Cardiovascular Complications in Survivors after BMT: Risk Factors and Strategies for Keeping your Heart Healthy

K. Scott Baker, MD, MS
Director, Pediatric Blood and Marrow Transplant and Survivorship Programs
Fred Hutchinson Cancer Research Center
Seattle, WA
Goals for today’s talk…

• To learn about what part of cancer treatment and/or bone marrow transplant affects the heart
• What do you need to know for screening and long-term follow-up
• What can you do to help prevent heart problems
Risk Factors for Late Complications

Cardiovascular Complications

Cardiac Dysfunction

Atherosclerosis

Arrhythmia

Reno-vascular

Narrowed coronary artery

Plaque (cholesterol and other fatty substances)
## Cardiovascular complication from cancer and cancer therapy

<table>
<thead>
<tr>
<th>Chemotherapy Induced</th>
<th>Radiation Induced</th>
<th>Multifactorial: Cancer and Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cardiomyopathy</td>
<td>• Valvular heart disease</td>
<td>• High Blood Pressure</td>
</tr>
<tr>
<td>• Heart dysfunction</td>
<td>• Pericardium (lining around heart) problems</td>
<td>• Cholesterol/ Lipid Problems</td>
</tr>
<tr>
<td>• Heart Failure</td>
<td>• Problem in the cardiac rhythm</td>
<td>• Metabolic Syndrome</td>
</tr>
<tr>
<td></td>
<td>• Blockage of the arteries</td>
<td>• Body composition abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cardiovascular Diseases (CVD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Heart attack, strokes, etc</td>
</tr>
</tbody>
</table>
CHEMOTHERAPY INDUCED CARDIOTOXICITY

Normal Heart

Heart muscle pumps blood out of the left ventricle.

Heart Failure

Weakened heart muscle cannot pump enough blood.
Congestive Heart failure is a chronic, progressive condition in which the heart muscle is unable to pump enough blood through to meet the body's needs for blood and oxygen.

Basically, the heart can't keep up with its workload.

– this can be asymptomatic!
Drugs that can induced cardiotoxicity

- **Anthracyclines**
  - Adriamycin (Doxorubicin, leukemias, lymphomas)
  - Daunorubicin (Cerubidine, leukemias)
  - Cyclophosphamide (Genoxal, Mitoxan)

- **Targeted Therapies**
  - Epirubicin (Ellence, breast cancer)
  - Osemertinib (Tagrisso, lung cancer)
    - Trastuzumab (Herceptin, breast cancer)
    - Bevacizumab (Avastin)
    - Sorafenib (Nexavar)
Anthracycline cardiotoxicity

Doxorubicin dose | Incidence of LV dysfunction
---|---
400 mg/m² | 3-5%
550 mg/m² | 7-26%
700 mg/m² | 18-48%

Ewer MS. Nat Rev Cardiol. 12; 547-558 2015
Defining cardiotoxicity: Echocardiogram

- Decrease of the left ventricular ejection fraction below the baseline after chemotherapy
- Normal LVEF ~50-70 %

The Ejection Fraction compares the amount of blood in the heart to the amount of blood pumped out. The fraction or percentage helps describe how well the heart is pumping blood to the body.
Symptoms of Congestive Heart Failure

- Shortness of breath
- Increased heart rate
- Severe fatigue preventing exercise
- Very swollen feet or ankles (so swollen that if a finger is pressed firmly on the area for few seconds it leaves an indentation)
- Cough and wheezing that doesn’t go away
- Lack of appetite, nausea
Which patients after BMT are at increased risk for developing cardiovascular disease?

Risk factors:

- High doses anthracycline (≥ 250 mg/m² doxorubicin, ≥ 600 mg/m² epirubicin)
- High doses radiation therapy (> 30 Gy)
- **Low doses anthracycline and radiation therapy**
- Low doses anthracycline or trastuzumab + 2 CV risk factors

Genetic factors:

- Age (U-Shape)
- Female gender

Smoking
- High BP
- Diabetes
- Dyslipidemia
- Obesity
- Sedentary lifestyle

Low ejection fraction < 50%
- Prior heart attack
- Heart valve disease
- Kidney disease
Clustering of CVD and Cancer Rates

Heart Disease Death Rates, 2014-2016
Adults, Ages 35+, by County

Rates are spatially smoothed to enhance the stability of rates in counties with small populations.

