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CREATING TOMORROW'S SOLUTIONS, TOGETHER
PREPARING THE TRANSPLANT COMMUNITY TO SERVE EVERY PATIENT IN NEED.
2012 COUNCIL MEETING

Caring for HCT Survivors

Navneet Majhail, MD, MS
Michelle Kolb

Financial Disclosure: None

Learning Objectives

- Identify the unique pre-, peri- and post-transplant exposures and risk factors associated with late complications of transplant
- Apply appropriate screening, testing and vaccinations based on the 2012 published guidelines for transplant recipients including additional recommendations for recipients based on individual exposures and risk factors
- Explain the role the multidisciplinary team in the long-term follow-up care of transplant recipients
- Discover transplant center practices for implementing 2012 recommended screening and preventive practices for long-term survivors of HCT

Caring for HCT Survivors: Monitoring Late Effects

Navneet Majhail, MD, MS
Medical Director, Health Services Research
National Marrow Donor Program
Adjunct Associate Professor of Medicine
University of Minnesota

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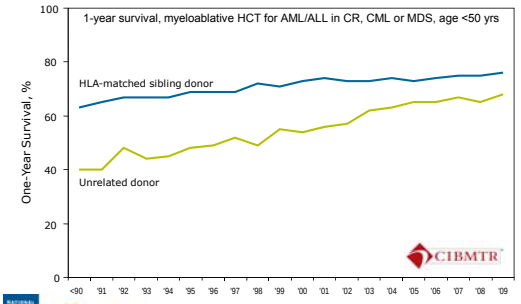
Topics

- Long-term survival and late complications in autologous and allogeneic hematopoietic cell transplant (HCT) recipients
- Screening and prevention guidelines for HCT survivors with 2012 updates
- Care of HCT survivors
- Resources for physicians and patients

Long-term Survival and Late Complications after HCT

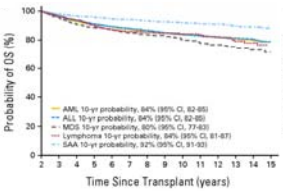
Outcomes of HCT have Improved



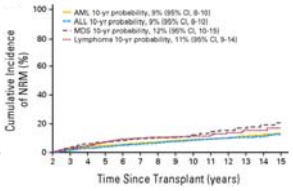
Long-term Survival after HCT

- CIBMTR study of 10,632 allogeneic HCT recipients surviving ≥ 2 years in remission (median followup 9 years)

Overall survival



Non-relapse mortality



J Wingard et al, JCO 2011 ; 29: 2230

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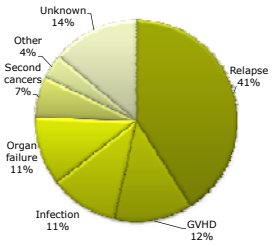
Long-term Survival after HCT

- Causes of death, ≥ 2 year survivors of allogeneic HCT
  - N = 1270 deaths
  - Chronic GVHD most common cause of death for SAA
- Main risk factors for late mortality on multivariate analysis
  - Older age at HCT
  - Chronic GVHD
- Relative mortality higher than age-, gender-matched general population at 15 years followup



Causes of death (malignant diseases)

J Wingard et al, JCO 2011 ; 29: 2230

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Long-term Survival after HCT

Reference	Patients	Overall Survival	CGVHD & Mortality Risk	Life Expectancy
AUTOLOGOUS HCT				
Bhatia et al (2007), BMT-SS	N=854, multiple ds (≥2 yr survivors)	69% @ 10 yrs	--	Same (for select pts)
Majhail et al (2009), CIBMTR	N=1367, lymphoma (≥2 yr survivors)	52-85% @ 10 yrs	--	Same
ALLOGENEIC HCT				
Bhatia et al (2007), BMT-SS	N=1479, multiple ds (≥2 yr survivors)	80% @ 15 yrs	√	↓ @ 15 yrs
Goldman et al (2010), CIBMTR	N=2444, CML (≥5 yr survivors)	87-88% @ 15 yrs	√	↓ @ 15 yrs
COMBINED				
Martin et al (2010), FHCRC	N=2574, multiple ds (≥5 yr survivors)	80% @ 20 yrs	√	↓ @ 30 yrs

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Long-term Survival after HCT

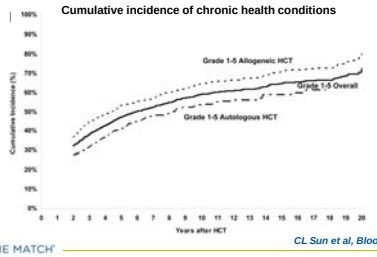
- More transplants + better outcomes = more survivors
  - ~100,000 HCT survivors in the US in 2009
  - ~250,000 survivors estimated by 2020

