Late Complications

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Objectives

• Review late complications in hematopoietic cell transplant (HCT) recipients
• Review screening and prevention guidelines for HCT survivors
• Review upcoming form changes for late complications

Long-term Survival after HCT

• CIBMTR study of 10,632 allogeneic HCT recipients surviving ≥2 years in remission (median followup 9 years)

Long-term Survival after HCT

• Causes of death, ≥2 year survivors of allogeneic HCT
  – N = 1270 deaths
  – Chronic GVHD most common cause of death for SAA
• Main risk factors for late mortality on multivariate analysis
  – Older age at HCT
  – Chronic GVHD
• Relative mortality higher than age-, gender-matched general population at 15 years followup

Long-term Survival after HCT

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Overall Survival</th>
<th>COVID &amp; Mortality Risk</th>
<th>Life Expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTOLOGOUS HCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bhate et al (2007), BMT-SS</td>
<td>N=2244, multiple ds (≥2 yr survivors)</td>
<td>87-88% @ 15 yrs</td>
<td>✓</td>
<td>✓ @ 15 yrs</td>
</tr>
<tr>
<td>Majhail et al (2009), CIBMTR</td>
<td>N=1367, lymphoma (≥2 yr survivors)</td>
<td>52.86% @ 10 yrs</td>
<td>– Same (for select pts)</td>
<td></td>
</tr>
<tr>
<td>ALLOGENEIC HCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bhate et al (2007), BMT-SS</td>
<td>N=1479, multiple ds (≥2 yr survivors)</td>
<td>80% @ 15 yrs</td>
<td>✓</td>
<td>✓ @ 15 yrs</td>
</tr>
<tr>
<td>Goldman et al (2010), CIBMTR</td>
<td>N=2444, CML (≥5 yr survivors)</td>
<td>87-88% @ 15 yrs</td>
<td>✓</td>
<td>✓ @ 15 yrs</td>
</tr>
<tr>
<td>COMBINED</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin et al (2010), FHCRC</td>
<td>N=2574, multiple ds (≥5 yr survivors)</td>
<td>80% @ 20 yrs</td>
<td>✓</td>
<td>✓ @ 10 yrs</td>
</tr>
</tbody>
</table>

Causes of death (malignant diseases)

J Wingard et al, JCO 2011; 29: 2230
Late Complications

- Transplant survivors are at risk for late complications
  - Organ toxicity
  - Infections
  - Secondary cancers
  - Growth and development issues
  - Psychosocial, sexual, fertility and QOL issues

Burden of Late Morbidity

- Late complications are significant issues for survivors
  - BMT-SS – 1022 auto and allo HCT 2-year survivors

Risk Factors for Late Complications

- Late Organ Dysfunction
  - Neurologic – cognitive dysfunction, neuropathy
  - Eye – sicca syndrome, cataracts
  - Oral – xerostomia, caries
  - Pulmonary – bronchiolitis obliterans
  - Cardiovascular – coronary artery disease, metabolic syndrome, cardiomyopathy
  - Liver – iron overload, hepatitis
  - Kidney – HTN, chronic kidney disease
  - Bone – osteoporosis, avascular necrosis
  - Endocrine – hypothyroidism, growth disturbance

Late Infections

- Increased risk for infections in patients with delayed immune reconstitution (e.g., chronic GVHD, prolonged steroid exposure)
  - Encapsulated bacteria, CMV, VZV, Aspergillus, PCP
- International consensus guidelines for prevention of early and late infections published in 2009
  - Transplant recipients need vaccinations to prevent late infections

Secondary 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
  - Post-transplant lymphoproliferative disorders (PTLD)
  - MDS/AML
  - Solid cancers
Secondary Cancer Risk Periods

- Results from EBV mediated B-cell proliferation
  - Incidence 1-2% after allo HCT, rare after auto HCT
  - Risk associated with degree of immune suppression
  - Surveillance and pre-emptive therapy for EBV reactivation in high-risk patients may reduce risk

