Manifestations and Management of Veno-occlusive Disease/Sinusoidal Obstruction Syndrome in the Era of Contemporary Therapies

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Abstract: The concept of veno-occlusive disease (VOD), along with our understanding of it, has historically been and remains an evolving phenomenon. This review presents a broad view of VOD, also known as sinusoidal obstruction syndrome (SOS), including (1) traditional hematopoietic stem cell transplant–associated VOD/SOS, (2) late-onset VOD/SOS, (3) pulmonary VOD, and (4) VOD/SOS associated with chemotherapy only. Several VOD/SOS management modalities exist that include modes for both prophylaxis and treatment. An extensive review of the literature on monoclonal antibodies, both approved and pending approval by the US Food and Drug Administration, reveals that only a few have been associated with an increased risk for VOD/SOS. In fact, bevacizumab appears to have a protective effect against the development of VOD/SOS. As the landscape of cancer treatment changes, careful attention needs to be focused on how new therapies affect the incidence of VOD/SOS.

Keywords
Monoclonal antibody, sinusoidal obstruction syndrome, veno-occlusive disease

Introduction

Published reports of veno-occlusive disease (VOD), also widely referred to as sinusoidal obstruction syndrome (SOS), first appeared in the early 1900s. These early cases occurred in toddlers who ingested herbal infusions, especially those made with *Senecio* or *Crotalaria*.[1,2] VOD/SOS remains a cause of morbidity and mortality today, but most cases result from cytotoxic chemotherapy or high-dose radiation, especially in patients who receive a hematopoietic stem cell transplant (HSCT).[3-10] VOD/SOS affects an estimated 0% to 77% of patients receiving HSCT, and the average mortality rate for severe cases is 84.3%.[11] Our understanding of VOD/SOS has historically been an evolving phenomenon, and currently, with the development of newer treatment modalities, such as monoclonal antibody (mAb) therapy, special attention and recognition need to be paid to the potential for emerging associations with VOD/SOS.

Clinical Presentation and Diagnosis

VOD/SOS may have a classic presentation, or the onset may be later. The pulmonary form of VOD develops in some patients, and in some, the disease develops in the absence of HSCT.

Classic Presentation

Classic signs and symptoms of VOD/SOS include ascites and painful hepatomegaly. Severe disease can lead to hepatic, respiratory, and renal failure, and the incidence of mortality secondary to multiple-organ failure (MOF) is high. VOD/SOS is a well-recognized complication of HSCT; however, although reports vary, the incidence appears to be decreasing over time.[11,12] This decrease is likely due to increased early recognition, along with the increasing use of reduced-intensity conditioning regimens.[13]

Traditionally, VOD/SOS was described as a clinical entity affecting the hepatic sinusoids that occurred within 21 days following HSCT, and it was diagnosed with either the Baltimore or the Seattle criteria (Table 1). However, with the evolution of conditioning regimens, chemotherapies, and novel immunotherapies, along with expanding knowledge in the field of HSCT, we have discovered that VOD/SOS is not always restricted to the first 21 days after HSCT and may also occur in the non-HSCT setting. Furthermore, it can occur without hyperbilirubinemia, which is a component of both the Seattle and the Baltimore criteria for VOD/SOS. Pulmonary VOD (PVOD) as a clinical entity is even more poorly understood than hepatic VOD/SOS.

Late-Onset Disease

Carreras and colleagues published an analysis of 739 patients undergoing autologous HSCT for multiple myeloma, in which VOD/SOS developed in 8% of patients receiving busulfan with melphalan for conditioning. Of note, the median time between HSCT and diagnosis was 29 days, with a range of 3 to 57 days.[14] The European Society for Blood and Marrow Transplantation (EBMT) recently published revised criteria for VOD/SOS in adults to provide an accurate diagnosis and the timely initiation of targeted VOD/SOS therapies. The EBMT criteria for late-onset SOS/VOD (Table 1) were developed following reports that 15% to 20% of cases were occurring more than 21 days after HSCT. Of note, EBMT also proposed new criteria for grading the severity of VOD/SOS in adults, classifying cases as mild, moderate, severe, and very severe. These classifications are designed to guide therapeutic interventions, especially for patients with severe or very severe disease.[15] It is important to recognize that VOD/SOS also can occur in the absence of elevated bilirubin, especially in the pediatric population. Myers and colleagues reported that 29% of their patients with VOD/SOS did not have hyperbilirubinemia at diagnosis.[16]

