Cardiovascular Considerations during Bone Marrow Transplantation

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Presenter Disclosure Information
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I will not discuss off label use or investigational use in my presentation.
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Cardiovascular (CV) Considerations during Bone Marrow Transplantation (BMT)

Objectives:
• Describe common cardiovascular issues encountered during BMT
• Identify high risk populations for cardiac complications during transplant
• Explain strategies to minimize complicating medical issues
• Recognize current clinical research gaps and discuss proposals for ongoing projects
Cardiovascular Considerations during BMT
Potential serious cardiac complications

- QT prolongation/Rhythm disturbances
- Heart Failure
- Myocardial injury
- Endovascular Infection

Cardiovascular Considerations during Bone Marrow Transplantation

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What is the best CV recommendation in preparation for BMT?
A case story

- 66 y/o M, with previous coronary disease (CAD) and aortic valve replacement (AVR) in 2006 developed NHL lymphoma, initially diagnosed in 1/2012
- He was initially treated with anthracycline based therapy for 4 cycles
- He tolerated this until he had heart failure (HF) and a resultant left ventricular ejection fraction (LVEF) of 35%
- Achieved remission at 4 cycles
Case study (cont’d)

- Past hx: Hypertension (HTN), hyperlipidemia, CAD s/p bypass x3 with AVR on carvedilol 6.25mg bid, atorvastatin 40 mg, aspirin, furosemide 40mg, and lisinopril 20mg.
- 3 months after chemo, he developed chest pain and reportedly got a drug eluting stent in the right coronary artery (8/2012)
- He was then seen in December 2012 and was asymptomatic
- Now he has recurrent disease, received 2 cycles of non-anthracycline based therapy (RICE), and is potentially getting a stem cell transplant

Physical Exam and Labs

- 124/77, HR 61, R 18, afebrile
- Jugular venous pressure (JVP) 8 cm. Lungs: few basilar crackles. Cardiac exam: loud S4, PMI enlarged
- No edema, good distal pulses
- Na 136, Cr .9, Cl 21.
- Hgb 11.5, plt 216, LDL 74
- B-type natriuretic peptide (BNP) 107, trop I 0.01

ECG Now
Echocardiography and BNP over time

• Echo 5/2013:
  AV velocity 3.1 m/sec
  LVEF 45-50%

• Previous echos:
  1/12 LVEF 60
  2/12 LVEF 53
  4/12 LVEF 35
  7/12 LVEF 20
  8/12 LVEF 34
  2/13 LVEF 45-50

• BNP
  327 (12/2012)
  147 (2/2013)
  107 (5/2013)
  296 (6/2013)

So what is the best recommendation?

- Further Pre-BMT evaluation?
- Stop clopidogrel, aspirin?
- Go ahead and take your shot?

What is the risk of a drug eluting stent prior to a procedure?
LVEF 38%; RVEF 42%
What do you say now?
- Is he stable to proceed?
- How risky is this BMT?
- Would you do anything else?
  - Consider dental evaluation

Pre-stem cell risk factors are very important

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Cardio-Oncology: How do we manage co-morbidities during BMT?

- 64 y/o with myeloma and amyloidosis (cardiac involvement) who is being treated with bortezomib, lenalidomide for 6 months (on maintenance now) and has achieved a remission
- He is being considered for an autologous BMT

Case 2: Myeloma with amyloid

- PMH: HTN, hyperlipidemia, chronic kidney disease, HF, CAD, AV nodal re-entry tachycardia with AV nodal ablation
- Deep venous thrombosis, sleep apnea
- Meds: carvedilol 6.25mg bid, aspirin, pravastatin 20mg, allopurinol, furosemide

Current ECG
Recent Echo Case 2: Phys Exam and Labs

- BP 130/78, P70
- 8-9 cm JVP, lungs clear, loud S4, 1+ edema
- BUN/Cr 58/2.0, trop I 0.09, BNP 221
- Maximal oxygen consumption (MVO2) = 12.7
- Recent cath: 40-60% circumflex, 30-40% right coronary artery
- Right heart cath: Pulmonary artery 44/20 mm Hg, mean wedge 22, Fick cardiac index 2.71 (CO=6.4 l/min)

BMT and CV Issues:
How do we manage these?

- So what are the effective pre-op evaluations?
- Can he be optimized better?
The further reduced the cardiac output, the worse the arrhythmia risk


Biomarkers may be helpful in identifying developing toxicity


Prevention of Cardiotoxicity is possible

Bosch, X et al, JACC 2013, p 2355
Cardiovascular Considerations during Bone Marrow Transplantation

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Patients with myeloma have marked and significant reductions in quantitative measures of physical function for years after the initial therapy

Tuchman, SA, et al, Clinical Lymphoma, Myeloma & Leukemia, 2014
Statin therapy prior to and during chemotherapy was protective

Are there things on the cancer therapy horizon that could be concerning for cardiomyopathy?

