Graft-vs-Host Disease: Looking Ahead

Amin M. Alousi, MD
Associate Professor of Medicine
Department of Stem Cell Transplantation

Learning Objectives

• Identify the Current Agents/Methods for GVHD prophylaxis and upcoming trials in Phase 1, 2 and 3 testing
• Outline the Current "Standard Treatment" for Newly Diagnosed Acute GVHD
• Distinguish important factors important for identifying a patient with "Low Risk" and "High Risk" newly diagnosed acute GVHD and how research aims will differ for these two populations.
• Identify the Impact of Lower GI GVHD on non-relapse mortality (NRM) and the importance of institutional strategies/pathways to evaluate and treat these patients.
• Compare limitations of performing drug trials in patients with chronic GVHD and recognize the current drug classes undergoing study consideration.
Yo-Yo of Competing Risks

- Relapse
- GVHD

Yo-Yo of Competing Risks

- Relapse
- GVHD

Yo-Yo of Competing Risks

- Relapse
- GVHD

Yo-Yo of Competing Risks

- Relapse
- GVHD
Looking Forward is Important; But One Must Know the Past First!!!

What is the impact of GVHD and GVHD Treatment on Disease Relapse?

A Truly Must Read for any Transplant Practitioner

Influence of immunosuppressive treatment on risk of recurrent malignancy after allogeneic hematopoietic cell transplantation

Yoshihiro Inamoto, Mary E. D. Flowers, Stephanie J. Lee, Paul A. Carpenter, Edus H. Warren, H. Joachim Dieg, Rainer F. Storb, Frederick R. Appelbaum, Barry E. Stoner and Paul J. Martin

2011 118: 456-463
Risk of early and late recurrent malignancy according to GVHD condition.

- Relapse Rates Gradually Fall for patients with either acute or chronic GVHD until at least 36 months.
- Patients with No GVHD, Relapse Rates fall for first 18 months, flat between 18 -> 30 months then fall again reaching similar rates to those with GVHD by 60 months.

Early (<18 months) and Late Relapse (>18 months) Rates based on Presence or Absence of Acute or Chronic GVHD

- Grade II, Grade III/IV Acute and Chronic GVHD are all associated with similar reductions in rates of late relapse.
- In those with Grade II/IV acute GVHD, subsequent development of chronic GVHD does not further reduce relapse.
- No interaction between donor type, HLA-mismatch, disease risk category and stem cell source.
• In patients with prior GVHD, the reduction in relapse persisted during immune suppressive therapy and after withdrawal.
  – Take Home Message: If patient has GVHD- don’t be in a hurry to stop IST and IST does not increase risk for relapse.

• In patients who do not develop GVHD, relapse rates during immune suppressive therapy peak between 6-9 months post SCT.
  – Take Home Message: If patient does not have GVHD taper immunosuppression per guidelines [MRD: ~3-4 months, MUD (others): ~6 months].

• During the first 12 months, relapse rates in patients w/o GVHD who d/c immune suppression were lower than those who continue IST.
  – Take Home Message: Same as above

• After 24 months, patients with no h/o GVHD and who stopped IST have higher late relapse than those with prior h/o GVHD.
  – Take Home Message: GVHD protects from late relapse and unfortunately even if you stop IST promptly in patients with no h/o GVHD rates for late relapse remain higher.

• Withdrawal of IST was not associated with a significantly decrease risk of late relapse in those with h/o GVHD.
  – Take Home Message: Once GVHD occurs, the withdrawal of IST does not add to benefit in reduction in relapse, i.e. don’t be in too much of a hurry to stop IST in patients with GVHD.

Alousi’s Take Home Message

• Forget the fact that untreated GVHD has high Mortality.
• Forget the fact that Dying of GVHD is no better (and probably worse) than Dying of Relapse.
• Forget the fact that Dying of GVHD is a terrible way to die.
• But don’t forget . . . treating GVHD does not increase the likelihood of relapse.
GVHD-Free, Relapse-Free Survival

• How Do we Measure Success?
  ✓ Alive
  ✓ In Remission
  ✓ No High-Risk Acute GVHD (Grade III/IV)
  ✓ No Chronic GVHD that needs systemic therapy

Happy Camper

GVHD-Free, Relapse-Free Survival

• How Do we Measure Success?
  ✓ Alive
  ✓ In Remission
  ✓ No High-Risk Acute GVHD (Grade III/IV)
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Happy Camper

GVHD-Free, Relapse-Free Survival

• How Do we Measure Success?
  ✓ Alive
  ✓ In Remission
  ✓ No High-Risk Acute GVHD (Grade III/IV)
  ✓ No Chronic GVHD that needs systemic therapy

GVHD-Free, Relapse-Free Survival (GRFS)
Composite endpoint of graft–versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation

by

Sherman G Holtan, Todd E DeFor, Aleksandr Lazaryan, Nelli Bejanyan, Moksh Arora, Claudia G Brunstein, Bruce R Blazar, Margaret L MacMillan, Daniel J Weisdorf

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GRFS: New Composite Endpoint for Clinical Trials

• Attempt to Measure “Cure” without “On-Morbidity”.
• Data from CIBMTR estimates roughly a quarter of patients meet this endpoint @ 1 year.
• Minnesota Examined Risk Factors for GFRS in 907 adult and pediatric allo-HCT recipients for malignant diseases from 2000-2012.

GRFS: New Composite Endpoint for Clinical Trials

• Roughly 30% of patients in this analysis were deemed GVHD and Relapse-Free Survivors @ 1 year (compared to DFS of ~50% and OS~60%).
• In-other-words, while roughly 60% of patients survive to 1 year, but only 1/3rd or so do so without major complication.
Stem Cell and Donor Type impacts GFRS: Dominant Contributors to Failure

- Sib Marrow: NO Acute GVHD III/IV, ↑ relapse
- Sib PB: ↑ Chronic GVHD; ↓ Relapse)
- MUD’s: ↑ Acute GVHD III/IV
- Cords: ↑ Death without Relapse or GVHD

What Impacts GVHD – Relapse-Free Survival Incidences?

- Donor Type
- Age
- Disease Risk
- Graft Type

- Pediatric MRD who received Marrow had the highest GFRS; numbers too small to determine whether there was a difference in adult MUD or MRD recipients between Marrow and Peripheral Blood.

