Graft-versus-Host Disease and Immunotherapy Lessons from the Clinic

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Disclosures

- **Research Support**: Pharmacyclics, Inc.; Incyte Corp.
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- **Consultant**: Pharmacyclics, Inc., CSL Behring
- **Major Shareholder**: No disclosure
- **Other**: I will be discussing “off-label” use of several treatments for chronic GVHD.
Outline

- Acute Myeloid Leukemia
- Graft-vs-host disease (GVHD)
  - Risks of acute and of chronic GVHD
  - Severity and impact on major transplant outcomes
  - Chronic GVHD after alternative donors
  - Insights on pathophysiology of chronic GVHD
  - Novel therapeutic modalities targeting mechanism of T/B/Treg cells
Major Conclusions of AML Trials <60

1. Maintenance improves DFS but not OS
2. CNS surveillance / prophylaxis unnecessary
3. Inclusion of at least two cycles of HDAC of benefit
4. Allogeneic HCT improves DFS and OS in intermediate and high risk patients
5. Gemtuzumab ozogamicin improves DFS and OS in low and intermediate risk patients
6. Midostaurin improves EFS and OS in patients with ITD and TKD FLT3 mutant AML

Slide courtesy of Fred Appelbaum
Outline

- Graft-vs-host disease (GVHD)
  - Risks of acute and of chronic GVHD
  - Severity and impact on major transplant outcomes
  - Chronic GVHD after alternative donors
  - Insights on pathophysiology of chronic GVHD
  - Novel therapeutic modalities targeting mechanism of T/B/Treg cells
Graft-versus-Host-Disease (GVHD)

- Major barrier of otherwise successful allogeneic hematopoietic stem cell transplantation (HCT)
- Results from an immunological assault of the allogeneic “graft” against the host
- Associated with lower risk of relapse via the graft-versus-leukemia/tumor effect (GVL/T)
NIH GVHD Consensus Project

- Emphasized the differences in clinical manifestations of chronic and acute GVHD
- Defined minimal criteria for diagnosis of chronic GVHD based on manifestations regardless of time after HCT
- Standardized criteria for scoring organ severity and for overall disease severity

Filipovich et al. Biol Blood Marrow Transplant 2005; 11: 945-956
Types of GVHD

**Acute GVHD**

- Classic onset
- Late Onset

- No Prior aGvHD
- Prior Active aGvHD
- Prior aGvHD

**Chronic GVHD**

- Diagnosis of Chronic GVHD
- Classic or Overlap CHRONIC GVHD

- No Prior aGvHD
- Prior Active aGvHD
- Prior aGvHD

**De Novo**
- Progressive
- Quiescent

- Day +100 after HCT
- LATE ACUTE GVHD
EBMT-NIH-CIBMTR Position Statement on Standardized Terminology and Guidance for GVHD Assessment

Schoemans H. et al. Submitted to BMT 10/24/2017
Acute GVHD

Incidence and Severity

Non-Relapse Mortality

Non-myeloablative transplantation: Storb et al., JCO 2013
Similarity in Risk Factors for Acute and Chronic GVHD

- Matching donor type
- Gender mismatch
- Graft type
- Diagnosis
- Conditioning regimen
- Age factors

Chronic GVHD

- Pleomorphic syndrome involving multiple organs with inflammatory and fibrotic clinical manifestations
- 20 to 60% cumulative incidence by 1 year after transplant
- Median onset 6 months after HCT, but ~10% of patients diagnosed beyond one year after transplant
- Median duration of treatment 2.5 – 3.5 years after initial Dx.
- 20% requires continued IS treatment beyond 7 years among those who did not relapse
- Associated with poor quality of life and function status
Risks for Chronic GVHD

Incidence ➪
- Peripheral blood as the graft source of stem cells
- Unrelated donor
- HLA-mismatching donor
- Female donor ➔ Male recipient
- Older age (patient or donor)

Incidence ➥
- T Cell Depletion (*in vitro* or *in vivo*)
- Cyclophosphamide post-transplant
- Umbilical cord blood graft source

