LATE EFFECTS OF TRANSPLANTS:
LESSONS LEARNED AND STRATEGIES TO IMPROVE THE
HEALTH OF THE HCT SURVIVOR

SARO ARMENIAN, DO, MPH
ASSOCIATE PROFESSOR, DEPARTMENTS OF PEDIATRICS AND POPULATION SCIENCES
DIRECTOR, DIVISION OF OUTCOMES RESEARCH
CITY OF HOPE COMPREHENSIVE CANCER CENTER
I have no relevant disclosures
Growing Number of HCT Survivors

Life Expectancy: 5-Year Survivors

Reduction in Life Expectancy
(Years)

Attained Age (Years)

Reduction in Life Expectancy
(%)

Attained Age (Years)

30% lower life expectancy than that of the U.S. population
Late Mortality: 5-year Survivors

Chronic health conditions account for 75% of late deaths

- Secondary Cancer: 28%
- GvHD: 11%
- Infection: 17%
- Relapse: 14%
- Unknown: 4%
- Respiratory: 7%
- Cardiovascular: 10%
Late complications after HCT

Early complication
0

3 months

Delayed events

2 years

Late events

10 years

Very late events

Respiratory complications
Chronic GvHD and infections
Ocular complications
Keratoconjunctivitis

Thyroid dysfunction
Growth failure
Gonadal failure
Chronic kidney disease
Avascular necrosis
Osteoporosis
Infertility
Sexual dysfunction
Metabolic disorders

Cardiovascular disease
Liver cirrhosis
Malignant complications

Physical and psychological performance, QoL and social integration

*Expert Rev Hematol.* 2(5), 2009
Cancer Survivorship Research to Improve Outcomes
Burden of Chronic Health Conditions Over Time

HCT Survivors: 3.5-fold risk of Severe/ life-threatening conditions compared to siblings

**Accelerated Aging in Survivors**

**Frailty:** State of increased vulnerability resulting from aging-related decline in reserve and function across multiple physiologic systems, compromising the ability to cope with everyday or acute stressors.

Adapted from *Clin Geriatr Med.* 1992;8:1-17
Frailty Phenotype and Cancer

- Five components of fitness
  - Cardiovascular Health Study (65-101 years of age)
    - Muscle wasting
    - Muscle weakness
    - Self-reported exhaustion
    - Slow walking speed
    - Low energy expenditure

- Frail = 3 components (prevalence: 7.2%)
- Pre-frail = 2 components (prevalence: 15%)
Frailty Phenotype and HCT

- High cumulative therapeutic exposures +/-
- Sequelae of chronic GvHD +/-
- Chronic health conditions post-HCT

Young HCT survivors vulnerable to frailty

Substantial Stressors

Pre-HCT Therapeutic Exposures
- Diagnosis of Primary Ca
- Pre-HCT relapse of Ca

HCT-related exposures
- HCT
- GvHD

Post-HCT Therapeutic Exposures
- Post-HCT relapse of Ca

Slide courtesy of M. Arora
PREVALENCE OF FRAILTY (<65Y) – HCT SURVIVORS AND SIBLINGS

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siblings</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>8.4 (2.0-34.5)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Adjusted for age at study, income, chronic health conditions
Frailty and Impact on Long-Term Survival

Frailty: 39.3% at 10 years
No frailty: 14.7% at 10 years

\[ P < .001 \]

<table>
<thead>
<tr>
<th></th>
<th>Hazards Ratio (95% CI)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>No frailty</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Frailty</td>
<td>2.76 (1.7-4.4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Beyond the Frailty Phenotype: "Aging Mimicry"?

Autologous HCT

- All second cancers
- Haematological second cancers
- Solid second cancers

Cumulative incidence (%)

Years from HCT

Bone Marrow Transplantation (2014) 49, 691–698

Allogeneic HCT

Relative risk

PTLD
Leukemia
Solid tumors
NHL/HD
GvHD

Blood Reviews (2002) 16, 135–146
Beyond the Frailty Phenotype: “Aging Mimicry”?
Cancer and Aging

Cancer and its treatment
- Chemotherapy
- Radiation
- Surgery
- Bio/Immunotherapy

Macromolecular damage
Metabolism
Stem cells and regeneration
Proteostasis
Adaptation to stress
Epigenetics
Inflammation
Premature Aging in Cancer Survivors
Biomarkers of Premature Aging in Cancer Survivors

Telomere Content and Risk of Second Malignant Neoplasm

Clin Cancer Res; 20(4); 904–11. ©2013

Table 3. Association between telomere content and SMN, cases versus controls

<table>
<thead>
<tr>
<th>SMN</th>
<th>Number of case–control pairs</th>
<th>Mean telomere content ± SD</th>
<th>Adjusted ORa</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>P</td>
</tr>
<tr>
<td>All SMN</td>
<td>147</td>
<td>0.56±0.21</td>
<td>0.58±0.26</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>68</td>
<td>0.55±0.18</td>
<td>0.55±0.25</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>48</td>
<td>0.54±0.21</td>
<td>0.63±0.30</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>31</td>
<td>0.63±0.27</td>
<td>0.54±0.23</td>
</tr>
</tbody>
</table>

aAdjusted for sex, race, family history, smoking status, and age at diagnosis of the primary disease.
Biomarkers of Premature Aging in Cancer Survivors

