CASE STUDY:
MINH, 32, ALL

VOD/SOS WITH RENAL AND PULMONARY DYSFUNCTION

following HSCT in an adult patient with relapsed/refractory acute lymphoblastic leukemia (ALL)

Data based on actual patient case experiences. Disease progression may vary and may not be indicative of all patients. Individual diagnosis and treatment decisions are at the discretion of the healthcare provider.

Indication

Defitelio® (defibrotide sodium) is indicated for the treatment of adult and pediatric patients with hepatic VOD, also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following HSCT.

IMPORTANT SAFETY INFORMATION

Contraindications

Defitelio is contraindicated in the following conditions:

- Concomitant administration with systemic anticoagulant or fibrinolytic therapy
- Known hypersensitivity to Defitelio or to any of its excipients

Please see additional Important Safety Information on back and accompanying full Prescribing Information.

HSCT=hematopoietic stem-cell transplantation; SOS=sinusoidal obstruction syndrome; VOD=veno-occlusive disease.

DEFITELIO® (defibrotide sodium) injection 80 mg/mL

PATIENT HISTORY OF PRESENT ILLNESS

Minh, a 32-year-old male with relapsed/refractory ALL treated with inotuzumab ozogamicin

PHYSICAL EXAM

- Vital signs within normal range
- No hepatomegaly
- No ascites
- Performance score: 90%

TREATMENT APPROACH

- Received twice daily fludarabine/cytarabine combination with inotuzumab ozogamicin (1.5 mg/m^2)
- Admitted for allogeneic peripheral blood stem cell transplantation with a haploidentical donor
- Reduced-intensity conditioning with fludarabine, melphalan, and total body irradiation (2Gy)
- GvHD prophylaxis: post-transplant cyclophosphamide + tacrolimus + mycophenolate mofetil
- VOD/SOS prophylaxis: ursodiol

RISK FACTORS FOR DEVELOPING VOD/SOS[1-3]

- Prior treatment with inotuzumab ozogamicin
- Allogeneic HSCT
- Cumulative effect of hepatotoxic drugs, including tacrolimus

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hemorrhage

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Concomitant systemic anticoagulant or fibrinolytic therapy may increase the risk of bleeding and should be discontinued prior to Defitelio treatment. Consider delaying Defitelio administration until the effects of the anticoagulant have abated.

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GvHD=graft-vs-host disease.

ADMISSION BASELINE (DAY -7)

PHYSICAL EXAM

- Weight: 74.3 kg
- Normal vital signs
- No hepatomegaly, no ascites
- Performance score: 90%

IMAGERY FINDINGS

- Baseline hepatic ultrasound performed and was normal

KEY CONSIDERATIONS

- Prior abdominal irradiation
- Prior treatment with inotuzumab (18% incidence of VOD/SOS in relapsed/refractory ALL patients)[4,a]
- Serum ferritin levels slightly elevated prior to transplant

RELEVANT LABORATORY FINDINGS	
CBC	WBC: 7.6 x 10^9/L Hemoglobin: 12 g/dL[b] Hematocrit: 35%[b] Platelets: 135,000/mcL[b]
Total serum bilirubin	0.3 mg/dL
Liver biochemistry	ALP: 55 U/L AST: 21 U/L ALT: 22 U/L
Serum creatinine	0.8 mg/dL[b]
GFR	100 mL/min
BUN	12 mg/dL
Ferritin	700 ng/mL[b]

[a]Data from a CIBMTR registry of US patients with ALL age ≥18 years old treated with inotuzumab ozogamicin, who proceeded to allogeneic HSCT, collected from August 2017 to August 2022.[4]

[b]Denotes lab value outside the reference ranges.[5]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CBC=complete blood count; CIBMTR=Center for International Blood and Marrow Transplant Research; GFR=glomerular filtration rate; WBC=white blood cell.