Data Sources:
- National Vital Statistics System
- National Center for Health Statistics
- www.cdc.gov/nchs/maps

Rates of Cancer Deaths in the United States
All Types of Cancer, All Ages, All Races/Ethnicities, Both Sexes

<table>
<thead>
<tr>
<th>Rate per 100,000 people</th>
</tr>
</thead>
<tbody>
<tr>
<td>127.9 - 155.1</td>
</tr>
<tr>
<td>155.5 - 164.1</td>
</tr>
<tr>
<td>164.6 - 174.8</td>
</tr>
<tr>
<td>177.4 - 199.3</td>
</tr>
</tbody>
</table>
The Metabolic Syndrome...

- A cluster of metabolic disorders related to insulin resistance that predisposes to type 2 diabetes and atherosclerotic disease.

Characterized by:

- Central obesity
- Glucose intolerance
- Dyslipidemia
- Hypertension
Third National Cholesterol Education Program Adult Treatment Panel III (ATP III) Criteria for Metabolic Syndrome:
3 or more of the following

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Adults</th>
<th>Adolescents*</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Triglyceride Level, mg/dL</td>
<td>≥150</td>
<td>≥110</td>
</tr>
<tr>
<td>Low HDL-C level, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>&lt;40</td>
<td>≤40</td>
</tr>
<tr>
<td>Females</td>
<td>&lt;50</td>
<td>≤40</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>waist circumference, cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>&gt;102</td>
<td>≥90th Percentile</td>
</tr>
<tr>
<td>Females</td>
<td>&gt;88</td>
<td>≥90th Percentile</td>
</tr>
<tr>
<td>High fasting glucose level, mg/dL</td>
<td>≥100</td>
<td>≥100</td>
</tr>
<tr>
<td>High blood pressure, mm Hg</td>
<td>≥130/85</td>
<td>≥90th Percentile</td>
</tr>
</tbody>
</table>

*ATP III criteria modification for adolescents (age 12-19 years) as described by Cook et al, 2003
Adjusted for age, sex, Tanner stage
CV Risk Factors - Lipid Levels

### Total Cholesterol

- **Effect Size**
  - All Survivors
  - TBI+CNS
  - TBI
  - Chemo Only

### Triglycerides

- **Effect Size**
  - All Survivors
  - TBI+CNS
  - TBI
  - Chemo Only

### HDL Cholesterol

- **Effect Size**
  - All Survivors
  - TBI+CNS
  - TBI
  - Chemo Only

### LDL Cholesterol

- **Effect Size**
  - All Survivors
  - TBI+CNS
  - TBI
  - Chemo Only

**No PFM Adjustment**

**Adjusted PFM**

Adjusted for age, sex, Tanner stage
CV Risk Factors - Insulin Metabolism

M-lbm

HOMA

Blood Glucose

Insulin

- No PFM Adjustment
- Adjusted PFM
  Adjusted for age, sex, Tanner stage
Summary

• Changes in body composition (loss of muscle mass, increased fat mass) result in normal BMI, but likely contributes to resistance to insulin

• Adverse impact of cancer therapies on body composition and development of insulin resistance may increase the risk of CV disease and diabetes in survivors
# Spectrum of Radiation Damage to Heart

<table>
<thead>
<tr>
<th>Structure</th>
<th>Abnormality</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardium</td>
<td>![Pericarditis Image]</td>
<td>Heart Failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abdominal distention</td>
</tr>
<tr>
<td>Heart Muscle</td>
<td></td>
<td>Heart Failure</td>
</tr>
<tr>
<td>Cardiac Valves damage</td>
<td>![Heart Valve Disease Image]</td>
<td>Murmur/ Heart Failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chest Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lightheadedness</td>
</tr>
<tr>
<td>Blockage of the arteries</td>
<td>![Heart Attack/ Stroke Image]</td>
<td>Heart Attack/ Stroke</td>
</tr>
<tr>
<td>Electrical complications</td>
<td>![ECG Recording Image]</td>
<td>Heart Block</td>
</tr>
</tbody>
</table>
Radiation therapy

Damage of the arteries and cardiac valves

- Fibrosis (scarring)

- Coronary artery disease
- Heart failure
- Pericardial constriction
- Valvular disease
- Stroke

**Risk factors:**
- Higher radiation dose
- Larger volume exposed
- Younger age
- Adjuvant chemo
- Type of radiation source
- CV risk factors

Chen-Scarabelli C et al. JNC 2016 May 25
## What about non-treatment Risk Factors?

