Long Term Follow-up after Hematopoietic Cell Transplant for Fanconi Anemia

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What is known about long-term complications after BMT specific to FA?

• Almost nothing
• Few publications in medical literature address this specifically for FA patients
• HOWEVER, what we know about late effects after BMT in non-FA patients and what we know about FA itself can be combined to guide us regarding what the issues are
Follow-up after Transplantation

- Acute
- Long-Term
- Late Effects

Diagram:
- Venn diagram with overlapping circles:
  - Blue circle: RADIATION
  - Green circle: CHEMOTHERAPY

The overlap represents the intersection of radiation and chemotherapy effects.
Assessment of Risk

- Age
- Gender
- Genetics
- Social
- Other Health
- Lifestyle
- Radiation
- Chemotherapy
## Overlapping Etiology of Late Effects

<table>
<thead>
<tr>
<th>Fanconi Anemia Related Conditions</th>
<th>BMT Related Late Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital Anomalies (GI, heart, kidney, urinary, dental)</td>
<td>Organ toxicities that may impact long term cardiac, kidney, liver function)</td>
</tr>
<tr>
<td>Endocrine abnormalities (diabetes, GH Deficiency, hypothyroidism</td>
<td>Same</td>
</tr>
<tr>
<td>Reproductive issues (infertility, high risk pregnancy, early menopause)</td>
<td>Same</td>
</tr>
<tr>
<td>Nutritional Issues (GI tract anomalies, poor oral intake)</td>
<td>Similar issues if chronic GHVD</td>
</tr>
<tr>
<td>Neurologic issues (vision, hearing)</td>
<td>Cataracts after radiation</td>
</tr>
<tr>
<td>Musculoskeletal issues/congenital anomalies</td>
<td>Low bone density, joint contractures with chronic GVHD</td>
</tr>
<tr>
<td>High risk of Malignancy</td>
<td>Risk of Malignancy</td>
</tr>
<tr>
<td>Psychosocial impact of chronic illness</td>
<td>Same</td>
</tr>
<tr>
<td>Iron overload from transfusions</td>
<td>Same</td>
</tr>
<tr>
<td>Androgen Toxicity</td>
<td>n/a</td>
</tr>
<tr>
<td>n/a</td>
<td>Graft vs. Host Disease</td>
</tr>
</tbody>
</table>
Care of the Long-Term Survivor
Transplant Specific Risks

What do we know?

Treatment exposures
Screening/Evaluation
Risk Modification
FA Specific Publications related to Long-Term Follow-up/Late Effects

• Sanders, et al. FHCRC, Seattle (Blood 2011)
  – 4 decades of follow-up after BMT for Aplastic Anemia, 15 with FA
  – 1971-2009, median f/u 22 years

  – 50 total pts, 31 with LTFU
  – 1981-1996, median f/u >6yr
Organ Specific Complications

- Endocrine (growth, fertility, thyroid)
- Bone Health
- Eye
- Cardiovascular/metabolic
- Neurologic
- Post transplant Malignancies
Endocrine: Treatment Exposures

Chemotherapy

– Gonadal (testicular/ovarian) Dysfunction and Infertility
  • Alkylators – Cyclophosphamide, but dose dependant, FA protocols are low dose

Radiation (dose dependent)

– Gonadal Dysfunction and Infertility
– Growth hormone deficiency
– Thyroid dysfunction– low, high, nodules, cancer
Endocrine Late Effects

Problem: Gonadal Dysfunction

**Evaluation-Males**

- Pubertal onset and development
- Testosterone, FSH, LH
- Testicular volume, semen analysis

**Evaluation-Females**

- Pubertal onset, menstrual history
- FSH, LH, estrogen

• Close follow-up of growth and pubertal development required for all survivors through adolescence

• Endocrinology consultation for most if not all
Endocrine Dysfunction-Growth

• Growth Hormone Deficiency (GH)
  – many receiving TBI will have GH deficiency
  – CNS radiation +/- TBI majority develop GH deficiency
  – catch up growth not usually seen, but further negative deviation away from normal does not occur
  – For FA: disease vs treatment?

Sanders: Growth rates normal (0 to -1 SDS), but FA combined with other forms of aplastic anemia

Socié: Growth rates below normal (-1 to -2 SDS) but difficult to say if from FA or BMT-- likely both.
Endocrine Late Effects

Problem: Thyroid Dysfunction

Sanders: none developed hypothyroidism
-11 had no XRT
-3 had 2 Gy TBI, 1 had 4.5 Gy

Socié: 4/31 hypothyroid (all got 5 Gy TAI)
Endocrine-Fertility

Screening
- History and physical exam
- Laboratory screening: LH, FSH, estradiol, testosterone

Risk modification
- Sperm/(egg) banking
- Evaluation by reproductive endocrinologist
- Fertility counseling
Osteopenia/Osteoporosis

- Risks
  - Steroids
  - Radiation therapy
  - Hypogonadism
  - Early menopause
  - Growth hormone deficiency
  - Hyperthyroidism
  - Nutritional status
Osteopenia/Osteoporosis