What are the severe manifestations of cGVHD
Sclerodermoid or fasciitis chronic GVHD manifestations

20% (95%CI, 18-23) at 3 years

Inamoto, Y. et al. Blood 2013
Risk for Sclerotic/Fasciitis Chronic GVHD

↑ Incidence
- Peripheral blood as the graft source of stem cells
- Mismatched adult unrelated donor
- > 450 cGy TBI in the conditioning regimen

↓ Incidence
- Cord blood as the graft source
- Haplo with cyclophosphamide post-transplant

Inamoto Y et al. Blood 2013
Fatobene G et al ASH 2017 (Abstract #73)
Severity of Chronic GVHD and Major Outcomes

- Non-relapse mortality
- Overall Survival
- Quality of life
- Graft-versus-Leukemia
### Severity of chronic GVHD and Major Outcomes

**NRM, OS and Graft-vs.-Leukemia**

#### A. Non-relapse mortality

<table>
<thead>
<tr>
<th>NIH global score</th>
<th>N. of patients*</th>
<th>Non-relapse mortality HR† (95% CI)</th>
<th>P</th>
<th>N. of patients*</th>
<th>Overall mortality HR† (95% CI)</th>
<th>P</th>
<th>N. of patients*</th>
<th>Recurrent malignancy HR† (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>196</td>
<td>1.00 (reference)</td>
<td></td>
<td>196</td>
<td>1.00 (reference)</td>
<td></td>
<td>194</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>455</td>
<td>4.27 (0.99-18.4)</td>
<td>0.051</td>
<td>455</td>
<td>2.79 (1.24-6.30)</td>
<td>0.013</td>
<td>447</td>
<td>1.26 (0.68-2.35)</td>
<td>0.46</td>
</tr>
<tr>
<td>Severe</td>
<td>320</td>
<td>17.1 (4.12-71.3)</td>
<td>&lt;0.001</td>
<td>320</td>
<td>7.59 (3.42-16.9)</td>
<td>&lt;0.001</td>
<td>314</td>
<td>1.27 (0.64-2.52)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

*Total number of patients contributing to the category at one or more visits.
†Models were adjusted for time after transplantation, transplant center, patients' age, stem cell source, disease risk, cytomegalovirus status, HLA and donor type, gender mismatch, conditioning intensity, prior acute GVHD and thrombocytopenia at the visit.

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Inamoto Y et al, Haematologica 2014: 99:1619
### Chronic GVHD associated with worse Functional Status

<table>
<thead>
<tr>
<th></th>
<th>cGVHD patients* (n=260)</th>
<th>Normal population** (n=260)</th>
<th>Difference score (cGVHD patient minus age-sex matched expected normal value)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>mean 40.94 std 10.83</td>
<td>mean 49.56 std 2.84</td>
<td>mean -8.61 std 10.65</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Role-Physical</td>
<td>mean 36.80 std 11.46</td>
<td>mean 49.71 std 2.24</td>
<td>mean -12.91 std 11.61</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>mean 45.44 std 10.83</td>
<td>mean 49.50 std 1.48</td>
<td>mean -4.05 std 11.03</td>
<td>0.0042</td>
</tr>
<tr>
<td>General Health</td>
<td>mean 41.10 std 9.59</td>
<td>mean 49.71 std 1.11</td>
<td>mean -8.60 std 9.68</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Vitality</td>
<td>mean 45.65 std 10.86</td>
<td>mean 50.77 std 1.50</td>
<td>mean -5.11 std 11.12</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>mean 40.28 std 12.30</td>
<td>mean 50.15 std 0.85</td>
<td>mean -9.87 std 12.32</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Role-Emotional</td>
<td>mean 44.20 std 12.80</td>
<td>mean 50.25 std 1.14</td>
<td>mean -6.04 std 12.84</td>
<td>0.0621</td>
</tr>
<tr>
<td>Mental Health</td>
<td>mean 49.47 std 9.90</td>
<td>mean 50.67 std 1.77</td>
<td>mean -1.21 std 9.97</td>
<td>0.1536</td>
</tr>
<tr>
<td>PCS</td>
<td>mean 38.99 std 9.69</td>
<td>mean 49.33 std 2.67</td>
<td>mean -10.34 std 9.84</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>MCS</td>
<td>mean 48.05 std 10.59</td>
<td>mean 50.83 std 1.83</td>
<td>mean -2.78 std 10.65</td>
<td>0.6606</td>
</tr>
</tbody>
</table>

