Management of Cardiotoxicity due to Systemic Cancer Therapy
Spectrum of Cardiotoxicity Associated with Anticancer Treatment

• Left Ventricular Dysfunction
  Type 1 cardiac dysfunction
  Type 2 cardiac dysfunction
• Vasospasm and cardiac ischemia (Type 3)
• Hypertension
• Hypotension
• Arrhythmias
• Miscellaneous (pericardial inflammation, valvular abnormalities... )
## Left Ventricular Dysfunction

<table>
<thead>
<tr>
<th><strong>Type 1 Cardiotoxicity</strong> (e.g. Doxorubicin)</th>
<th><strong>Type 2 Cardiotoxicity</strong> (e.g. trastuzumab)</th>
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<td>- May lead to cellular death</td>
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<td>- Permanent damage</td>
<td></td>
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Potential Type 1 Toxicity Intensifiers

- Cyclophosphamide
- Ifosfamide
- Mitomycin C
- Etoposide
- Melphalan
- Vincristine
- Bleomycin
- Paclitaxel
Type 1 Cardiotoxicity

**Anthracyclins**
- Daunorubicin
- Doxorubicin
- Epidoxorubicin
- Idarubicin
  - Lipozomal formulations

**Anthraquinones**
- Mitoxantrone
Type 1 Cardiotoxicity-Pathogenesis

• Free radical induced oxidative stress

• Myocyte membrane peroxidation

• Influx of intracellular Ca^{++}

• Mitochondrial membrane lipid peroxidation
Congestive heart failure as a function of cumulative dose with bolus doxorubicin

Type 1 Cardiotoxicity

Cumulative dose
Congestive heart failure incidence 5 %

Doxorubicin     ---  450-500 mg /m²
Epirubicin      ---  900 mg/m²
Mitoxantrone    ---  140 mg/m²

* CHF rate for Doxorubicin
  550mg/m²₂  %18
  600mg /m²   %36
Type 1 Cardiotoxicity-Morphological Changes

Doxorubicin was given IV every 3-4 weeks. Biopsy specimens were taken approximately 3 weeks following last doxorubicin dose. *Identified by electron microscopy and graded based on the systems of Billingham and Mackay.

Clinical Spectrum of Cardiotoxicity due to Anthracyclins

- Acute (during administration)
- Early (several days to months)
- Late (years to decades)
Clinical Spectrum of Cardiotoxicity due to Anthracyclins

• Damage can start with first administration

• Clinical manifestations of early injury are subtle
  Nonspecific repolarization
  Electrocardiographic changes
  Arrhythmias (atrial fibrillation)
  Symptoms of myocarditis-pericarditis

• These signs and symptoms are generally transient.
Clinical Spectrum of Cardiotoxicity due to Anthracyclins

- Subsequent dosages of anthracyclines add to the initial cardiotoxicity

- With low cumulative dosages, the heart compensates well

- The ejection fraction usually remains normal until the ability of the heart to compensate for myocyte loss has been exceeded
Clinical Spectrum of Cardiotoxicity due to Anthracyclins

- Even with significant loss of myocytes and some drop in resting ejection fraction, the patient may remain fully asymptomatic.

- Some patients progress over weeks.

- Sometimes over decades (nonischemic dilated cardiomyopathy).
Clinical Spectrum of Cardiotoxicity due to Anthracyclins

Prolonged tachycardia following exertion

↓

Tachycardia at rest

↓

Shortness of breath on exertion

↓

Increasing cardiac size

↓

Congestive heart failure.
## Risk Factors for Increased Cardiotoxicity of Type 1 Agents

<table>
<thead>
<tr>
<th>Category</th>
<th>Factors</th>
</tr>
</thead>
</table>
| General                                     | • Previous treatment with the same or any other anthracycline or anthracenedione  
|                                             | • Advanced age                                                          |
|                                             | • Pediatric age                                                         |
|                                             | • Irradiation with a field overlying the heart                          |
| Underlying cardiovascular conditions         | • Aortic stenosis and other valvular abnormalities                       |
|                                             | • Systemic hypertension                                                 |
|                                             | • Cardiomyopathy of any type                                            |
|                                             | • Congenital heart disease                                              |
|                                             | • Any condition associated with an increased left ventricular end-diastolic pressure |
| Other medications                           | Cyclophosphamide                                                        |
|                                             | Trastuzumab                                                             |
|                                             | Paclitaxel                                                              |
|                                             | Mitomycin C                                                             |
## Techniques for Assessing Cardiac Damage of Patients Receiving Type 1 Agents