- Treatment
  - Destroy B-cells (Rituxan)
  - Replete T-cells (DLI, EBV cytotoxic T cells)
  - Chemotherapy, antiviral drugs

MDS/AML

- Primarily occurs in auto HCT recipients
  - Incidence 5-15%, latency period of 2-5 years
  - Associated with specific cytogenetic abnormalities (e.g., t11q23, del 5)
- Rare in allo HCT survivors (donor derived AML/MDS)
- Risk mediated by pre-, peri-, post-HCT exposures
- Aggressive disease – long-term survival <15%
  - Allogeneic HCT as treatment if feasible

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

Exposures Mediate Late Organ Toxicity

- Chronic GVHD
  - Dry eye, caries, xerostomia, bronchiolitis obliterans, genitourinary issues
  - Squamous cell cancer of skin and oral mucosa
- Exposure to corticosteroids/CSA
  - Osteoporosis, HTN, kidney disease, myopathy
- TBI
  - Coronary artery disease, caries, dry eye, cataracts, endocrine dysfunction
  - Breast cancer

Recommended Screening and Preventative Practices for Long-Term Survivors after HCT
Guidelines History

- Initial work in 2006 by CIBMTR, ASBMT and EBMT
  - Co-published in BBMT and BMT
- Guidelines group reconvened in 2011
  - Greater international representation – CIBMTR, ASBMT, EBMT, APBMT, BMTSanz, EMBMT, SBMTM
  - Literature review and conference calls to discuss and finalize consensus recommendations
  - Co-published in March 2012 issues of 4 journals to maximize international dissemination
  - Emphasis on exposures and called out “special populations” (e.g., GVHD, TBI, children, steroids)

Organ Systems/Issues Considered

- Immune system
- Ocular
- Oral
- Respiratory
- Cardiac and vascular
- Liver
- Renal and genitourinary
- Muscle and connective tissue
- Skeletal
- Nervous system
- Endocrine
- Mucocutaneous
- Second cancers
- Psychosocial and sexual
- Fertility
- General Health

Example: Oral Complications

- All HCT recipients
  - Educate about preventive oral health and dental maintenance
  - Counsel to avoid smoking and chewing tobacco, avoid intraoral piercing
  - Clinical oral evaluation at 6 mo, 1 yr and then yearly
  - Dentist or oral medicine specialist evaluation at 1 yr and then yearly
- Pediatric recipients
  - Assessment of teeth development
- Chronic GVHD patients
  - Clinical oral evaluation every 6 mo
  - More frequent dentist or oral medicine specialist consultations may be considered

Guideline Limitations

- Working Group acknowledged limitations – based guidelines on available literature and expert consensus opinion regarding best practice
  - Limited number of clinical trials and prospective studies
  - Evolution of HCT practice – late effects take time to develop and characterize
  - Implementation in resource limited countries
  - General health recommendations vary by country
- Recognized the need for ongoing research and for periodic update of the guidelines

Example

- 35 year old female, 100 days after unrelated donor HCT for AML in CR1
  - Healthy prior to diagnosis of AML
  - Exposures include 1 cycle of induction chemotherapy, myeloablative conditioning using Bu-Cy
  - No history of acute GVHD

