AML: Fast track to transplant

John M. Pagel, M.D., Ph.D., Chief of Hematologic Malignancies and Director of Stem Cell Transplantation, Swedish Cancer Institute

Steve Spellman, MBS, Director – Immunobiology Research, CIBMTR

November 10, 2018
The following faculty and planning committee staff have the following financial disclosures:

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Disclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td>John M. Pagel, M.D., Ph.D.</td>
<td>Swedish Cancer Institute</td>
<td>Actinium Pharmaceuticals</td>
</tr>
<tr>
<td>Steve Spellman, MBS</td>
<td>CIBMTR</td>
<td>None</td>
</tr>
<tr>
<td>Misty Evans</td>
<td>Vanderbilt University</td>
<td>Jazz Pharmaceuticals, Monetary, Speakers Bureau</td>
</tr>
<tr>
<td>Maria Brown</td>
<td>CIBMTR</td>
<td>None</td>
</tr>
</tbody>
</table>
Learning Objectives

• At the conclusion of this session, attendees will be able to:
  • Describe the diagnosis of AML and Risk assessment
  • List traditional treatment options
  • Understand outcomes with allogeneic transplantation using different donor stem cell sources
  • Evaluate results of SWOG 1203 trial
  • Recall Intervention at diagnosis opportunities
Survival in Acute Myeloid Leukemia

Initial Therapy for Adult AML Patient Fit for Curative Therapy

- 49 year old woman with hypertension
- Presented for evaluation of fever, weight loss
- WBC 53,840 with 44% blasts, HgB 8.5 gram/dL, PLT 68,700
- Bone marrow biopsy: AML with del(5q)
- Neutrophilic dermatosis, grade 3 transaminase elevation prior to induction
Current Paradigm for the Initial Treatment of AML

Initial Diagnosis of AML → Induction therapy

- Complete response
- Primary refractory

Risk Stratify → Consolidation chemotherapy

- Relapse?
- Salvage therapy

Complete response?

→ Allogeneic Hematopoietic Stem Cell Transplant
S1203: Treatment Arms

• 7+3:
  • Induction: Ara-C 100 mg/m² CI IV daily x 7 and Daunorubicin* 90 mg/m² IV QD days 1-3
  • Consolidation: Ara-C 3 gram/m² IV every 12 hours on days 1, 3, and 5 x 4 cycles

• IA+V Induction:
  • Vorinostat 500 mg po TID QD X 3 days (days 1-3), Idarubicin 12 mg/m² QD x 3 (days 4-6), Ara-C 1.5 gram/m² CI QD X 4 (days 4-7)

• IA+V Consolidation (x 4 cycles):
  • Vorinostat 500 mg po TID QD X 3 days (days 1-3), Idarubicin 8 mg/m² QD x 2 (days 4-5), Ara-C 0.75 gram/m² CI QD X 3 (days 4-6)
  • Maintenance: vorinostat 200 mg po TID x 14 days every 28 days

• IA as IA+V (without vorinostat)
<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>7+3 (N=261)</th>
<th>IA (N=261)</th>
<th>IA+V (N=216)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>460 (62%)</td>
<td>164 (63%)</td>
<td>166 (64%)</td>
<td>130 (60%)</td>
<td>0.58</td>
</tr>
<tr>
<td>CRi</td>
<td>111 (15%)</td>
<td>33 (13%)</td>
<td>41 (16%)</td>
<td>37 (17%)</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>167 (23%)</td>
<td>64 (25%)</td>
<td>54 (21%)</td>
<td>49 (23%)</td>
<td></td>
</tr>
</tbody>
</table>
S1203: Early mortality

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>7+3</th>
<th>IA</th>
<th>IA+V</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died ≤ day 30</td>
<td>31 (4)</td>
<td>7 (3)</td>
<td>16 (6)</td>
<td>8 (4)</td>
<td>0.013</td>
</tr>
<tr>
<td>Died ≤ day 60</td>
<td>53 (7)</td>
<td>12 (5)</td>
<td>22 (9)</td>
<td>19 (9)</td>
<td>0.097</td>
</tr>
</tbody>
</table>

Grab your cape.
S1203: Overall Survival

IA+V vs IA  p = 0.6
IA+V vs 7+3 p = 0.67
IA vs 7+3  p = 0.92

Grab your cape.