Prevention of GVHD
Overview GVHD Prophylaxis

- Standard GVHD Prophylaxis:
  - CNI + Short Course Methotrexate: The most common regimen for myeloablative Allo HCT.
  - CNI + Mycophenolate Mofetil: The most common prophylaxis for non-myeloablative Allo HCT and UCT.

- Despite the use of these regimens, 25-70% of recipients develop acute and/or chronic GVHD; main contributor to NRM.
- Can we improve upon this?
- Recent Attempts and Future Direction

BMT CTN Protocol 0402
A Phase III Randomized, Multicenter Trial of GVHD Prophylaxis Regimens After HLA-Matched, Related PBSCT

Sirolimus / Tacrolimus
Versus
Tacrolimus / Methotrexate

Study Conduct

- **Eligibility:**
  - AML/ALL in CR, CML CP/AP, MDS
  - Matched Sibling Donor (HLA-A, B, DRB1)
  - Age 2-60
  - No prior transplant or uncontrolled infection
  - Adequate organ function

- **Conditioning:**
  - Cy or VP-16 + TBI (>12 Gy)
  - Initially BuCy was included but removed due to excess toxicity

- **Supportive Care:**
  - No planned G-CSF unless clinically indicated
Study Findings

- **Engraftment**: Tac/Siro results in quicker engraftment
  - Neutrophils: 14 vs. 16 days, p=0.001
  - Platelets: 16 vs. 19 days, p=0.03
  - Time to hospital discharge not different

- **Incidence of Acute GVHD by Day 100**:
  - Grade II-IV: Siro/Tac 26% vs. Tac/MTX 34%, p=0.17
  - Grade III/IV: Siro/Tac 8% vs. Tac/MTX 15%, p=0.05

- **Chronic GVHD**: Higher for Tac/Siro (54% vs. 43%, p=0.044).

- **TRM by Day 100, DFS and OS @ 2 years**: Identical.

- **Within the context of TBI-based, MAC MRD AHCT, Siro/Tac is a suitable alternative to Tac/MTX.**

- **Remains Unknown if Results would differ if MUD’s were studied.**


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GVHD Prophylaxis: Current Strategies being Investigated

- Recent wealth of novel GVHD prevention strategies examined in early phase, single-center trials with encouraging results.

- In addition, two “older” methods of *ex vivo* and *in vivo* T-cell Depletion remain areas of active research.

- Current challenge will be in selecting the most promising approach to move forward into multi-center trials.
Ex Vivo T-cell Depletion: Evidence for and Against

Comparative Analysis of CD34+ Selected, T-Cell Depleted HLA-Matched Sibling Grafts on Allogeneic Hematopoietic Cell Transplantation for Patients with Acute Myeloid Leukemia in Complete Remission

Comparison Outline

BMT CTN 0101

Patients Randomized N=600

No Transplant N=1

Received Transplant N=599

BMT CTN 0303

Patients Randomized N=44

No Transplant N=1

Received Transplant N=43

Eligibility Criteria:
- Age 18-65
- HLA Match-Sibling
- PBSC
- AML in CR1 or CR2

Patients meeting eligibility N=84

AML CR1 N=65

AML CR2 N=19

AML CR1 N=27

AML CR2 N=7
Cumulative Incidences of Chronic GVHD

P=0.001

0101, 50% @ 2 years
0303, 19% @ 2 years


Cumulative Incidence of Treatment-related Mortality

P=0.95

0303, 21% @ 2 years
0101, 19% @ 2 years


Cumulative Incidence of Leukemia Relapse

P=0.57

0101, 27% @ 2 years
0303, 24% @ 2 years

CD34 Selected (TCD) AHCT: Case For and Against

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consistently low rates of Acute GVHD</td>
<td>• Primarily studied/ applied to patients in</td>
</tr>
<tr>
<td>• Lower rates of Chronic GVHD</td>
<td>first CR</td>
</tr>
<tr>
<td>• Comparable TRM</td>
<td>• Requires Ablative Conditioning</td>
</tr>
<tr>
<td>• No apparent impact on DFS &amp; OS for</td>
<td>• So if acute and chronic is lower shouldn’t</td>
</tr>
<tr>
<td>patients in CR1</td>
<td>TRM be less (not the same)?</td>
</tr>
<tr>
<td>• If patients have same survival but</td>
<td>• Death from poor immune reconstitution</td>
</tr>
<tr>
<td>less GVHD (especially chronic) isn’t</td>
<td>and toxicity from conditioning is no better</td>
</tr>
<tr>
<td>this desirable?</td>
<td>than death from GVHD (death is death).</td>
</tr>
<tr>
<td></td>
<td>• Should the bar be lower GVHD which translates into improved OS?</td>
</tr>
</tbody>
</table>

BMT CTN 1301: The PROGRESS II Trial: Prevention and Reduction of GVHD and Relapse Enhancing Survival after Stem Cell Transplantation

Comparison of Two CNI-Free Prophylaxis Regimens: Post-CY versus CD34-Selection in Patients with Acute Leukemia in Remission receiving Myeloablative Conditioning

In Vivo T-cell Depletion: Evidence for and Against
Finke et al. Lancet Oncology. 10(9): 855-64. 2009

Randomized To
ATG-Frensenius 60mg/kg
Or
No Drug

MA Conditioning (TRI-based or Bu/CY)

MTX [15, 10mg/m²]
Days +1, +3, +6, +9, +11

Inclusion Criteria
• Age 2-60 years
• Acute Leukemia/ CML/NOS
• 8/8 HLA-MUD

Cyclosporine Day -3 through Day +100

ATG-F

Finke et al. Lancet Oncology. 10(9): 855-64. 2009

<table>
<thead>
<tr>
<th>Acute GVHD II/IV or Death by Day 100</th>
<th>Acute GVHD III/IV</th>
<th>Chronic GVHD @ 2-years</th>
<th>NRM @ 2-years</th>
<th>Relapse @ 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATG-F</td>
<td>27%</td>
<td>21.7</td>
<td>10.8%</td>
<td>28.3%</td>
</tr>
<tr>
<td>No ATG-F</td>
<td>34%</td>
<td>24.5</td>
<td>28.9%</td>
<td>23.6%</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.59 (0.3-1.7)</td>
<td>0.5 (0.25-1.01)</td>
<td>0.34 (0.21-0.55)</td>
<td>0.68 (0.38-1.22)</td>
</tr>
<tr>
<td>P-Value</td>
<td>0.1</td>
<td>0.011</td>
<td>0.014</td>
<td>0.20</td>
</tr>
</tbody>
</table>

• Primary Endpoint of Acute GVHD III/IV Day 100 Survival: NS
• More EBV PTLD in ATG-F Arm (5 vs. 1 cases)
• Encouraging reduction in Acute and Chronic GVHD
• No apparent impact on relapse
• Randomized Study currently underway in the U.S.A.

