Future Trends in Blood and Marrow Transplantation

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Agenda

- Hematopoietic Cell Transplantation
  - Historical Perspective
  - Current status
- Competing technologies
- Future trends
- Summary
HCT Historical Perspective

August 1949
Russians succeed in developing a nuclear weapon

Egon Lorenz 1892-1954

John Freeman Loutit together with David Barnes Demonstrate the existence of A graft vs leukemia effect
Hematopoiesis

Stem Cells

T-lymphocytes
B-lymphocytes

Granulocytes
Monocytes
Eosinophils
Basophils
Erythrocytes
Megakaryocytes
Platelets
Dr. E Donnell
Thomas receives Nobel Prize in 1990

...the bone marrow was obtained from a patient with blood type 0, C(+) who had died from a brain hemorrhage. The ribs were removed under sterile conditions between 1 hour and 30 minutes and 2 hours and 5 minutes after death. The bone marrow was extracted from the ribs and suspended in tissue culture media...
Allogeneic Transplantation
First Registry Report

Table 1. Results of 263 reported human bone marrow transplants

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of patients</th>
<th>No. with EN regimen</th>
<th>No. with registry disease</th>
<th>No. of autografts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplastic anemia</td>
<td>92</td>
<td>48</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Leukemia</td>
<td>34</td>
<td>23</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>31</td>
<td>22</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Immune deficiency</td>
<td>15</td>
<td>3</td>
<td>11</td>
<td>7</td>
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<tr>
<td>Total</td>
<td>263</td>
<td>125</td>
<td>48</td>
<td>11+</td>
</tr>
</tbody>
</table>

* Three alive at the time of this report.
Tumors that exhibit dose response effect to chemotherapy:
- Leukemia
- Lymphoma
- Testicular Cancer
- Neuroblastoma
- Breast Cancer

Tumors that don't:
- Lung
- Kidney
- Colon

Rationale for high-dose therapy:
- Cures 100%
- Lethal bone marrow toxicity
- Lethal toxicity to other organs
Stanley Dudrick develops TPN in the 1970’s

Jean Dausett, Jan van Rood y Paul Terasaki. HLA pioneers in the 1970’s

Development of Laminar air flow rooms, new antibiotics, antivirals, antifungals 1970-present

Development of central venous access catheters Hickman–Boviac - Hohn
One Hundred Patients With Acute Leukemia Treated by Chemotherapy, Total Body Irradiation, and Allogeneic Marrow Transplantation

By E. Donnell Thomas, C. Dean Buckner, Meera Banaji, Reginald A. Clift, Alexander Fefer, Nancy Flournay, Brian W. Goodell, Robert O. Hickman, Kenneth G. Lerner, Paul E. Neiman, George E. Sale, Jean E. Sanders, Jack Singer, Mary Stevens, Rainer Storb, and Paul L. Weiden

From bloodjournal.hematologylibrary.org on October 12, 2012. For personal use only.

Abstract

Treatment of a 5-month-old lymphopenic immunological deficiency utilizing immunologically competent cells from peripheral blood buffy coat and bone-marrow of a sibling donor resulted in reconstitution of both cellular and humoral immunity. Fatal graft-versus-host disease was circumvented by using a histocompatible and HLA-matched donor. A mild graft-versus-host disease was diagnosed at 8 days post-implantation and resolved spontaneously. Biopsies of rectal mucosa and skin indicate a continuing round-cell infiltration of host tissue 2 months post-implantation. The patient, however, remains clinically well.

Robert Good MD, PhD: first successful HCT in the world in a patient with SCID
PROBABILITY OF RELAPSE AFTER HLA-IDENTICAL SIBLING TRANSPLANTS FOR EARLY LEUKEMIA

PROBABILITY OF RELAPSE, %

YEARS

T Depletion (N=401)
Twins (N=70)
No GVHD (N=433)
AGVHD Only (N=738)
CGVHD Only (N=127)
AGVHD + CGVHD (N=485)
Timeline Showing Numbers of Bone Marrow Transplantations and Advances in the Field, 1957–2006.