Non-HSCT Disease

VOD/SOS in oncology patients was initially described in 2 patients with leukemia who were receiving 6-thioguanine,[3] so it has long been known to occur outside the HSCT setting. It has been described in patients receiving chemotherapy and immunosuppression without HSCT, especially following the use of 6-thioguanine, actinomycin D, azathioprine, dacarbazine, inotuzumab ozogamicin (INO), gemtuzumab ozogamicin (GO), oxaliplatin, vincristine, or radiation, with less reported incidence following carmustine, cisplatin, irinotecan, bleomycin, cyclophosphamide, and vincristine.[17-25]

Pulmonary VOD

Several emerging reports describe PVOD, which is poorly understood and difficult to diagnose. PVOD occurs in a wide variety of patients and has been reported in association with pre-existing exposure to chemotherapy, especially to bleomycin, cisplatin, carmustine, cyclophosphamide, and mitomycin.[26] It also has been reported following autologous HSCT and allogeneic HSCT (allo-HSCT).[27-30] The main feature that PVOD shares with VOD/SOS is vascular and endothelial damage. PVOD affects small pulmonary veins and venules, causing post-capillary pulmonary venular obstruction and pulmonary vascular congestion. These may lead to clinical manifestations such as exercise intolerance, hypoxemia, pulmonary hypertension, and right-sided heart failure.[28,31] Although the pathogenesis is similar in the 2 conditions, PVOD is distinct from hepatic VOD/SOS. PVOD is likely underdiagnosed and remains very challenging to treat.

Troussard and colleagues were the first ones to report on HSCT-associated PVOD, which developed in a 7-year-old patient on day 44 after sibling donor HSCT for acute lymphoblastic leukemia (ALL).[32] Since then, multiple cases of PVOD in HSCT recipients have been reported. In a review by Bunte and colleagues, the time of onset following HSCT ranged from 6 to 343 days after transplant, with very high mortality rates.[28]

Although the etiology remains unknown, the manifestations, diagnostic characteristics, and inciting factors of PVOD have been described (Table 1). Definitive diagnosis requires lung biopsy, but other noninvasive diagnostic modalities may helpful, such as high-resolution computed tomography (CT), arterial blood gas measurement, pulmonary function tests, and bronchoalveolar lavage. Resten and colleagues reviewed high-resolution CT scans of the chest obtained from 15 patients who had pathologically confirmed PVOD and compared them with scans from patients who had primary pulmonary hypertension. Key characteristic findings for patients with PVOD on CT scan were ground-glass opacities, thickened interlobular septa, and mediastinal adenopathy.[33] Although pulmonary function tests report a variety of findings, the most characteristic finding is a diffusing capacity of the lung for carbon monoxide (DLCO) of less than 55%.[34]

Table 1. Comprehensive Overview of VOD/SOS

	Acute	Late-Onset	Non–HSCT-Associated	Pulmonary
Manifestations	Painful hepatomegaly Ascites Hyperbilirubinemia Edema	Same as acute	Same as acute	Pulmonary hypertension Dyspnea Hypoxemia Exercise intolerance Pulmonary infiltrates Pulmonary hemorrhage Right-sided heart failure
Diagnosis	Modified Seattle criteria[83,84] *≥2 of the following within 20 days of HSCT:* - Bilirubin ≥2 mg/dL - Painful hepatomegaly - Weight gain >2% OR Baltimore criteria[10] *Bilirubin ≥2 mg/dL within 21 days of HSCT and ≥2 of the following:* - Hepatomegaly - Weight gain >5% - Ascites OR Histologically proven SOS/VOD	Classic VOD/SOS beyond day 21 Histologically proven VOD/SOS ≥2 of the following criteria: - Bilirubin ≥2 mg/dL - Painful hepatomegaly - Weight gain >5% - Ascites AND Hemodynamic and/or ultrasound evidence[15]	Histologically proven VOD/SOS Clinical suspicion in patient with history of recent exposure to inciting factor	Lung biopsy (fibrous intimal proliferation of pulmonary venules and small veins) Chest CT (septal lines, ground-glass opacities, enlarged nodes) PFT (decreased DLCO) ABG (lower Pao_2) BAL (hemorrhage)
Inciting factors	Previous liver disease Second allo-HSCT Sirolimus Busulfan/total-body irradiation Gemtuzumab ozogamicin Inotuzumab ozogamicin Concomitant hepatotoxic drug exposure (azoles) Radiation exposure Iron overload Myeloablative→reduced-intensity conditioning Allo-HSCT→auto-HSCT Osteopetrosis/neuroblastoma Hemophagocytic lymphohistiocytosis[37,52,85]	No factors unique to late-onset VOD/SOS identified	Actinomycin D Azathioprine Bleomycin Carmustine Cisplatin Cyclophosphamide Dacarbazine Gemtuzumab ozogamicin Inotuzumab ozogamicin Irinotecan Oxaliplatin Procarbazine 6-Thioguanine Vincristine[17-24,26,86-88]	Autoimmune disorders Chemotherapy[a] Genetic predisposition HIV HSCT[a] Pulmonary Langerhans cell histiocytosis Radiation therapy Sarcoidosis Solid-organ transplant Tobacco exposure[35,89]

