Management of Steroid Refractory Chronic GVHD

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Leukemia BMT Program of British Columbia
Disclosures

Advisory Board:
Jazz Pharmaceuticals
Janssen
Gilead

Clinical Trials Participation:
Pharmacyclics
Novartis
Gilead

Honorarium:
Otsuka
Learning Objectives

Describe current understanding of pathophysiology of cGVHD

Outline how this understanding has lead to new targets for treatment

Describe the results supporting the use of novel agents as targeted therapy
TS ♂ 37 yrs old

September 2012 - Stage 4B Double Hit lymphoma
February 2013 - 10/10 MUD Cy/TBI transplant
75% day 10 Methotrexate

Acute GVHD skin – steroid dependent

Basiliximab March - May 2013

Progressed to chronic while on steroids, CNI & and basiliximab
July 2015 - COP
  high dose prednisone
  ECP

Stabilisation of PFTs & lichenoid skin changes

Scleroderma
  Imatinib – progressive changes
  flare in LFTs & thrombocytopenia

Renal involvement
  Ibrutinib – stable disease

Closure of compassionate access program
  Ruxolitinib
Remains on steroids

Steroid complications
diabetes
osteoporosis
Graft versus Host Disease

Caused by antigenic differences between the donor (graft) and patient (host)

MHC match

Donor T cell

Recipient APC

self peptides + mHA

MHC mismatch

Donor T cell

Recipient APC

self peptides + mHA

donor’s immune system mounting an immune attack causing tissue damage

Koyama & Hill; Blood, 2016)
Development of GVHD after transplant

Acute GVHD:
Red skin rash, GI symptoms, liver

Chronic GVHD
Skin, eyes, mouth, gastrointestinal, liver, musculoskeletal, lung, genitourinary

3-48%
13-82%

Day 0 50 100 180 1 y 2 y 3 y 5 y

Vogelsang & Paveltic: Chronic Graft Versus Host Disease: Interdisciplinary Management (2009)
Chronic GVHD

- Most common complication of HCT
- Leading cause of late non-relapse mortality
- Median onset 5-6 months post transplant
- Affects 30-70% of patients @ 1 year
- 5-10% diagnosed beyond one year
- Median duration of treatment 2.5 – 3.5 years
- 15% require 7+ years of IST
Vogelsang & Paveltic: Chronic Graft Versus Host Disease: Interdisciplinary Management (2009)
Sites affected by Chronic GVHD

Flowers et al Blood 2002
Oral Manifestations

Treister et al, BBMT 2010
## Who Needs Therapy?

<table>
<thead>
<tr>
<th>cGVHD manifestations based on Global Severity Score</th>
<th>Systemic Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 2 sites involved (no lung), all with mild scoring (asymptomatic, not interfering with function), no high risk features</td>
<td>No</td>
</tr>
<tr>
<td>≤ 2 sites involved (no lung), all mild scores + high risk features</td>
<td>Yes</td>
</tr>
<tr>
<td>≤ 2 sites involved including lung</td>
<td>Yes</td>
</tr>
<tr>
<td>&gt; 2 sites</td>
<td></td>
</tr>
<tr>
<td>** Moderate or Severe**</td>
<td></td>
</tr>
<tr>
<td>Any site</td>
<td>Yes</td>
</tr>
</tbody>
</table>

High risk features: platelet count <100,000, bilirubin >34, on steroids at onset

*Inamoto & Flowers COH 2011*
Initial Treatment of cGVHD

Prednisone 1mg/kg/day (Level A1)

Addition of calcineurin inhibitor to prednisone (Level CII)
- Steroid sparing but doesn’t increase response rate

Administration of other agents is not beneficial

<table>
<thead>
<tr>
<th>Author</th>
<th>Arms Compared</th>
<th>Double Blind</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koc</td>
<td>CSP/Prednisone ± thalidomide</td>
<td>Yes</td>
<td>51</td>
<td>Toxicity</td>
</tr>
<tr>
<td>Arora</td>
<td>CSP/Prednisone ± thalidomide</td>
<td>No</td>
<td>54</td>
<td>No benefit</td>
</tr>
<tr>
<td>Martin</td>
<td>CNI/Prednisone ± MMF</td>
<td>Yes</td>
<td>151</td>
<td>No benefit</td>
</tr>
<tr>
<td>Gilman</td>
<td>CNI/Prednisone ± hydroxychloroquine</td>
<td>No</td>
<td>54</td>
<td>Terminated early</td>
</tr>
<tr>
<td>Carpenter &amp; Arora</td>
<td>Sirolimus/Prednisone ± CNI</td>
<td>No</td>
<td>151</td>
<td>Terminated early</td>
</tr>
</tbody>
</table>

