Long-Term Outcomes After Hematopoietic Cell Transplantation

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Conflicts of Interest

- No relevant financial conflicts of interest

Objectives

- Review data on long-term survival after allogeneic HCT
- Review risk-factors for late mortality
- Review common late complications of HCT
- Review followup recommendations for HCT survivors

Early HCT Outcomes Have Improved

One-year survival after MA HCT for AML, ALL, CML, or MDS

Who is a Long-Term Survivor

- Patients who survive the initial intense post-transplant period
- At risk for morbidity and mortality from long-term complications of HCT

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
- Related and unrelated donors
- Final study population = 10,632
- Median followup ~9 years

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>Overall survival</td>
<td>84%</td>
<td>84%</td>
<td>80%</td>
<td>84%</td>
<td>92%</td>
</tr>
<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>
</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
- Chronic GVHD was major driver of late mortality

Survival Vs. General Population

- At 15 years post-transplantation, higher rates of overall mortality compared to age-/gender- matched healthy peers

Conclusions of This Study

- 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

Late Complications of HCT
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
- Can range from mild to life-threatening

Late Complications
- Organ dysfunction/toxicity
- Late infections
- Second cancers
- Growth/development issues
- Psychosocial, sexual and QOL issues

Risk Factors for Late Complications
- Pre-HCT exposures
- Primary therapy (chemotherapy/RT)
- Conditioning regimen
- Post-HCT exposures (infections, medications)
- Genetic factors
- Age & Gender
- Lifestyle factors

Organ Specific Toxicity
- Neurologic – cognitive dysfunction
- Eye – sicca syndrome, cataracts
- Oral – xerostomia, caries
- Lungs – bronchiolitis obliterans
- Heart – coronary artery disease
- Liver – iron overload, hepatitis
- Kidney – HTN, chronic kidney disease
- Bone – osteoporosis, avascular necrosis
- Endocrine - hypothyroidism

Pre- and Post-HCT Exposures Mediate Late Complications
- Chronic GVHD
  - Dry eye, caries, xerostomia, bronchiolitis obliterans, genitourinary issues
- Exposure to corticosteroids/CSA
  - Osteoporosis, HTN, kidney disease, myopathy
- TBI
  - Coronary artery disease, caries, dry eye, cataracts, endocrine dysfunction
Screening and Prevention

- International consensus guidelines
- NS Majhail et al, "Recommended screening and preventive practices for long-term survivors after HCT"
- Will be published in March 2012
- Biol Blood Marrow Transplant
- Bone Marrow Transplant
- Hem Onc Stem Cell Therapy
- Brazilian BMT society journal

Late Infections

Vaccination Guidelines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Recommended for use after HCT</th>
<th>Time post-HCT to initiate vaccine</th>
<th>No. of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal conjugate (PCV)</td>
<td>Yes</td>
<td>3-6 months</td>
<td>3-4</td>
</tr>
<tr>
<td>Tetanus, diphtheria, acellular pertussis</td>
<td>Yes</td>
<td>6-12 months</td>
<td>3</td>
</tr>
<tr>
<td>Haemophilus influenza conjugate</td>
<td>Yes</td>
<td>6-12 months</td>
<td>3</td>
</tr>
<tr>
<td>Meningococcal conjugate</td>
<td>Follow general population recommendations</td>
<td>6-12 months</td>
<td>1</td>
</tr>
<tr>
<td>Inactivated polio</td>
<td>Yes</td>
<td>6-12 months</td>
<td>3</td>
</tr>
<tr>
<td>Recombinant hepatitis B</td>
<td>Follow general population recommendations</td>
<td>6-12 months</td>
<td>3</td>
</tr>
<tr>
<td>Inactivated influenza</td>
<td>Yearly</td>
<td>4-6 months</td>
<td>1-2</td>
</tr>
<tr>
<td>Measles-mumps-rubella (live)</td>
<td>Measles: All children and seronegative adults</td>
<td>24 months</td>
<td>1-2</td>
</tr>
</tbody>
</table>

Biology of Blood and Marrow Transplantation, 2009, Volume 15 (10), 1143-1238
Bone Marrow Transplantation, 2009, Volume 44 (8), 521-526

