Roswell Park Cancer Institute Blood and Marrow Transplantation (BMT) Update

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Blood and Marrow Transplant Program
Roswell Park Cancer Institute
2015
The presentation will include off-label use of drugs for multiple myeloma treatment

<table>
<thead>
<tr>
<th>Role</th>
<th>Conflicts of Interest</th>
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<tr>
<td>Research Support/P.I.</td>
<td>No relevant conflicts of interest to declare</td>
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<tr>
<td>Employee</td>
<td>No relevant conflicts of interest to declare</td>
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<tr>
<td>Consultant</td>
<td>Bristol Myers Squibb, Celgene, Janssen, Karyopharm, Millenium, Onyx, Sanofi, The Binding Site</td>
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<tr>
<td>Major Stockholder</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Speakers Bureau</td>
<td>No relevant conflicts of interest to declare</td>
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<td>Honoraria</td>
<td>Bristol Myers Squibb, Celgene, Janssen, Karyopharm, Millenium, Onyx, Sanofi, The Binding Site</td>
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<tr>
<td>Scientific Advisory Board</td>
<td>No relevant conflicts of interest to declare</td>
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Disclosures

- The presentation will include off-label use of drugs for treatment of hematologic malignancies and cellular therapies
- Consultation, Advisory Board participation and Honoraria from The Binding Site, Bristol Myers Squibb, Celgene, Janssen, Karyopharm, Takeda/Millenium and Sanofi
Acute lymphocytic leukemia (ALL): Case Report

- 01/14: 28 y.o. male: precursor B cell ALL, 6 cycles of Hyper-CVAD, plan for allogeneic BMT but delayed
- 10/14: Bone marrow test: 78% blasts, CD 10+, CD20+, CD22+, partial trisomy 9 by FISH. Re-induced as per CALGB 10403 (dose intensive regimen for AYA patients)
- 11/14: Bone marrow test: 30% blasts, liposomal vincristine complicated by myopathy, started on prednisone
- 12/14: Goesto MSKCC for CD19 CAR-T-cell rx, 2 CAR-T cell infusions beginning 01/15
- 04/15: Bone marrow test: 78% blasts, Blinatumomab (bi-specific T-cell engager, CD3 and CD19) for 1 cycle
- 05/15: Hypercalcemia, acute kidney injury, Bone marrow test: 100% blasts, FLAG-IDA re-induction & liposomal vincristine, Bone marrow test: ~50% blasts
- 06/15: Severe abdominal pain/ileus, inotuzumab ozogamicin (anti-CD22 & calicheamicin) for 3 doses over 2 weeks, bone marrow test <1% blasts with molecular clonality and +MRD by flow (0.02%) Cytogenetics: Absent trisomy 9
- 07/15: Sibling (female) allogeneic blood stem cell transplant after fludarabine and melphalan, Day +22 bone marrow test NED by flow, 500/500 female cells & clonal B cell gene re-arrangement, Day +38 bone marrow aspirate NED by flow and cytogenetics, B cell gene rearrangement pending
Bone Marrow and Cord Blood Units

http://hematopoiesis.info/2008/10/04/private-cord-blood-banking-worth-your-money/
Mobilization of Stem Cells into the Peripheral Blood

Fig 1. Kinetics of CD34+ cells (A) and CFU-GM (B) in the peripheral blood of healthy donors treated with G-CSF 5 µg kg (n = 2) or G-CSF 10 µg kg (n = 6). Measurements were performed before administration of G-CSF on the corresponding day.

Dreger et al BJH 1994
Types of Transplants

- **Syngeneic**
  - Identical twin

- **Allogeneic**
  - From another person
    - family member (sibling, parent, other relative)
    - unrelated donor

- **Autologous**
  - Self
RPCI BMT Program

- Autologous up to age 80
- Allogeneic
  - Myeloablative up to age 60
  - Reduced Intensity up to age 80
- Goal: Increasing patient access with decreasing mortality and improved outcome
  - Reduce the toxicity of chemotherapy and radiation therapy
  - Reduce the toxicity of Graft-versus-Host Disease (GvHD) and preserve the Graft-versus-Tumor (GvT) effect
RPCI Cord Blood Transplant Experience

- First CBT: May 1997, most recent CBT: Sept 2015
- 36 total, 33 Single CB, 3 Double CB, 7 alive, 6 disease free, 3 are >15 years from CBT
- Deaths: Infection n=8, Relapse of disease: n=7, GvHD n=5, RRT n=4, Cardiac disease n=2, hemorrhage n=1, second cancer n=1
- There are several strategies to overcome the risk of infection, relapse, severe GvHD and toxicity
RPCI BMT Program Outcomes

