Hot Topics in Pediatric Hematopoietic Stem Cell Transplantation

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Presentation Information

- This presentation was delivered during the BMT Pharmacists Conference as part of the American Society for Blood and Marrow Transplantation (ASBMT) and Center for International Blood & Marrow Transplant Research (CIBMTR) Tandem Meetings Annual Conference in Orlando, FL, February 24-28, 2010

Disclosures

- I have received honoraria for services (Speakers' Bureau participation and CE programming) from Enzon Pharmaceuticals, Genzyme Oncology and sanofi-aventis
- I am a member of the Pediatric Central Institutional Review Board through the National Cancer Institute/National Institutes of Health
- Most of the products mentioned in this presentation are not currently FDA-approved for use in patients under the age of 18 years

Objectives

- Identify current trends in the field of pediatric hematopoietic stem cell transplantation with respect to transplant procedures, supportive care practices and long-term surveillance
- Analyze selected data recently published on current trends in pediatric hematopoietic stem cell transplantation
- Incorporate recent published data to augment current institutional practice standards for the care of pediatric hematopoietic stem cell transplant recipients

Disease States

Acute Lymphoblastic Leukemia (ALL)

- Most common malignancy in childhood
  - Accounts for approximately 1 in 4 cancer diagnoses in children less than 15 years old
  - Peak incidence: 2 to 5 years old
  - Five-year survival rates 85-90%
- Risk determination
  - Age, gender and white blood cell count at diagnosis
  - Cytogenetics
    - Favorable – hyperdiploid; presence of t(12;21)
    - Unfavorable – hypodiploid; presence of t(4;11) or t(9;22)

Acute Lymphoblastic Leukemia (ALL)

• Role of stem cell transplantation (USA)
  - Matched related donor allogeneic SCT is recommended over chemotherapy in very high-risk Ph+ patients in 1st complete remission
  - Matched related donor allogeneic SCT in 2nd or subsequent remission may be equivalent to or better than chemotherapy alone
  - Some patients with late relapses achieve extended leukemia-free survival with autologous purged SCT (but insufficient evidence to determine if better than chemotherapy alone)


Acute Lymphoblastic Leukemia (ALL)

• There is insufficient evidence to:
  - Support a recommendation for unrelated donor allogeneic SCT vs. chemotherapy in 2nd or subsequent remission
  - Support the use of autologous unpurged SCT
  - Compare outcomes of related vs. unrelated donor allogeneic SCT
  - Support a recommendation of autologous versus allogeneic SCT


Acute Lymphoblastic Leukemia (ALL)

• Role of stem cell transplantation (Europe)

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>Donor Type</th>
<th>Well matched</th>
<th>1 antigen mismatched</th>
<th>Autologous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission (CR) 1 (low risk)</td>
<td>Generally not recommended</td>
<td>Generally not recommended</td>
<td>Generally not recommended</td>
<td>Generally not recommended</td>
</tr>
<tr>
<td>CR1 (high risk)</td>
<td>Standard of care</td>
<td>Standard of care</td>
<td>Clinical option</td>
<td>Generally not recommended</td>
</tr>
<tr>
<td>CR2</td>
<td>Standard of care</td>
<td>Standard of care</td>
<td>Clinical option</td>
<td>Clinical option</td>
</tr>
<tr>
<td>&gt; CR2</td>
<td>Standard of care</td>
<td>Standard of care</td>
<td>Clinical option</td>
<td>Clinical option</td>
</tr>
</tbody>
</table>


Acute Lymphoblastic Leukemia (ALL)

• Philadelphia-chromosome positive (Ph+) ALL
  - Occurs in only 3-5% of children with ALL compared to 25% incidence in adults
  - Associated with a poor outcome (< 40% survival)
  - Daily oral doses of imatinib have found to be safe and effective in children
    - Doses: 260 – 570 mg/m²/day
    - Well tolerated: adverse events similar to adults
  - What is the utility of imatinib given in combination with multi-agent chemotherapy?