Screening

– Dual energy X-ray absorptiometry (DXA)
– Sanders: 5 pts had normal DXA scans

Risk modification

– Vitamin D
– Calcium
– Bisphosphonates
– Hormone replacement therapy
Ophthalmologic Problems

• Cataracts secondary to TBI
  – single dose TBI: incidence at 5 yr 80%
  – fractionated TBI:
    • 50% incidence at dose > 1200 cGy
    • 30-35% at < 1200 cGy
    • FA dose=2-4.5 Gy, Socie, 4/31 (13%)
  – chemo only regimen: 20% incidence

• Infections
  – primarily related to cGVHD
  – Viral (CMV, Varicella, herpes)
The Metabolic Syndrome...

• A cluster of metabolic disorders related to insulin resistance that predisposes to type 2 diabetes and atherosclerotic cardiovascular disease.

Characterized by:

➢ Central obesity
➢ Glucose intolerance
➢ Dyslipidemia
➢ Hypertension
Cardiovascular and Metabolic

• Survivors after BMT have been found to be:
  – More resistant to insulin
  – Not obese, but higher percent of “internal” body fat and loss of muscle mass
  – More likely to have abnormal lipid levels (high bad cholesterol and low good (HDL) cholesterol
  – More likely to have high blood pressure

• Higher risk after exposure to total body irradiation

• Higher risk of CV related mortality in long-term follow-up

• What does this mean for FA survivors after BMT?
Cardiovascular and Metabolic

**Screening (Annual)**
- Lipid profile
- Fasting glucose +/- glucose tolerance test
- Blood pressure

**Risk modification**
- Avoid smoking
- Limit alcohol
- Diet – low fat, low cholesterol
- Exercise
Neuropsychologic

Risk Factors

• BMT unlikely to significantly increase risk unless more severe complications, prolonged hospitalization, cGHVD, BMT are very young age

Evaluation

• Careful history
  – cognitive development, memory, school performance, behavior changes, motor dysfunction, seizures
• Vision and hearing screening
• Neuropsychological testing
• EEG, MRI if indicated
Malignancies after BMT in FA Survivors

• Issue of great concern for FA patients after BMT
• Risk of hematologic malignancies (leukemia) will be decreased to population risk level in fully engrafted patients
  – Abnormal bone marrow has been replaced
• Solid Tumors: is risk greater after BMT???
Risk of solid tumors

• Estimate is about 40% probability by 20 yrs post-BMT* (5/79 patients)
  – All were squamous cell carcinomas of head/neck
  – Peak risk was at 9 yrs after BMT

• Does exposure to radiation therapy increase this risk?
  – Only one study* has addressed this issue and did not find increased risk associated with radiation
  – Risk was increased in those that had GVHD

• Does normalization of bone marrow and immune system function decrease solid tumor risk?
  – Unknown

*Deeg, Blood 87: 386, 1996
Risk of solid tumors

• Sanders (2011): 2/15 developed malignancy 9 and 12 yrs after BMT (squamous cell carcinoma, colon cancer)

• Socié (1998): 6/50, head/neck cancers, all had cGVHD, mean 8.2 yrs after BMT (5-16)

• Alter (2003): 4 cancers in 3 pts out of 44 who had BMT (lymphoma, head/neck (2), vulvar (1))
  – Rate in BMT survivors was higher than non-BMT but small numbers and not statistically significant

• Possible that treatment better tolerated after BMT since normal bone marrow function
Important Points in Evaluation of Transplant Survivors

• Identification of treatment exposures
  – Chemotherapy drugs utilized, (doses)
  – Doses and sites of radiation therapy

• Knowledge of potential late effects of therapies received

• Plan for screening/evaluation and follow-up

• Plan for modification of risk factors

• How to get this: Survivorship Programs
Survivorship Program Services

• Coordination of care and integration with primary care physicians
• Referrals for medical or other services, physical and occupational therapy, nutrition, social work, vocational and rehabilitation therapy and other sub-specialties as needed
• Educational information on physical, emotional and daily living issues specific to HCT survivors
• Navigation to locate community and web-based resources
• Educational classes and events
Eligibility — Transfer to Long Term Follow-up

Patients may be transferred to FA LTFU clinic for ongoing long-term follow-up

• 2 years from transplant
• No active chronic GVHD
• Clinic staffed by FA specialist as well as BMT physician with expertise in transplant survivorship issues
Survivorship Clinical Evaluations Include:

- Cancer Treatment Summary/Survivorship Care Plan
- Screening of medical history and current needs
- Physical examination and lab tests focused on long-term and late effects
- Guidelines and recommendations for follow-up monitoring, including for healthy lifestyle and general health maintenance
- Subspecialty referrals as needed
- Communication back to primary hematologist and primary care provider
Survivorship Treatment Summary and Care Plan (1)

- **Diagnosis and History:** age, pre-HCT medical conditions, congenital malformations, pre-HCT treatments/surgical procedures

