Long-Term Survival After Allogeneic Hematopoietic Cell Transplantation

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Scientific Director
Late Effects Working Committee

Conflicts of Interest
• No relevant financial conflicts of interest

Objectives
• Review data on long-term survival after allogeneic HCT
• Compare survival of HCT recipients to general population
• Review risk-factors for late mortality

Early HCT Outcomes Have Improved

One-year survival after MA HCT for AML, ALL, CML, or MDS (1990-2007)

What Is Long-term Survival?
• Likelihood of survival after the intense early post-transplant period
  • E.g. survival among patients who have survived 1 or 2 years post-transplant
  • Mortality and morbidity are more likely due to late complications

What Are Late Complications?
• Medical conditions that occur months to years after transplant
  • Can start during treatment and persist long-term
  • Can be new late-onset medical problems
• Late effects can be:
  • Disturbance in growth and development
  • Organ loss or dysfunction
  • Second cancers
  • Psychosocial problems
• Can range from mild to life-threatening
Risk Factors for Late Complications

Long-term Survival after Allogeneic HCT for Acute Leukemia, MDS, Lymphoma and SAA
JR Wingard, et al.
Journal of Clinical Oncology, 2011

Study Population
- Allogeneic HCT for AML, ALL, MDS, lymphoma or SAA between 1980-2003
- Survived in CR for ≥2 years
- Myeloablative conditioning

Patient Selection Criteria
- Inclusion criteria:
  - Diagnosis of AML, ALL, MDS, lymphoma, SAA
  - Myeloablative HCT
  - HCT between 1980-2003
- Exclusion criteria:
  - Syngeneic HCT and UCB recipients
  - Death, relapse or second HCT within 2-years of HCT
  - Teams with inadequate followup information (completeness index <80% at 5 years) (N = 4615)

Final Study Population
N = 33553

Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AML (N=1021)</th>
<th>ALL (N=1030)</th>
<th>MDS (N=941)</th>
<th>Lymphoma (N=137)</th>
<th>SAA (N=2171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs</td>
<td>28</td>
<td>16</td>
<td>34</td>
<td>74</td>
<td>18</td>
</tr>
<tr>
<td>Cy+TBI conditioning</td>
<td>53%</td>
<td>74%</td>
<td>45%</td>
<td>70%</td>
<td>17%</td>
</tr>
<tr>
<td>Related donor</td>
<td>75%</td>
<td>65%</td>
<td>52%</td>
<td>80%</td>
<td>81%</td>
</tr>
<tr>
<td>BM graft</td>
<td>85%</td>
<td>91%</td>
<td>80%</td>
<td>74%</td>
<td>99%</td>
</tr>
<tr>
<td>Grade 2-4 acute GVHD</td>
<td>39%</td>
<td>46%</td>
<td>45%</td>
<td>42%</td>
<td>25%</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>47%</td>
<td>41%</td>
<td>56%</td>
<td>50%</td>
<td>33%</td>
</tr>
<tr>
<td>Median followup, mos</td>
<td>110</td>
<td>108</td>
<td>92</td>
<td>102</td>
<td>109</td>
</tr>
</tbody>
</table>

Outcomes at 15-years after HCT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AML</th>
<th>ALL</th>
<th>MDS</th>
<th>Lymphoma</th>
<th>SAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>9%</td>
<td>9%</td>
<td>10%</td>
<td>6%</td>
<td>--</td>
</tr>
<tr>
<td>Non-relapse mortality</td>
<td>9%</td>
<td>9%</td>
<td>10%</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Overall survival</td>
<td>84%</td>
<td>84%</td>
<td>80%</td>
<td>84%</td>
<td>92%</td>
</tr>
</tbody>
</table>
### Multivariate Analysis: Overall Survival

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chronic GVHD (Relative risk [95% CI])</th>
<th>Other risk-factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>1.6 (1.4-1.9)</td>
<td>Older age, advanced disease</td>
</tr>
<tr>
<td>ALL</td>
<td>1.3 (1.1-1.6)</td>
<td>Older age, advanced disease, PB graft</td>
</tr>
<tr>
<td>MDS</td>
<td>1.7 (1.1-2.4)</td>
<td>Older age, acute GVHD</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1.6 (1.0-2.6)</td>
<td>Older age, unrelated donor</td>
</tr>
<tr>
<td>SAA</td>
<td>2.2 (1.5-3.0)</td>
<td>Older age, acute GVHD</td>
</tr>
</tbody>
</table>

### Causes of Death

- Disease recurrence most common cause of death for AML, ALL, MDS and lymphoma (20-34%)
- GVHD most common cause of death for SAA (21%)
- Other common causes of death
  - GVHD
  - Infections
  - Organ failure