Years since randomization

7+3 (N = 261, deaths = 99)
IA (N = 261, deaths = 96)
IA+V (N = 216, deaths = 88)
Cytogenetics remains the most common and reproducible estimate of prognosis for patients with AML

- Using cytogenetics, patients can be categorized as having favorable, intermediate, or unfavorable (high) risk disease
- The unfavorable risk group comprises ~30% of all patients
  - Has a first CR1 rate of 54% and an estimated survival at 5 years of 11%
    - outcomes that were significantly worse than seen in intermediate- or favorable-risk patients
- Among patients with high-risk disease allogeneic transplantation has a ~44% survival at 5 years with allogeneic transplantation versus 15% with chemotherapy alone
- Unfortunately only 40% of patients assigned to allogeneic HCT are actually transplanted.
- Allogeneic transplantation has been recommended for adults age ≤60 years with high-risk AML in CR1
Current Use and Trends in Hematopoietic Cell Transplantation in the United States

- The number of both autologous and allogeneic transplants for treatment of malignant diseases continues to increase.
- Between 1991 and 1997, 7% of allogeneic HCTs were performed in patients age ≥50 years
  - Between 2000 and 2015, this percentage increased to 38%.
- In 2015, 25% of all allogeneic HCT recipients were age ≥60 years, up from 5% in 2000
  - 4.4% were age ≥70 years in 2015, compared with 0.4% in 2000

D’Souza et al, BBMT, 2017
Indications for Hematopoietic Cell Transplant in the US, 2016

- Allogeneic (Total N=8,519)
- Autologous (Total N=14,181)

Number of Transplants

- Myeloma / PCD
- NHL
- AML
- MDS / MPN
- ALL
- HD
- Other Cancer
- Other Non-Malignant
- Aplastic Anemia
- CML
- CLL
Common Conditioning Regimens in AML or MDS Allogeneic HCT in the US in 2000-2015

MAC

- MA Bu+Cy+/-others: 8%
- MA Bu+Flu+/-others: 31%
- MA TBI+/-others: 34%
- MA Others: 27%

RIC

- RIC Bu+Flu+/-others: 12%
- RIC Flu+Mel+/-others: 32%
- RIC TBI+/-others: 30%
- RIC Others: 26%
Patient Eligibility: Factors associated with transplant-related problems

Disease-related
- Diagnosis & molecular characteristics
- Prior therapy
- Remission vs Relapse
- Early vs late in disease course

Patient-related
- Age
- Performance status
- Co-morbidities

Treatment-related
- Intensity of the conditioning regimens

• Stem cell source
Legend: MRD- matched related donor; MMRD- mismatched related donor; MUD-BM/PB- matched unrelated donor-bone marrow/peripheral blood
Survival after HLA-Matched Sibling Donor HCT for AML, 2005-2015

- Early (n=8,254)
- Intermediate (n=2,089)
- Advanced (n=2,766)

Probability, %

Years

p < .0001
Survival after Unrelated Donor HCT for AML, 2005-2015

- Early (n=10,739)
- Intermediate (n=4,585)
- Advanced (n=4,688)

p < .0001
Survival after HLA Matched Sibling Donor HCT for AML, Age <18 Years, 2005-2015

Early (n=918)
Intermediate (n=234)
Advanced (n=160)

p < .0001
Adjusted Probability of Survival After Transplantation for AML

- HLA-id Sib (N=624)
- 7/8 MUD (N=406)
- 8/8 MUD (N=1,193)

Impact of Donor Type on one-year mortality of after HCTs done in 2013-2015

Sib N=7438

8/8 MUD N=8642

p=0.6914
Survival After Unrelated Donor Transplantation
Age <50 years, myeloablative conditioning, acute leukemia in remission or MDS

Adjusted 1-year Overall Survival

Odds of 1-year survival increased by 6% per year (95% CI, 7-9%) on average between 1990 and 2015

Grab your cape.
Is a hapolidentical donor the best option for AML in the absence of HLA-identical donor?