J Pidala et al, Blood 2011, 17: 1114
Superior patient-reported outcomes in 5-year survivors who received marrow vs. PB unrelated donor transplant

Long-term results of this randomized trial:

Recipients of unrelated donor BM had better psychological well-being, less burdensome chronic GVHD symptoms, and were more likely to return to work than recipients of PB at 5 years after transplantation.

Lee S et al, *JAMA Oncol.* 2016 Dec 1;2(12):1583-1589
Comparison of Chronic GVHD and Functional Status after Alternative Donor Transplantation

- Retrospective study
- All patients > 18 y/o
- First alternative donor hematopoietic cell transplant for any diagnosis in Seattle between 2006 to 2015

Alternative hematopoietic cell donors included:
- 1 allele mismatched unrelated adult
- Cord blood unrelated
- Haploidentical related

Chronic GVHD after Cord Blood, Haploidentical Related and 1-Allele Mismatched Unrelated Donor transplantation

- 396 alternative donor HCT recipients
- 129 developed cGVHD and included in the study.
- Chronic GVHD developed after HCT in:
  - 29 of 163 UCB recipients (3-year CI, 18%)
  - 21 of 88 R-HAPLO recipients (3-year CI 24%)
  - 79 of 145 1-mMUD recipients (3-yeat 55%)
Chronic GVHD severity, function status and duration of IS treatment by type of alternative donors
Severe chronic GVHD manifestation according to Alternative Donor HCT

Conclusions

- UCB and R-HAPLO HCT recipients were less likely to develop cGVHD compared to 1-mMUD group.
- Among those with cGVHD:
  - UCB and R-HAPLO HCT recipients were less likely to develop severe manifestations,
  - had less protracted cGVHD (a shorter duration of systemic treatment), and
  - higher likelihood of resuming work or school,
  - suggesting better QoL compared to 1-mMUD HCT recipients.
Insights in Pathobiology
Pathophysiology of chronic GVHD ~ 3-step model ~

**Phase 1**
Acute inflammation & Tissue injury

**Phase 2**
Chronic inflammation & Dysregulated immunity

**Phase 3**
Aberrant tissue repair & fibrosis

Innate immunity

Adaptive immunity

CD8+ T cell

B cell

CD4+ T cell

NK cell

Pathophysiology of chronic GVHD ~ 3-step model ~

**Phase 1**
Acute inflammation & Tissue injury
- Mature T cell in the donor graft
- Antigen-presenting cells

**Phase 2**
Chronic inflammation & Dysregulated immunity
- Residual activated T cell derived from donor graft
- Self-reactive T & B cells derived from stem cell

**Phase 3**
Aberrant tissue repair & fibrosis
- Follicular helper T cell
- Plasma cells
- Macrophage
- Fibroblast

Treg

Abnormal Cytokine Environment in the Severe Lymphopenia

**Effectors**

- Tcon cells: IL-7↑, IL-15↑
- B cells: BAFF↑
  - Excessive homeostatic proliferation
  - Self-reactive T & B clones↑

**Suppressors**

- Treg cells: IL-2↓
  - Collapse of homeostasis

**Unbalanced immune recovery**
Aberrant B-Cell Signaling in Active Chronic GVHD

- Syk ↑ in cGVHD patients
- B cells from cGVHD ↑ sensitivity to Entospletinib
Potential Targets for GVHD Treatment (2017)

