Why care about CV toxicities in MM?

• Median age 72 years
• About 2/3 have CV disease at baseline
• 70% experienced CV events over a 6 year period
• CV events are common causes of early death after diagnosis
• Patients are living longer


Auguston JCO 2005
Case

- 63 year old female with MM diagnosed in 2013
- PMH hypertension controlled on atenolol
- Cyclophosphamide, bortezomib and dexamethasone induction
- High-dose melphalan/Autologous stem cell transplant 4/2013
- Post transplant consolidation with Lenalidomide, bortezomib, dexamethasone
  - stopped for dyspnea due to pneumonitis (likely bortezomib)
  - Lenalidomide maintenance stopped for recurrent infections – 12/2013
- Relapse 11/2015 – treated with lenalidomide and dexamethasone until 5/2016, complicated by PE, placed on rivaroxaban
- Relapse 10/2016 – carfilzomib and dexamethasone recommended
Case - continued

- Hypertension on atenolol - BP 129/75
- Baseline echocardiogram, LVEF 60%, mild diastolic dysfunction
- NTproBNP 414, Troponin T <0.01
- Received carfilzomib 20/27 mg/m² over 30 min with 500 mL fluid pre and post-infusion in local oncologist’s office
- Presented weekly to ED with shortness or breath, headaches and low grade temperatures
- Returns on C2D11 with severe headaches, orthopnea, PND
- Exam showed BP 188/123 HR 69 97% RA, JVP to angle of jaw
- NT-proBNP 19,247, Troponin T 0.18
- Echocardiogram: LVEF 33%, PASP 57, mild RV dilatation
Agenda

• Overview of myeloma and its therapies
• Cardiovascular and pulmonary toxicities of myeloma regimens
  – Immunomodulatory drugs
  – Proteasome inhibitors
• Management of potential cardio-pulmonary toxicities
  – Identification of those at risk
  – Preventive strategies
  – Monitoring strategies
Multiple myeloma

• Cancer of bone marrow plasma cells
• "Multiple myeloma" = multiple bone marrow tumors
• Epidemiology
  – 1% of all cancers
  – Most common hematologic malignancy in African-Americans
  – About 25,000 new cases annually in the US
  – About 90,000 patients living with myeloma
• Median Age ~72
• Modestly strong association with obesity
Timeline of progress in MM therapy

1965
- Melphalan and prednisone

1995
- HDM/Autologous stem cell transplant
- Pamidronate

2000
- Thalidomide
- Zoledronic acid

2005
- Bortezomib
- Lenalidomide

2010
- Carfilzomib
- Pomalidomide

2015
- Panobinostat
- Daratumumab
- Elotuzumab
- Ixazomib

“Novel agents”

- Alkylator
- High-dose alkylator
- Bisphosphonates
- Immunomodulatory drugs
- Proteasome inhibitors
- Histone deacteylase inhibitor
- Monoclonal antibodies
- Steroids
There has been more progress in MM than any other cancer – incurable but controllable

Overall survival Mayo Clinic 1971-2006

Daratumumab, lenalidomide and dexamethasone v. lenalidomide and dexamethasone

Standard treatment approach to newly diagnosed MM

**Induction**
- ~4 cycles
- Bortezomib
- Lenalidomide
- Dexamethason

**Consolidation**
- Collect Stem Cells
- High dose melphalan/Autologous stem cell transplant

**Maintenance**
- Lenalidomide
  - or
  - Bortezomib

**Induction**
- ~9 cycles
- Bortezomib
- Lenalidomide
- Dexamethason

**Transplant Eligible***
- Fit
- Frail

**Transplant Ineligible**
- Fit
- Frail

*"Physiologic" age <70, no significant co-morbidities, CrCl >30, LVEF≥50, DLCO≥50
Treatment at relapse

Early relapses
1-3 prior lines of therapy

- Carfilzomib
- Lenalidomide
- Dexamethasone
- Clinical trials

Later relapses

- Pomalidomide
- Dexamethasone
- Clinical trials

- Panobinostat
- Bortezomib
- Dexamethasone

- Carfilzomib
- Dexamethasone

- Dexamethasone

- Thalidomide
- Cisplatin
- Adriamycin
- Cyclophosphamide
- Etoposide

HDM/Autologous stem cell transplant
What are the cardiovascular and pulmonary toxicities of myeloma agents?