Scenarios: With and Without Chronic GVHD

<table>
<thead>
<tr>
<th>Organ</th>
<th>No GVHD</th>
<th>GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system</td>
<td>Vaccinations</td>
<td>Vaccinations</td>
</tr>
<tr>
<td></td>
<td>PCP prophylaxis x 6 mo</td>
<td>PCP &amp; encapsulated organism prophylaxis for duration of immune suppression</td>
</tr>
<tr>
<td></td>
<td>Monitor CMV based on risk factors</td>
<td>Monitor CMV based on risk factors</td>
</tr>
<tr>
<td>Ocular</td>
<td>Clinical evaluation at 6 mo, 1 yr and then yearly</td>
<td>Clinical evaluation at 6 mo, 1 yr and then yearly</td>
</tr>
<tr>
<td></td>
<td>Ophthalmologic exam at 1 yr, subsequent as needed</td>
<td>Ophthalmologic exam at 1 yr, subsequent as needed</td>
</tr>
<tr>
<td></td>
<td>Both may be performed more frequently if needed</td>
<td>Both may be performed more frequently if needed</td>
</tr>
<tr>
<td>Oral</td>
<td>Clinical evaluation at 6 mo, 1 yr and then yearly</td>
<td>Clinical evaluation at 6 mo, 1 yr and then yearly</td>
</tr>
<tr>
<td></td>
<td>Evaluation by dentist at 1 yr and then yearly</td>
<td>Evaluation by dentist at 1 yr and then yearly</td>
</tr>
<tr>
<td></td>
<td>May be performed more frequently</td>
<td>May be performed more frequently</td>
</tr>
</tbody>
</table>
### Scenarios: With and Without Chronic GVHD

<table>
<thead>
<tr>
<th>Organ</th>
<th>No GVHD</th>
<th>GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Clinical evaluation at 6 mo, 1 yr and then yearly</td>
<td>Clinical evaluation at 6 mo, 1 yr and then yearly</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Assess cardiovascular risk at 1 yr and then yearly</td>
<td>Assess cardiovascular risk at 1 yr and then yearly</td>
</tr>
<tr>
<td>Muscle</td>
<td>General population guidelines for physical activity</td>
<td>General population guidelines for physical activity</td>
</tr>
<tr>
<td>Second cancers</td>
<td>Encourage skin self exam</td>
<td>Encourage skin self exam</td>
</tr>
<tr>
<td></td>
<td>Mammogram starting at age 40</td>
<td>Mammogram starting at age 40</td>
</tr>
<tr>
<td>Muco-cutaneous</td>
<td>Annual gynecologic exam</td>
<td>Annual gynecologic exam</td>
</tr>
<tr>
<td></td>
<td>May be performed more frequently if indicated</td>
<td></td>
</tr>
</tbody>
</table>

... + other organ systems

### Resources Based on Guidelines

- **Print Version – Post-Transplant Care**
  - **Recommended Post-Transplant Care**

- **Print Version – Screening/Prevention**
  - **Screening Immunization GVHD**

- **App Version**
  - Patient and physician versions
  - Choose risk factors (age group, gender, GVHD, steroid exposure, TBI) and get individualized recommendations
  - Email functionality
  - Links to references – can be opened in a browser
  - Referral timing guidelines and outcomes data
  - Link to Advances in Transplantation newsletter
Resources for Patients and Physicians

- HCT Quick Reference Guidelines for physicians - marrow.org/md-guidelines
  - Print and online
  - Mobile (search ‘transplant’)

- Patient guidelines include - marrow.org/patients
  - Simple medical descriptions
  - Checklist to bring to physician visits
  - Glossary of medical terms

CIBMTR Form Revisions: Focus on Late Complications

CIBMTR Research on Late Complications

- Late Effects Committee studies have focused on:
  - Long-term survival
  - Second cancers
  - Disease specific late complications
  - Organ specific late complications
  - Quality of life
- Capturing data on late complications has challenges
  - Patient issues
  - Physician/center issues
- Important component of CIBMTR research portfolio

CIBMTR Forms Revision

- Forms that capture late complications information
  - Form 2450 (Post-TED), Form 2100 (100 Days), Form 2200 (6 Months to 2 Years), Form 2300 (>2 Years)
- Form revision process ongoing
  - Input from center physician and CRP/DM colleagues
  - Input from experts in transplant late complications
- Some areas with notable changes
  - Pulmonary complications
  - Liver complications
  - Post-transplant lymphoproliferative disorder (PTLD)

