Mission of Long-Term Follow Up

To provide life-long medical consultation to hematopoietic stem cell transplant recipients (and their physicians) that were treated at The Hutchinson Center (FHCRC) and the Seattle Cancer Care Alliance (SCCA).

Clinical LTFU Activities

- Prepare patients for departure home
- Provide telephone consultation with patients and referring physicians
- Evaluate LTFU patients on site in clinic visits
- Evaluate results of studies done at home
- LTFU support group

Research LTFU Activities

- Send yearly questionnaires and keep track of health outcomes of survivors
- Conduct research protocols relating to chronic GVHD treatment and other long-term problems

LTFU Telemedicine Nursing Office
Our LTFU Patient Charts

LTFU Telemedicine
- Close to 60 phone calls/week
- Half are from patients, half are from local providers
- About half of callers have questions that can be answered within RN scope of practice
- About half go to rounds for LTFU Attending input with RNs communicating recommendations back to local providers

Telemedicine Rounds

Improved Early Survival

Long-term Survival Odds

Among 2 year disease-free survivors, subsequent survival:
90% at 5 years
85% at 10 years
80% at 15 years

Among 5 year disease-free survivors, subsequent survival:
80% at 20 years

Study Compared
N = 1418 vs. 1148
Showed ↓ in day 200 non-relapse mortality by 60%
Showed ↓ in overall mortality by 41%

100 day survival | 1 year survival | 5 year survival
89% | 65% | 35%

SCCA survival rates are typically better than most transplant centers
Return to Work

About 70% of our BMT Survivors return to work/school.

Transplant Related Mortality

- *Relapse* is the number one cause of late transplant related mortality in autologous AND allogeneic patients.
- Other causes of late death are second cancers, infections, chronic GVHD, respiratory diseases and cardiovascular diseases.

Life after Transplant

- The majority of long-term survivors recover to a “new normal” that is acceptable to them.
- VERY FEW make it through transplant without some degree of long-term changes that affect health and well-being.
- The minority of long-term survivors suffer serious morbidity post-transplant to a degree that causes chronic disability and/or suffering.

Was it worth it?

A surprising 95% of patients answered affirmatively with either a “4” which means “Quite a Bit” or a “5” which means “Very Much” on a 1-5 scale when asked to agree with the following statement: “Having a transplant was worth it.”

Long-Term Complications

- Neurologic
- Endocrine
- Sexual
- Fertility
- Renal/Urinary
- Musculoskeletal
- Dental
- Ocular
- Emotional
- Chronic GVHD
- Infection
- Relapse
- New malignancy
- Pulmonary
- Cardiac

Neurologic

- Learning Disabilities
  - Higher risk with:
    - Prior cranial irradiation
    - Intrathecal chemotherapy
    - Younger age at time of transplant
  - Psychometric testing to assess problem
  - School support for specialized learning plans
- Cognitive Dysfunction
  - Poor memory, concentration, word-finding difficulty
  - Biggest dip around day 80
  - Patients recover until one year post-transplant
  - Residual cognitive impairment can be assessed with Neuropsych testing and managed with behavioral interventions
Endocrine: Diabetes

- Reported in 7.6% of HSCT survivors and 3.1% of siblings
- Exposure to TBI is associated with an increased risk along with greater BMI and older age

Endocrine: Thyroid

- Risk factors
  - Most frequent in patients receiving total body irradiation (29%)
  - Occurs in about 14% of those receiving chemo only
  - More frequent after cranial irradiation
  - Common with I-131 containing regimens
- Screening
  - Thyroid testing annually for life
- Symptoms
  - Fatigue
  - Depression
  - Weight gain
  - Sleep disturbances
  - Dry skin
  - Thinning hair
- Diagnosis
  - Elevated TSH
- Treatment
  - Thyroid replacement hormone

Endocrine: Growth and Development

- Risk Factors for impaired growth
  - Cranial irradiation
  - Total body irradiation
  - Age less that 6 years at time of transplant
  - Underlying Fanconi’s Anemia
- Treatment
  - Growth Hormone: Stimulates growth of epiphyseal cartilage and bone
  - Greatest response to treatment results when started before the height drops to below the third percentile
  - Early use allows for longer period of treatment/growth

