28-30 JUNE 2018

MASCC/ISOO
ANNUAL MEETING ON SUPPORTIVE CARE IN CANCER

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#MASCC18
Assessment of Cardiac Injury and Toxicity From Cancer Chemotherapy

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Head Non-invasive Imaging
Division pediatric Cardiology
Connecticut Children’s Medical Center
Objectives

- Discuss cardiotoxicity of most commonly used chemotherapeutic agents
- Risk stratification of patients exposed to cardiotoxic medications
- Early imaging and biomarkers for assessment of cardiac injury
- Take-home points
- Future directions
Chemotherapeutic Agents
Anthracycline Induced Cardiotoxicity

1. Oxidative stress model of cardiotoxicity
   - Anthracycline antibiotics (e.g., doxorubicin)
   - Oxidative stress
   - Reactive oxygen species
   - Protein, nucleic acid, lipid oxidation
   - Cellular dysfunction
   - Cell death

2. Topoisomerase-II dependent cell death model of cardiotoxicity
   - Disrupted TopIIβ activity
   - Double-stranded DNA breaks
   - p53 activation, mitochondrial dysfunction, ROS, cell dysfunction and cell death
   - Unwound DNA
   - Supercoiled DNA

3. Alterations in MDR efflux proteins
   - MDR
   - Alterations

4. Decreased mesenchymal and circulating progenitor cells

Carrie G. Lenneman, and Douglas B. Sawyer Circ Res. 2016;118:1008-1020
HER2/ERBB2- Targeted Therapies

Carrie G. Lenneman, and Douglas B. Sawyer Circ Res. 2016;118:1008-1020
Small-molecule tyrosine kinase and VEGF inhibitors

Carrie G. Lenneman, and Douglas B. Sawyer Circ Res. 2016;118:1008-1020
Cardiovascular Side Effects of Chemotherapy and Radiation

Carrie G. Lenneman, and Douglas B. Sawyer Circ Res. 2016;118:1008-1020
Fulminant Myocarditis with Combination Immune Checkpoint Blockade

- Checkpoint inhibitors Cytotoxic T-lymphocyte antigen 4 (PD-1, CTLA-4)

Fulminant Myocarditis with Combination Immune Checkpoint Blockade
Types Anthracycline Cardiotoxicity

**Acute:** vasodilation, hypotension, arrhythmias

**Early onset:** acute myocyte damage with associated left ventricular dysfunction and less commonly pericarditis

**Late Onset Cardiotoxicity**

**Occult:** Structural heart disease without signs and symptoms of heart failure, occurs at least a year after exposure to AC

**Clinically Evident:** 10-20 years after the termination of therapy
Anthracycline Induced Cardio-toxicity

Zeiss C, Gatty D, Toro-Salazar et al, manuscript in progress
Chronic Cardiotoxicity

Zeiss C, Gatty D, Toro-Salazar et al, manuscript in progress
Diffuse Cardiac Fibrosis in AIC

Zeiss C, Gatty D, Toro-Salazar et al, manuscript in progress
Genetic Diversity in AIC

Zeiss C, Gatty D, Toro-Salazar et al, manuscript in progress
Stages in the development of HF and recommended therapy by stage based on published guidelines (ACC/AHA)

- **CANCER TREATMENT**
  - Long term follow-up begins
  - At risk of heart failure
  - Clinical heart failure

- **STAGE A** At high risk for HF but without structural heart disease or symptoms
- **STAGE B** Structural heart disease but without symptoms of HF
- **STAGE C** Structural heart disease with symptoms of HF
- **STAGE D** Refractory HF requiring interventions

**Primary prevention**
- Preventing the initial development of disease
  - Limit lifetime anthracycline exposure
  - Less cardiotoxic analogues
    - Epirubicin
    - Idarubicin
    - Mitoxantrone
  - Alternative drug administration schedules
    - Bolus versus continuous infusion
  - Cardioprotectants
    - Dextrazoxane