Wolff D, et al. BBMT, 2010
Steroids fail to control GVHD in 40-60% of patients

Flowers et al BBMT 2008
Steroid refractory/dependent cGVHD

Steroid Refractory

- Progression after 2-4 weeks of first line treatment
- No response after 1-2 months

Steroid Dependent

- Can not taper < 0.25mg/kg
Second Line treatment of cGVHD

- Extracorporeal photopheresis
- Mycophenolate mofetil
- Thalidomide
- Sirolimus or everolimus
- Rituximab
- Pentostatin
- Methotrexate
- Tacrolimus
- Imatinib
- Thoraco-abdominal irradiation
- Pulse steroid
- Mesenchymal stem cells
- Etretinate
- Etanercept
- Clofazimine
- Chloroquine
- Alefacept

20 – 82% ORR

Martin et al Korean J Hematol 46 (3) 153-63
# Second line therapy of cGVHD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study type</th>
<th>No of Pts</th>
<th>% OR</th>
<th>OS %</th>
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</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>Phase I/II</td>
<td>19</td>
<td>79</td>
<td>84 1.5 yr</td>
</tr>
<tr>
<td></td>
<td>Phase I/II</td>
<td>9</td>
<td>22</td>
<td>78 1.5yr</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>14</td>
<td>50</td>
<td>75 1.5yr</td>
</tr>
<tr>
<td>MMF</td>
<td>Retrospective</td>
<td>23</td>
<td>26</td>
<td>96 1 yr</td>
</tr>
<tr>
<td></td>
<td>Retrospective</td>
<td>11</td>
<td>64</td>
<td>67 1 yr</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Retrospective</td>
<td>34</td>
<td>76</td>
<td>72 3 yr</td>
</tr>
</tbody>
</table>

*Modified Inamoto & Flowers – COH, 2011*
Second Line treatment of cGVHD

40% alive 1 yr following change in Rx without change in therapy or relapse

Martin et al Korean J Hematol 46 (3) 153-63
Better treatments require understanding of pathophysiology of cGVHD
Biologic Phases of cGVHD

**Phase 1**
Acute inflammation & Tissue injury
- Innate immunity

**Phase 2**
Chronic inflammation & dysregulated immunity
- Adaptive immunity
  - Thymic Injury and dysfunction
  - T cells
  - B cells
  - NK cells
  - Antigen presenting cells
  - Regulatory Cells
    - Treg, Breg
    - IL-10 producing regulatory T cells (Tr1)

**Phase 3**
Aberrant tissue repair & fibrosis
- Innate & adaptive
  - TGFβ
  - PDGFα
  - TNFα
  - IL-17
  - Macrophages
  - Fibroblasts

*Cooke K, et al BBMT: 2017*
Continuum of acute – chronic GVHD
Targets for Blockade of cGVHD

1. APC activated, move to LN
2. APC activate Th1, Th17, Tfh T cells
3. Tfh support Ab-producing B cells
4. T- & B-cells infiltrate tissue
5. Ab deposition and cytotoxic attack

Im, A et al Leukemia: 2017
T regulatory cells

- ~5% of CD4$^+$ T cells in human PB
- Police of the immune system
- Suppress many different types of cells' immune responses
  - CD4$^+$ and CD8$^+$ T cells, B cells, NK cells, APCs
- Constitutively express IL-2R$\alpha$ (CD25)
Mouse Models of Tregs & GVHD

