Hepatic Sinusoidal Obstructive Syndrome (SOS/VOD)

Background

Definition

Hepatic Sinusoidal Obstruction Syndrome (SOS), also known as hepatic Veno-occlusive Disease (VOD) is a serious and potentially fatal complication that can occur following Blood or Marrow Transplantation (BMT) in both adult and paediatric patients.

Pathophysiology

SOS/VOD is caused by toxic injury to hepatic venules and sinusoidal endothelial cells from the conditioning therapy of BMT and manifests with hepatomegaly and/or right upper quadrant pain, jaundice and fluid retention. This toxic injury causes a cascade of events, leading to platelet and coagulative material deposition in the sub endothelium and occlusion caused by fibrosis of the terminal venous venules and sinusoids. These processes can lead to hepatocellular necrosis, liver failure, multi-organ dysfunction and death.

Incidence/prevalence

Incidence rates for SOS/VOD are varied but are reported to occur in 5-15% of patients undergoing BMT – being more common after myeloablative allogeneic BMT (5-15%) than after allogeneic BMT with reduced-intensity conditioning or autologous transplant (< 5%). The severity of SOS/VOD varies from mild disease, which resolves without specific therapy, to a more severe from, characterised by progression to multi-organ failure and a mortality rate of over 80% if left untreated.

Onset/duration

SOS/VOD typically occurs in the first 30 days post BMT (and often in the first 7-14 days post-BMT), although it can occur later.

Risk factors

The probability and severity of SOS/VOD can be influenced by a range of patient-related, donor-related and transplant-related factors.

Patient Related

- age greater than 60 or less than 1-2 years
- poor performance status (Karnovsky <90%)
- advanced disease (beyond second CR or relapsed/refractory disease)
- female (especially if receiving norethisterone)
- underlying haemoglobinopathy (thalassaemia or sickle-cell disease)
- diagnosis of primary haemophagocytic lymphohistiocytosis, adrenoleucodystrophy or osteopetrosis
- prior abdominal or hepatic irradiation
- reduced DLCO (less than 70% predicted)
- pre-existing liver disease including cirrhosis
- elevated AST (>2.5 upper limit of normal) or bilirubin (>1.5 upper limit of normal)
- active viral hepatitis B or C
- pre-existing hepatic fibrosis or elevated serum ferritin
- prior autologous or allogeneic transplant
- prior treatment with gemtuzumab ozogamicin, inotuzumab ozagomicin or PD-1 inhibitors (pembrolizumab or nivolumab)
- metabolic syndrome
- genetic factors (GSTM1 polymorphism, C282Y allele, MTHFR 677CC/1298CC haplotype)

Donor Related

- Haematopoietic Progenitor source
    - peripheral blood stem cells (PBSC) confer a lower risk than bone marrow sourced stem cells in autologous transplant (ASCT)
    - allogeneic BMT has a higher risk of SOS/VOD than autologous transplant
- donor-recipient HLA disparity

Transplant Related (type and intensity of transplant conditioning and GvHD prophylaxis)

- reduced intensity conditioning regimens have a lower risk compared to myeloablative regimens (<5% vs 5-15%)
- non T-cell depleted transplant has a higher risk than T-cell depleted transplant
- autologous SCT has a lower risk than allogeneic BMT (<5% vs 5-15%)
- second transplant has a higher risk than first transplant
- multiple sequential ASCT (eg. for neurological solid tumours) has a higher risk than single ASCT
- TBI-based conditioning is associated with a higher risk than non-TBI-based conditioning
- busulfan-based conditioning has a higher risk than other chemotherapy agents, with; oral busulfan associated with a higher risk of SOS/VOD than intravenous busulfan (including with autologous regimens) and busulfan followed by cyclophosphamide conditioning associated with a higher risk of SOS/VOD than cyclophosphamide followed by busulfan
- GvHD prophylaxis with sirolimus and tacrolimus

Assessment and Diagnosis

Symptoms and signs

Early diagnosis of SOS/VOD is important so that treatment can be initiated. Clinical assessment and diagnostic interventions play a crucial role in identifying patients as high risk of SOS/VOD and detecting the symptoms of SOS/VOD. Assessment should be conducted and documented at baseline and then throughout treatment in order to identify any changes.

