How to Evaluate the Heart of Elderly Patients

Special considerations regarding cardiotoxicity

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The University of Texas
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Why Discuss Cardiac Disease and Cancer in the Elderly? Let’s Consider...

• These are the two most common disease conditions in the aging population in the developed world:
  – Cardiac disease may pre-exist cancer therapy or may be caused/exacerbated either by it or its treatment
  – Cancer therapy is more effective than ever before at treating cancer, but has a price...
    ▪ Too much cardiac damage and the tumor doesn’t matter
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These Are by Far the Two Most Common Disease Conditions in the Developed World...

Lifetime risk of developing coronary heart disease at age 40 years (U.S.)

Lifetime risk of developing cancer (U.S.)

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## Five-year Relative Survival (%)* During Three Time Periods by Cancer Site

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>50</td>
<td>53</td>
<td>66</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>75</td>
<td>79</td>
<td>89</td>
</tr>
<tr>
<td>Colon</td>
<td>51</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>Leukemia</td>
<td>35</td>
<td>42</td>
<td>49</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>13</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Melanoma</td>
<td>82</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>48</td>
<td>53</td>
<td>63</td>
</tr>
<tr>
<td>Ovary</td>
<td>37</td>
<td>40</td>
<td>45†</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Prostate</td>
<td>69</td>
<td>76</td>
<td>100</td>
</tr>
<tr>
<td>Rectum</td>
<td>49</td>
<td>57</td>
<td>66</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>73</td>
<td>78</td>
<td>82</td>
</tr>
</tbody>
</table>

5-year relative survival rates based on follow up of patients through 2003.

†Recent changes in classification of ovarian cancer have affected 1996-2002 survival rates.

There Is Considerable Confusion!

Even the drug companies sometimes have the wrong idea
Drug firm says cancer drug can raise heart risk
Herceptin significantly increases 'cardiotoxicity' in patients, Genentech says

WASHINGTON - An early review of a recent study showed Genentech Inc.'s cancer drug Herceptin can significantly increase the risk of heart problems, the company said in a letter released by U.S. regulators Wednesday.
How Accurate Is Clinician Reporting of Chemotherapy Adverse Effects?

- Comparative study of patient reporting of eight symptoms with physician reporting of same symptoms

- Physician sensitivity = 47%*

- Physician specificity = 68%*

- **BUT:** elderly patients often do not recognize or do not report their symptoms!

*JCO 2004 22:3485-3490*
Classic Triad of Heart Failure

• **Dyspnea** → common in the elderly for a variety of reasons beyond heart failure

• **Lower extremity edema** → common in the elderly for a variety of reasons beyond heart failure

• **Fatigue** → common in the elderly for a variety of reasons beyond heart failure
Difficulties in Diagnosing “Heart Failure” in the Elderly

- Can be a wide range of presentations
- Many of the symptoms of heart failure overlap with other disease states such as:
  - COPD, obesity, nephrotic syndrome, drug induced or vascular edema, cirrhosis, sleep apnea, and cancer
- How to effectively and efficiently differentiate between these entities?
How to Differentiate Non-specific Signs and Symptoms?

• Lab tests: sometimes helpful
• Natural progression of the process: very helpful
• History and Physical: often the most useful
Principles for the Management of Cardiac Disease Benefit Cancer Patients

- Biomarkers used in Cardiology are also used in Oncology
- Cardiac specific therapy allows for more effective cancer treatment
  - ACE-inhibitors and Beta-blockers for heart failure
  - Anti-anginal treatments for spasm
Are Interventions More Important in the Elderly?

Shorter life expectancy must be balanced with increased vulnerability
Remember, There Is Significant Reversibility of LV Dysfunction With Trastuzumab-related Cardiac Toxicity

Recovery of LV Dysfunction With Standard HF Therapy

Significant Improvement in EF After Optimal HF Therapy

Lenihan et al, HFSA 2008
Carvedilol Appears Protective During Adriamycin-based Chemotherapy

Kalay et al. JACC. Dec 2006. 48:2258-62
ACE Inhibition may be Important for Prevention of Toxicity

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
<th>Total (n=114)</th>
<th>ACEI Group (n=56)</th>
<th>Control Subjects (n=58)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td></td>
<td>0.49*</td>
</tr>
<tr>
<td>Acute pulmonary failure</td>
<td>4 (3)</td>
<td>0 (0)</td>
<td>4 (7)</td>
<td></td>
<td>0.07*</td>
</tr>
<tr>
<td>Heart failure</td>
<td>14 (12)</td>
<td>0 (0)</td>
<td>14 (24)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arrhythmias requiring treatment</td>
<td>11 (10)</td>
<td>1 (2)</td>
<td>10 (17)</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Cumulative events</td>
<td>31</td>
<td>1</td>
<td>30</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Fisher exact test.*

