Secondary Cancers after Transplant

Celebrating a Second Chance at Life Survivorship Symposium

April 29 – May 5, 2023

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What is a "second cancer"?

- Second cancers are cancers that occur months to years after a bone marrow or stem cell transplant (hematopoietic cell transplant, or HCT)
- These cancers are different from the one for which the transplant was performed
- People who have received HCTs are at significantly increased risk of developing another cancer because of the effects of high dose chemotherapy, radiation, immune suppression, and certain infections.

Learning Points

- Second cancers are common after HCT
  - Autologous and allogeneic HCT recipients experience different risks for different types of cancer.
  - Pediatric HCT recipients are at significant risk as well.
- Screening and prevention are essential and can make a difference in long-term outcomes
  - Adhering to recommended screening practices and choosing healthy lifestyles can be lifesaving.
- We are learning more about why some people develop these cancers and others don't, which we hope will inform personalized approaches to improve the health of HCT recipients in the future.

Allogeneic HCT Outcomes are Improving

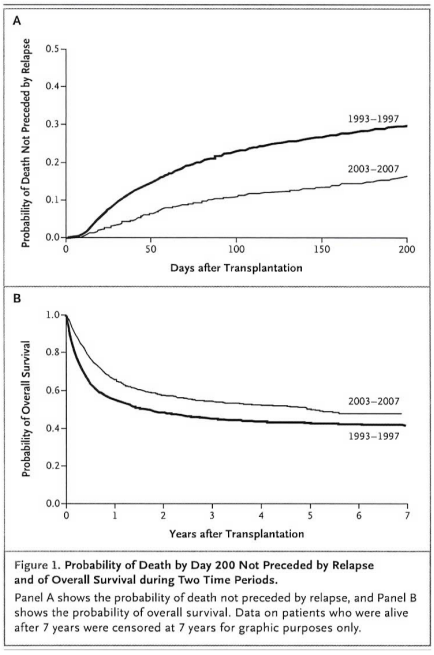
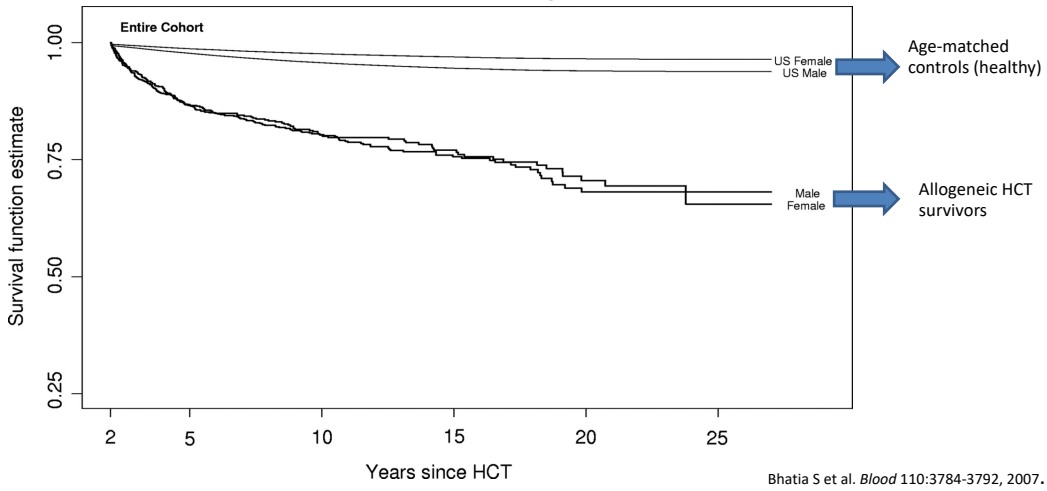


Figure 1. **Probability of Death by Day 200 Not Preceded by Relapse and of Overall Survival during Two Time Periods.**
Panel A shows the probability of death not preceded by relapse, and Panel B shows the probability of overall survival. Data on patients who were alive after 7 years were censored at 7 years for graphic purposes only.