- Most recent outcomes report
- 1/1/2010-12/31/2012 with follow-up to 12/31/2013
- N=148 patients
- Actual 1-year survival rate = 70.9%
- Predicted 1-year survival rate = 62.2%
- 95% CI predicted 1-yr survival rate = 55.1%-69.6%
- Result: RPCI actual 1-year survival is statistically significantly higher than predicted
Hematopoietic Stem Cell Transplantation - Classification -

**Allogeneic**
- HLA-identical sibling
- Other relative
- Unrelated

**Syngeneic**

**Autologous**

**Donor**

**Non-myeloablative**
- Umbilical cord blood

**Reduced Intensity**
- Bone Marrow
- Peripheral Blood

**Myeloablative**
- Peripheral Blood
- Bone Marrow

**Conditioning Regimen Intensity**
- Reduced Intensity
- Myeloablative

**Graft Source**
- Ex vivo expansion
- In vivo selection

**Graft manipulation**

Courtesy M Pasquini, CIBMTR
Autologous BMT

High dose Chemo +/- XRT

Blood or Marrow Collection

Patient

Freezer
Allogeneic BMT

Donor

High dose Chemo +/- XRT

Recipient
Location of Centers Participating in the CIBMTR 2013
Indications for Hematopoietic Stem Cell Transplants in the US, 2011

- **Allogeneic** (Total N=7,892)
- **Autologous** (Total N=12,047)

### Number of Transplants

- **Multiple Myeloma**
- **NHL**
- **AML**
- **ALL**
- **MDS/MPD**
- **CML**
- **Aplastic Anemia**
- **CLL**
- **Other Non-Malignant Disease**
- **Other Cancer**
- **HD**

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

8
Cumulative Plot of Transplant Recipients in the US by Transplant Type

- **Autologous**
- **Allogeneic**

* 2013 Data incomplete
Graft-versus-Host Disease (GvHD) and Graft-versus-Tumor (GvT)

- Graft-versus-Host Disease (GvHD) is caused by the immune activation of donor cells recognizing recipient cells as foreign.
- Acute GvHD occurs ~ 100 days after BMT and affects Skin, GI tract and Liver.
- Chronic GvHD occurs after acute GvHD; up to 3 years following BMT.
- GvHD is the most frequent cause of mortality after allogeneic BMT.
- However, GvHD is accompanied by a Graft-versus-Tumor (GvT) effect that can result in eradication of the underlying cancer.
MECHANISM OF GVHD

Afferent phase

1. Ag presentation
2. Cell activation
3. Clonal proliferation & differentiation

Efferent phase

1. Lymphokine dysregulation
2. Target cell Death
3. NK
4. CTL
5. M

Courtesy of Mohamed Soliman
RPCI Flow Cytometry
GVHD is associated with GVL response

![Graph showing the relationship between GVHD and GVL response over time.](image)

No genetic disparity, No GVL → Twins (N=70)

No T cells, Very little GVL → T Depletion (n=401)

Subclinical GVHD, Some GVL → No GVHD (n=433)

More GVHD, More GVL → AGVHD Only (n=738)

CGVHD Only (N=127)

AGVHD + CGVHD (N=485)

Probability of Relapse After 2,254 HLA-identical Sibling Transplants for Early Leukemia, SlideCourtesy Wei Du
Transplant regimens

Immunosuppression

Myelosuppression

Flu-Cy
Flu-Cy-ATG
Flu-low dose TBI
Flu ATG

Flu-Mel
Flu-Bu
Flu-Mel-TBI

Cy-TBI
Bu-Cy

Regimen Related Toxicity

Later Graft-versus Disease Effect

Relapse

Earlier Anti-Disease Effect

Myelosuppression
Bi-specific T-cell Engaging (BiTE) antibody therapy for cancer: Blinatumomab (anti-CD 19)

Nagorsen and Baeuerle Exp Cell Research 2011

ALL Activity: Schedule to be determined in NHL
Inotuzumab ozogamicin (Anti-CD22)

Inotuzumab (HzIgG4SerPro) - Lys-NH$_2$ (random)

Calicheamycin = (2 to 3 per IgG)

http://www.dddmag.com/articles/2013/05/antibody-drug-conjugates-carbon-14-labeling-requirements
Car T Cell: Clinical trial overview

1. Gene transfer
2. Antibody-coated beads
3. Cells
4. Activation expansion
5. Bead removal and formulation
6. 8-11 days
7. Infusion of T cells to eradicate CD19+ tumor
8. Lymphodepleting chemotherapy

Courtesy D Porter
Targeting CD19+ CLL with CAR-Modified T cells

- CARs combine an antigen recognition domain of antibody with intracellular signaling domains into a single chimeric protein.
- Gene transfer (lentiviral vector) to stably express CAR on T cells confers novel antigen specificity.