Clinical assessment should include:

- risk assessment for SOS/VOD prior to commencing therapy
- baseline and then twice daily weight
- strict fluid balance monitoring including input, output and balance
- baseline measurement of abdominal girth followed by daily measurements if any suspicion of SOS/VOD, to detect fluid retention and ascites. Ensure the same area is measured and the area is marked i.e. 2.5 cm under the umbilicus
- daily urinalysis
- skin integrity for signs of breakdown and jaundice
- abdominal examination for right upper quadrant pain and distension
- signs of bleeding
- baseline blood tests and then daily or as clinically indicated: EUC, LFT, bilirubin, FBC, coagulation profile and drug levels for hepatotoxic and nephrotoxic drugs
- respiratory assessment to detect pulmonary oedema
- regular vital signs, including blood pressure

Investigations and diagnosis

The differential diagnosis of deranged liver function tests following BMT is wide and includes graft-versus-host disease (GvHD), infection and drug toxicity. The main role of diagnostic techniques including histopathology and imaging investigations is to exclude other diagnoses as the diagnosis of SOS/VOD can primarily be based on clinical criteria.

Hepatic ultrasound (specifically reversed hepatic venous flow with new onset of hepatomegaly and ascites) may assist in the diagnosis of SOS/VOD and be useful in excluding other causes of deranged liver function post-BMT. More definitive diagnostic tests, including liver biopsy and measurement of hepatic venous gradient pressure through the jugular vein are far more accurate but are more invasive and as such are uncommonly used.

Clinical algorithms for diagnosis and staging of SOS/VOD

A number of clinical algorithms have been used to diagnose SOS/VOD. The most well-validated, the Seattle and Baltimore criteria, are both based on the presence of clinical findings (jaundice, weight gain, hepatomegaly and ascites) not attributable to any other cause in the first 3 weeks after BMT. The revised EBMT criteria for diagnosing and assessing SOS/VOD in adults (Mohty et al, 2016) and in children (Corbacioglu et al, 2018) may provide a means for addressing the apparent lack of specificity and sensitivity of existing clinical algorithms but are yet to be validated in prospective studies.

BMTSANZ

Criteria	Definition
Seattle	At least 2 of the following within 30 days after transplant: • hepatomegaly and right upper quadrant pain • jaundice • unexplained weight gain or ascites
Modified Seattle	At least 2 of the following within 20 days after transplant • hepatomegaly and right upper quadrant pain • ascites • unexplained weight gain of more than 2% from baseline
Baltimore	Bilirubin greater than or equal to 34µmol/L within 21 days after transplant and at least 2 of the following: • painful hepatomegaly • ascites • weight gain of more than 5% from baseline
EBMT 2018 Paediatric Criteria	No limitation for time of onset of SOS/VOD Presence of two or more of the following: • Unexplained consumptive or transfusion-refractory thrombocytopenia • Unexplained weight gain on 3 consecutive days despite the use of diuretics or weight gain >5% above baseline value • Hepatomegaly (best confirmed by imaging) above baseline value • Ascites • Rising bilirubin from a baseline value on 3 consecutive days or bilirubin > 34µmol/L within 72 hours
EBMT 2016 Adult Criteria	**Classical SOS/VOD** (In the first 21 days post-BMT) Bilirubin 34µmol/L and two of the following criteria must be present: • Painful hepatomegaly • Weight gain >5% from baseline • Ascites
	Late onset SOS/VOD (>21 Days post-BMT) Classical VOD/SOS beyond day 21 OR Histologically proven SOS/VOD OR Two or more of the following criteria must be present: • Bilirubin > 34µmol/L • Painful hepatomegaly • Weight gain>5% • Ascites AND Hemodynamic or/and ultrasound evidence of SOS/VOD

Grading

SOS/VOD can be classified into mild, moderate or severe disease depending on the clinical course within the first 100 days post BMT:

Mild stage

- meets diagnostic criteria
- requires no specific intervention
- is self limiting

Moderate stage

- evidence of liver injury
- requires active treatment for excess fluid and pain management
- resolves in most patients

Severe stage

- persistent hepatic dysfunction with severe hyperbilirubinaemia
- does not resolve within 100 days post BMT
- associated with multi organ failure
- can lead to:
    - renal insufficiency
    - confusion/disorientation
    - cardiac failure
    - bleeding requiring transfusion support
- untreated SOS/VOD may be associated with a mortality rate of over 80% (it must be noted however, that these outcomes were reported prior to the development of effective therapies for SOS/VOD, such as defibrotide)

The EBMT (Mohty et al, 2016) has developed criteria for severity grading of suspected SOS/VOD based principally on the time since first onset of clinical symptoms of SOS/VOD, the bilirubin level and kinetics, transaminases, weight increase and renal function (below). The EBMT SOS/VOD Risk Assessment App is available at https://itunes.apple.com/au/app/ebmt-educational-tools/id1350943950?mt=8.