Pulmonary Complications

- Current questions
  - Form 2100 and 2200:
    - Detailed questions on IPn/IPS
    - Limited questions on bronchiolitis obliterans, pulmonary hemorrhage and cryptogenic organizing pneumonia
  - Form 2300 – very limited questions on pulmonary toxicity
- Proposed revisions
  - Detailed data to confirm diagnosis
  - Questions piloted at few sites with very positive feedback from CRP/DM’s

Pulmonary Complications - Revision*

*Work in progress – not finalized
**Pulmonary Complications - Revision* Diagnostic Tests**

- **Diagnostic Tests**
  - "Yes" or "No" answers are selected by:
  - Bronchial wall thickening
  - Bronchial wall thickening
  - Bronchiectasis
  - Centrilobular opacities
  - Diffuse infiltrates
  - Ground glass infiltrates
  - Lung nodules
  - Presence of air trapping

**Liver Complications**

- **Current questions**
  - Form 2100, 2200 and 2300 – very limited questions on liver toxicity

- **Proposed revisions**
  - Detailed data to confirm diagnosis and treatment
  - Questions piloted at few sites with very positive feedback from CRP/DM's

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*Work in progress – not finalized*
Liver VOD - Revision*

**Diagnosis**

438. Venous-occlusive disease (VOD) or venous obstruction syndrome (VOS)?
   - Yes = go to question 439
   - No = go to question 440

Specify diagnosis of liver toxicity by clinical signs and symptoms / evaluation:

439. Ancestry
   - Yes
   - No
   - Also asks about biopsy, autopsy

440. Ultrasound / VUS / Doppler (colour / spectral arterial flow
   - Yes = go to question 441
   - No = go to question 442

441. X-ray, CT scan, or MRI
   - No
   - Also asks about uncooked, other therapy

*Work in progress – not finalized

**Treatment**

431. Did the recipient receive therapy for VOD (including continuation of prophylactic medications)?
   - Yes = go to question 432
   - No = go to question 433

Specify therapy:

432. Ceftriaxone
   - Yes
   - No

433. N-acetylcysteine
   - Yes
   - No

434. TPA
   - Yes
   - No

*Work in progress – not finalized

Liver VOD - Revision*

**Severity/Prognosis**

438. Bilirubin at date of death for this report

439. Maximum bilirubin in first 100 days

440. Maximum bilirubin in first 100 days

441. Date maximum weight documented

432. Was there concurrent multi-organ failure (e.g. renal, respiratory, neurological)?
   - Yes
   - No

*Work in progress – not finalized

PTLD

- Current questions
  - 430. Lymphoma or lymphoproliferative disease (yes, no)
  - 431. Date of diagnosis
  - 432. Is the tumor EBV positive (yes, no)

- Proposed revisions
  - Emphasis on details needed to answer research questions on PTLD

PTLD - Revision*

**Diagnosis and Patient Status**

PTLD - Revision*

**Diagnostic Tests**

*Work in progress – not finalized
### PTLD - Revision*

#### Sites of Involvement

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>581. Was PTLD confirmed by biopsy?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>584. Specify sites of PTLD involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>585. Bone marrow</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>586. Central nervous system (brain or cerebrospinal fluid)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

- Also asks about involvement of liver, lung, lymph nodes, spleen, other sites
- Requests copies of relevant investigations (e.g., pathology report, CT scan)

### PTLD - Revision*

#### Treatment

<table>
<thead>
<tr>
<th>R44. What therapy given? (for R/D of involvement and/or PTLD)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes – de-escalation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No – escalation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>587. Renal failure (Renal, Malfunction)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>588. Chemotherapy (e.g., CHOP, COPP)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>589. De novo cellular infiltration (DCI)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

- Also asks about withdrawal of immunosuppression and other therapies

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**Questions?**

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*Work in progress – not finalized*