Caution!!!
Benefit of ATG may not apply Broadly
Results of CIBMTR Analysis:
Impact of anti-T-cell antibodies on the outcome of RIC HCT for hematologic malignancies:

<table>
<thead>
<tr>
<th>ATG-containing vs. T-cell Replete Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Acute GVHD II/IV</td>
</tr>
<tr>
<td>Acute GVHD III/IV</td>
</tr>
<tr>
<td>Chronic GVHD</td>
</tr>
</tbody>
</table>

Impact of anti-T-cell antibody infusion on outcomes in Reduced Intensity Conditioned HCT.


Non-Relapse Mortality

Relapse

Disease-Free Survival

Overall Survival

ASH 2014 Updates: ATG for Prophylaxis

- Prevention of Chronic GVHD after HLA-matched Sibling PB +/- ATG 30mg/kg days 3 to 7 (Neovi®) before MAC: Prospective, Multi-center, Phase III. Bonifazi et al.
  + Engraftment Delayed in ATG arm.
  + No difference in Acute GVHD (I-IV or III/IV).
  + Less Chronic GVHD @ 2 years (36% versus 73%, p<0.0001).
  + No apparent difference in TRM, RFS or OS.

- Thymoglobulin Decreases the Need for IST @ 12 months after MA and NMA Conditioned MUD HCT: CBMTG 0801: A RCT. Walker et al.
  + PB or BM Allowed, MA or NMA Allowed.
  + Dose of rabbit: ATG was 4.5mg/kg.
  + Freedom from IST @ 1 year was twice as high in ATG –arm (37% vs. 17%, p<0.0001).
  + Benefit seen in MA and NMA groups.
  + No difference in NRM, Relapse or OS.

ASH 2014 Updates: ATG for Prophylaxis

- Higher Dose of ATG (rabbit ATG) increases the Risk of Relapse in AML Patients undergoing MRD HCT in CR1: An Analysis from the Acute Leukemia Working Party of EBMT. Devillier et al.
  + EBM Registry Data, AML CR1, PB and RIC.
  + High Dose ATG >/=6mg/kg (median 7.5mg/kg) vs. Low Dose ATG <6mg/kg (median dose 5mg/kg).
  + Dose did not appear to impact the rates of Acute GVHD II-IV, Chronic GVHD or NRM.
  + Cum Incidence of Relapse was higher in high-dose ATG group (HR 2.3, p=0.003) leading to worst LFS and OS.
New Approaches: Cellular Therapy with Regulatory T-cells (Tregs) to Reduce GVHD

The University of Minnesota Experience in Umbilical Cord Transplantation

Patient Eligibility: Phase I UCB Treg Trial in UCB Transplant Recipients

HLA: 4-6/6
ABO Compatible

HLA: 4-6/6

HLA: 4-6/6

HLA: 4-6/6
**Phase I Treatment Plan for Human UCB Tregs**

- **UCB Treg cell culture**
- Non-myeloablative conditioning
- **Days Post-Transplant**
  - -18
  - -9 ...
  - -3 ...
  - 0
  - +1
  - +15

**UCB Tregs**

**Phase I semi-log dosing:**

1 – 30 x 10^5/kg/dose

**MMF**

**CSA or Rapa**

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**Major Outcomes of Phase I Treatment Plan**

**Primary Endpoint:** No Dose-Limiting Toxicities Seen

- **Grade II-IV Acute GVHD**
- **Viral + Fungal Infections**
- **Relapse at 1 year**

**Cumulative Incidence**

- **Historical**
  - 60%
  - 40%
  - 40%

- **Treg**
  - 43%
  - 39%
  - 35%

**Days Post-Transplant**

- **P = 0.05**
- **P = 0.02**
- **P = 0.43**

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**Future Direction: Tregs**

- University of Minnesota is planning a f/up phase 1 trial utilizing a new expansion method to achieve $T_{\text{effector}} : T_{\text{reg}}$ ratios approaching that found beneficial in mouse models.

- Similar Trial planned at MDACC.
ASH 2014: Increasing Tregs a Pharmacologic Strategy

- Zhao et al. Low Dose Interleukin-2 Therapy Could Prevent Chronic GVHD: A Randomized Study.
  - Preclinical work suggested that low dose IL-2 may preferential expand NK cells and Tregs following allo HCT.
  - Performed a Randomized Control Trial to see if this would translate into prevention of Chronic GVHD.
  - Treatment started on Day 60.
  - Preliminary Analysis of 88 randomized patients (short follow-up, majority less than 1 year).
  - Less Severe Chronic GVHD and TRM in treatment group.
  - Appeared to Expand Regulatory Treg and NK cells while not affecting conventional T cells, Th1 T-cells or Th17 T-cells.

HDAC Inhibitors & Experimental GVHD

- Histone deacetylase inhibitors (HDACi) remodel chromatin, regulate gene expression, and have demonstrable efficacy as anti-cancer agents.
- HDACi reduce pro-inflammatory cytokines, increase regulatory T cell numbers, and attenuate experimental GVHD.
- HDAC inhibition in murine model reduced GVHD with no apparent impact on GVL.

**Pre-clinical Study of SAHA for GVHD Prevention**

- In the mouse model of GVHD where BALB/c mice are transplanted into C57BL/6 after TBI.
- Treating the mice with nanomolar concentrations of SAHA from days+3 to +7 post BMT reduced:
  - inflammatory cytokines,
  - reduced clinical severity scores of GVHD
  - improved survival when compared to control.
- SAHA did not appear to inhibit donor T-cell proliferative or cytotoxic responses.
- Concluded SAHA may reduce GVHD while preserving GVL.