2016 EBMT Criteria for Severity Grading of Suspected SOS/VOD in adults				
	Mild	**Moderate**	**Severe**	**Very severe (MOD/MOF)**
Time since first clinical symptoms of SOS/VOD	>7 days	5-7 days	<4 days	Any time
Bilirubin (µmol/L)	≥34 and <51	≥51 and <85	≥85 and <136	≥136
Bilirubin kinetics			Doubling within 48 hours	
Transaminases	≤2 x normal	>2 and ≤5 x normal	>5 and ≤8 x normal	>8 x normal
Weight increase	<5%	≥5% and <10%	≥5% and <10%	≥10%
Renal function	<1.2 x baseline at transplant	≥1.2 and >1.5 x baseline at transplant	≥1.5 and <2 x baseline at transplant	≥2 x baseline at transplant or other signs of MOD/MOF

Interpretation:

1. MOD = Multi-organ dysfunction
2. MOF = Multi-organ failure
3. Patients belong to the category that fulfils two or more criteria. If patients fulfil two or more criteria in two different categories they must be classified in the most severe category.
4. Patients weight increase ≥5% and <10% is considered by default as a criterion of severe SOS/VOD unless they fulfil no other criteria for severe SOS/VOD – in which case they are classified as having moderate SOS/VOD.
5. Patients with multi-organ dysfunction must be classified as very severe.
6. Time from the date when the first signs/symptoms of SOS/VOD began to appear (retrospectively determined) to the date when the symptoms/signs fulfilled SOS/VOD diagnostic criteria.

Management: Prevention and Treatment

Prevention

Preventive measures for SOS/VOD include:

1. Pre-BMT risk assessment
2. Reversal of SOS/VOD risk factors where possible
3. Pharmacoprophylaxis

Risk Assessment

Most low-risk patients do not require specific prophylaxis for SOS/VOD.

Patients at high risk of SOS/VOD include those who are receiving an allogeneic stem cell transplant AND have at least one of the following additional risk factors for SOS/VOD:

- pre-existing liver disease (cirrhosis or elevated ALT/AST - 2 x upper limit of normal)
- prior autologous or allogeneic transplant
- allogeneic transplant for leukaemia beyond second relapse
- conditioning with busulfan containing regimens; with a greater risk of SOS/VOD associated with oral busulfan than with IV busulfan (including with autologous regimens)
- prior treatment with gemtuzumab ozogamicin, inotuzumab ozagomicin or PD-1 inhibitors (pembrolizumab or nivolumab)
- diagnosis of primary haemophagocytic lymphohistiocytosis, adrenoleucodystrophy or osteopetrosis
- haemoglobinopathy (thalassaemia or sickle cell disease)
- prior abdominal irradiation
- reduced DLCO (less than 70% predicted)
- hepatitis B or C positive (not Ab positive)
- pre-existing hepatic fibrosis or iron overload
- GVHD prophylaxis with sirolimus and tacrolimus

Reversal or remediation of SOS/VOD risk factors

The majority of patient-related risk factors are difficult or impossible to reverse (particularly within the time constraints of BMT). Where possible the following strategies can be considered in patients at high risk of SOS/VOD:

- Delay of BMT until reversible conditions have resolved
- Use of reduced intensity conditioning for allogeneic transplant in preference to myeloablative conditioning
- Use of non-TBI-based conditioning
- Use of intravenous rather than oral busulfan as conditioning
- Change in conditioning chemotherapy sequencing to CyBU rather than BuCy
- Avoidance of hepatotoxins

Pharmacoprophylaxis

Ursodeoxycholic Acid Prophylaxis (UCDA)

Should a decision be made that prophylaxis is necessary, ursodeoxycholic acid (UCDA) can be used. A systematic review by Tay et al, pooled the results from three randomised studies comparing UDCA to no treatment and demonstrated a reduced risk of SOS/VOD in patients receiving UDCA (relative risk,

0.34; 95% confidence interval 0.17–0.66). EBMT Position statements have also recognised the potential benefits of UCDA in preventing SOS/VOD.