Acute Lymphoblastic Leukemia (ALL)

Children’s Oncology Group AALL0031 Study

Frontline Induction/Consolidation (4-15 weeks) Consolidation (3 weeks) x 2 courses Stem Cell Transplantation Reinduction (3 weeks) Intensification (9 weeks) X 2 courses of each Maintenance (8 weeks) X 12 cycles

160 patients


Acute Lymphoblastic Leukemia (ALL)

Imatinib Therapy for Non-Transplant Patients

Acute Lymphoblastic Leukemia (ALL)

Outcome of adding imatinib to standard chemotherapy regimens


Chemotherapy + imatinib compared to stem cell transplantation + imatinib


Summary & Conclusions
- Preliminary data suggests outcome with continuous administration of imatinib in combination with chemotherapy is as good as results with imatinib and stem cell transplantation
- Safety profile of imatinib therapy is acceptable
  - Hepatotoxicity can be augmented by breaks in therapy
  - Cardiac toxicity not seen in children as reported in adults
- Follow-up study using dasatinib is ongoing
- Issues
  - Long-term efficacy and safety data
  - Incorporation of tyrosine kinase inhibitors
  - Role of transplantation

Reduced Intensity Conditioning Regimens
- Role of reduced intensity conditioning (RIC) regimens in adults is well established
- Exact place in therapy of RIC is not clear in pediatrics
  - Tolerance to transplant process is usually greater in children
  - Stem source of umbilical cord blood or bone marrow has been preferred in children
    - Survival data
    - Ethical issues
  - Safety and efficacy data is limited to single institutional center experiences

Transplant Process
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What are our experiences?
- Non-malignant diseases (66-100% overall survival)
  - Sickle cell disease
  - Congenital neutropenia
  - Severe aplastic anemia
  - Hemophagocytic lymphohistiocytosis
  - Severe combined immunodeficiency disorder
- Malignant diseases (66-93% overall survival)
  - Acute lymphoblastic leukemia
  - Chronic myeloid leukemia
  - Non-Hodgkin’s lymphoma
  - Neuroblastoma
  - Hodgkin’s disease

Complications

Reduced Intensity Conditioning Regimens

**Commonly Used Transplant Regimens in Pediatrics**

<table>
<thead>
<tr>
<th>Reduced Intensity</th>
<th>Ablative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced Intensity Conditioning Regimens</td>
<td></td>
</tr>
<tr>
<td>Non-myeloablative</td>
<td>Reduced Intensity</td>
</tr>
<tr>
<td>Busulfan 16mg/Fludarabine/Alemtuzumab</td>
<td>TBI/Cyclophosphamide/Thiotepa</td>
</tr>
<tr>
<td>Busulfan 8mg/Fludarabine/Fludarabine/Alemtuzumab</td>
<td>TBI/Cyclophosphamide</td>
</tr>
<tr>
<td>TBI/Cyclophosphamide/Thiotepa</td>
<td></td>
</tr>
</tbody>
</table>

**Immunosuppression**

- Haplo
- MUD
- MRD

**Myelosuppression**


**Myelosuppression**


**Reduced Intensity Conditioning Regimens**

- Disease status and treatment
  - ALL – morphologic remission
  - AML – M1/M2 acceptable
  - JMML/MDS – less than 5% blasts
  - CML – first chronic phase, accelerated phase, or subsequent chronic phase with less than 5% blasts
  - NHL/HD – responsive disease /no persistent masses > 5 cm

**Results – 47 patients (25 males)**

- Median age 11 years (range 2-20)
- 60% qualified with prior myeloablative transplant
- 10 patients had organ toxicity/3 invasive fungal infections
- Median follow-up 24 months (range 11-53)

- 2 year EFS and OS were 40.2% and 44.5%

**Survival in relation to history of myeloablative transplantation**

Reduced Intensity Conditioning Regimens

Survival in relation to disease status


Chronic graft-versus-host disease

- Leading cause of late morbidity and non-relapse mortality following HSCT
- Different disease and process in children
  - Recovery of the immune system
  - Stem cell source utilization patterns
  - Response to and effects of immunosuppression
- Treatment options
  - Standard of care: corticosteroids + calcineurin inhibitor
  - Salvage regimens
  - Need remains for well-tolerated therapy that is easy to administer and monitor


