Acute Graft versus Host Disease

Mukta Arora MD. MS.
Acute Graft-versus-Host Disease

- Demographics and population at risk
- Diagnosis and staging
- Clinical presentation, response to treatment
- BMT CTN trials
- Form 2100
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

In children

In Adults

CIBMTR summary slides
Increasing use of PBSCT

![Bar chart showing the increasing use of PBSCT in different age groups and time periods.](image_url)
More frequent use of reduced intensity conditioning

![Bar graph showing the comparison between Reduced Intensity Conditioning and Standard Myeloablative Conditioning from 1998 to 2006. The graph indicates a trend of increased use of reduced intensity conditioning over the years, with data for 2006 marked as incomplete.](image-url)
Incidence of acute GVHD

Incidence of grade II-IV acute GVHD has been reported to vary between 20-85%
AGVHD is major cause of non-relapse mortality

HLA-identical Sibling

- Relapse: 41%
- GVHD: 13%
- Other: 16%
- Infection: 17%
- IPn: 3%
- Organ toxicity: 10%

Unrelated Donor

- Relapse: 34%
- GVHD: 14%
- Other: 16%
- Infection: 20%
- IPn: 6%
- Organ toxicity: 10%

CIBMTR Summary slides
Timing, Diagnosis and Organ Stage/ Grade of acute GVHD
Transplant Events

-8 -1 0 1mo 3mo 6mo

Conditioning Transplant Engraftment

Mucositis
Organ toxicity (VOD)

Acute GVHD ← Chronic GVHD

Infections
Bacterial  CMV  Varicella
Fungus
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

Skin: Lichen planus, Hyper/ hypo pigmentation, ichthyosis, onychodystrophy, morphea, scleroderma, hair changes.
Oral: sicca, atrophy, lichenoid, Hyperkeratosis
GI: wasting, dysphagia, odynophagia, strictures
Eye: keratoconjunctivitis sicca
Lungs: Bronchiolitis obliterans
Others: myofascial, genital

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><strong>Acute GVHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic AGVHD</td>
<td>≤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><strong>Chronic GVHD</strong></td>
<td></td>
<td></td>
<td></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>Skin</th>
<th>Liver</th>
<th>Gut</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% BSA</td>
<td>Bilirubin (mg/dl)</td>
<td>Diarrhea (ml/day)</td>
</tr>
<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>Generalized erythroderma</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: Methylprednisone

<table>
<thead>
<tr>
<th>Grade</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>443</td>
<td>27%</td>
</tr>
<tr>
<td>Grade II</td>
<td></td>
<td>60%</td>
</tr>
<tr>
<td>Grade III/IV</td>
<td></td>
<td>13%</td>
</tr>
</tbody>
</table>

Factors associated with CR/PR

- 28 d % CR: 35%
- %PR: 20%

Factors associated with mortality

- Survival@ 1 year: 53%
- Age, higher grade, unrelated donor.

BBMT 2002, MacMillan et al.
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:?
# Secondary treatment of Acute GVHD

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyclonal anti T cell Abs</td>
<td>ATG</td>
</tr>
<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>
</tr>
</tbody>
</table>
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 CR

Overall Survival

A

B

Probability

Days After Randomization

MMF: D28: 67%, D56: 82%
Denileukin Diftitox: D28: 65%, D56: 76%
Pentostatin: D28: 55%, D56: 74%
Etanercept: D28: 44%, D56: 61%

Probability

Days After Randomization

MMF: D270: 64% (95% C.I.: 48 - 76)
Denileukin Diftitox: D270: 49% (95% C.I.: 34 - 62)
Pentostatin: D270: 47% (95% C.I.: 31 - 62)
Etanercept: D270: 47% (95% C.I.: 32 - 61)
### 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
Form 2100