Complications of HCT: Late Effects

WBMT Congress 2014

Naeem A Chaudhri MD FACP

King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
BMT Complications and Management

- Approximately 50,000 patients undergo HCT worldwide each year.
- Advances in technology and supportive care.
- Survive long term after HCT.
- Complications related to pre, peri, and post transplant exposure and risk factors.
One-year Survival by Year of Transplant, Donor and Age, Worldwide

- HLA-matched siblings, Age ≥ 50
- Unrelated donors, Age ≥ 50
- HLA-matched siblings, Age < 50
- Unrelated donors, Age < 50

Acute Leukemia, CML or MDS early disease status.
Late Effects

**Introduction**

- Practice is continuously changing.
- Emerging indications for HSCT.
  - Autoimmune, sickle cell disease
- New donor sources.
  - Umbilical cord and haploidentical
- Novel therapies.
  - Post HCT maintenance. Myeloma/Leukemia
- Increasing age limit.
  - RIC and NMA
- Change in risks and constellation of complications
- **A broad facet of medical issues faced by late survivors (≥ 6 months) is presented**
Causes of Death after Autologous Transplants done in 2010-2011

- Primary Disease: 69%
- Infection: 18%
- Organ Failure: 4%
- Second Malignancy: 8%
- Other: 1%
Causes of Death after HLA-identical Sibling Transplants done in 2010-2011

- Primary Disease: 49%
- Second Malignancy: 17%
- Infection: 12%
- Organ Failure: 15%
- GVHD: 5%
- Other: 1%
Causes of Death after Unrelated Donor Transplants done in 2010-2011

- Primary Disease: 38%
- GVHD: 17%
- Infection: 19%
- Organ Failure: 7%
- Second Malignancy: 1%
- Other: 17%

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH
Complications/Late Effects and Management

- Immunity and Infections
- Ocular Complications
- Oral complications
- Respiratory complications
- Cardiac and Vascular complications
- Liver complications
- Renal and genitourinary complications
- Complications of Muscle and Connective tissue
- Skeletal complications
- Central and Peripheral Nervous System
- Endocrine
- Muco-cutaneous
- Secondary cancers
- Psychosocial adjustment and sexual complications
- General screening and preventive health
Immunity and Infections

• Immune recovery occurs gradually (12-18 mths)
  – Slower in allo/UCB. HLA mismatch/TCD. GVHD and prolonged IS
• Risk highest in 1-2 years, but may be long term.
• Assessment by T-Cell function
  – CD4 count, CD4/CD8 ratio may guide for prophylaxis
• Chronic GVHD:
  – Opsonization is impaired.
• Late infections:
  – Aspergillus of the lungs.
  – Late CMV with increasing pro/preemptive therapy
  – VZV frequently in the first year
  – PCP generally during first 6 months, longer in cGVHD.
  – Certain geographic areas. e.g., TB, malaria

BBMT 2009:15:1143
Immunity and Infections: Recommendations

- **CGVHD:**
  - Antibiotic prophylaxis for encapsulated organism as long as IS therapy administered.
  - Antiviral and antifungal prophylaxis.
  - CMV screening based on risk factors.

- **Prophylaxis for oral procedures:**
  AHA guideline for endocarditis

- **PCP prophylaxis:**
  - Allo/Auto HCT: Prophylaxis 6 months. Longer if steroids in use or CGVHD with IS

- **Immunization with inactivated vaccines starting 6-12 months**

*BBMT 2009:15:1143*
<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 c</td>
<td>Yes</td>
<td>6-12 months</td>
<td>3</td>
</tr>
<tr>
<td>Haemophilus influenzae conjugate</td>
<td>Yes</td>
<td>6-12 months</td>
<td>3</td>
</tr>
<tr>
<td>Meningococcal conjugate</td>
<td>Follow country recommendations for general population</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 country recommendations for general population</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>
Ocular complications

1) Anterior segment.
   Kerato-conjunctivitis sicca syndrome
   Ocular sicca syndrome: also with xerostomia, vaginitis, skin dryness associated with chronic GVHD.
   40-60% of pts with CGVHD