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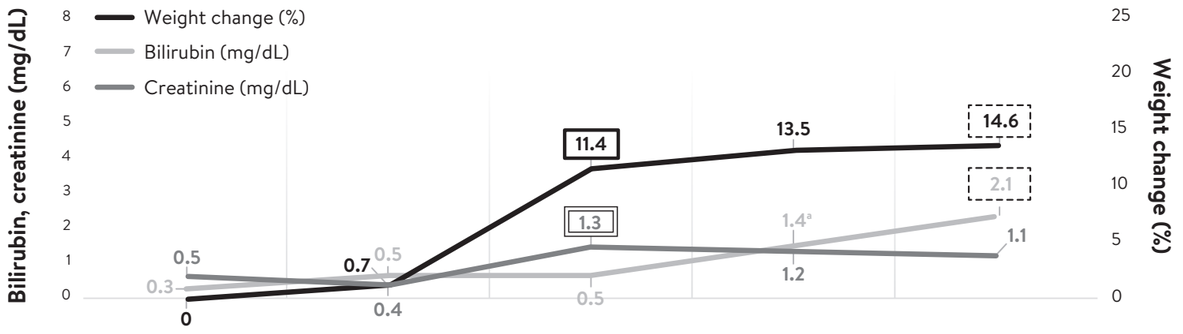
CASE SUMMARY



BASELINE: DAY -7	DAY +10	DAY +12	DAY +13	DAY +14
Normal baseline hepatic ultrasonography	Increase in ALP levels (177 U/L)[a]	AST: 21 U/L ALT: 22 U/L	AST: 40 U/L ALT: 28 U/L	AST: 1335 U/L[a] ALT: 507 U/L[a]
	O_2 saturation on RA: 88%	Minimal pleural effusion (x-ray)	•	Minimal pleural effusion (x-ray)
		Mild ascites	•	Severe ascites
		Hepatomegaly	•	Hepatomegaly
			Abdominal distension	Abdominal distension
				Portal flow impairment

▭ Met Cairo/Cooke diagnostic criteria for VOD/SOS[1]

▭ Met EBMT diagnostic criteria for VOD/SOS[3,6]

▭ First evidence of renal/pulmonary dysfunction[3]

• Symptom remained the same

[a]Denotes lab value outside the reference ranges.[5]

EBMT=European Society for Blood and Marrow Transplantation; RA=room air.

ADDITIONAL CONSIDERATIONS

Day +10– Patient presented with Grade 2 diarrhea and skin GvHD.

- Differential diagnosis included: infection, liver disease, bone disorder
- Patient showed first sign of pulmonary dysfunction with oxygen saturation levels at 88%. Patient required an intranasal cannula to deliver fresh oxygen

Day +12– Patient presented with hepatomegaly, mild ascites, forward flow of portal/hepatic veins on Doppler with increased peak velocity. An x-ray showed minimal pleural effusion of the lung. Patient had a progressive weight gain >10% baseline body weight, direct hyperbilirubinemia, and hypoalbuminemia.

- Differential diagnosis included: infection, fluid overload, VOD/SOS
- Patient met Cairo/Cooke diagnostic criteria for VOD/SOS with mild ascites, hepatomegaly, and a weight change of 11.4%
- Patient showed first sign of renal dysfunction with a creatinine level of 1.3 mg/dL

Day +13– Patient presented with slightly elevated AST/ALT levels and abdominal distension (abdomen swollen outward). Ascites worsened from mild to moderate and pleural effusion continued. Weight continued to increase as did hyperbilirubinemia (1.4 mg/dL) and hypoalbuminemia.

- Differential diagnosis included: infection, fluid overload, VOD/SOS, acute kidney injury

After being clinically diagnosed with VOD/SOS with renal and pulmonary dysfunction on Day +12, patient started on a 21-day course of Defitelio (6.25 mg/kg every 6 hours) beginning on Day +13.

Day +14– Patient had worsening hyperbilirubinemia, hypoalbuminemia, and hepatomegaly (liver 18.9 cm), with elevated ALT and AST levels. Intraperitoneal drain inserted for massive refractory ascites. Liver biopsy not performed due to concerns with shortness of breath, coagulopathy, and sepsis.

- Differential diagnosis included: infection, fluid overload, VOD/SOS, acute kidney injury
- Patient fulfilled EBMT criteria for post-transplant VOD/SOS

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hypersensitivity Reactions

Hypersensitivity reactions including rash, urticaria, and angioedema have occurred in less than 2% of patients treated with Defitelio. One case of an anaphylactic reaction was reported in a patient who had previously received Defitelio. Monitor patients for hypersensitivity reactions, especially if there is a history of previous exposure. If a severe hypersensitivity reaction occurs, discontinue Defitelio, treat according to the standard of care, and monitor until symptoms resolve.

