Organ Function and Long-term Outcomes following HSCT

November 16th, 2022
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WELCOME

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Late Effects and Survivorship

Following Pediatric Hematopoietic Stem Cell Transplantation

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Potential Late Effects

- Chronic GVHD
- Infection
- Pulmonary dysfunction
- Cardiovascular disease
- Hypogonadism
- Growth hormone deficiency
- Renal insufficiency
- Iron overload
- Osteoporosis/AVN
- Cataracts
- Dental anomalies
- Neurocognitive dysfunction
- Psychological
- Secondary Malignancy
Etiology of Late Effects

- Primary disease
- Previous treatment for primary disease
- Pre-transplant co-morbidities
- Type of transplant (source, match, manipulation)
- Conditioning regimen
- Patient age at transplant
- Acute transplant complications
- GVHD
Case Study
R.E. is an 11-year-old female with history of SCID (Omenn’s) -10 years status post a 9/10 HLA matched unrelated donor BMT. -Her conditioning regimen was busulfan, cytoxan and ATG. -Severe GVHD of the GI tract and skin., treated with steroids. -Infectious complications including disseminated aspergillosis, due to immunosuppression. Treated with prolonged amphotericin

Late Effects:
• Chronic GVHD
• Delayed immune reconstitution/multiple infections
• Endocrine dysfunction: growth disturbance, adrenal insufficiency (steroids)
• Chronic kidney disease
• Pulmonary fibrosis (mild)
• Osteoporosis
• Neurocognitive Dysfunction
• Cataracts
Chronic Graft-versus-Host Disease

Incidence

▪ varies greatly, from 20 to 85%

Risk varies based on:

▪ Transplant source
▪ Donor characteristics
▪ Patient characteristics
▪ History of acute GVHD

Surveillance: Screening consists of thorough clinical examination, laboratory data (CBC, CMP), Pulmonary function testing, assess joints

Treatment: First line for moderate to severe cGVHD usually consists of steroids ± calcineurin inhibitor
Figure 2  Phases of opportunistic infections among allogeneic HCT recipients. HHV6, human herpesvirus 6; NK, natural killer; PTLD, post transplant lymphoproliferative disease.

Mackall et al. (2009) Bone Marrow Transplant, 44, 457-462.
Endocrinopathies

Risk factors:
- Age at transplant
- Previous therapy
- Conditioning regimen
- Prolonged treatment with steroids

Late effects:
- Hypothyroidism
- Hypoadrenalism
- Growth hormone deficiency
- Linear growth disturbance
- Gonadal failure
Endocrine Dysfunction: Adrenal Insufficiency

Risk Factors
- Prolonged steroid use
- Radiation

Prevention
- Slow wean of steroids

Surveillance:
- Clinical symptoms
- AM cortisol levels and ACTH stimulation testing, if indicated

Treatment
- Stress doses of steroids for illness and procedures
Endocrine: Growth Disturbance

**Definition:** decrease in growth velocity that is inappropriate for age

**Incidence:** occurs in up to 1/3 of patients post-HSCT

**Risk factors:** TBI and cranial radiation, steroids, age at transplant, previous primary disease treatment history

**Surveillance:**
- Height/weight
- Tanner Staging

**Treatment:**
- Referral to endocrinology for possible growth hormone therapy (patient must be over a year off of therapy)
Case Study 2: Renal Dysfunction

R.E. is an 11-year-old female with history of SCID (Omenn’s)
- 10 years status post a 9/10 HLA matched unrelated donor BMT.
- Her conditioning regimen was busulfan, cytoxan and ATG.
- Severe GVHD of the GI tract and skin., treated with steroids.
- Infectious complications including disseminated aspergillosis, due to immunosuppression. Treated with prolonged amphotericin

Late Effects:
• Chronic GVHD
• Delayed immune reconstitution/multiple infections
• Endocrine dysfunction
• Chronic kidney disease
• Osteoporosis
• Cataracts
Chronic Kidney Disease

**Definition:** irreversible kidney function and/or reduction of kidney function, with at least one of the following

- GFR <60 mL/min per 1.73 m² for greater than 3 months
- GFR >60 mL/min per 1.73 m² that is accompanied by structural damage or other markers of function kidney abnormalities (proteinuria, albuminuria, renal tubular disorders, pathologic abnormalities by histology or imaging)

**Incidence:** estimated at 20%

**Risk factors:** acute renal failure, h/o antihypertensive treatment, GVHD, nephrotoxic agents

**Surveillance:** BP monitoring, annual metabolic panel and UA

**Treatment:** BP control, dialysis
Pulmonary Complications

Late effects
- Restrictive disease: total lung capacity (TLC) < 80% predicted
- Obstructive disease: forced expiratory volume-1/forced vital capacity (FEV1/FVC) ratio of less than 70%. (ex. Bronchiolitis obliterans)