INDICATIONS FOR BLOOD AND MARROW TRANSPLANTATION IN NORTH AMERICA
2002

Allogeneic (Total N = 7,200)
Autologous (Total N = 10,500)
Indications for Hematopoietic Stem Cell Transplants in the US, 2012

- **Allogeneic (Total N=7,554)**
- **Autologous (Total N=11,145)**

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

Number of Transplants
HCT Current Status
Indications for Hematopoietic Stem Cell Transplants in the US, 2013

- **Allogeneic** (Total N=8,197)
- **Autologous** (Total N=11,258)

**Number of Transplants**

- Myeloma / PCD
- AML
- ALL
- CML
- NHL
- HD
- MDS / MPD
- CLL
- Aplastic Anemia
- Other Non-Malign Dis
- Other Cancer
34 550 HSCT’s 2006 – 2008
Transplant rates allogeneic HSCT: acute leukemias

TR per 10 mil Pop.: Acute Leukemias:
Allo HSCT 2006-2008
(average N. HSCT over 3 year period)

- 0 or no report
- < 25
- 25.1 – 50
- 50.1 – 100
- > 100

Worldwide Network for Blood and Marrow Transplantation
Five Phases of Transplant

Complications:
- Acute and/or chronic GvHD
- Viral infections (CMV, VZV, PCP, IP)
- Bacterial infections
- HSV, mucositis
- VOD
- Secondary tumors, cataracts, endocrine changes, QoL

BMT Process:
- High-dose myeloablative therapy
- Phase 1 Chemo Phase
- Marrow Failure
- Phase 2 Low Count Phase
- Phase 3 Early Recovery 3-4 weeks post SCT
- Phase 4: Early Convalescence 1-12 months
- Phase 5: Late Convalescence >12 months

Supportive Therapy:
- Antiemetics
- Nutrition
- Antibiotics
- Growth factors
- Stem cell infusion
- Marrow function
- Immune function
- Red cell transfusions
- Platelet transfusions
- Chemo XRT
- Marrow function

TIME LINE
-12 0 0.5 2 6 >12 months

Disease State:
- Marrow failure
- Phase 2 Low Count Phase
- Phase 3 Early Recovery 3-4 weeks post SCT
- Phase 4: Early Convalescence 1-12 months
- Phase 5: Late Convalescence >12 months
Traditional Inpatient HCT in Protective Environment
Modern BMT Inpatient Unit
Outpatient Stem Cell Transplantation

Patients live in an extended living facility proximal to the hospital (30 minutes)

Come back and forth daily to receive care
  Evaluation healthcare professional
  Laboratory assessment
  Intervention (fluids, electrolytes and transfusion)
Percent Need Met (Actual / Calculated Demand)

US Pediatric Market Areas (Age < 20)
Allogeneic Stem Cell Transplant Rates as Percent of Need (2010)

US Adult Market Areas (Ages 20 - 54)
Allogeneic Stem Cell Transplant Rates as Percent of Need (2010)

US Adult Market Areas (Ages 55 - 74)
Allogeneic Stem Cell Transplant Rates as Percent of Need (2010)

© 2011 National Marrow Donor Program
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Number of newly diagnosed cases

Number of first AHPCT

AHPCT “utilization rate”

Costa et al.
Center Size Categories

- Based on 2010 total HCT volume (N=84 centers)
Effect of Race on Utilization of HCT
Caucasian- vs. African-Americans

Likelihood of undergoing HCT 1997-2002; CIBMTR & SEER data

Joshua TV et al, Cancer; 2010
HCT Current Status
Increasing Access/Breaking Barriers
Age
Contribution of Allografting to Treatment of Cancer

**ESTIMATED NUMBERS OF POTENTIAL TRANSPLANT CANDIDATES vs TRANSPLANT RECIPIENTS IN U.S.**

- **NHL:**
  - Allografts: 57,000
  - Autografts: 4,700
- **MM:**
  - Allografts: 13,700
  - Autografts: <65
- **AML:**
  - Allografts: 9,200
  - Autografts: 4,700
- **HD:**
  - Allografts: 7,200
  - Autografts: 3,600
- **CML:**
  - Allografts: 4,700
  - Autografts: 3,600
- **ALL:**
  - Allografts: 4,700
  - Autografts: 3,600
Conditioning Regimen Effects