Cataracts
   TBI exposure. At 10 years 40-70%. Older age. Steroids: 45% at 10 years. Allo HCT (risk higher than ASCT)

2) Posterior segment.
   • Ischemic micro vascular retinopathy, appears to be related to radiation exposure +/- CSA (lesions resolve on withdrawal of IS Rx)
   • Infectious retinitis/edema/hemorrhage
Ocular complications: Recommendations

- Routine clinical evaluation: 6 months, 1 year, then yearly.
- Ophthalmology referral, sooner with CGVHD. Frequency may depend on symptoms and presence or absence of CGVHD.
- Visual symptoms require ocular exam urgently.
Oral Complications

• Common after HCT

• Risk factors:
  – Oral chronic GVHD
  – Radiation use and dose to head and neck region
  – Fanconi’s anemia
  – Age

• Long term sequelae may continue despite resolution of GVHD
  – Peri-oral fasciitis or skin sclerosis. Xerostomia.
  – Decrease in saliva: infection/dental decay.
  – Oral cancers (fanconi, cGVHD are at higher risk)

• Young age and TBI use may lead to mandible and teeth development problems.

Blood 2005;105
Blood 2009;113
Blood 2011;117
Oral Complications: Recommendations

• Effective cGVHD management.
• Education.
  – Avoid smoking, decrease sugar containing beverages
  – Clinical oral exam: 6mth, 1 yr and yearly.
  – High risk(cGVHHD, Fanconi): every 6 month evaluation
• Dental/Oral Medicine evaluation especially for children for tooth development.
Respiratory Complications

- **Allo HCT higher risk then Auto**
- **Idiopathic pneumonia syndrome**
  - Commonly early
  - Factors: allo HCT, TBI and GVHD. Chemo may enhance TBI effects or direct damage (BCNU/BU)
- **Bronchiolitis obliterans syndrome (BOS)**
  - 2-14%. Pulmonary GVHD? Obstructive lung disease
  - PFT’s: FEV1/FVC ratio < 0.7, FEV1 < 75%
  - Chest CT with air trapping/Bronchiactasis
  - Absence of infection in the respiratory tract
- **Cryptogenic organizing pneumonia (COP)/BOOP**
  - Typically in 6-12 mths. Restrictive pattern. Treatment with steroids
- **Sino-pulmonary infections.**
  - Usually with delayed immune recovery.
Respiratory Complications: Recommendations

• Effective treatment of GVHD and infectious complications likely to reduce COP/BOS
• Adequate steroid treatment for patient with COP
• Routine clinical assessment: 6 month, 1yr, then yearly
• Earlier and more frequent assessments in patients with CGVHD
• Counseling for smoking and passive smoking
• Pts with Symptoms and signs require focused radiological assessment and PFT’s
Cardiac and Vascular Complications

- Clinically evident complications are rare. Possibly underestimated.
- Cardiac toxic death: Auto 2%. Allo 3%
- **Factors involved:**
  - Cumulative anthracyclines
  - Chest radiation
  - Pre HCT cardiac function
  - Iron overload in non-malignant diseases.
  - Advancing age
  - Established CV risk factors
  - Conditioning regimens
Univariate analysis of risk factors for a cardiovascular event.

Cumulative incidence of an arterial event stratified by age of the patients at time of HSCT. (A) The cumulative incidence at 20 years is 8.7% for patients younger than 20 years, 20.2% for patients between 20 and 40 years, and 50.1% for patients between 40 and 60.