**Secondary prevention**
- Prevention of disease before onset of signs and symptoms of illness

**Tertiary prevention**
- Reducing impact of the disease

Adoption of healthy lifestyle
- Aggressive management of modifiable risk factors (hypertension, diabetes)
- Pharmacologic intervention
  - ACE inhibitors
  - β-blockers
Cardiotoxicity Model

Risk Factors:
- Genetic disposition
- Higher cumulative dose
- Female gender
- Radiation therapy
- Greater follow-up timespan
- Prescribed other cardiotoxic medications
- Young age at diagnosis

Exposure to anthracyclines

Acute cardiotoxicity:
- Loss of extracellular matrix
- Stress response (apoptosis)

Compensation

Chronic cardiotoxicity:
- Cardiac hypertrophy
- Microscopic fibrosis

 Decompensation

Heart failure
## The Effect of Risk Factors on Development of Persistent Cardiomyopathy

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Unadjusted OR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years post-chemo</td>
<td>0.93</td>
<td>0.86, 1.01</td>
<td>0.09</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>1.06</td>
<td>0.99, 1.14</td>
<td>0.11</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Gender</td>
<td>0.63</td>
<td>0.25, 1.60</td>
<td>0.33</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Cumulative dose</td>
<td>1.00</td>
<td>1.00, 1.01</td>
<td>0.16</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Radiation to chest</td>
<td>3.16</td>
<td>1.17, 8.54</td>
<td>0.02</td>
<td>2.33</td>
<td>0.77, 6.96</td>
<td>0.13</td>
</tr>
<tr>
<td>Vinca Alkaloids</td>
<td>1.01</td>
<td>0.33, 3.09</td>
<td>0.99</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>BMT</td>
<td>4.66</td>
<td>1.71, 12.76</td>
<td>0.003</td>
<td>4.17</td>
<td>1.37, 12.69</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous heart disease†</td>
<td>5.05</td>
<td>1.84, 13.85</td>
<td>0.002</td>
<td>6.04</td>
<td>2.10, 17.34</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardio-protective drugs</td>
<td>1.92</td>
<td>0.42, 8.67</td>
<td>0.40</td>
<td>---</td>
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<td>---</td>
</tr>
</tbody>
</table>

*The 3 significant risk factors upon univariate analysis were selected as covariates for the multiple logistic regression model (radiation to the chest, BMT and previous heart disease).

†Previous heart disease defined as: presence of congenital heart disease, pericardial effusion/tamponade, SVC syndrome, myocardial dysfunction prior to chemotherapy.

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Toro-Salazar et al. Cardio-Oncology. 2015;1(1).
Effect of Previous Myocardial Dysfunction on Survival

- SF>29%: Cumulative survival was 88% at 10 yrs from diagnosis, 85% at 15 yrs, 84% at 20 yrs, and 82% at 25 yrs in subjects with SF >29%

- SF<29%: Cumulative survival of 71% at 10 years, 66% at 15 yrs 62% at 20 yrs and 54% at 25 yrs in subjects with SF < 29%
# The Effect of Risk Factors on All Cause Mortality