Pentostatin in Steroid-Refractory Chronic GVHD

- Potent inhibitor of nucleoside deaminase
- Markedly reduces CD4 and CD8 cells as well as B-cells with IgG levels
- Results in chronic GVHD favorable in adults
  - Phase II study: 55% objective response in 58 heavily pre-treated patients
  - Phase II study in children conducted by the Pediatric Blood and Marrow Transplant Consortium recently published


Graft-versus-Host Disease

- Therapy
  - Pentostatin 4 mg/m² IV every other week
  - Duration of therapy was 6-12 months
  - Other immunosuppression therapy
    - Corticosteroid taper started 8-12 weeks after starting study
    - Calcineurin inhibitor continued throughout study
    - All other therapies tapered starting at 3 months from study entry
  - Infection prophylaxis strongly recommended
    - Penicillin
    - Acyclovir
    - Fluconazole
    - Trimethoprim-sulfamethoxazole


Pediatric Blood and Marrow Transplant Consortium study

- Allogeneic HSCT of any stem cell source in patients less than 21 years of age
- Treatment-refractory cGVHD
  - Development of 1 or more new sites while on active therapy
  - Progression of existing site(s) while on active therapy
  - Failure to improve while on standard therapy for at least 1 month [at least 1 mg prednisone (or other steroid equivalent)/kg every other day or other immunosuppression regimen if intolerant of steroids]
- Could not have failed more than 2 prior regimens and must have reasonable performance status and organ function

Graft-versus-Host Disease

- Evaluation occurred at baseline and every 3 months
  - Grading in 9 domains: rash, sclerosis, oral, fasciitis, joint, liver, lung, gastrointestinal and ocular
- Monthly toxicity grading
- Results
  - 51 patients treated (53% male)
    - Median age 9.8 years (range 0.9-20.7)
    - Median time from HSCT to GVHD 5.0 months (1.4-26.1)
    - Median time from GVHD to study entry 6.2 months (0.1-42.1)
    - Myeloablative transplants 73%
    - 96% subjects on corticosteroids at study entry for a median time of 3.9 months (range 0-24.9)


Graft-versus-Host Disease

- Response by domain


Graft-versus-Host Disease

- Toxicity


Graft-versus-Host Disease

- Overall survival (secondary endpoint)


Other Complications

Invasive Fungal Infections:
Focus on Echinocandins

- Study importance
  - Confirmation of response in children
  - Response to sclerotic manifestations of cGVHD
  - Tempo of response
  - Largest reported pediatric cGVHD trial to date
  - Tools for staging and assessing response to cGVHD
  - Next step → assessment in newly diagnosed, high risk pediatric patients with cGVHD

- Incorporation of pentostatin in treatment algorithms

**Invasive Fungal Infections**

- **Frequency and severity of invasive fungal infections**
  - Estimated that 10-40% of pediatric patients will experience an infection at some point during allogeneic HSCT
  - Susceptibility of the host
  - Use of broad-spectrum antibiotics
  - Most common causes: *Candida* spp and *Aspergillus* spp
  - Leading cause of morbidity and mortality in children
  - Candidemia 16-31% mortality rate
  - Aspergillosis: mortality rate as high as 77%
  - Newer treatment options

*Anidulafungin* open label noncomparative study

*Caspofungin*: Only evaluation has been with micafungin in this setting

Micafungin as safe and effective as liposomal amphotericin B in 35% feces

No data

**Study limitations**

February 2006

- 2 mg/kg/day (100 mg/day if > 40 kg) vs. 3 mg/kg/day
  - Patients < 8 years old may need 1.3
  - Evaluated versus fluconazole up to a month after HSCT