Risk factors:
- GVHD
- Age
- Infection
- Conditioning regimen

Assessment
- Clinical presentation variable
- Pulmonary Function Tests
- High-resolution chest CT

Treatment
- Supportive (not GVHD-related)
- Immunosuppression (bronchiolitis obliterans/GVHD)
Skeletal: Osteopenia and Osteoporosis

**Osteoporosis definition** (pediatrics): bone mineral density Z score below -2.0 in combination with a fracture

**Risk Factors:**
- TBI
- steroids
- ovarian failure

**Surveillance:**
- Bone density via DEXA scans, annual vitamin D-25(OH) levels

**Prevention/Treatment:**
- Weight-bearing exercise
- calcium and vitamin D supplements
- hormone replacement therapy (if indicated)
Endocrine Dysfunction: Gonadal Failure

Definition:
• Female: irregular or absent menses and FSH in postmenopausal range
• Male: elevated FSH and low testosterone levels causing primary testicular failure and impaired spermatogenesis

Clinical presentation: delayed pubertal development based on Tanner staging, amenorrhea, early menopausal symptoms

Risk factors: Busulfan, TBI

Monitoring: Annual LH, FSH, and testosterone level (males)/estradiol level (females)

Surveillance: Annual gynecologic exams and annual mammograms after the age of 35 (or earlier depending upon family history)

Treatment:
▪ Sperm banking and freezing eggs when possible prior to therapy
▪ Hormone replacement therapy
▪ Management of menopausal symptoms
Skeletal: Avascular Necrosis

**Definition:** necrosis of bone tissue due to lack of blood supply often leading to destruction of joint articular surfaces
- Hip joint is most often affected
- Can be seen as late as 10 years post-transplant

**Incidence:** 4-10% at one year post-transplant

**Risk factors:** Steroids, gender (male), age > 16 years old

**Treatment:** Joint replacement surgery
Dental

Risk factors:
- Conditioning regimen
- Chronic GVHD
- Age at transplant

Late effects
- Poor root development
- Premature apical closure
- Dental caries
- Enamel dysplasia
- Abnormal eruption
- Periodontal disease

Surveillance: Twice yearly dental examination, radiographic studies
Liver Dysfunction

**Risk factors:** PRBC transfusions, TPN, and medication toxicities

**Late effects:**
- Iron overload
- Fatty liver disease
- chronic GVHD
- Hepatitis

**Surveillance:** Annual LFTs; hepatitis screening at 1, 2, and 5 years post-transplant; and ferritin levels, T2* MRI

**Treatment:**
- Iron overload: oral iron chelation or monthly therapeutic phlebotomy
Neurocognitive Dysfunction

**Neurocognitive disabilities** are significant and common late effects of HSCT, including difficulty with:

- Reading,
- Verbal and nonverbal memory,
- Defects in verbal fluency,
- Impaired memory,
- Shortened attention span,
- Poor school performance

**Surveillance:** neuropsychological testing, esp prior to school starting.

**Management:**

- IEP, 504 plan
- Strong communication with the school
Psychological Dysfunction

- Depression
- Anxiety
- Adjustment disorder
- Post-traumatic stress disorder (PTSD)
PIDTC Data:
Retrospective Data for patients > 2 years post HSCT

- Manuscript in preparation (being submitted soon, Eissa et al)

- Retrospective data from 662 patients on SCID patients treated with one transplant between 1982 and 2012.

- Of the 662 patients: exclusion of 263 patients:
  150 expired prior to 2 years
  64 received a second transplant
  49 were lost to follow up and did not have any data available

- Total used in this study was 399 patients.
  76% male/ 24% female
  median age at dx: 131 days (0 to 6781 days)
  median follow up: 8.2 years (2-32.2 years)
  median age at tx: 178 days (7 – 7067 days)
Patient Transplant Characteristics

Infection Status at time of transplant
- no infection: 28.1%
- active infection: 40.1%
- resolved infection: 28.1%
- unknown data: 3.8%

Conditioning
- No Conditioning: 69.6%
- Reduced intensity: 9%
- Myeloablative: 20.6%
- unknown dose: 0.8%

Donor Source
- Matched sibling: 18.3%
- Other donor: 5.3%
- MMRD: 58.1%
- URD: 18.3%

Product type
- Cord Blood: 11.3%
- BM: 75.4%
- PBSC: 13.3%
## Prevalence of Chronic Late Effects

