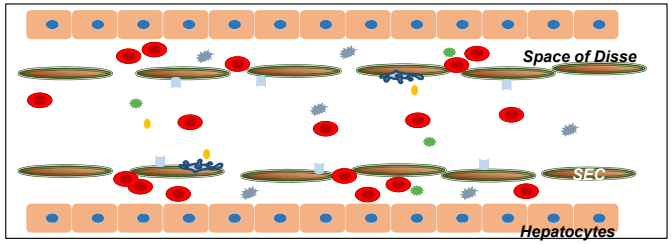
- **Definition**
  - Also known as SOS
  - Hepatomegaly (painful), jaundice (bilirubin ≥2 mg/dL)
  - Fluid retention, weight gain (≥5%), ascites
  - Onset first 3-4 weeks post-HSCT, other causes absent
- **Pathophysiology**
  - Primary injury to SECs, hepatocytes, stellate cells

Venular microthrombosis, fibrin deposition, ischemia, fibrogenesis

Portal hypertension, hepatorenal syndrome, MOF, death

SEC = sinusoidal endothelial cell; MOF = multi-organ failure.
Ho VT, et al. *Semin Thromb Hemost*. 2007;33(4):373-388; EBMT-ESH handbook [website]. https://ebmtonline.forumservice.net. Accessed September 6, 2017. Bearman SI. *Blood*. 1995;85(11):3005-3020.

Activation and Damage to the Sinusoidal Endothelium (SEC)

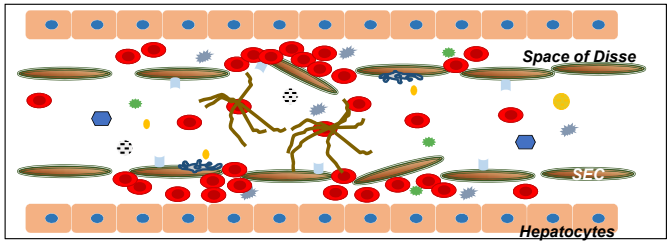


↑TNF-α, ICAM-1, VCAM-1, PAI-1, vWF, TF, heparanase, ↓t-PA

ICAM-1 = intercellular adhesion molecule 1; VCAM-1 = vascular adhesion molecule 1; PAI-1 = plasminogen activator inhibitor 1; vWF = von Willebrand factor; TF = tissue factor, t-PA = tissue-plasminogen activator.

Richardson PG, et al. *Expert Opin Drug Saf.* 2012;12(1):123-136.

Gap Formation, Fibrin Deposition, and Narrowing of the Sinusoids



↑TNF-α, ICAM-1, VCAM-1, PAI-1, vWF, TF, heparanase, ↓t-PA

Richardson PG, et al. *Expert Opin Drug Saf.* 2012;12(1):123-136.

Risk Factors for VOD

Biologic/Environmental	Iatrogenic
Pre-existing liver disease	Inotuzumab ozogamicin, gemtuzumab ozogamicin
Heparanase gene single nucleotide polymorphisms	HSCT conditioning with: - Busulfan/cyclophosphamide - Melphalan
Pyrrolizidine alkaloids	Abdominal irradiation
	Second myeloablative transplantation or transplantation beyond 2nd remission

Valla DC, et al. *Clin Res Hepatol Gastroenterol.* 2016;40:378-385.

Clinical Criteria for the Diagnosis of VOD

Seattle Criteria	Baltimore Criteria
Presence before day 30 post-SCT of two or more of the following • Jaundice • Hepatomegaly, right upper quadrant pain • Ascites +/- unexplained weight gain	Hyperbilirubinemia >2 mg/dL before day 21 post-SCT and at least two of the following • Hepatomegaly • Ascites • Weight gain ≥5% from baseline

Modified Seattle Criteria
Presence before day 20 post-SCT of two of the following • Bilirubin >2 mg/dL (~34 µmol/L) • Hepatomegaly, right upper quadrant pain of liver origin • Unexplained weight gain of >2% baseline because of fluid accumulation

- Both have high specificity of 91% to 92%, but low sensitivity

McDonald GB, et al. *Hepatology.* 1984;4(1):116-122. McDonald GB, et al. *Ann Intern Med.* 1993;118(4):255-267. Jones RJ, et al. *Transplantation.* 1987;44(6):778-783. Carreras E, et al. *Ann Hematol.* 1993;66(2):77-80.