Courtesy D Porter

CAR, chimeric antigen receptor; TCR, T-cell receptor.
Treatment Regimens

A 0604

- Cy 50 mg/kg
- BMT
  - Day -6 to 0
  - Fludarabine 40 mg/m^2/day
  - Double UCB Infusion
  - TBI 200 cGy
  - G-CSF
  - MMF tid
  - Cyclosporine

B 0603

- Cy 14.5 mg/kg/day
- BMT
  - Day -6 to 0
  - Fludarabine 30 mg/m^2/day
  - Bone Marrow Infusion
  - TBI 200 cGy
  - G-CSF
  - MMF tid
  - Tacrolimus
  - Cy 50 mg/kg/day
Non-relapse mortality and relapse

Non-relapse mortality

Relapse

Cumulative Incidence, %

Months Post Transplant

BMT CTN 0603/0604

Non-relapse mortality and relapse
The results of BMT CTN 0603 and 0604 provide equipoise for a randomized phase III clinical trial with progression-free survival as the primary endpoint.

BMT CTN 1101 Hypothesis: Two year PFS is similar after related haplo-BM donor transplantation or after dUCB transplantation.
BMT CTN 1101 Schema

Patient ≥ 18 and ≤ 70 yrs.
Acute leukemia or lymphoma
Available both
1) 4-6/6 HLA-matched
   UCB units
2) 4-6/8 HLA matched
   related donor

Randomization
Stratified by Transplant Center

Adequate organ function
Performance score ≥ 70

Double UCB

Haplo-BM
The Hematopoietic Stem Cell (HSC)

- Hematopoiesis is a hierarchical process with HSCs at the apex
- $10^{12}$ new blood cells produced daily
- HSCs differentiate into multipotent progenitors (MPP) and eventually produce all blood cells

Courtesy of M Nemeth
HSC Proliferation is Associated with Differentiation

Long-term HSCs (LT-HSCs) are quiescent (G\(_0\))

- LT-HSC
- ST-HSC
- MPP
- Committed Progenitors

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>G(_0)</th>
<th>G(_1)</th>
<th>S/G(_2)/M</th>
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</thead>
<tbody>
<tr>
<td>LT-HSC</td>
<td>&gt; 1.0%</td>
<td>&gt; 1.0%</td>
<td>&lt; 0.01%</td>
</tr>
<tr>
<td>ST-HSC</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MPP</td>
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% of Whole Bone Marrow

Courtesy of M Nemeth
Hypothesis

Ryk mediates the effect of Wnt5a on HSC proliferation and long-term function

Courtesy of M Nemeth
Effect of Ryk Inhibition on Quiescence

p < 0.05

p < 0.01  p < 0.05

% G0

Control  Wnt5a  Wnt5a + α-Ryk  α-Ryk

Courtesy of M Nemeth
Blockade of Ryk inhibits the effect of Wnt5a on HSC proliferation and long-term function

Povinelli and Nemeth
*Stem Cells, 2014*

Povinelli, *et al*
*Exp Hematol, 2015*

Courtesy of M Nemeth
Hematopoietic Stem Cell Ontogeny

AGM: aorta-gonads-mesonephros
FL: Fetal Liver
WBM: Whole bone marrow

http://daleystem.hms.harvard.edu/

Slide courtesy of Dr. Vladislav Sandler, HemoGenyx LLC
CD144⁺CD45⁺CD34⁺ Adult Hemogenic Endothelium (AHE) Cells are found in cord blood. Postnatal Hemogenic Endothelium (PHE) is a better name for these cells in the cord and cord blood.

The prediction of engraftment of one of two CB units may depend on the CD34+ and CD34+CD144+ cells.

Slide courtesy of Dr. Vladislav Sandler, HemoGenyx LLC
CD144⁺CD45⁺CD34⁺ AHE Cells From Umbilical Cord Engraft in Immune-Compromised Mice

Slide courtesy of Dr. Vladislav Sandler, HemoGenyx LLC

Every circle is a separate NOD mouse (Taconic)
Intrinsic and Extrinsic Modes of Glycosylation

Intrinsic Glycosylation

Extrinsic Glycosylation

ST6Gal-1: a Glycosyltransferase mediating attachment of sialic acid residues
- Abundant intracellularly
- Abundant as a freely circulating, catalytically active protein in blood
Hematopoietic arrest at GMP stage by rST6G
rST6G infusion mitigates acute inflammation

