Microtransplantation for Elderly Patients with AML

Anthony Sung, MD
Division of Hematologic Malignancies and Cellular Therapy
Duke University Medical Center
April 22, 2017
Disclosures

• Research funded by Novartis (unrelated) and Cellective Biotherapy (unrelated)

• Thanks to Ephraim Fuchs and Kai-Xun Hu for slides
Overview

• AML in the Elderly
• What is Microtransplantation?
• Microtransplantation in Newly Diagnosed AML
• Microtransplantation in Other Diseases
AML and Incidence by Age
AML and Relative Survival by Age

SEER data
# AML in the Elderly: Outcomes

<table>
<thead>
<tr>
<th>Age Category</th>
<th>CR %</th>
<th>Median OS (months)</th>
<th>Mortality within 30 days of induction %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;55 years N=364</td>
<td>64 %</td>
<td>18.8</td>
<td>2.7 %</td>
</tr>
<tr>
<td>Age 55-65 years N=242</td>
<td>46 %</td>
<td>9.0</td>
<td>11.2 %</td>
</tr>
<tr>
<td>Age 65-75 years N=270</td>
<td>39 %</td>
<td>6.9</td>
<td>20 %</td>
</tr>
<tr>
<td>Age &gt;75 years N=79</td>
<td>33 %</td>
<td>3.5</td>
<td>31.6 %</td>
</tr>
</tbody>
</table>

- CR: Complete Remission
- Median OS: Median Overall Survival
- Mortality within 30 days of induction

Source: Appelbaum FR et al., Blood 2006;107(9):3481-3485
What to do?

Microtransplantation!
What is Microtransplantation?

Infusion of allogeneic cells without substantial engraftment (i.e. resulting in microchimerism, <2% donor chimerism), thereby avoiding GVHD while still enhancing anti-tumor immunity.
Early Hints...

• 1960: Remission of metastatic melanoma induced by infusion of 250 cc whole blood from a donor with melanoma in spontaneous remission

  W. Sumner and A. Foraker, Cancer, 13: 79-81, 1960

• 1964: Rat sarcomas treated effectively by DLI from tumor-immunized, allogeneic donors
  • Infused cells were not found in spleen nor in tumors
  • Prior splenectomy prevented benefit from DLI


• 1966: Remissions in 9 of 21 acute leukemia patients (6 CR) by infusions of buffy coat cells from CML patients

Additional Studies


No. treated: 2 1 19 8 13 10 13 30 101 28 1 4
No. who sustained CR: 0 1 5 2 3 10 5 12 77 12 0 3

Irradiated PBMCs
Steady-state PBMCs
G-CSF-mobilized, unselected PBMCs
NK-cell purified product

Krakow EF et al., Blood Rev 2014;28(6):249-61
A rose by any other name...

- Adoptive Cellular Therapy (ACT)
- Donor Lymphocyte Infusion (DLI)
  - Non-engrafting Donor Lymphocyte Infusion
  - Non-engrafting Allogeneic Cellular Therapy (NEACT)
- Allogeneic Cellular Therapy Without Substantial Engraftment (ACT-WiSE)
- Microtransplantation
## Infusion of HLA-mismatched peripheral blood stem cells improves the outcome of chemotherapy for acute myeloid leukemia in elderly patients

Mei Guo, Kai-Xun Hu, Chang-Lin Yu, Qi-Yun Sun, Jian-Hui Qiao, Dan-Hong Wang, Guang-Xian Liu, Wan-Jun Sun, Li Wei, Xue-Dong Sun, Ya-Jing Huang, Jun-Xiao Qiao, Zheng Dong and Hui-Sheng Ai

<table>
<thead>
<tr>
<th>Outcome</th>
<th>7+3</th>
<th>7+3+MT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>42.8%</td>
<td>80.0%</td>
</tr>
<tr>
<td>2-yr DFS</td>
<td>10%</td>
<td>38.9%</td>
</tr>
<tr>
<td>Count recovery</td>
<td>16/20 days</td>
<td>11/14.5 days</td>
</tr>
</tbody>
</table>

![Graph A](image1.png)

*Graph A: Disease-free survival distribution. p=0.01*

![Graph B](image2.png)