- **Chemokines**
  - CXCL9, -10, -11
  - CXCL3

- **Cytokines**
  - TGFβ
  - TNFα
  - IFNγ
  - IL-2
  - IL-1
  - IL-4
  - IL-6
  - IL-10
  - IL-15
  - IL-17
  - IL-21
  - MCP-1
  - BAFF

- **Abs**
  - PDGFR
  - H-Y
  - αdsDNA
  - ANA
  - ACLA

- **T regs**
- **T conv**
- **Th17/Tc17**
- **TFH/TFR**
- **B cells**
  - Transitional, B regs
- **Endothelial cell**
- **Monocytes/Macrophages**

*Slides courtesy of S. Lee*
**Corticosteroids is the Primary Therapy**

<table>
<thead>
<tr>
<th>Author</th>
<th>Trial No</th>
<th>Treatment Description</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sullivan</td>
<td>179</td>
<td>Prednisone +/- azathioprine</td>
<td>Don't use azathioprine initially</td>
</tr>
<tr>
<td>Sullivan*</td>
<td>61</td>
<td>Steroids qod, CSA</td>
<td>Combination therapy better</td>
</tr>
<tr>
<td>Arora</td>
<td>54</td>
<td>Steroids, CSA +/- thalidomide</td>
<td>No benefit, closed early</td>
</tr>
<tr>
<td>Koc</td>
<td>51</td>
<td>Steroids, CSA/FK +/- thalidomide</td>
<td>No benefit, closed early</td>
</tr>
<tr>
<td>Koc</td>
<td>307</td>
<td>Steroids +/- CSA</td>
<td>No benefit (PDN+CNI less AVN)</td>
</tr>
<tr>
<td>Gilman</td>
<td>42</td>
<td>Steroids, CSA +/- HCQ</td>
<td>No benefit, closed early</td>
</tr>
<tr>
<td>Martin</td>
<td>151</td>
<td>Steroids, CSA +/- MMF</td>
<td>No benefit, closed early</td>
</tr>
<tr>
<td>Carpenter</td>
<td>138</td>
<td>Steroids, Sirolimus +/- CNI (CTN Trial)</td>
<td>No benefit, closed early</td>
</tr>
</tbody>
</table>

* Phase II

- Initial treatment is with steroids at 0.5-1.0 mg/kg/d
- About 30% respond and never need additional therapy
- Median duration of treatment 2-3 years
Treatment of chronic GVHD

- High-dose of glucocorticoids associated with increased risks for serious infections and other severe comorbidities

- Corticosteroids fail to control GVHD in about 40% to 60% of patients
<table>
<thead>
<tr>
<th>Therapies reported in cGVHD beyond First line</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Azathioprine</td>
</tr>
<tr>
<td>- ATG /Atgam</td>
</tr>
<tr>
<td>- Alemtuzumab</td>
</tr>
<tr>
<td>- Alafacept</td>
</tr>
<tr>
<td>- Acitretin</td>
</tr>
<tr>
<td>- Bortezomib</td>
</tr>
<tr>
<td>- Clofazimine</td>
</tr>
<tr>
<td>- Daclizumab</td>
</tr>
<tr>
<td>- ECP (extracorporeal photopheresis)</td>
</tr>
<tr>
<td>- Etanercept</td>
</tr>
<tr>
<td>- Enbrel</td>
</tr>
<tr>
<td>- Hydroxychloroquine</td>
</tr>
<tr>
<td>- Ibrutinib</td>
</tr>
<tr>
<td>- Infliximab</td>
</tr>
<tr>
<td>- Interleukin-2 (IL-2)</td>
</tr>
<tr>
<td>- Mega dose of steroids</td>
</tr>
<tr>
<td>- Methotrexate</td>
</tr>
<tr>
<td>- Mycophenolate mofetil</td>
</tr>
<tr>
<td>- Mesenchymal cells Inf.</td>
</tr>
<tr>
<td>- Pentostatin</td>
</tr>
<tr>
<td>- Proteosome inhibitors</td>
</tr>
<tr>
<td>- Remicaide</td>
</tr>
<tr>
<td>- Rituximab</td>
</tr>
<tr>
<td>- Sirolimus</td>
</tr>
<tr>
<td>- TAI/TLI</td>
</tr>
<tr>
<td>- Thalidomide</td>
</tr>
<tr>
<td>- TKI (imatinib, Nilotinib)</td>
</tr>
<tr>
<td>- T-regulatory cells infusion</td>
</tr>
</tbody>
</table>
Therapies reported in cGVHD beyond First line

