Post Allogeneic Hematopoietic Cell Transplant Care for Pediatric Transplant Survivors

Monica Bhatia, MD
Director, Pediatric Stem Cell Transplantation Program
Associate Professor of Pediatrics
Columbia University, New York
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• No conflict of Interests

Abbreviation
AlloHCT: Allogeneic hematopoietic cell transplantation = Bone marrow transplantation (BMT) = Peripheral blood stem cell (PBSC) = Umbilical cord blood transplantation (UCBT)
Outline

• **Early Post-AlloHCT care (6-12 months)**
  • Organ functions
  • Infections
  • Disease recurrence

• **Intermediate care (12-24 months)**
  • Vaccination
  • Bone health
  • Endocrine health

• **Long term follow up (>2 years)**
  • Organ dysfunction
  • Screening for second malignant neoplasm
  • Growth monitoring
  • Emotional wellbeing
Introduction

• AlloHCT has curative potential for both malignant and non-malignant disease

• Over last two decades, survival has significantly improved

• Increase in number of long term survivors

• Higher burden of serious chronic conditions

• Impairments can virtually involve every organ system

• Significant impact on quality of life and health care utilization
Toxicities of HCT

Short Term
- Seizures, CVA, PRES
- Mucositis
- Veno-Occlusive Disease of the Liver
- Acute Graft versus Host Disease
- Infections

Long Term
- Learning Disabilities
- Bronchiolitis Obliterans
- Cardiac Dysfunction
- Infertility
- Chronic Graft Versus Host Disease
- Infections Endocrine
- Abnormalities: Thyroid, Growth

Short Term vs Long Term
Clinical Vignette: Longitudinal Follow-up

• 10 year old child (M/F) received an unrelated alloHCT(BM/PBSC/UCB) for relapsed leukemia (ALL/AML) 6 months back.

**Important pertinent history**

- Pre-BMT chemotherapy exposure
- Conditioning for BMT- Myeloablative/reduced intensity, Total body irradiation vs. Busulfan
- Infections: recurrent bacterial infection, CMV, EBV reactivation
- Graft-versus-host disease: prophylactic agents utilized, treatment, taper plan.
- Organ injury
- Disease status
First follow up at your clinic

- Looks well, ambulatory, in good spirits
- Vitals: age appropriate, dryness of skin, stria, no central line, hirsutism.
- Medications: bactrim, fluconazole, valganciclovir and cyclosporine (taper)

What would I do

- Complete blood count with differential
- Liver and renal function test, cyclosporine levels
- T-cell panel
- Immunoglobulin levels
- Viral PCR: no
- Hormone levels: no
- Parents would like to know about: diet, visitors and school.
Results

• WBC:4 x10⁹/L, ANC-1 x10⁹/L, Hemoglobin-10 gm/dl, plt-100 x10⁹/L.
• ALT- 180U/mL (4-5x upper limit of normal), Bili-0.8mg/dl, Serum creatinine-0.8mg/dL.
• CD4 count-100/µL, CD8-count-200/µL.
• IgG level-500mg/dL.

Now what?

• Look back: previous LFT’s, medications, GVHD, viral infections.
• Repeat CBC and liver function test: CBC-unchanged, ALT-220 U/mL.
• Most likely drug induced. However, check ferritin, could be early sign of chronic GVHD, rarely infection.
• Stop: ? Bactrim, fluconazole, valganciclovir
• Repeat labs in 2 weeks.
Follow up #3, 7 months post-AlloHCT

ALT

Improving

ALT <100

Restart anti-infection PPX

Duration of anti-infection PPX

Worse

Develops skin changes suggestive of cGVHD

Starts steroids and Increase CSA

Worse

Increase CSA
One year follow up

• Disease work-up-BMA aspirate, Spinal tap, IT-chemo???

• CBC, LFT’s, Chem10, Ferritin, T-cell panel, Immunoglobulin levels

• Echo/EKG, Pulmonary function test

• Thyroid function test, FSH, LH, testosterone levels, GH

• Vaccination
Routine Bone Marrow and CSF Analyses Following AlloHCT in Children with Leukemia: Lack of Consensus and Questionable Utility: Levinson et al, BBMT 2017

Q2 Do you perform routine bone marrow analyses after AlloHCT in all patients with acute lymphoblastic leukemia (ALL) who are not enrolled on a research study?

As clinically indicated: 24.19% (45)
No: 9.68% (17)
Yes: 66.13% (11)

Q4 Do you perform routine bone marrow analyses after AlloHCT in all patients with acute myeloid leukemia (AML) who are not enrolled on a research study?