<table>
<thead>
<tr>
<th>Risk Factors¹*</th>
<th>Unadjusted OR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years post-chemo</td>
<td>0.62</td>
<td>0.54, 0.70</td>
<td>&lt;0.001</td>
<td>0.62</td>
<td>0.54, 0.71</td>
<td>&lt;0.001</td>
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<tr>
<td>Age at Diagnosis (yrs)</td>
<td>1.05</td>
<td>1.01, 1.10</td>
<td>0.02</td>
<td>0.94</td>
<td>0.87, 1.02</td>
<td>0.12</td>
</tr>
<tr>
<td>Gender</td>
<td>0.69</td>
<td>0.42, 1.16</td>
<td>0.16</td>
<td>---</td>
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</tr>
<tr>
<td>Cumulative dose</td>
<td>3.77</td>
<td>2.12, 6.71</td>
<td>&lt;0.001</td>
<td>3.17</td>
<td>1.14, 8.85</td>
<td>0.03</td>
</tr>
<tr>
<td>Radiation to chest</td>
<td>1.32</td>
<td>0.66, 2.67</td>
<td>0.43</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Vinca Alkaloids</td>
<td>0.32</td>
<td>0.19, 0.54</td>
<td>&lt;0.001</td>
<td>0.37</td>
<td>0.13, 1.08</td>
<td>0.07</td>
</tr>
<tr>
<td>Previous SF &lt; 29%</td>
<td>4.52</td>
<td>2.62, 7.79</td>
<td>&lt;0.001</td>
<td>6.54</td>
<td>2.40, 17.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMT</td>
<td>4.21</td>
<td>2.19, 8.09</td>
<td>&lt;0.001</td>
<td>5.22</td>
<td>1.57, 17.37</td>
<td>0.007</td>
</tr>
<tr>
<td>Previous heart disease</td>
<td>1.66</td>
<td>0.76, 3.61</td>
<td>0.20</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Cardio-protective drugs</td>
<td>0.71</td>
<td>0.21, 2.39</td>
<td>0.58</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Solid Tumor Diagnosis</td>
<td>3.2</td>
<td>1.94, 5.42</td>
<td>&lt;0.001</td>
<td>4.13</td>
<td>1.72, 9.87</td>
<td>0.001</td>
</tr>
</tbody>
</table>

1 Risk factors for cardiotoxicity include increased length of post-chemotherapy interval (years), younger age at diagnosis, female gender, total cumulative dose ≥240 mg/m², radiation therapy to the chest, treatment with vinca alkaloids, previous shortening fraction < 29%, bone marrow transplant, previous heart disease, non-use of cardio-protective drugs, solid tumor diagnosis

*The 7 significant risk factors upon univariate analysis were selected as covariates for the multiple logistic regression model (increased length post-chemotherapy interval, younger age at diagnosis, total cumulative dose anthracyclines > 240 mg/m², use of vinca alkaloids, previous SF<29%, BMT, and solid tumor diagnosis)
Risk Stratification

CLINICAL CARE PATHWAY
Cardiac Care Guidelines for Chemotherapy Patients

This is a recommended algorithm that applies to patients receiving cardiotoxic chemotherapy medication.

*Time of diagnosis: baseline echo:

LOW RISK

- Obtain echocardiogram
- Encourage compliance with exercise regimens
- Complete fasting lipid profile following induction therapy
- Cardiac MRI, if indicated based on echo
- High risk group: obtain echo every 150 mg/m² cumulative dose until 200 mg/m², then obtain every 50 mg/m²
- Cardiac MRI, observation if needed
- Determine if referral to PT is warranted based on results

MODERATE RISK

- Obtain echocardiogram
- Dexrazoxane unless contraindicated
- Baseline stress testing:
  - Performed following induction therapy for ambulatory patients
  - For ALL patients, it will be performed following induction and at start of maintenance
  - For solid tumor and AML patients, it will be performed off therapy
- Fitnessgram (PACER)
- Encourage compliance with exercise regimens
- Complete fasting lipid profile following induction therapy

HIGH RISK

- Obtain echocardiogram
- To which risk category does the patient belong?

Major risk categories:
- Age:
  - 25 years: 0
  - 1-4 years: 1
  - <1 year: 2
- Gender:
  - Male: 0
  - Female: 1
- Radiation to heart region:
  - None: 0
  - <30 Gy: 1
  - 30-40 Gy: 2
  - >40 Gy: 3
- Alkylating agents:
  - None: 0
  - Vinca alkaloid: 1
- Anthracycline cumulative dose:
  - <101 mg/m²: 0
  - 101 to 150 mg/m²: 1
  - 151 to 200 mg/m²: 2
  - 201 to 250 mg/m²: 3
  - 251 to 300 mg/m²: 5
  - >300 mg/m²: 8
- High dose Cyclophosphamide:
  - None: 0
  - Cyclophosphamide: 1
- Previous heart disease:
  - None: 0
  - Not affecting myocardium: 1
  - Affecting myocardium: 2
- Iron overload:
  - No: 0
  - Yes: 1
- Hypertension:
  - Normal: 0
  - Elevated/Pre-Hypertension: 1
  - Stage 1: 2
  - Stage 2: 3
- Bone Marrow Transplant:
  - None: 0
  - Antithymocyt: 1
  - Allogeneic: 2
- Congestive Heart Failure:
  - No: 0
  - Yes: 1