New EBMT Criteria for VOD/SOS Diagnosis in Children and Adults

Children

- No limitation for time of onset of VOD/SOS

***Presence of ≥2 of the following*[a]:**

- Unexplained consumptive and transfusion-refractory thrombocytopenia[b]
- 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)[c] above baseline value
- Ascites (best if confirmed by imaging)[c] above baseline value
- Rising bilirubin from a baseline value on 3 consecutive days

OR

bilirubin ≥2 mg/dL within 72 hours

Adults

Classical VOD/SOS (≤21 days post-HSCT)

Bilirubin ≥2 mg/dL and 2 of the following:

- Painful hepatomegaly
- Weight gain >5%
- Ascites

Late-onset VOD/SOS (>21 days post HSCT)

Classical VOD/SOS beyond day 21

OR

Histologically proven VOD/SOS

OR

Presence of ≥2 of the following:

- Bilirubin ≥2 mg/dL (or 34 µmol/L)
- Painful hepatomegaly
- Weight gain >5%
- Ascites

And **hemodynamic and/or ultrasound evidence of VOD/SOS**

[a]With the exclusion of other potential differential diagnoses; [b]≥1 weight-adjusted platelet transfusion/day to maintain institutional guidelines; [c]Suggested: imaging (ultrasound, computed tomography, or magnetic resonance imaging) immediately before HSCT to determine baseline value for both hepatomegaly and ascites.

Corbacioglu S, et al. *Expert Rev Gastroenterol Hepatol.* 2017;11(10):885-898.

Prognosis of VOD/SOS

- **Most useful** } **Bearman model**
  - Rate of rise of bilirubin
  - Rate of weight gain
  - MOF
    - Oxygen requirement
    - Renal dysfunction
    - Encephalopathy
- **sVOD**
  - MOF has emerged as the best parameter (to date) for predicting bad outcome
  - All-cause mortality >80%
  - Previous standard: best supportive care

sVOD = severe veno-occlusive disease.

Bearman SI, et al. *J Clin Oncol.* 1993;11(9):1729-1736. Cesaro S, et al. *Haematologica.* 2005;90(10):1396-1404. Coppell JA, et al. *Biol Blood Marrow Transplant.* 2010;16(2):157-168. McDonald GB, et al. *Ann Intern Med.* 1993;118(4):255-267. Bulley SR, et al. *Pediatr Blood Cancer.* 2007;48(7):700-704. Lee SH, et al. *Bone Marrow Transplant.* 2010;45(8):1287-1293. Wadleigh M, et al. *Curr Opin Hematol.* 2003;10(6):451-462. Pihusch M, et al. *Transplantation.* 2005;80(10):1376-1382. Cheuk DK, et al. *Bone Marrow Transplant.* 2007;40(10):935-944.

Management of VOD

- Management strategies primarily consist of supportive measures
  - Diuresis, paracentesis, hemofiltration, mechanical ventilation, and hemodialysis
  - Not all of these strategies lead to improved outcome
- Heparin plus t-PA
  - Response in up to 30% of patients, but survival is poor
  - Associated with increased risk of life-threatening bleeding
  - Not recommended in patients with sVOD who have already developed MOF
  - Should also be avoided in patients with pulmonary or renal failure

DeLeve LD, et al. *Hepatology.* 2009;49(5):1729-1764. Helmy A. *Aliment Pharmacol Ther.* 2006;23(1):11-25. Bearman SI, et al. *Blood.* 1997;89(5):1501-1506.

t-PA with or without Heparin for the Treatment of VOD

Author	No. of Patients	Dose (mg/d)	Duration (d)	Heparin (yes/no)	No. of Responses	Life-Threatening Hemorrhage
Baglin, et al (1990)	1	50	4	No	1	0
Bearman, et al (1997)	42	5.4-120	2-4	Yes	12	10
Leahey, et al (1996)	9	5-10	2-4	Yes	5	0
Goldberg, et al (1996)	1	20	4	Yes	1	0
Higashigawa, et al (1995)	1	2-5	4	Yes[a]	1	0
Lee, et al (1996)	3	10-20	7-14	Yes	3	0
Yu, et al (1994)	3	0.25-0.5[b]	4	No	2	0
Schriber, et al (1999)	37	30-40	1-25	Yes	13[c] (2)[d]	13
Kulkarni, et al (1999)	17	10	1-12	Yes[e]	6	0

[a]Patient also received PGE; [b]Dose reported as mg/kg; [c]In patients who were suspected of VOD; [d]In patients who were diagnosed with VOD; [e]12 patients received heparin.