As clinically indicated: 22.58% (14)
No: 14.52% (9)
Yes: 62.90% (39)

ALL:
Number of Bone Marrow Analyses in First Year

Number of Practitioners

<table>
<thead>
<tr>
<th>Number of Analyses Per Year</th>
<th>Number of Practitioners</th>
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<tbody>
<tr>
<td>1</td>
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AML:
Number of Bone Marrow Analyses in First Year

Number of analyses/year

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<thead>
<tr>
<th>Number of Analyses Per Year</th>
<th>Number of Practitioners</th>
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Follow up at one year

- Still on Immunosuppression
- Complains of exercise intolerance: ? Lungs, heart or bone
- CBC, LFT’s, Chem 10, ferritin, T-cell panel, Immunoglobulin levels
- Echo/EKG, Pulmonary function test
- Thyroid function test, FSH, LH, testosterone levels, GH,
- Vaccination
Vaccination
When should vaccinations begin for the typical BMT recipient?

- As early as 6 months: Conjugated vaccines
- Not receiving any chemotherapy maintenance
- No graft-versus-host disease
- No anti-CD20 monoclonal antibody administration in last 6 months
- Did not Receive IVIG in last 2 months
- AlloHCT recipients should be vaccinated despite protective titers
<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 a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal conjugate (PCV)</td>
<td>Yes</td>
<td>3-6 months</td>
<td>3-4 b</td>
</tr>
<tr>
<td>Tetanus, diphtheria, acellular pertussis c</td>
<td>Yes</td>
<td>6-12 months</td>
<td>3 d</td>
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<tr>
<td><strong>Haemophilus influenzae conjugate</strong></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 e</td>
</tr>
<tr>
<td>Measles-mumps-rubella (live) t g</td>
<td>Measles: All children and seronegative adults</td>
<td>24 months</td>
<td>1-2 h</td>
</tr>
</tbody>
</table>

a. Please refer to the specific guidelines for each vaccine.

b. Depending on the specific vaccine, the number of doses may vary.
c. Acellular pertussis vaccine.
d. Depending on the dose and schedule.
e. Depending on the specific vaccination program.
f. Live vaccines require careful consideration.
h. Depending on seronegative status.
Specific interval between doses

Following the primary series of three PCV doses, a dose of the 23-valent polysaccharide pneumococcal vaccine (PPSV23) to broaden the immune response might be given.

For patients with chronic GVHD who are likely to respond poorly to PPSV23, a fourth dose of the PCV should be considered instead of PPSV23.

DTaP is preferred. However, DTaP is not licensed for adults, administer Tdap.

Acellular pertussis vaccine is preferred, but the whole-cell pertussis vaccine should be used if it is the only pertussis vaccine available.
When and how should MMR vaccination be given after BMT?

• It is considered safe to give live attenuated MMR when recipients are
  >2 years out from BMT,
  >1 year off all systemic immunosuppression,
  >8 months out from any prior IVIG dose (the “2-1-8” mnemonic).
• Relaxation of this rule to some extent is considered when community outbreaks occur.
• Antibody titers are unnecessary before or after vaccination.
Who should be offered varicella vaccine and when is it safe to do so?

• Varivax recommended for VZV-seronegative recipients

• Timing of varicella vaccination can be remembered as for MMR by the “2-1-8” rule.

• A second dose of varicella vaccine is needed 1 month after the first.
How soon after BMT can I give the flu vaccine?

• Administer at >6 months post-BMT regardless of conditioning regimen or BMT type.

• During community outbreaks flu vaccine may be given at 3 to 4 months post-BMT, in which case a second dose is given 1 month later.

• Children aged >6 months and <9 years who never had flu vaccine post-transplant need 2 flu shots given 1 month apart.

• Patients who require protective isolation or are hospitalized should not be exposed to live attenuated influenza vaccine.

• All household contact should receive inactivated flu vaccine.
Need aggressive long term follow up
Long Term effects: Triad of Troubles
Late effects of blood and marrow transplantation.