TOTAL SCORE

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Cancer Therapeutics–Related Cardiac Dysfunction (CTRCD)

- CTRCD defined as a decrease in the LVEF of >10 percentage points, to a value <53% (normal reference value for two-dimensional (2D) echocardiography (2DE) in adults
- No pediatric guidelines available
- Need to go beyond quantification of EF to evaluation of myocardial deformation and adaptive microstructural and microvascular changes

Measurements of Global Systolic Function

Comparison of LVEF following the initiation of AC vs. one year following completion of AC. Percent change in LVEF from initiation of AC to one year following completion of AC.

Early Cardiotoxicity (EF, ESVI)

TCD Low Dose: 158-200 mg/m²
TCD High Dose: 442-450 mg/m²

Late Cardiotoxicity

Myocardial Mechanics: Moving beyond the basics (EF limitations)

- EF is the gold standard for global functional assessment
- Does not consider regional contractile dysfunction
- EF insensitive to alterations in regional performance and may conceal underlying regional dysfunction
Myocardial Strain

3D Circumferential-radial-longitudinal Coordinate System Used For Strain Calculation

Myocardial Strain: The Gold Standard by Tagged Imaging

- Visualization of myocardial deformation without implanting physical markers
HARP Analysis of SA Tagged-Images

![Graph showing data points for Basal, MID, and Apical with respective trend lines.](image-url)
Ultra fast strain imaging with strain-encoding (SENC)

- Left Movie: Short-axis view shows longitudinal strain
- Right Movie: Long-axis view shows circumferential strain
- Each movie took less than a second to acquire and produce from the scanner
- The color scale shows peak strain values in the myocardium
- Arrows point to infarction

Courtesy from Nael Osman, Ph.D. CTO, Myocardial Solutions, Inc.
Tagged Imaging Strain/Early Cardiotoxicity

TCD Low Dose: 158-200 mg/m²
TCD High Dose: 442-450 mg/m²

Occult Cardiotoxicity in Childhood Cancer Survivors Exposed to Anthracycline Therapy

Olga H. Toro-Salazar, Eileen Gillan, Michael T. O'Loughlin, Georgine S. Burke, Joanna Ferranti, Jeffrey Stainsby, Bruce Liang, Wojciech Mazur, Subha V. Raman and Kan N. Hor

Circ Cardiovasc Imaging. 2013;6:873-880; originally published online October 4, 2013; doi: 10.1161/CIRCIMAGING.113.000798

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Print ISSN: 1941-9651. Online ISSN: 1942-0080
Myocardial Strain Magnitude Late Cardiotoxicity

T2 mapping – identifies myocardial edema

- **Basis:** increase myocardial water content changes magnetic relaxation properties influencing the CMR signal (normal value < 60 ms, range 46-80 ms)
- **Example:** acute myocardial infarction with bright areas on T2 mapping, T2-weight STIR and LGE images
T1 Mapping – Detects Diffuse Fibrosis

- Basis: signal intensity of pixels is based on the relaxation of hydrogen nuclei protons – varies between different tissue
- Myocardium with diffuse fibrosis has greater retention of contrast material (ie shorter T1 times)

Chronic Cardiotoxicity

Higher mean ECV was observed in patients with cumulative dose $\geq 400\text{mg/m}^2$ (0.27 vs. 0.21, $p<0.05$)
Correlation of ECV with A) anthracycline dose, B) peak VO$_2$, C) LVmass/LVEDV and D) LV wall thickness/height.
Feasibility of Echocardiographic Techniques to Detect Subclinical CTRCD among High-Dose Patients When Compared with CMR