- *Increase immediate anti-tumor effect*
- *Increase toxicity*
- *Rely on later graft versus disease effect*
- *Decreased regimen related toxicity*

*conditioning regimen spectrum*

Low Intensity

High Intensity

Number of candidates for HCT
Allografting an Aging Population
Lessons Learned from AML/MDS

- Should there be an age limit for allografting?
- How old is too old?
- Who should be considered?
Trends in Transplants by Type and Recipient Age*
2001-2010

* Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma
Trends in Allogeneic Transplants by Recipient Age*

- **<60 years**
- **≥60 years**

*Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma*
Future Trends

1. HCT will be used increasingly more frequently in older patients
   - Stress on system
   - Need for comprehensive rehabilitation
   - QOL and functional performance will become increasingly important outcomes
Overcoming Barriers
Increasing Donor Pool
Clinical Problem: Finding a Donor for Allogeneic Transplantation for all Patients

**PROBABILITY OF HAVING A BONE MARROW DONOR**

- **No Donor**
- **Matched sibling**: 30%

HSCT from an alternative donor is the only option:
- matched unrelated donor
- unrelated cord blood unit
- mismatched family donor
Access to HCT – Donor Availability

- 2001-2003
- 114 AML/MDS patients in CR 1
- 15 underwent allo HCT in CR1
  - Donor identified in 59% of patients
  - No donor most common stated reason for not proceeding to HCT

- Mawad et al JCO 2013
- 2008 – 2011
- 137 AML patients in CR1
- 79 (57%) underwent HCT.
- Reasons for not proceeding to HCT.
  - Early relapse (31%)
  - Poor performance status (21%)
  - Financial and psychosocial issues (21%).
7/8 and 8/8 Allele, Available-Match Rates in the US Adult Donor Registry

8 of 8  7 of 8
Adult Cord Match Rates in the Cord Blood Registry, Cell Dose ≥2.5/Kg
Post-Transplant Cyclophosphamide
A Disruptive Technology
Use of alternative donor sources for HCT
Relative risks and benefits of different cell sources: clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>UD</th>
<th>Cord</th>
<th>Haplo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engraftment</td>
<td>Fast</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Graft failure</td>
<td>Rare</td>
<td>More common</td>
<td>Rare with new techniques</td>
</tr>
<tr>
<td>GvHD</td>
<td>High (esp with mismatch)</td>
<td>Lower than expected with mismatch</td>
<td>Low due to techniques</td>
</tr>
<tr>
<td>Relapse</td>
<td>Possibly lower than sibling</td>
<td>Possibly lower than sibling</td>
<td>Higher</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>Many recent studies show equivalence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drafted in 2015!!
Future Trends

• 1. HCT will be used increasingly more frequently in older patients
  – Stress on system
  – Need for comprehensive rehabilitation
  – QOL and functional performance will become increasingly important outcomes

• 2. HCT will be used increasingly with alternative donors, particularly in developing countries with post transplant cyclophosphamide.

• Head to head comparisons between donor sources will be needed to determine patient and disease specific donor selection algorithms.
Overcoming Barriers
Patient advocacy
What if you remove insurance barriers?
HCT for MDS over age 65 and CMS coverage
The Referral Bias as a Barrier
The Myeloma Example
More than a third of myeloma patients are not receptive to HCT as frontline treatment

...and 10-15% are never offered the procedure

... the perception of many patients and physicians is that the procedure is dangerous, or toxic, or limited to younger patients.
Questions

• Is the HCT message being delivered to patients accurate?

• Is the HCT message being delivered to patients in an optimal manner?

• Would patients be more receptive to HCT if the message was delivered by an HCT expert?