Late Complications

- Transplant survivors are at risk for late complications
  - Organ toxicity
  - Infections
  - Secondary cancers
  - Growth and development issues
  - Psychosocial, sexual, fertility and QOL issues

Burden of Late Morbidity

- Late complications are significant issue for survivors
  - BMT-SS – 1022 auto and allo HCT 2-year survivors



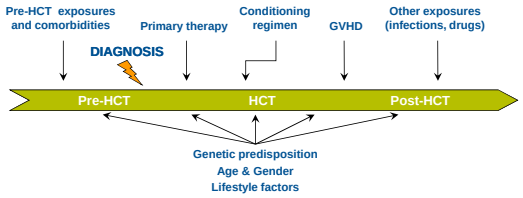
CL Sun et al, Blood 2010 ; 116: 3129

Burden of Late Morbidity

- Late complications impact recovery and QOL
  - FHCRC study of 1,087 auto and allo HCT 1-year survivors
  - Cumulative incidence of 14 late effects at 5-years
    - 45% among auto and 79% among allo HCT survivors
    - ≥ 3 late effects in 3% auto and 26% allo HCT survivors
  - Survivors with ≥ 3 late effects reported
    - Worse physical functioning
    - Higher moderate/severe limitation of usual activities
    - Lower likelihood of full-time work or study

N Khera et al, JCO 2012 ; 30: 71

Risk Factors for Late Complications



Late Organ Dysfunction

- Neurologic – cognitive dysfunction, neuropathy
- Eye – sicca syndrome, cataracts
- Oral – xerostomia, caries
- Pulmonary – bronchiolitis obliterans
- Cardiovascular – coronary artery disease, metabolic syndrome, cardiomyopathy
- Liver – iron overload, hepatitis
- Kidney – HTN, chronic kidney disease
- Bone – osteoporosis, avascular necrosis
- Endocrine – hypothyroidism, growth disturbance

Exposures Mediate Late Organ Toxicity

- Chronic GVHD
  - Dry eye, caries, xerostomia, bronchiolitis obliterans, genitourinary issues
- Exposure to corticosteroids/CSA
  - Osteoporosis, HTN, kidney disease, myopathy
- TBI
  - Coronary artery disease, caries, dry eye, cataracts, endocrine dysfunction

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Late Infections

- Increased risk for infections in patients with delayed immune reconstitution (e.g., chronic GVHD, prolonged steroid exposure)
  - Encapsulated bacteria
  - CMV, VZV
  - Aspergillus, PCP
- International consensus guidelines for prevention of early and late infections published in 2009
  - Recommendations for vaccinations in transplant recipients

M Tomblyn et al, Biol Blood Marrow Transplant, 2009, 15, 1143
M Tomblyn et al, Bone Marrow Transplant, 2009, 44, 521

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Vaccination Guidelines

Vaccine	Recommended for use after HCT	Time post-HCT to initiate vaccine	No. of doses
Pneumococcal conjugate (PCV)	Yes	3-6 months	3-4
Tetanus, diphtheria, acellular pertussis	Yes	6-12 months	3
Haemophilus influenzae conjugate	Yes	6-12 months	3
Meningococcal conjugate	Follow general pouplation recommendations	6-12 months	1
Inactivated polio	Yes	6-12 months	3
Recombinant hepatitis B	Follow general population recommendations	6-12 months	3
Inactivated influenza	Yearly	4-6 months	1-2
Measles-mumps-rubella (live)	Measles: All children and seronegative adults	24 months	1-2

M Tomblyn et al, Biol Blood Marrow Transplant, 2009, 15 , 1143
M Tomblyn et al, Bone Marrow Transplant, 2009, 44, 521

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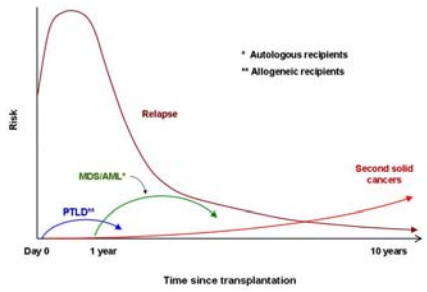
Secondary Cancers

- Cancers that occur after transplant
  - Different from the cancer for which transplant was performed
  - Cancer treatments may cause them or increase their risk
- Types of second cancers
  - Post-transplant lymphoproliferative disorders (PTLD)
  - MDS/AML
  - Solid cancers