Current Management of VOD

- Liver transplantation can be beneficial
  - Only considered in patients with severe liver failure; feasibility a challenge
  - Generally contraindicated in cases of malignancy due to high rates of recurrence
- TIPS
  - Shown to relieve ascites in some patients (but in others, it worsened the process)

TIPS = transjugular intrahepatic portosystemic shunt.
Helmy A. *Aliment Pharmacol Ther.* 2006;23(1):11-25. Richardson PG, et al. *Acta Haematol.* 2001;106(1-2):57-68. DeLeve LD, et al. *Hepatology.* 2009;49(5):1729-1764. Azoulay D, et al. *Bone Marrow Transplant.* 2000;25(9):987-992.

Rationale for Development of New Therapies for VOD/SOS

- Treatments are supportive and are associated with significant risk of bleeding
- sVOD remains a serious complication of SCT with a high mortality rate (>80%)

There is an urgent, unmet clinical need for effective therapies for the treatment and prevention of VOD/SOS

Helmy A. *Aliment Pharmacol Ther.* 2006;23(1):11-25. Bearman SI, et al. *Blood.* 1997;89(5):1501-1506. Coppell JA, et al. *Biol Blood Marrow Transplant.* 2010;16(2):157-168.

Novel Therapeutic Approaches: Goals

- Modulate endothelial cell (EC) injury without causing systemic bleeding or other toxicity
- Protect host without compromising anti-tumor effect of cytotoxic therapy
- Preferably have activity in spectrum of vascular injury syndromes during SCT (eg, TTP/HUS, DAH/IP)
- Possible role in other syndromes underpinned by endothelial damage (eg, GvHD)

TTP = thrombotic thrombocytopenic purpura; HUS = hemolytic-uremic syndrome; DAH = diffuse alveolar hemorrhage; IP = interstitial pneumonitis.
Richardson P, et al. *Br J Haematol.* 1999;107(3):485-493.

Proposed Mechanism of Action of DF

- DF: A polydisperse oligonucleotide shown to exert protective effects on the endothelium
- Precise mechanism of action of DF is yet to be determined
- Proposed to involve two distinct elements
  - Protection of ECs
  - Restoration of the thrombotic–fibrinolytic balance
- DF
  - Decreases the influx of inflammatory mediators (↓ICAM-1 and heparanase)
  - Activates the fibrinolytic system (↑t-PA, TFPI and thrombomodulin, ↓PAI-1, TF and vWF)

TFPI = tissue factor pathway inhibitor.
Richardson PG, et al. *Expert Opin Drug Saf.* 2012;12(1):123-136. Guglielmelli T, et al. *Expert Opin Biol Ther.* 2012;12(3)353-361. Pellegatta F, et al. *Br J Pharmacol.* 1996;118(3):471-476. Echart C, et al. *Bone Marrow Transplant.* 2010;45(suppl 2);S281. Ostrovsky O, et al. *Blood.* 2010;115(11):2319-2328. Falanga A, et al. *Leukemia.* 2003;17(8):1636-1642. Morabito F, et al. *Expert Opin Biol Ther.* 2009;9(6):763-772. Palomo M, et al. *Biol Blood Marrow Transplant.* 2011;17(4):497-506. Zhou Q, et al. *Thromb Hemost.* 1994;71(4):507-510. Cella G, et al. *Clin Appl Thromb Hemost.* 2001;7(3):225-228.

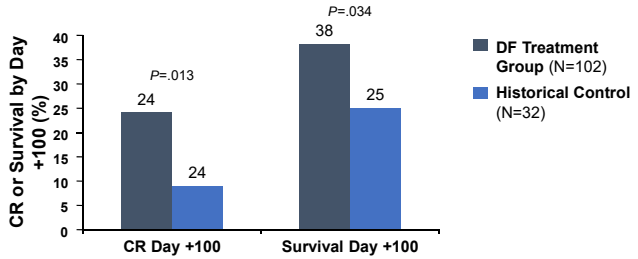
Pivotal Treatment Trial: Historically Controlled, Multi-Center, Open-Label, Phase 3 Study; 2005-01