• Would patients be more receptive to HCT if the message was delivered in a uniform way?
Can we develop effective strategies that reduce symptom burden?
MSKCC Program to reduce post HCT symptom burden

- Host Factors
  - Mood
  - Education
  - Comorbid Conditions
  - Genetic Predisposition
- Treatment Factors
  - Drug Specific Toxicities
  - Dose Intensity
  - Inflammatory Cytokines
- Preventive Factors
  - Anti-nausea meds
  - Pain Control
  - Supportive Care
- Environmental Factors
  - Treatment Environment
  - Team Approach
- Outpatient SCT
- Homebound SCT
- Light Therapy
- Predictors of Severe Symptom Burden
- PK Directed Melphalan Therapy
  - New Melphalan formulations
- Acupuncture
  - Deng et al.
  - IL6 Blockade
  - Kosuri et al.
Is there anything we can do about this?

Importance of Community-Transplant Center Relationships
Case 1

- 49 y/o man with diploid cytogenetics AML s/p induction and re-induction chemo with cytarabine and idarubicin still pancytopenic
- Latest marrow – MDS no overt leukemia
- Primary induction failure, with 9% blast and marrow consistent with prior MDS. Diploid cytogenetics. 2% circulating blasts
- Still pancytopenic
  - Good performance status KPS 80
  - Rectal fistula/abscess
  - No other comorbidities (Prostate hypertrophy and prior orthopedic surgeries
  - CT Chest normal
  - CT Sinus normal
What Next

• If patient had been seen by the BMT Service upfront he would have had a donor identified and could proceed straight to HCT.
• Otherwise he will need continued treatment until a cell source is identified which could take 4-6 weeks.
• Does it matter?
Increasing Access
Shared care model in HCT
Traditional Care Model for HCT for Patients in the Community AML

Community Oncologist

Refer for HCT Assessment

HCT Specialist in Transplant Center

Proceed to HCT

HCT Center/Team

Perform most pre HCT testing

Conditioning and HCT

Post HCT care for 3-4 months if no complications

Frequent follow up more if complications

Communication with Community Oncologist sporadic

Diagnosis
Disease risk assessment
Induction strategy
Assessment of response
Patient & Family Disease education

HCT eligibility assessment
HLA Typing
Donor Searching
Patient and Family HCT Education

Risk assessment
HCT eligibility assessment
Assessment of response
HLA Typing
Donor Searching
Patient and Family HCT Education

Return home to community oncologist
PROS & CONS OF TRADITIONAL MODEL

PROS
• Minimizes number of providers seeing patients at early points of a difficult disease process
• Maintains local control
• Historical precedence
• Reimbursement issues clearly delineated

CONS
• Many times delays the search and procurement process
• Not conducive to rapid adoption of a HCT strategy
• Maintains the HCT and community oncologist as separate
  – HCT expert only establishes a relationship late in course of disease
  – HCT team only releases patient back to community when they feel comfortable that medical events are unlikely to happen
• Non HCT expert delivering HCT specific content and making HCT relevant decisions
Shared Care Model for HCT for Patients in the Community AML

Community Oncologist

Diagnosis
- Disease risk assessment
- Induction strategy
- Assessment of response
- Patient & Family Disease education
- HCT eligibility assessment
- HLA Typing
- Donor Searching
- Patient and Family HCT Education
- Pre HCT work up

Refer for HCT Assessment

HCT Specialist in Transplant Center

Proceed to HCT

HCT Center / Team
- Performs most pre HCT testing
- Conditioning and HCT
- Post HCT care for 3-4 months if no complications
- Frequent follow up more if complications
- Communication with Community Oncologist sporadic

Return home to community oncologist

Length of stay
- 3-4 months if no complications
- More frequent follow up if complications
PROS & CONS OF SHARED CARE MODEL

PROS

• Expedites search and procurement process even for patients in whom HCT is not considered frontline treatment option
• Allows HCT team to meet the patient early and become a member of the local treatment team.
• HCT expertise delivered locally through local or HCT Center nurse navigator or both
• Facilitates transition back and forth from community to HCT center
• Brings HCT expertise into the community