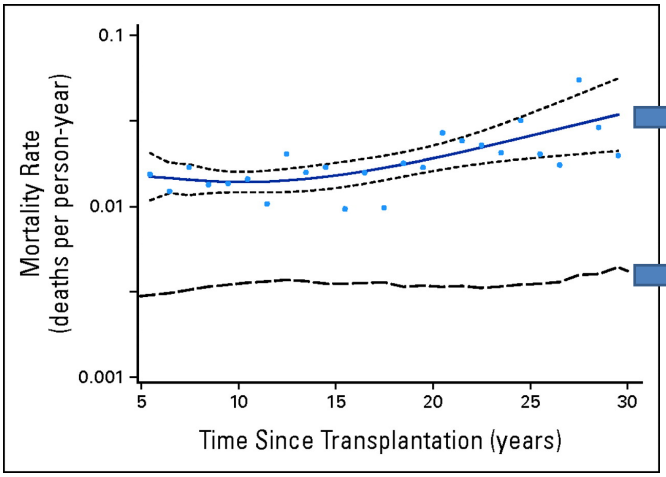
Gooley TA et al *NEJM* 363: 2091-2101, 2010.

But Long-Term Survivors Do Not Live as Long as The General Population



Bhatia S et al. *Blood* 110:3784-3792, 2007.

Mortality Rate: Transplant Survivors vs. U.S. Population



Martin PJ et al. *J Clin Oncol* 28:1011-1016, 2010.

Causes of Death

- Allogeneic HCT:
  - Relapse (30%)
  - Chronic graft-vs-host disease (GVHD) (15-20%)
  - Second cancer (5-10%)
  - Infection (5-15%)
  - Other organ dysfunction (15-20%)
- Autologous HCT:
  - Relapse (50-60%)
  - Second cancer (25%)
  - Cardiopulmonary (5%)
  - Other treatment related (13%)

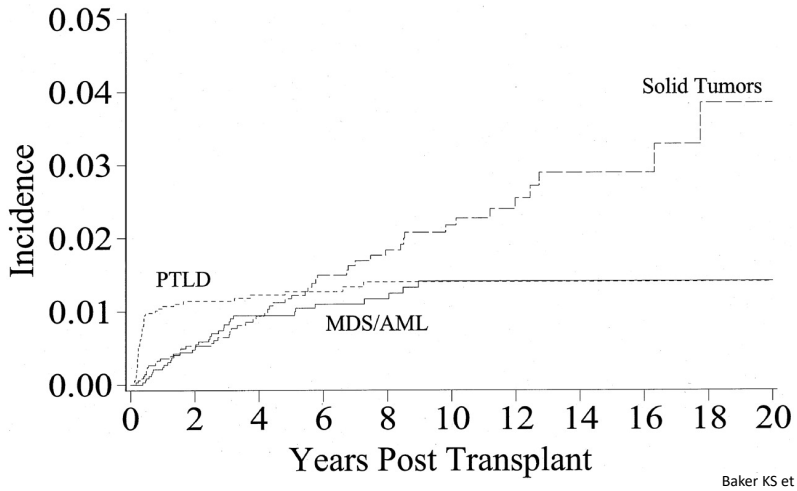
Wingard JR et al. *J Clin Oncol* 29:2230-2239, 2011.
Bhatia S et al. *Blood* 105:4215-4222, 2005.

Second Cancers

- Risk is 4–11 fold higher than general population
  - 7.5% of transplant survivors vs 1.6% of sibling controls
- Incidence of 13% at 15 years post alloHCT
- Three distinct groups:
  - Therapy-related blood cancers
  - Lymphoma (post-transplant lymphoproliferative disorder, PTLD)
  - "Solid" cancers (breast, skin, soft tissue, cervical, gastrointestinal, etc.)

