Cardiovascular Risk in Patients Undergoing Bone Marrow Transplant: How to Assess?

Saro Armenian, DO, MPH
Joerg Hermann, MD
General indications for BMT/HCT

- Dose intensity for malignant tumor
- Graft vs. Tumor
- Marrow failure
- Graft vs. Autoimmune process (GVHI)
- Gene replacement or therapy
Practical BMT/HCT

Allogeneic

• Stem cell source: other
• High dose therapy with immunotherapy
  – Anti-tumor and building better immunity
• Related
• Unrelated: matched, haploidentical
• Cord blood

Autologous: no immunologic conflict

• Stem cell source: self; as “rescue” from high dose chemo
  – “marrow lethal dose”
Elements of BMT/HCT

- **Selection of donor**
  - Based on tissue typing of 6-10 HLA antigens in allogeneic transplantation
  - Tissue typing unnecessary in autologous transplantation

- **Harvest of stem cells from donor**
  - Bone marrow harvest or pheresis of peripheral blood

- **Preparative regimen**
  - Chemo-radiation for ablation and immune suppression

- **Stem cell infusion**

- **Post-transplant supportive care**
  - Autologous 100 days
  - Allogeneic 180 days or longer for tolerance to develop
Increasing number of transplants

Annual Number of Transplant Recipients in the US by Transplant type

- Autologous
- Allogeneic

* 2013 Data incomplete
Long-term Survival after HCT

Growing number of long-term survivors


HCT Survivors: Projections

All Survivors

Number of Survivors, $x10^3$

Year

2009 109
2015 164
2020 242
2025 354
2030 502

Autologous
Allogeneic Related Donor
Allogeneic unrelated Donor

Survivors by Transplant Type

Number of Survivors, $x10^3$

Year

2009 67
2015 94
2020 137
2025 202
2030 294

HCT Survivors: Projections

Chronic Health Conditions after HCT

Cardiovascular complications

Cardiac Dysfunction/
heart failure

Atherosclerosis

Reno-vascular

Arrhythmia
Cardiovascular disease: HCT Survivors

- Cardiovascular Death
- Cardiomyopathy or Heart Failure
- Ischemic Heart Disease
- Stroke
Cardiovascular risk factors: \textit{HCT Survivors}

\begin{itemize}
\item Hypertension
\item Renal Disease
\item Dyslipidemia
\item Diabetes Mellitus
\end{itemize}
Cardiovascular risk factors and CVD

Blood, 2012, 120: 4505-12
Nature of the problem

↑ Baseline CV Risk Factors ➔ Cancer Diagnosis ➔ ↓ Cardiovascular Reserve Capacity (CVRC) ➔ CV Toxicity

Direct

Therapy-related (Pre-, During, Post-HCT) exposures

Indirect

Aging
Modifiable CV Risk Factors (HTN, Obesity, Dyslipidemia, Diabetes)
Heart failure HCT survivors: Cumulative anthracycline dose

\[ \text{J Clin Oncol, 2008, 26: 5537-43} \]
\[ \text{Blood, 2011, 118: 6023-9} \]

\[ \text{↑ Female} \]
\[ \text{↑ Chest Radiation} \]

\text{Conditioning-related exposures do not contribute to long-term HF risk}
CV Risk Factors and Heart Failure: 

**HCT Survivors**

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† p<0.05

*Blood, 2011, 118: 6023-9*
Premature atherosclerosis

- Primary disease
  - Familial risk factors
  - Pre-HCT exposures
  - Comorbidities
- HCT
  - Conditioning
  - GVHD
- Clinical event
  - De novo CV risk factors
  - Clinically apparent cardiovascular disease

Vascular endothelial lesions

Enhancement of atherosclerosis

If the iliac clot enlarges to completely block the artery at vessel supplied by that artery begins to die below the stenosis.
Arterial disease by HCT type
Case #1