Acute airway inflammation elicited by oropharyngeal instillation of NTHI

rST6G mitigated inflammation by at least 2 ways
1. Suppressed new inflammatory cell production
2. Suppressed release of inflammatory mediators

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Manipulating circulating ST6Gal-1

• Depleting circulating ST6Gal-1 (e.g. by Mab)
  – Enhance hematopoietic repopulation after myeloablative events

• Raising circulating ST6Gal-1 (e.g. by rST6G)
  – Myeloproliferative syndromes
  – Suppression of inflammation
Molecular pathways that contribute to GVH and GVL activity

Van den Brink et al Nat Rev. 2002

Courtesy W Du, N Leigh, X Cao
GzmB is required for allogeneic CD8\(^+\) T cells to cause lethal GVHD


Courtesy W Du, N Leigh, X Cao
GzmB\(^{-/-}\) CD8\(^{+}\) T cells exhibit significantly enhanced GVL effect

This result was repeated with different donor and host combinations and three more tumor models.

GzmB diminishes the ability of CD4+T_{eff} cells to cause lethal GVHD

Donor T cell dose: 5×10^4

MHC-mismatched

C57BL/6 (H-2b) → BALB/C (H-2d)

Percent survival vs. time after BMT injection (days)

- BM only n=8
- WT CD4+T_{eff} n=12
- GzmB−/- CD4+T_{eff} n=12

* p=0.0296

Du et al, J Immunol Accepted for publication

Courtesy W Du, N Leigh, X Cao
GzmB diminishes the ability of CD4+T_{eff} cells to cause lethal GVHD
GzmB is required for CD4+T_{eff} cell-mediated optimal GVL response

Donor T cell dose: $1 \times 10^4$

Du et al, J Immunol Accepted for publication

Courtesy W Du, N Leigh, X Cao
GzmB diminishes the ability of CD4+ T_{eff} cells to cause lethal and pathological GVHD.

GzmB contributes to the optimal GVL activity of CD4+ T_{eff} cells.

GzmB plays opposite roles in CD4+ Teff vs. CD8+ T cell in mediating GVHD and GVL effect.

Du et al, J Immunol Accepted for publication

Courtesy W Du, N Leigh, X Cao
Baseline tumor growth and immune control in laboratory mice are significantly influenced by subthermoneutral housing temperature

Kathleen M. Kokolus, Maegan L. Capitano, Chen-Ting Lee, Jason W.-L. Eng, Jeremy D. Waight, Bonnie L. Hylander, Sandra Sexton, Chi-Chen Hong, Christopher J. Gordon, Scott I. Abrams, and Elizabeth A. Repasky
Housing temperature-induced stress is suppressing murine GVHD through β2-adrenergic receptor signaling

Leigh N, Kokulus K et al Submitted to JI 2015
Propranolol, β1 and 2-adrenergic blocker worsens GvHD at room temperature receptor signaling

Leigh N, Kokulus K et al Submitted to JI 2015
The effect of temperature on GvHD is mediated in part by the \( \beta_2 \)-adrenergic system

Leigh N, Kokulus K et al Submitted to JI 2015
Conclusions

• Understanding the patient’s immune status pre/post alloHSCT may lead to the design of strategies to control disease and prevent relapse

• Can protective immune reconstitution to prevent infections occur without the development of GvHD following alloHSCT?

• Can the GvT/GvL effect be preserved while eradicating the morbidity and mortality of GvHD

• Can CBT be enhanced to decrease the risk of infection

• Can other therapies enhance the host’s ability to eradicate disease and/or have direct anti-tumor effects?
  – Antibodies +/- conjugate; +/- IMiD,
  – Targeted cellular therapies for Hematologic malignancies
  – Targeted Checkpoint Inhibition
People and Services who make the BMT program possible

- S Balderman
- G Chen
- C Ho
- M Ross
- M Aungst
- K Arnold
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- M Everett
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- P Paplham
- S Flavin
- H McAdoo
- S Stack
- H Werner
- K Farrell
- H Jacobson
- S Oakley
- K West
- J Pleskow
- M Cimino
- T Hahn
- S Schinnagel
- S Zhao
- M Steward
- D Swinnich
- D Cipolla
- K Dubel
- P Lipka
- S Siconofi
- C Warren
- L Yoerg
- T Glow
- RKumpf
- G Wilding
- ID service
- Rad Onc Service
- Radiology Svc
- Surgery Svc
- Pathology Svc
- Lab Medicine
- Stem Cell Lab
- Apheresis Unit
- Managed Care and Finance Svc
- P Wallace
- L Sucheston Campbell
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- L Regan
- S Boehm
- C Paddon
- J Kapinos
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- Hospitalist Staff
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