N Majhail. Br J Haematol, 2011, 154, 301

Secondary Cancer Risk Periods



Risk Factors for Second Cancers

- Alkylating chemotherapy – MDS/AML after autologous HCT
- EBV – PTLD after allogeneic HCT
- Chronic GVHD – squamous cell cancers (skin, oro-pharynx)
- Total body irradiation – non-squamous cell cancers (breast cancer)

Quality of Life After HCT

- Affects all domains of QOL
  - Autologous HCT - Lowest at ~2 weeks, returns to baseline by 3 months to 1 year
  - Allogeneic HCT - Lowest at ~4 weeks, returns to baseline by 3 months to 1 year in absence of GVHD
  - Patients with chronic GVHD have persisting QOL deficits
- Continued long-term impairments compared to healthy controls
- QOL impairments and psychosocial issues in caregivers

Need for More Research on Late Effects

- Longer followup of survivors to understand complete burden and impact of late complications
- Survivorship issues related to newer transplant modalities (older age patients, NMA/RIC regimens, UCB)
- Genetic and molecular pathogenesis of late effects
- Interventions to prevent or mitigate late complications
- Interventions to enhance patient education and compliance
- Optimal care models for transplant survivor care

Recommended Screening and Preventative Practices for Long-Term Survivors after HCT

Co-published in:

Biology of Blood and Marrow Transplantation, 2012; 18: 348
Bone Marrow Transplantation, 2012; 47: 337
Hematology Oncology and Stem Cell Therapy, 2012; 5: 1
Revista Brasileira de Hematologia e Hemoterapia, 2012; 34: 109

Guidelines History

- Initial work in 2006 by CIBMTR, ASBMT and EBMT
  - Co-published in BBMT and BMT
- Guidelines group reconvened in 2011
  - Greater international representation – CIBMTR, ASBMT, EBMT, APBMT, BMTSANZ, EMBMT, SBTMO
  - Literature review and conference calls to discuss and finalize consensus recommendations
  - Co-published in March 2012 issues of 4 journals to maximize international dissemination

Key Differences 2012 vs. 2006

- Combined autologous and allogeneic HCT recipients
  - Greater emphasis on exposures and risk factors
- Called out 'special populations'
  - Pediatric recipients
  - TBI recipients
  - Exposure to steroids
  - GVHD
- Post HCT vaccinations included
- Implementation in countries with limited resources

Guidelines Presentation

- Narrative review of each organ system with references
- Specific recommendations at end of each section
- Supporting tables
  - By organ system
  - By time post HCT
  - By selected exposures and risk factors ('special populations')
  - Vaccinations
  - Links to other guidelines

Organ Systems/Issues Considered

- Immune system
- Ocular
- Oral
- Respiratory
- Cardiac and vascular
- Liver
- Renal and genitourinary
- Muscle and connective tissue
- Skeletal
- Nervous system
- Endocrine
- Mucocutaneous
- Second cancers
- Psychosocial and sexual
- Fertility
- General Health

Example: Oral Complications

- All HCT recipients
  - Educate about preventive oral health and dental maintenance
  - Counsel to avoid smoking and chewing tobacco, avoid intraoral piercing
  - Clinical oral evaluation at 6 mo, 1 yr and then yearly
  - Dentist or oral medicine specialist evaluation at 1 yr and then yearly
- Pediatric recipients
  - Assessment of teeth development
- Chronic GVHD patients
  - Clinical oral evaluation every 6 mo
  - More frequent dentist or oral medicine specialist consultations may be considered

General Health Recommendations

- General health maintenance
  - Hypertension, cholesterol, diabetes, depression and other psychological issues, sexually transmitted diseases
- Secondary cancer screening
- Osteoporosis
- Healthy lifestyle – diet and exercise