Troponin I Is Valuable in Detecting Cardiotoxicity

<table>
<thead>
<tr>
<th>Cardiac Events in the Study Groups</th>
<th>Total (n=703)</th>
<th>Tnl−/− (n=495)</th>
<th>Tnl+/− (n=145)</th>
<th>Tnl+/+ (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden death</td>
<td>3 (0.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2 (0.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Acute pulmonary failure</td>
<td>3 (0.4)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>47 (7)</td>
<td>1 (0.2)</td>
<td>18 (12)</td>
<td>28 (44)</td>
</tr>
<tr>
<td>Asymptomatic left ventricular dysfunction</td>
<td>37 (5)</td>
<td>2 (0.4)</td>
<td>24 (17)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Life-threatening arrhythmias</td>
<td>17 (2)</td>
<td>2 (0.4)</td>
<td>10 (7)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Conduction disturbances requiring pacemaker implantation</td>
<td>2 (0.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Cumulative events</td>
<td>111 (16)</td>
<td>5 (1)</td>
<td>53 (37)*</td>
<td>53 (84)*†</td>
</tr>
</tbody>
</table>

Values are given as n (%).
*P<0.001 vs Tnl−/− group; †P<0.001 vs Tnl+/− group.
BNP, a Marker of Volume Overload, May Also Be an Effective Marker of Subsequent Myocardial Damage

# How Do We Best Detect Cardiotoxicity by Echo?

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Low dose</th>
<th>Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ejection fraction (%)</strong></td>
<td>63.92 ± 8.65</td>
<td>62.00 ± 7.11</td>
<td>59.10 ± 7.05(^3,^5)</td>
</tr>
<tr>
<td><strong>Sa (cm/s)</strong></td>
<td>11.42 ± 3.17</td>
<td>10.92 ± 2.81</td>
<td>10.02 ± 0.30(^2,^5)</td>
</tr>
<tr>
<td><strong>Fractional shortening (%)</strong></td>
<td>40.84 ± 7.86</td>
<td>39.46 ± 7.22</td>
<td>37.29 ± 7.06(^2)</td>
</tr>
<tr>
<td><strong>E/A ratio</strong></td>
<td>1.07 ± 0.31</td>
<td>1.07 ± 0.38</td>
<td>1.03 ± 0.37</td>
</tr>
<tr>
<td><strong>Ea (cm/s)</strong></td>
<td>11.87 ± 3.88</td>
<td>12.26 ± 4.41</td>
<td>11.36 ± 4.54</td>
</tr>
<tr>
<td><strong>E:Ea ratio</strong></td>
<td>6.97 ± 2.32</td>
<td>6.55 ± 2.00</td>
<td>6.76 ± 2.06</td>
</tr>
<tr>
<td><strong>Tei ratio</strong></td>
<td>0.41 ± 0.12</td>
<td>0.47 ± 0.14(^2)</td>
<td>0.51 ± 0.16(^4)</td>
</tr>
</tbody>
</table>

Sa = longitudinal (annular) systolic contraction, E = transmitral E wave velocity, A = transmitral A wave velocity, Ea = longitudinal (annular) early diastolic relaxation velocity.

*P < 0.05 compared to baseline. \(^2\)P < 0.01 compared to baseline. \(^3\)P < 0.001 compared to baseline. \(^4\)P < 0.0001 compared to baseline. \(^5\)P < 0.05 compared to low dose.

How Do We Best Detect Cardiotoxicity by Echo?

- Ejection fraction
  - Imperfect
- Other parameters of systolic function
  - Sometimes used but probably no advantage
- Diastolic parameters
  - Some feel they offer greater sensitivity

Considerations

• Anthracycline-induced cardiotoxicity is well known and frequently limits treatment, especially in the elderly

• The severity of myocardial damage is dependent on several factors

• Current monitoring techniques, such as MUGA or Echo, have substantial limitations and only detect LV dysfunction after it occurs
So...how big is the problem of cardiotoxicity in the elderly?

It depends on who you ask!
We don’t really know

• **Consider:**
  – Some LV dysfunction may be reversible, and in afflicted patients the problem may not be as great
  – The methods for diagnosing are imperfect
    ▪ Over-inclusive LV determinations

• **But:**
  – Patients are surviving longer
  – There is a better understanding for what heart-failure really is
    ▪ Where should we draw the threshold?
    ▪ When does it become a problem?
Conclusion

• The ability to predict and identify elderly patients who develop cardiotoxicity with chemotherapy needs improvement

• Biomarkers may actually identify those patients long before heart failure is present

• Establishing a method to easily and reliably detect cardiotoxicity can have a profound impact on outcomes

• Treatment for heart failure is especially important in the elderly because of increased risk factors and co-existing disease