- ESV values > 29 mL/m²
- 3DE GLS magnitude > −17%
- Decrease in early atrial myocardial velocity of <10 cm/sec at the IVS
- 3DE EF correlated best with EF obtained by CMR

Doppler LV Inflow

Variables Measured:

- Peak E
- Deceleration Time
- Peak A
- A Duration
Doppler Diastolic Waveforms

Transmitral, Pulm. Vein, Mitral annulus
3DE Strain
## Echocardiographic Myocardial Deformation Parameters

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Anthracycline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global (GCS) ¹ (%)</strong></td>
<td>-29.6±3.2</td>
<td>-25.9±3.5</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Global (GCS) ² (%)</strong></td>
<td>-30.0±2.5</td>
<td>-25.5±3.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Longitudinal (GLS) ³ (%)</strong></td>
<td>-20.1±3.4</td>
<td>-19.3±3.6</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Longitudinal (GLS) ⁴ (%)</strong></td>
<td>-21.5±2.0</td>
<td>- 17.6 ±2.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Longitudinal (GLS) ⁵ (%)</strong></td>
<td>-22.5±1.9</td>
<td>-19.7±2.9</td>
<td>0.005</td>
</tr>
</tbody>
</table>

¹ Global (GCS): 2D (Anthracycline n=53; control n=12)  
² Global (GCS): 3D (Anthracycline n= 51)  
³ Longitudinal (GLS) 4ch (anthracycline n=53; control n=12)  
⁴ Longitudinal (GLS) 3D (anthracycline n=51; control n=12)  
⁵ Longitudinal (GLS) 2D 4ch_2ch average (n=48; control n=12)
Effect of Dexrazoxane on Myocardial Injury in Doxorubicin-Treated Children with ALL

July 8, 2004

Figure 2. Percentage of Patients with at Least One Elevated Cardiac Troponin T Level Overall, before Treatment with Doxorubicin, and during Treatment.

An elevated level of troponin T was defined as one that exceeded 0.01 ng per milliliter. The number of patients in whom troponin T was measured at least once during the specified intervals is shown in each bar.
NT-proBNP

- Few studies have shown that higher baseline concentrations of NT-proBNP can predict the development of overt heart failure after cardiotoxic chemotherapy
- Cut-offs of natriuretic peptides that could play a predictive role are still elusive
- A level of NT-proBNP between 300 ng/l and 500 ng/l may indicate patients with a higher propensity for further heart failure
- Further studies needed to validate this findings
Use of integrated imaging and serum biomarker profiles to identify subclinical dysfunction in pediatric cancer patients treated with anthracyclines

Olga H. Toro-Salazar¹,⁷⁺, Ji Hyun Lee¹, Kia N. Zellars², Paige E. Perreault², Kathryn C. Mason², Zhu Wang¹, Kan N. Hor³, Eileen Gillan¹, Caroline J. Zeiss⁴, Daniel M. Gatti⁵, Brooke T. Davey¹, Shelby Kutty⁶, Bruce T. Liang⁷, and Francis G. Spinale²
Micro RNAs
MicroRNAs

Oatmen, Toro-Salazar OH, et al, AJPHeart, in review.
Genetic Susceptibility
Take Home Points

• Need for validated biomarkers that are surrogate end points for clinically important cardiovascular disease and treatments that prevent or control CTRCD

• A cross-disciplinary approach has the best chance to identify and treat cancer patients at risk for cardiotoxicity
Future Directions

• Comprehensive, evidence-based personalized prevention, detection, and treatment strategies for CTRCD are needed

• New knowledge on molecular mechanisms that dictate susceptibility or resistance to CTRCD will inform new therapeutic approaches

• Insights into the regulatory pathways responsible for CTRCD and developing a biomarker signature of early myocardial dysfunction will allow us to identify patients most at risk for severe toxicity, as well as to evaluate new preventive therapies for CHF
Acknowledgement