CONS

• Another resource needs to be developed. Local and Transplant Center HCT Nurse Navigator
• “More cooks in the kitchen”
• Telemedicine and communication tools need to be developed.
• Patient and physician buy in is key.
• Reimbursement issues need to be figured out
• It has never been done by us before, although successful shared care models do exist (Canada).
Homebound Stem Cell Transplantation

- Delivery of all or part of stem cell transplant care within the patients home or “home like environment”
- Swedish and Spanish Experience demonstrate it is feasible and effective

- How to implement in our environment?
- What research agenda can we build around it?
- What are the barriers?
New challenges for HCT

• Competing technologies
  – CART cells
  – Checkpoint blockade
  – Targeted therapies
    • Ibrutinib
• Continued perception that therapy is dangerous, complicated and very toxic
• Access to HCT Centers
  – Healthcare economics
  – Financial viability
  – Workforce issues
Competing technologies
Immuno-therapy
Immune Surveillance

- T cell, MDSC, DC, TGFβ, Adenosine, Tumor cells
- Escape: Decreased MHC class 1, Persistent tolerogenic antigen, Decreased antigen quantity/variety, Increased number of MDSCs, Increased inhibitory cytokines and ligands, Poor antigen presentation
- Equilibrium: Adaptive immunity, Persistent tolerogenic antigen
- Elimination: Increased MHC class 1, Increased antigen quantity/variety, Innate and adaptive immunity (TLRs, DAMPs), Increased costimulatory molecules, Increased antigen presentation

Immunotherapy
• **Powerful:** Attacks the cancer systemically

• **Specific:** Trains the immune system to recognize & target only cancer cells

• **Memory:** Capacity for memory means durability of protection

• **Universal:** Treatment approach applicable to nearly all cancers
Advantages of CAR T cell therapy

- HLA-independent antigen recognition, therefore universal application
- Active in both CD4\(^+\) and CD8\(^+\) T cells
- Target antigens include proteins, carbohydrates and glycolipids
- Rapid generation of tumor specific T cells
- Minimal risk of GvHD
- A living drug
- Additional modification capability
<table>
<thead>
<tr>
<th>T Cell Product</th>
<th>Age, med (range)</th>
<th>No. of Pts.</th>
<th>T Cell Dose</th>
<th>CR/MRD-CR</th>
<th>Survival</th>
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<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-28z (JCAR015-MSK)*</td>
<td>45 (22-74)</td>
<td>39</td>
<td>1-3x10^6 CAR T cells/kg</td>
<td>87/70%</td>
<td>All cohorts: Med OS: 8.5 mos 6m OS: 59% (39-74) MRD-CR cohorts: Med. OS: 10.8 mos 6m OS: 75% (50-89)</td>
</tr>
<tr>
<td>19-4-1BBz (CTL019-UPenn)*</td>
<td>N/A</td>
<td>12</td>
<td>4x10^7 - 1x10^9 CAR T cells</td>
<td>89</td>
<td>N/A</td>
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<tr>
<td>19-4-1BBz (JCAR017-FHRC)*</td>
<td>N/A</td>
<td>20</td>
<td>2x10^5-10^7 CAR T cells/kg</td>
<td>83</td>
<td>N/A</td>
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<tr>
<td><strong>Pediatrics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>19-4-1BBz (CTL019-CHOP)</td>
<td>10 (5-22)</td>
<td>30</td>
<td>~3x10^6 CAR T cells/kg</td>
<td>90/77%</td>
<td>6m EFS:63% (47-84) 6m OS: 78% (63-95)</td>
</tr>
<tr>
<td>19-28z (KTE-C19-NCI)</td>
<td>14 (5-27)</td>
<td>20</td>
<td>1-3x10^6 CAR T cells/kg</td>
<td>70/60%</td>
<td>All cohorts: 6m OS: ~65% MRD-CR cohorts: 6m RFS: ~80%</td>
</tr>
</tbody>
</table>

Adverse Events

• Cytokine release syndrome (CRS)
  – Fever
  – Hypotension
  – Respiratory insufficiency

• Neurological changes
  – Delirium
  – Global encephalopathy
  – Aphasia
  – Seizure-like activities/seizure
Armored CARs

Figure 1.