### Relative Mortality: AML

### Relative Mortality: ALL

### Relative Mortality: MDS
Conclusions

- Patients who receive myeloablative allogeneic HCT for AML, ALL, MDS, lymphoma and SAA and survive in CR for 2-years have very favorable long-term survival
- Chronic GVHD increases risks of overall late mortality
- Late relapse most common cause of death
  - Patients need long term surveillance for relapse
- High risks of non-relapse mortality
  - Patients need screening and surveillance for late complications

Long-term Survival after Allogeneic HCT for CML

JM Goldman, et al.
Journal of Clinical Oncology, 2010

Study Population

- Allogeneic HCT for CML CP1 between 1978-1998
- Survived in CR for ≥5 years
- Myeloablative conditioning

Patient Selection Criteria

Inclusion criteria
- Diagnosis of CML
- Myeloablative HCT
- HCT between 1978-1998

N = 8738

Exclusion criteria
- Disease status > CP1
- Syngeneic HCT and UCB recipients
- Death, relapse or second HCT within 5-years of HCT
- Teams with inadequate followup information (completeness index <80% at 5 years)

N = 6294

Final Study Population

N = 2444
### Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Related Donor (N=1692)</th>
<th>Unrelated Donor (N=752)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>35 (2-59) years</td>
<td>34 (1-58) years</td>
</tr>
<tr>
<td>Time since dx &lt;12 mos</td>
<td>63%</td>
<td>43%</td>
</tr>
<tr>
<td>Bone marrow graft</td>
<td>94%</td>
<td>99%</td>
</tr>
<tr>
<td>TBI conditioning</td>
<td>52%</td>
<td>79%</td>
</tr>
<tr>
<td>MTX+CSA GVHD prophy</td>
<td>70%</td>
<td>74%</td>
</tr>
<tr>
<td>Acute GVHD (grade 2-4)</td>
<td>25%</td>
<td>61%</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>58%</td>
<td>70%</td>
</tr>
<tr>
<td>Median followup (range)</td>
<td>133 (60-303) mos</td>
<td>124 (60-231) mos</td>
</tr>
</tbody>
</table>

### Relapse by Chronic GVHD

### NRM by Chronic GVHD

### Overall Survival by Chronic GVHD

### Overall Survival by Donor Type

### Multivariate Analysis: Overall Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Survival (Relative Risk 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 40-49 years at HCT</td>
<td>3.0 (1.5-6.0)</td>
</tr>
<tr>
<td>Age ≥50 years at HCT</td>
<td>5.0 (2.4-10.7)</td>
</tr>
<tr>
<td>Bu-Cy conditioning (vs. TBI)</td>
<td>0.6 (0.4-0.9)</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>2.5 (1.6-4.0)</td>
</tr>
</tbody>
</table>
Causes of Death

- Infections – 15%
- Organ failure – 17%
- GVHD – 14%
- Relapse – 7%

Relative Mortality: CML

Conclusions

- CML CP1 patients who receive MA allo HCT and survive in CR for 5-years have very favorable long-term survival
- Chronic GVHD protects against relapse, but increases risks of non-relapse and overall late mortality
- Late relapse relatively uncommon, but can occur
  - Patients need long term surveillance for relapse
- High risks of non-relapse mortality
  - Patients need screening and surveillance for late complications

Followup Care for HCT Survivors

It Takes a Village...

- Models of care must meet specialized needs of high risk population
- Partner with
  - Wide range of specialists
  - Primary care physicians
  - Mid-level providers
  - Patients and caregivers

‘Lost In Transition’

- Cancer patient – Cancer survivor
- Medical provider
- Survivor
- Health-care system

Systematic care – Non-systematic care
**Individual Risks for Late Effects**

10 year old with Hodgkin’s lymphoma treated with autologous HCT

60 year old with AML treated with allogeneic HCT and has GVHD

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**Take Home Points**

- Allo HCT recipients who survive in remission for 2-5 years have 80-90% long term survival
- Older age at HCT and chronic GVHD are important risk-factors for late mortality
- Relapse is uncommon, but can occur late after HCT
  - Survivors need surveillance for relapse
  - Optimal surveillance strategy needs to be defined

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**Summary**

- Treatment related causes are important contributors of late mortality
  - Survivors need screening and prevention of late effects
- Till 10-15 years post-HCT, mortality rates remain higher than age and gender matched general population for majority of HCT survivors
  - Longer followup needed to evaluate if rates will eventually be similar to that of general population

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**Summary**

- Obtaining information on long-term followup and late complications can be challenging
  - Very important component of HCT research
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