Published in final edited form as:

Leuk Lymphoma. 2012 August ; 53(8): 1552–1557. doi:10.3109/10428194.2012.661052.

Clinicopathologic Features of Late Onset Veno-Occlusive Disease/Sinusoidal Obstructive Syndrome After High Dose Busulfan and Hematopoietic Cell Transplantation

Rish K. Pai, M.D.¹, Koen van Besien, M.D.², John Hart, M.D.³, Andrew S. Artz, M.D.², and Peter H. O'Donnell, M.D.^{2,4}

¹Department of Anatomic Pathology, Cleveland Clinic, Cleveland, OH

²Section of Hematology Oncology, Department of Medicine, The University of Chicago, Chicago, IL

³Department of Pathology, The University of Chicago, Chicago, IL

⁴Committee on Clinical Pharmacology and Pharmacogenomics, The University of Chicago, Chicago, IL

Abstract

Most cases of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) occur <21 days after allogeneic hematopoietic stem cell transplantation (HCT). Rarely, however, VOD/SOS can occur later, and can be confused with other causes. We report the clinicopathologic features of 8 patients with advanced hematologic malignancies developing VOD/SOS >30 days after dose-escalated busulfan/fludarabine/alemtuzumab and HCT. Median time to diagnosis=52 days (range: 33–77). For 7 patients, VOD/SOS was confirmed by liver biopsies showing classical features including reticulin deposition within sinusoids, central vein occlusions, hepatocyte atrophy/necrosis, sinusoidal/perivenular hemorrhage, and sparing of portal tracts. VOD/SOS risk was directly related to higher busulfan plasma exposures. Two patients died from VOD/SOS, and in another two patients VOD/SOS was contributory to death. Late-onset VOD/SOS may be underrecognized and should be considered in the differential diagnosis of patients undergoing HCT, particularly after high dose busulfan. Liver biopsy should be entertained even late in the course if appropriate signs/symptoms exist.

Keywords

veno-occlusive disease; sinusoidal obstruction syndrome; stem cell transplantation; late-onset; busulfan

INTRODUCTION

Hepatic veno-occlusive disease (VOD) was first described in 1920 in South Africans who ingested pyrrolizidine alkaloids contained in Senecio tea [1]. Ingestion of this tea resulted in occlusion of the terminal hepatic venules resulting in “senecio cirrhosis”. A similar disease was noted in Jamaica after ingestion of Jamaican bush tea [2, 3]. In the developed world the overwhelming number of cases of veno-occlusive disease occur after allogeneic stem cell transplantation [4, 5]. Current work suggests that the primary insult is actually to the sinusoidal lining cells rather than the terminal hepatic venules which has led to the term sinusoidal obstruction syndrome (SOS) [6]. While VOD/SOS is commonly related to allogeneic hematopoietic stem cell transplantation (HCT), cases of this entity have been reported with chemotherapeutic agents and immunosuppressive medications outside of the stem cell transplant setting [7–9].

The incidence of VOD/SOS after HCT varies considerably across studies with ranges between 5% and 60% reported in the literature [4, 10–13]. This marked variability is most likely a result of differences in clinical reporting of mild cases and in diagnostic criteria. VOD/SOS is clinically characterized by weight gain, ascites, hepatomegaly and jaundice occurring within the first 30 days after HCT. While there are several entities that can give rise ascites, jaundice and weight gain and potentially mimic VOD/SOS, many of these entities can be excluded given the strong temporal association of VOD/SOS occurring shortly after HCT and its association with certain conditioning agents such as busulfan and total body irradiation [14–18].

Reports of VOD/SOS occurring >21 days after transplant are rare [14, 19–21], but the diagnosis may be underrecognized. Late diagnosis, especially, can be confused with other causes of liver dysfunction such as acute graft versus host disease (GVHD), viral hepatitis, drug-induced liver disease, sepsis, or other causes. We report the clinicopathologic features of 8 patients with advanced hematologic malignancies developing late-onset VOD/SOS, all >30 days after HCT.

MATERIALS AND METHODS

All patients provided written informed consent to participate in a previously-described 36-patient phase I study of dose-escalated intravenous busulfan along with fludarabine/alemtuzumab as conditioning chemotherapy prior to HCT [22]. The eight cases observed within this study were retrieved from the surgical and autopsy pathology files at the University of Chicago. In the four patients where the pathology was obtained from liver biopsy, a transjugular approach by an interventional radiologist was used, and none of these patients had biopsy-related complications. A chart review was performed to obtain pertinent clinical information including type of hematologic malignancy, GVHD prophylaxis, liver function tests, and imaging studies. All H&E slides as well as reticulin and trichrome stains were reviewed by two hepatopathologists (R.K.P. and J.H.).