Clinical and biological markers of premature aging after autologous SCT in childhood cancer

Bone Marrow Transplant. 2017 Apr;52(4):600-605

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survivors (n = 19)</th>
<th>Controls (n = 20)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>22.3</td>
<td>22.1</td>
<td>0.966</td>
</tr>
<tr>
<td>Sex/female n (%)</td>
<td>11 (57.9)</td>
<td>11 (55.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Potential biological markers of frail health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telomere length (AU)</td>
<td>0.66</td>
<td>0.97</td>
<td>0.043</td>
</tr>
<tr>
<td>S-hsCRP (mg/L)</td>
<td>2.98</td>
<td>0.42</td>
<td>0.001</td>
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</tbody>
</table>
Biomarkers of Premature Aging in Cancer Survivors

Clonal Hematopoiesis Associated With Adverse Outcomes After Autologous Stem-Cell Transplantation for Lymphoma

J Clin Oncol 35. © 2017
Physiologic Measures of Premature Aging

$\text{VO}_2\text{peak}$

Product of cardiac output and A-V oxygen difference

Inversely correlated with death from CV disease and all-cause mortality

*Sedentary adult women*

*Patients with breast cancer*

*Biol Blood Marrow Transplant. 2017 Apr;23(4):700-705*
Non-Relapse Mortality

Risk of All-Cause Mortality
HR: 1.4, p=0.002*

*Adjusted for: Age, race/eth, risk of relapse, KPS, HCT source, aGVHD
Cancer Survivorship Research to Improve Outcomes

Cancer Diagnosis and Treatment

"Primary" Prevention

"Secondary" Prevention

Implementation

CANCER SURVIVORS

Evidence-based Clinical Care Guidelines

Health-related and QOL Outcomes

High-risk Groups

Development of Intervention Strategies

Clinical Trials of Efficacy
Cancer/HCT Survivorship Screening Recommendations

Children’s Oncology Group
Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer

Version 4.0 – October 2013

Recommended Screening and Preventive Practices for Long-Term Survivors after Hematopoietic Cell Transplantation

Navneet S. Majhail,1,2 J. Douglas Rizzo,3 Stephanie J. Lee,4 Mahmoud Aljurf,5 Yashiko Atsuta,6 Carmem Bonfim,2 Linda J. Burns,8 Noeem Chaudhri,7 Stella Davies,9 Shinichiro Okamoto,10 Adriana Seber,11 Gerard Socie,1,2 Jeff Szer,11 Mario Teresa Van Lint,14 John R. Wingard,1,5 Andre Tichelli16 for the Center for International Blood and Marrow Transplant Research (CIBMTR), American Society for 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)
Utility of screening/surveillance

Screening value

Benefits

Harms plus costs

Harms

Costs

Low Value

High Value

Low Value

Screening intensity

Low

Optimal

High

Measuring cost-effectiveness of screening/surveillance

ACC/AHA Classification
- Stage A: At high risk for CHF, without heart disease
- Stage B: Asymptomatic LV dysfunction
- Stage C: Symptomatic heart disease
- Stage D: Symptomatic, advanced heart disease requiring interventions

Life Cycle Model AC-exposed CCS
- No heart abnormality
- Asymptomatic LV dysfunction
- Symptomatic heart disease
- Death

10 million simulations

Transition probabilities

At risk for heart failure

At risk for heart failure

Clinical heart failure

Anthracycline
Improving accuracy of late effects risk prediction in HCT survivors

45% of cases with CHF exposed to <250 mg/m$^2$

Cases  
(Heart Failure)

Controls  
(No Heart Failure)

For a given exposure, there is marked variation in prevalence and severity of heart failure that is not explained exclusively by clinical risk factors.

Clinical risk factors:
- Age at exposure
- Female gender
- Anthracycline dose
- Comorbidities

Genetic risk factors:
- Drug metabolism and Transport
- Generation of reactive oxygen species
- Anti-oxidant defense
- DNA repair pathways
- Renin-angiotensin system

Therapy-Related Heart Failure
**Anthracycline**

- **Prescribed dose**
  - ABCC1, ABCC2

- **Internal dose**
  - CBR1, CBR3

**NAD(P)H oxidase multi-enzyme complex**

- **Dox-quinone**
  - NQO1
  - Aconitase/IRP1
  - Loss of Fe Homeostasis

**Energy/Redox Impairment**

<table>
<thead>
<tr>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>2.9</td>
</tr>
<tr>
<td>Chest XRT</td>
<td>4.7</td>
</tr>
<tr>
<td>HFE (rs1799945), GC/GG</td>
<td>2.5</td>
</tr>
<tr>
<td>RAC2 (rs13058338), TA/AA</td>
<td>2.8</td>
</tr>
<tr>
<td>ABCC2 (rs818710), GA/AA</td>
<td>4.3</td>
</tr>
</tbody>
</table>