Kolb HJ et al. *Ann Int Med* 131(10): 738-744, 1999.
Baker KS et al. *Leukemia* 24:2039-2047, 2010.
Socie G et al. *Biol Blood Marrow Transplant* 18(1):S139-S150, 2012

Incidence of Second Cancers after All Types of Hematopoietic Cell Transplants



Baker KS et al. *J Clin Oncol* 21:1352-1358, 2003.

Second Cancers:
Therapy-Related Blood Cancers

- These include myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML)
- Risk almost exclusively in autologous HCT recipients
- Typically occur 6 months to 5 years post-transplant
- Cumulative incidence ~2% at 10 years
- Possible association with radiation exposure and etoposide mobilization

Tarella C et al. *J Clin Oncol* 29:814-824, 2011.
Bhatia S et al. *Blood* 95:1588-1593, 2000.
Stone RM et al. *J Clin Oncol* 12:2535-2542, 1994.

Second Cancers:
Post-Transplant Lymphoproliferative Disorder (PTLD)

- Risk almost exclusively in allogeneic HCT recipients
- Onset within 2 years post-transplant
- Epstein Barr Virus (EBV)-driven B-cell proliferation
- Strongly associated with impaired T-cell function
  - Immune deficiency as indication for transplant
  - T-cell depletion (ATG or *ex vivo*)
  - Mismatched and/or unrelated donor
  - Severe acute GVHD or chronic GVHD
- Incidence approaches 8%
- Previously had poor prognosis, likely improving due to better surveillance and more effective treatment

Loren AW et al. *Bone Marrow Transplant* 31:145-155, 2003.
Curtis RE et al. *Blood* 94:2208-2216, 1999

Second Cancers:
Solid Tumors

- Risk greater in allogeneic HCT than autologous HCT
  - Allogeneic: Standardized Incidence Ratio (SIR) 2.1
  - Autologous: SIR 1.4 for all cancers and 20.6 for MDS/AML
- Cumulative incidence ~5% at 15 years and continues to increase over time
- Risk factors:
  - Radiation, particularly age < 30 at HCT
  - Immunosuppression/chronic GVHD
  - Viruses: human papilloma virus (HPV), hepatitis viruses (HBV, HCV)
  - Reason for transplant: acute leukemia > CML > SAA

Bilmon IA et al. *Bone Marrow Transplant* 95:691-698, 2014.
Socie G and Rizzo JD. *Semin Hematol* 49:4-9, 2012.
Rizzo D et al. *Blood* 113:1175-1183, 2008.
Bhatia S et al. *J Clin Oncol* 19:464-471, 2001.

Incidence of Second Cancers in Allo HCT
with Busulfan/Cyclophosphamide (Bu/Cy) Conditioning

Majhail N et al. *Blood* 117:316-322, 2011.

Second Cancers: Risk Factors

- Radiation at age < 10 years:
  - 9 – 10 x increase in non-squamous cell cancers
- Radiation most strongly associated with thyroid, bone, soft tissue, brain, breast, melanoma
- Presence of cGHVD:
  - 11 x increase in squamous cell carcinoma (SCC) of skin and 5 x SCC of oral cavity
- Male sex:
  - 12 x increase in SCC of the skin
- Donor T-cell depletion:
  - 3 x increase in melanoma
- Myeloablative conditioning
  - Reduced intensity transplants associated with similar cancer risk to general population

Rizzo JD et al. *Blood* 113:1175-1183, 2009.
Ringden O et al. *Biol Blood Marrow Transplant* 20:1777-1784, 2014.

Second Cancers Increased After HCT

	SIR (Observed/Expected Cases)	
Melanoma	1.4 – 8.3	
Oral cavity	7.0 – 16.0 (as high as 20x for lip, tongue, salivary gland)	
Brain	3.8 – 9.5	
Esophagus	8.5 - 11	
Liver	6.3 – 28	
Thyroid	5.8 – 6.6	
Breast	2.6 – 4.6	
Bone	8.5 - 13	
Soft tissue	6.5 - 8	
Lung	2.6	Bu/Cy only

Rizzo et al. *Blood* 113:1175-1183, 2009.
Majhail N et al. *Blood* 117:316-322, 2011.
Inamoto Y et al. *Bone Marrow Transplant* 50: 1013-1023, 2015.
MacDonald AM et al. *J Clin Oncol* 28:2876-2882, 2020.