<table>
<thead>
<tr>
<th>What You Can Change?</th>
<th>What You Can’t Change?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Activity</td>
<td>Age</td>
</tr>
<tr>
<td>Life Stress</td>
<td>Gender</td>
</tr>
<tr>
<td>High Blood Pressure</td>
<td>Family History</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>High Cholesterol &amp; Triglycerides</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Unhealthy Diet (HIGH in saturated fat &amp; calories; LOW in fresh fruit, veggies, whole grains &amp; fish)</td>
<td></td>
</tr>
</tbody>
</table>
### Always Know Your Numbers!

<table>
<thead>
<tr>
<th>Test</th>
<th>Ideal Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Cholesterol</strong></td>
<td>&lt;200 mg/dl</td>
</tr>
<tr>
<td><strong>“Bad Cholesterol” LDL</strong></td>
<td>&lt;100 mg/dl (best)</td>
</tr>
<tr>
<td>(Low Density Lipoprotein Cholesterol)</td>
<td>&lt;130 mg/dl (OK)</td>
</tr>
<tr>
<td><strong>“Good Cholesterol” HDL</strong></td>
<td>&gt;50 mg/dL women</td>
</tr>
<tr>
<td>(High Density Lipoprotein Cholesterol)</td>
<td>&gt;40 mg/dL men</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td>&lt;150 mg/dl</td>
</tr>
<tr>
<td><strong>Fasting Glucose</strong></td>
<td>&lt;100 mg/dl</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td>&lt;120/80 mmHg</td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td>&lt;25</td>
</tr>
<tr>
<td><strong>Waist Circumference</strong></td>
<td>&lt;35 inches women</td>
</tr>
<tr>
<td></td>
<td>&lt;40 inches men</td>
</tr>
<tr>
<td>Screening (condition)</td>
<td>BMT Survivors</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Check at every office visit or at least annually, more frequent if on medications</td>
</tr>
<tr>
<td>Fasting lipids (dyslipidemia)</td>
<td>Annually, more frequent if on therapy</td>
</tr>
<tr>
<td>EKG / Echo (cardiomyopathy)</td>
<td>Depends upon risk factors and/or symptoms (anthracycline dose, radiation exposure, etc) - Talk to your BMT Team</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>Annually, more frequent if high/borderline high</td>
</tr>
</tbody>
</table>
Allogeneic and Autologous Transplant Guidelines
• **Discuss with your healthcare provider:**
  – Reasonable weight goals
  – Physical activity restrictions, if any
  – Diet/nutrition counseling
  – Help with tobacco cessation
  – *Control of high blood pressure, cholesterol, and diabetes if relevant*
Check your weight status

Healthy Weight

Healthy Weight

Assessing Your Weight

Body Mass Index (BMI)

About Adult BMI

Adult BMI Calculator

This calculator provides BMI and the corresponding BMI weight status category. Use this calculator for adults, 20 years old and older. For children and teens, 2 through 19 years old, use the BMI Calculator for Children and Teens.

For the information you entered:

Height: 5 feet, 9 inches

Weight: 170 pounds

Your BMI is 25.1, indicating your weight is in the Overweight category for adults of your height.

For your height, a normal weight range would be from 125 to 169 pounds.

People who are overweight or obese are at higher risk for chronic conditions such as high blood pressure, diabetes, and high cholesterol.

Search: “CDC BMI calculator”
But…. if you have had a BMT remember that a normal BMI may not give you the full picture of your body composition/body fat status and a DXA scan or some other test may be required.
Are you getting enough exercise?

**Physical Activity**

**Physical Activity Basics**

How much physical activity do you need?

Regular physical activity helps improve your overall health and fitness, and reduces your risk for many chronic diseases.

Fitting regular exercise into your daily schedule may seem difficult at first, but the 2008 Physical Activity Guidelines for Americans are more flexible than ever, giving you the freedom to reach your physical activity goals through different types and amounts of activities each week. It’s easier than you think!