Expanded Treg

+ CD4\(^+\) T cells

Taylor et al; Blood 2002
Extracorporeal Photopheresis (ECP)
Proposed MOA of ECP

Goussetis et al; Transfusion and Apheresis Science 2002
## Summary of ECP for cGVHD Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Complete or partial response (skin)</th>
<th>Complete or partial response (liver)</th>
<th>Complete or partial response (oral)</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besnier et al. (1997)</td>
<td>5</td>
<td>4/4</td>
<td>1/1</td>
<td>—</td>
<td>5/5</td>
</tr>
<tr>
<td>Smith et al. (1998)</td>
<td>18</td>
<td>4/10</td>
<td>3/13</td>
<td>2/7</td>
<td>7/18</td>
</tr>
<tr>
<td>Child et al. (1999)</td>
<td>11</td>
<td>10/10</td>
<td>1/6</td>
<td>—</td>
<td>10/11</td>
</tr>
<tr>
<td>Miller et al. (1998)</td>
<td>8</td>
<td>5/7</td>
<td>0/1</td>
<td>0/2</td>
<td>7/8</td>
</tr>
<tr>
<td>Salvaneschi et al. (2001)</td>
<td>14</td>
<td>10/12</td>
<td>6/9</td>
<td>8/12</td>
<td>11/14</td>
</tr>
<tr>
<td>Apisarnthanarax et al. (2003)</td>
<td>32</td>
<td>19/32</td>
<td>—</td>
<td>—</td>
<td>19/32</td>
</tr>
<tr>
<td>Sniecinski et al. (1998)</td>
<td>26</td>
<td>12/15</td>
<td>5/12</td>
<td>7/8</td>
<td>—</td>
</tr>
<tr>
<td>Zic et al. (1999)</td>
<td>11</td>
<td>6/8</td>
<td>2/5</td>
<td>2/10</td>
<td>—</td>
</tr>
<tr>
<td>Padua (2002)</td>
<td>19</td>
<td>15/18</td>
<td>7/9</td>
<td>—</td>
<td>17/19</td>
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<tr>
<td>Greinix (2005)</td>
<td>47</td>
<td>41/44</td>
<td>21/25</td>
<td>40/42</td>
<td>42/47</td>
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<tr>
<td>Kanold et al. (2003)</td>
<td>63</td>
<td>31/51</td>
<td>24/33</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Messina et al. (2003)</td>
<td>44</td>
<td>20/36</td>
<td>12/20</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bisaccia et al. (2003)</td>
<td>6</td>
<td>4/6</td>
<td>3/3</td>
<td>2/2</td>
<td>6/6</td>
</tr>
<tr>
<td>Rubegni et al. (2005)</td>
<td>32</td>
<td>22/27</td>
<td>18/23</td>
<td>23/25</td>
<td>—</td>
</tr>
<tr>
<td>Foss et al. (2005)</td>
<td>25</td>
<td>15/25</td>
<td>0/6</td>
<td>6/13</td>
<td>—</td>
</tr>
<tr>
<td>Percentage of patients who responded to ECP (CR/PR in %)</td>
<td>—</td>
<td>72 (40-100)</td>
<td>63 (0-100)</td>
<td>74 (0-95)</td>
<td>—</td>
</tr>
</tbody>
</table>

ECP

Only 1 published prospective, randomised, cross over controlled trial
100 patients randomised 1:1 ratio + IST vs IST alone

1° endpoint was to determine the effect of ECP on skin

Flowers et al, Blood; 2008
Results

Figure 4. Cumulative incidence of complete or partial skin response.

Table 3. Total Skin Score (TSS) and corticosteroid response to ECP treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 12</th>
<th></th>
<th></th>
<th>Week 24</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ECP, n = 48</td>
<td>Control, n = 47</td>
<td>P</td>
<td>ECP, n = 48</td>
<td>Control, n = 47</td>
<td>P</td>
</tr>
<tr>
<td>Median percent change from baseline in TSS</td>
<td>–14.5</td>
<td>–8.5</td>
<td>.48</td>
<td>–31.4</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>&gt; 50% reduction in corticosteroid dose, n (%)†</td>
<td>12 (25)</td>
<td>6 (12.8)</td>
<td>.13</td>
<td>19 (39.6)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>&gt; 50% reduction in corticosteroid dose and</td>
<td>4 (8.3)</td>
<td>0 (0.0)</td>
<td>.04</td>
<td>11 (22.9)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>&gt; 25% improvement in TSS, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 50% reduction in corticosteroid dose and final</td>
<td>10 (20.8)</td>
<td>3 (6.4)</td>
<td>.04</td>
<td>17 (35.4)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>corticosteroid dose of &lt; 10 mg/day, n (%)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Flowers et al, Blood; 2008
ECP & Tregs