Endocrine: Puberty

- Chemotherapy
  - Cytoxan only: If prepubertal at time of transplant, normal progression of puberty
  - Busulfan: Evidence of primary ovarian failure in girls and decreased sex hormone production in some boys
  - Need to be follow closely from 12 years of age
- TBI
  - Delayed sexual development in 46% of girls and 56% of boys
  - Sex hormones (estrogen and testosterone) necessary for the promotion of pubertal growth spurt and sexual maturation
  - The expertise of an endocrinologist is needed

Sexuality: Men

- Manifestations:
  - Elevated FSH levels
  - Azospermia
  - Low testosterone levels
  - Decreased libido
  - Premature ejaculation
  - Impotence
- Management:
  - Annual testing of free and total testosterone
  - Treatment with testosterone may be warranted after risks/benefits explored

Sexuality: Women

- Manifestations
  - Permanent ovarian failure common in most patients
  - Elevated FSH and LH levels and decreased estradiol are common
  - Both sexuality and bone health adversely affected
  - Decreased libido, vaginal dryness, hot flashes, night sweats, vaginal atrophy and adhesions, emotional and cognitive changes, sexual dysfunction, discomfort with intercourse
- Management:
  - Annual testing of estradiol level
  - Systemic hormonal therapy for some women may be warranted after risks/benefits carefully explored
  - Topical estrogens may relieve some symptoms and improve sexual function
Fertility

- BMT survivors are 36X more likely to report no conception as compared to their sibling(s)
- Most patients will require fertility specialist to get pregnant and all patients should be treated as high risk once they get pregnant
- Newer therapies can help preserve fertility in advance of BMT
- Lead time for egg harvest is down to two weeks

Fertility: Pregnancy Outcomes

- 1522 Disease-Free Survivors were studied for pregnancy and birth outcomes
  - 146 Pregnancies in 76 patients
  - 115 Live births to 67 patients
- Birth defects in line with general population, however, LBW and pre-term labor higher and spontaneous abortion higher (TBI)
- ? Cancer risk in offspring d/t patient’s own disease/risk factors or pretreatment damage to sperm
- Theoretical risk of relapse when pregnant d/t immunosuppressed state during pregnancy

Renal/Urinary

- Bladder
  - Late hemorrhagic cystitis d/t BK virus, polyome virus or adenovirus
  - Women with vaginal/vulvar cGVHD can get frequent UTIs
- Kidney
  - Renal impairment from CNIs, antibiotics, TBI or underlying disease (MM)
  - Hemolytic Uremic Syndrome
  - Nephrotic syndrome related to cGVHD

Musculoskeletal: Osteoporosis and Osteopenia

- Risk Factors:
  - Steroid Use
  - Hypogonadism
  - Radiation
  - Inactivity
- Incidence
  - Up to 40% of patients have reduced bone mass density at one-year after transplant
- Management
  - DEXA scan at one year and yearly if on prednisone/at risk
  - Bisphosphonates
  - Calcium/Vitamin D supplementation
  - Hormonal therapy for select patients
  - Weight-bearing exercise

Musculoskeletal: Avascular Necrosis

- Incidence
  - Reported in 4-10% of patients
  - Hip most common site
  - Most patients have >1 joint affected
- Risk Factors
  - Steroid use
  - TBI
  - Male gender
  - Older age
  - AML or AA diagnoses
- Diagnosis
  - MRI gold standard
- Treatment
  - Core decompression for early-stage AVN
  - Joint replacement

Musculoskeletal: Body Composition

- Loss of mean muscle mass as compared to healthy siblings
- Even if weight the same, percent fat mass is higher than lean body mass percent
- From outside, patient can look healthy, or even underweight, but this leads to metabolic issues

BMT Survivor
- Weight: 62kg
- LBM: 37kg
- BMI: 23
- PFM: 34%

Sibling
- Weight: 70kg
- LBM: 47kg
- BMI: 24
- PFM: 28.6%
Dental

- Decreased salivary gland function and increased sensitivity, tooth decay, and gingivitis
- Avoid elective dental work in the first 6 months and while immunosuppressed, including routine cleaning (d/t risk of seeding pathogens)
- Use fluoride rinse and or gel and good oral hygiene
- Risk of osteonecrosis with bisphosphonate use
- If dental work is needed during first 6 months or if immunosuppressed:
  - Prophylactic (and possibly post-procedure) antibiotics
  - Dental dam, high-flow suction