- **Primary objective**
  - To demonstrate the efficacy of DF 25 mg/kg/d in patients with severe VOD in terms of CR rate by day +100 post-HSCT
    - CR defined as total bilirubin <2 mg/dL and resolution of MOF
- **Secondary objectives**
  - To compare survival rates at day +100 and day +180 post-HSCT in patients receiving DF with those in the HC cohort
  - To assess the safety of the selected dose and schedule of DF in patients with severe VOD
- **134 eligible patients** (based on Baltimore criteria by day +21 and either renal and/or pulmonary failure by day +28)
  - DF arm (n=102), DF 25 mg/kg/d[a], median treatment duration: 22 days (range, 1-60 days), minimum 21 days
  - HC arm (n=32), subjects selected by an independent Medical Review Committee blinded to outcome

[a]DF given IV in four divided doses ~every 6 hours.

Richardson PG, et al. *Blood*. 2016;127(13):1656-1665. Richardson PG, et al. *Blood*. 2009;114(22):2009.

Phase 3 Results: DF Significantly Increased CR and Survival at Day +100

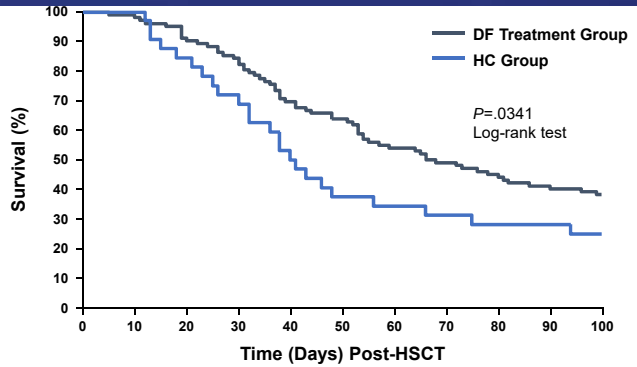


- **AEs**
  - Hemorrhagic AEs were similar between treatment and control arms (65% vs 69%)
  - 18% of treated patients experienced a drug-related toxicity that led to discontinuation

AE = adverse event.

Richardson PG, et al. *Blood*. 2016;127(13):1656-1665. Richardson PG, et al. *Blood*. 2009;114(22):2009.

Phase 3 Results: DF Demonstrates a Significant Survival Benefit at Day +100 in Patients with Severe VOD



Richardson PG, et al. *Blood*. 2016;127(13):1656-1665. Richardson PG. Oral presentation at EBMT 2013, London, UK.

Phase 3: Summary

- DF improves CR and survival at day +100 post-HSCT
- DF was generally well tolerated
- Toxicities observed in this study were similar to those observed in previous studies

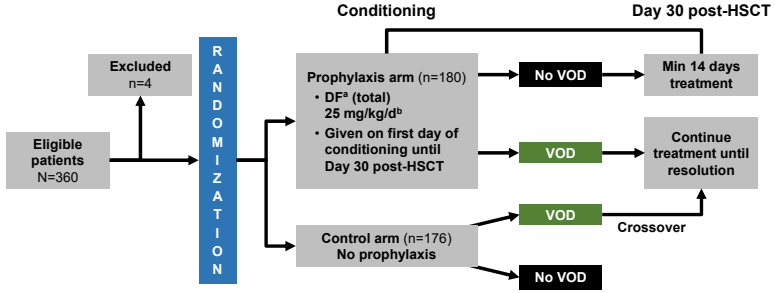
Richardson PG, et al. *Blood*. 2016;127(13):1656-1665. Richardson PG, et al. *Blood*. 2009;114(22):2009.

EBMT Phase 3 Study with DF for the Prevention of VOD in HSCT Patients

- Open-label, randomized controlled trial in pediatric patients (aged <18 years)
- Objective: To assess whether prophylactic use of DF can reduce the incidence and severity of VOD in high-risk pediatric patients undergoing HSCT
- Primary endpoint: Development of VOD by day 30 post-HSCT
- Secondary endpoints: Assessment of VOD severity and incidence and severity of acute GvHD (aGvHD)
- 356 eligible patients randomized to
  - Prophylaxis arm (n=180), DF[a] (total) 25 mg/kg/d[a] given on first day of conditioning until day 30 post-HSCT
  - Control arm (n=176), no prophylaxis

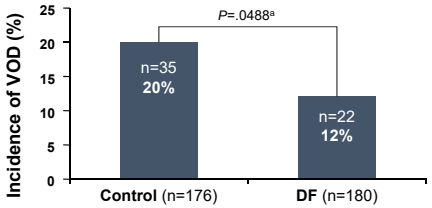
[a]DF given IV in four divided doses of 6.25 mg/kg over 2 hours.
Corbacioglu S, et al. *Lancet.* 2012;379(9823):1301-1309.