- Research Team at CCMC
- Echo lab team at CCMC
- MRI lab team at Hartford Hospital (Michael O’Loughlin, MD)

- Division Pediatric Oncology CCMC (Eileen Gillan, MD, Andrea Orsey, MD, Chin Lau, MD, PhD)

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- Milena Furtado, PhD, The Jackson Laboratory – Bar Harbor

- Caroline Zeiss BVSc, Diplomate ACVP & ACLAM, PhD. Professor, Comparative Medicine Yale University School of Medicine

- Dr. Frank Spinale MD, PhD (Biomarker Lab)
- University of South Carolina

- Dr. Bruce Liang MD – Dean of University of Connecticut Med School
- University of Connecticut Health Center

- Dr. Kan Hor MD
- Caroline Wilhelm, MD
- Nationwide Children’s Hospital

- Dr. Wojciech Mazur MD, The Christ Hospital – Ohio
THANK YOU
Molecular Pathways Involved In Cardiotoxicity
Anthracycline Cardio-toxicity

- Anthracycline toxicity is highly prevalent
- Traditional assessment by ejection fraction is inadequate to detect subclinical anthracycline toxicity
- Early cardiac injury is characterized by a progressive decline in global average circumferential (εcc) and longitudinal strain magnitude (εll)
- Tissue characterization (T1 mapping, T2 mapping) identify myocardial edema (early) and microscopic fibrosis (late).
- Biomarkers
Cardiac Matrix Alterations Caused by Adriamycin

Normal

Denuded

Diffuse fibrosis

Caulfield and Bittner (Am J Pathol 1988, 133:298-305)
Anthracycline Protocol

S → Function, myocardial tagging 20 minutes → T1 and T2-mapping → GAD → T1 10 & 20 min → PC: RUPV/MV → MDE
Diagnosis

- Measurement of global and regional myocardial function:
  - Global systolic function: SF, EF
  - Regional Myocardial function (global longitudinal and circumferential strain magnitude)
  - Indices of diastolic function
- CMR tissue characterization (T1 and T2 mapping), MDE
- Biomarkers
  - Biomarkers of inflammation and oxidative stress (CRP and TNF-α)
  - Myocyte injury (Troponin, Caspase-3) and
  - Heart failure: BNP or NT-proBNP)
  - Extracellular matrix (PICP, CITP, MMPs and TIMPs)
  - Growth cell and viability: sRAGE and VEGEF
  - MiRNA
# Pediatric Chemotherapy Agents with Cardiotoxic Potential

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Danorubicin, Doxorubicin (including pegylated liposomal form), Epirubicin, Idarubicin, Mitoxantrone (anthraquinone)</td>
</tr>
<tr>
<td>Ankylating agents</td>
<td>Busulfan, Carboplatin, Cisplatin, Cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide, Mitomycin, Trabectedin</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Clofarabine, Cytarabine, 5-fluorouracil, Methotrexate</td>
</tr>
<tr>
<td>Antimicrotubule agents</td>
<td>Docetaxel, Paclitaxel, Vinblastine, Vincristine, Vinorelbine</td>
</tr>
<tr>
<td>Interleukins</td>
<td>Aldesleukinh</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Alemtuzumab, Bevacizumab, Rituximab, Trastuzumab</td>
</tr>
<tr>
<td>Small-molecule tyrosine kinase and VEGF inhibitors</td>
<td>Dasatinib, Imatinib, Pazopanib, Sorafenib, Sunitinib</td>
</tr>
<tr>
<td>Topoisomerase inhibitor</td>
<td>Etoposide</td>
</tr>
<tr>
<td>Miscellaneous agents</td>
<td>All-trans-retinoic acid, Arsenic, Asparaginase, Bleomycin, Lenalidomide, 6-mercaptopurine, Thalidomide</td>
</tr>
</tbody>
</table>
Concept of Myocardial Strain

- Strain = Myocardial Deformation
- Strain analysis – detects myocardial deformation
- Positive strain = stretching
- Negative strain = shortening