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**Phase II Study: Targeting Histone Deacetylases for GVHD Prevention**

- Safety and Efficacy of vorinostat for reduction in GVHD in patients undergoing matched related donor RIC AHCT.
- **Controls:** Comprised of similarly treated patients using standard GVHD prophylaxis (Tac/MMF).
- **PRIMARY ENDPOINT:** Cumulative incidence of grade 2-4 acute GVHD by day 100 with a target risk of 25%.

Choi et al. Lancet Oncol. 15:87-95. 2014

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**Vorinostat for GVHD Prophylaxis Treatment Schema**

Vorinostat 100mg oral twice daily (days: -10 to +100)

Presented at ASH 2012 by Choi et al.
Phase II Study: Vorinostat for GVHD Prevention

<table>
<thead>
<tr>
<th>Probability of GVHD (%)</th>
<th>Days since Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>0.2</td>
<td>20</td>
</tr>
<tr>
<td>0.4</td>
<td>50</td>
</tr>
<tr>
<td>0.6</td>
<td>75</td>
</tr>
<tr>
<td>0.8</td>
<td>100</td>
</tr>
</tbody>
</table>

STUDY (N=47) vs. CONTROL (N=25)

22 vs. 42%, p=0.03

4 vs. 19%, P=0.07

Choi et al. Lancet Oncol. 15:87-95. 2014

Post-Transplant Cyclophosphamide (Cy) as sole GVHD Prophylaxis

- Researchers at Johns Hopkins Cancer Center have explored methods for GVHD prophylaxis that avoids prolonged immunosuppression.

- Hypothesized that by avoiding prolonged exposure to calcineurin inhibitors would result in quicker immune reconstitution.

- In so doing, they predicted that the main post-transplant complications, GVHD and infections, would be minimized.

Post-Transplant Cyclophosphamide (Cy) as sole GVHD Prophylaxis

- Cy Lacks toxicity to hematopoietic stem cells and spares Tregs which express aldehyde dehydrogenase.

- In mouse models they were able to demonstrate that timed use of post-transplant Cy depletes allo-reactive T-cells and minimizes graft failure and GVHD.

- Previous work has shown that targeting allo-reactive T-cells leads to immunotolerance.

- Basic principle: antigen stimulation → proliferation of T-cells → selective elimination of proliferating allo-reactive T-cells.

Post-Transplant Cy as Prophylaxis

- Reconstitution of Immune System & Development of Tolerance
- Ablation of Alloreactive T-cells
- Antigen Presentation
- Up-regulation of Minor Ags
- Inflammatory Cytokines

- Conditioning Regimen

Post-Transplant Cyclophosphamide (Cy) as sole GVHD Prophylaxis

- 117 patients with various hematologic malignancies treated.
- Incidence of Acute GVHD II-IV and III-IV was 43% and 10%.
- Day 100 NRM was 9%.
- Low infection Rates.
- Chronic GVHD incidence was 10%.
- Only 3 patients remained on immunosuppression at last follow-up.

Can Post-transplant CY be used with less intense Conditioning?

MD Anderson Protocol 2008-0261: Reduced Intensity Bu/Flu followed by Post-transplant Cy for Older-age / Frail Pts with Hematologic Malignancies

Alousi. ASH. 2012. Alousi et al. BBMT. In press. 2015

Treatment Plan

<table>
<thead>
<tr>
<th>Day</th>
<th>BU Test Dose</th>
<th>FLU Test Dose</th>
<th>CY Test Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/m²</td>
<td>mg/m²</td>
<td>mg/kg</td>
</tr>
<tr>
<td>0</td>
<td>32</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>+1</td>
<td>BU</td>
<td>FLU</td>
<td>CY**</td>
</tr>
<tr>
<td>+2</td>
<td>BU</td>
<td>FLU</td>
<td>CY**</td>
</tr>
<tr>
<td>+3</td>
<td>BU</td>
<td>FLU</td>
<td>CY**</td>
</tr>
<tr>
<td>+4</td>
<td>BU</td>
<td>FLU</td>
<td>CY**</td>
</tr>
</tbody>
</table>

* Only MUD's received ATG
** No additional immunosuppression unless developed GVHD
*** Bone Marrow preferred (but not mandated) over Peripheral Blood HCT

Post-transplant CY vs. Matched-Controls**

<table>
<thead>
<tr>
<th></th>
<th>Post-transplant CY</th>
<th>Tacrolimus/MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[95% CI]</td>
<td>[95% CI]</td>
</tr>
<tr>
<td>Acute GVHD-Gd II/IV</td>
<td>10% (5-20)</td>
<td>10% (9-16)</td>
</tr>
<tr>
<td>Acute GVHD-Gd III/IV</td>
<td>14% (9-25)</td>
<td>14% (10-18)</td>
</tr>
<tr>
<td>Chronic GVHD-1 yr</td>
<td>22% (12-40)</td>
<td>22% (12-40)</td>
</tr>
<tr>
<td>MNH @ 2 years</td>
<td>13% (10-16)</td>
<td>13% (10-16)</td>
</tr>
<tr>
<td>OS @ 5 years</td>
<td>52% (25-67)</td>
<td>52% (25-67)</td>
</tr>
<tr>
<td>OS @ 10 years</td>
<td>52% (25-67)</td>
<td>52% (25-67)</td>
</tr>
</tbody>
</table>

* 49 patients enrolled for which matching could be done (37/47 non-matched patient outcomes did not differ).
** Patient matching using a computer-generated algorithm in order of priority: Age, Diagnosis, Disease Status, Donor Type, Graft Source

Alousi. ASH. 2012. Alousi et al. BBMT. In press. 2015
Two Trials of Bu/Flu followed by Post-CY. Kanaky et al. vs. Alousi et al.

- Bu/Flu MA: AUC 5,000 (vs. 4,000)
- Median Age: 49 years (vs. 62 years with a median CMI of 3)
- Acute GVHD II-IV: 51% (vs. 53%)
- Acute GVHD III/IV: 15% (vs. 22%)
- Chronic GVHD: 14% (vs. 18%)
- Relapse: 22% (vs. 36%)
- OS @ 2 years: 67% (vs. 33%)

- Identical Rates of GVHD but differing Survival
- Impact of Higher rates of Acute GVHD in older, more frail population.
- NRM related to GVHD differs based on patient population.