2009;15:613

Micafungin alone or in combination was safe and effective in 50 kg: 50 mg/day micafungin vs. 400 mg/day fluconazole

71% feces

Estimated that 10

February 2006

- Arylsulfatase

**Invasive Fungal Infections**

- **Prophylaxis in pediatric HSCT**
  - Only evaluation has been with micafungin in this setting
  - Evaluated versus fluconazole up to a month after HSCT
    - > 50 kg: 50 mg/day micafungin vs. 400 mg/day fluconazole
    - < 50 kg: 1 mg/kg/day vs. 8 mg/kg/day
  - Micafungin more successful than fluconazole in preventing systemic fungal infections prior to and through first 4 weeks after transplantation
  - Rates of candidal colonization: more with micafungin (except for *C. glabrata*)
  - Micafungin found to be as effective as fluconazole and may be an alternative agent for antifungal prophylaxis

**Invasive Fungal Infections**

- **Treatment of pediatric invasive candidiasis**
  - Evaluations with caspofungin and micafungin
  - Largest randomized double-blind comparative trial evaluated use of micafungin
    - Micafungin vs. Ambisome®
      - 4 mg/kg/day (100 mg/day if > 40 kg) vs. 3 mg/kg/day
      - 4 mg/kg/day (200 mg/day if > 40 kg) vs. 5 mg/kg/day if persistent fever after 5 days or positive infection
    - Minimum treatment for 14 to a maximum of 4 weeks (in some cases up to 8 weeks)
    - Similar safety and efficacy
    - Micafungin as safe and effective as liposomal amphotericin B in pediatric invasive candidiasis
  - Patients < 8 years old may need 1.3-1.5 times higher doses

**Invasive Fungal Infections**

- **International Pediatric Fungal Network (Duke University)** (pfn.pediatrics.duke.edu)

**Recent safety concerns**

- Liver toxicity associated with micafungin
  - Micafungin shown to induce irreversible foci of altered hepatocytes and liver tumors in rats after 3 months of treatment
  - European Medicines Agency (EMEA)
    - "Black box warning" on micafungin labeling
      - Use micafungin only if other antifungal agents are not appropriate

**Role and dose of echinocandins in therapy**


**Invasive Fungal Infections**

- **Echinocandin Pharmacokinetic Parameters in Children 2-17 Years of Age**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Caspofungin</th>
<th>Micafungin</th>
<th>Anidulafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA approval</td>
<td>January 2001</td>
<td>March 2005</td>
<td>February 2006</td>
</tr>
<tr>
<td>Peptide</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CL</td>
<td>1.5-2.0 L/kg</td>
<td>0.9-1.6 L/kg</td>
<td>0.41-0.9 L/kg</td>
</tr>
<tr>
<td>T1/2</td>
<td>14.0-16.0 hr</td>
<td>12.1-17.3 hr</td>
<td>18.0-20.0 hr</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hydroxylation &amp; Acetylation</td>
<td>Acetylation &amp; catechol-O-methyl transferase</td>
<td>Hydroxylation</td>
</tr>
<tr>
<td>Elimination</td>
<td>30% (faster); 41% (same); 46% (unchanged)</td>
<td>71% (faster)</td>
<td>30% (faster)</td>
</tr>
<tr>
<td>Dosing</td>
<td>Load: 7.5 mg/kg; Maint: 5.5 mg/kg/day or in neonates</td>
<td>1.6 mg/kg/day; Maint: 0.75-1.5 mg/kg/day</td>
<td>Data lacking in neonates</td>
</tr>
<tr>
<td>Dose (2)</td>
<td>Moderate hepatic insufficiency</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>


**Invasive Fungal Infections**

- **Histoplasmosis in Pediatric HSCT**
  - Evaluation using caspofungin, micafungin, and anidulafungin
  - Micafungin showed the best results across all age groups
  - No differences in toxicity

**Invasive Fungal Infections**

- **Susceptibility of the host**
  - Use of broad-spectrum antibiotics
  - Most common causes: *Candida* spp and *Aspergillus* spp
  - Leading cause of morbidity and mortality in children
  - Candidemia 16-31% mortality rate
  - Aspergillosis: mortality rate as high as 77%