58 yo female, referred for Cardiology Consultation for cardiomyopathy

• No cardiopulmonary symptoms of any kind currently
• 2 months ago palpitations, dyspnea, chest tightness at the time of apheresis
• 1 month ago severe upper respiratory infection, pneumonia with respiratory failure, requiring hospitalization
Case #1 - Past Medical History

- Stage I (T1c, N0, M0) right breast infiltrating ductal carcinoma 6 years ago, s/p doxorubicin + cyclophosphamide x 4 cycles, followed by 12 weekly cycles of paclitaxel, XRT, lapatinib and Herceptin
- GIST 4 years ago, resected and treated with imatinib x 5 months
Case #1 - Past Medical History

• AML, 4 years ago, s/p induction with Idarubicin plus Cytarabine (3+7) and one cycle of high dose Cytarabine consolidation therapy, allo PBSCT with Flu/Bu conditioning
• Chronic GVHD involving skin, eyes, esophagus and liver
• Cardiomyopathy (EF 48% 3 years ago)
• Hypothyroidism
• Hyperlipidemia
Case #1 - Medications

- Carvedilol 3.125 mg BID
- Flovent HFA 220 mcg/actuation Aerosol 2 puffs BID
- Levothyroxine 100 mcg tablet 1 tablet by moth one time daily
- Lisinopril 7.5 mg one time daily
- Montelukast 10 mg every evening
- Omeprazole 40 mg one time daily
- Pravastatin 20 mg one time daily
- Sirolimus 1 mg one time daily
Case #1 - ECG
Case #1 - Echocardiogram

Final Impressions
1. Technically difficult images.
2. Focused study per left ventricular chemotherapy protocol.
3. Left ventricular enlargement.
4. Estimated left ventricular ejection fraction range: 30% – 35%.
5. Generalized left ventricular hypokinesis.
7. Indeterminate left ventricular diastolic function grade.

Findings
# Case #1 - Serial Echocardiograms

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<tr>
<td>SV Index (cc/m²)</td>
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</table>
Case #1 – Cardiac MRI
Case #1 - Cardiac MRI

- Borderline left ventricular enlargement, global hypokinesis with no regional wall motion abnormalities, LVEF 31%.
- Normal right ventricle size and systolic function. RVEF 53%.
- Mild mitral regurgitation.
- Reduced perfusion of ventricular septum at basal and mid levels, at rest and with stress. No regional wall motion abnormalities.
- No delayed myocardial enhancement.
- Small pericardial effusion. Normal pericardial thickness. Small pericardial effusion. No pericardial edema or enhancement. No MRI evidence of ventricular interdependence or constrictive physiology.
What is the Most Likely Etiology of the Reduced Cardiac Function?

A. Hypothyroidism
B. Coronary artery disease
C. Viral myocarditis
D. Anthracycline exposure
E. High dose conditioning therapy for allogenic HCT
F. HER-2 inhibitors (Trastuzumab/Lapatinib)
Heart failure HCT survivors: 
Cumulative anthracycline dose

\[ J \text{ Clin Oncol, 2008, 26: 5537-43} \]
\[ Blood, 2011, 118: 6023-9 \]

↑ Female
↑ Chest Radiation
Anthracycline Dose and Correlation With LVEF Reduction and Heart Failure

Cardiac Function Dynamics
Pediatric Cancer Patients After Doxorubicin

Cardiac Function Dynamics
Pediatric Cancer Patients After Doxorubicin

Anthracyclines \( \geq 250 \text{ mg/m}^2 \)

Chest radiation \( \geq 15 \text{ Gy} \)

Anthracyclines \( \geq 100 \text{ mg/m}^2 \) + Chest radiation \( \geq 10 \text{ Gy} \)

Echo-cardiographic surveillance starting 2 years after therapy, again 5 years after diagnosis, and then every 5 years thereafter

ESMO Clinical Practice
Guideline 2012

Baseline cardiologic evaluation, ECHO

Tnl evaluation at each cycle

Tnl POS
- Enalapril for 1 year
- ECHO end CTh, 3-6-9 months
- ECHO 12 m
- ECHO every 6 months for 5 years