<table>
<thead>
<tr>
<th>Technique</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electron-microscopic evaluation of cardiac biopsy</td>
<td>• Gold standard&lt;br&gt;• Invasive, potentially dangerous, and expensive&lt;br&gt;• Presently almost never used for clinical assessment</td>
</tr>
<tr>
<td>Changes in the absolute LVEF values</td>
<td>• Late finding&lt;br&gt;• Cannot determine the extent of damage present or the likelihood of clinically relevant damage from subsequent treatments</td>
</tr>
<tr>
<td>MUGA (multigated acquisition cardiac blood-pool scan)</td>
<td>• Radiation exposure&lt;br&gt;• More costly than echocardiography</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>• Additional information on cardiac structure&lt;br&gt;• May be subject to greater interobserver variability</td>
</tr>
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</table>
# Weaknesses of ejection fractions

## Is the change in ejection fraction real?
- Technical variation as a function of the method used to estimate the ejection fraction
- Intraobserver variation

## If the change in ejection fraction is real, is that change related to the drug?
- Is the change sufficiently large for clinical decision making?
- Is the change caused by other biologic variables?
  - Anemia
  - Hormonal variation
  - Tumor shunting
  - Other cardiac stressors, volume status changes...
Monitoring Cardiotoxicity

- Perform **baseline** radionuclide angiocardiography at rest prior to administration of **100 mg/m2 doxorubicin**.

- **Patients with normal baseline LVEF (50 percent)**
  - Perform a second study after **250 to 300 mg/m2**.
  - Repeat study after **400 mg/m2** in patients with known heart disease, radiation exposure, abnormal electrocardiographic results, or cyclophosphamide therapy; **450 mg/m2** in the absence of any these risk factors.

- **Patients with abnormal baseline LVEF (50 percent)**
  - Doxorubicin therapy should **not be initiated with baseline LVEF 30 percent**.
  - In patients with LVEF >30 percent and <50 percent, sequential studies should be obtained prior to each dose.
Discontinue anthracycline

• Decrease of > 15 percentage points within the normal range

• Drop of > 10 percentage points to a level below the lower limit of normal
Cardiac Biomarkers

- Serum Troponins (troponin T and I)
- Brain Natriuretic Peptide (BNP)
  NT-pro-BNP (N-terminal amino acid fragment)
Cardiac troponins predict left ventricular dysfunction from chemotherapy

In a study of 204 patients, left ventricular ejection fraction (LVEF) was significantly reduced at seven months, compared to baseline, in those who who had an elevated level of troponin I (cTnI +) during chemotherapy. In contrast, patients who did not have elevated cTnI (cTnI-) had a transient reduction in LVEF at three months, which returned to baseline at seven months.

* p < 0.001 versus baseline (month 0).
• P < 0.001 cTnI+ versus cTnI-. groups.

# Strategies for Cardioprotection for Anthracycline Type 1 Toxicity

<table>
<thead>
<tr>
<th>Goal</th>
<th>Strategies to achieve goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative dose limitation</td>
<td>Anthracycline dose 200-240 mg/m²</td>
</tr>
<tr>
<td>Reduction of risk factors</td>
<td>• Control dyslipidemia&lt;br&gt;• Eliminate tobacco use</td>
</tr>
<tr>
<td>Modification of the infusion schedule</td>
<td>• Weekly administration&lt;br&gt;• Prolonged infusion (24-96 hrs)</td>
</tr>
<tr>
<td>Alteration of the molecule</td>
<td>Epirubicin</td>
</tr>
<tr>
<td>Alteration of the delivery system</td>
<td>Pegylated and nonpegylated liposomal formulations</td>
</tr>
<tr>
<td>Cardioprotection</td>
<td>Dexrazoxane</td>
</tr>
<tr>
<td>Reduce cardiac wall stress</td>
<td>• Control hypertension&lt;br&gt;• Beta-adrenergic blockers&lt;br&gt;• Angiotensin-converting enzymes&lt;br&gt;• Angiotensin-receptor blockers</td>
</tr>
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</table>
Dexrazoxane- ASCO Guidelines