[a] highest incidence occurs with chemotherapy exposure and prior to HSCT.

→, followed by; ABG, arterial blood gas; allo-HSCT, allogeneic HSCT; auto-HSCT, autologous HSCT; BAL, bronchoalveolar lavage; CT, computed tomography; DLCO, diffusing capacity of lungs for carbon monoxide; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; PFT, pulmonary function test; SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease.

Owing to the rarity of this diagnosis, no trials targeting treatment for PVOD have been conducted. Instead, treatment recommendations have been based on expert consensus. General recommendations include limiting physical activity and avoiding medications that may aggravate pulmonary hypertension. First-line therapy includes supplemental oxygen for hypoxemia, warfarin anticoagulation, and diuretics to prevent right ventricular overload. Additional therapies for pulmonary hypertension, such as endothelin receptor antagonists, phosphodiesterase inhibitors, or prostacyclins, can be considered. Pulmonary vasodilators can be very harmful, causing or exacerbating severe pulmonary edema in patients with PVOD. Although these agents may be needed as a bridge to lung transplant, they must be used with extreme caution. Despite all potential supportive therapies, PVOD remains incurable without a lung transplant.[35]

Risk Factors in the Era of Contemporary Therapies

Multiple risk factors for VOD/SOS in the HSCT setting have been identified; these include patient, disease, and transplant characteristics.[14] However, the therapeutic landscape for malignancies continues to broaden, and additional risk factors—such as the use of targeted therapies—have been introduced and continue to be established. Here we discuss the implications of these therapies with regard to the incidence of VOD/SOS.

mAbs have been incorporated into both frontline and salvage chemotherapy regimens for a multitude of malignancies.[36] Recent advances in the use of mAbs, such as administering them in combination with bispecific T-cell engagers (BiTEs) or in conjugation with cytotoxic drugs (antibody-drug conjugates), have improved our ability to target specific tumor antigens and augment anticancer activity. Clinical data show that these modifications yield promising outcomes compared with the outcomes of conventional chemotherapy in the setting of relapsed or refractory Hodgkin lymphoma and B-cell ALL. The improved outcomes translate to higher eligibility rates for HSCT, the only known curative option in this setting.[25,37-39]

Although targeted therapies inherently minimize systemic toxicities, each mAb has its own side-effect profile, which can be amplified when the agent is linked to a cytotoxic drug. This has proved true for 2 antibody-drug conjugates known for their role in acute leukemia: GO and INO. Both have been associated with an increased incidence of VOD/SOS in HSCT and non-HSCT settings.

Gemtuzumab Ozogamicin

GO is a humanized anti-CD33 mAb that is conjugated to calicheamicin, a potent cytotoxic compound derived from *Micromonospora echinospora*. The US Food and Drug Administration granted an accelerated approval to GO in 2000 for the treatment of patients with CD33-positive acute myeloid leukemia (AML) who were older than 60 years; however, commercial marketing was discontinued in 2010 owing to concerns over efficacy and hepatotoxicity. Still, GO remains available for investigational use.[40] In phase 2 trials, grade 3/4 hyperbilirubinemia occurred in 23% of patients. VOD/SOS was reported in 11% of patients who underwent HSCT, with no cases diagnosed outside the HSCT setting.[41] In postmarketing data, the incidence of VOD/SOS and fatal hepatotoxicity increased in various settings (GO before HSCT, GO after HSCT, and GO without HSCT.) We report below on the literature.

