Surviving the Cure: Guidelines for BMT Long-Term Follow-Up Care

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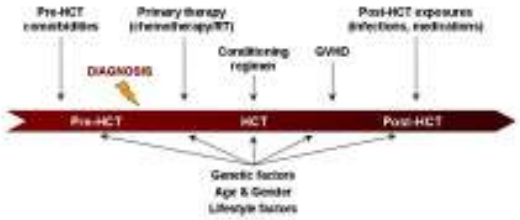
"It Takes a Village…."

- Meet specialized needs of BMT patients
- Aim for best possible outcomes through:
  - Prevention
  - Early detection
  - Minimizing disabilities
- Requires partnership:
  - Primary care physicians and specialists
  - Nurses, advanced practice professionals, pharmacists, social workers, allied health providers
  - ***Patients and their families***

Objectives

- Understand late effects and known risk factors by organ system
- Understand the 2012 expert panel guidelines for screening and preventive practices for long term survivors
- Be able to implement recommendations for your patients

Risk Factors for Late Complications



Majhail NS, Rizzo JD. Late complications: screening and management. Wingard JR, Gastineau DA, Leahter HL, Snyder E, Szczepiorkowski ZM, eds. Hematopoietic Stem Cell Transplantation: A Handbook for Clinicians. Bethesda, MD: American Association of Blood Banks (AABB). 2009.

Recommended Screening and Preventive Practices for Long-term Survivors after HCT

Navneet S Majhail, J Douglas Rizzo, Stephanie J Lee, Mahmoud Aljurf, Yoshiko Atsuta, Carmem Bonfim, Linda J Burns, Naeem Chaudhri, Stella Davies, Shinichiro Okamoto, Adriana Seber, Gerard Socie.

For the Center for International Blood and Marrow Transplant Research (**CIBMTR**), American Society of Blood and Marrow Transplantation (**ASBMT**), European Group for Blood and Marrow Transplantation (**EBMT**), Asia-Pacific Blood and Marrow Transplantation Group (**APBMT**), Bone Marrow Transplant Society of Australia and New Zealand (**BMTSANZ**), East Mediterranean Blood and Marrow Transplantation Group (**EMBMT**) and Sociedade Brasileira de Transplante de Medula Ossea (**SBTMO**)

Biol Blood Marrow Transplant. 18:348-371, 2012

Late Complications Affect All Organ Systems

- Immune system
- Ocular problems
- Lips and mouth
- Pulmonary
- Cardiovascular
- Renal
- Bone health
- Nervous
- Endocrine
- Psychosocial
- Second cancers

Immunity and Infections

- Infectious risk highest in the first 1-2 years after transplantation; allo HCT >> auto HCT
- Risk continues long-term for patients with cGHVD
- Patients and their primary care providers should be educated regarding immune status

Immunity and Infections - Recommendations

- Patients with chronic GVHD:
  - Antibiotic prophylaxis targeting encapsulated organisms for at least as long as immunosuppressive therapy is administered
  - Antiviral and antifungal prophylaxis should be considered
- Screening for CMV reactivation should be based on risk factors, including intensity of immunosuppression.
- Prophylactic antibiotics for oral procedures
  - American Heart Association guidelines for endocarditis prophylaxis.

Immunity and Infections - Recommendations

- *Pneumocystis jirovecii* prophylaxis
  - Allogeneic HCT
    - Engraftment until as long as immunosuppressive therapy is given
  - Autologous HCT
    - 3 to 6 months for those with substantial immunosuppression (purine analogues, high dose steroids)

Vaccinations

Vaccine	Time post-HCT to Initiate	No. of Doses
Pneumococcal	3-6 months	3-4
Tetanus, Diptheria, acellular Pertussis	6-12 months	3
Haemophilus influenza	6-12 months	3
Meningococcal	6-12 months	1
Inactivated polio	6-12 months	3
Hepatitis B	5-12 months	3
Inactivated influenza	4-6 months	1-2
MMR*	**24 months**	**1-2**

*Not recommended <24 months post-HCT in patients with active GVHD or on immune suppressive therapy