Breast cancer

• **Initial use in patients with metastatic breast cancer**
  It is recommended that dexrazoxane *not routinely be used*

• **Delayed use in patients with metastatic breast cancer who have received 300 mg/m² of doxorubicin**
  It is suggested that the use of dexrazoxane *be considered for received 300 mg/m²* of doxorubicin in the metastatic setting

• **Use in patients receiving adjuvant chemotherapy for breast cancer**
  The use of dexrazoxane in the adjuvant setting is *not suggested* outside of a clinical trials
Other malignancies

• Use in adult patients with other malignancies

The use of dexrazoxane can be considered in adult patients who have received 300 mg/m2 of doxorubicin-based therapy. Caution in doxorubicin-based therapy which has been shown to improve survival.

• Use in pediatric malignancies

There is insufficient evidence to make a recommendation.

• Use in patients with cardiac risk factors

There is insufficient evidence.

• Dose of dexrazoxane

At a ratio of 10:1 with the doxorubicin dose, administered via slow IV push or short IV infusion 15 to 30 minutes before doxorubicin administration.
Left Ventricular Dysfunction

**Type 1 Cardiotoxicity**  
(eg. Doxorubicin)

- May lead to cellular death
- Damage starts with the first administration
- Changes upon biopsy
- Cumulative dose related
- Permanent damage

**Type 2 Cardiotoxicity**  
(e.g. trastuzumab)

- Cellular dysfunction
- No typical biopsy changes
- Not related to cumulative dose
- Mostly reversible
Type 2 Cardiotoxicity

Functional (contractile) dysfunction without myocyte death

• Trastuzumab

• Lapatinib  asymptomatic CHF--- 0.1 %
  symptomatic CHF--- 1.3 %

• Other agents (some of tyrosine kinase inhibitors ?)
Trastuzumab and Cardiotoxicity

- HER2 is required for cardiac development.

- HER2 expression is high in the fetal myocardium and is required for the development of ventricular muscle and heart valves.

- Cardiac stress increases the expression of neuregulin, a paracrine peptide messenger that activates HER2 by inducing its phosphorylation.
Clinical Spectrum of Trastuzumab Cardiotoxicity

- Asymptomatic fall in LVEF
- Tachycardia may be an early clinical indicator
- Dilated, hypokinetic congestive disease is its late manifestation
- Is not cumulative dose-dependent
- More treatable and more likely to be fully reversible
Trastuzumab and Cardiotoxicity

- Initial anthracycline injury is important
- Secondary insult of trastuzumab acts as a sequential stress
## Trastuzumab and Cardiotoxicity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Congestive Heart Failure %</th>
</tr>
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<tbody>
<tr>
<td>Trastuzumab alone</td>
<td>3-4 %</td>
</tr>
<tr>
<td>Antracycline alone</td>
<td>11 %</td>
</tr>
<tr>
<td>Trastuzumab + anthracycline</td>
<td>27 %</td>
</tr>
<tr>
<td>Paclitaxel alone</td>
<td>1 %</td>
</tr>
<tr>
<td>Trastuzumab+ paclitaxel</td>
<td>13 %</td>
</tr>
</tbody>
</table>
Trastuzumab and Cardiotoxicity

• The timing of the exposure is important

• If the secondary insult of trastuzumab is administered during a period when the anthracycline injury has not yet been stabilized, the resulting damage appears to be far greater

**Adjuvant trastuzumab trials**
NSABP B-31    interval 3 weeks----- 4.1%
HERA           interval 90 days----- 0.8%

**Meta-analysis**  10955 patients
Symptomatic CHF    1.9% (trastuzumab) --- 0.3%
Asymptomatic CHF   13.3% (trastuzumab)--- 6.1%
Monitoring Trastuzumab Cardiotoxicity

