Gastrointestinal complications after stem cell transplantation

Jervoise Andreyev
Consultant Gastroenterologist in Pelvic Radiation Disease
London, UK
100 consecutive patient audit

In hospital
• impact of GI symptoms: 100% major

After discharge
• impact of GI symptoms: 100% daily/several times per week
• 63% GI symptoms most difficult problem throughout

Dr. Bronwen Shaw
personal communication
Gl bleeding
Liver disease
Mucositis
Dysphagia
Gut GvHD
Endoscopic assessment
Neutropaenic enterocolitis
Infection
Diarrhoea
Nutrition
Not enough multidisciplinary working
What do GI symptoms mean?

Very little
Hannah

32, cord blood transplant - ALL

<table>
<thead>
<tr>
<th>Week</th>
<th>Diarrhoea:</th>
<th>Procedure:</th>
<th>Microorganism</th>
<th>Treatment:</th>
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<tbody>
<tr>
<td>Week 7</td>
<td></td>
<td>Flexi sig</td>
<td></td>
<td>GvHD</td>
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<td></td>
<td>Diarrhoea:</td>
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<td></td>
<td>Rx tacrolimus +</td>
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<td></td>
<td>steroids -</td>
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<td>settled</td>
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<td></td>
<td>Diarrhoea:</td>
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<td></td>
<td>Rx ciprofloxacin -</td>
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<td>SIBO</td>
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<td></td>
<td>settled</td>
<td></td>
<td>Klebsiella</td>
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<tr>
<td>Week 14</td>
<td>Diarrhoea:</td>
<td>OGD/Flexi sig</td>
<td></td>
<td>SIBO</td>
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<tr>
<td></td>
<td></td>
<td>+D2 aspirate</td>
<td>Ecoli</td>
<td>(Ecoli)</td>
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<tr>
<td>Week 17</td>
<td>Diarrhoea: valgancyclovir - settled</td>
<td>OGD/Flexi sig +D2 aspirate</td>
<td>CMV</td>
<td></td>
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<td>Week 20</td>
<td>Diarrhoea</td>
<td>OGD/Flexi sig</td>
<td></td>
<td>SI Candida</td>
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<td></td>
<td></td>
<td>+D2 aspirate</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Rx fluconazole/amphotericin- settled</td>
<td></td>
<td></td>
<td>Lansoprazole</td>
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<td>Week 35</td>
<td>Diarrhoea</td>
<td>History</td>
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Why diarrhoea?

Two critical concepts
1. The physiological model

Any insult → Inflammatory changes

- Oedema
- Cell death

Atrophy / loss of stem cells

Unrelated factors
- medication side effects
- stress
- sepsis
- premorbid conditions

Potentially alter specific GI physiological function(s)

ischaemia

Symptoms
2. Range of physiology

Upper GI tract

- Carbohydrate malabsorption
- Dysmotility promoting bacterial overgrowth
- Fat malabsorption
- Change in fluid secretion
- Vitamin and bile acid malabsorption
- Visceral neuropathy

Any insult

Nutrient metabolism

- Nutrient and fluid reabsorption
- Gut hormones
- Contraction

Permeability

- Colon
- Ileo-caecal valve
- Altered fermentation
- Altered motility
- Altered sphincter function

Microbiota

200 mls

Change in fluid secretion

Visceral neuropathy

Acute GVHD

Diarrhoea

1. > 500ml / 24 hours
2. > 1,000ml / 24 hours
3. > 1,500ml / 24 hours
4. Pain with / without ileus
92% identified on clinical grounds have GvHD

BUT

Personal observations

- Volume as a measure of severity is flawed
- Majority of patients do not have GvHD
What is GI toxicity?
## Physiological causes for diarrhoea

<table>
<thead>
<tr>
<th>Cause</th>
<th>Chemotherapy</th>
<th>Radiotherapy</th>
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<tbody>
<tr>
<td>Lactose intolerance</td>
<td>11-50%</td>
<td>50%</td>
</tr>
<tr>
<td>Malabsorption of other disaccharides</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Bile acid malabsorption</td>
<td>?</td>
<td>50%</td>
</tr>
<tr>
<td>Small bowel bacterial overgrowth</td>
<td>?</td>
<td>25%</td>
</tr>
<tr>
<td>Rapid transit</td>
<td>?</td>
<td>100%</td>
</tr>
<tr>
<td>Viral infection</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>C. Difficile</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Drug related (non chemotherapy)</td>
<td>?</td>
<td>10%</td>
</tr>
<tr>
<td>Other</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Malabsorption of carbohydrates

**Figure 1**
The role of short-chain fatty acids (SCFA) and colonic microbiota in modifying osmotically induced colonic fluid secretion associated with reduced small intestinal absorption of dietary carbohydrate(s) (CHO).
Malabsorption of carbohydrates

Figure 6
Effect of PEG (blue squares) and lactulose (red circles) on stool water in normal subjects.
Malabsorption of carbohydrates

**Figure 7**

Diagrams representing overall fluid balance in normal subjects (a) and in patients with clinical cholera (b) and during treatment with standard iso-osmolar oral rehydration solution (ORS) (c) or with resistant starch (RS)-ORS (d). RS is digested by colonic enteric bacteria to SCFA, CO₂, and H₂. The size of the arrows represents magnitude of fluid movement. See text.
Bile acid malabsorption

No data but.....
Enterohepatic circulation of bile acids

1. terminal ileal dysfunction = BAM


2. increased hepatic production, overwhelming absorptive mechanisms = BAD

FGF19
Symptoms of BAM

- Loose 100%
- Urgent 80%
- Frequent 72%
- Fatty 71%
- Crampy 68%
- Incontinent 62%