CV complications: Recommendations

• Proper pre HCT selection of patients and assessment of expected cardiac toxicity.
• Routine clinical assessment at 1 year then yearly.
• More frequent evaluations in pts with risk factors.
• Education on “healthy life style”
• Treatment of cardiac risk factors.
Liver Complications/Late Effects

- **Chronic GVHD** is the major cause.
  - Exclude other causes.
  - Liver biopsy if Liver dysfunction is the only manifestation of GVHD and systemic IS therapy is required.
  - Ursodeoxycholic acid may be used as adjunct.
  - Liver transplant has been performed in rare cases of liver failure. *(liver transpl;2005;11)*

- Liver complications commonly related also to, medications, hepatitis B or C, Iron overload.
- PCR testing for Hep B and C. Antiviral therapy
- Iron chelation and or phlebotomy as required.
Renal and Genitourinary Complications/Late Effects

- Exposures during pre-, peri- and post HCT
- Incidence of CKD 5-65%. Apparent after 6-12 months
  - TMA, glomerulonephritis, nephrotic syndrome
  - TBI may cause radiation nephritis
  - Majority are idiopathic

- **Risk Factors:**
  - Older age, diagnosis (e.g. myeloma), baseline renal function, AGVHD, cGVHD, calcineurin inhibitors.
  - Infections, drugs, TBI
  - Post HCT H. cystitis.
  - cGVHD vulva/vagina: recurrent UTI’s
Renal and Genitourinary Complications: Recommendations

- Identifying high-risk patients and early as well as frequent assessment.
- Modifications in drugs and treatment of conditions causing kidney injury.
- HTN screening and treatment.
- Consideration of changing IS from CSA to non-nephrotoxic IS.
- Renal function assessment to include urinary protein.
- Workup including US or Bx in CKD or late onset renal dysfunction.
- Routine assessment every 6-12 months on long-term survivors.
Muscle and Connective Tissue

• Steroid induced myopathy
• Fasciitis/scleroderma
• Polymyositis
• Up to 35% of pts at 10 yrs with Musculo-skeletal symptoms
  • \textit{JCO 2005;23:6596}

• Long term sequelae of cGVHD
  – Myositis/ Polymyositis, skin sclerosis
  – Fibrosis, joint contractures
  – Requires prolonged and aggressive IS
Skeletal Complications/Late Effects

• Bone density loss a well recognized complication
  – Osteoporosis 25%, Osteopenia 50%, AVN 4-19%
  – Rapid loss within 6-12 months
  – Elderly, women, BMI <20-25, inactivity, steroid use(≥5mg/d for >3 months)

• Other possible factors
  – Hypogonadism, sec. hyperparathyroidism, toxicity from conditioning.
Skeletal Complications: Management and Recommendations

- Dual photon densitometry at 1 year for all adult women, all allo-HCT recipients and high risk patients.

- Treatment and preventive choices:
  - Activity, vitamin D and calcium supp, bisphosphonates
  - Hormone replacement therapy
  - Screening for AVN is not recommended
HCT Late Effects and Management

• **Central and Peripheral Nervous System**
  
  Drug related, infections and metabolic encephalopathy. Exposure to TBI and intrathecal chemo at higher risk. Cognitive function decline may be subclinical. 
  Assessment at 1 year for all and frequent for higher risk.

• **Endocrine complication**
  
  Subclinical hypothyroid in 7-15% in 1\textsuperscript{st} year
  Gonadal dysfunction(92% males, 99% females)
  
  Growth in children should be monitored
  Yearly evaluation and management as required
Mucocutaneous Late Effects and Management

- CGVHD patients with skin involvement approx. 70%
  - Lichen planus-like
  - Sclerosis, alopecia, thinning of scalp hair, nail dystrophy, skin depigmentation, sweat impairment, genital GVHD
  - Secondary cancers of the skin

- Clinical screening and preventive measures
Late Effects of Secondary Cancers and Management

- **Secondary Cancers**
  - 2 to 3 fold increase of developing solid tumors
  - Nearly all cancer types

- **Risk factors:**
  - Radiation therapy (sarcoma, breast, thyroid)
  - Chronic GVHD (SCC)
  - Length and intensity of IS
  - Children with cranial radiation: Brain tumors
  - Fanconi’s anemia: oro-pharyngeal cancers
  - Auto HCT: risk of sec leukemia/MDS
  - Post transplant lymphoproliferative disorders

- Earlier screening program
- Avoidance of exposure to UV rays, tobacco.
HCT Late Effects and Management