• Control LVEF with 3 month intervals

• If the LVEF decreases by >10 points but is >50 percent, continue trastuzumab

• Reassess the LVEF in two to four weeks. If the LVEF is stable or improved, continue trastuzumab

• If there is a further decrease in the LVEF, discontinue trastuzumab

• If the LVEF has decreased more than 30 points, discontinue trastuzumab

• Reassess the LVEF in two to four weeks. Do not resume trastuzumab unless the LVEF improves to >45 percent
Antineoplastic Agents Associated with Ischemia

- 5-Fluorouracil
- Capecitabine
- Vinblastine
- Vincristine
- Bleomycin
- Cisplatin
- Biological response modifiers
Fluoropyrimidines and Cardiotoxicity

• Vascular spasm in reaction to the parent drug and its catabolites (fluoro-beta-alanine and fluoroacetate)

• Decrease in Nitric Oxide (NO) synthetase

• Vasoconstriction in smooth muscle rings, which is reversible with nitrates

• Coronary angiography following the 5-FU cardiotoxic syndrome has not revealed ongoing cardiac spasm
**Fluoropyrimidines and Cardiotoxicity**

**Clinical Spectrum**
Chest pain, anginal symptoms  
Atrial/ventricular arrhythmias  
Myocardial infarction, cardiogenic shock (1.6%)

- Incidence of clinical and/or ECG findings (4%)
- Continuous infusion had a higher rate of cardiotoxicity (6%)
- Addition of leucovorin?

- Prior history of cardiac disease significantly increases risk (15.1% vs. 1.5%, with no cardiac disease history)
Taxanes and Cardiotoxicity

- Paclitaxel causes acute **asymptomatic bradycardia** in up to 30% of patients
- **Early series - 5%** incidence of serious arrhythmias and MI
- **Larger database - 0.1%** of patients suffered from serious bradycardias
- Taxanes **interfere with the metabolism and excretion of anthracyclines** and potentiate anthracycline-induced cardiotoxicity
- Slow infusion of paclitaxel and doxorubicin or **increased time between** doxorubicin and paclitaxel treatments decreased cardiotoxicity
- When combined with paclitaxel, the cumulative doxorubicin dose should not exceed 360 mg/m2, and **doxorubicin should be given before paclitaxel**
Antineoplastic Agents Associated with Arrhythmia

- Paclitaxel
- IL-2
- Vinca alcaloids
- Bleomycin
- Rituximab
- Arsenic trioxide
- Cisplatin
Antineoplastic Agents Associated with Hypertension

• Bevasizumab (8-18%)
• Sunitinib
• Sorafenib
• Cisplatin
Radiation-Induced Heart Disease

- Pericardial disease
- Acute pericarditis during irradiation
- Delayed acute pericarditis
- Pericardial effusion
- Constrictive pericarditis
- Myocardial dysfunction
- Valvular heart disease
- Electrical conduction abnormalities
- Congestive Heart Disease
The "sliding doors" concept, an example of diverse outcomes based on first diagnosis

Female patient, age 75 y, with occult colorectal carcinoma and ischemic heart disease

Depending on whether the patient first sees:

**Oncologist:**
- Detects fecal blood
- Colonoscopy reveals tumor
- Surgery, FOLFOX+Bevacizumab
- 5-FU induced cardiotoxicity
- Thrombosis, hypertension
- Progressive heart failure -Cardiac insufficiency

**Cardiologist:**
- Finds ischemic heart disease
- Medical therapy and cardiac monitoring
- GI tract bleeding
- Colon cancer detected
- Liver metastases
- Chemotherapy with heart monitoring
- Metastatic disease

**Cardio-Oncologist**

Prevention of Metastasis and HF

A possible cardio-oncology team flowchart

Examples of major mechanisms causing cardiotoxicity of anticancer treatments (black text), clinically used therapeutic agents (green text), and potential protective agents (blue cursive text)
