Acute Graft versus Host Disease

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Factors affecting acute graft versus host disease

Increased risk
- Unrelated donor
- Peripheral blood stem cell
- Older age
- HLA mismatch
- Transplant from alloimmune female donor
- Higher dose TBI

Decreased risk
- Cord Blood (severe acute GVHD)
- Non myeloablative conditioning
- T cell depletion

Increasing number of allogeneic HCT

Increasing frequency of URD HCT

Increasing use of PBSCT
More frequent use of reduced intensity conditioning

Incidence of acute GVHD
Incidence of grade II-IV acute GVHD has been reported to vary between 20-85%

Clinical Manifestations of acute GVHD

- Skin
  - Maculopapular rash

- Upper GI
  - Nausea, vomiting or both

- Lower GI
  - Watery diarrhea
  - Severe
  - Bloody diarrhea or ileus (after exclusion of infectious causes)

- Liver
  - Cholestatic hyperbilirubinaemia
Clinical Manifestations of chronic GVHD

**Skin**
Dyspigmentation, new-onset alopecia, poikiloderma, lichen planus-like eruptions, or sclerotic features

**Nails**
Nail dystrophy or loss

**Mouth**
Xerostomia, ulcers, lichen-type features, restrictions of mouth opening from sclerosis

**Eyes**
Dry eyes, sicca syndrome, cicatricial conjunctivitis

**Muscles, fascia, joints**
Fasciitis, myositis, or joint stiffness from contractures

Clinical Manifestations of chronic GVHD

**Female genitalia**
Vaginal sclerosis, ulcerations

**GI**
Anorexia, weight loss, oesophageal web or strictures

**Liver**
Jaundice, transaminitis

**Lungs**
Restrictive or obstructive defects on pulmonary function tests, bronchiolitis obliterans, pleural effusions

**Marrow**
Thrombocytopenia, anemia, neutropenia

Diagnosis of acute GVHD

- **Dermatitis** + **Hepatitis** + **Enteritis**

Acute GVHD  Chronic GVHD

Diagnosis of GVHD

<table>
<thead>
<tr>
<th>Category</th>
<th>Time after HCT or DLI</th>
<th>AGVHD Features</th>
<th>CGVHD Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GVHD</td>
<td>≤100 d</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Classic AGVHD</td>
<td>&gt;100 d</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Persistent, recurrent, or late-onset AGVHD</td>
<td>&gt;100 d</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>No time limit</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Classic CGVHD</td>
<td>No time limit</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Overlap syndrome</td>
<td>No time limit</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

This patient presented at day 110 with skin rash
Acute or chronic?

Presented at day 80 with mouth pain
Acute or chronic?
Acute or chronic?

Acute or chronic?

Acute GVHD: Clinical Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>% BSA</th>
<th>Bilirubin (mg/dl)</th>
<th>Diarrhea (ml/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;25</td>
<td>2-3</td>
<td>500-1000</td>
</tr>
<tr>
<td>II</td>
<td>25-50</td>
<td>3.1-6</td>
<td>1000-15000</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td>6.1-15</td>
<td>&gt;1500</td>
</tr>
<tr>
<td>IV</td>
<td>Bullae</td>
<td>&gt;15</td>
<td>Pain+/-ileus</td>
</tr>
</tbody>
</table>

Acute GVHD: Clinical Grade

<table>
<thead>
<tr>
<th>Overall Grade</th>
<th>Skin</th>
<th>Liver</th>
<th>GI</th>
<th>Upper GI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>1-3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>2-3</td>
<td>2-4</td>
<td>2-3</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>-</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Presentation
Clinical Case I

- 62 years old woman with AML
- Reduced intensity conditioning followed by an HLA matched URD transplant
- GVHD prophylaxis: CSA + MMF
- Day 28: Diffuse maculopapular rash + diarrhea 1100 ml/day. A skin biopsy is performed.
- Dx: AGVDH skin +++, GI + +
- Grade: ?

Clinical Case II

- 45 years old male with ALL
- Myeloablative conditioning: Cy/ TBI, matched sibling donor transplant
- GVHD prophylaxis: CSA + MTx
- Neutropenic fever, mucositis
- Day 35: diffuse maculopapular skin rash + diarrhea: 700 ml/day +hyperbilirubinemia: 2.5 mg/dl
- Dx: AGVHD: skin ++++, GI: liver: +
- Grade: ?