<table>
<thead>
<tr>
<th>First generation CAR</th>
<th>Second generation CAR</th>
<th>Third generation CAR</th>
<th>“Armored” Fourth generation CAR</th>
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<tbody>
<tr>
<td>scFv (V(<em>{\alpha}) + V(</em>{\beta}))</td>
<td>(\zeta) signaling domain</td>
<td>CD28 costimulatory domain</td>
<td>41BB costimulatory domain</td>
</tr>
<tr>
<td>Transmembrane domain</td>
<td>Flexi-cytokine</td>
<td>Costimulatory ligand</td>
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Cytokine transgene

Costimulatory ligand transgene

J. Park EBMT 05 April 2016: CAR T cells in hematologic malignancies
Targeted Therapies
Targeted therapies

Reprinted with permission.
Dohner, H. Blood 2010.
ASP2215 (Gilteritinib) - Astellas

• **Potent inhibitor of FLT3, FLT3/ITD, kinase domain mutations**
  – Long half-life (2+ days)
  – CYP3A4 metabolized (as are all FLT3 TKIs)

• **Planned dose 120 mg/day**
  – Placebo available January 2016.

• **Clinical Results**
  – 127 relapsed/refractory FLT3+ AML patients treated.
  – ORR 58% in FLT3-mutated patients
  – Extremely well-tolerated
  – MTD 300 mg/day
  – DLT (at 450 mg/day): transaminitis, diarrhea

Courtesy, M. Levis
AG-221, an Oral, Selective, First-in-Class, Potent Inhibitor of the IDH2 Mutant Enzyme, Induces Durable Responses in a Phase 1 Study of IDH2 Mutation Positive Advanced Hematologic Malignancies

Eytan M Stein¹, Jessica K Altman², Robert Collins³, et al.

Isocitrate dehydrogenase (IDH) is a critical enzyme of the citric acid cycle

IDH mutations occur in a spectrum of solid and hematologic tumors¹
  IDH2 mutations: 9–13% of AML and 3–6% of MDS
  IDH1 mutations: 6–10% of AML and 3% of MDS

IDH1/2 mutations confer a gain-of-function²:
  increased histone and DNA methylation
  impaired cellular differentiation
Interim Analysis of a Phase 1 Trial of SGN-CD33A in Patients with CD33-positive Acute Myeloid Leukemia (AML)

- Eytan M. Stein, MD¹; Anthony S. Stein, MD², Roland B. Walter, MD, PhD, MS (Epi)³, et al.
Looking Ahead
Probability of Death by Day 200 Not Preceded by Relapse and of Overall Survival during Two Time Periods.

![Graph A](image1)

![Graph B](image2)

Leukemia relapse remains unchanged in the last two decades despite improvements in supportive care and transplant related mortality.
Optimal timing of HCT

Early HCT

Delayed HCT

Appropriate timing of HCT
Improved immune recovery predicts improved OS/Relapse Risk
J Goldberg/M. Perales/G Heller

Immune recovery parameters assessed as continuous variables over time

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio for death</th>
<th>p-value</th>
<th>Hazard Ratio for relapse</th>
<th>p-value</th>
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<tbody>
<tr>
<td>ALC</td>
<td>0.88</td>
<td>0.006</td>
<td>0.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4</td>
<td>0.79</td>
<td>&lt;0.001</td>
<td>0.55</td>
<td>&lt;0.001</td>
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<tr>
<td>CD8</td>
<td>0.83</td>
<td>&lt;0.001</td>
<td>0.53</td>
<td>&lt;0.001</td>
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<tr>
<td>NK</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CD45RA</td>
<td>0.77</td>
<td>&lt;0.001</td>
<td>0.67</td>
<td>0.002</td>
</tr>
<tr>
<td>PHA</td>
<td>0.76</td>
<td>0.064</td>
<td>0.49</td>
<td>0.010</td>
</tr>
</tbody>
</table>
Strategies to enhance T cell reconstitution following allo-HSCT
Improving HCT Outcomes