EBMT Phase 3 Prevention: Study Design



[a]Designated an orphan drug by the FDA and EMA; [b]DF given IV in four divided doses of 6.25 mg/kg over 2 hours.
Corbacioglu S, et al. *Lancet.* 2012;379(9823):1301-1309.

Phase 3 Prevention Results: DF Significantly Reduced the Incidence of VOD in Children



- No significant difference between VOD-associated mortality at 100 days after HSCT in DF vs control group (2% vs 6%, *P*=.10)
- However, mortality was four times higher in patients with VOD than those without VOD (25% vs 6%, *P*<.0001)

[a]Z test for competing risk analysis.
Corbacioglu S, et al. *Lancet.* 2012;379(9823):1301-1309.

Updated Results from a Large Treatment IND Study Using DF for Patients with Hepatic VOD

Paul G. Richardson, MD; Angela R. Smith, MD, MS; Brandon M. Triplett, MD; Nancy A. Kernan, MD; Stephan A. Grupp, MD, PhD; Sally Arai, MD; Joseph H. Antin, MD; Leslie Lehmann, MD; Valeria Bandiera; Maja Miloslavsky, PhD; Robin Hume, MS; Alison L. Hannah, MD; Bijan Nejadnik, MD; Robert J. Soiffer, MD; and the Defibrotide Study Group

2015 BMT Tandem Meetings, February 11-15, San Diego, California

- Inclusion by one of the following
  - Clinical VOD diagnosis
    - Originally, severe VOD (with MOF) per Baltimore criteria post HSCT was required
    - Study was amended to include non-severe VOD and VOD per modified Seattle criteria following HSCT or chemotherapy
  - Biopsy-proven VOD
- Exclusion: Clinically significant bleeding or the need for ≥2 vasopressors, concurrent use of medication that increases risk of hemorrhage

Jones RJ, et al. *Transplantation.* 1987;44(6):778-783. McDonald G, et al. *Ann Intern Med.* 1993;118(4):255-267. Carreras E, et al. *Ann Hematol.* 1993;66(2):77-80.

Pivotal Phase 3 Trial vs Treatment-IND

Inclusion Criteria

Pivotal Phase 3
Baltimore Criteria + MOF

Treatment-IND
Baltimore Criteria + MOF
↓
Baltimore Criteria
↓
Modified Seattle Criteria

	Pivotal Phase 3		T-IND
	DF	Control	DF
sVOD/MOF	102	32	279
VOD (no MOF)	0	0	247
Total post-HSCT	102	32	526

Jones RJ, et al. *Transplantation*. 1987;44(6):778-783. McDonald G, et al. *Ann Intern Med*. 1993;118(4):255-267. Carreras E, et al. *Ann Hematol*. 1993;66(2):77-80. Richardson PG, et al. *Blood*. 2009;114(22):654. Richardson PG, et al. *Blood*. 2016;127(13):1656-1665.

Summary of AEs

- Tolerability and low rate of DF-associated toxicities consistent with prior studies

Category	Overall, n (%) (N=641)
≥1 AE	429 (67)
≥1 Grade 3/4/5 AE	346 (54)
≥1 AE leading to discontinuation	176 (28)
≥1 Treatment-related AE[a]	135 (21)

[a]Considered to be possibly, probably, or definitely related to DF treatment. Missing relationships were analyzed as "possibly related."
Richardson P, et al. *Blood*. 2009;114(22):654. Richardson P, et al. *Biol Blood Marrow Transplant*. 2010;16(7):1005-1017.