- Azathioprine
- ATG / Atgam
- Alemtuzumab
- Alafacept
- Acitretin
- Bortezomib
- Clofazimine
- Daclizumab
- ECP (extracorporeal photopheresis)
- Etanercept
- Enbrel
- Hydroxychloroquine
- Ibrutinib (Only one approved for cGVHD)

- Infliximab
- Interleukin-2 (IL-2)
- Mega dose of steroids
- Methotrexate
- Mycophenolate mofetil
- Mesenchymal cells Inf.
- Pentostatin
- Proteosome inhibitors
- Remicaide
- Rituximab
- Sirolimus
- TAI/TLI
- Thalidomide
- TKI (imatinib, Nilotinib)
- T-regulatory cells infusion
Ibrutinib for steroids dependent/refractory chronic GVHD – Results of Phase I/II (n = 42)

- 65% best overall response observed at median 14 month FU
- 71% of responders had sustained responses at 20 wks
- Most patients with multiple cGVHD organ involvement had a multiorgan response.
- Biomarker changes support Ibrutinib effect on both B- and T- cells in chronic GVHD
- No new safety signals seen with Ibrutinib in this study.
- Most common adverse events were: 
  - fatigue, diarrhea, cramps, nausea, bruising, infections
- Ibrutinib for frontline treatment of cGVHD is underway.

Novel therapeutic modalities targeting mechanism of T/B/Treg

T-targeted therapy

Treg-based therapy

B-targeted therapy

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

Allo-reactive T cells

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

Allo and auto-reactive B cells

Inhibit B cell signaling
- BTK inhibition - ibrutinib
- SYK inhibition - fostamatinib
- entospletinib
## Current clinical trials

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Agent</th>
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<tbody>
<tr>
<td>T-regulatory cells</td>
<td>Infusions +/- sirolimus, IL-2 +/- ECP</td>
</tr>
<tr>
<td>Interleukin-2-inducible T Cell-kinase inhibition</td>
<td>Ibrutinib (ITK)</td>
</tr>
<tr>
<td>B cells/BCR signaling</td>
<td>Ibrutinib (BTK) Entospleteninib, Fostamatinib (SYK) Ofatumumab (CD20)</td>
</tr>
<tr>
<td>IMIDs (immunomodulatory drugs)</td>
<td>Pomalidomide</td>
</tr>
<tr>
<td>Proteosome inhibition</td>
<td>Bortezomib, carfilzomib, ixazomib</td>
</tr>
<tr>
<td>JAK 1/2 inhibition</td>
<td>Baricitinib, ruxolitinib</td>
</tr>
<tr>
<td>ROCK2 inhibition</td>
<td>KD025</td>
</tr>
<tr>
<td>Hedgehog inhibition</td>
<td>LDE225, Vismodegib</td>
</tr>
<tr>
<td>Cellular therapy</td>
<td>Mesenchymal stem cells Dendritic cells</td>
</tr>
</tbody>
</table>
Factors in the Choice of Treatment

Organ involved and severity
Coexisting co-morbidity
Risk of infections
Relevant drug interactions
Intensity of the monitoring needed
Treatment accessibility (distance, cost, etc.)
Treatment Goals

• Adequate control GVHD manifestations aimed to decreased morbidity and prevent progression to more severe disease

• Systematic monitor for early signs of manifestations associated with high morbidity (i.e., deep sclerosis, lung involvement)

• Minimize corticosteroids use without losing control of the disease

• Effective treatment should result in durable responses and without increasing risk of infections, other toxicities or lost of GVL/T effect