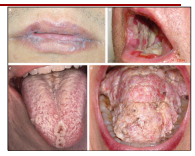
Ocular Late Effects

- Cataracts
  - 5-20% without TBI; 40-70% with TBI
  - Risk factors: TBI, age, corticosteroids
- Ocular sicca syndrome
  - Incidence 20-60%
  - Risk factors: TBI, chronic GVHD
- Ischemic microvascular retinopathy
  - Not seen post auto-HCT
  - Risk factors: TBI, cyclosporine, chronic GVHD
- Posterior segment
  - Hemorrhage
  - Optic disc edema
  - Infectious retinitis (CMV, toxoplasma, fungi)

Ocular Recommendations

- Routine clinical evaluation of visual history and symptoms at 6 months, 1 year and yearly thereafter for all patients
- Ophthalmology evaluation for visual acuity and fundus exam at 1 year for all patients
- Patients with any visual symptoms should undergo ocular exam immediately
- cGHVD – refer to ophthalmology sooner and at first clinical sign of cGHVD

Oral Late Effects



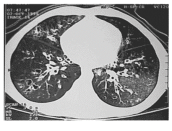
- Sicca syndrome
  - Xerostomia occurs in ~50%
  - Risk factors: TBI, chronic GVHD
- Dental caries
  - Risk factors: TBI, chronic GVHD, dry mouth
- Head and neck malignancies
  - Risk factors: chronic GVHD, head and neck radiation, Fanconi's anemia

Oral Recommendations

- Educate patients about preventive oral health and routine dental maintenance
  - Pre-HCT dental evaluation for all patients
  - Avoid smoking and chewing tobacco
  - Decrease intake of sugar containing beverages
  - Avoid intraoral piercing
- Clinical oral evaluation at 6 months, 1 year and yearly
  - Patients at high risk: every 6 months, and educated on meticulous oral hygiene and taught self oral inspection
  - Include history of xerostomia, review high risk habits, perform oral, head and neck and oral exam
- Dental evaluation at 1 year for all, then yearly
  - More frequent for those with oral GVHD or Fanconi's anemia

Pulmonary Late Effects: BOS

- Bonchiolitis obliterans syndrome (BOS)
  - Incidence 2-14% (allogeneic HCT)
  - Risk factors: chronic GVHD ("pulmonary GVHD")
  - Clinically manifests as DOE, cough, wheezing
  - Obstructive lung defect on PFTs
  - CT findings: Bronchiolar obstruction & air trapping
  - May respond to steroids, azithromycin; high mortality



Pulmonary Late Effects: COP

- Cryptogenic organizing pneumonia (COP; BOOP)
  - Rare, no specific early screening tests
  - Risk factors: variety of toxic, immunological, inflammatory injuries
  - Usually presents in first 6-12 months post-HCT; later onset may occur in patients with chronic GVHD
  - Clinical presentation: non-productive cough, DOE, low grade fevers
  - CT findings: Patchy infiltrates: restrictive PFT's
  - Responsive to corticosteroids; 80% of patients recover

Pulmonary Recommendations

- Routine clinical assessment at 6 months,1 year and yearly
- Some recommend more frequent clinical assessments including PFTs in patients with chronic GVHD
- Counseling regarding risks of smoking and smoking cessation

Cardiovascular Late Effects

- Any cardiac dysfunction (cardiomyopathy, valvular anomaly, conduction anomaly)
- Vascular: Cerebrovascular disease, ischemic heart disease, peripheral arterial disease
- Metabolic syndrome (hypertension, abdominal obesity, diabetes)
- Incidence and Risk Factors:
  - 2-3% of late deaths; may be underestimated and may increase with longer follow-up
  - Risk factors: Radiation to chest and neck, cumulative anthracycline dose, iron overload, cardiac function pre-HCT
  - General population risk factors (e.g., smoking, lipids, diabetes)