Wadleigh and colleagues reported on 62 patients with previously treated AML/myelodysplastic syndrome, 14 of whom received GO prior to HSCT in which a cyclophosphamide-based conditioning regimen was used. Rates of VOD/SOS were significantly higher in the patients who received GO (64% vs 8%; $P<.001$) than in those without GO exposure prior to HSCT.[42] A retrospective review of 23 patients who were treated with GO for relapsed AML after HSCT noted that VOD/SOS was diagnosed in 35% of the patients. Clinical manifestations typically occurred 7 to 10 days after the administration of GO, with peak elevations in hepatic function tests occurring 8 to 22 days after infusion. A trend toward a dose-dependent effect on the incidence of VOD/SOS was observed but was not statistically significant.[43] The overall rate of VOD/SOS that Tallman and colleagues observed in a prospective observational review was 9.1% (Table 2), which corresponded to a 2.7% risk for death. In patients who had received prior HSCT, the incidence of VOD/SOS was 27%.[44] An analysis of pooled data on patients (older than 18 years) in a first recurrence of AML who were treated with GO showed comparable results. HSCT affected the rates of VOD/SOS as follows: prior HSCT, 19%; subsequent HSCT, 17%; no HSCT, 0.9%. Still, VOD/SOS has been described in patients who received GO with no prior cytotoxic therapy.[45]

Inotuzumab Ozogamicin

INO, a humanized anti-CD22 mAb bound to calicheamicin, currently is being evaluated for the treatment of refractory Hodgkin lymphoma and B-cell ALL. A dose-finding study in patients with B-cell non-Hodgkin lymphoma who had not received prior allo-HSCT did not find INO to be well correlated with the incidence of VOD/SOS, even when more than the maximum tolerated dose of 1.8 mg/m^2 was given. Nonetheless, VOD/SOS was diagnosed in 1 patient. It is noteworthy that

Table 2. Monoclonal Antibodies Associated With VOD/SOS

Author	Incidence of VOD/SOS, N (%)	Median Time to Onset of VOD/SOS (Range), d	Median Time Between mAb and HSCT (Range)
Gemtuzumab ozogamicin			
Giles et al, 2001[45]	GO: 14 (12)	NR	NA
Larson et al, 2005[90]	HSCT→GO: 5 (19) GO→HSCT: 8 (17) GO: 2 (0.9)	NR NR NR	11.7 mo (4.3-112.4) NR NA
Rajvanshi et al, 2002[43]	HSCT→GO: 8 (35)	NR	131 d (17-967)
Tallman et al, 2013[44]	Overall: 44 (9.1) HSCT→GO: 12 (15.8)	NR	NR
Wadleigh et al, 2003[42]	HSCT: 4 (8) GO→HSCT: 9 (64)	22 (10-27) 13 (7-21)	NR 2.3 mo (0.7-3.5)
Inotuzumab ozogamicin			
Advani et al, 2010[38]	HSCT→INO: 1 (1.3)	NR	NA
Kantarjian et al, 2012[91]	INO→HSCT: 5 (23)	NR	6 wk (4-14)
Kantarjian et al, 2013[39]	INO→HSCT: 6 (16.7)	NR	NR
Kantarjian et al, 2016[25]	CC→HSCT: 1 (5) INO→HSCT: 10 (20.8) HSCT→INO: 2 (11.8) INO: 3 (4.9)	16 (3-39)	NR NR NR NA
Kebriaei et al, 2013[37]	INO→HSCT: 5 (19.2)	23 (3-55)	40 d[a] (NR)

[a] Median days between mAb and start of HSCT preparative regimen.

→, followed by; CC, conventional chemotherapy; d, days; GO, gemtuzumab ozogamicin; HSCT, hematopoietic stem cell transplant; INO, inotuzumab ozogamicin; mAb, monoclonal antibody; mo, months; NA, not applicable; NR, not reported; VOD, veno-occlusive disease; wk, weeks.