Post-CY

- Post-transplant CY may need to be combined with additional immunosuppression when used with less intensive conditioning and/or older/frailer patients.
- Post-transplant CY has combined with Tacrolimus/MMF
  - Studied in recipients of T-cell replete bone marrow grafts from haploidentical donors following non-myeloablative conditioning with low rates of GVHD.
  - Incidence of Acute GVHD II-IV 34%
  - Incidence of Extensive Chronic GVHD 5%.


Bortezomib for GVHD Prevention

- Proteasome inhibitor bortezomib has immunomodulatory properties that may be beneficial as GVHD prophylaxis.
- Researchers at the Dana-Farber performed a Phase I/II study in 45 recipients of T-cell replete, peripheral blood grafts from 1 or 2-loci MM Unrelated Donors following RIC.
- Bortezomib was given on Days +1, +4, +7 in combination with Tacrolimus/Methotrexate.

Bortezomib for GVHD Prophylaxis

Treatment Schema


Bortezomib for GVHD Prevention

- Acute GVHD II-IV and III/IV @ Day 180= 22% and 7%.
- Chronic GVHD @ 1-year= 29%.
- NRM @ 2-years= 11% with minimal toxicity from study drug.
- GVHD and Survival outcomes compared favorably to a contemporaneous Cohort who received a 8/8 MUD PB HCT with Sirolimus-based GVHD prophylaxis at their center.


Prevention of GVHD through Controlling T-cell Trafficking to GVHD target tissues
**Modified Billingham’s Criteria: Requirements for GVHD**

- Graft must contain immunocompetent cells.
- Host cells must have antigens (proteins) for which the graft cells recognize as foreign.
- The host must be unable to mount an attack against the graft (must be immunosuppressed).
- **Effector cells have to traffic to GVHD organs.**

**Background for Maraviroc Phase I/II Trial**

- Chemokine Receptor 5 and its natural ligands CCL3/4 and 5 have been implicated in the pathogenesis of GVHD and solid organ rejection.
- Maraviroc (MVC) is the first drug in the class of CCR5 antagonists.
- Noncompetitive, slowly reversible small-molecule antagonist that prevents signaling by all three ligands.
- Drug is licensed for use in combination therapy for patients infected with a HIV subtype which is dependent solely on the CCR5 co-receptor to enter cells (CCR5-tropic HIV).

**Background Studies for Phase I/II Study**

- Hypothesized that MVC use early after allogeneic HCT might inhibit lymphocyte trafficking and decrease the incidence of acute GVHD (especially Gut and Liver).
- **Good Safety Profile**
  - No effect on T cell function.
  - In vitro tests on CD8+ T cells exposed to CMV peptide in presence or absence of MVC demonstrated no impact on antigen-specific proliferation and cytotoxicity.
  - No impact stem cell proliferation.
Treatment Schematic: Phase I/II Study

Bu 6.4mg/kg
Flu 120mg/m2

PBSCT

MVC

+ Tacro

Day -2
Day 0
MTX

15mg/m2,
10mg/m2

+30

MVC given as 150mg or 300mg
Oral twice daily until day 30
Suspended for mucositis or toxicity.

Clinical Trial Outcomes of Acute GVHD, Moderate-to-Severe Chronic GVHD, and Organ-Specific Acute GVHD.

- Gd II/IV: 14.7%
- Gd III/IV: 2.9%
- Day 180 Gd II/IV: 24%
- Day 180 III/IV: 6%

Minimal GI and Liver GVHD

BMT CTN Protocol 1203
A Randomized, Multi-center, Phase II Trial Comparing Novel Approaches for Prevention of Graft-versus-Host Disease

- Age > 18 years
- All Diseases
- Marrow Remission or Chemosensitive tumor
- MRD or MUD Donors
- Peripheral Blood
- RIC/NMA Conditioning

Post-transplant Cy + Tacrolimus/MTX
Maraviroc + Tacrolimus/MTX
Bortezomib + Tacrolimus/MTX

Prospectively Matched CIBMTR Cohort
Acute GVHD Therapy

Therapy of Acute GVHD

- Grade I (Less than 50% BSA Rash):  
  - Initial therapy is usually topical steroids alone.  
  - Systemic Steroids given for rash that persists/ worsens or new organ.

- Isolated Upper GI GVHD:  
  - High response Rate with Prednisone 1mg/kg followed by rapid taper with or without non-absorbable steroid.

Therapy of Acute GVHD

- Grade II-IV Acute GVHD:  
  - Standard Therapy: Methylprednisone (or Prednisone) @ 2mg/kg.  
  - Day 28 RR is approximately 55%, worst for Lower GI versus other organs.  
  - What is the appropriate steroid starting dose?  
  - No improvement in response rate or outcome by addition of 2nd agent.  
    - ATG  
    - Anti-interleukin-2 Receptor Antibodies (Daclizumab)  
    - Anti-TNF alpha agent (infliximab)  
    - Mycophenolate mofetil
Initial Dose of Steroids for Acute GVHD

- Prospective randomized study of high versus low dose steroids:
  - Grade Ila AGVHD (Upper GI GVHD, Stool Volume < 1 liter, rash <50% and no liver involvement)
    - Randomized
    - 1.0 mg/kg/day vs. 0.5 mg/kg/day

  Prednisone-equivalent dosing

Mielcarek. ASH. 2013

Initial Dose of Steroids for Acute GVHD

- Prospective randomized study of high versus low dose steroids:
  - Grade IIb to IV AGVHD (Rash > 50% BSA, Stool Volume > 1 liter and any liver involvement)
    - Randomized
    - 2.0 mg/kg/day vs. 1.0 mg/kg/day

  Prednisone-equivalent dosing

Mielcarek. ASH. 2013

No Impact on Reduction in Cumulative Dose

- Primary Outcome: 33% Reduction in Day 42 Cumulative Dose of Steroids.
  - Grade Ila Cohort: 1mg/kg vs. 0.5mg/kg/day Initial Dose
    - 27mg/kg vs. 22 mg/kg (18% reduction, p=0.08)
  - Grade IIb-IV Cohort: 2mg/kg vs. 1mg/kg/day Initial Dose
    - 41mg/kg vs. 38mg/kg (7% reduction, p=0.4)

