Veno-Occlusive Disease: “New Perspectives”

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Veno-occlusive disease

- VOD, also known as sinusoidal obstruction syndrome, is a potentially life-threatening complication of HSCT
- The conditioning regimens given before HSCT result in the production of toxic metabolites by the hepatocytes in the liver
- These metabolites trigger the activation, damage and inflammation of the endothelial cells that line the sinusoids
  - Sinusoids are small capillary-like blood vessels found in the liver
- This ultimately leads to VOD, which is characterised by
  - Increased thrombosis and decreased fibrinolysis
  - Sinusoidal damage and narrowing
  - Inflammation

Cell toxicity resulting from chemotherapy damages the lining of the liver sinusoids

Toxic metabolites resulting from the HSCT conditioning regimen damage and activate the sinusoidal endothelial cells

Activation of sinusoidal endothelial cells can trigger multiple pathways, resulting in inflammation and narrowing of the sinusoids.

The accumulation of cells and debris in the space of Disse, the perisinusoidal space located between the endothelium and the hepatocyte, lead to narrowing of the sinusoids.

VOD is characterised by increased clot formation and reduced clot breakdown.

The narrowing of the sinusoids, embolised endothelial cells and increased clot formation lead to the endpoint of VOD, namely obstruction of the sinusoids.

PAI-1, plasminogen activator inhibitor-1; TF, tissue factor; t-PA, tissue plasminogen activator
Pathophysiology of VOD

- Activation and damage due to conditioning regimen-mediated injury. Damage is both directed and mediated by cytokines such as:
  - TNF-α, IL-1β, IL-6
- Increased expression of adhesion molecules ICAM-1 and VCAM-1 of endothelial cell surface
- Activation of leukocytes that release additional inflammatory cytokines
- Digestion of extracellular matrix
- Portal vein hypotension
- Hepatic venous outflow obstruction

ICAM, intracellular adhesion molecule; IL, interleukin; TNF, tumour necrosis factor; VCAM, vascular cell adhesion protein
Summary of VOD pathophysiology

• The conditioning regimen given prior to HSCT increases endothelial cell activation, resulting in damage to the SECs and hepatocytes.

• The accumulation of cells in the space of Disse (the perisinusoidal space), increased inflammation and formation of clots lead to narrowing of the sinusoids.

• This results in VOD, which is characterised by blockage of the sinusoids, portal vein hypotension and reduced hepatic venous outflow.
Severe VOD/SOS: Case study

• 37-year-old lady
• September 2008 – CML. p210 BCRABL
• Rx imatinib – haematological toxicity
• Switched to dasatinib – more haematological toxicity
• October 2009 Philadelphia chromosome negative
• September 2012 CML transforming to AML

VOD, Veno-occlusive disease; SOS, Sinusoidal obstruction syndrome; CML, Chronic myeloid leukaemia; Rx, Prescription; BM, Bone marrow; AML, Acute myeloid leukaemia
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Severe VOD/SOS: Case study

- September 2012 dasatinib stopped
- October 2012 Cycle 1 DAT 3+10
- December 2012 Cycle 2

- Conditioning – IV Busulfan/Cyclophosphamide
- February 2013 sibling allogeneic bone marrow transplant
Nursing assessment

- Weigh patients daily
- Measure abdominal girth
- Monitor urea and electrolytes
- Monitor fluids in/out
- Assess all sites for bleeding
- Assess pain level and source
- Blood tests

Conditioning and stem-cell transplant

- % Weight Gain
- Cr, umol/L
- Bili, umol/L

Bu/Cy

Sib AlloBMTx  TPN/ANC  -0

Cr, Creatinine; Bili, Bilirubin; Sib AlloBMTx, Sibling allogeneic bone marrow transplantation; Tx, Treatment; TPN, Total parenteral nutrition; ANC, Absolute neutrophil count

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Risk factors for VOD

• Patient-related\(^1,2,3\)
  - Age
  - Malignant disease
  - Disease relapse
  - **Status of the liver** (eg cirrhosis, fibrosis)
  - **High AST/ALT ratio**
  - Previous liver radiation
  - Viral hepatitis\(^4\)
  - Iron overload\(^4\)

• Transplant-related\(^1,2,3\)
  - **Allogeneic transplant**
  - Donor type
  - Bone marrow-derived stem cell origin (vs peripheral-derived)
  - Fever in conditioning
  - Second transplant
  - Abdominal irradiation
  - Prior treatment with gemtuzumab (Mylotarg\(^\text{®}\))
  - **Conditioning regimen**
  - **Hepatotoxic drugs**

Several risk factors have an additive effect on the incidence of VOD\(^2\)

The most important risk factors are highlighted in bold.
AST/ALT, aspartate amino transferase/alanine amino transferase
Which of the following patient characteristics represent VOD risk factors?