this patient had previously undergone autologous HSCT and radiotherapy to the liver.[38] Despite cases of hyperbilirubinemia and transaminitis, Ogura and colleagues did not report any cases of VOD/SOS when INO was given in combination with conventional chemotherapy for non-Hodgkin lymphoma.[46] Data from the acute leukemia setting suggested that with regard to toxicity, including liver function abnormalities, weekly doses (0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on days 8 and 15) were more favorable than single doses (1.8 mg/m^2) administered every 3 to 4 weeks. Patients who proceeded to HSCT did so 2 to 14 weeks after their last dose of INO. VOD/SOS was observed in 17% of patients, all of whom had undergone HSCT (Table 2). In this small subset of patients, a dual alkylator preparative regimen was associated with an increased incidence of VOD/SOS (38% vs 5%; *P*=.02).[39] Similar rates of VOD/SOS (19%) occurred 3 to 55 days after HSCT in patients who received prior therapy with INO (Table 2).[37] A phase 3 trial recently confirmed an increased risk for VOD/SOS after INO compared with conventional chemotherapy, particularly in patients who received INO before conditioning chemotherapy for HSCT (21% vs 5%); however, VOD/SOS during INO therapy occurred even outside the HSCT setting (Table 2).[25]

Several hypotheses for the cause of hepatotoxicity associated with GO and INO have been proposed. Possibilities include endocytosis via mannose receptors on sinusoidal epithelial cells and the existence of CD33-positive cells in the hepatic sinusoids.[43,47]

Bevacizumab

Results of studies on the effect of bevacizumab (Avastin, Genentech) on VOD/SOS are discordant. Agarwal and colleagues suggest a causal relationship between VOD/SOS and bevacizumab.[48] Conversely, reduced rates and severity of VOD/SOS, potentially owing to the inhibition of von Willebrand factor–rich platelet thrombus formation, have been noted in patients with metastatic colorectal cancer.[49-51]

Sirolimus

Although sirolimus is not a novel agent, it has been associated with hepatic VOD/SOS in patients who have had HSCT. Following conditioning based on cyclophosphamide and total-body irradiation (TBI), patients

who received sirolimus in combination with tacrolimus and methotrexate experienced significantly higher rates of VOD/SOS compared with patients who received a graft-versus-host disease (GVHD) regimen of tacrolimus/methotrexate or tacrolimus/sirolimus (21% vs 7% vs 11%).[52] A phase 1/2 study in pediatric patients noted an 11% incidence of VOD/SOS following HSCT with cyclophosphamide/TBI-based conditioning. The investigators noted potentially increased toxicity when sirolimus was initiated before transplant and given concurrently with cyclophosphamide. Subsequently, in a phase 3 trial, the addition of sirolimus to tacrolimus/methotrexate in pediatric patients undergoing HSCT with cyclophosphamide/TBI-based conditioning resulted in a nonstatistically significant increase in the incidence of VOD/SOS (21% vs 9%; *P*=.06).[53,54] Although limited data are available suggesting that this finding may correlate with higher sirolimus levels,[55] a potential association between sirolimus and VOD/SOS needs to be further explored and understood.

Management of VOD/SOS

General Supportive Care

The most critical steps in the management of VOD/SOS are careful risk assessment for the development of VOD/SOS and early identification to allow early intervention. Risk factors for VOD/SOS are summarized in Table 1, and preventive measures should be taken in high-risk patients. General supportive measures to minimize further exacerbation of the VOD/SOS state include minimizing fluid overload, closely monitoring weight, and minimizing extracellular fluid while maintaining intravascular fluid volume so that the kidneys maintain adequate perfusion. The use of colloids, such as albumin or red cells, sometimes is effective in this setting.[56,57] Additionally, if symptomatic ascites develops and the patient requires paracentesis, small-volume taps of up to 1 L per day in adults should be used to avoid decreased renal perfusion and hepatorenal syndrome. Finally, in patients with severe VOD/SOS and MOF, monitoring in the intensive care unit and hemodialysis may become necessary. Varieties of agents have been used for the prevention and treatment of VOD/SOS, mainly in the setting of HSCT; these are reviewed in the next sections.

Prevention

Ursodeoxycholic acid, also known as ursodiol, is a hydrophilic bile acid that has been used for the prophylaxis and treatment of a variety of hepatic conditions, including VOD/SOS. It has been tested in prospective randomized trials, with mixed results. Daily doses ranging from a flat 600 mg to 12 mg/kg for up to 90 days after transplant have been studied. In 2 randomized prospective studies, a significant reduction in the incidence of VOD/SOS was noted, but no difference in survival.[58,59] However, the largest randomized study, by Ruutu and colleagues, failed to show a reduction in VOD/SOS incidence, but it notably showed a significant reduction in grades 3 and 4 acute hepatic GVHD and significantly better 1-year survival in the ursodiol-treated group (71% vs 55%; *P*=.02).[60] A systematic review of pooled randomized studies comparing ursodiol with no treatment showed a significant reduction in the rates of VOD/SOS (relative risk [RR], 0.34; 95% CI, 0.17-0.66).[61] Therefore, ursodiol is generally recommended as a prophylactic agent for VOD/SOS and is listed in the transplant guidelines published by the British Society of Blood and Marrow Transplantation (BSBMT)[62] and the EBMT.[15]