• Haplo is gaining ground because of:
  − Rapid availability of donor in a high-risk disease
  − Potential budgetary advantages
  − Less transplant related mortality?
• But still open questions:
  • Long term reports still scarce
  • Higher rate of relapse?
### AML CR1; Haploidentical *versus* Matched Sibling

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Haploidentical (n=231)</th>
<th>Identical sibling (n=219)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y, median (range)</strong></td>
<td>28 (15-57)</td>
<td>40 (17-60)</td>
</tr>
<tr>
<td><strong>Cytogenetic risk group,</strong> no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate, normal</td>
<td>99 (43)</td>
<td>110 (50)</td>
</tr>
<tr>
<td>Intermediate, abnormal</td>
<td>84 (36)</td>
<td>77 (35)</td>
</tr>
<tr>
<td>High</td>
<td>48 (21)</td>
<td>32 (15)</td>
</tr>
<tr>
<td><strong>Courses required for CR (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>155 (67)</td>
<td>156 (71)</td>
</tr>
<tr>
<td>2</td>
<td>60 (26)</td>
<td>50 (23)</td>
</tr>
<tr>
<td>3-4</td>
<td>16 (7)</td>
<td>13 (6)</td>
</tr>
<tr>
<td><strong>Graft type, no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM + PB cell</td>
<td>231 (100)</td>
<td>124 (57)</td>
</tr>
<tr>
<td>BM</td>
<td>14 (6)</td>
<td></td>
</tr>
<tr>
<td>PB cell</td>
<td>81 (37)</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-up time from CR, mo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of evaluable patients</td>
<td>188 (81%)</td>
<td>184 (84%)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>36 (16-63)</td>
<td>37 (14-66)</td>
</tr>
</tbody>
</table>

Wang et al., Blood 2015; 125: 3956-3962
Myeloablative Conditioning for Sibling vs Haplo

• HLA-haploidentical related:
  • Cytarabine (4 g/m2/d -10, -9)
  • Busulfan (3.2 mg/kg/d -8, -7, -6)
  • cyclophosphamide (1.8 g/m2/d -5, -4)
  • Me-CCNU (250 mg/m2/d -3)
  • ATG (2.5mg/kg/d -5 to -2)

• HLA-identical sib:
  • hydroxycarbamide (80mg/kg -10)
  • cytarabine (2 g/m2/d -9)
  • Rest of regimen the same without ATG

• GVHD prophylaxis: CSP, MMF, MTX

Grab your cape.

Wang et al., Blood 2015; 125: 3956-3962
Outcomes after Transplantation According to Donor Source

Non-relapse Mortality

Relapse

P = .13

P = .98

Grab your cape.

Wang et al., Blood 2015; 125: 3956-3962
GvHD According to Donor Source

Acute GVHD Grades II-IV

Chronic GVHD

Wang et al., *Blood* 2015; 125: 3956-3962
Survival According to Donor Source

Wang et al., Blood 2015; 125: 3956-3962

Grab your cape.