Tnl NEG
- ECHO 12 m
- ECHO every year

Anthracycline-CTh

Tnl not evaluated during CTh

ECHO at end CTh
- No LVD
- ECHO 3 months
- No LVD
- ECHO 6 months
- No LVD
- ECHO 9 months
- No LVD
- ECHO 12 months
- No LVD
- ECHO every year

LVD

ACE + BB

Clinical follow-up

ECHO every year

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Sara H. Amerian, Christina Luchetti, Ana Bals, Joseph Gerson, Louis S. Cornblow, Nadine Dandulski, Susan Demi, Pamela S. Douglas, Jean-Bernard Davard, Michael Ewer, Carol Fabian, Melissa Halpin, Mark Behr, Lee W. Jones, Bonnie Ky, Erica J. Mayer, Janel Matta, Kevin Offinger, Katherine Ray, Kathrynn Ruddy, and Daniel Leshin

ABSTRACT

Purpose
Cardiac dysfunction is a serious adverse effect of certain cancer-directed therapies that can interfere with the efficacy of treatment, decrease quality of life, or impact the actual survival of the patient with cancer. The purpose of this effort was to develop recommendations for prevention and monitoring of cardiac dysfunction in survivors of adult-onset cancers.

Methods
Recommendations were developed by an expert panel with multidisciplinary representation using a systematic review (1996 to 2016) of meta-analyses, randomized clinical trials, observational studies, and clinical experience. Study quality was assessed using established methods, per study design. The guideline recommendations were drafted in part using the Guidelines Into Decision Support methodology.

Results
A total of 104 studies met eligibility criteria and compose the evidence base for the recommendations. The strength of the recommendations in these guidelines is based on the quality, amount, and consistency of the evidence and the balance between benefits and harms.

Recommendations
It is important for health care providers to initiate the discussion regarding the potential for cardiac dysfunction in individuals in whom the risk is sufficiently high before beginning therapy. Certain higher-risk populations of survivors of cancer may benefit from prevention and screening strategies implemented during cancer-directed therapies. Clinical suspicion for cardiac disease should be high and threshold for cardiac evaluation should be low in any survivor who has received potentially cardiotoxic therapy. For certain higher-risk survivors of cancer, routine surveillance with cardiac imaging may be warranted after completion of cancer-directed therapy, so that appropriate interventions can be initiated to halt or even reverse the progression of cardiac dysfunction.

J Clin Oncol 34, © 2016 by American Society of Clinical Oncology

INTRODUCTION

Recent advances in cancer treatment and supportive care have resulted in a growing number of survivors of cancer. With longer survival, attention to the chronic and long-term adverse treatment effects has become increasingly important. Heart failure (HF), presenting during or after completion of cancer treatment, is a well-recognized complication impacting survival and quality of life. The American College of Cardiology (ACC) and American Heart Association (AHA) describe HF as a progressive disease. This process begins with risk factors known to be associated with the development of HF, including the toxicity of chemotherapy and/or radiation (RT) stage A, and is commonly progressive after structural changes to the heart occur. The initial manifestation may be asymptomatic cardiac dysfunction (stage B), which precedes eventual development of overt signs and symptoms (stages C and D). In patients with cancer, onset of either asymptomatic or symptomatic disease may also be responsible for interruption or disqualification of cancer-directed therapy, potentially reducing
5. What are the preferred surveillance and monitoring approaches after treatment in patients at risk for cardiac dysfunction?