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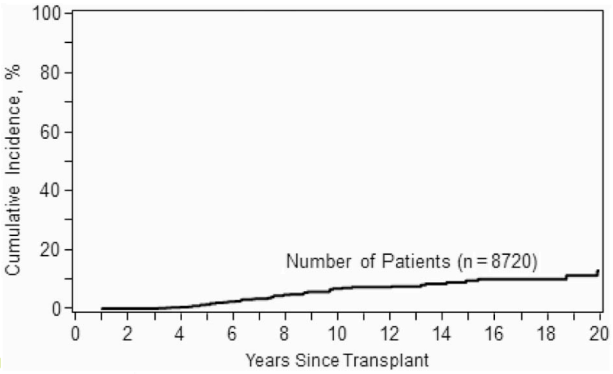
2023 SURVIVORSHIP SYMPOSIUM

Pediatric Allogeneic HCT Survivors and Central Nervous System (CNS) Tumors

- 33-fold increased risk
- Radiation exposure and presence of CNS disease prior to transplant were greatest risk factors



Gabriel M et al. *Biol Blood Marrow Transplant* 23(8):1320-1326, 2017.
Bowers DC et al. *Lancet Oncol* 14:e321-328, 2013.

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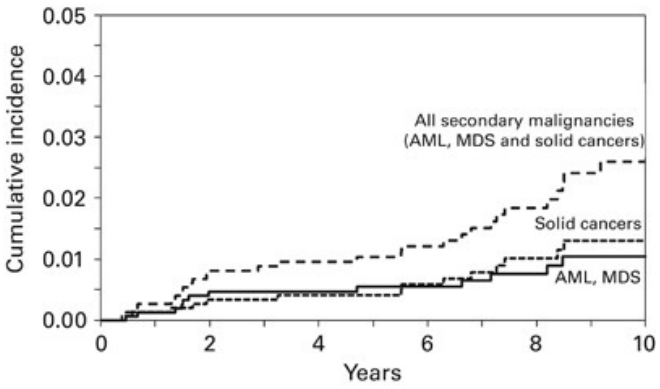
2023 SURVIVORSHIP SYMPOSIUM

Pediatric Autologous HCT Survivors

- 24-fold increased risk of solid cancers
  - Primarily thyroid, soft tissue / bone, brain, MDS/AML
  - Risk increases over time (40-fold increase at > 10 years post HCT)



Danner-Koptik KE et al. *Bone Marrow Transplant* 48:363-368, 2012.

Emerging Evidence for Genetic Predisposition

- Genes that increase risk of cancer
  - Unable to repair damaged DNA
- Genetic variation in metabolism of chemotherapy
- Telomere length and thyroid cancer
- Polygenic risk scores and risk of breast, thyroid, CNS cancer

Man TK et al. *Cancer Epidemiol Biomarkers Prevention* 31:453-460, 2022.
Bhatia S. *Hematology: ASH Education Program* 1:245-250, 2022.
Wang Z et al. *Clin Cancer Res* 24:6230-6235, 2018.
Wang X et al. *J Clin Oncol* 35:3688-3696, 2017.
Bhatia S. *Cancer* 121:648-663, 2015.

Screening and Prevention

- **Skin:** Annual evaluation by Dermatology
  - Total body irradiation (TBI), graft-versus-host disease (GVHD)
- **Thyroid:** Annual exam or ultrasound
  - TBI
- **Oropharyngeal:** Exam every 6-12 months (dentist)
  - TBI, GVHD
- **Esophageal:** Upper endoscopy if symptoms of reflux or difficulty swallowing
  - TBI, GVHD
- **Colorectal:** Colonoscopy age ≥ 45
  - TBI, GVHD

Inamoto Y et al. *Bone Marrow Transplant* 50: 1013-1023, 2015.