Let's go!
Outcomes Haplo vs MUD for AML – CIBMTR

- 2,174 pts with AML (21-70 yrs) transplanted between 2008-2012
- 1,982 pts had 8/8 MUD, 192 pts haplo with postCy
- **MA** - 1245 had MUD, 104 haplo
- **RIC/NMA** - 737 had MUD, 88 haplo
- Very similar characteristics except:
  - RIC MUD transplants older (median 62 vs. 57 yrs), more likely to have a PS< 80%
  - Haplo transplants less likely to be in CR1 and had longer interval diagnosis – transplant
- Median follow-up – approx. 3 years for all groups
- No transplant center effect on survival

Leukemia-Free Survival
Adjusted for DRI, performance score, secondary AML

Grade II-IV Acute Graft vs Host Disease

Myeloablative

HR 4.41 (95% CI 1.82-10.70), p=0.001

MUD 23% (21-26)

HAPLO 6% (2-12)

Reduced Intensity

HR 1.53 (95% CI 0.76-3.07), p=0.23

MUD 16% (13-19)

HAPLO 11% (5-20)

Cumulative Incidence, %

**Myeloablative**

HR 2.18 (95% CI 1.49-3.19), p<0.0001

MUD 52% (50-55)

HAPLO 29% (20-38)

**Reduced Intensity**

HR 2.02 (95% CI 1.36-2.99), p=0.0004

MUD 51% (47-54)

HAPLO 32% (23-43)

Non Relapse Mortality

Myeloablative

- MUD 20% (18-22)
- HAPLO 14% (8-22)

Reduced Intensity

- MUD 23% (19-26)
- HAPLO 9% (4-16)

HR 1.32 (95% CI 0.78-2.23), p=0.31

HR 0.73 (95% CI 0.54 – 1.00), p=0.05

Relapse

Cumulative Incidence, %

Myeloablative

Reduced Intensity

HR 0.89 (95% CI 0.66-1.21), p=0.46

HAPLO 44% (34-53)

MUD 39% (37-42)

HR 0.73 (95% CI 0.54-1.00), p=0.05

HAPLO 58% (46-68)

MUD 42% (38-45)

Umbilical Cord Blood Stem Cell Grafts

• Advantages
  • Readily available stem cells source
  • Tolerance across HLA barriers
  • Nearly 30 year of experience
  • Less chronic GvHD vs. Matched Unrelated donor
    • Eapen M et al Lancet 2010
  • Potent anti-tumor activity
    • Milano F et al NEJM 2016

• Disadvantages
  • Low stem cell dose
    • Delayed hematopoietic recovery
    • Delayed immunologic recovery
  • Increased resource utilization

Potential Solution
Ex-vivo Expansion Cord Blood Stem Cells
Strategies to improve outcomes after SCT in AML

• **Pre-HCT strategies**
  • Improving conditioning regimens
  • Graft engineering
  • Donor selection

• **Post-HCT strategies**
  • Prophylactic and preemptive chemotherapeutic approaches
  • Prophylactic and preemptive immune-mediated approaches

Finding a donor and actually getting to a transplant

Grab your cape.
Background

• AML patients with high-risk cytogenetics have a significantly worse survival
  • compared to similarly treated intermediate- or favorable-risk patients

• Better outcome in high-risk AML patients in CR1 who undergo allogeneic HCT
  • compared with consolidation chemotherapy
  • only 40% of patients proceed to HCT

• Alternative donors are available for the large majority of high-risk AML patients
  • outcomes after allogeneic HCT from URD are similar to those following MRD transplantation
  • the lack of a matched sibling donor (available in about 33%) should not be a barrier to HCT
Feasibility of Allogeneic HCT Among High-Risk AML Patients in First Complete Remission

Results of the Transplant Objective from the SWOG (S1203) Randomized Phase III Study of Induction Therapy Using Standard 7+3 Therapy or Idarubicin with High-Dose Cytarabine (IA) versus IA plus Vorinostat

Clinical Trials Registry: NCT #01802333

SWOG 1203 Transplant Objectives

• To determine if a prospective organized effort could rapidly identify alternative donors to improve the historical 40% allogeneic HCT rate

Primary Objective
• To determine whether it is possible to get 60% or more of adults ≤ age 60 with high-risk AML in CR1 to allogeneic HCT