Cardiovascular Recommendations

- Routine clinical assessment and CV risk factor evaluation for all at 1 year and yearly
  - More frequent evaluations for high-risk (e.g. mediastinal radiation; amyloidosis; pre-existing abnormalities)
- Education and counseling on "heart" healthy life style
  - Regular exercise, dietary counseling, healthy weight, no smoking
- Treat risk factors, including diabetes, hypertension and dyslipidemia (for patients on therapy: fasting lipid panel every 6-8 weeks until treatment goal is achieved, then every 4-6 months)
- Endocarditis prophylaxis per AHA recommendations

Hepatic Late Effects

- Medication toxicity
- Chronic GVHD
  - Major cause of liver toxicity post-HCT
  - Liver biopsy should be done for diagnosis if only manifestation
- Iron overload
  - Prevalence: 25%
  - Risk factors: Red cell transfusions; ineffective erythropoiesis; carrier state for hereditary hemochromatosis
- Viral hepatitis
  - Prevalence: 3-6%
  - Hepatitis B – mild to moderate liver disease
  - Hepatitis C – often asymptomatic; cumulative incidence for cirrhosis is 11% at 15 yrs and 24% at 20 yrs; extrahepatic disease and genotype 3 are associated with progression to cirrhosis

Hepatic Recommendations

- LFTs every 3-6 months for first year, then yearly thereafter; more frequent on individual basis
- Iron overload
  - Serum ferritin at 1 year for all patients who received RBCs either pre- or post- transplant
  - Additional diagnostic testing (liver bx, MRI) if therapy contemplated
- Hepatitis B and C patients
  - Monitor viral load
  - Consult liver and infectious disease specialists
  - May recommend liver biopsy, particularly at 8-10 years post-HCT

Renal and Genitourinary Late Effects

- Chronic kidney disease (GFR less than 60 ml/min)/1.73m^2
  - Incidence: 5-65%
  - Common manifestations
    - Progression of early onset acute renal failure
    - Thrombotic microangiopathy
    - Glomerulonephritis
    - Nephrotic syndrome
    - Interstitial fibrosis

  - Risk factors: older age, radiation (TBI, involved field), GVHD, drugs, hypertension, infections (CMV)
- Bladder wall scarring and contraction
  - Risk factors: substantial hemorrhagic cystitis
- Recurrent urinary tract infections
  - Risk factors: immunosuppressive therapy; women with GVHD of vulva/vagina

Renal and Genitourinary Recommendations

- Check blood pressure at every clinic visit and treat hypertension appropriately

- Avoid nephrotoxins

- Evaluate renal function at 6 months, 1 year and at least yearly thereafter for all patients (more frequently for high risk patients)
  - BUN, creatinine, urine protein
  - Early referral to nephrologist for any sign of CKD or progressive disease
  - Further w/u: renal ultrasound, renal biopsy as clinically indicated

Muscle and Connective Tissue Late Effects

- 35% of 10-year survivors report musculoskeletal stiffness, cramps, weakness and joint swelling
- Steroid myopathy
  - Proximal muscle weakness (quadriceps muscle most severely affected) secondary to long-term steroid use
  - May be associated with increased risk of mortality
  - Easy test: observe patient changing position from supine to sitting or sitting to standing

Muscle and Connective Tissue Late Effects

- Fasciitis/scleroderma
  - Diagnostic feature of chronic GVHD
  - Early involvement of fasciae and tendons manifests clinically as edema; progresses to fibrosis and joint contractures
  - Most common in fingers, wrists, shoulders, elbows and ankles
- Myositis or polymyositis
  - Rare; distinctive feature of chronic GVHD; usually occurs 2-5 years post-HCT
  - Majority of patients have elevated serum creatinine kinase; myopathic pattern on EMG; peri-fascicular lymphocytic infiltration on muscle biopsy
  - Responds favorably to immunosuppressive therapy

Muscle and Connective Tissue Recommendations

- All HCT recipients should follow age-specific guidelines for physical activity
- Patients with chronic GVHD
  - Frequent joint ROM assessment
  - Patients should be instructed on self-assessment of ROM
- Patients on steroids
  - PT consult to establish baseline function and provide ROM and muscle strengthening exercises
  - Frequent clinical evaluation for myopathy