Mielcarek. ASH. 2013
No Impact on Reduction in Cumulative Dose

- Secondary Outcomes:
  - Measures of prednisone toxicity (infections, hyperglycemia)
  - Possible harm (progression to Grade III/IV GVHD, secondary therapy for refractory GVHD, non-relapse mortality, recurrent malignancy).
- Grade III-IV Cohort:
  - No difference in NRM, Relapse and OS.
  - Patients who started treatment with lower-dose prednisone were more likely to require secondary systemic immunosuppressive therapy than those who started treatment with higher-dose prednisone (41% vs 7%, \( p < 0.001 \)).
  - Trend suggested an increase in the risk of progression to Grade III-IV acute GVHD (19% vs 7%, \( p = 0.2 \)).
  - The risks of infection and measures of glycemic control were not affected by initially assigned prednisone dose.

Conclusions:

- Acute GVHD Limited to Upper GI GVHD and Skin Rash <50%.
  - Patients started on 0.5mg/kg/day vs. 1mg/kg/day:
    - Trend for lower cumulative dose of steroids
    - No impact on secondary outcomes (benefit or adverse effect).
- Rash >50%, Stool > 1 Liter and/or Liver Involvement.
  - 2mg/kg/day should remain the starting dose.
  - No Reduction in Cumulative Dose
  - Worst secondary Outcomes (much more likely to need secondary therapy and trend for progression to higher grade GVHD).

Incorporation of Biomarkers to Identify High-Risk Patients with New Onset GVHD

*Who are the patients identified as High-Risk?*

**Answer:**

Patients with or who will develop Unresponsive lower GI GVHD.

---

* Slides and Data Compliments of John Levine
  EEBMT. 2014. (Current Oncology in Press)
ANN ARBOR SCORES
BIOMARKERS AND GI GVHD

- TNFR1: TNFα amplifies GI injury  
  Schmaltz Blood 2003
- ST2 and its ligand IL33 regulate inflammatory bowel disease activity  
  Pastorelli PNAS 2010
- REG3α protects intestinal epithelial cells from damage  
  Ogawa Inflamm Bowel Disease 2003
- 80% of GVHD-related NRM occurs in pts with poorly responsive GI GVHD  
  unpublished data (UM/Regensburg)

Acute GVHD Clinical Grade and Biomarker Grade (called Ann Arbor) @ GVHD Onset

<table>
<thead>
<tr>
<th>Acute GVHD Clinical Grade (Glucksberg Grading)</th>
<th>Ann Arbor I (Biomarker Grade)</th>
<th>Ann Arbor II (Biomarker Grade)</th>
<th>Ann Arbor III (Biomarker Grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I (n=51)</td>
<td>23%</td>
<td>59%</td>
<td>18%</td>
</tr>
<tr>
<td>Grade II (n=183)</td>
<td>25%</td>
<td>56%</td>
<td>19%</td>
</tr>
<tr>
<td>Grade III/IV (n=69)</td>
<td>26%</td>
<td>49%</td>
<td>25%</td>
</tr>
<tr>
<td>Total: 303 patients</td>
<td>25%</td>
<td>55%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Biomarker Grading Can Outperform Clinical Grading by Identifying Seemingly Low-Risk Patients who are Actually High-Risk and vice-versa

GVHD BIOMARKER SCORES

- Goal: Identify high risk patients at onset (not max)
  - 3 biomarkers: TNFR1, ST2, REG3α
- Onset GVHD samples
  - 492 UM and Regensburg pts (training and validation)
  - 300 BMT CTN pts (multicenter validation)
- Use of 6 mo NRM as clean objective endpoint
  - Statistical model in training set (n=328) provides NRM probability for each patient
- Rank order the probabilities and identify thresholds that stratify patients such that 6m NRM:
  - Ann Arbor 1: ≤10%
  - Ann Arbor 2: 10%-40%
  - Ann Arbor 3: ≥40%
- Correlate scores with d28 treatment response
- Validate thresholds in two independent cohorts

* Slides and Data Compliments of John Levine  
  EEBMT 2014 (Lancet Oncology In Press)
ANN ARBOR GVHD SCORES

BMT CTN (n=300)

TREATMENT RESPONSE

* Slides and Data Complements of John Levine
EEBMT 2014 (Lancet Oncology In Press)
SUMMARY

- Identifies a high risk population across clinical severity presentations
  - Ann Arbor 3 GVHD = ~22% of mild, moderate, or severe GVHD
- Ann Arbor 3 enriches for HR GI GVHD
- Incorporating clinical grading into the algorithm does not improve stratification but increases size of strata 1 and 3
- (Similar effect on strata size can be achieved by adjusting thresholds in the biomarkers only algorithm)

Evaluation of GI GVHD

- Have an institutional pathway for patients with suspected GI GVHD.
- Admit when need to expedite work-up or for severe symptoms (unable to tolerate diet, severe diarrhea resulting in dehydration).
- Flex Sigmoid with Random Rectal Biopsies correlates with Pathology from Proximal Bowel.
- EGD (with duodenal biopsy) + Flex Sig has highest yield.*
- Do not give Prep with flex sig as can induce grade 1 histologic changes in path.

Most Important Slide of Lecture!!

Do Not Delay Therapy for Lower GI GVHD
Chronic GVHD

Who Needs Systemic Treatment?

<table>
<thead>
<tr>
<th>Chronic GVHD manifestations based on Global Severity Score</th>
<th>Systemic Treatment Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td></td>
</tr>
<tr>
<td>- ≤ 2 sites involved (no lung), all with mild scoring on Global Severity Score (asymptomatic or symptoms not interfering function), no high risk features*</td>
<td>No</td>
</tr>
<tr>
<td>- ≤ 2 sites involved (no lung), all with mild scoring on Global Severity Score (asymptomatic or symptoms not interfering function), but with high-risk features**</td>
<td>Yes</td>
</tr>
<tr>
<td>- ≤ 2 sites but one is lung.</td>
<td>Yes</td>
</tr>
<tr>
<td>- &gt; 2 sites.</td>
<td>No</td>
</tr>
</tbody>
</table>

Any site Moderate or Severe

Yes

*High-risk feature: Platelets < 100,000, skin involvement > 50% BSA, Progressive-Onset (Chronic GVHD already being treated with steroids > 0.5mg/kg) at chronic manifestation onset.