• Clinical trials is the only way to advance treatment of chronic GVHD and often the most appropriate treatment for an individual patient
Negative Impact of Chronic GVHD
What Can Be Done

• Prevention
• Pre-emptive treatment
• Improvement of initial treatment
Prevention Strategies

- Successful prevention principles:
  - Effective in preventing chronic GVHD associated with poor quality of live and mortality and
  - Maintain the graft-vs-malignancy effect
Prevention Strategies

Antithymocytes globulin (ATG)
Cytoxan posttransplant
Selective naïve T cells manipulated graft
Selective Depletion of Naïve T cells (T_N) from PBSC Grafts

Will selective T_N depletion reduce GVHD relative to T cell-replete HCT?

Will add-back of T_M by T_N depletion improve immune reconstitution relative to TCD HCT?

Courtesy from Marie Bleakley
Results of the first 30 patients enrolled in the 1st trial of naïve T cell depletion from PBSC

Major reduction in chronic GVHD without an increase in relapse

Chronic GVHD
NIH criteria LTFU team

Relapse

Bleakley, Heimfeld, Shlomchik, Riddell et al BBMT 2014
### GVHD Prevention after PBSCT

**ATG vs. PTCy vs. $T_N$ Depl Graft**

<table>
<thead>
<tr>
<th></th>
<th>ATG-F (RCT)‡</th>
<th>PTCy (SCCA)</th>
<th>$T_N$ Depl. (SCCA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>83 (vs. 72)</td>
<td>43</td>
<td>35</td>
</tr>
<tr>
<td><strong>Median Age (range)</strong></td>
<td>41 (19-55)</td>
<td>38 (3-66)</td>
<td>37 (18-64)</td>
</tr>
<tr>
<td><strong>Donors (Rel. / Unrel.)</strong></td>
<td>Matched (100% / 0%)</td>
<td>Matched (28% / 72%)</td>
<td>Matched (100% / 0%)</td>
</tr>
<tr>
<td><strong>MRD negative</strong></td>
<td>?</td>
<td>51%</td>
<td>63%</td>
</tr>
<tr>
<td><strong>Prep. Regimen</strong></td>
<td>a) 12Gy + Cy or VP16   b) Bu/Cy</td>
<td>a) 12Gy</td>
<td>a) 13.2Gy + TT + Flu</td>
</tr>
<tr>
<td><strong>Chronic GVHD</strong></td>
<td>32% (vs. 69%)*</td>
<td>16%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Acute GVHD, Gr. 3-4</strong></td>
<td>2% (vs. 8%)</td>
<td>0%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>NRM, 2 yrs</strong></td>
<td>14% (vs. 12%)</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Relapse, 2 yrs</strong></td>
<td>32% (vs. 25%)</td>
<td>17%</td>
<td>21%</td>
</tr>
<tr>
<td><strong>Survival, 2 yrs</strong></td>
<td>74% (vs. 78%)</td>
<td>70%</td>
<td>78%</td>
</tr>
</tbody>
</table>

‡ Walker et al., Lancet Onc. 2015

* “Traditional” cGVHD grading

Slide courtesy of Marco Mielcarek
Conclusions

• Advances in pathobiology and better clinical trials design resulted in the 1st FDA approved therapy for chronic GVHD

• An explosion of novelty approaches targeting mechanism involved in chronic GVHD have been emerging in recent years.

• Un-manipulated peripheral blood as the source of stem cells graft when standard GVHD prophylaxis (CNI+MTX) is used alone should be avoided.

• Counseling patients about alternative donor should include the risk of severe chronic GVHD after cord blood or haplo versus mismatched adult URD without T depletion.
Perspective

• Many approaches in preserving GVL without causing severe GVHD are under active investigations

• Better interventions to improve patient outcomes will come from advances in science, BUT
  ....they do take time,
  ....need financial support and
  ....a lot of patience
Acknowledgments

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Dan Egan
Elizabeth Krakow
Rachel Salit

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