Treatment of Chronic Graft versus Host Disease

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University of Minnesota

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# Transplant Events

<table>
<thead>
<tr>
<th></th>
<th>Conditioning</th>
<th>Transplant</th>
<th>Engraftment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Mucositis</td>
<td>Organ toxicity (VOD)</td>
<td>Acute GVHD</td>
</tr>
<tr>
<td>1mo</td>
<td>Acute GVHD</td>
<td>Chronic GVHD</td>
<td>Engraftment</td>
</tr>
<tr>
<td>3mo</td>
<td>Fungus</td>
<td>Engraftment</td>
<td>Infected</td>
</tr>
<tr>
<td>6mo</td>
<td>Infected</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Infections**
  - Bacterial
  - CMV
  - Varicella
  - Fungus
Factors affecting chronic GVHD

**Increased risk**
- Unrelated donor
- Peripheral blood stem cell
- Older age
- Prior acute GVHD
- HLA mismatch
- Transplant from alloimmune female donor

**Decreased risk**
- Cord Blood
GVL accompanies GVHD
Clinical Presentation
Response to Treatment
Duration of Immunosuppression
Dermatitis + Hepatitis + Enteritis

Acute GVHD

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

Chronic GVHD

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
Organ Involvement with cGVHD

- Skin: P = 0.2
- Oral: P = 0.9
- GI: P = 0.5
- Eyes: P = 0.9
- Liver: P = 0.3
- Lungs: P = 0.3
Treatment of CGVHD: Response to Immunosuppressive therapy

Arora et al, BBMT 2003
Overall Survival and Cumulative Incidence of Discontinuation of Immunosuppression

Overall Survival

Cumulative Incidence

96% (85-100%)

3+ years median Rx

Arora et al BBMT 2003
Factors predicting poor prognosis

- Progressive onset of disease
- Thrombocytopenia
- Extensive skin involvement
- Lichenoid histology
- Elevated bilirubin
- Lung disease
- Older age
- Poor KPS
TREATMENT of CGVHD

Standard Risk pts (Plt > 10^5)  High Risk pts (Plt < 10^5)

- Prednisone + placebo
- Prednisone + AZA
- Prednisone
- CSP / Prednisone

- Prednisone
- CSP / Prednisone
- CSP / Prednisone
Randomized Trials: Initial therapy using steroids with or without additional agents: additional immunosuppression not beneficial

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>NRM</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone + Azathioprine</td>
<td>N= 126</td>
<td>21 % vs. 40%</td>
<td>61% vs. 47%</td>
</tr>
<tr>
<td>Prednisone + cyclosporine</td>
<td>307</td>
<td>13% vs 17%</td>
<td>72% vs. 67%</td>
</tr>
</tbody>
</table>

Sullivan et al, Blood 1988
Koc et al, Blood 2002
Alternate – day treatment

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Survival</th>
<th>Non relapse mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>145</td>
<td>72%</td>
<td>17%</td>
</tr>
<tr>
<td>CSP / Prednisone</td>
<td>142</td>
<td>67%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Toxicity of cGvHD treatment with Steroids

NRM according to steroid dose at cGvHD diagnosis

Blood. 2004;104:3501-3506
Similar incidence of discontinuation of immunosuppression in single & two drug arms

Koc et al, Blood 2002
**Thalidomide as Initial Therapy: Similar response and survival**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Outcome Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹Prednisone and CNI + Thalidomide</td>
<td>52</td>
<td>OS 49% vs. 47% at 3 years. Similar outcomes, drug not well tolerated.</td>
</tr>
<tr>
<td>²Prednisone and CNI + Thalidomide</td>
<td>54</td>
<td>OS 66% vs 54% at 2 years. Similar response and survival.</td>
</tr>
</tbody>
</table>

¹Koc et al, Blood 2000, ²Arora et al BBMT2001
MMF as Initial therapy

Randomized multicenter double blind placebo controlled trial

Martin et al, Blood, 2009
Eligible CGVHD Patients

Randomize

Steroids + CNI + MMF
N = 74

Steroids + CNI + Placebo
N = 77

Primary Endpoint: resolution of chronic GVHD & withdrawal of systemic treatment within 2 years without secondary treatment

Paul Martin et al, 2009
Similar discontinuation of immunosuppression but more treatment failure with MMF