Individual organ severity scoring within global severity categories

More than 90% of patients will have Moderate or Severe Chronic GVHD Based on NIH Severity Scoring
Treatment of Chronic GVHD

- Steroids 1mg/kg +/- CNI
- No FDA Approved Therapy for Chronic GVHD
- Previous Randomized Study of MMF closed early due to higher death (and trend for higher relapse) in MMF arm compared to steroids alone
- Large Case Series for ECP in chronic GVHD.
- Randomized study of ECP/ steroids versus steroids, what was learned?
  - *Greinix et al. BBMT. 17:1775-82. 2011.*

Prospective, Randomized Control Trial of ECP in Chronic GVHD

- Only published prospective, randomized control trial of ECP in chronic GVHD.
- This single-blind, multicenter study randomized 100 patients in a 1:1 ratio to ECP therapy in addition to conventional immunosuppression versus conventional immunosuppression alone.
- Eligible patients received at least 2 weeks of steroids and were considered steroid-refractory, dependent or intolerant.

*Flowers M E D et al. Blood 2008;112:2667-2674*

Prospective, Randomized Control Trial of ECP in Chronic GVHD

- ECP was administered on 3 days for the first week, and then twice weekly (on consecutive days) through 12 weeks.
- Patients in the ECP arm who responded were allowed to continue with 2 ECP sessions every 4 weeks until week 24.
- Control arm patients were allowed to cross-over to ECP if progressed or after completion of 12 weeks.

*Flowers M E D et al. Blood 2008;112:2667-2674*
Prospective, Randomized Control Trial of ECP in Chronic GVHD

- The primary objective was to determine the effect of ECP treatment on the cutaneous manifestations of cGVHD at week 12.
- Skin was the only organ studied in primary study.
- Non- or poorly validated Total Skin Score was used as primary measure of response.
- Blinded, trained expert assessed baseline and 12 week evaluation.


Improvement in Total Skin Score (TSS) and reduction in steroid dose through week 12.

- Median changes in TSS from baseline until week 12: ECP(14.5%) and control (8.5%) arms were not statistically different (p=.48).
- 25.0% (n = 12) of ECP-patients and 12.8% (n = 6) of control-patients had a 50% reduction in steroids (P = .15).
- % of patients having both a 50% or > reduction in daily steroid dose and a 25% or > reduction in the TSS was higher in the ECP group than the control group (8.3%; 4 patients vs 0 patients; P = .04).
- 25.0% the ECP-patients and 6.4% of the control-patients had a 50% or > reduction in steroid dose and a daily dose of < 10 mg/day (P = .04).


Median Absolute Change in TSS Through Week 24

Greatest Reduction in TSS Seen After 12 weeks
Un-blinded assessment of Skin Involvement by an Experienced Clinical Investigator

Cumulative incidence of complete or partial skin response

Study Week

Probability of a Response

ECP

Control

p < 0.0001

Disposition of patients enrolled in initial randomized and crossover open-label ECP study

Hildegard T. Greinix, Koen van Besien, Ahmet H. Elmaagacli, Uwe Hillen, Andrew Grigg, Robert Knobler, Dennis...

Progressive Improvement in Cutaneous and Extracutaneous Chronic Graft-versus-Host Disease after a 24-Week Course of Extracorporeal Photopheresis—Results of a Crossover Randomized Study

Biology of Blood and Marrow Transplantation, Volume 17, Issue 12, 2011, 1775 - 1782

Greatest Reduction seen after 12 weeks.
How Do We Know if Our Chronic GVHD Therapy is Working?

How do we measure response?

Clinical Benefit of Response in Chronic Graft-versus-Host Disease

Inamoto / Lee et al. on behalf of the Chronic GVHD Consortium. Biology of Blood and Marrow Transplant. 18: 1517-24. 2012
Chronic GVHD Patient Consortium

- 283 patients prospectively assessed.
- Roughly 80% “Overlap”/ 20% “Classic” Chronic
- Median age was 51 years (2-79)
- Skin, Mouth, liver, lungs and Eyes most commonly involved.
- 28% severe, 59% moderate and 13% mild chronic GVHD based on NIH Severity Classification.

Calculated response overall and in individual organs at 6 months after enrollment, according to the provisional algorithm

Survival outcomes according to overall response at 6 months.
(A) OS. (B) NRM.
NIH Consensus Response Does not Translate into improvement in QOL

<table>
<thead>
<tr>
<th>QOL Measure</th>
<th>Clinical Meaningful Change</th>
<th>Prevalent Cases</th>
<th>Incident Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 PCS</td>
<td>4.8</td>
<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>5.2</td>
<td>0.9</td>
<td>0.1</td>
</tr>
<tr>
<td>FACT-BMT</td>
<td>9.9</td>
<td>5.4</td>
<td>0.14</td>
</tr>
<tr>
<td>HAP-MAS</td>
<td>6.3</td>
<td>4.0</td>
<td>21.9</td>
</tr>
<tr>
<td>HAP-AAS</td>
<td>8.3</td>
<td>3.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Inamoto, Lee, et al.  
Clinical Benefit of Response in Chronic Graft-versus-Host Disease  
Biology of Blood and Marrow Transplantation, 2012; 1517 – 1524.

How Do we Assess Response?  
**Answer: We have No Idea!!**

- "Physician Knows Best": not stringent, too subjective.
- NIH Global Severity Response Assessment: too stringent and inadequately captures clinically meaningful responses.

Challenging (if not impossible) to show benefit in a randomized study in Chronic GVHD when there is no valid end-point:

*How does one define (show) response (benefit)*?