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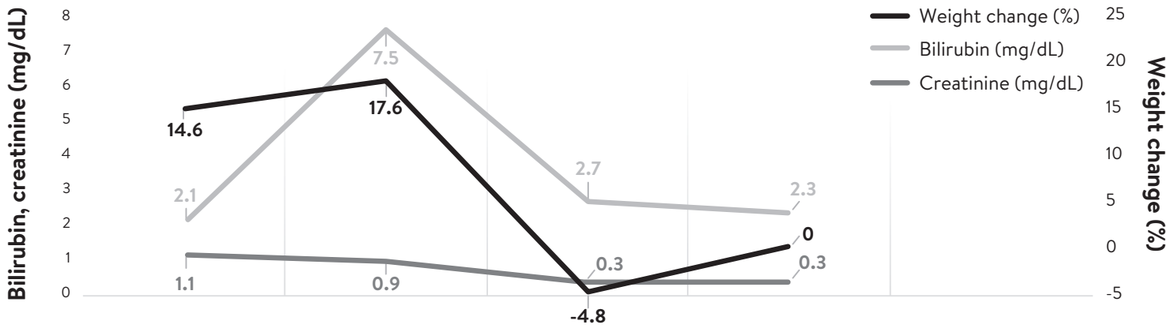
TREATMENT AND CLINICAL STATUS POST-VOD/SOS DIAGNOSIS



DAY +14	DAY +20	DAY +34 → +49	DAY +65	DAY +730
AST: 1335 U/L[a] ALT: 507 U/L[a]	AST: 432 U/L[a] ALT: 106 U/L[a]	AST: 22 U/L ALT: 23 U/L	AST: 23 U/L ALT: 21 U/L	AST: 23 U/L ALT: 21 U/L
Minimal pleural effusion (x-ray)	•	•	O_2 saturation on RA: 95%	
Severe ascites	•	Ascites resolved; drain removed		Alive in MRD-remission
Hepatomegaly	•	Hepatomegaly decreasing	Hepatomegaly resolved	Normal liver function
Abdominal distension	RUQ pain	No RUQ pain		
Portal flow impairment	•	Liver function improving	Normal hepatic venous flow	

DAY +13 Patient started on Defitelio

DAY +34 Patient completed course of Defitelio

• Symptom remained the same

During treatment with Defitelio, patient was monitored for bleeding and other potential adverse reactions, such as hypotension, diarrhea, vomiting, nausea, and epistaxis.[7]

This case discusses an individual patient. Outcomes depicted are not indicative of those achieved for all patients.

[a]Denotes lab value outside the reference ranges.[5]

MRD=minimal residual disease; RUQ=right upper quadrant.

ADDITIONAL CONSIDERATIONS

Day +20–AST/ALT levels had decreased close to normal range. Patient continued to present with refractory ascites, hepatomegaly, and right upper quadrant pain. Hepatic portal flow continued to be impaired.

Day +34– Patient completed his 21-day course of Defitelio.

Day +35 through Day +49– Decrease in hepatomegaly was observed by Doppler ultrasound.

Day +49–Patient experienced complete resolution of ascites, and intraperitoneal drain was removed. Liver function started to improve with no persistent right upper quadrant pain.

Day +65–Patient's hepatomegaly completely resolved, and portal flow was normal through hepatic veins. Oxygen saturation on RA was >95%. Patient was discharged from the hospital that evening.

Nearly two years later, patient continues to do well and is in MRD-negative complete remission. Liver function is normal.

IMPORTANT SAFETY INFORMATION

Most Common Adverse Reactions

The most common adverse reactions (incidence ≥10% and independent of causality) with Defitelio treatment were hypotension, diarrhea, vomiting, nausea, and epistaxis.

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RECENT ADVANCES IN DIAGNOSTIC CRITERIA FOR VOD/SOS DIAGNOSIS

Historically, the Baltimore (1987) and modified Seattle (1984) criteria have been used for diagnosis of VOD/SOS.[8-10]

EBMT diagnostic criteria for VOD/SOS in adults[3]

VOD/SOS THAT OCCURS ≤21 DAYS POST HSCT	LATE-ONSET VOD/SOS >21 DAYS POST HSCT
Baltimore criteria[a]: **Presentation of bilirubin ≥2 mg/dL and at least 2 of the following:** • Painful hepatomegaly • Weight gain (>5%) • Ascites	**Baltimore criteria[a] beyond Day 21** **OR** histologically proven VOD/SOS **OR** 2 or more of the following criteria must be present: • Bilirubin ≥2 mg/dL (or 34 µmol/L) • Painful hepatomegaly • Weight gain (>5%) • Ascites **AND** hemodynamic or/and ultrasound evidence of VOD/SOS (hepatomegaly, ascites, and decrease in velocity or reversal of portal flow)

These proposed criteria have not been prospectively validated in clinical trials.