Neuropsychological effects
- Depression, anxiety
- Post-traumatic stress disorder
- Neurocognitive deficits

Pulmonary diseases
- Bronchiolitis obliterans syndrome
- Cryptogenic organizing pneumonia
- Pulmonary hypertension

Kidney diseases
- Thrombotic microangiopathy
- Nephrotic syndrome
- Idiopathic chronic kidney disease
- Persistent acute kidney injury
- BK virus nephropathy

Iron overload

Bone diseases
- Osteopenia
- Osteoporosis
- Avascular necrosis

Endocrine diseases
- Thyroid dysfunction
- Gonadal dysfunction
- Diabetes
- Dyslipidemia
- Metabolic syndrome
- Adrenal insufficiency

Solid cancer
- Oral cavity
- Skin
- Breast
- Thyroid
- Other sites

Cardiovascular diseases
- Cardiomyopathy
- Congestive heart failure
- Valvar dysfunction
- Arrhythmia
- Pericarditis
- Coronary artery disease

Liver diseases
- Hepatitis B, Hepatitis C, liver cirrhosis
- Nodular regenerative/focal nodular hyperplasia

Gonadal dysfunction/infertility

Infectious diseases
- Pneumocystis jirovecii
- Encapsulated bacteria
- Fungi
- Varicella-zoster virus
- Cytomegalovirus
- Respiratory syncytial virus
- Influenza virus
- Parainfluenza virus
Total Body Irradiation (Top to Bottom Injury)

- Neurocognitive deficits
- GH deficiency
- Leukoencephalopathy
- Cataract
- Dental abnormalities
- Cardiac toxicity
- Pulmonary toxicity
- Renal toxicity
- Gonadal dysfunction
- Uterine vascular insufficiency
- Musculoskeletal
- Hypothyroidism, thyroid cancer
- Renal toxicity
- Hypothyroidism, thyroid cancer
- Pulmonary toxicity
- Renal toxicity
- Uterine vascular insufficiency
- Cataract (busulfan)
- Pulmonary fibrosis (busulfan)
- Gonadal dysfunction
- Therapy-related AML/MDS
- Bladder cancer
Chronic GVHD

- Xerophthalmia
- Xerostomia, dental abnormalities
- Pulmonary toxicity
- Gastrointestinal strictures
- Genitourinary strictures
- Skin and joint changes
- Immune deficiency
- Second cancers, especially skin, oral, cervical, lymphoma
Long Term Follow up:

Evaluation

• Endocrine
• Bone Health
• Dental abnormalities
• Renal toxicity
• Increased risk of second cancers
• Adverse psychosocial/quality of life effects
• Mental health disorders, risk behaviors
• Psychosocial disability due to pain, fatigue
Endocrine Complications

- Most prevalent chronic conditions seen after HCT in children 50% to 85%

- Infertility tends to be very common in both genders, whereas hormonal dysfunction is more likely in females than in males.

- Metabolic syndrome, characterized by adiposity, dyslipidemia, glucose intolerance, and hypertension
Gonadal Function

• TBI, alkylating, and similar DNA interstrand crosslinking agents

• Toxic to spermatogonial germ cells (high dose busulfan and cytoxan).

• Leydig (testosterone-producing) cells tend to be more resilient.

• Permanent azoospermia likely after 6-10 Gy of TBI, whereas testosterone insufficiency in Leydig cells may not occur until 20 Gy
Gonadal Functions

- Infertility associated with lower radiation doses among pubertal versus pre-pubertal girls (5-10 Gy vs. 10-15 Gy, respectively).

- At-risk males, morning testosterone should be evaluated beginning no later than age 14 and as clinically indicated.

- At-risk females, luteinizing hormone, follicle stimulating hormone, and estradiol should be evaluated beginning no later than age 13.
Avascular Necrosis of Bone after AlloHCT in Children

- The median time from HCT to the onset of AVN: 14 months
- 37% of patients AVN occurs within 1 year of HCT.
- 59% AVN occurs 1 to 5 years after HCT
- Risk factors
  - Age at transplant (≥5 years)
  - Female gender, and
  - chronic graft-versus-host disease (GVHD)

Late osteonecrosis by BMT donor type in 1346 BMT recipients.

Smita Bhatia et al. Blood 2017;130:1302-1314
• Infectious complications: Important cause of late morbidity and mortality in long-term survivors of childhood HCT.

• Long-term survivors treated with TBI had nearly an 8-fold increased risk of death from infection compared with population norms.