① Malignant disease
② Conditioning with busulfan
③ Allogeneic transplantation
④ All of the above

37-year-old lady
CML. p210 BCRABL
Rx imatinib – haematological toxicity
Switched to dasatinib – more haematological toxicity
Philadelphia chromosome negative
CML transforming to AML
Cycle 1 DAT 3+10
Conditioning – IV Busulfan/Cyclophosphamide
Sibling allogeneic transplant
Which of the following patient characteristics represent VOD risk factors?

- ① Malignant disease
  - 0%
- ② Conditioning with busulfan
  - 13%
- ③ Allogeneic transplantation
  - 10%
- ④ All of the above
  - 77%

37-year-old lady
CML. p210 BCRABL
Rx imatinib – haematological toxicity
Switched to dasatinib – more haematological toxicity
Philadelphia chromosome negative
CML transforming to AML
Cycle 1 DAT 3+10
Conditioning – IV Busulfan/Cyclophosphamide
Sibling allogeneic transplant
Initial symptoms of VOD

WG, Weight gain
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What was the first symptom suggesting the development of VOD?

① Post-transplant nausea
② Neutropenic sepsis
③ Weight gain >3%
④ CML transforming to AML
**VOD/SOS Diagnosis**

- **Modified Seattle Criteria**
  - Within 20 days
    - Elevated bilirubin (> 34µmol/L)
    - RUQ pain. No hepatomegaly
    - > 2% weight gain

- **Baltimore Criteria**
  - Within 21 days
    - Elevated bilirubin (> 34µmol/L)
    - No hepatomegaly
    - > 5% weight gain
    - Ascites

RUQ, Right upper quadrant pain
VOD can also be classified by severity

- VOD presents with a wide spectrum of severity and is typically categorised as mild, moderate or severe\(^1,2\)

<table>
<thead>
<tr>
<th>Severity of VOD</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| Mild            | • Self-limiting  
                  • No treatment required |
| Moderate        | • Evidence of liver injury  
                  • Requires treatment (pain medication, diuretics and other supportive care)  
                  • Patients usually recover |
| Severe          | • Unresolved symptoms or death before 100 days post-HSCT  
                  • Multi-organ failure, severe hyperbilirubinemia with rapid weight gain |

### VOD symptoms classified by severity

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain before Day 20, % increase(^1)</td>
<td>7.0 (±3.5)</td>
<td>10.1 (±5.3)</td>
<td>15.5 (±9.2)</td>
</tr>
<tr>
<td>Maximum total serum bilirubin before Day 20, mg/dL(^1)</td>
<td>4.7 (±2.9)</td>
<td>7.9 (±6.6)</td>
<td>26.0 (±15.2)</td>
</tr>
<tr>
<td>Patients with oedema, %(^1)</td>
<td>23</td>
<td>70</td>
<td>85</td>
</tr>
<tr>
<td>Patients with ascites, %(^1)</td>
<td>5</td>
<td>16</td>
<td>48</td>
</tr>
<tr>
<td>Mortality rate before Day 100, %(^1)</td>
<td>9</td>
<td>23</td>
<td>98</td>
</tr>
</tbody>
</table>

- Renal/cardiac failure\(^1\)–\(^3\)
- Respiratory failure and pleural effusion\(^1\)–\(^3\)
- Encephalopathy\(^4\)
- Haemorrhagic complications (intestinal and pulmonary)\(^2,3\)
- Increased risk of infectious complications\(^1\)–\(^3\)
- Multi-organ failure syndrome\(^1\)–\(^4\)

Nursing management of VOD

Management of VOD is mainly supportive

- Restrict fluid intake
- Administer analgesia
- Position patient comfortably
- Administer blood products
- Administer electrolytes
- Administer medications
- Provide psychological support
- Provide family support

### Traditional treatment of VOD

<table>
<thead>
<tr>
<th>Current management strategies: primarily supportive measures&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Diuresis to minimise oedema</td>
<td></td>
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<tr>
<td>Sodium and fluid restriction</td>
<td></td>
</tr>
<tr>
<td>Haemofiltration and haemodialysis</td>
<td></td>
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<tr>
<td>Analgesia</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Heparin + rt-PA</strong></th>
<th></th>
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<tbody>
<tr>
<td>Response in up to 30% of patients, but overall survival is poor&lt;sup&gt;2,3,4&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Associated with increased risk of life-threatening bleeding&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Not recommended in patients with sVOD who have already developed multi-organ failure&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Should be avoided in patients with pulmonary or renal failure&lt;sup&gt;2,4&lt;/sup&gt;</td>
<td></td>
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Rationale for development of new therapies for VOD

• Traditional strategies are supportive, and treatments are associated with significant risk of bleeding\(^1, 2\)

• However, severe VOD remains a serious complication of HSCT with a high mortality rate (> 80%)\(^3\)