Secondary Objective
• To determine if transplanting significantly more adults with high-risk AML in CR1 would lead to an improved outcome compared with the historical RFS of 22%
Patients and Methods

Treatment Naïve AML Patients Between 18-60

↓

Buccal Swab Obtained (all patients)

↓

Standard Cytarabine + Daunorubicin (7+3; n=261)

↓

Idarubicin with high-dose cytarabine (IA; n=261)

IA with vorinostat (IA+V; n=216)

↓

All patients with high-risk cytogenetics underwent expedited HLA-typing; Typing to be completed within 5 business days

Grab your cape.
Expedited Donor Identification and HCT

1. Preliminary search results sent to referring physician/HCT Center

2. HLA type siblings and activate formal search

   - Matched sibling available
     - Yes
       - HCT
     - No

   - Identify and qualify URD or dUCB
     - Procure URD or dUCB

Grab your cape.
Consort Flow Diagram Displaying Randomization and Distribution of Patients

Assessed for eligibility (n=754)

Randomised (n=738)

7+3 (n=261) Received treatment (n=260) Did not receive treatment (n=1)
High-risk (n=60)
Achieved CR (n=38)
Transplant in CR1 (n=22)

High-dose AraC (n=261) Received treatment (n=258) Did not receive treatment (n=2)
High-risk (n=61)
Achieved CR (n=49)
Transplant in CR (n=28)

High-dose AraC + Vorinostat (n=216) Received treatment (n=211) Did not receive treatment (n=5)
High-risk (n=38)
Achieved CR (n=29)
Transplant in CR (n=20)

Ineligible (n=16)
- Insufficient blasts (n=7)
- No evidence of AML (n=3)
- Ph+ (n=1)
- APL (n=1)
- Receiving valproic acid (n=1)
- Intubation (n=1)
- Inadequate cardiac function (n=1)
- TB positive (n=1)

Analyzed for outcomes transplant (n=70)

Grab your cape.
Frequency of HCT in CR1 Among High-Risk AML

- 738 eligible patients
  - median age 49 years (range, 18-60)
  - 159 (22%) had high-risk cytogenetics
    - 60 (38%) 7+3
    - 61 (38%) IA
    - 38 (24%) IA+V
- HCT in 317 of all 738 patients (43%)
- 107 of 159 high-risk patients achieved CR/CRi (67%)
  - 68 (64%) of the high-risk patients received a HCT in CR1
    - p<0.001 compared to historical rate of 40%
  - 39 high-risk CR1 patients did not receive a transplant in CR1
Reasons for 39 high-risk CR1 patients not receiving a transplant in CR1

<table>
<thead>
<tr>
<th>Reason</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-morbidities</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>6</td>
</tr>
<tr>
<td>No insurance</td>
<td>1</td>
</tr>
<tr>
<td>No donor</td>
<td>1</td>
</tr>
<tr>
<td>Physician decision</td>
<td>3</td>
</tr>
<tr>
<td>Patient decision</td>
<td>3</td>
</tr>
<tr>
<td>Relapse</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
</tr>
</tbody>
</table>
Transplant Data

<table>
<thead>
<tr>
<th>HCT Donor Status</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD</td>
<td>25 (37%)</td>
</tr>
<tr>
<td>MUD</td>
<td>31 (45%)</td>
</tr>
<tr>
<td>Mismatched related donor</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Mismatched unrelated donor</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>UCB</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

- 66 high-risk patients transplanted in CR/CRi have detailed data
  - Median time to HCT from CR1 was 76 days (range, 20-365)
  - 57 patients (86%) received a myeloablative regimen
  - 9 (14%) received reduced-intensity conditioning
Cumulative Incidence of Transplant among High-Risk Patients in CR1 and all High-risk Patients

Grab your cape.
Grab your cape.
Grab your cape.
OS after transplant in CR1, high-risk cohort