Denney et al, Transplantation; 2017
Low dose IL-2 is a growth factor for Tregs

Malek & Bayer, Nat Rev Immun 2004
Low dose IL-2 for SR cGVHD

Single arm, open label study, 35 patients

Eligibility
Steroid refractory
≥2 lines of prior therapy
No CNI or sirolimus

Treatment
1 x 10^6 IU/m2/day for 12 weeks

Outcome
CR/PR @ 12 weeks 57%

Koreth et al, NEJM, 2011
Results

Predictor of response: time from cGVHD to initiation of IL-2

Koreth et al, NEJM, 2011
Immunological outcomes

Koreth et al, Blood, 2016
B cell function and their role in cGVHD

Shimabukuro-Vornhagen et al, Blood 2008
Dysregulation of B-cell compartment is hallmark of cGVHD
Clinical features of autoimmune disease

Targets for Blockade of cGVHD

Non-lymphocyte targets:
- Hedgehog inhibitors
- Neutrophil elastase inhibitors

Expand thymopoiesis:
- KGF
- IGF
- IL-7
- Steroid blockade

Block T activation & cytokine-induced lineages:
- JAK inhibitors (Ruxolitinib, Baricitinib)
- Proteasome inhibitors
- CTLA4-Ig fusion protein

Block trafficking of effectors from LN:
- Ponésimod (S1P1R)

Deplete B cells:
- Rituximab
- Block B activation:
  - Bevlimumab (BAFF)
  - Fostamatinib (Syk)
  - Cerdulatinib (Syk)
  - Ibrutinib (BTK)

1. APC activated, move to LN
2. APC activate Th1, Th17, Tfh T cells
3. Tfh support Ab-producing B cells
4. T & B cells infiltrate tissue
5. Ab deposition and cytotoxic attack

*Im, A et al Leukemia: 2017*
Targeting B cells - depletion

Monoclonal antibody against CD20 – results in B cell lymphopenia

<table>
<thead>
<tr>
<th>Reference(s)</th>
<th>ORR, no./total no. (%)</th>
<th>Response site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratanatharathorn et al$^{95}$</td>
<td>4/8 (50)</td>
<td>Cut, Lu, Ms, O</td>
</tr>
<tr>
<td>Canninga–van Dijk et al$^{98}$</td>
<td>5/6 (83)</td>
<td>Cut, Li</td>
</tr>
<tr>
<td>Okamoto et al$^{100}$</td>
<td>NA</td>
<td>Cut</td>
</tr>
<tr>
<td>Zaja et al$^{97}$</td>
<td>(65)</td>
<td>Cut, Li, Ms, Lu, Gi, O</td>
</tr>
<tr>
<td>Cutler et al$^{101}$</td>
<td>14/20 (70)</td>
<td>Cut, Ms, Li</td>
</tr>
<tr>
<td>Mohty et al$^{99}$</td>
<td>10/15 (66)</td>
<td>Cut, Gi, Li, O</td>
</tr>
<tr>
<td>von Bonin et al$^{103}$</td>
<td>9/13 (69)</td>
<td>Cut, Ms, O</td>
</tr>
<tr>
<td>Teshima et al$^{102}$</td>
<td>3/7 (43)</td>
<td>Cut, Ms, O</td>
</tr>
</tbody>
</table>
Rituximab