**Recommendation 5.1.** Clinicians should complete a careful history and physical examination in survivors of cancer previously treated with potentially cardiotoxic therapies. (Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

**Recommendation 5.1.1.** In individuals with clinical signs or symptoms concerning for cardiac dysfunction, the following approaches should be offered as part of recommended care:

- Echocardiogram for diagnostic workup (Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)
- Cardiac MRI or MUGA if echocardiogram is not available or technically feasible (eg, poor image quality), with preference given to cardiac MRI (Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)
- Serum cardiac biomarkers (troponins, natriuretic peptides) (Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)
- Referral to a cardiologist based on findings (Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

**Recommendation 5.2.** An echocardiogram may be performed between 6 and 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk (Recommendation 1.1) of cardiac dysfunction. (Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

**Recommendation 5.2.1.** Cardiac MRI or MUGA may be offered for surveillance in asymptomatic individuals if an echocardiogram is not available or technically feasible (eg, poor image quality), with preference given to cardiac MRI. (Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

**Recommendation 5.3.** Patients identified to have asymptomatic cardiac dysfunction during routine surveillance should be referred to a cardiologist or a health care provider with cardio-oncology expertise for further assessment and management. (Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong)

**Recommendation 5.4.** No recommendations can be made regarding the frequency and duration of surveillance in patients at increased risk (Recommendation 1.1) who are asymptomatic and have no evidence of cardiac dysfunction on their 6- to 12-month post-treatment echocardiogram. (Informal consensus; relative balance of benefits and harms; Evidence quality: insufficient)

**Recommendation 5.5.** Clinicians should regularly evaluate and manage cardiovascular risk factors such as smoking, hypertension, diabetes, dyslipidemia, and obesity in patients previously treated with cardiotoxic cancer therapies. A heart-healthy lifestyle, including the role of diet and exercise, should be discussed as part of long-term follow-up care. (Evidence based and consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)
5. What are the preferred surveillance and monitoring approaches after treatment in patients at risk for cardiac dysfunction?

Recommendation 5.1. Clinicians should complete a careful history and physical examination in survivors of cancer previously treated with potentially cardiotoxic therapies.

Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong

Recommendation 5.2. An echocardiogram may be performed between 6 and 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk of cardiac dysfunction.

Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong

Cardiac MRI or MUGA if echocardiogram is not available or technically feasible (eg, poor image quality), with preference given to cardiac MRI

Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate

Serum cardiac biomarkers (troponins, natriuretic peptides)

Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate

Referral to a cardiologist based on findings

Informal consensus; benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: strong

Recommendation 5.2.1. An echocardiogram may be performed between 0 and 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk (Recommendation 1.1) of cardiac dysfunction.

Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate

Recommendation 5.2.2. Cardiac MRI or MUGA may be offered for surveillance in asymptomatic individuals if an echocardiogram is not available or technically feasible (eg, poor image quality), with preference given to cardiac MRI.

Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate

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Informal consensus; relative balance of benefits and harms; Evidence quality: insufficient

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Evidence based and consensus; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate
Case #1 – Take Home Points

• pre-HCT anthracycline dose and CV risk factor assessment to determine risk status (low vs. high) is the key initial step for post-HCT cardiomyopathy surveillance efforts

• echocardiogram in at risk patients recommended 6-12 after completion of anthracycline-containing chemotherapy, thereafter the surveillance schedule remains undefined (unless pediatric patients and radiation therapy)

• Important to evaluate for factors that cause cardiomyopathy by itself or reduce the anthracycline threshold
Case #2

39 yo female, referred for Cardiology Consultation

- 10 days ago chest discomfort while lying in bed, initially sharp, then heaviness into the arms
- mild dyspnea and diaphoresis
- resolution of symptoms after 30 minutes
Case #2 – Past Medical History

• AML, dx 10 years ago, s/p chemotherapy (daunorubicin, cytarabine, etoposide, high-dose Ara-C) and matched unrelated donor allogeneic BMT 8 years ago, complicated by late-onset chronic graft-versus-host disease involving skin and GI tract
• Steroid-related DM
• Hyperlipidemia
• Nicotine dependence
• Depression
Case #2 - Medications

- Albuterol 90 mcg/Act 2 puffs q4h PRN
- Aspirin 81 mg per day
- Atorvastatin 80 mg per day
- Metoprolol 25 mg twice a day
- Xanax 0.5 mg twice a day PRN
Case #2 - ECG
What is Your Recommendation?