*Graph B: Overall survival distribution. p=0.0006*
Updates from ASH 2016

- 179 Patients
- 79% CR rate
- 3/10, unrelated donors
- 52% microchimerism
- 2 patients with GVHD
# Updates from ASH 2016

<table>
<thead>
<tr>
<th></th>
<th>All (n=169)</th>
<th>60-64 (n=66)</th>
<th>65-69 (n=43)</th>
<th>70-74 (n=37)</th>
<th>75-85 (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR rate (%)</strong></td>
<td>81.7</td>
<td>78.8</td>
<td>83.7</td>
<td>91.9</td>
<td>69.6</td>
</tr>
<tr>
<td><strong>Early death (%)</strong></td>
<td>8.7</td>
<td>7.7</td>
<td>13.9</td>
<td>5.9</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>GVHD (%)</strong></td>
<td>1.2</td>
<td>0</td>
<td>4.6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Slide courtesy of Hui-Sheng Ai and Kai-Xun Hu
Microchimerism

Fig 4. The kinetics of donor microchimerism after the microtransplantation. (A) Normal data; (B) (log10 of data in part A. Donor microchimerism was detected in 20 of 23 patients (range, 0.000000697 to 0.46 gene expression copies compared with the internal control gene β-globin [1.0 copy]). The kinetics of donor microchimerism showed that microchimerism emerged on day 2 and reached its peak on days 7 through 14 after microtransplantation. The longest persistent time of donor microchimerism was 1,020 days. MST, micro stem-cell transplantation.
Microtransplantation at Duke
Phase 1, single center, fixed dose
Fifteen Patients Evaluable

- CR after IND1: 4/4 standard risk, 5/11 high risk
- Compare to Blood 2011: 17/18 standard risk, 7/12 high risk
- Of the 6 with refractory disease:
  - 2 underwent re-induction with 7+3+DLI without response
  - 1 was treated with MEC without response
  - 3 went to hospice
Fifteen Patients Evaluable
Results

• No therapy-related deaths
• No GVHD
• Seven patients with fevers/chills during or immediately after infusion
  • Including all 4 patients still in CR
Cytokine Release Syndrome

Table 2. HIS Characteristics in the 30 Patients in the $1 \times 10^8$ to $2 \times 10^8$ CD3+ Cells/kg Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperpyrexia, day 0 to 1 (100%)</td>
<td>Median onset, 14 hours. 100% resolution by 6 hours with steroid administration. (Steroids administered for hyperpyrexia lasting &gt;72 hours)</td>
</tr>
<tr>
<td>Malaise (100%)</td>
<td>Seen in 30 of 30 patients</td>
</tr>
<tr>
<td>LFT aberration (93%)</td>
<td>Seen in 28 of 30 patients</td>
</tr>
<tr>
<td>Morbilliform rash (60%)</td>
<td>Seen in 18 of 30 patients</td>
</tr>
<tr>
<td>Diarrhea (73%)</td>
<td>Seen in 22 of 30 patients</td>
</tr>
<tr>
<td>Skin and colon biopsies</td>
<td>No acute GVHD</td>
</tr>
</tbody>
</table>

GVHD, graft-versus-host disease.
Microtransplantation at Other Centers and in Other Diseases
<table>
<thead>
<tr>
<th>Center</th>
<th>Investigators</th>
<th>Disease</th>
<th>Source</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keck/USC</td>
<td>Preet Choudhary, Giri Ramsingh</td>
<td>Elderly AML, newly diagnosed</td>
<td>G-PBSC Haplo, 7+3</td>
<td>NA</td>
</tr>
<tr>
<td>Hospital Universitario Puerta de Hierro</td>
<td>Rafael Fores, Rafael Duarte</td>
<td>AML, CMML blast crisis, RAEB2</td>
<td>G-PBSC Haplo, 7+3</td>
<td>13/13 CR</td>
</tr>
<tr>
<td>University of Sydney</td>
<td>David Gottlieb, Emily Blythe</td>
<td>AML in CR</td>
<td>Discarded Cells, 5-7/10, cytarabine</td>
<td>n=4, microchimerism</td>
</tr>
<tr>
<td>Brown University</td>
<td>Peter Quesenberry, John Reagan</td>
<td>newly Diagnosed; refractory/relapsed; heme malig</td>
<td>Unmobilized haplo; G-PBSC haplo; various regimens</td>
<td>mixed</td>
</tr>
<tr>
<td>Johns Hopkins University</td>
<td>Ephraim Fuchs</td>
<td>Heme Malig</td>
<td>Cy + unmobilized; 3rd Party, CD8 depleted, 5-7/10</td>
<td>TBD</td>
</tr>
</tbody>
</table>
Microtransplantation and Consolidation