*Looking Ahead: We need to know how to study this disease!!*
**Thinking Ahead: Strategies for Increasing Tregs in Patients with Chronic GVHD**

- ECP
- Rapamycin
- Ex-vivo Expanded Tregs
- Low-dose IL-2

**ASH 2014: Low-Dose IL-2 for Steroid Refractory Chronic GVHD: Phase 2 and Long Term Efficacy, Safety and Immune Correlates. Koreth et al.**

- 35 Patients with St. Refractory chronic GVHD, Median 4 organs involved, Median of 2 concurrent therapies at enrollment, median dose of steroids was Prednisone 20mg.
- Dose $1 \times 10^6$ IU/m²/day Sub-Q for 12 weeks.
- Well tolerated: 2 patients withdrew; 5 patients (out of 35) requiring dose reduction.
- Objective Response Rate at week 12 was 21/33 patients with 2 patients progressing.
"It Takes a Whole Medical Center to Care for a BMT Patient"

- Gynecology
- Nursing
- Pharmacy
- Pulmonary Medicine
- Dermatology
- Ophthalmology
- Gastroenterology
- Infectious Disease
- Nutrition
- Radiology
- Pathology
- Transfusion Services

GVHD Clinic

- Amin M. Atousi, MD
- Sharon Hymes, MD
- Joyce Neumann, PhD., APN
- Tamera Alexander, PA
- Bethany Overmann, RN
- Nutrition
- Pathology
- Nursing
- Pulmonary Medicine
- Gastroenterology
- Infectious Disease
- Ophthalmology
Impact of Age on GFRS: Pediatrics- Relapse Accounts for Higher Amount of Failures; Adults- Death without Relapse or GVHD

Conditioning Impact on GFRS: Relapse Accounts for Higher Amount of Failures in RIC
**Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ECP + Steroids N=48</th>
<th>Control Arm N=47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, years</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>Corticosteroid-status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Corticosteroid-dependent</td>
<td>28 (58%)</td>
<td>25 (53%)</td>
</tr>
<tr>
<td>• Corticosteroid-refractory</td>
<td>7 (15%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>• Corticosteroid-intolerant</td>
<td>13 (27%)</td>
<td>17 (36%)</td>
</tr>
<tr>
<td>Median days from BMT to cGVHD (range)</td>
<td>140 (69-637)</td>
<td>129 (70-1389)</td>
</tr>
<tr>
<td>Median days from cGVHD to randomization (range)</td>
<td>569 (25-2743)</td>
<td>830 (1-2248)</td>
</tr>
<tr>
<td>Dropout type of cGVHD, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Progressive</td>
<td>28 (58%)</td>
<td>25 (53%)</td>
</tr>
<tr>
<td>• Quiescent</td>
<td>5 (10%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>• de novo</td>
<td>15 (32%)</td>
<td>16 (34%)</td>
</tr>
<tr>
<td>TSS at baseline, median (range)</td>
<td>9.4 (0.6-23.6)</td>
<td>9.2 (1.0-20.7)</td>
</tr>
</tbody>
</table>

**Patient Characteristics (continued)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ECP + Steroids N=48</th>
<th>Control Arm N=47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracutaneous GVHD involvement, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ocular</td>
<td>27 (56.3%)</td>
<td>28 (59.6%)</td>
</tr>
<tr>
<td>• GI</td>
<td>2 (4.2%)</td>
<td>9 (18.5%)</td>
</tr>
<tr>
<td>• Liver</td>
<td>14 (28.3%)</td>
<td>14 (29.8%)</td>
</tr>
<tr>
<td>• Lung</td>
<td>9 (18.8%)</td>
<td>7 (14.9%)</td>
</tr>
<tr>
<td>• Oral mucosa</td>
<td>30 (62.5%)</td>
<td>30 (61.8%)</td>
</tr>
<tr>
<td>• Joints</td>
<td>18 (37.5%)</td>
<td>16 (34%)</td>
</tr>
<tr>
<td>Median duration (wks) of corticosteroid usage for cGVHD before study entry (range)</td>
<td>52 (2.7-426)</td>
<td>55 (1.9-310)</td>
</tr>
</tbody>
</table>


Disposition of patients enrolled into the study.

Audience Response Question #1
Which of the following statements is true regarding the interaction of gvhd, gvhd therapy and relapse:

A. Acute GVHD III/IV is associated with less relapse than lower grades acute gvh.
B. Patients who have both acute and chronic gvh have a lower likelihood of relapse than patients with just acute or chronic.
C. GVHD protects from early relapse (relapse which occurs in the first 18 months post-HCT.
D. Treating patients who have GVHD does not increase their risk of relapse.

Audience Response Question #2
GVHD-Free, Relapse-Free Survival [GRFS] is a new composite endpoint which defined as being Alive, in Remission, without history of Grade III/IV Acute GVHD and without Chronic GVHD that requires systemic treatment. At 1-year, what is the estimated likelihood that a recipient of an allogeneic HCT will meet this definition:

A. 15-25%
B. 25-35%
C. 35-50%
D. 50-65%

Audience Response Question #3
With respect to anti-thymocyte globulin (ATG) for GVHD prophylaxis, which is a true statement:

A. Fresenius ATG has been shown to lower the incidence of chronic GVHD in a randomized, control trial in recipients of MUD grafts following myeloablative conditioning.
B. It is clearly been shown that the benefits of ATG extend to all forms of conditioning intensity (ablative versus non-myeloablative).
C. Outcomes are the same regardless of the dose of rabbit ATG as long as the total dose is less than 10mg/kg.
D. All the above are true.
Audience Response Question #4

With respect to initial dose of corticosteroids in patients with newly-diagnosed acute GVHD, a single-center, randomized trial of 1mg/kg versus 2mg/kg for patients with grades IIb and higher (rash more than 50%, stool output more than 1 liter/day and/or any liver involvement) showed that patients randomized to 1mg/kg experienced which of the following:

A. Less toxicity (infections and need for insulin).
B. Lower cumulative dose of steroids.
C. Higher likelihood of needing a second-line therapy.
D. Less likely to progress to higher grade acute GVHD.

Audience Response Question #5

Which is true regarding treatment of patients with chronic GVHD:

A. The 2005 NIH Consensus Guidelines for measuring response to therapy have been validated and shown to correlate with non-relapse mortality and quality-of-life.
B. Newer strategies are focusing on methods of increasing regulatory T-cells (Tregs) to promote tolerance.
C. Patients with 2 organs involved, all classified as mild severity on NIH scoring generally are treated with systemic steroids.
D. All of the above.