Clinical Case III

- 62 years old with NHL
- Reduced intensity conditioning followed a matched URD transplant
- GVHD prophylaxis: CSA and MMF
- Day 45 post HCT: has persistent nausea, intermittent vomiting and weight loss, has skin rash involving face and both forearms
- Upper GI endoscopy + biopsy: diagnostic of acute GVHD
- Stage: skin: stage I, upper GI: stage I; grade?

Standard therapy for AGVHD

- Grade I (skin stage I or II): Topical steroids
- Moderate to Severe: Methylprednisolone

<table>
<thead>
<tr>
<th>N</th>
<th>443</th>
</tr>
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<tbody>
<tr>
<td>Grade I</td>
<td>27%</td>
</tr>
<tr>
<td>Grade II</td>
<td>60%</td>
</tr>
<tr>
<td>Grade III/IV</td>
<td>13%</td>
</tr>
<tr>
<td>28 d % CR</td>
<td>35%</td>
</tr>
<tr>
<td>%PR</td>
<td>20%</td>
</tr>
<tr>
<td>Survival@ 1 year</td>
<td>53%</td>
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</tbody>
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Factors associated with CR/PR

- Related donor, GVHD prophylaxis other than MTx alone
- Age, higher grade, unrelated donor

Secondary treatment of Acute GVHD

<table>
<thead>
<tr>
<th>Polyclonal anti T cell Abs</th>
<th>ATG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti cytokine agents</td>
<td>Infliximab, Etanercept</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>MMF, Pentostatin</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Sirolimus, Tacrolimus</td>
</tr>
<tr>
<td>Anti T cell fusion proteins</td>
<td>Denileukin Diftitox</td>
</tr>
<tr>
<td>Monoclonal anti T cell Abs</td>
<td>Daclizumab, Visilizumab</td>
</tr>
<tr>
<td>Monoclonal anti T &amp; B cell Abs</td>
<td>Alemtuzumab</td>
</tr>
<tr>
<td>Photopheresis</td>
<td>ECP</td>
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Clinical Case I contd.

- 62 year old female diagnosed with grade III acute GVHD at day 28, started therapy with systemic steroids.
- 1 week later: Rash is still present (less prominent), no change in diarrhea.
- Treatment: ?
Clinical Case I contd.
• 62 year old female diagnosed with grade III acute GVHD at day 28, started therapy with systemic steroids.
  • 1 week later: Rash is less prominent, no change in diarrhea.
  • Treated with ATG: rash and diarrhea respond.
  • Develops CMV reactivation along new pneumonia.
  • BAL: + CMV

Clinical Case II contd.
• 45 years old diagnosed with grade II acute GVHD at day 35
  • Treated with systemic steroids
  • Responds well, and is gradually tapered off steroids, during taper
  • Develops a dry mouth with ulcerations and dry eyes.
  • Lip biopsy + chronic GVHD

Clinical Case III contd.
• 62 years old diagnosed with grade II acute GVHD at day 45
  • Treated with systemic steroids and gradually tapered off steroids.
  • Able to completely discontinue all immunosuppression by 6 months and has no active GVHD

Update on BMT CTN Clinical Trials

Phase II randomized clinical trial of Etanercept, mycophenolate, Denileukin or pentostatin along with corticosteroids for acute GVHD

N = 180 patients, median follow up: 9 months
Cumulative Incidence of toxicities, infections and relapse

<table>
<thead>
<tr>
<th>Cumulative Incidence</th>
<th>Etanercept %</th>
<th>Mycophenolate %</th>
<th>Denileukin %</th>
<th>Pentostatin %</th>
</tr>
</thead>
<tbody>
<tr>
<td>D 56 grade 3-5 toxicity</td>
<td>76</td>
<td>80</td>
<td>76</td>
<td>67</td>
</tr>
<tr>
<td>Severe infections at day 270</td>
<td>47</td>
<td>44</td>
<td>62</td>
<td>57</td>
</tr>
<tr>
<td>Relapse at day 180</td>
<td>15</td>
<td>11</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>

Conclusion

Efficacy and toxicity data suggest the use of MMF plus corticosteroids is the most promising regimen to compare against corticosteroids alone in a definitive phase 3 trial.

BMT CTN: 0802 A Multi-center Randomized, Double Blind, Phase III Trial Evaluating Corticosteroids with Mycophenolate Mofetil versus Corticosteroids with Placebo as Initial Systemic Treatment of Acute GVHD

Primary Objective: To estimate the GVHD free survival at day 56 after randomization without additional therapy