Presentation of Guidelines

Tissues/Organs	Complications and Tests	Preventive Measures	Recommended Timing: 6 mo	12 mo	Annually
Skeletal	Complications: • Osteopenia/osteoporosis • Avascular necrosis Tests: • Dual photon densitometry • MRI	All HCT recipients			
		Dual photon densitometry for adult women, all allogeneic HCT recipients and patients who are at high risk for bone loss (e.g., prolonged corticosteroid exposure); subsequent testing determined by defects or to assess response to therapy		✓	•
		Counseling about physical activity, vitamin D and calcium supplementation to prevent loss of bone density	✓	✓	✓
		Additional measures for special populations*			
		Consider dual photon densitometry at an earlier date in patients with prolonged corticosteroid or calcineurin inhibitor exposure	✓ GVHD ✓ Steroids	✓ GVHD ✓ Steroids	• GVHD • Steroids
Nervous system	Complications: • Leukoencephalopathy • Neuropsychological and cognitive deficits • Late infections • Calcineurin neurotoxicity • Peripheral neuropathy Tests: • MRI • Neuropsychological testing	All HCT recipients			
		Clinical evaluation for symptoms and signs of neurologic dysfunction. Diagnostic testing (e.g., radiographic, nerve conduction studies) for those with symptoms or signs	•	✓	✓
		Evaluate for changes in cognitive function, which may be subtle in adults	•	✓	✓
		Additional measures for special populations*			
		Assessment for cognitive development milestones		✓ Pediatric	✓ Pediatric

Key:
• ✓ = recommended preventive measures
• • = Assessment recommended for patients with pre-existing conditions, if clinically indicated, if abnormal testing in a previous time period, or with new signs/symptoms
*Special populations = GVHD (patients with GVHD), Steroids (patients with ongoing significant corticosteroid exposure), Pediatric (pediatric patients), TBI (patients who have received total body irradiation)

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Potential Limitations

- Working Group acknowledged limitations – based guidelines on available literature and expert consensus opinion regarding best practice
  - Limited number of clinical trials and prospective studies
  - Evolution of HCT practice – late effects take time to develop and characterize
  - Implementation in resource limited countries
  - General health recommendations vary by country
- Recognized the need for ongoing research and for periodic update of the guidelines

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Example

- 35 year old female, 100 days after unrelated donor HCT for AML in CR1
  - Healthy prior to diagnosis of AML
  - Exposures include 1 cycle of induction chemotherapy, myeloablative conditioning using Bu-Cy
  - No history of acute GVHD

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Scenarios: With and Without Chronic GVHD

Organ	No GVHD	GVHD
Immune system	- Vaccinations - PCP prophylaxis x 6 mo	- Vaccinations - PCP & encapsulated organism prophylaxis for duration of immune suppression - Monitor CMV based on risk factors
Ocular	- Clinical evaluation at 6 mo, 1 yr and then yearly - Ophthalmologic exam at 1 yr, subsequent as needed	- Clinical evaluation at 6 mo, 1 yr and then yearly - Ophthalmologic exam at 1 yr, subsequent as needed - Both may be performed more frequently if needed
Oral	- Clinical evaluation at 6 mo, 1 yr and then yearly - Evaluation by dentist at 1 yr and then yearly	- Clinical evaluation at 6 mo, 1 yr and then yearly - Evaluation by dentist at 1 yr and then yearly - May be performed more frequently

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Scenarios: With and Without Chronic GVHD

Organ	No GVHD	GVHD
Pulmonary	- Clinical evaluation at 6 mo, 1 yr and then yearly	- Clinical evaluation at 6 mo, 1 yr and then yearly
Cardiac	- Assess cardiovascular risk at 1 yr and then yearly	- Assess cardiovascular risk at 1 yr and then yearly
Muscle	- General population guidelines for physical activity	- General population guidelines for physical activity - Periodic clinical evaluation for myopathy
Second cancers	- Encourage skin self exam - Mammogram starting at age 40	- Encourage skin self exam - Mammogram starting at age 40 - Clinical/dental evaluation with focus on oropharyngeal cancer
Muco-cutaneous	- Annual gynecologic exam	- Annual gynecologic exam - May be performed more frequently if indicated

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... + other organ systems

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Care of HCT Survivors

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Challenges

- Transplant center
  - Limited resources, competing priorities
  - Difficult to follow and collect data on long-term survivors
- Patient
  - Distance and resources
  - Complex medical issues
  - Not aware of their risks
- Referring and primary care physicians
  - Competing priorities
  - Lack of knowledge and resources

It Takes a Village…

- Models of care must meet specialized needs of high risk population
- Take into account individual patient exposures
- Multidisciplinary approach
  - Patients and caregivers
  - Transplant centers
  - Wide range of specialists
  - Referring and primary care physicians
  - Other health care providers

Individual Risks for Late Effects

10 year old with Hodgkin's lymphoma treated with autologous HCT

RISKS ARE NOT SAME

60 year old with AML treated with allogeneic HCT and has GVHD

Survivor Care Plan

- Treatment summary and care plan
  - Individualized plans based on exposures
- No standard instrument for HCT survivors
  - General cancer specific tools available
  - LIVESTRONG Care Plan www.livestrong-careplan.org
  - Passport for Cure® www.txch.org/passportforcure
- Guidelines can be used as a template for developing care plans for patients