• **Psychosocial Adjustment and Sexual Complications**
  – Routine evaluations at 6 monthly period
  – Fertility issues

• **General screening and preventive health**
  – Recommended screening for all patients
  – Sex specific recommendations
    • Prostate for males
    • Breast ca, Cervical ca, osteoporosis for females
  – Healthy lifestyle recommendations for all patients
Late Effects and Management Conclusions

- Late Effects Management Guidelines Implementation
  - Applicable to all patients.
  - Resource availability issues
    - Specialists
    - Procedures
    - Healthcare access

- Comprehensive evaluation and follow-up
  - Individual exposures and risk factors
Late Effects and Management
Conclusions

• HCT patients require comprehensive evaluation, management and long term FU
• Survivorship care plan
  • Appropriate surveillance
  • Late effects
  • Relapse
  • Care outside HCT centers.
  • Close communication with primary care providers
• Multidisciplinary approach
• Late Effects clinics in Transplant centers?
Recommended Screening and Preventive Practices for Long-term Survivors after Hematopoietic Cell Transplantation

Navneet S Majhail\textsuperscript{1,2}, J Douglas Rizzo \textsuperscript{3}, Stephanie J Lee\textsuperscript{4}, Mahmoud Aljurf\textsuperscript{5}, Yoshiko Atsuta\textsuperscript{6}, Carmem Bonfim\textsuperscript{7}, Linda J Burns\textsuperscript{8}, Naeem Chaudhri\textsuperscript{5}, Stella Davies\textsuperscript{9}, Shinichiro Okamoto\textsuperscript{10}, Adriana Seber\textsuperscript{11}, Gerard Socie\textsuperscript{12}, Jeff Szer\textsuperscript{13}, Maria Teresa Van Lint\textsuperscript{14}, John R Wingard\textsuperscript{15}, Andre Tichelli\textsuperscript{16}

CIBMTR, ASBMT, EBMT, APBMT, BMTSANZ, EMBMT, SBTMO collaborative work.

\textit{Biology Blood Marrow transplant 18:348, 2012}
\textit{Bras Hematol Hemoter. 2012;34(2):109-33.}
\textit{Hematology Oncology Stem Cell Therapy, V1,Q1 2012.}
\textit{Bone Marrow Transplant. 2012 Mar;47(3):337-41.}
Thank You
Thank You
## Global Activity Survey 2006

<table>
<thead>
<tr>
<th>Region</th>
<th>Allogeneic 1st Tx.</th>
<th>Autologous 1st Tx.</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia/NZ</td>
<td>319 (28%)</td>
<td>818</td>
<td>1137</td>
</tr>
<tr>
<td>Brazil</td>
<td>800 (53%)</td>
<td>703</td>
<td>1503</td>
</tr>
<tr>
<td>Canada</td>
<td>416 (46%)</td>
<td>498</td>
<td>914</td>
</tr>
<tr>
<td>EMRO</td>
<td>682 (67%)</td>
<td>330</td>
<td>1012</td>
</tr>
<tr>
<td>Europe</td>
<td>9661 (39%)</td>
<td>15389</td>
<td>25050</td>
</tr>
<tr>
<td>Japan</td>
<td>1946 (66%)</td>
<td>1008</td>
<td>2954</td>
</tr>
<tr>
<td>US</td>
<td>4840 (44%)</td>
<td>6164</td>
<td>11004</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>18664 (43%)</strong></td>
<td><strong>24910</strong></td>
<td><strong>43574</strong></td>
</tr>
</tbody>
</table>

Preliminary data
Transplant activity worldwide
1980-2009

- Autologous
- Allogeneic

Transplants

Year: 80's - 90's - 00's - 01's - 02's - 03's - 04's - 05's - 06's - 07's - 08's - 09's
One-year survival after myeloablative conditioning for acute leukemias in any remission phase, CML or MDS, age <50 years, by year of transplant and graft source, 1988-2008

- Sibling Donor
- Unrelated Donor