RESULTS

None of the 8 patients developing VOD/SOS during this 36-patient phase I study exhibited early-onset (standard) VOD/SOS. All were late-onset occurrences. The clinicopathologic features of the 8 patients are summarized in Table I.

Case 1 (Patient #7)

61 year-old male with chronic myelogenous leukemia (CML) receiving matched, sibling transplant. He presented on day +48 with weight gain, right upper quadrant abdominal pain, and hyperbilirubinemia. Ultrasound showed ascites and hepatomegaly. He was treated with supportive care for a clinical diagnosis of VOD/SOS and improved, but died at day +172 from CMV pneumonia.

Case 2 (Patient #12)

58 year-old male with a history of regular alcohol consumption and acute myeloid leukemia (AML) diagnosed 4 months prior to matched, related-donor transplant. He presented at day +60 with nausea/vomiting, jaundice, and abdominal distension. Liver biopsy was performed (Figure 1A, 1B). The patient's condition deteriorated despite steroids and he died with sepsis on day +85.

Case 3 (Patient #14)

49 year-old female with relapsed Philadelphia chromosome-positive acute lymphoblastic leukemia undergoing matched, related-donor transplant. At day +56, she presented with abdominal pain. Liver biopsy showed marked centrilobular congestion and focal hepatocyte necrosis, with complete occlusion of most central veins by reticulin. She was treated with supportive care measures but died on day +69 from VOD/SOS complications including pulmonary hemorrhage.

Case 4 (Patient #19)

61 year-old male with myelodysplastic syndrome with refractory cytopenia and multi-lineage dysplasia undergoing matched, unrelated-donor transplant. He developed ataxia/lethargy on day +33. Liver biopsy showed hepatocyte necrosis, hemorrhage, and extensive mild reticulin deposition within the sinusoids and central veins. Defibrotide was given, with temporary improvement. However, he had persistent portal hypertension and died on day +909 with liver failure and post-transplant lymphoproliferative disease involving the liver.

Case 5 (Patient #31)

41 year-old male with chronic lymphocytic leukemia diagnosed 3 years prior who underwent syngeneic transplant. On day +69, he presented with abdominal pain/distension. Liver biopsy was performed (Figure 1C, 1D). VOD/SOS completely resolved with supportive care. The patient experienced disease relapse at day +717, but remains currently alive at day +1186 of follow-up.

Case 6 (Patient #33)

51 year-old male with non-Hodgkin lymphoma (NHL) diagnosed 1 year prior who was transplanted (matched, related) with refractory disease. He developed fever and nausea/vomiting on day +37. Total bilirubin reached a maximum of 22.9 mg/dL. Defibrotide was started however the patient deteriorated and died on day +45. At autopsy, liver examination revealed bridging necrosis and hemorrhage, unremarkable bile ducts, no evidence of GVHD, but mild reticulin fiber deposition within centrilobular sinusoids and central veins. Microscopic deposits of residual lymphoma were scattered throughout the parenchyma.

Case 7 (Patient #35)

54 year-old male with follicular NHL diagnosed 2 years prior who proceeded to matched, related-donor transplant. He presented at day +77 with increasing abdominal girth and pain, edema, weight gain, and jaundice. Liver biopsy was remarkable for prominent reticulin deposition in centrilobular sinusoids and narrowing of the central veins by reticulin. Supportive measures including diuresis were used, and VOD/SOS resolved. Although NHL recurred at day +259, the patient is currently alive (+1057 days post-transplant).

Case 8 (Patient #36)

57 year-old male with refractory AML and a history of heavy alcohol use who was previously treated with allogeneic transplant 11 months prior (fludarabine/melphalan/alemtuzumab) but developed recurrent disease and proceeded to second matched, unrelated-donor transplant. New lower extremity edema developed on day +37. The patient developed worsening mental status, bacteremia, and renal failure. Peripheral blood examination showed 23% circulating blasts. Autopsy on day +40 showed 1000mL of ascitic fluid in the abdomen. Microscopic liver sections revealed centrilobular hepatocyte necrosis with prominent hemorrhage, extensive deposition of reticulin within centrilobular sinusoids, and complete occlusion of central veins by reticulin fibers (Figure 1E, 1F).