Second Cancers

- Cancers that occur after transplant
- Different from the cancer for which transplant was performed
- Cancer treatments may cause them or increase their risk
- Types of second cancers
  - PTLD
  - MDS/AML
  - Solid cancers
Secondary Cancer Risk Periods

- PTLD
  - Origin in donor B-lymphocytes
  - Results from EBV mediated B-cell proliferation → lymphoma
  - Incidence 1-2% after allogeneic HCT, rare after autologous HCT
  - 80% of cases occur within 1-year
  - Risk associated with degree of immune suppression

- PTLD
  - Surveillance and pre-emptive therapy for PTLD reactivation in high-risk patients may reduce risk
  - Treatment
    - >80% mortality
    - Destroy B-cells (e.g., rituxan)
    - Replete T-cells (e.g., DLI, EBV cytotoxic T cells)
    - Chemotherapy, antiviral drugs

PTLD

- MDS/AML
  - Autologous HCT
    - Incidence 5-15%
    - Latency period of 2-5 years
    - Associated with specific cytogenetic abnormalities (e.g., t11q23, del5)
  - Allogeneic HCT
    - Donor derived AML/MDS – very rare

Risk Factors for MDS/AML

- Host factors
  - Age
  - Genetic diseases
  - DNA repair polymorphisms

- Lifestyle factors
  - Smoking
  - Environmental exposures

- Transplant factors
  - Chemotherapy exposure
  - TBI

- Pre-HCT treatment factors
  - Chemotherapy exposure
  - Allogeneic HCT

Treatment of MDS/AML

- Long term survival <15%
- Typically aggressive disease
- Less likely to achieve response to chemotherapy
- Allogeneic HCT preferred treatment
Secondary Solid Cancers

- Latency period of 3-5 yrs, incidence increases with time
  - ~1-2% at 5 yrs, ~1-6% at 10 yrs, ~2-15% at 15 yrs after HCT
- Absolute risk is low, but is higher than general population

Solid cancers among 28,874 allogeneic HCT recipients

Risk Factors for Solid Cancers

- Chronic GVHD
- Squamous cell (epithelial) cancers
  - Skin
  - Oral cavity, tongue and oro-pharynx
- Total body irradiation
- Non-squamous cancers
  - Breast cancer
  - Soft tissue sarcoma
  - Central nervous system cancer

Screening for Solid Cancers

<table>
<thead>
<tr>
<th>Site</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Mammogram annually starting age 40; begin at 25 or 6 years after RT if chest has received ≥ 20 Gy</td>
</tr>
<tr>
<td>Cervix</td>
<td>PAP smear annually (for regular test) or every 2 years (for liquid based test)?</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Fecal occult blood annually and/or flexible sigmoidoscopy or barium enema every 5 years or colonoscopy every 10 years starting age 50?</td>
</tr>
<tr>
<td>Skin</td>
<td>Yearly skin exam†</td>
</tr>
<tr>
<td>Lung</td>
<td>Yearly pulmonary exam with imaging as appropriate</td>
</tr>
<tr>
<td>Oral</td>
<td>Yearly oral cavity exam</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Yearly thyroid exam</td>
</tr>
</tbody>
</table>

* Adapted from Children's Oncology Group guidelines and EBMT/CIBMTR/ASBMT guidelines
† Similar to American Cancer Society recommendations for general population cancer screening

Quality of Life

QOL After HCT

- Affects all domains of QOL
  - Autologous HCT - Lowest at ~2 weeks, returns to baseline by 3 months to 1 year
  - Allogeneic HCT - Lowest at ~4 weeks, returns to baseline by 3 months to 1 year
  - Patients with GVHD have persisting QOL deficits
  - Continued long-term impairments compared to healthy controls
  - QOL impairments in caregivers

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'

Individual Risks for Late Effects
- RISKS ARE NOT SAME

Survivor Care Plan
- No standard instrument for HCT survivors
- NMDP Patient Services Advisory Group (Chair, Dr Naynesh Kamani)
  - In the works – care plan instrument that can be used by centers

Take Home Points
- HCT recipients who survive in remission for 2-5 years have 80-90% probability of long term survival
- Chronic GVHD is important risk-factor 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 complications are important contributors of late mortality and morbidity
- Survivors need screening and prevention of late effects
- Obtaining information on long-term followup and late complications can be challenging
  - Very important component of HCT research
  - Try your best!!

www.marrow.org/md-guidelines