[a]Defined as classical VOD/SOS in EBMT criteria.

CAIRO/COOKE DIAGNOSTIC CRITERIA FOR VOD/SOS

REVISED DIAGNOSTIC CRITERIA FOR ADULT AND PEDIATRIC PATIENTS[1,b]		
***Any 2* of the following after HSCT:**	**OR**	***Any 1* of the following after HSCT:**
• Elevated bilirubin (≥2 mg/dL) or greater than upper institutional limits[c] • Unexpected weight gain (≥5% compared to baseline weight pre-HSCT) • Excessive platelet transfusions consistent with refractory thrombocytopenia post HSCT • Hepatomegaly for age or increased size over pre-HSCT • Right upper quadrant pain • Ascites confirmed by physical exam and/or imaging studies • Reversal of portal venous flow (hepatofugal flow) by Doppler ultrasound		• Hepatic biopsy consistent with VOD/SOS • Unexplained elevated portal venous wedge pressure Though it is not recommended, a liver biopsy or direct portal wedge pressure measurements can be used when making a diagnosis of VOD/SOS, if necessary.[1]

These proposed criteria have not been prospectively validated in clinical trials.

IMPORTANT SAFETY INFORMATION

Contraindications

Defitelio is contraindicated in the following conditions:

- Concomitant administration with systemic anticoagulant or fibrinolytic therapy
- Known hypersensitivity to Defitelio or to any of its excipients

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[b]Probably or definitely secondary to VOD/SOS and not other etiologies.[1]

[c]In patients with an already elevated bilirubin prior to HSCT conditioning, this criterion should not be utilized in the diagnostic criteria.[1]

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EFFICACY OF DEFITELIO WAS EVALUATED IN 689 PATIENTS[7,11]

STUDIES INCLUDED A BROAD RANGE OF ADULT AND PEDIATRIC PATIENTS WITH VOD/SOS WITH RENAL OR PULMONARY DYSFUNCTION FOLLOWING HSCT[7,11,12]

	Study 1[7,13]	Study 2[7]	Study 3[11,12]
Study design	Phase 3 prospective	Phase 2 prospective	Expanded access study
Number of patients	**102**	**75**	**512**
VOD/SOS associated with:	Multi-organ dysfunction (pulmonary, renal, or both)[a]	Multi-organ dysfunction[b]	Renal or pulmonary dysfunction[c]
Median number of days on treatment (days) (range)	21.5 (1, 58)	19.5 (3, 83)	21[d] (1, 91)
Treatment dose of Defitelio	6.25 mg/kg infusion every 6 hours		
Median age (years) (range)	21 (<1, 72)	32 (<1, 61)	14 (<1, 69)
Type of transplant, n (%)			
Allogeneic	90 (88)	67 (89)	450 (88)
Autologous	12 (12)	8 (11)	61 (12)
Ventilator or dialysis dependent at study entry, n (%)	34 (33)	8 (11)	225 (42)

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hemorrhage

Defitelio may increase the risk of bleeding in patients with VOD after HSCT. Do not initiate Defitelio in patients with active bleeding. Monitor patients on Defitelio for signs of bleeding. If bleeding occurs, withhold or discontinue Defitelio.

Concomitant systemic anticoagulant or fibrinolytic therapy may increase the risk of bleeding and should be discontinued prior to Defitelio treatment. Consider delaying Defitelio administration until the effects of the anticoagulant have abated.