Most Common Treatment-Related AEs

AE[a] (Incidence ≥5%)	Overall, n (%) (N=641)
Hypotension	86 (13)
Respiratory failure	49 (8)
Diarrhea	48 (8)
Pyrexia	47 (7)
Pulmonary hemorrhage	44 (7)
Renal failure	44 (7)
Vomiting	38 (6)
Gastrointestinal hemorrhage	35 (6)
Hypoxia	35 (6)
Epistaxis	33 (5)
Nausea	32 (5)

[a]Other than worsening MOF and VOD.
Richardson P, et al. *Blood*. 2009;114(22):654. Richardson P, et al. *Biol Blood Marrow Transplant*. 2010;16(7):1005-1017.

Survival at Day +100 Pediatric and Adult Subgroups

- Survival at day +100 in post-HSCT patients was 58% in the pediatric subgroup and 45% in the adult subgroup

Subgroup	Pediatric (≤16 years) Survival Day +100 n/N (%)	Adult (>16 years) Survival Day +100 n/N (%)
All HSCT patients	163/283 (58)	109/243 (45)
sVOD/MOF	79/157 (50)	46/122 (38)
VOD (no MOF)	84/126 (67)	63/121 (52)
All post-chemotherapy patients	39/47 (83)	9/15 (60)

Note: Chemotherapy patients with non-sVOD not analyzed separately.
Richardson P, et al. *Blood*. 2009;114(22):654. Richardson P, et al. *Biol Blood Marrow Transplant*. 2010;16(7):1005-1017.

Survival at Day +100 Allograft and Autograft Subgroups

- Survival at day +100 in post-HSCT patients was 50% in allograft patients and 66% in autograft patients

Subgroup	Allografts Survival Day +100 n/N (%)	Autografts Survival Day +100 n/N (%)
All HSCT patients	234/467 (50)	37/56 (66)
sVOD/MOF	109/252 (43)	16/27 (59)
VOD (no MOF)	125/215 (58)	21/29 (72)

Richardson P, et al. *Blood.* 2009;114(22):654. Richardson P, et al. *Biol Blood Marrow Transplant.* 2010;16(7):1005-1017.

Survival at Day +100

- Survival at day +100 in post-HSCT patients was 52%

Subgroup	Survival Day +100 n/N (%)
All HSCT patients	272/526 (52)
sVOD/MOF	125/279 (45)
VOD (no MOF)	147/247 (60)
All post-chemotherapy patients	48/62 (77)

Richardson P, et al. *Blood.* 2009;114(22):654. Richardson P, et al. *Biol Blood Marrow Transplant.* 2010;16(7):1005-1017.

Conclusions

- Largest prospective evaluation of DF to date in VOD
- DF was generally well tolerated in this population, with manageable toxicity, and highly consistent with prior studies of DF in this setting
  - Tolerability was consistent with the low incidence of DF-associated toxicities reported in prior studies
- Day +100 survival
  - Favorable results shown in pediatric, adult, allograft, and autograft subgroups post HSCT or chemotherapy with sVOD/MOF and VOD (no MOF)
  - Higher survival rate in VOD without MOF indicates further study is warranted to determine impact of treatment earlier in the course of VOD
- Future directions
  - Prophylaxis in allogeneic and high-risk autologous HSCT
  - Earlier treatment

Richardson PG, et al. *Blood.* 2009;114(22):654. Richardson P, et al. *Biol Blood Marrow Transplant.* 2010;16(7):1005-1017. Corbacioglu S, et al. *Lancet.* 2012;379(9823):1301-1309. Dignan FL, et al. *Br J Haematol.* 2013;163(4):444-457. Richardson PG, et al. *Blood.* 2013;122(21):2470.

Defibrotide

- DF open-label studies in patients with hepatic VOD and MOD following HSCT
  - In one trial, treatment with DF was associated with a 38.2% survival rate compared with a 25% rate in matched historical controls
  - In another trial, the survival rate was 44%

MOD = multi-organ dysfunction.
Med Lett Drugs Ther. 2016;58(1503):120.

Socioeconomic Burden of VOD

- Existing burden of patients undergoing HSCT is already high
- Individuals with VOD are faced with
  - Increased hospital length of stay (average, 28 days)
  - Almost $50,000 increase in health-related costs (~$120,000 total)
  - Six times higher risk of mortality compared with patients without VOD

Dvorak CC, et al. *Biol Blood Marrow Transplant.* 2016;22(3):S275.