Pre HCT Therapy
Tallman/Younes/Moskowitz/Landgren

Pre HCT
Early referral
Leukemia Registration Protocol
Identify barriers to HCT and impact of psychosocial factors on HCT outcomes
Giralt/Tallman/Gyurkocza/Duhameel/Applebaum/Gany

Risk Profile
Refractory patients
Targeted maintenance therapy
Shaffer/Stein/Tallman/Giralt

Prep Regimen
BuMelFlu
Clo Mel Thio
Midi for Cords
Novel radiotherapy
Anti CD45
radioconjugate
Gyurkocza
New antibodies anti CD33a
Shaffer

New Graft Sources
Cord Blood
Barker/Ponce/Dahi
Haplo: Shaffer

Graft Engineering
CD34 Selection

Supportive Care
CMV CTL
Oreilly/Koehne/Prockop
EBV CTL Prockop/Oreilly
Enhancing Immune reconstitution
Perales/vandenBrink
Tamari/Giralt
GVHD Prevention
Ponce/Hanash/Perales/Barker
Microbiota
Jenq/vandenbrink/Gyurkocza/Shaffer

Relapse Prevention
Drugs
Oral Aza Papa/Giralt
Subq Aza: Tamari
Targetted Shaffer
Cells
WT1: Koehne/Oreilly
Car T cells:
Sadelain/Brentjens/Park/Riviere/Sauter
HCT focus on value, quality and cost effectiveness
Figure 1j. Center-Specific Results

2014 Report Card

Predicted and Actual Survival Rates for Transplant Centers with Over 270 Transplants

Box indicates predicted survival with 95% confidence interval. Dashed line indicates overall network survival rate of 67.1%.
Dot indicates a center's actual survival; a dot below (above) the box indicates an under (over)-performing center relative to the network.
Quick win
AML in the elderly

- 2000-2009
- 8336 pts
  - Not Treated = 5009
  - Treated = 3327
  - Transplanted = 276
    (increased from 50)
- Prior MDS = high risk
- HR for Transplant
  - \( \leq 75 = 0.63 \ (0.53-0.75) \)
  - \( >75 = 1.2 \ (0.95-1.52) \)

Largest Potential Impact: Low-grade lymphoma

Less than 5% of patients with early relapse are being considered for autograft.

Cost of newly approved drugs for this indication > 100K yearly.

MSKCC 4 patients a year for the last 5 years.
Showing the value of BMT in Follicular Lymphoma

Follicular Lymphoma Relapsed Within 24 months of 1ry therapy
Likely to maintain most treatment within the MSKCC System

Aggressive Salvage Therapy
Chemo + High Dose Therapy Plus Maintenance

Conventional Therapy
Chemo + Maintenance

- X year Disease Outcomes
  - OS/PFS
  - Time to Next Treatment

- X year Symptom Burden Outcomes
  - Longitudinal Symptom Burden
  - Patient Reported Outcomes

- X year Cost Outcomes
  - Healthcare expenditures
  - Out of pocket expenses

- X year Societal Outcomes
  - Time off work

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Figure 1j. Center-Specific Results

Predicted and Actual Survival Rates for Transplant Centers with Over 289 Transplants

Box indicates predicted survival with 95% confidence interval. Dashed line indicates overall network survival rate of 68.0%. Dot indicates a center’s actual survival; a dot below (above) the box indicates an under (over)-performing center relative to the network.
Summary

- Both autologous and allogeneic HCT activity is likely to continue to increase in the future.
- Optimal utilization will require continued comparative effectiveness analysis between HCT and alternative treatments.
- It is essential to make HCT easier and less toxic.
- Although novel immune therapies and targeted therapies are likely to impact the timing and utilization of HCT. They will also likely enhance efficacy and potentially increase access.
- Access will continue to be a major problem unless a concerted effort at increasing the number of HCT centers and enhancing the efficiency of existing centers. APPs will be essential in these efforts.
- Optimal utilization of HCT for patients with blood cancers will require close collaboration between community oncologist and HCT Centers
- The traditional way of doing business like the traditional Triple P transplant (push the drugs-pour the cells and pray that it all works out) will not move the field forward nor enhance access to HCT