The dose of UCDA is 12 mg per kg per day orally given in 2 to 4 divided doses, commencing the day prior to conditioning and continuing until day +90. (UCDA prophylaxis may be ceased before day +90 in patients who have stable engraftment and no signs of SOS/VOD as 'late' SOS/VOD is extremely uncommon in these patients).

Heparin (unfractionated and low molecular weight)

While unfractionated and low molecular weight heparins may be useful for prevention of venous thromboembolic events, there is no evidence that they have any role in the prevention of SOS/VOD.

Defibrotide

A number of studies in both adults and children have reported significant reductions in the incidence of post-BMT SOS/VOD following the prophylactic use of defibrotide. Defibrotide is a sodium salt of complex single-stranded oligodeoxyribonucleotides derived from porcine mucosal DNA that appears to stabilise endothelial cells, reduce endothelial-cell activation and restore the thrombofibrinolytic balance. Importantly, defibrotide is not associated with a significantly increased bleeding risk despite reducing procoagulant activity, increasing fibrinolysis and modulating platelet activity.

While the optimal dose, duration of prophylaxis and route of administration remains unknown, and it is uncertain whether prophylaxis with defibrotide is superior to early treatment, the mortality from established SOS/VOD is sufficiently high to justify prophylaxis in high-risk paediatric (where evidence is strongest) and adult patients.

- The recommended dose is 6.25 mg/kg intravenously four times a day, every 6 hourly (total daily dose of 25mg/kg) given as a 2 hour IV infusion in sodium chloride or 5% dextrose via a 0.2um in-line filter. (Final concentration is 4-20 mg/mL).
- Defibrotide should be commenced on the day prior to conditioning and continued until day +14 or until engraftment has occurred.

The use of defibrotide in combination with UDCA in patients at high risk of developing VOD may be considered at the discretion of the treating physician.

In this regard it is important to note that as of August 2018 defibrotide has been registered by the FDA in the United States and is approved in the EU for treatment of SOS/VOD but is not TGA registered in Australia or listed on the PBS. The cost of defibrotide is also substantial: for an average 70kg adult patient defibrotide costs $4696/day - $65,000 for a 14 day course.

Treatment (of established SOS/VOD)

The management of established SOS/VOD includes supportive care and specific pharmacotherapy.

Supportive care

It is vitally important to provide adequate supportive care for patients with SOS/VOD. This includes:

- adequate analgesia
- maintenance of intravascular volume
- avoidance of nephrotoxins
- diuretics and salt restriction, to avoid and treat fluid overload
- dialysis
- respiratory support
- drainage of ascites and pleural effusions

Early consultation with a specialist hepatology unit is advised regarding the medical and surgical management of severe SOS/VOD, including consideration of Transjugular Intrahepatic Portosystemic Shunt (TIPS).

Pharmacotherapy

Systemic anticoagulants or thrombolytics such as tissue plasminogen activator (tPA) have been associated with significant bleeding complications, including fatal events, thus limiting their utility, and do not demonstrate any survival benefit and so cannot be recommended.

Defibrotide has been shown in phase II and III trials to improve complete response and survival in patients with severe post-BMT SOS/VOD. It is currently the most effective agent available for the treatment of SOS/VOD with approximately ~ 50% of patients with severe SOS/VOD, including those with multi-organ failure, achieving a complete response.

The recommended dose for the treatment of SOS/VOD is 6.25 mg/kg intravenously four times a day (total daily dose of 25mg/kg) given as a 2-hour infusion in sodium chloride or 5% dextrose via a 0.2um in-line filter. (Final concentration is 4-20 mg/mL). The dose should be based on baseline weight, defined as weight on admission date. No dose adjustment is required for renal or hepatic impairment. Although further study is necessary to establish the optimal duration of therapy it is currently recommended that treatment should continue for at least 21 days and until the symptoms of SOS/VOD resolve.

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