Cost-Effectiveness: DF

- The recommended dosage of DF is 6.25 mg/kg given as a 2-hour IV infusion every 6 hours for a minimum of 21 days
- The cost of 21 days of treatment with DF for a patient weighing 70 kg is $155,925
- Budget impact model from the perspective of a bone-marrow transplantation center
  - Estimated that 2.3% of adults and 4.2% of children would develop VOD with MOD following HSCT
- Incremental cost-effectiveness ratio (ICER) was $47,736
  - 88% probability DF was cost-effective at a $100,000/QALY threshold

QALY = quality-adjusted life year.
Veenstra DL, et al. *J Med Econ.* 2017;20(5);453-463.

Cost-Effectiveness Prophylaxis: DF

- Evaluation of the cost-effectiveness of DF
  - Of 438 pediatric patients identified as having undergone HSCT,138 were at risk of VOD (total incidence of VOD was 7.4%)
- Total calculated costs for prophylactic DF in 138 patients at risk was almost six times higher than the incremental costs for patients with VOD
- Concluded DF prophylaxis is not cost-effective
- Limitation: Cost analysis included all patients undergoing HSCT and not just those at risk of developing severe VOD

Pichler H, et al. *Biol Blood Marrow Transplant.* 2017;23(7):1128-1133.

Medications for VOD

Prevention[a]

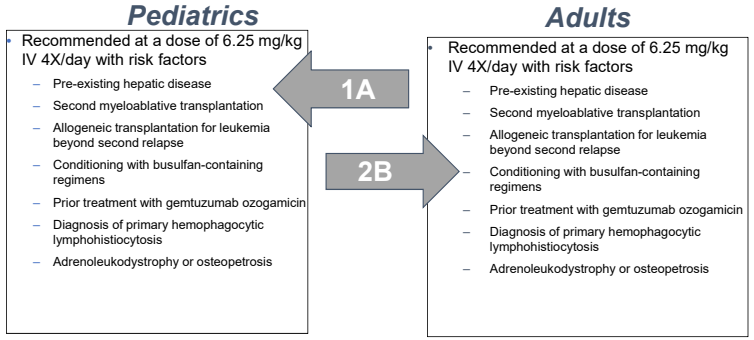
- DF: Recommended based on risk
- Heparin: No longer recommended
- UDCA: Has shown reduction in VOD
- Pentoxifylline: Not recommended
- Antithrombin: Not recommended
- Prostaglandin E1: Not recommended

Treatment

- DF: Recommended
- Tissue plasminogen activator: Not recommended
- N-acetylcysteine: Not recommended
- Methylprednisolone: May be considered
- Judicious clinical care: Recommended (fluid balance)
- Early discussions with specialists (critical care/hepatology)

[a]DF is currently not approved for preventative treatment but is in clinical trials for this indication.
UDCA = ursodeoxycholic acid.
Dignan FL, et al. *Br J Haematol.* 2013;163(4):444-457. ClinicalTrials.gov [website]. Study comparing efficacy and safety of defibrotide vs best supportive care in the prevention of hepatic veno-occlusive disease in adult and pediatric patients. Last updated April 27, 2018. Accessed May 18, 2018.

DF Prophylaxis



Gokce M, et al. *Exp Clin Transpl.* 2013;11:440-446.

Treatment Stratification

- Preventive measures
  - Resolve reversible risk factors (eg, acute hepatitis, iron overload)
  - Irreversible risk factors: Include patients on prophylaxis when possible (eg, second HCST, previous liver disease, radiation, or treatment with gemtuzumab ozogamicin)
- Monitor for VOD/SOS: Diagnose when appropriate and treat
- Severe VOD/SOS: Consider DF (start immediately in patients with multiple organ failure)

Carreras E. *Br J Haematol.* 2015;168(4):481-491.

Summary

- VOD/SOS is a potentially life-threatening complication of HSCT
- In cases of sVOD/MOF, mortality rate can be as high as 80% or more
- Diagnosis of VOD/SOS relies on clinical criteria
- Current management of VOD/SOS primarily involves supportive care
- There is an urgent unmet need for better treatment strategies for the treatment and prevention of VOD/SOS
  - DF, a polydisperse oligonucleotide (which has orphan drug status for the treatment and prevention of VOD) is EMA-approved and commercially launched in the EU
  - The FDA approved DF on March 31, 2016, for the treatment of adult and pediatric patients with VOD with renal or pulmonary dysfunction following HSCT
- Phase 3 trial of DF prophylaxis in very high-risk pediatric and adult patients is ongoing

Questions?