Only one published, prospective, randomised controlled trial

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Study Entry</th>
<th>1 Year</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate, no./no. total (%)</td>
<td>NA</td>
<td>14/20 (70)</td>
<td></td>
</tr>
<tr>
<td>Complete response rate, no./no. total (%)</td>
<td>NA</td>
<td>2/20 (10)</td>
<td></td>
</tr>
<tr>
<td>Prednisone dose, median mg/d</td>
<td>40</td>
<td>10</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Discontinued prednisone, no./no. total (%)</td>
<td>NA</td>
<td>4/19 (21)</td>
<td></td>
</tr>
<tr>
<td>Prednisone reduction of at least 50%, no./no. total (%)</td>
<td>NA</td>
<td>13/19 (68)</td>
<td></td>
</tr>
<tr>
<td>No change, or higher dose, no./no. total (%)</td>
<td>NA</td>
<td>6/19 (32)</td>
<td></td>
</tr>
<tr>
<td>Cutaneous involvement, median %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body surface area</td>
<td>42</td>
<td>20</td>
<td>.02</td>
</tr>
<tr>
<td>Sclerodematous involvement</td>
<td>35</td>
<td>20</td>
<td>.19</td>
</tr>
<tr>
<td>Lichenoid involvement</td>
<td>19.5</td>
<td>3</td>
<td>.17</td>
</tr>
<tr>
<td>Rheumatologic involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS pain score, median</td>
<td>4</td>
<td>1.5</td>
<td>.02</td>
</tr>
<tr>
<td>VAS fatigue score, median</td>
<td>5</td>
<td>2</td>
<td>.50</td>
</tr>
<tr>
<td>Preston dynamometer, average left and right hand, lb</td>
<td>62.5</td>
<td>71.5</td>
<td>.13</td>
</tr>
<tr>
<td>Oral involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathology score</td>
<td>11.75</td>
<td>12.5</td>
<td>.63</td>
</tr>
<tr>
<td>Ocular involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schirmer test, average left and right eye, mm</td>
<td>1</td>
<td>3.75</td>
<td>&lt; .99</td>
</tr>
</tbody>
</table>

Cutler et al, Blood, 2006
Prospective, randomised trial comparing rituximab with imatinib in patients with skin sclerosis

1° end point – sig. clinical response

• 27% in both groups

Crossover design – 72 patients

• 18 patients crossed over to rituximab: 5 experienced a SCR by 6 months after crossover (31%)

• 23 patients crossed over to imatinib: 4 experienced a SCR by 6 months after crossover (19%)

Arai et al, Clin Can Res
2016
Targeting B cells - Ibrutinib

Ibrutinib

Single arm, open-label study, 42 patients

Ibrutinib 420mg/day

1-3 prior therapies; steroid dependent/refractory

CR/PR in 28/42 patients; CR 9/42 patients

- 21/28 tapered prednisone to < 0.15mg/kg/day
- 5/28 stopped steroids
- 20/28 sustained response > 20 weeks

Health Canada Approval

Miklos et al, Blood, 2017
Targets for Blockade of cGVHD

1. APC activated, move to LN
2. APC activate Th1, Th17, Tfh T cells
3. Tfh support Ab-producing B cells
4. T- & B-cells infiltrate tissue
5. Ab deposition and cytotoxic attack

Block T activation & cytokine-induced lineages:
- JAK inhibitors (Ruxolitinib, Baricitinib)
- Proteasome inhibitors
- CTLA4-Ig fusion protein

Non-lymphocyte targets:
- Hedgehog inhibitors
- Neutrophil elastase inhibitors

Expand Tregs:
- IL-2

Expand thymopoiesis:
- KGF
- IGF
- IL-7
- Steroid blockade

Deplete B cells:
- Rituximab

Block B activation:
- Belimumab (BAFF)
- Fostamatinib (Syk)
- Cerdulatinib (Syk)
- Ibrutinib (BTK)
JAK Inhibitors

- Reduce proliferation of T-effector cells
- Suppresses pro-inflammatory cytokines - inflammation, tissue damage, and fibrosis
- Impairs function of dendritic cells (antigen-presenting B-cells) resulting in decreased alloreactive T-cell activation

Teshima T, Blood, 2014
Ruxolitinib

41 patient retrospective survey

Refractory to steroids for ≥ 3 weeks

29/41 (70.7%) multiple organ involvement

6/41 (14.6%) moderate; 35/41 (85.4%) severe

Most patients beyond 2nd line treatment

Median # of prior therapies = 3 (1-10)

ORR 35/41 (85.4%) – 32/41 PR (78%); 6/41 CR (14.6%)

Median time to response 3 weeks (1-25 weeks)

Zeiser et al, Leukemia, 2015
29/41 (70.7%) multiple organ involvement

6/41 (14.6%) moderate; 35/41 (85.4%) severe

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Median time to response 3 weeks (1-25 weeks)