- **Care Providers:** Treatment facility and Pre-HCT health care providers and PCP with contact information, transplant center and providers

- **Treatment details:** Type of transplant, Chemotherapy, with selected cumulative doses, radiotherapy doses and fields, surgical procedures, blood product exposures
Survivorship Care Plan (2)

- **Complications** on/off treatment with long-term implications, acute/chronic GVHD, infections

- Associated **potential risks** of treatment including second cancers or specific organ toxicity with screening and follow-up recommendations

- Sent to survivor and healthcare providers
### Long Term Follow-up Plan

<table>
<thead>
<tr>
<th>Return Visit</th>
<th>1 year</th>
<th>2 year</th>
<th>3 year</th>
<th>4 year</th>
<th>5 year</th>
<th>Every 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiology</strong></td>
<td></td>
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<tr>
<td>Lipid profile (Fasting)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>Fasting Glucose</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>ECHO</td>
<td>X</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>X</td>
<td>X</td>
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<tr>
<td><strong>Pulmonary</strong></td>
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<tr>
<td>Pulmonary Function Tests/DLCO</td>
<td>X</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>X</td>
<td>C</td>
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<tr>
<td><strong>Endocrine</strong></td>
<td></td>
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<tr>
<td>TSH, FT4</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Insulin Level (Fasting)</td>
<td>X</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<tr>
<td>LH/FSH† (begin age 10 for females, 11 for males)</td>
<td>X</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<tr>
<td>Ultrasensitive Estradiol† Females &gt;10 yr</td>
<td>X</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<tr>
<td>Testosterone† (males &gt;11 yr)</td>
<td>X</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<tr>
<td>Bone age (females &gt;10 yr, males &gt;11 yr)</td>
<td>X</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<tr>
<td>DEXA Scan</td>
<td>X</td>
<td>X</td>
<td>R</td>
<td>R</td>
<td>X</td>
<td>C</td>
</tr>
</tbody>
</table>

X = to be done, C = consider, check with MD/PNP, R = repeat if previously abnormal
### Long Term Follow-up Plan

<table>
<thead>
<tr>
<th>Return Visit Post Transplant</th>
<th>1 year</th>
<th>2 year</th>
<th>3 year</th>
<th>4 year</th>
<th>5 year</th>
<th>Q5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Growth and Development</strong></td>
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<tr>
<td>Height and Weight</td>
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<td>X</td>
<td>X</td>
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<td>Growth chart</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neuropsychology evaluation</td>
<td>X*</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td><strong>Hepatic Function:</strong></td>
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<tr>
<td>ALT, BILI, ALK Phos, Albumin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HBSAG, HBSAB, Hep. C. ab</td>
<td>X</td>
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<td></td>
<td></td>
<td>C</td>
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<tr>
<td><strong>Renal</strong></td>
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<tr>
<td>Creatinine, Urinalysis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td><strong>Immunology</strong></td>
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</tr>
<tr>
<td>Ig G, A, M, E.</td>
<td>X</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Immunizations (per schedule)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>QOL</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td><strong>ENT/Audiology</strong></td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td><strong>Ophthalmology</strong></td>
<td></td>
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<td></td>
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<td>C</td>
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<tr>
<td><strong>Dental (Home Dentist)</strong></td>
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<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
</tbody>
</table>
Additional Issues to Consider

• ENT screening for head and neck cancers
• GYN evaluation for females
• Endocrinology consultation when necessary
• Neuropsychological screening assessment
• Other consultations as appropriate
  – Pulmonary, cardiology, GI, etc.
Care for the Whole Person

- Neurocognitive deficits
- Anxiety
- Depression
- Social Withdrawal
- Loss
- School/work re-entry
- Insurance
Late Effects

Future Directions

Prevention of Toxicities

• Preparative regimens with reduced toxicities
  – Fludarabine, possibly avoiding radiation, targeted therapies that can eliminate bone marrow and/or immune function but not “normal” cells

• Prevention of GVHD
  – Better matching
  – Improvements in prophylaxis/treatment, T cell depletion

• Gene Therapy
Long Term Survivors

Future Directions

• Find ways to identify which patients are at highest risk for late effects secondary to therapy

• Determine what parts of the treatment are causing the most significant long term problems and find ways to modify the treatment or prevent late effects
Long Term Survivors

Future Directions

• Education of pediatric hematologists/oncologists, primary care physicians, parents, survivors and the community about late effects in FA patients who are BMT survivors so these patients can be properly monitored followed and treated after transplantation.
Survivorship Resources

• Beyond the Cure
  – www.beyondthecure.org

• National Marrow Donor Program
  – www.marrow.org

• Children’s Oncology Group
  – www.survivorshipguidelines.org

• American Cancer Society
  – www.cancer.org

• National Coalition for Cancer Survivorship
  – www.canceradvocacy.org

• Center for Disease Control (CDC)
  – www.cdc.gov/cancer/survivorship
Fanconi Anemia Center
Seattle Children’s Hospital
Seattle Cancer Care Alliance
Fred Hutchinson Cancer Research Center

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