**Invasive Fungal Infections**

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  - Most common causes: *Candida* spp and *Aspergillus* spp
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  - European Medicines Agency (EMEA)
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  - Use micafungin only if other antifungal agents are not appropriate

**Invasive Fungal Infections**

- **Role and dose of echinocandins in therapy**


Invasive Fungal Infections

- Dosing “equivalents” for micafungin
  - Hope WW, et al
    - 100 mg/day \( \rightarrow \) 3.38 x weight \(-0.25\) mg/kg/day
    - 150 mg/day \( \rightarrow \) 5.07 x weight \(-0.25\) mg/kg/day
    - 200 mg/day \( \rightarrow \) 6.77 x weight \(-0.25\) mg/kg/day
  - Seibel NL, et al
    - 50 mg/day \( \rightarrow \) 1 mg/kg/day
    - 100 mg/day \( \rightarrow \) 2 mg/kg/day
    - 150 mg/day \( \rightarrow \) 3 mg/kg/day
    - 200 mg/day \( \rightarrow \) 4 mg/kg/day

- Children 2-8 years of age may need 1.5 times higher dosing


Survivorship and Follow-Up in Adulthood

“Pediatric SCT survivors may have decades of life to live following transplant, thus making this lasting support critical for ensuring survivors are able to become well adjusted, functioning members of society.”

Dreyer ZE. Bone Marrow Transplant. 2009;43:433.

Physical Functioning After SCT

- 214 SCT survivors (> 5 years) analyzed
  - April 1972 – November 1994
  - Mean age 28.7 years (range: 18.8-45.9 years); 55% male
  - Mean age at transplant: 11.9 years (range: 1.8 – 17.9 years)
  - Medical Outcome Study Short Form 36 Health Survey (SF-36)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>SCT Mean Score</th>
<th>Control Mean Score</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical component (PCS)</td>
<td>51.1</td>
<td>55.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical function</td>
<td>89.1</td>
<td>94.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Role physical</td>
<td>84.5</td>
<td>91.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>79.2</td>
<td>82.9</td>
<td>0.05</td>
</tr>
<tr>
<td>General health</td>
<td>70.1</td>
<td>81.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


Metabolic Syndrome

- Originally described by Reaven in 1988 as “Syndrome X”
- Constellation of complications which predispose patients to the development of cardiovascular disease (CVD) and diabetes
  - Dysglycemia
  - Obesity (central adiposity)
  - Elevated blood pressure
  - Elevated triglycerides
  - Decreased high-density lipoprotein (HDL) cholesterol
  - Pro-inflammatory and pro-thrombotic states
- Exact pathogenesis remains ill-defined
  - Relation to insulin resistance
  - Role of leptin, adiponectin, growth hormone and C-reactive protein


Metabolic Syndrome

- Definition and diagnostic criteria more ill-defined
  - World Health Organization (WHO) first definition in 1998
  - European Group for the Study of Insulin Resistance (EGIR)
  - National Cholesterol Education Program (NCEP)
  - American Association of Clinical Endocrinologists (AACE)
  - International Diabetes Federation (IDF)
  - American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI)
  - In 2008, 27 articles identified 46 “definitions” for pediatric patients
  - 28 ~ NCEP  9 ~ WHO  3 ~ EGIR  1 ~ AACE  5 unique
  - Difficulties with definitions

Metabolic Syndrome

**Example of a pediatric-specific criteria**

<table>
<thead>
<tr>
<th>International Diabetes Federation criteria for metabolic syndrome in children. Diagnose requires the presence of two of the following five criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group</strong>:</td>
</tr>
<tr>
<td>&lt; 10</td>
</tr>
<tr>
<td>10 - 16</td>
</tr>
<tr>
<td>10 - 16</td>
</tr>
<tr>
<td>&gt; 16</td>
</tr>
</tbody>
</table>