A

Leukemia-Free Survival (probability)

Time (months)

Prognosis
- Low-risk group
- Intermediate-risk group

B

Overall Survival (probability)

Time (months)

Prognosis
- Low-risk group
- Intermediate-risk group

C

Leukemia-Free Survival (probability)

Time (months)

CD3+ T/kg
- < 1.1
- ≥ 1.1

D

Overall Survival (probability)

Time (months)

CD3+ T/kg
- < 1.1
- ≥ 1.1

Guo M et al., J Clin Oncol 2012; 30:4084-90
MST and MDS

• 21 patients
• decitabine + cytarabine
• 81% response, 52% CR
• 2 yr PFS 43%, 2 yr OS 85%
### MST and Relapsed/Refractory Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>N</th>
<th>CR</th>
<th>PR</th>
<th>Overall response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML(^1-3)</td>
<td>32</td>
<td>6</td>
<td>2</td>
<td>25%</td>
</tr>
<tr>
<td>ALL(^1)</td>
<td>15</td>
<td>4</td>
<td>2</td>
<td>40%</td>
</tr>
<tr>
<td>MDS(^4)</td>
<td>21</td>
<td>11</td>
<td>-</td>
<td>52%</td>
</tr>
<tr>
<td>B cell NHL(^5-7)</td>
<td>32</td>
<td>13</td>
<td>7</td>
<td>63%</td>
</tr>
</tbody>
</table>

2. DJ Medina Leuk Res. 32:1842-8, 2008
## MST and Myeloma/PCL

<table>
<thead>
<tr>
<th></th>
<th>F/M</th>
<th>RISK</th>
<th>type</th>
<th>DONOR</th>
<th>Induction chemo</th>
<th>MST</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M- 53</td>
<td>I</td>
<td>IgGIIA</td>
<td>4, related URD</td>
<td>DVDx4VGPR</td>
<td>11</td>
<td>CR48m, progress, 72m Die</td>
</tr>
<tr>
<td>2</td>
<td>M -42</td>
<td>H</td>
<td>IgDIIIIB</td>
<td>related</td>
<td>VDx2VGPR</td>
<td>4</td>
<td>CR30m, progress, 40m Die</td>
</tr>
<tr>
<td>3</td>
<td>M-53</td>
<td>I</td>
<td>IgGIIA</td>
<td>related</td>
<td>VADx1VGPR</td>
<td>2</td>
<td>CR58m, CR78m</td>
</tr>
<tr>
<td>4</td>
<td>F-45</td>
<td>I</td>
<td>IgGIIA</td>
<td>related</td>
<td>VTDX2CR</td>
<td>4</td>
<td>CR18m, then lost</td>
</tr>
<tr>
<td>5</td>
<td>F -70</td>
<td>I</td>
<td>IgAIIIA</td>
<td>related</td>
<td>VMDX1VGPR</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M-58</td>
<td>I</td>
<td>IgGIIA</td>
<td>related</td>
<td>VT DX2VGPR</td>
<td>3</td>
<td>CR72m</td>
</tr>
<tr>
<td>7</td>
<td>M-49</td>
<td>I</td>
<td>IgDIIIA</td>
<td>related</td>
<td>VT DX2VGPR</td>
<td>2</td>
<td>CR43m</td>
</tr>
<tr>
<td>8</td>
<td>M-60</td>
<td>I</td>
<td>IgGIIA</td>
<td>related</td>
<td>VT DX3VGPR</td>
<td>1</td>
<td>CR36m</td>
</tr>
<tr>
<td>9</td>
<td>F-68</td>
<td>I</td>
<td>IgGIIA</td>
<td>related</td>
<td>VT DX3VGPR</td>
<td>1</td>
<td>CR36m, TD</td>
</tr>
<tr>
<td>10</td>
<td>F-58</td>
<td>H</td>
<td>IgGIIA</td>
<td>related</td>
<td>VD, VMDVAD-PR</td>
<td>2m</td>
<td>progress, die</td>
</tr>
<tr>
<td>11</td>
<td>M-62</td>
<td>I</td>
<td>IgDIIIA</td>
<td>related</td>
<td>VDX3VGPR</td>
<td>3</td>
<td>CR36m Infection, MODS, Die</td>
</tr>
<tr>
<td>12</td>
<td>M-52</td>
<td>H</td>
<td>PCL</td>
<td>related</td>
<td>VTDX2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>M-51</td>
<td>H</td>
<td>PCL</td>
<td>URD</td>
<td>VTDX2</td>
<td>2</td>
<td>CR 6m</td>
</tr>
<tr>
<td>14</td>
<td>M-51</td>
<td>I</td>
<td>IgGIIIA</td>
<td>related</td>
<td>VDX2, VMDX3</td>
<td>2</td>
<td>VGPR 8m</td>
</tr>
<tr>
<td>15</td>
<td>F-74</td>
<td>I</td>
<td>IgGIIIA</td>
<td>related</td>
<td>VTDX2</td>
<td>2</td>
<td>VGPR 15m</td>
</tr>
<tr>
<td>16</td>
<td>M-60</td>
<td>I</td>
<td>IgAIIIA R2</td>
<td>related</td>
<td>17(VD/VCD/V AD)</td>
<td>4</td>
<td>VGPR 7m</td>
</tr>
<tr>
<td>17</td>
<td>F-59</td>
<td>H</td>
<td>K R2</td>
<td>URD</td>
<td>16(VD/VDV/ CD)</td>
<td>2</td>
<td>CR 12m</td>
</tr>
<tr>
<td>18</td>
<td>F-40</td>
<td>I</td>
<td>IgGIIA</td>
<td>related</td>
<td>VDX3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Survival