Both unfractionated heparin and low-molecular-weight heparin have been studied in VOD/SOS prophylaxis. Prospective studies in children and adults showed mixed results,[62] but a systematic review and meta-analysis of 12 studies in which unfractionated heparin and low-molecular-weight heparin were used for prophylaxis of VOD/SOS showed that anticoagulation did not significantly reduce the risk for VOD/SOS (RR, 0.90; 95% CI, 0.62-1.29).[63]

Antithrombin (AT) has a protective effect on the vascular endothelium, and levels are low in VOD/SOS. Therefore, AT has been tested in a number of trials. It may be beneficial very early in the course of VOD/SOS, but it is contraindicated for the treatment of severe VOD/SOS with MOF owing to the risk for hemorrhage.[62] In a retrospective study of 48 patients with VOD/SOS who received early treatment with AT, the overall 100-day mortality was 17%, much lower than would be expected without AT.[64] Haussmann and colleagues reported on a prospective study testing AT doses of 50 to 100 U/kg in children who had AT levels of 70% or less. When VOD/SOS incidence was compared with that in historical controls, no difference was noted between the 2 groups.[65]

Defibrotide (Defitelio, Jazz Pharmaceuticals) is a sodium salt of complex single-stranded oligodeoxyribonucleotides derived from porcine intestinal mucosa DNA.[66,67] Its mechanism of action is not completely defined, but it is believed to play a role in endothelial protection and restoration of the thrombotic-fibrinolytic balance. It has not been associated with an increased risk for bleeding despite reducing procoagulant activity, increasing fibrinolysis, and modulating platelet activity.[68,69] Although it is the only agent approved for the treatment of VOD/SOS, it is not licensed for use in prevention. However, results in retrospective and prospective studies are encouraging. Chalandon and colleagues reported on 52 patients with a

median age of 36.5 years (range, 5-60 years) who received a daily dose of defibrotide of 10 to 25 mg/kg from the day before myeloablative conditioning until 20 days after allo-HSCT.[70] All patients also received unfractionated heparin. There were no cases of VOD/SOS in the treatment group vs 10 of the 52 patients in the control group; event-free survival also was higher in the treatment group (P=.02).[70] Cappelli and colleagues reported on a series of 63 children who underwent allo-HSCT for β-thalassemia and were considered to be at very high risk for the development of VOD/SOS.[71] Defibrotide at a daily dose of 40 mg/kg was administered orally starting on the day of the conditioning regimen. In the absence of VOD/SOS, defibrotide was tapered on day 30 and discontinued by day 45 after HSCT. VOD/SOS developed in 1 patient, and this patient had stopped defibrotide early owing to concerns about bleeding.[71] Similarly, Corbacioglu and colleagues reported a low VOD/SOS rate in a series of 9 children who were undergoing allo-HSCT for osteopetrosis and were considered to be at very high risk for VOS/SOS compared with historical controls (1 of 9 in the defibrotide group vs 7 of 11 in the control group).[72] Based on these encouraging results in children, a phase 3 randomized controlled trial was conducted in 356 children who underwent autologous or allo-HSCT with myeloablative conditioning. Patients had 1 or more risk factors for VOD/SOS. The treatment group received defibrotide intravenously at a dose of 6.25 mg/kg every 6 hours from the start of HSCT conditioning to day 30 following HSCT. VOD/SOS developed in 12% of the treatment group vs 20% in control group (P=.05).[73] Notably, the incidence of acute GVHD also was significantly lower in the treatment group (P=.0046), perhaps owing to the anti-inflammatory effects of defibrotide on the endothelial cells of the skin, gastrointestinal tract, and liver.[73] A multicenter, prospective study that includes children and adults is ongoing, and results are eagerly awaited. Defibrotide is recommended for prophylaxis in children and adults with high-risk factors by the BSBMT guidelines.[62]