Zeiser et al, Leukemia, 2015
<table>
<thead>
<tr>
<th>Study Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of Chronic Graft Versus Host Disease With Arsenic Trioxide</td>
</tr>
<tr>
<td>Treatment of Chronic Graft-Versus-Host Disease With Mesenchymal Stromal Cells</td>
</tr>
<tr>
<td>Continuous Alloreactive T Cell Depletion and Regulatory T Cell Expansion for the Treatment of Steroid-refractory or Dependent Chronic GVHD</td>
</tr>
<tr>
<td>Extracorporeal Photopheresis and Low Dose Aldesleukin In Treating Patients With Steroid Refractory Chronic Graft-Versus-Host Disease</td>
</tr>
<tr>
<td>A Phase I Study of Abatacept in the Treatment of Patients With Steroid Refractory Chronic Graft Versus Host Disease (cGVHD)</td>
</tr>
<tr>
<td>Vismodegib in Treating Patients With Steroid-Refractory Chronic Graft-Versus-Host Disease</td>
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<tr>
<td>Ruxolitinib for Steroid-refractory GVHD</td>
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<tr>
<td>A Phase 1/2 Trial of Donor Regulatory T-cells for Steroid-Refractory Chronic Graft-versus-Host-Disease</td>
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<tr>
<td>Glasdegib in Refractory Patients With Sclerotic Chronic Graft-Versus-Host Disease</td>
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<tr>
<td>Therapeutic Effects of Hydrogen on Steroid-refractory/or Steroid-dependent cGVHD</td>
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<tr>
<td>A Study of Ruxolitinib vs Best Available Therapy (BAT) in Patients With Steroid-refractory Chronic Graft vs. Host Disease (GvHD) After BMT(REACH3)</td>
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<tr>
<td>Extracorporeal Photopheresis Using Theraflex ECPâ„¢ for Patients With Refractory Chronic Graft Versus Host Disease (cGVHD)</td>
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<td>Safety and Efficacy of AMG 592 in Subjects With Steroid Refractory Chronic Graft Versus Host Disease</td>
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<tr>
<td>Study of Baricitinib, a JAK1/2 Inhibitor, in Chronic Graft-Versus-Host Disease After Allogeneic Hematopoietic Stem Cell Transplantation</td>
</tr>
</tbody>
</table>
Understanding of the pathophysiology has improved leading to identification of therapeutic targets but it too early to evaluate success

Choice of second line agent depends on
• Availability – varies province to province
• Cost
• Side effect profile
• Patient compliance
• Mode of delivery
Multi-disciplinary approach

Chronic GVHD Clinic

- Respirology
- Psychosocial
- Gastroenterology
- Infectious Disease
- Ophthalmology
- Oral Medicine
- Gynaecology
- Rheumatology
- Endocrinology
- Nutrition
- Dermatology
- Physiotherapy
Non-relapse mortality & Survival

Arai et al, Blood 2011

<table>
<thead>
<tr>
<th>Severity</th>
<th>2 yr NRM</th>
<th>2 yr OS</th>
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</thead>
<tbody>
<tr>
<td>Severe</td>
<td>32%</td>
<td>62%</td>
</tr>
<tr>
<td>Moderate</td>
<td>9%</td>
<td>86%</td>
</tr>
<tr>
<td>Mild</td>
<td>3%</td>
<td>97%</td>
</tr>
</tbody>
</table>
Adverse health outcomes by cGVHD status

Fraser et al Blood 2006
cGVHD increases late effects of HCT

- Cataracts
- Keratoconjunctivitis sicca
- Thyroid cancer
- Hypothyroidism
- Bronchiolitis obliterans (related to GVHD)
- Chronic infections
- Liver dysfunction
- Hepatitis B and C
- Iron overload
- Osteoporosis
- Avascular neurosis
- Sexual dysfunction
- Infertility
- Memory loss
- Depression/anxiety
- Post-traumatic stress disorder
- Dry mouth
- Oral cancer
- Coronary artery disease
- Congestive heart failure
- Renal failure
- Infections
- Recurrent malignancy
- Secondary malignancy
- GVHD
- Skin cancer
L/BMT cGVHD Clinic

- Weekly clinic instituted in 2008 – 2 physicians
- Steroid refractory/dependent patients
- ~30 patients per year
- Review conducted of first 5 years (112 patients)
  - 65% had prior acute GVHD
  - 55% severe cGVHD
  - 22% died – 12 from GHVD; 13 relapse
  - Unable to identify effective therapy
L/BMT Algorithm