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[a]A diagnosis of VOD/SOS was made using Baltimore criteria (bilirubin ≥2 mg/dL and at least 2 of the following: hepatomegaly, ascites, and weight gain >5% by Day +21 post HSCT).[8,13]

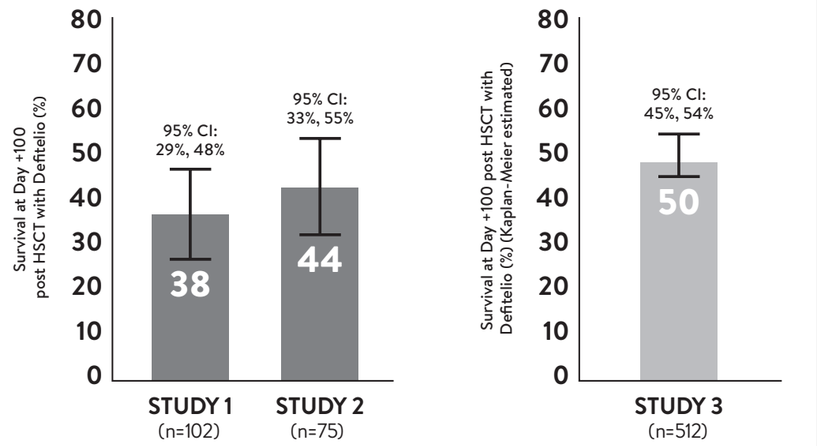
[b]A diagnosis of VOD/SOS was made using Baltimore criteria (bilirubin ≥2 mg/dL and at least 2 of the following: ascites, weight gain >5% from baseline, hepatomegaly, or right upper quadrant pain) by Day +35 post HSCT.[8,14]

[c]A diagnosis of VOD/SOS was made using Baltimore criteria (bilirubin ≥2 mg/dL and at least 2 of the following: hepatomegaly, ascites, and weight gain >5%) by Day +35 post HSCT or modified Seattle criteria (presentation by Day 20 post HSCT of at least 2 of the following: bilirubin >2 mg/dL, hepatomegaly or right upper quadrant pain, and weight gain >2% of baseline).[6,8,9,11,13]

[d]Duration of treatment from first dose to last dose is presented because days without treatment were not captured for the expanded access study.[7]

DEFITELIO WAS PROVEN TO IMPROVE SURVIVAL AT DAY +100 CONSISTENTLY ACROSS 3 STUDIES[7,11]

SURVIVAL AT DAY +100 POST HSCT WITH DEFITELIO ACROSS STUDIES IN ADULT AND PEDIATRIC PATIENTS[7,11]



Expected Day +100 survival with supportive care: 21% to 31%

Based on published reports and analyses of patient-level data for individuals with hepatic VOD/SOS with renal or pulmonary dysfunction who received supportive care or interventions other than Defitelio.[7]

DELAYS IN DEFITELIO INITIATION WERE ASSOCIATED WITH INCREASED MORTALITY AT DAY +100[11]

IN AN EXPLORATORY POST HOC ANALYSIS FROM STUDY 3[11]

- Analysis of Study 3 indicated that **increased mortality at Day +100 was associated with longer delays in Defitelio administration** following a diagnosis of VOD/SOS with renal or pulmonary dysfunction (confirmed by the Cochran-Armitage trend test; $P<0.001$)
  - Analysis based on adult and pediatric patients (n=512) with a diagnosis of VOD/SOS with renal or pulmonary dysfunction[e]
  - The reason for initiation delay following diagnosis was not assessed in this expanded access study

[e]All patients received Defitelio at a dose of 6.25 mg/kg infused every 6 hours.

CI=confidence interval.

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SAFETY PROFILE

ADVERSE REACTIONS INDEPENDENT OF CAUSALITY ≥10% ANY GRADE OR GRADE 4–5 ≥2% OF DEFITELIO-TREATED PATIENTS[7,a]

Adverse reaction	Defitelio (n=176) n (%)	
	Any grade	Grade 4–5[b]
Hypotension	65 (37)	12 (7)
Diarrhea	43 (24)	0
Vomiting	31 (18)	0
Nausea	28 (16)	0
Epistaxis	24 (14)	0
Pulmonary alveolar hemorrhage	15 (9)	12 (7)
Gastrointestinal hemorrhage	15 (9)	5 (3)
Sepsis	12 (7)	9 (5)
Graft-vs-host disease	11 (6)	7 (4)
Lung infiltration	10 (6)	5 (3)
Pneumonia	9 (5)	5 (3)
Pulmonary hemorrhage	7 (4)	4 (2)
Infection	6 (3)	4 (2)
Hemorrhage intracranial	5 (3)	4 (2)
Hyperuricemia	4 (2)	4 (2)
Cerebral hemorrhage[c]	3 (2)	3 (2)