Ocular: Cataracts

- Risk factors:
  - TBI
  - Steroid use
  - Cranial irradiation
- Incidence
  - About 40% of TBI patients
  - About 20% of non-TBI patients
  - Long term prednisone use doubles incidence
  - Affects children and adults

Emotional

- Patients report many emotional issues after transplant: uncertainty, fatigue, reduced attention span, STMS, depression, sexual dissatisfaction, low self-esteem and PTSD
- No significant different between BMT survivors and those given maintenance chemotherapy
- Physical recovery happens earlier than psychologic or work recovery
- Transplant-related distress slower to resolve in allogeneic vs autologous patients and those with poorer social supports
- By 5 years, most survivors report good psychologic health in addition to minimal physical symptoms and return to work
- Fatigue, lack of energy, sexual dissatisfaction remain long-term problems for many survivors

CHRONIC GVHD

- Increased Risk Of Developing Chronic GVHD
  - Prior acute GVHD
  - Greater HLA disparity
  - Increasing patient age
  - Female donor/male patient
  - Peripheral blood stem cells versus bone marrow
  - Donor Lymphocyte Infusion

- Chronic GVHD Incidence
  - Approximately 50% of allogeneic patients will develop chronic GVHD
  - Onset is generally 75 days to 2 years post transplant
  - Uncommon for first diagnosis of cGVHD to be after 2 years
  - If new symptoms common to GVHD present after 2 years in a patient with no GVHD, suspect other causes
Acute vs Chronic GVHD: Timing

- Acute
  - Tends to be near time of engraftment
- Chronic
  - Tends to be after day +75

Acute vs Chronic GVHD: Presentation

- Acute
  - Tends to be abrupt onset
  - Tends to be “angry”
  - Tends to demand attention
- Chronic
  - May be insidious
  - May be “explained away”
  - May be less obvious

Acute vs Chronic GVHD: Sites

- Acute
  - Skin
  - Gut
  - Liver
- Chronic
  - Skin
  - Oral
  - Liver
  - Lung
  - Ocular
  - Genital (F>M)
  - Joints/Fascia
  - Gut
  - Labs (Eos, Plts)

Acute vs Chronic GVHD: Treatment

- Acute
  - HD Steroids as a short course, followed by a rapid taper
  - Will resolve (over weeks to months) or become refractory
  - After resolution, no permanent damage
  - Refractory difficult to treat, may result in death
- Chronic
  - HD Steroids as a longer course, followed by slow taper
  - Steroid-sparing agent
  - Will resolve (over months to years) or become refractory or progressive with additional sites
  - After resolution, may leave permanent damage
  - Refractory and progressive difficult to treat, may result in death
Chronic GVHD of the Eye

Chronic GVHD Oral Exam

Lacy patch?
Keratotic patch?
Erythema?
Ulcers?
Mucoceles?
GVHD: Other Manifestations

- Esophageal webs, strictures or stenosis
- Vaginal scarring and stenosis with painful or inability to have intercourse and penile changes
- Thrombocytopenia, eosinophilia, inflammatory marker elevation
- Pericardial or pleural effusions
- Nephrotic syndrome, ascites, peripheral neuropathy and myasthenia gravis

Decrease The Risk Of Chronic GVHD

- Compliance with immunosuppressive medication
- Avoid sunburns
- Avoid infections

May Require Treatment for 3-5 Years and with Multiple Lines of Therapy

**Systemic Therapy**
- Prednisone
- Cyclosporine (Neoral)
- Tacrolimus (FK-506)
- Mycophenolate Mofetil (Cellcept)
- Sirolimus (Rapamycin)
- Methotrexate
- Rituxan
- PUVA
- Extracorporeal Photopheresis
- Imatinib
- Azathioprine (Imuran)

**Local Therapy**
- Vaginal/Vulvar
- Oral
- Skin
- Ocular
- Lung
- Gut
Effects of Treatment

- Immunosuppression
- Increased infections
- Osteoporosis
- Avascular necrosis
- Diabetes
- Cataracts
- Nephrotoxicity
- Deconditioning
- Depression