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Acknowledgements

Guidelines Working Group
- Navneet Majhail (US)
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- Patient Services (Elizabeth Murphy and team)

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New Clinical & Patient Resources

Michelle Kolb
Medical Marketing
National Marrow Donor Program

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The Guidelines Evolution

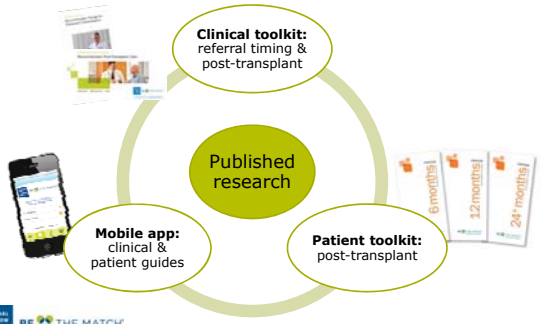
2004
Referral guidelines

2006
Patient post-transplant guide

2007
Clinical guidelines toolkit

2010
Mobile app + online tool

2012 Guidelines



Clinical Toolkit

- Referral guidelines—with recommendations for 18 diseases
- Three-part long-term survival guidelines:
  1. Long-term screening recommendations (more robust)
  2. Vaccinations (new)
  3. GVHD screening recommendations, including photo atlas

marrow.org/HCT-guide

Patient Toolkit

- Patient-friendly version of the long-term screening recommendations
- 6, 12, 24+ month guides
- Each guide provides tests, evaluations & glossary
- Checklist to prepare for checkup
- Space for notes

BeTheMatch.org/careguide

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Free Mobile App

- Create customized lists, view latest outcomes data, access GVHD photo atlas—for patients & clinicians

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Education & Awareness Efforts

Transplant Centers
Education, mailing, email, conferences

Referring Physicians
MedScape CME, mailing, banner ads, conferences

NMDP Patients
Education, mailing, email, conferences, banner ads

Non-NMDP Patients
Online, conferences, banner ads

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Targeted Mailings

- Information & order forms sent to TCs
- Guide sent to 2+ year transplant recipients
- Mailing to referring MDs in January

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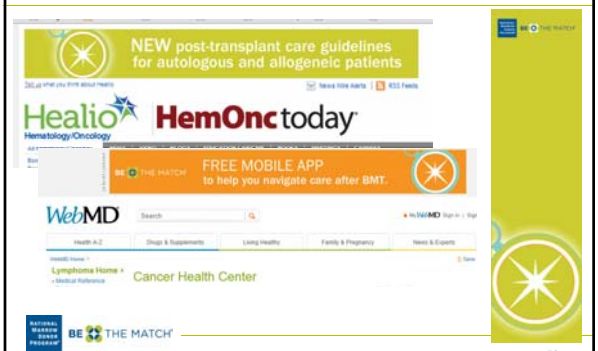
Online Banner Ads



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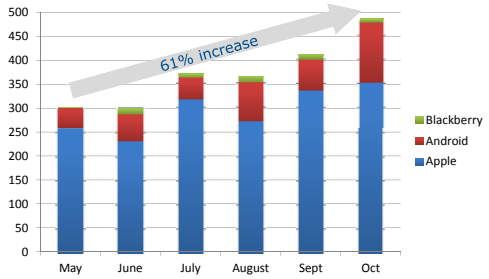
Early Results: App Downloads



Over 9000 total app downloads

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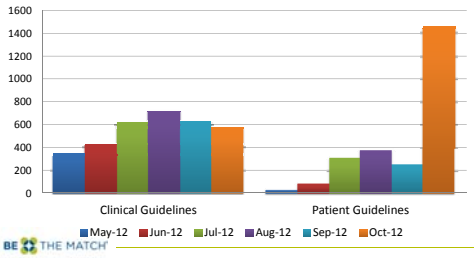
Results: Orders + Web Traffic

- **5800 guidelines distributed**: 1850 clinical, 3950 patient
- **Unique visitors** to guidelines promotional pages:



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Multiple formats, all absolutely free

- **Online**: marrow.org/HCT-guide
- **Download** the app—iPad, iPhone, Android
- **Order** resources here or at NMDP Connection Lounge
- **Email** us anytime: medicaleducation@nmdp.org

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Questions?

For Physicians:
www.marrow.org/md

For Patients:
www.marrow.org/patient

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