Screening and Prevention

- **Lung:** Screening CT chest if smoking history
  - General population: age ≥ 50 and ≥ 30 pack-years **OR** ≥ 50 and ≥ 20 pack-years + one other risk factor (like HCT!)
- **Breast:** Annual mammogram **and** breast MRI
  - TBI, certain chemotherapies, younger age at transplant
    - Radiation: Start screening 8 years after treatment or age 25, whichever is earlier, but not later than age 40
- **Cervical:** Annual Pap and HPV screen
  - Women post-HCT do not get appropriately screened (< 40%)
  - Women with GVHD, who are at the highest risk, are 50% less likely to be screened

Hwang J et al. *Biol Blood Marrow Transplant* 24:1094-1098, 2018.
Inamoto Y et al. *Bone Marrow Transplant* 50: 1013-1023, 2015.

Screening and Prevention

- **Endometrial, ovarian, prostate, testis, brain/CNS and sarcoma**
  - No specific screening but close attention to symptoms
  - Significant knowledge gap particularly for female genital tract cancers
- Other important prevention strategies:
  - Avoid smoking
  - Use sunscreen SPF 30 or higher
  - Healthy lifestyle – diet & exercise

Inamoto Y et al. *Bone Marrow Transplant* 50: 1013-1023, 2015.
Chang HA et al. *J Natl Compr Canc Netw* 16: 211-218, 2018.

Future Research Directions

- Establish multicenter mechanisms to conduct large long-term studies of HCT survivors that capture detailed data on all transplantation exposures
  - Define magnitude of risks for specific cancers
  - Evaluate interaction between traditional risk factors (eg, smoking) with HCT-related risk factors
  - Bank cryopreserved donor and recipient blood and marrow cells along with cancer tissue for laboratory investigations
  - Assess genetic risk factors
  - Investigate validity, cost-effectiveness, magnitude of risk reduction, optimal techniques and timing of screening for specific cancers
  - Validate cancer prevention interventions (eg, HPV vaccination)

Battiwalla M, Tichelli A, Majhail NS. *Biol Blood Marrow Transplant* 23:184-192, 2017.

Take Home Points

- Understand that HCT is a lifesaving therapy. Although imperfect, it's the best treatment we have for many blood cancers and other life-threatening diseases.
- Talk to your transplant team about screening for cancer, and be sure to complete all your testing at the appropriate time.
  - Be clear on who is going to be responsible for ordering your testing – Your transplant team? Your primary care provider? Your gynecologist? Your gastroenterologist?
- Take good care of yourself – eat a healthy diet, exercise regularly, don't smoke!
- Be an advocate for yourself. Not every provider will know about the special needs of HCT survivors.

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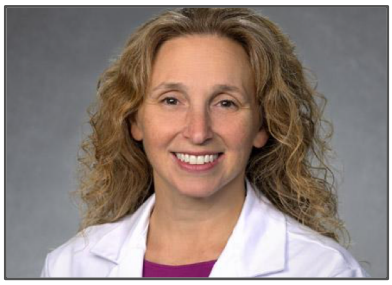
QUESTIONS?



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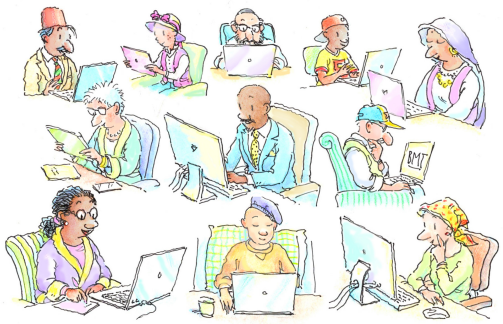
LET US KNOW HOW WE CAN HELP YOU



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