Infection: Immune Reconstitution

- Takes about 6 months post-autologous
- Takes about 12 month post-allogeneic
- Longer if chronic GVHD present as immune reconstitution not complete until off all IST
- Re-vaccination begins at one year after transplant with the inactivated vaccines, live vaccines delayed
- Flu shot can be given at 6 months post-transplant and should be given annually for life

Infection: Common Pathogens

- sinus Infections – More common with chronic GVHD
- Sepsis – More common if central line
- Pneumonias and Viral URIs
- CMV reactivation – Monitored if at high risk
- Fungal Infections – Most common if on prolonged high dose steroids

Prevention of Infection

- Patients follow safe living guidelines
- Pneumocystis prophylaxis for the first 6 months and Varicella Zoster prophylaxis for the first year after transplant or as long as on immunosuppression
- Hand hygiene

Common Questions Asked

<table>
<thead>
<tr>
<th>Questions Often Asked</th>
<th>After Transplant</th>
<th>Time after Transplant</th>
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<tbody>
<tr>
<td></td>
<td>All Patients</td>
<td>Less than 6 Months</td>
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<tr>
<td>School</td>
<td>No</td>
<td>No</td>
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<td>Hot tubs (1)</td>
<td>No</td>
<td>Yes (1)</td>
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<tr>
<td>Swimming (1) (avoid head submersion &amp; diving, use sun screen)</td>
<td>No</td>
<td>Yes (1)</td>
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<tr>
<td>Gardening (digging in soil, moving the lawn, raking leaves)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Having plants in the home (not handling)</td>
<td>OK</td>
<td>OK</td>
</tr>
<tr>
<td>Making/feeding yeast bread</td>
<td>No</td>
<td>OK</td>
</tr>
</tbody>
</table>

Relapse of Disease

- Most common in first 1-2 years but there have been late relapses at 10+ years
- Poor prognosis if relapse is in first year
- Monitor for relapse
  - BCR/ABL testing in CML patients, Ph+ ALL patients
  - Myeloma labs for MM patients
- Withdrawal of IST, standard chemotherapy or radiation (for localized disease), donor lymphocyte infusion or a 2nd transplant are options
New Malignancies

- Transplant recipients have 7 to 8% higher risk of developing a new cancer than the general population.
- Skin, oral, MDS and breast cancers are most common and occur more frequently 5 to 10 years after transplant, the incidence increasing with years of survival with no plateau.
- Risk factors:
  - TBI
  - Chronic GVHD
  - Alkylating agents used pre transplant
  - EB Virus
  - Younger age at time of transplant.
- Screening:
  - Annual mammograms (for >35, and age 25 or 8 years from TBI, whichever comes first).
  - Annual dental exams.
  - Annual full-body naked skin exams.
  - Plus all the standard screenings.

Oral Cancers

Pulmonary

- Late-onset pulmonary complications occur in 7-26% of patients.
- Infections need to be ruled out first in a patient presenting with pulmonary issues.
- TBI is a major risk factor.
- PFTs are done pre-transplant and then at one-year post as well as with new cGVHD or pulmonary symptoms.
- Common late pulmonary issues are: Bronchiolitis Obliterans (BO), Cryptogenic Organizing Pneumonia (COP) or Idiopathic Pneumonitis (IPS).

Cardiac

- Increased Risk of:
  - Cardiovascular Events
  - Hypertension
  - Hyperlipidemia

Incidence of Cardiovascular (CV) Events is Increased after HCT

Want to Learn More?
Internet Resources

• FHCRC LTFU Web Site

• CIBMTR Post-Transplant Guidelines

• Pediatric Survivorship Guidelines
  – http://www.survivorshipguidelines.org/

• National Marrow Donor Program
  – https://bethematch.org/For-Patients-and-Families/Life-after-transplant/

My name is Ric Packard. I live in Pocatello, ID. I had a transplant in June of 2012 for AML. It saved my life and allowed me to go kayaking today with my grandchildren. I just can’t say enough about the nurses at SCCA and UW. It was so hard for so long and they were so patient and kind. I probably never thought I was as sick as I was because the staff was so positive and pleasant. Having AML was the best experience of my life because it, out of necessity, brought me closer to my wife and my God. Thank you all again and again and again...