- **ROS**

- **Mitochondrial dysfunction**

- **Myocyte apoptosis**

- **Maladaptive LV Remodeling**

- **Asymptomatic ↓ LVEF/FS**

- **Heart Failure**
Improving accuracy of late effects risk prediction in HCT survivors

Clinical and Genetic Determinants of Cardiomyopathy Risk among Hematopoietic Cell Transplantation Survivors

Biol Blood Marrow Transplant 22 (2016) 1094–1101

Hyaluronan Synthase 3 Variant and Anthracycline-Related Cardiomyopathy: A Report From the Children’s Oncology Group


CELF4 Variant and Anthracycline-Related Cardiomyopathy: A Children’s Oncology Group Genome-Wide Association Study

TRANSLATING OBSERVATIONAL STUDIES INTO PREVENTION
Subsequent Malignancy: Breast Cancer

Radiation exposed Survivors of Childhood and AYA Cancer N=230

Low Dose Tamoxifen for Radiation-Induced Breast Cancer Risk Reduction (R01 CA140245 [Palomares])

- Tamoxifen 5mg x 2 yr (N=115)
- Placebo x 2 years N=115

Endpoints: Mammographic Density, Histologic & Circulating Markers
Cardiovascular Disease: Heart Failure

**Phase IIb randomized placebo-controlled clinical trial**

Childhood CA survivors treated with high dose anthracycline (≥250 mg/m²)

- **N= 250**
  - 2wk run-in 3.125mg/day
  - If tolerating, escalate
  - Carvedilol 12.5mg/day total 2 yrs
  - N=125

- 6.25mg/day x 1 month Carvedilol

- Equivalent evaluation and dose mod.

- Placebo x 2 years
  - N=125

NIH/NCI: R01CA196854 (Armenian)
Leukemia & Lymphoma Society
St. Baldrick’s Foundation
Subsequent Malignancy: HPV Vaccination

Cancer Survivors
Age 9-26 years; 12-60 months following completion of systemic cancer therapy

R01 CA166559 (Landier, Klosky)

Specific Aim 1
Cross-Sectional Survey
Prevalence of vaccine initiation
Determinants of vaccine non-initiation
Sociodemographic
Behavioral
Medical
Willing to receive 3-dose HPV vaccine series?
HPV vaccine initiation?
Yes
No
Recruited for Aim 1?
Yes
No
Meets Eligibility for Aim 2?
Yes
No
STOP

Specific Aim 2
Single Arm Phase II Open Label Trial
Stratified by age and gender
3-dose HPV vaccine series
- Safety/Tolerability
- Immunogenicity
- Response/Persistence

Abbreviations: GMT = HPV-specific geometric mean titer; SP= Seropositivity; Quant Ig = Quantitative immunoglobulins; Total Ig = HPV-specific total immunoglobulins
Bridging the Gap in Follow-up Through Innovation

Cancer Epidemiol Biomarkers Prev 2007; 16(4): 834

Bridging the Gap in Follow-up Through Innovation

Traditional paternalistic model of care

Empowered Physician ➔ Empowered Patient

- Patient completely reliant on HCP to receive information, diagnosis and referral
- Difficult for patients to navigate within and between health and social care
- Interventions usually in response to physical evidence from patient

Empowered patient sharing ownership

Empowered Physician ➔ Empowered Patient

- Patient informed whenever and wherever, using their interoperable medical record
- Co-creation of care packages, proactive prevention, rapid access to services
- Technology enabled support and self-management
Caltech-COH Biomedical Research Initiative (Armenian [COH], Gharib [Cal Tech])
R21 CA178344 (Armenian)
Organization of the LTFU visit

- Survivorship care plan
  - History and treatment summary
  - Comorbidities
  - HCT-specific information
    - Type of HCT
    - Conditioning
    - GvHD

- Risk profile for late complications
  - Present
  - Possible

**Preparation**
- Review all relevant documents
- Organize visit according to risk profile
- Team meeting (roles)

**Clinic visit**
- Medical consultation
- Specialized investigations
- Psychosocial assessment
- Counseling & answering questions

**Follow-up**
- Assemble and summarize information
- Multidisciplinary discussion of probs.
- Recommendations for follow-up
Take home messages

- Late effects of HCT a reality, but not a fatality
  - Cardiovascular complications, Osteopenia, infertility

- The occurrence of late effects and well-being not a contradiction
  - Regular systematic screening allows prevention and early treatment of late complications
  - Counseling re: healthy lifestyle part of long-term care

- Long-term survivorship care should also include
  - Training and education of healthcare providers
  - Healthcare agencies/resources of need for lifelong care
  - Research opportunities to address gaps in knowledge