Martin et al, 2009
Secondary Therapy of cGVHD

• No standard second line therapy available

• Several agents tested
  - case series
  - phase II trials

• Not comparable
  - heterogenous patient population
  - different response criteria
<table>
<thead>
<tr>
<th>Therapy</th>
<th>N</th>
<th>Response</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus</td>
<td>98</td>
<td>63-93%</td>
<td>41-89%</td>
</tr>
<tr>
<td>Rituximab</td>
<td>35</td>
<td>50-83%</td>
<td>-</td>
</tr>
<tr>
<td><strong>ECP</strong></td>
<td>276</td>
<td>40-80%</td>
<td>19-93%</td>
</tr>
<tr>
<td>MMF</td>
<td>65</td>
<td>46-72%</td>
<td>83-92%</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>161</td>
<td>20-59%</td>
<td>41-64%</td>
</tr>
</tbody>
</table>
## Other Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>Inclusion</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulsed steroids</td>
<td>61</td>
<td>Refractory</td>
<td>48% major, 27% minor response</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>4</td>
<td>Steroid resistant</td>
<td>1 CR, 2 PR</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>22</td>
<td>Persistent symptoms</td>
<td>55% PR</td>
</tr>
<tr>
<td>Etanercept</td>
<td>10</td>
<td>Steroid dependent</td>
<td>1 CR, 5 PR</td>
</tr>
<tr>
<td>Low dose MTX</td>
<td>14</td>
<td>Refractory</td>
<td>71% required &lt; 1mg/kg PSE</td>
</tr>
<tr>
<td>Etretinate</td>
<td>32</td>
<td>Refractory sclerodermatous</td>
<td>74% improvement</td>
</tr>
</tbody>
</table>
BMT CTN 0801

A Phase II/III Randomized Trial Comparing
- Sirolimus + Prednisone (test arm- ↑ T-regs)
- Sirolimus + CNI + Prednisone (control arm)
- Sirolimus + ECP + Prednisone (test arm- ↑ T-regs)

Study Chairpersons:
Paul Carpenter MBBS. & Mukta Arora M.D.
Screen for eligibility
(High-risk cGVHD at diagnosis and/or inadequate response after < 12 weeks of steroids)

Non-ECP Center

Randomize

1:1

Non-ECP Center P+SRL

Non-ECP Center P+CNI+SRL

ECP Center P+CNI+SRL

ECP Center P+SRL+ECP

Evaluate comparator Arms from Non-ECP + ECP Centers for analysis
### 0801 Enrollment Challenges

<table>
<thead>
<tr>
<th></th>
<th>2009-2010</th>
<th>allografts</th>
<th>~cGVHD(40%)</th>
<th>Enrollment</th>
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<tbody>
<tr>
<td>Non ECP Centers</td>
<td>2077</td>
<td>831</td>
<td></td>
<td>25</td>
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<tr>
<td>ECP Centers</td>
<td>3085</td>
<td>1234</td>
<td></td>
<td>5</td>
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BMT CTN 0801 Study Schema

Screen for eligibility
(High-risk cGVHD at diagnosis and/or inadequate response after < 12 weeks of steroids)

Non-ECP Center

Yes

Randomize

1:1

Non-ECP Center P+SRL

Non-ECP Center P+CNI+SRL

ECP Center P+CNI+SRL

ECP Center P+SRL+ECP

Evaluate comparator Arms from Non-ECP + ECP Centers for analysis
Non Relapse Mortality: CGVHD Severity Score

Arai et al, Blood 2011
Survival: CGVHD Severity Score

- Mild, HR 1.0
- Moderate, HR 4.3 (0.6-32)
- Severe, HR 13.3 (1.8-97)

Overall p<0.0001

Arai et al, Blood 2011
Worse Survival with Late onset acute GVHD simulating CGVHD

Arora et al, BMT 2009
CGVHD Overlap: Influence on non-relapse mortality

Overlap acute and chronic GVHD
Classical chronic GVHD

Non-relapse mortality

Months since enrollment

CGVHD Consortium, 2011
Key Points

cGVHD therapy remains frustrating

Incidence is increasing

Thrombocytopenia and progressive onset are markers of poor prognosis

Treatment requires prolonged immunosuppression

Infections are the commonest cause of death