DISCUSSION

We report here 8 cases of late-onset VOD/SOS, all occurring >30 days after dose-escalated intravenous busulfan and HCT, representing to our knowledge the largest such series. Previously, the two main groups reporting diagnostic criteria for VOD/SOS have required presentation within 21 days of transplant. In the modified Seattle criteria, at least two of the three following features must be present within 20 days post-transplantation: hyperbilirubinemia with serum bilirubin >2 mg/dL, hepatomegaly with right upper quadrant pain, and weight gain >2% from baseline body weight due to fluid [4]. The Baltimore criteria are similar in that a diagnosis of VOD/SOS requires hyperbilirubinemia >2 mg/dL within 21 days after transplant along with at least two of the following: hepatomegaly, weight gain >5%, and ascites [12]. While sharing these clinical features, our cases of VOD/SOS (7 biopsy-confirmed) in contrast all occurred beyond the usual immediate time frame: median time to diagnosis in our series was 52 days (range: 33–77 days). All 8 patients were treated on a 36-patient protocol using dose-escalated intravenous busulfan along with fludarabine/alemtuzumab as conditioning [22], for a VOD/SOS incidence of 22% (all late-onset).

The idea of delayed-onset VOD/SOS with busulfan was perhaps first noted in HCT-treated patients receiving high-dose busulfan, melphalan, and thiotepa [23], wherein the authors observed VOD/SOS occurring significantly later than in patients treated with cyclophosphamide-based regimens. However, the median time of onset in the busulfan group in this study was only day +9. To our knowledge, only one other large series of 21 patients, and three smaller reports describing 11 total patients undergoing HCT and exhibiting true late-onset VOD/SOS have been previously published [14, 19–21]. Carreras et al. [14] reported an 8% incidence of VOD/SOS among 240 multiple myeloma patients receiving busulfan/melphalan for HCT in which the median time to VOD/SOS was 29 days (range: 3 – 57 days), still considerably shorter than observed in our present series. Toh et al. [19] retrospectively reported on four such patients (all of whom were treated with busulfan and cyclophosphamide as their conditioning regimen), but all four manifested VOD/SOS between 24 and 42 days—also not nearly as late as in our series. Another case report more recently described a patient with clinical features of VOD/SOS after treatment with busulfan/melphalan and autologous HCT [20] in which the patient presented with VOD/SOS at day +55, similar to our experience. Finally, an interesting study of everolimus/tacrolimus as GVHD prophylaxis with busulfan/fludarabine also reported late VOD/SOS in 6 patients [21], at a median 32 days post-HCT (range: 10–51 days), although the authors hypothesized that the VOD/SOS risk in this study was perhaps predominantly due to the everolimus/tacrolimus combination. Nevertheless, with our cases added to this body of literature, it appears that the incidence of busulfan-related late-onset VOD/SOS is in the range of 5–25%, and that the diagnosis is probably underrecognized.

While the clinical criteria for recognizing VOD/SOS are essential, a liver biopsy is the definitive method of determining the diagnosis. In the early stages of VOD/SOS, there is sinusoidal congestion and hemorrhage of red blood cells into the space of Disse and around the terminal hepatic veins resulting from injury to the sinusoidal lining cells. This is most prominent in zones 3 and 2. This results in obstruction of the sinusoidal blood flow which can result in sinusoidal dilatation, hepatocyte atrophy and necrosis in severe cases. With time, there is deposition of collagen fibers in the sinusoids and terminal hepatic veins. The fact that the same, classic pathologic features were observed in our patients as in those with typical-onset VOD/SOS cases suggests a common, unifying underlying disease process that was simply of delayed onset in our patients. The most likely cause is that this was due to factors specific to the novel dosing strategy we used.

In our treatment protocol, intravenous busulfan was dose-escalated above standard dose levels based upon real-time pharmacokinetic area under the curve (AUC) monitoring [22]. Risk of VOD/SOS was busulfan AUC-related, with no patients with a measured AUC < 4800 $\mu\text{mol}\cdot\text{min}/\text{L}$ exhibiting VOD/SOS, while 4/9 and 3/7 patients with AUCs between 5800–6800 or > 6800 $\mu\text{mol}\cdot\text{min}/\text{L}$, respectively, developed VOD/SOS [22]. VOD/SOS is a well-known complication of busulfan [15–17], and the unique higher dosing of intravenous busulfan in our study seemed clearly related. Of the eight VOD/SOS patients in our series, six had received prophylactic ursodeoxycholic acid. Clinical risk factors for VOD/SOS (patient age, donor type, human leukocyte antigen mismatch, active disease) were not identified as being associated with VOD/SOS development in our patients. Others have shown that the timing of busulfan administration in relation to other chemotherapeutic

agents like cyclophosphamide may be important in VOD/SOS development [24], and while our protocol employed no cyclophosphamide (nor methotrexate, which is also often implicated in VOD/SOS risk), it may be that the presence (and timing of administration) of another VOD/SOS-related chemotherapy drug in conjunction with busulfan is what poses the greatest risk of precipitating early-onset VOD/SOS, whereas late-onset VOD/SOS may be favored when patients are exposed only to high dose busulfan without other hepatotoxins.