Diagnosis
SeHCAT scanning (nuclear medicine) is 98-100% sensitive & specific
Lenalidomide

• New effective therapy for multiple myeloma
• Needs to be used long term
• Diarrhoea problematic in 5%

Lenalidomide

Patients

• 5 men, 7 women
• 6 previous transplant
• Median 66 years (48-79)
• GI function deteriorated 6 months (range 1-15) after lenalidomide

- Diarrhoea (100%)
- Frequency 6/day (range 1-10)
- Urgency (92%)
- Faecal incontinence (58%)
- Abdominal cramps (42%)

Pawlyn Blood 2014
Lenalidomide

Investigations:

• Bloods - incl CRP, TFTs, Coeliac screen
• Glucose hydrogen methane breath test
• OGD + D2 biopsies and D2 aspirate
• Trial of lactose free diet
• 7 day food diary assessed for dietary indiscretion
• Colonoscopy + biopsies
• Stool for pancreatic faecal elastase
• SeHCAT scan
Lenalidomide

Results
Abnormal SeHCAT all patients

- Severe BAM n=9 patients
- Moderate BAM n=2
- Mild n=1

Treatment

- n=2, low fat diet alone
- n=10 colesevelam (off label)
- All -> reduction in stool frequency & improvement in BSC
- 50% -> normal bowel habit
- No dose reduction or cessation of lenalidomide due to diarrhoea.

Pawlyn  Blood 2014
Small intestinal bacterial overgrowth
# Symptoms associated with SIBO

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Abdominal pain</td>
<td>10-50</td>
</tr>
<tr>
<td>Belching</td>
<td>54</td>
</tr>
<tr>
<td>Bloating</td>
<td>13-86</td>
</tr>
<tr>
<td>Borborygmi</td>
<td>63</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>13-89</td>
</tr>
<tr>
<td>Flatulence</td>
<td>55</td>
</tr>
<tr>
<td>Gastric stasis</td>
<td>20</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>23-27</td>
</tr>
<tr>
<td>Steatorrhoea</td>
<td>11-38</td>
</tr>
<tr>
<td>Nocturnal defaecation</td>
<td>-</td>
</tr>
<tr>
<td>Mucus discharge</td>
<td>-</td>
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</tbody>
</table>

Grace AP&T 2013
Methods: Diagnosis

Test

1. Glucose hydrogen /methane breath test

2. Duodenal aspirate

> $10^3$ colony forming units/ml

Treat

- Positive test results or empirically
- Microbial sensitivities (if available)
- Antibiotics, 7-14 day course

Bjorneklett 1982; Flatz 1985; Grace 2013
Permeability: a key role

Intestinal permeability & allografts?

- Intestinal permeability often abnormal at baseline
- Worsens after conditioning
-Severity of toxicity predicts change in permeability
-Change in permeability predicts GvHD severity
- Normalisation of permeability reduces risk of GvHD
- Citrulline low circulating levels found in severe intestinal damage
- Levels correlate with GvHD

Future: a key step is selective protection of the GI mucosa and reduction in pancreatic secretions
How to assess diarrhoea?
Assessment for diarrhoea

1. Blood tests
2. Review drugs (especially PPIs)
3. Sepsis screen
4. Assess for bacterial overgrowth
5. Assess pancreatic function
6. Assess for bile acid malabsorption
7. Lactose free/ low fat diets?
8. Tests for disaccharidase malabsorption
9. Imaging?
10. Very early endoscopy
Which endoscopy?
Symptoms are not useful in guiding the type of endoscopic assessment

Ross Am J Gastroenterology 2008

Serial endoscopic examinations are of reliable diagnostic value

Martinez Bone Marrow Transplantation 2012
Endoscopic diagnosis of GvHD

- Grade 1 requires biopsy for diagnosis
- 25% will have unexpected CMV
- Gastroscopy plus flexisigmoidoscopy 93%
- Colonoscopy with ileal biopsies 87%
- Bowel preparation in critically ill?
- Up to 20% die within 30 days of colonoscopy
- Wireless capsule endoscopy inconsistent data

Figure 2 | Diagnosis of GI-AGVHD based on biopsy location in the gastrointestinal tract.

Liu et al. 2013
Figure 3 | Diagnosis of CMV infection based on biopsy site.

Liu 2013
Infection: especially CMV
- many unnecessary deaths
- diagnosis is too late
Endoscopic investigation of choice:

Very early and if necessary repeated

1. Upper GI endoscopy 
   + oesophageal / gastric / duodenal biopsies 
   + duodenal aspirate to microbiology

AND

2. Flexible sigmoidoscopy + biopsies
Conclusions

- GI toxicity is the number 1 cause of morbidity during stem cell transplantation
- Symptom control / treatment is usually generic rather than directed
- GI toxicity predicts for post transplant complications
- Promising biomarkers are being identified
- Research in this area would transform transplantation
Conclusions

Modern oncology needs to reconsider fundamentally the way it measures, assesses and manages GI symptoms
GvHD: Treatment

- 1mg/kg/day of methylprednisolone for grade II GvHD (2B)
- 2mg/kg/day of methylprednisolone for grades III-IV GvHD (1A)
- The use of “nonabsorbable” steroids can be considered for acute intestinal GvHD in order to reduce systemic steroids (2B)
- The following agents are suggested for use in the second line treatment of steroid refractory acute GvHD: ECP, Anti-TNF antibodies, m-TOR inhibitors, MMF, interleukin 2 receptor antibodies (2C)
- The following agents are suggested as third line treatment options in acute steroid refractory GvHD: Alemtuzumab, Pentostatin, mesenchymal stem cells and methotrexate (2C)