5 years

DFS: 73.3%
OS: 86.7%
Conclusion

• Microtransplantation is safe and may be effective
• Correlative studies are necessary to understand its mechanisms

Next Steps:
• Randomized International Phase 3 Trial of Microtransplantation in Newly Diagnosed Elderly AML
Acknowledgments

**Duke Pilot**
- Nelson Chao
- David Rizzieri
- Arati Rao

Donor Screening, Stem Cell Collection
- Amy Harder
- Angelica DeOliviera
- Barbara Waters-Pick

**Research Team**
- Rachael Stowe
- Kristi Romero
- Julia Lloyd-Cowden

**Clinical Team**
- Joey Misuraca
- Physicians
- Nurses
- Patients & Families

**Laboratory Collaborators**
- Kent Weinhold (Duke)
- Janet Staats (Duke)
- Greg Sempowski (Duke)
- Dongfeng Chen (Duke)
- VK Gadi (FHCRC)
- Chris Hourigan (NHLBI)

**Phase 3 Collaborators**
- Hui-Sheng Ai
- Kai-Xun Hu
- Winston Wu

**Funding**
- 5KL2TR001115-03
- ASH RTAF

anthony.sung@duke.edu
But how does this work?

These findings suggested that the original results could be explained best by an indirect process initiated by the short-lived donor cells but carried to completion by the cells of the host. This raised the question of using
Donor CD4 cells

Cyclophosphamide (Cy) 200 mg/kg IP
Day: -1
Tumor + mismatched lymphocytes (DLI) IV
Day: 0
Follow survival

Survival (%)

No DLI
Tumor alone
CD4⁺/8⁻ DLI
CD8⁻ DLI

Days after IV tumor

0 20 40 60 80 100

p = .04

Recipient CD8 cells

CD8 replete hosts

Mismatched DLI prolongs survival of hosts that have CD8+ T cells

CD8 depleted hosts

Mismatched DLI fails to prolong survival of hosts that lack CD8+ T cells

Reversal of T cell exhaustion

Fuchs model

Blood and marrow

Leukemia antigens

Host antigen-presenting cell

“HELP”

Infused alloreactive CD4 T cell

Exhausted host CD8+ T cell

PD-1

Slide courtesy of Ephraim Fuchs
Male Donors to Female Recipients

![Graph showing DFS and OS survival rates for different time points.](image-url)
Expression of activating KIR
Possible mechanisms?

• Graft-versus-Leukemia
• Host-versus-Graft
• Donor CD4 -> Host PC
• NK/KIR