Long-Term Survival After Allogeneic Hematopoietic Cell Transplantation

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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

Pre-HCT comorbidities

Primary therapy (chemotherapy/RT)

Post-HCT exposures (infections, medications)

DIAGNOSIS

Conditioning regimen

GVHD

Pre-HCT

HCT

Post-HCT

Genetic factors
Age & Gender
Lifestyle factors
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 $\geq 2$ 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
N = 22921
N = 10632
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AML (N=4017)</th>
<th>ALL (N=2895)</th>
<th>MDS (N=930)</th>
<th>Lymphoma (N=619)</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>34</td>
<td>18</td>
</tr>
<tr>
<td>Cy+TBI conditioning</td>
<td>53%</td>
<td>74%</td>
<td>45%</td>
<td>76%</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>95%</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>12%</td>
<td>11%</td>
<td>--</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
- GVHD
- Organ Failure
- Infections

- AML
- ALL
- MDS
- Lymphoma
- SAA
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

![Graph showing relative risk over years for AML patients.](image)
Relative Mortality: ALL
Relative Mortality: MDS

![Graph showing relative risk over years for MDS](image-url)
Relative Mortality: Lymphoma
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 $\geq 5$ years
- Myeloablative conditioning
Patient Selection Criteria

Inclusion criteria

• Diagnosis of CML
• Myeloablative HCT
• HCT between 1978-1998

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)

Final Study Population

N = 8738
N = 6294
N = 2444
<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>35%</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

![Graph showing incidence of relapse by years with Chronic GVHD. The graph indicates a steady increase in incidence over time for both Yes and No categories.](image)
Overall Survival by Donor Type

- Sibling donor
- Unrelated donor

Years

0 10 20 30 40 50 60 70 80 90 100

Probability, %

0 10 20 30 40 50 60 70 80 90 100

CIBMTR
# Multivariate Analysis: Overall Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Survival</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

Years post-transplant

Hazard

CIBMTR
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

Systematic care

Non-systematic care

BARRIERS

Medical provider
Survivor
Health-care system
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

RISKS ARE NOT SAME
Take Home Points
Summary

- 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
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
Summary

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