• Patients with active chronic GVHD:
  - Functionally asplenic
  - Impaired lymphocyte function
  - Antibiotic prophylaxis against encapsulated organisms for the duration of immunosuppressive therapy.
  - Broad spectrum parenteral antibiotics for fevers
## Screening Guidelines

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Risk factors</th>
<th>Screening guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>TBI, cranial radiation, abdominal radiation, corticosteroids, obesity</td>
<td>Fasting serum glucose or hemoglobin A1C every 2 y</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>TBI, calcineurin inhibitors</td>
<td>Lipid panel every 2 y</td>
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<tr>
<td>Hypertension</td>
<td>Corticosteroids</td>
<td>Annual manual BP monitoring</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Anthracyclines, pre-BMT chest RT, CVRFs</td>
<td>Echocardiograms (every 1 to 5 y depending on the risk factors)</td>
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<tr>
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<td>Screening for modifiable CVRFs (diabetes, dyslipidemia, hypertension)</td>
</tr>
<tr>
<td>Condition</td>
<td>Risk Factors</td>
<td>Screening Guidelines</td>
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<tr>
<td>Iron overload</td>
<td>Multiple transfusions</td>
<td>Serum ferritin 1 y post-BMT, as clinically indicated</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Ifosfamide, platinum-based chemotherapy, methotrexate, TBI, calcineurin inhibitors</td>
<td>1 y post-BMT and as clinically indicated; Yearly urinalanalysis for proteinuria, BP monitoring</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Alkylating agents, TBI, cranial radiation, pelvic radiation, testicular radiation</td>
<td>LH, FSH, testosterone (males)</td>
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<tr>
<td></td>
<td></td>
<td>LH, FSH, estradiol (females)</td>
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<tr>
<td></td>
<td></td>
<td>History of sexual dysfunction and infertility</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Corticosteroids, growth hormone deficiency, hypogonadism, lack of physical activity, Vitamin D deficiency</td>
<td>DXA scan 1 y after BMT, then as clinically indicated</td>
</tr>
</tbody>
</table>
# Screening Guidelines

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk Factors</th>
<th>Follow-up/Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteonecrosis</td>
<td>Corticosteroids, calcineurin inhibitors, radiation</td>
<td>X-ray/MRI (in the event of symptoms)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>Radiation to the neck, TBI</td>
<td>Annual TSH, FT4</td>
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<td>Annual palpation of thyroid gland for nodules</td>
</tr>
<tr>
<td>Cataracts, xerophthalmia</td>
<td>TBI, cranial radiation, corticosteroids, cGVHD</td>
<td>History of visual acuity</td>
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<td></td>
<td>Annual ophthalmologic examination</td>
</tr>
<tr>
<td>Neurocognitive impairment</td>
<td>Cranial radiation, TBI, high-dose methotrexate and cytarabine</td>
<td>Annual screening for educational/ vocational difficulties</td>
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<tr>
<td></td>
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<td>Formal neuropsychological evaluation if difficulties identified</td>
</tr>
<tr>
<td>Pulmonary dysfunction</td>
<td>Bleomycin, busulfan, nitrosoureas, chest radiation, TBI, cGVHD</td>
<td>Pulmonary function tests at 1 y after BMT, then as clinically indicated</td>
</tr>
</tbody>
</table>
Conclusions

• Children following HCT are at risk of late effects
• Late effects results in significant morbidity
• Morbidity associated with late effects results in significant psychosocial challenges
• Collaborative efforts among COG, CIBMTR, ASBMT and EBMT will have impact on reduction late effects
• Modifiable risk factors:
  - Replacing TBI
  - Decreasing chronic GVHD.
References


• **Carpenter** PA, **Englund** JA. How I vaccinate blood and marrow transplant recipients. Blood. 2016 Jun 9;127(23):2824-32.
Questions?

Thank you!
SECOND CANCERS

• Subsequent malignant neoplasms can be classified into 3 groups:
  
• Therapy-related myelodysplasia and acute myeloid leukemia (t-MDS/AML)
  
• Lymphoma, including lymphoproliferative disorders
  
• Solid tumors

Smita Bhatia et al. Blood 2017;130:1302-1314
Therapy Related Myelodysplastic Syndrome
Secondary Acute Myeloid Leukemia

• Major cause of nonrelapse mortality after autologous HCT and is less common after allogeneic HCT.
• Transplantation-specific risk factors:
  - Use of peripheral blood stem cells (compared with bone marrow),
  - Stem cell mobilization with etoposide,
  - Conditioning with TBI, and
  - Multiple transplantations.
• Latency of t-MDS/AML development can be longer after alkylating agents or radiation compared with after topoisomerase II inhibitors (4 to 7 years versus < 5 years)
Solid Tumors

• Incidence: As high as 11% at 15 years after transplantation,

• More than 2-fold what would be expected in the general population matched on age and sex.

• Risk appears to be greater after allogeneic than after autologous HCT

• Skin cancers (melanomas, basal cell, and squamous cell carcinomas)