**Example of adult criteria**

**American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI)**


**Methotrexate**

**Cisplatin**

**Steroids**

**Cranial radiotherapy**

**Vincristine**

**Anthracyclines, Cyclophosphamide**

**Homocysteine**

**Magnesium**

**Central adiposity**

**Gait or balance disturbances**

**Physical inactivity**

**Cardiac fitness**

**Cardiovascular disease**

**Risk factors**

**Insulin resistance**

**Lipin levels**

**Nothing clearly identified**

**Growth hormone deficiency**

**越来越高 to see high triglycerides and low HDL-C**

**Not common to see hypertension or obesity**

**Does not appear to associate with GVHD**

**Annalora et al**

**Majhail et al**

**Taskinen et al**

**Current Recommended Waist Circumference Thresholds for Abdominal Obesity**

<table>
<thead>
<tr>
<th>Population</th>
<th>Organization</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>AHA/NHLBI</td>
<td>≥ 102 cm</td>
<td>≥ 88 cm</td>
</tr>
<tr>
<td>Canada</td>
<td>Health Canada</td>
<td>≥ 102 cm</td>
<td>≥ 88 cm</td>
</tr>
<tr>
<td>European</td>
<td>European Cardiovascular Societies</td>
<td>≥ 102 cm</td>
<td>≥ 88 cm</td>
</tr>
<tr>
<td>Japanese</td>
<td>Japanese Obesity Society</td>
<td>≥ 85 cm</td>
<td>≥ 90 cm</td>
</tr>
<tr>
<td>Middle East, Mediterranean</td>
<td>IDF</td>
<td>≥ 94 cm</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>Caucasian</td>
<td>WHO</td>
<td>≥ 94 cm</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>Europoid</td>
<td>IDF</td>
<td>≥ 94 cm</td>
<td>≥ 80 cm</td>
</tr>
</tbody>
</table>

**Updated criteria**

* Recommended that International Diabetes Federation (IDF) cut points be used for non-Europeans and either IDF or American Heart Association (AHA) cut points be used for people of European origin until more data is available.

* Most common drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High dose ω-3 fatty acids should be used with caution.

* Most people with type 2 diabetes will have the metabolic syndrome by the Proposed criteria.

HDL-C, high-density lipoprotein-cholesterol.
Metabolic Syndrome

GOALS

Risk factors/Co-morbidities
- Fasting lipid profile, smoking history, family history, blood pressure, BMI, fasting glucose, physical activity

MODERATE RISK
- BMI < 90%ile for age/sex
- BP < 95%ile for age/sex/ht%ile
- LDL-C < 130 mg/dL
- Fasting glucose < 100 mg/dL
- HgbA1C < 7%

At Risk
- BMI < 95%ile for age/sex
- BP < 95%ile + 5 mm Hg for age/sex/ht%ile
- LDL-C < 160 mg/dL
- Fasting glucose < 100 mg/dL
- HgbA1C < 7%

Interventions
- A: Assessment/Aspirin
- B: Blood pressure control
- C: Cholesterol management
- D: Diabetes prevention/diet
- E: Exercise

Avascular Necrosis

- Exact pathogenesis is poorly understood
  - Subchondral bone ischemia
- Estimated to develop in 4-10% of HSCT survivors
  - Median time of onset is 12 months (range 2-132 months)
- Most likely to occur in the hip
- Identifiable risk factors
  - Steroids?
  - Age > 16 years
  - Diagnosis of aplastic anemia or acute leukemia

Avascular Necrosis

- 75 patients developed AVN
  - Cumulative incidence: 3.7% at 5 years and 5% at 10 years
  - Type of transplant: Cumulative incidence at 5 and 10 years
    - 20 autologous (2.5% and 2.9%)
    - 44 matched related (3.6% and 5.4%)
    - 11 unrelated (13.2% and 14.7%)
  - 160 joints affected (median per patient = 2; range 1-8)
    - 106 hips
    - 26 knees
    - 19 shoulders
    - 2 ankles
    - 4 wrists
    - 3 elbows
  - Median 3.2 years (range 1-16.6 years)