**Physical Activity Guidelines**

- **Children**: 6 to 17 years old
- **Older Adults**: 65 years or older
- **Adults**: 18 to 64 years old
- **Pregnant or Postpartum Women**

[https://www.cdc.gov/physicalactivity/basics/index.htm](https://www.cdc.gov/physicalactivity/basics/index.htm)
Adults (18-64) need at least:

- 2 hours and 30 minutes (150 minutes) of **moderate-intensity aerobic activity** (i.e., brisk walking) every week

  **OR**

- 1 hour and 15 minutes (75 minutes) of **vigorous-intensity aerobic activity** (i.e., jogging or running) every week

  **AND**

- **Muscle-strengthening activities** on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders, and arms).

*10 minutes at a time is fine!*
Exercise & Cancer Prevention

• Exercise is definitely safe for cancer survivors *(American College Sports Medicine 2010)*
  – Improves quality of life
  – Reduces fatigue

• May reduce recurrence of some cancers
  – Suggestive evidence for breast, colorectal, prostate
  – Mainly from “observational” studies and not from randomized trials
Analyze your diet

There is more than one way to eat healthfully and every day is an opportunity to try new foods to get the most nutrition and meet your personal health needs. Choose foods from each food group and limit saturated fat, sodium, and sugar. A healthy eating style is sustainable, affordable, and enjoyable.

Everything You Eat and Drink Matters

What and how much you eat and drink, along with regular physical activity, can help you maintain a healthy weight and lower your risk of disease.
Stay Healthy

Many cancer deaths could be prevented by making healthy choices like not smoking, staying at a healthy weight, eating right, keeping active, and getting recommended screening tests. In this section you can learn how to help lower your chances of getting cancer, plus what screening tests the American Cancer Society recommends, and when.

Stay Healthy Topics

- Stay Away from Tobacco
- Eat Healthy and Get Active
- Be Safe in the Sun
- Other Ways to Protect Yourself
- Find Cancer Early
- ACS Programs to Help You Stay Well
- Information for Health Care Professionals

Tools and Calculators
To Do’s

- Find out your treatment history (radiation, anthracycline chemotherapy)
- If you’re still smoking, talk to your doctor about trying to quit. Consider enrolling in a tobacco cessation program.
- Try to exercise and eat better – these things may make a difference; certainly can’t hurt! (except sore muscles)
- If you haven’t had a regular check-up in a while, talk to your primary care provider about whether you should be screened for high blood pressure, cholesterol problems, and diabetes.
- If you already have any of these conditions, please take your medicines or talk to your primary care provider about making sure those conditions are well-controlled.
- If your primary care provider is unsure about the best guidelines for a cancer survivor like you, consider asking for a referral to a SURVIVORSHIP program.
QUESTIONS?
Survivorship Program

K. Scott Baker, MD - Director
Karen Syrjala, PhD - Co-Director
Emily Jo Rajotte, MPH, Program Mgr
Elizabeth Kaplan, MD
Leslie Heron, ARNP
Deb Loacker, RN
Emy Jensen, Program Assistant
Joli Bartell, Project Coordinator
Gabriela Emond, Program Assistant

Phone: (206) 667-2814
survivor@fhcrc.org
What are the Priorities in the Cardiovascular Care of Oncology Patients?

Prior to Cancer Therapy
- Identify high cardiovascular risk patients
- Mitigate cardiotoxicity risk

During Cancer Therapy
- Monitoring to identify cardiotoxicity
- Avoid dose interruptions
- Prevent CV events

After Cancer Therapy
- Decrease risk of late Cardiovascular events
- Improve long-term health

Armenian et al. J Clin Oncol 35:893-911
Obesity

- Dyslipidemia
- Hypertension
- INSULIN RESISTANCE (Hyperinsulinemia)
- Type 2 Diabetes
- Atherosclerotic Cardiovascular Disease
Impact of Sedentary Lifestyle
Full range of disease

- Baseline ECG
- Baseline LVEF assessment

Diagnostic Testing → Cancer Diagnosis → Treatment/Prevention

- "Primordial Prevention"

- Treat comorbidities
- Lifestyle modification
- Limit anthracycline dose
- Consider cardioprotective meds
- Exercise training
- Consult cardiology
- Interrupt cardiotoxic therapy
- Initiate HF therapies
- Check cardiac biomarkers
- Consider exercise testing
- Rule out other HF causes
- Repeat LVEF evaluations