Overall survival probability

- Matched related, N = 25, deaths = 16
- Matched unrelated, N = 32, deaths = 17

Log-rank p-value = 0.45

Months since transplant

Grab your cape.
Transplant Survival Outcomes

- The 2-year RFS estimate in the entire high-risk cohort is 32%
  - significantly higher than the 22% historical rate (p=0.05)
- Median RFS in the high-risk CR1 cohort (n=107) was 10 months [range, 1-32* (censored) months]
- Median OS
  - among all patients in the high-risk cohort (n=159) was 12 months [range, 1-33* (censored) months]
  - 18 months [range 3-33* (censored) months] for those transplanted in CR1
### 1 Year Estimates of Survival for High-Risk Patients Transplanted in CR1

<table>
<thead>
<tr>
<th></th>
<th>RFS (95% CI)</th>
<th>OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MRD</strong></td>
<td>40% (25%, 65%)</td>
<td>44% (28%, 69%)</td>
</tr>
<tr>
<td><strong>MUD</strong></td>
<td>50% (35%, 71%)</td>
<td>56% (41%, 76%)</td>
</tr>
</tbody>
</table>

The HR (reference = related) for RFS after transplant was 0.69 (0.36, 1.32) and for OS after transplant was 0.77 (0.39, 1.52)
Conclusions

• In newly diagnosed adults with AML age 18-60 with early cytogenetic testing with an organized effort to identify a suitable allogeneic HCT donor
  • CR1 transplant rate of 64% in the high-risk group
  • significant improvement in RFS over historical controls
Approaches to Radioimmunotherapy for AML

• Radioimmunoablation
• Targeted $\beta$ particle therapy
Rationale for RIT in HCT Regimens

- AML is highly radiosensitive.
- TBI is effective in HCT regimens at high doses.
- TBI dose cannot be escalated safely.
- RIT can increase radiation doses to bone marrow while minimizing exposure of normal tissues.

Trace-labeled \textsuperscript{131}I-Anti-CD45

Therapeutically-labeled \textsuperscript{131}I-Anti-CD45

Stem Cell Infusion

Day -21 -14 -4 0

Biodistribution and Dosimetry Studies

• Recommended therapeutic dose delivered 24 Gy to the liver.
• Mean absorbed dose to bone marrow was 36 Gy.
• Mean absorbed dose to spleen was 101 Gy.

$^{131}$I-Anti-CD45 Dosimetry

![Graph showing radiation dose (cGy/mCi $^{131}$I) for different tissues: Marrow, Spleen, Liver, Lung, Kidney, and Total Body. The graph compares Radiation Dose to Leukemia Cells and Normal Tissue.]


Grab your cape.

Let's go!
Conditioning with $^{131}$I-Anti-CD45/Flu/TBI: Outcomes of Patients Receiving MTD

Grab your cape.

Primary Endpoint: Durable CR rate, lasting at least 6 months.

Bone marrow aspirate and biopsy performed in all patients at ~1 and/or 2 months after the last day of intervention to determine response and at 6 months after CR has been established to confirm CR duration in groups labeled.
General Comments

- Relapse after HCT remains the leading cause of death for AML.
- Now almost all patients can have a donor.
- Matched sibling/unrelated donor are not the ONLY standards.
  - Haploidentical HCT
- Better outcomes in poor prognosis AML patients may be achieved simply by rapidly finding unrelated donors and performing allogeneic HCT in CR1 as soon as possible.
Our Vision

Democratize Cell Therapy

*Equal Outcomes for All*

INCREASE
- Service level
- Event–free survival
- Volume

ELIMINATE
- Disparity

Grab your cape.
The Strategic Themes

Innovate for the customer
Grow with purpose
Simplify everything
Be There responsively serving
Intervention at Diagnosis

The Idea: HLA type and match every AML patient at the time of diagnosis and provide tools to identify high risk patients and to simplify the road from diagnosis to transplantation.
Equal Outcomes for All
Thank you!