Treatment

With the recent availability of an effective therapeutic agent for VOD/SOS—namely, defibrotide—the diagnosis and initiation of therapy are being re-examined. A recent position paper from the ESBMT recommends using revised diagnostic criteria and new criteria for grading the severity of VOD/SOS in adults.[15] In general, 75% to 80% of cases of VOD/SOS are reversible with supportive measures only.[57] Therefore, mild VOD/SOS does not require therapeutic intervention. However, therapy should be initiated immediately in severe or very severe VOD/SOS. Patients with moderate disease require close monitoring because VOD/SOS is a dynamic process, and therapy may be warranted. The decision to treat should be guided clinically and should not be based on the initial etiology and inciting factors.

Defibrotide is the only approved agent for the treatment of VOD/SOS in children and adults. In the pivotal phase 3 study, 102 adult and pediatric patients in whom VOD/SOS and MOF had been diagnosed according to the Baltimore criteria were treated daily with defibrotide at a dose of 25 mg/kg for a minimum of 21 days.[74] The primary endpoint of the study was survival at 100 days after HSCT, and observed rates were 38% in the defibrotide group and 25% in the historical controls (P=.01). Observed complete response rates on day 100 were 25.5% for treated patients vs 12.5% for historical controls (P=.016).[74] The control group consisted of 32 rigorously selected, similar patients. Owing to the promising activity of defibrotide noted in prior, smaller series,[75,76] it was felt to be unethical to deprive patients of the drug. Data from the defibrotide international compassionate use program were recently published and provide further important insights.[77] Between 1998 and 2009, 1129 patients in whom HSCT-associated or chemotherapy-associated VOD/SOS had been diagnosed by the Baltimore or modified Seattle criteria received defibrotide on a compassionate basis, and data were collected from 710 patients. Patients with a median age of 25 years (range, 0.2-70 years) received a median daily dose of defibrotide of 25 mg/kg (range, 10-80 mg/kg) for a median of 15 days (range, 1-119 days). Survival at 100 days after HSCT for the entire group was 54%. Survival by dose ranged from 43% to 61%; survival for the recommended dose of 25 mg/kg per day was 58%. Additionally, survival was better for children (65%) vs adults (46%), absence of MOF (65%) vs presence of MOF (40%), and nonsevere disease (67%) vs severe disease (44%),[77] with severity defined by the criteria of Bearman and colleagues.[78]

A variety of other agents, including tissue plasminogen activator (tPA)[79] and high-dose corticosteroids, were tried before the availability of defibrotide. tPA is not recommended owing to the high risk for bleeding, but high-dose corticosteroids, especially if initiated early, have shown compelling results. Methylprednisolone at 0.5 mg/kg twice daily for 14 doses was administered to 48 patients with a diagnosis of VOD/SOS by the Seattle criteria; MOF was present in 31% of the patients. The response rate was 63%, with 58% alive at 100 days after HSCT.[80] In another study, Myers and colleagues treated 9 children with methylprednisolone at 500 mg/m^2 twice daily for 6 doses and reported responses in 6 of the 9 children.[81] Therefore, high-dose methylprednisolone is listed as a therapeutic agent, with a recommendation category of 2C in the BSBMT guidelines.[62]

Conclusions

VOD/SOS is an important cause of morbidity and mortality, especially in HSCT recipients. It includes acute disease and the less-recognized phenomena of non–HSCT-related disease, pulmonary disease, and late disease. The management of VOD/SOS involves both treatment and potential prevention.

Disease-specific mAb therapy has brought significant advances to cancer treatment, but it also has affected the incidence of VOD/SOS. Of these mAb agents, 3 have been linked to an increased incidence of the condition, whereas bevacizumab may have a protective effect against VOD/SOS. The risk for VOD/SOS is greatest when GO or INO is used before or following HSCT. The toxicity associated with GO and INO is likely a result of the hepatic uptake of the antitumor agent calicheamicin, not of the mAb itself.[82] Providers should conduct meticulous risk assessments and thorough examinations of the patients receiving these agents, especially as part of investigative combination chemotherapy regimens.

Information regarding VOD/SOS has evolved significantly over the last several decades, as have our current treatment modalities. Careful attention needs to be focused on the potential positive and negative effects of the changing treatment landscape for cancer, including the incidence of VOD/SOS in high-risk patients.

Disclosures

The authors have no relevant financial disclosures.

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