Demographic and Clinical Factors and Risk of AVN: Multivariate Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Overall Relative risk (95% CI)</th>
<th>Allogeneic Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous</td>
<td>1.00</td>
<td>---</td>
</tr>
<tr>
<td>Related donor</td>
<td>2.39 (1.35-4.36)</td>
<td>1.00</td>
</tr>
<tr>
<td>Unrelated donor</td>
<td>5.82 (2.58-13.11)</td>
<td>1.67 (0.82-3.43)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>2.26 (1.33-3.85)</td>
<td>2.10 (1.12-3.95)</td>
</tr>
<tr>
<td>Presence of GVHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>---</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>---</td>
<td>2.22 (1.02-4.82)</td>
</tr>
</tbody>
</table>


Avascular Necrosis

Demographic and Clinical Factors and Risk of AVN: Multivariate Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Allogeneic Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs used for GVHD prophylaxis/treatment</td>
<td></td>
</tr>
<tr>
<td>No cyclosporine (CSA)</td>
<td>1.00</td>
</tr>
<tr>
<td>CSA alone</td>
<td>2.26 (0.46-11.32)</td>
</tr>
<tr>
<td>CSA + prednisone (pred)</td>
<td>5.17 (0.78-34.39)</td>
</tr>
<tr>
<td>CSA + tacrolimus (FK506)</td>
<td>9.83 (2.34-41.23)</td>
</tr>
<tr>
<td>CSA + pred + FK506 + mycophenolate mofetil</td>
<td>7.98 (1.76-36.18)</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>


Role of bisphosphonates

- Studies in children in the setting of HSCT
- Several challenges
  - Risk to benefit ratio favors the use in existing conditions rather than prevention
  - Establishment of dosing thresholds remains to be completed
  - Effects of normal growth and development on efficacy and outcomes
  - Number of patients to complete a trial is excessively large
  - Safety and long-term data lacking


What’s Going to Be Hot?

- COG ASCT0431/PBMT ONC051
  - Sirolimus-based GVHD prophylaxis in select CR1/CR2 ALL
- COG ASCT0521/PBMT SUP051
  - Etanercept for treatment of idiopathic pneumonia syndrome
- COG ASCT0631/PBMT SCT051
  - Phase III randomized trial of filgrastim-stimulated BM vs. conventional BM as a stem cell source in MSD transplants
- BMT CTN 0601
  - MUD HSCT using a RIC regimen for severe sickle cell disease
- PBMT ONC051
  - MUD HSCT using a RIC regimen for severe thalassemia

Self Assessment Questions

1. In the recently published study by Campbell et al (Cancer 2009), the development of avascular necrosis (AVN) is a recognizable complication following hematopoietic stem cell transplantation (HSCT). Which one of the following risk factors was not identified by the authors in predisposing patients to developing AVN after allogeneic HSCT?
   A. Male gender
   B. Female gender
   C. Development of chronic graft versus host disease
   D. Exposure to at least three of the following drugs: prednisone, cyclosporine, tacrolimus and/or mycophenolate mofetil

Self Assessment Questions

2. Although micafungin remains to be studied across the pediatric continuum, there is data to suggest that neonates require higher daily doses compared to adult patients. Which of the following micafungin dose ranges may be most appropriate for a neonate with mild hepatic insufficiency?
   A. 1-3 mg/kg/day
   B. 3-5 mg/kg/day
   C. 5-7 mg/kg/day
   D. 7-9 mg/kg/day
Self Assessment Questions

3. What is the role of allogeneic hematopoietic stem cell transplantation in pediatric patients with high-risk ALL?
   A. It is the standard of care for all patients achieving a CR1
   B. It should be offered only to those patients with a matched-sibling donor after CR1
   C. It is the standard of care for all patients only after CR2 when disease relapse occurs on therapy or within 6 months of completing initial therapy
   D. Its use remains controversial and individual patient situations should be carefully assessed