<table>
<thead>
<tr>
<th># of individuals experiencing &gt; 1 CLE (N= 399)</th>
<th>2 years</th>
<th>5 years</th>
<th>10 years</th>
<th>15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 organ system</td>
<td>100 (25%)</td>
<td>24.8</td>
<td>30.66</td>
<td>35.13</td>
</tr>
<tr>
<td>2 organ system</td>
<td>26 (6.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 organ system</td>
<td>10 (2.5%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4 organ system</td>
<td>4 (1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 organ system</td>
<td>1 (0.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 organ systems</td>
<td>1 (0.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ System</td>
<td>Prevalence</td>
<td>2 year</td>
<td>5 year</td>
<td>10 year</td>
</tr>
<tr>
<td>---------------</td>
<td>------------</td>
<td>--------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>Neuro</td>
<td>34 (8.5%)</td>
<td>5.51</td>
<td>6.89</td>
<td>8.73</td>
</tr>
<tr>
<td>Development</td>
<td>31 (7.8%)</td>
<td>6.02</td>
<td>7.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Dental</td>
<td>30 (7.5%)</td>
<td>0.25</td>
<td>4.12</td>
<td>8.47</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>26 (6.5%)</td>
<td>5.26</td>
<td>6.41</td>
<td>6.88</td>
</tr>
<tr>
<td>MSK</td>
<td>24 (6%)</td>
<td>3.26</td>
<td>4.14</td>
<td>6.21</td>
</tr>
<tr>
<td>Hepatic</td>
<td>18 (4.5%)</td>
<td>2.26</td>
<td>2.51</td>
<td>3.91</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>15 (3.8%)</td>
<td>1</td>
<td>2.32</td>
<td>3.62</td>
</tr>
<tr>
<td>Endocrine</td>
<td>15 (3.8%)</td>
<td>0.75</td>
<td>1.6</td>
<td>2.93</td>
</tr>
<tr>
<td>GI</td>
<td>5 (1.3%)</td>
<td>0.25</td>
<td>0.52</td>
<td>0.52</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Malignancy</td>
<td>9</td>
<td>0.5</td>
<td>1.41</td>
<td>1.41</td>
</tr>
</tbody>
</table>
Neuro Complications

- Motor Disturbances (2.8%)
- Hearing/ Speech/ and or visual Disturbances (2.3%)
- Seizures (2%)

- Other Complications (<1% each)
  - Cerebral palsy
  - Headache
  - Neuropathy
  - TIA
Developmental Complications

- Global developmental delays
- Behavioral Delays

- 6 patients reported depression
- 6 patients reported ADD/ADHD
- 3 patients reported autism disorders
- 1 patient reported severe anxiety

Some patients reported depression in addition to anxiety/ADHD.
Dental Complications

- caries/ decay
- mal-development
- missing permanent teeth
- poor dentition

** many of the children have not had all of their teeth in place
Growth

- 2-5 years post HSCT
  44% had a Z score < 25%ile
  23% had a Z score < 5%

- 6-10 years post HSCT
  46.4% had a Z score < 25%
  21.5% had a Z score < 5%
Malignancies

2.3% of patients developed a malignancy
   - lymphoma/ lymphoproliferative disease (0.9%)
   - non-melanoma skin malignancy (0.6%)
Reproduction

- 97 females*
  - 33 females > 14 yrs
  - 80% achieved menarche
  - (11NC, 5 IS, 3RIC, 5MAC)
  - 3 of those who received an unconditioned transplant had a child

- 302 males*
  - 3 reported fathering a child, none of the 3 received conditioning
FACTORS for Chronic Late Effects

- Pre-transplant infections (esp neurologic complications)

- RIC/ MAC conditioning regimens (growth, dental and endocrine abnormalities)

- cGVHD (autoimmune, hepatic and GI CLE)

- Artemis patients (DCLRE1C) had the greatest numbers of CLE
Take Aways

• Patients who undergo HSCT are at high risk of chronic health conditions

• Consistent long-term follow up is key to identifying and treating late effects of therapy

• More research is needed
Concerns for this retrospective data

1. Most centers did not collect the same data and we had to rely on what the center had available. Data managers extracted what was written in the notes, which may not have captured all information.

2. Although many patients were in follow up at the same center, many patients stopped going to their doctor when they felt well. Therefore information regarding reproduction is only descriptive.
QUESTIONS???
Q&A SESSION:
YOUR QUESTIONS ANSWERED
Have more Questions?

primaryimmune.org/ask-idf
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NEXT PROGRAM

SCID Compass Lunch & Learn: Pain Management & Coping for Kids in a Medical Setting

Samantha Childs, CCLS
November 30th, 2022
1:00-2:00 PM ET

www.scidcompass.org/events
THANK YOU!

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