A. No further testing
B. Chest CT PE protocol
C. Exercise treadmill stress test
D. Exercise stress echocardiogram
E. Coronary angiogram
F. Cardiac troponin T
Case #2 – Laboratory Parameters

CBC

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E’lytes

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<td>142</td>
<td>106</td>
<td>11</td>
<td>128</td>
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</tbody>
</table>

Cardiac biomarkers

- cTnT 0.18, CK-MB 1.7
- NT-pro-BNP 749
Case #2 – Coronary Angiogram
Case #2 – Coronary Angiogram
Case #2 – Coronary Angiogram
Case #2 – CV Risk Evaluation 3 months prior

- FRS 2.6%
- TC 212, HDL 36, LDL 127, TG 243 mg/dL
- BP 116/81 mmHg
- FPG 93 mg/dL
- BMI 19 kg/m²

- Chest CT: “scattered arterial calcifications including coronary”
Premature atherosclerosis

Familial risk factors

Pre-HCT exposures Comorbidities

Conditioning GVHD

De novo CV risk factors

Clinically apparent cardiovascular disease

Vascular endothelial lesions

Enhancement of atherosclerosis
Arterial disease by HCT type
Risk score:
arterial hypertension, dyslipidemia, diabetes, being overweight, smoking, physical inactivity (1 point each)

GVHD, radiation, and age not included!
Case #2 - Take Home Points

• Patients after HCT have an increased risk of (premature) atherosclerosis and represent a vulnerable population
• Traditional risk scores (Framingham) may not be adequate for this population
• Unique risk factors include chemotherapy and radiation exposure as well as graft versus host disease
• Modifiable risk factors should be managed as optimally as possible
Case #3

67-year-old woman, referred for a cardiology consultation

• Starting a few days ago, exertional dyspnea and significant bilateral lower extremity swelling
• Subsequently orthopnea and chest tightness
• Also fever, mucositis, urinary spasms, diarrhea, nausea, and general malaise
Case #3 – Past Medical History

• Stage IV Hodgkin lymphoma, 2 years ago, initial remission after ABVD chemotherapy, recurrence 6 months ago, treatment with bendamustine and brentuximab with CR, then autologous bone marrow transplant 2 weeks ago after BEAM conditioning (BiCNU (Carmustine), Etoposide, Ara-C (Cytarabine), Melphalan)

• Depression
Case #3 - Medications

- Pantoprazole 40 mg IV BID
- Acyclovir 400 mg PO BID
- Cefepime 2 gr IV BID
- Filgrastim 300 mcg SQ per day
- Fluconazole 400 mg IV per day
Case #3 – Vital Signs

- Height: 160.0 cm
- Weight: 62.70 kg
- BMI: 24.492 KG/M²
- Blood pressure: 110/57 mmHg
- Pulse rate: 115/minute
- Respiratory rate: 20/minute
Case #3 – Physical Exam

- General: Patient appears tired.
- Skin: No stasis dermatitis or ulceration.
- Vessels: No carotid bruits. Normal pedal pulses.
- Abdomen: Normal-sized liver and spleen. No abdominal masses or tenderness.
- Extremities: No clubbing or cyanosis. Pitting 2+ to 3+ lower extremity edema to the level of the knee.
## Case #3 – Laboratory Parameters

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### Additional parameters

- AST 33, ALP 96, total bilirubin 0.7, albumin 3.0
- NT-pro-BNP 7396
Case #3 - CXR
Case #3 - Echocardiogram

Final Impressions
1. Normal left ventricular chamber size.
2. Estimated left ventricular ejection fraction: 35%.
3. Generalized left ventricular hypokinesis. Systolic function of the apical segments is best preserved.
4. Borderline decrease in right ventricular systolic function.
5. Moderate mitral valve regurgitation (2 jets).
7. Compared to the report of 09/04/2014 the following changes have occurred: The left ventricular ejection fraction has decreased. Mitral regurgitation is now moderate and there are bilateral pleural effusions.