There is a balance between protein synthesis and degradation
A report of 6 cases describing carfilzomib related cardiac dysfunction and the patterns of cardiotoxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
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<tbody>
<tr>
<td>Carfilzomib Exposure Dosing (mg/m²)</td>
<td>20x1 then 27</td>
<td>27</td>
<td>20</td>
<td>20</td>
<td>27</td>
<td>20x1 then 27</td>
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<tr>
<td>Duration of Therapy (mos)</td>
<td>35</td>
<td>6</td>
<td>13</td>
<td>3</td>
<td></td>
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<tr>
<td>Total Cumulative Dose (mg/m²)</td>
<td>405</td>
<td>903</td>
<td>972</td>
<td>141</td>
<td>540</td>
<td>444</td>
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<tr>
<td>Baseline NYHA Class</td>
<td>III</td>
<td>III</td>
<td>I</td>
<td>III</td>
<td>I</td>
<td>III</td>
</tr>
<tr>
<td>LVEF</td>
<td>50</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>N/A</td>
<td>79*</td>
<td>594*</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Troponin</td>
<td>N/A</td>
<td>&lt;0.05</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Worst NYHA Class</td>
<td>III</td>
<td>II</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>Nadir of LVEF (%)</td>
<td>25</td>
<td>30</td>
<td>4</td>
<td>7</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Highest BNP or NT-proBNP† (pg/mL)</td>
<td>1837†</td>
<td>170†</td>
<td>2988†</td>
<td>2026</td>
<td>640</td>
<td>744</td>
</tr>
<tr>
<td>Highest Troponin</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>2.5</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Recovery Carfilzomib Discontinuation</td>
<td>Permanent</td>
<td>Temporary</td>
<td>Permanent</td>
<td>Permanent</td>
<td>Permanent</td>
<td>Temporary</td>
</tr>
<tr>
<td>Heart Failure Therapy Initiated</td>
<td>Beta-blocker; ACE-I; loop diuretic</td>
<td>None</td>
<td>Beta-blocker; ARB</td>
<td>Beta-blocker; ACE-I</td>
<td>Beta-blocker; aldosterone antagonist</td>
<td>Beta-blocker; aldosterone antagonist; loop diuretic</td>
</tr>
<tr>
<td>Best NYHA Class</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>I</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Highest LVEF</td>
<td>40</td>
<td>50</td>
<td>55</td>
<td>50</td>
<td>48</td>
<td>68</td>
</tr>
<tr>
<td>Lowest BNP (pg/ml)</td>
<td>65</td>
<td>104</td>
<td>2032</td>
<td>39</td>
<td>470</td>
<td>110</td>
</tr>
</tbody>
</table>

Properties of bortezomib and the second-generation proteasome inhibitors

<table>
<thead>
<tr>
<th>Proteasome Inhibitor</th>
<th>K_{cat}/K_{m} (nM)</th>
<th>I_{50} NF (nM)</th>
<th>Dissociation K_{d} (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>2.4-7.0/590-3200/24-74 (16,18,25)</td>
<td>36-40 (14,25,39)</td>
<td>110 [18]</td>
</tr>
<tr>
<td>MLN224808 [18]</td>
<td>3.4/5500/31</td>
<td>62</td>
<td>18</td>
</tr>
<tr>
<td>CEP-13770 [18,26]</td>
<td>3.8-100-100</td>
<td>NR</td>
<td>NR — slowly reversible</td>
</tr>
<tr>
<td>Carfilzomib [14]</td>
<td>6/3600/2400</td>
<td>NR</td>
<td>Inversible</td>
</tr>
<tr>
<td>PR-047 [21]</td>
<td>36/NR/NR</td>
<td>NR</td>
<td>Inversible</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; WCL, mantle cell lymphoma; MM, multiple myeloma; NR, not reported; SC, subcutaneous.
CV Considerations during BMT

Conclusion

- Pre-stem cell assessment and medical optimization is crucial
- During BMT careful adjustment and monitoring can prevent major issues
- Risk factor modification after BMT is needed
- Collaboration among disciplines is the key
**ARS Question #1**

What major cardiac concerns are there when a patient undergoes BMT?

a. Arrhythmias/QT prolongation  
b. Heart Failure  
c. Myocardial injury  
d. All of the above

**ARS Question #2**

Identify which one of the major baseline cardiac risk factors for the development of cardiac events is least important:

a. Chest radiation  
b. Prior anthracycline use  
c. Hypertension  
d. Coronary Disease

**ARS Question #3**

Treatment with what cardiac medications is not beneficial before or during chemotherapy or bone marrow transplant?

a. Clopidogrel  
b. Atorvastatin  
c. Enalapril  
d. Carvedilol