Dx & Staging of cGVHD

Prednisone 0.5-1mg/kg prednisone

±

CNI

2nd line
ECP
Mouth, skin

2nd line
Rituximab*
MSK, Skin

Imatinib
Scleroderma, lung

Ibrutinib
MSK, mouth, skin

TAI
Skin (not Scl)

Sirolimus

Methotrexate

MMF
<table>
<thead>
<tr>
<th>Attributes for selecting IST</th>
<th></th>
</tr>
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<tbody>
<tr>
<td><strong>Attributes for 1\textsuperscript{st} line therapy</strong></td>
<td><strong>Attributes for 2\textsuperscript{nd} line therapy</strong></td>
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<tr>
<td>• Achieves high complete response rates</td>
<td>• Achieves high complete response rates</td>
</tr>
<tr>
<td>• Rapid onset of action</td>
<td>• Rapid onset of action</td>
</tr>
<tr>
<td>• Low immunosuppression</td>
<td>• Low immunosuppression</td>
</tr>
<tr>
<td>o (as possible)</td>
<td>o (as possible)</td>
</tr>
</tbody>
</table>
RS 48 yr old

Would ibrutinib have potential benefit for joints/fascia
FFS after primary treatment of cGVHD

Inamoto et al Blood 124 (8) 1363-1371
Second Line treatment of cGVHD

Inamoto et al Blood 2013 121 (12) 2340-2346
Better treatments require understanding of pathophysiology of cGVHD

MacDonald et al Blood: 2017
# Second line therapy of cGVHD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study type</th>
<th>No of Pts</th>
<th>% OR</th>
<th>OS %</th>
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<tbody>
<tr>
<td>ECP</td>
<td>Phase II</td>
<td>23</td>
<td>70</td>
<td>78</td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td>43</td>
<td>65</td>
<td>70 1 yr</td>
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<tr>
<td>Retrospective</td>
<td></td>
<td>67</td>
<td></td>
<td></td>
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<tr>
<td>Rituximab</td>
<td>Phase II</td>
<td>37</td>
<td>86</td>
<td>72 1 yr</td>
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<tr>
<td>Meta-analysis</td>
<td></td>
<td>111</td>
<td>66</td>
<td></td>
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<tr>
<td>Imatinib</td>
<td>Phase I/II</td>
<td>19</td>
<td>79</td>
<td>84 1.5 yr</td>
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<tr>
<td>Phase I/II</td>
<td></td>
<td>9</td>
<td>22</td>
<td>78 1.5yr</td>
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<tr>
<td>Retrospective</td>
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<td>14</td>
<td>50</td>
<td>75 1.5yr</td>
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<tr>
<td>MMF</td>
<td>Retrospective</td>
<td>23</td>
<td>26</td>
<td>96 1 yr</td>
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<tr>
<td>Retrospective</td>
<td></td>
<td>11</td>
<td>64</td>
<td>67 1 yr</td>
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<tr>
<td>Sirolimus</td>
<td>Retrospective</td>
<td>34</td>
<td>76</td>
<td>72 3 yr</td>
</tr>
</tbody>
</table>

*Modified Inamoto & Flowers*
Mechanistic Intervention for Prevention & Treatment

**Stem cell graft engineering**
- Anti-thymocyte globulin
- Post-transplant cyclophosphamide
- CD34 selection
- Ex vivo pan-T cell depletion
- Ex vivo selective T cell depletion
- Donor IL-2 therapy

**Inhibit T cell signaling**
- ITK inhibition - ibrutinib
- JAK1/2 inhibition - ruxolitinib
- ROCK2 inhibition - KD025
- bortezomib

**Adoptive Treg Therapy**
- Purified donor Treg
- Ex vivo expanded Treg
- Antigen-specific Treg

**CD4⁺ FoxP3⁺ Regulatory T cells**

**Treg-sparing therapy**
- sirolimus
- mycophenolate mofetil
- ruxolitinib
- bortezomib

**In vivo Treg expansion**
- ECP
- low-dose IL-2

**B cell depletion in vivo**
- rituximab
- ofatumumab
- obinutuzumab

**Inhibit B cell signaling**
- BTK inhibition - ibrutinib
- SYK inhibition - fostamatinib

*Cutler C, et al Blood: 2017*