Findings
OTHER ECHO FINDINGS: Normal inferior vena cava size with normal inspiratory collapse (>50%). Normal abdominal aorta Doppler flow pattern. No intracardiac mass or thrombus, but the left atrial appendage cannot be visualized adequately with transthoracic echo to exclude thrombus in this location. No pericardial effusion. Bilateral pleural effusion. Echo pictures not adequate for strain imaging.
Case #3 – Baseline Echocardiogram

Final Impressions
1. Global averaged left ventricular longitudinal peak systolic strain is normal at −19 % (normal = more negative than −18%).
2. Normal left ventricular chamber size.
3. Calculated 2-D biplane volumetric left ventricular ejection fraction; 59 %.
4. Left atrial enlargement.
5. Mild tricuspid valve regurgitation.
6. Estimated right ventricular systolic pressure 32 mmHg (systolic blood pressure 122 mmHg).

Findings
Which HCT Conditioning Drug has the Highest Cardiotoxicity Risk?

A. Carmustine
B. Cytarabine
C. Cyclophosphamide
D. Fludarabine
E. Ifosfamide
F. Melphalan
# Cardiotoxicity of Conditioning

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<th>Risk factors</th>
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<th>Increased mortality (%)</th>
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<td>Cardiac dysfunction&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Doxo ≥ 400 mg/m²&lt;sup&gt;b&lt;/sup&gt;</td>
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Two single center series from the 1977-1997 era<sup>1,2</sup>:

- <5% cardiovascular complications
- 0.9-1.8% life-threatening CV event

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<sup>1</sup> Bone Marrow Transplant 2001;28:283
<sup>2</sup> J Clin Oncol 1994; 12:998
Risk Factors and Prevention

Dosage
Schedule of administration

Concomitant agents
History of chest wall radiation
History of prior anthracycline treatment

Older age
Overweight
LVEF < 50%

Total dose ≤ maximum-tolerated dose as single agent
Adopt the least cardiotoxic schedule (e.g., multifractionated schedule for HD cyclophosphamide)

>10 studies - overall balance in favor of:
Baseline resting LVEF is not predictive of severe CV events

Morandi P et al. Bone Marrow Transplant 2005;35:323-34
Cyclophosphamide-Induced Heart Disease

- Fulminant acute heart failure in 5-28% and pericardial tamponade in 19% with high dose therapy (180 mg/kg over four days), commonly with cytarabine

- Toxic endothelial damage with extravasation of toxic metabolites $\Rightarrow$ cardiomyocyte dysfunction

- Interstitial hemorrhage and edema $\Rightarrow$ LV wall thickening

- Fibrinous pericarditis with spotty pericardial hemorrhage

Cyclophosphamide-Induced Heart Disease

- Fulminant acute heart failure in 5-28% and pericardial tamponade in 19% with high dose therapy (180 mg/kg over four days), commonly with cytarabine
- LV function with wall thickening 5-15 days after initiation of therapy

Fulminant acute heart failure in 5-28% and pericardial tamponade in 19% with high dose therapy (180 mg/kg over four days), commonly with cytarabine

LV function with wall thickening 5-15 days after initiation of therapy

Ominous sign: declining ECG voltage

Acute mortality up to 20%

Long-term prognosis good

Aggressive support, even use of mechanical support devices to bridge to recovery

Cyclophosphamide-Induced Heart Disease

Case #3 - Take Home Points

• Conditioning therapies for HCT have variable acute (and largely reversible) cardiotoxicity risk
• Any variables that influence drug distribution and metabolism are important (e.g. obesity, older age)
• Risk is increased with combination therapies, prior anthracycline exposure or radiation exposure of the heart and possibly with any reduced cardiac function
• No established CV drug prevention strategies