The overall VOD/SOS incidence after HCT may be recently declining, especially with the advent of new prophylactic and treatment therapies [25, 26]. Still, while many cases of VOD/SOS are mild, up to 30% of cases can result in death [4, 10]. This was unfortunately true among our affected patients. We hope through our description of these late-onset cases, that VOD/SOS will be considered even after 21 days post-HCT. Appropriate clinical signs and symptoms and classic VOD/SOS changes on liver biopsy can importantly confirm the diagnosis even when VOD/SOS may not typically be high on the differential.

Acknowledgments

KVB received an unrestricted grant from Otsuka Pharmaceutical Group to support the clinical trial in which these patients participated.

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Figure 1.

(A) Liver biopsy from Patient #12 demonstrated marked sinusoidal congestion and hemorrhage with associated hepatocyte atrophy. There was no significant sinusoidal inflammatory cell infiltrate. The sampled portal tracts were unremarkable (H&E x100). (B) A reticulin stain performed on this biopsy demonstrated extensive deposition of reticulin fibers in the hepatic sinusoids confirming the diagnosis of VOD/SOS (x200). (C) Liver biopsy from Patient #31 demonstrated marked sinusoidal congestion as well as hemorrhage around a central vein (*) (H&E x100). There was no confluent necrosis and only scattered acidophil bodies were identified. The sinusoids also contained a mild inflammatory cell infiltrate composed of small lymphocytes as well as Kupffer cell aggregates. (D) A reticulin stain performed on this biopsy demonstrated deposition of reticulin fibers within the sinusoids and underneath the central vein endothelium (x200). (E) Section from the liver at autopsy from Patient #36 demonstrating complete occlusion of some central veins with associated hepatocyte dropout and hemorrhage (H&E x200). (F) A reticulin stain highlights the complete occlusion of some central veins (x200).

Case descriptions of eight patients developing late VOD/SOS after treatment with dose-targeted busulfan, fludarabine, and alemtuzumab and allogeneic hematopoietic stem cell transplantation

Supportive care included in all cases careful diuresis and fluid management plus any additional appropriate medical management of VOD/SOS-related infectious complications. The busulfan AUC represents the average of both plasma AUC measurements after conditioning doses 1 and 3, except for Patient #14, in whom only one measurement (after dose 3) was available.

Table 1

Patient no.	Measured Busulfan AUC (μmol·min/L)	Day of VOD/SOS Diagnosis after Transplant	Clinical Signs/Symptoms	Ursodiol prophylaxis?	Ultrasound Findings	Maximum Bilirubin at Time of VOD/SOS (mg/dL)	Pathologic Confirmation of VOD/SOS	Typical VOD/SOS Pathology	VOD/SOS Treatment	Clinical Outcome
7	6436	+48	ascites, weight gain, right upper quadrant abdominal pain	no	ascites, hepatomegaly (liver 20 cm)	3.6	none	n/a	supportive care	VOD/SOS improved, died day +172 from CMV pneumonia
12	16,286	+60	nausea/vomiting, ascites, jaundice	yes	ascites, hepatomegaly (liver 19.2 cm)	11.7	liver biopsy	Yes	supportive care, steroids	Died day +85 from VOD/SOS, plus E. Coli sepsis
14	9960	+56	ascites, abdominal pain	yes	ascites, hepatomegaly (liver 18.4 cm)	12.0	autopsy	Yes	supportive care	Died day +69 from VOD/SOS, plus pulmonary hemorrhage
19	4922	+33	ataxia, lethargy	no	ascites, hepatomegaly (liver 18.1 cm)	6.0	liver biopsy	Yes	defibrotide, supportive care	VOD/SOS improved temporarily, but had persistent portal hypertension and died day +909 from post-transplant lymphoproliferative disease also involving the liver
31	6718	+69	abdominal pain, distension	yes	ascites, hepatomegaly (liver 19.3 cm)	2.3	liver biopsy	Yes	supportive care	VOD/SOS resolved, currently alive at day +1186
33	6610	+37	fever, nausea/vomiting	no	ascites, hepatomegaly (liver 20 cm)	22.9	autopsy	Yes	defibrotide, supportive care	Died day +45 from liver infiltration of persistent lymphoma, VOD/SOS, hypoxic respiratory failure, hypotension
35	7707	+77	increased abdominal girth, abdominal pain, edema, weight gain, jaundice	yes	ascites, hepatomegaly (liver 20.3 cm)	1.5	liver biopsy	Yes	supportive care	VOD/SOS resolved, currently alive at day +1057
36	6256	+37	edema	yes	ascites, hepatomegaly (liver 21 cm)	1.3	autopsy	Yes	supportive care	Died day +40 from persistence of circulating blasts, VOD/SOS, bacteremia

n/a = not available.