Bone Issues
Osteopenia and Osteoporosis

Decrease in bone mass and increased risk for fracture

Normal

Osteoporosis

Numerous mechanisms of bone loss in HCT recipients

Contributing factor	*Mechanism*
Increase in bone resorption	
Renal dysfunction	Decrease in 1,25 $(OH)_2$ vitamin D3 production, secondary hyperparathyroidism
Calcineurin inhibitors	Decrease in renal function, osteoclast activation
Chemotherapy/irradiation	Hypogonadism causing decrease in estrogen and testosterone
Corticosteroids	Osteoclast activation, secondary hyperparathyroidism
Decrease in bone production	
Malabsorption (e.g. GVHD, mucositis)	Decrease in calcium and vitamin D absorption
Renal dysfunction	Magnesium and calcium wasting
Chemotherapy	Direct inhibitory effect on osteoblast formation and activity
TBI/cranio-spinal irradiation	Direct inhibitory effect on osteoblast formation and activity, decrease in growth hormone and IGF-1 production
Corticosteroids	Apoptosis of osteoblasts; inhibition of osteoblastogenesis; decrease in calcium levels due to inhibition of gastrointestinal absorption and increase in renal excretion

McClune BL et al. Bone Marrow Transplant. 2011. 46:1-9.

Avascular Necrosis/Osteonecrosis

- Avascular necrosis
  - 4-19% of survivors
  - Risk factors: same as for post-HCT bone loss PLUS inflammatory microvascular changes related to GVHD
  - Joint pain is first clinical sign
  - Hip most common (over 80% of cases/bilateral in >60%; other joints include knees, wrists, and ankles)
  - MRI is test of choice
  - Surgical approaches: core decompression in early cases; joint replacement

Skeletal Recommendations

- Bone Loss
  - Screening dual photon densitometry at 1 year in adult women, all allogeneic HCT recipients, and sooner in high risk patients
  - Evaluate gonadal function in patients with bone loss
  - Counsel patients about preventative measures
    - Maintain high level of suspicion in patients at risk
    - Weight bearing exercise
    - Fall prevention
    - Vitamin D and calcium supplementation
    - Hormone replacement therapy considered
    - Consider bisphosphonates for patients with osteopenia, at high risk for bone loss, and for evidence of progressive bone loss
- Screening for AVN is not recommended on routine basis

Central and Peripheral Nervous System Late Effects

- Manifestations
  - May be subtle
  - Memory loss, cognitive and learning problems in up to 10-20% of patients
  - Long term deficits in >40% of survivors
  - Leukoencephalopathy
  - Peripheral neuropathy

- Risk factors
  - Age, prior cognitive and learning problems
  - Chemotherapy/TBI and immunosuppressive drugs
  - Infections
  - More common in allogeneic HCT than auto
  - Growing evidence for GVHD effect on CNS (cerebral angiitis like syndrome; Guillain-Barre like syndrome)

Central and Peripheral Nervous System Recommendations

- Clinical assessment for symptoms and signs at 1 year and yearly
- Evaluation for cognitive developmental milestones at least annually in pediatric patients; adults should be queried annually
- Earlier and more frequent evaluations in high-risk patients

Endocrine Late Effects

- Hypothyroidism
  - Subclinical: 7-15% in first year
  - Median time to diagnosis is 4 years
  - Risk factors: TBI, busulfan/cy
- Autoimmune thyroiditis
  - Risk factor: radiation
- Hypogonadism
  - Some degree in >90% survivors (male and female)
  - Risk factors: age, gender, TBI, busulfan
- Low incidence of primary adrenal failure
- Growth disturbance in children

Endocrine Recommendations

- Thyroid function tests (TSH, T3 and free T4) at 1 year and yearly thereafter
- Clinical and endocrinologic gonadal assessment:
  - At 1 year for all women post-pubertal at HCT with annual gynecologic evaluation
  - In men (FSH, LH, testosterone) if symptoms warrant
  - At 6 months for pre-pubertal boys and girl; endocrinologist care vital
- Slow terminal tapering of steroids; give stress doses during acute illness