[a]Excludes events considered to be due to the underlying disease: multi-organ failure, veno-occlusive disease, respiratory failure, renal failure, and hypoxia.[7]

[b]Adverse reactions considered life-threatening or fatal.[7]

[c]Cerebral hemorrhage has been included in the table due to clinical relevance.[7]

TREATMENT MODIFICATIONS FOR SPECIFIC EVENTS OR PROCEDURES

TREATMENT MODIFICATIONS FOR TOXICITY OR INVASIVE PROCEDURE[7]

Event	Recommended action
Hypersensitivity reaction • Severe or life-threatening (anaphylaxis)	**1.** Discontinue Defitelio permanently; do not resume treatment.
Bleeding • Persistent, severe, or potentially life-threatening	**1.** Withhold Defitelio. **2.** Treat the cause of bleeding and give supportive care as clinically indicated. **3.** Consider resuming treatment (at the same dose and infusion volume) when bleeding has stopped and the patient is hemodynamically stable.
• Recurrent significant bleeding	**1.** Discontinue Defitelio permanently; do not resume treatment.
Invasive procedures	**1.** There is no known reversal agent for the profibrinolytic effects of Defitelio. Discontinue Defitelio infusion at least 2 hours prior to an invasive procedure. **2.** Resume Defitelio treatment after the procedure, as soon as any procedure-related risk of bleeding is resolved.

DRUG INTERACTIONS[7]

- Defitelio may enhance the pharmacodynamic activity of antithrombotic/fibrinolytic drugs such as heparin or alteplase. Concomitant use of Defitelio with antithrombotic or fibrinolytic drugs is contraindicated because of an increased risk of hemorrhage

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Indication

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Most Common Adverse Reactions

The most common adverse reactions (incidence ≥10% and independent of causality) with Defitelio treatment were hypotension, diarrhea, vomiting, nausea, and epistaxis.

Please see accompanying full Prescribing Information.

For additional information, visit **defitelio.com**
or call Jazz Pharmaceuticals Customer Service at 1-800-833-3533.

References: 1. Cairo MS, Cooke KR, Lazarus HM, et al. Modified diagnostic criteria, grading classification and newly elucidated pathophysiology of hepatic SOS/VOD after haematopoietic cell transplantation. *Br J Haematol.* 2020;190(6):822-836. **2.** Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives—a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant.* 2015;50(6):781-789. **3.** Mohty M, Malard F, Abecassis M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2016;51(7):906-912. **4.** De Lima MJG, Kebriaei P, Lanza F, et al. A registry-based, observational safety study of inotuzumab ozogamicin (InO) treatment in patients (pts) with B-cell precursor acute lymphoblastic leukemia (ALL) who proceeded to hematopoietic stem cell transplant (HSCT). Poster presented at: European Hematology Association (EHA), June 9–17, 2021. Virtual congress. https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.7017. **5.** Merck Manual, Professional Version. Blood tests: normal values. https://www.merckmanuals.com/professional/resources/normal-laboratory-values/blood-tests-normal-values. Accessed November 22, 2022. **6.** McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Ann Intern Med.* 1993;118(4):255-267. **7.** Defitelio [package insert]. Palo Alto, CA: Jazz Pharmaceuticals. **8.** Carreras E. Early complications after HSCT. In: Apperley J, Carreras E, Gluckman E, et al, eds. *The EBMT Handbook.* 6th ed. Paris, France: European School of Haematology; 2012:176-195. **9.** Jones RJ, Lee KS, Beschorner WE, et al. Venoocclusive disease of the liver following bone marrow transplantation. *Transplantation.* 1987;44(6):778-783. **10.** McDonald GB, Sharma P, Matthews DE, et al. Venoocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. *Hepatology.* 1984;4(1):116-122. **11.** Kernan NA, Grupp S, Smith AR, et al. Final results from a defibrotide treatment-IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome. *Br J Haematol.* 2018;181(6):816-827. **12.** Data on file. DEF-2018-022. Palo Alto, CA: Jazz Pharmaceuticals. **13.** Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood.* 2016;127(13):1656-1665. **14.** Richardson PG, Soiffer RJ, Antin JH. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. *Biol Blood Marrow Transplant.* 2010;16(7):1005-1017.

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