Effective therapies are therefore required for both the prophylaxis and treatment of severe VOD
Initiation of active treatment

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Defibrotide

- Defibrotide is a mixture of oligonucleotides derived from porcine intestinal mucosa
- Prepared by controlled depolymerisation of DNA
- Defibrotide is approved in the EU for the treatment of severe hepatic VOD in patients undergoing HSCT
  - It is indicated in adults and in adolescents, children and infants over 1 month of age
- Defibrotide is recommended by the EBMT and BCSH/BSBMT for the treatment of VOD in adults and children
- The BCSH/BSBMT also recommended defibrotide for the prophylaxis of VOD

BCSH, British Committee for Standards in Haematology; BSBMT, British Society for Blood and Marrow Transplantation; EBMT, European Society for Blood and Marrow Transplantation; EU, European Union
Defibrotide – mechanism of action

Defibrotide

- Protects endothelial cells
- Restores thrombofibrinolytic balance

### Intravenous Use

- **Dose:** 6.25 mg/kg body weight
- **Frequency:** every 6 hours
- **Dilution and Infusion:** Dilute NS or G5% and infuse over 2 hours. Final concentration for infusion 4–20 mg/mL.
- **Duration:** For a minimum of 21 days and continued until the symptoms and signs of severe VOD resolve.

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#### Defibrotide Administration

Defitelio® (Defibrotide)

Defibrotide – contraindications, warnings and interactions

<table>
<thead>
<tr>
<th>Precautions for defibrotide use:</th>
</tr>
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<tbody>
<tr>
<td>• When used with products that increase the risk of haemorrhage</td>
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<tr>
<td>• When used with anticoagulant therapy</td>
</tr>
<tr>
<td>o Warfarin</td>
</tr>
<tr>
<td>o Heparin</td>
</tr>
<tr>
<td>o Direct thrombin inhibitors</td>
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<tr>
<td>o Direct factor Xa inhibitors</td>
</tr>
<tr>
<td>• With products that affect platelet aggregation</td>
</tr>
<tr>
<td>o NSAIDs</td>
</tr>
<tr>
<td>• Defibrotide is not recommend for:</td>
</tr>
<tr>
<td>o Patients who have or develop significant acute bleeding requiring blood transfusion</td>
</tr>
<tr>
<td>o Patients who have haemodynamic instability</td>
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</tbody>
</table>

Defibrotide – adverse reactions and side effect

Defibrotide is generally well tolerated. In a historically-controlled trial, the incidence of haemorrhagic adverse events was similar between the controls and the patients receiving defibrotide (69% vs 65%).

Common adverse reactions (occurring between 1/10 and 1/100 people)

- Haemorrhage
  - Catheter site
  - Gastrointestinal
  - Pulmonary
  - Cerebral

- Haemorrhage
- Catheter site
- Gastrointestinal
- Pulmonary
- Cerebral

Uncommon adverse reactions (occurring between 1/100 and 1/1000 people)

- Hypersensitivity
- Anaphylaxis
- Haematoma
- Haemothorax
- Diarrhoea/nausea

- Epistaxis
- Haematuria
- Hypotension
- Coagulopathy
- Vomiting

- Hypersensitivity
- Anaphylaxis
- Haematoma
- Haemothorax
- Diarrhoea/nausea

- Haematenesis
- Rash
- Pruritus
- Petechiae
- Ecchymosis

Which of the following is not a precaution or contraindication when using defibrotide?

1. Anti-coagulant use
2. Haemodynamic instability
3. Right upper quadrant pain
4. NSAIDs

When used with products that increase the risk of haemorrhage
When used with anticoagulant therapy
With products that affect platelet aggregation
Patients who have or develop significant acute bleeding requiring blood transfusion
Patients who have haemodynamic instability
Resolution and post-VOD care

• Day +40 discharged from HSCT unit
  – Attended day unit daily
  – LFTs – bilirubin 23; Alk Phos 178; GGT 87; AST 30
• Day +43 bilirubin within normal range
  – No clinical signs of VOD
• 10 months post-transplant all LFTs returned to normal
• One-year post-transplant
  – In remission
  – Normal FBC
  – No GvHD
  – Normal liver function tests
  – Returning to work

LFT, Liver function test; Alk Phos, Alkaline phosphatase; GGT, Gamma glutamyl transpeptidase; AST, Aspartate transaminase; FBC, Full blood count; GvHD, Graft-versus-host disease
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Summary

• VOD remains a significant cause of morbidity and mortality following HSCT

• New treatment options give grounds for optimism

• Nurses play a major role
  – Early recognition
  – Supportive care

• We find defibrotide an effective treatment for severe VOD within our patient group

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EBMT VOD Learning Programme

• Card in your binder

• Available at Eusapharma Booth