Muco-Cutaneous Late Effects

- Nearly 70% of patients with chronic GVHD (skin, alopecia, nail dystrophy, sweat impairment)
- Women with hypo-estrogenism due to premature menopause
- Genital chronic GVHD
  - Develops in 12% of women with OR without associated systemic GVHD
    - Initial symptoms may be mild and nonspecific
    - Excoriated or ulcerated mucosa, fissures
    - Narrowing of introitus
    - Vaginal scarring or obliteration
  - Less common in men
    - Phimosis

Muco-Cutaneous Recommendations

- Skin:
  - Patients should be instructed in self examination, and in avoiding excess sunlight and use of sunscreens
- Genital
  - All women post allo-HCT should be instructed about self examination, general hygiene, early recognition of symptoms; annual gynecologic exam
  - Women with established chronic GVHD should have gynecological exam to screen for genital involvement

Psychosocial Adjustment

- Depressive symptoms and psychological distress are frequent
  - Both in patients, caregivers, spouses and family members
- May increase at transition from acute convalescence to long-term follow-up
  - Changes in roles
  - Employment situations
  - Financial difficulties

- Caused by multiple factors
  - Anemia, drugs, endocrine dysfunction, emotional distress, change in sleep patterns, sexual dysfunction
  - Underlying medical cause has to be ruled out

Psychosocial Adjustment

- Screen for depression throughout recovery period, at 6 months, at one year, and yearly thereafter
- Mental health professional assessment if needed
- Inquire as to level of spousal/caregiver psychological adjustment and family functioning
- Query sexual function in adults at 6 months, 1 year, and yearly thereafter

Secondary Cancers

- Devastating late complication
- Allo HCT recipients have a 2- to 3- fold increased risk of solid tumors
  - Risk factors: radiation therapy (sarcoma, breast, thyroid), immunosuppression, chemotherapy, cGHVD
  - Risk increased with time, and continue to increase even after 10 years post HCT
- Auto HCT = risk of tAML/MDS; 4% at 7 years; median onset 2.5 years
  - Risk factors: alkylators, prolonged conventional chemotherapy, pre-transplant irradiation
- PTLD – rare; 1% at 10 years; usually eary (6 months) but may be late; EBV association

Secondary Cancers - Recommendations

- Advise patients of risk
- Avoid high risk behaviors
- Screening clinical assessments yearly should include symptom review for secondary malignancies
- Women with radiation exposure (>800 cGy to chest) - begin screening mammography age 25 or 8 years post radiation, whichever is later, but no later than age 40
- Pay particular attention to oral exam for patients with history of cGHVD of the mouth and Fanconi's anemia pts

Additional Topics

- General screening guidelines and preventive health
- Fertility
- Sex-specific screening guidelines
- Healthy lifestyle guidelines
- Implementation of guidelines in resource limited countries
- Variety of links and tables for easy access, including screening and prevention of late complications by selected exposures and risk-factors

Free Guidelines for Patients

- Recommended screening/preventive practices for:
  - 6-months post-transplant
  - 12-months post-transplant
  - 24+ months/annual appointments
- Patient guidelines include:
  - Simple medical descriptions
  - Checklist to take to physician visits
  - Glossary of medical terms

Visit: BeTheMatch.org/careguide

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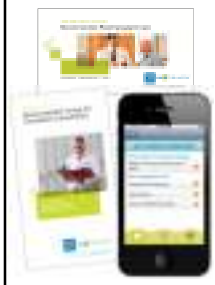
Free Guidelines for Careproviders



Recommendations for autologous and allogeneic patients, including:

- Timing for transplant consultation for 16 diseases, plus outcomes data
- Post-transplant screening and vaccinations
- GVHD screening (with photo atlas)

Available through mobile app, online and print
  - From your mobile store, search "transplant"

Visit: marrow.org/md-guidelines

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Conclusions

- Late complications may affect any organ system
- Increased risk for patients with cGHVD
- Heightened vigilance, prevention, therapy are imperative
- Develop a partnership with "patients and their villages" for life-long preventative and therapeutic medical care