<table>
<thead>
<tr>
<th>Corticosteroids</th>
<th>Immunomodulatory drugs</th>
<th>Proteasome inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>Thalidomide</td>
<td>Bortezomib</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Lenalidomide</td>
<td>Carfilzomib</td>
</tr>
<tr>
<td></td>
<td>Pomalidomide</td>
<td>Ixazomib</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Autonomic dysfunction</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>Fluid retention</td>
<td>Arrhythmias</td>
</tr>
<tr>
<td>Adrenergic stimulation</td>
<td>Venous thromboembolism</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Hyperglycemia/DM</td>
<td>Arterial thromboembolism</td>
<td>Hypertensive urgency</td>
</tr>
<tr>
<td></td>
<td>Pneumonitis</td>
<td>Dyspnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluid retention/edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonitis</td>
</tr>
</tbody>
</table>
Cardiovascular toxicity of myeloma regimens

Early relapses
1-3 prior lines of therapy

- Carfilzomib
- Lenalidomide
- Dexamethasone
- HDM/Autologous stem cell transplant

- Ixazomib
- Lenalidomide
- Dexamethasone

- Elotuzumab
- Lenalidomide
- Dexamethasone

- Daratumumab
- Lenalidomide
- Dexamethasone

Later relapses

- Pomalidomide
- Dexamethasone
- HDM/Autologous stem cell transplant

- Panobinostat
- Bortezomib
- Dexamethasone

- Carfilzomib
- Dexamethasone

- Dexamethasone
- Thalidomide
- Cisplatin
- Adriamycin
- Cyclophosphamide
- Etoposide
# VTE and immunomodulatory drugs

<table>
<thead>
<tr>
<th>Regimen</th>
<th>VTE Incidence (%)</th>
<th>NDMM</th>
<th>RRMM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thalidomide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>4</td>
<td>3-4</td>
<td></td>
</tr>
<tr>
<td>+ Dexamethasone</td>
<td>12-26</td>
<td>4-9</td>
<td></td>
</tr>
<tr>
<td>+ Melphalan</td>
<td>18-20</td>
<td>11-13</td>
<td></td>
</tr>
<tr>
<td>+ Doxorubicin</td>
<td>26-27</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>+ Multiagent chemotherapy</td>
<td>26</td>
<td>16-31</td>
<td></td>
</tr>
<tr>
<td><strong>Lenalidomide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>NA</td>
<td>0-13</td>
<td></td>
</tr>
<tr>
<td>+ Dexamethasone</td>
<td>19-75</td>
<td>11-15</td>
<td></td>
</tr>
</tbody>
</table>

Modified from Li JAMA Onc 2016
Algorithm for thromboprophylaxis in multiple myeloma

Pre-treatment risk assessment

**Individual factors**
- Obesity BMI ≥30
- Prior VTE
- Central venous catheter
- Known inherited thrombophilia
- Immobilization
- Surgery
- Smoking
- Comorbidities: DM, CKD
- Acute infection

**Disease state factors**
- Newly diagnosed
- Hyperviscosity
- Pulmonary hypertension

**Therapy-specific factors**
- High-dose dexamethasone (≥480 mg/month)
- Erythropoietin
- IMiD + high-dose dexamethasone
- IMiD + anthracycline
- IMiD + multiagent chemotherapy

≤1 Factor, except prior VTE → Aspirin 81-325 mg

Prior VTE → LMWH at prophylactic dose

≥2 Factors → LMWH at prophylactic dose, preferred over aspirin 325 mg

Modified from Palumbo Leukemia 2007, Li JAMA Onc 2016
Proteasome inhibitors (PI) in MM

• The ubiquitin-proteasome system (UPS) is charged with degrading proteins tagged with ubiquitin
• MM cells produce large quantities of immunoglobulin
• UPS is near saturation in MM cells
• MM cells are uniquely sensitive to proteasome inhibition
## Approved proteasome inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Use</th>
<th>CV toxicities (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib (2003)</td>
<td>Reversible</td>
<td>Newly diagnosed Relapsed</td>
<td>2-3%</td>
</tr>
<tr>
<td>Carfilzomib (2012)</td>
<td>Irreversible</td>
<td>Relapsed ≥1 prior line Relapsed 1-3 priors with lenalidomide, dexamethasone</td>
<td>15-20%</td>
</tr>
<tr>
<td>Ixazomib (2015)</td>
<td>Reversible</td>
<td>Relapsed 1-3 priors with lenalidomide, dexamethasone</td>
<td>No clear signal</td>
</tr>
</tbody>
</table>
Carfilzomib’s cardiovascular toxicities are diverse

- Heart failure
- Arrhythmia
- Pulmonary hypertension
- hypertensive urgency
- Dyspnea
- Edema
- VTE

- Why?
  - Multiple mechanisms
  - Endothelial injury
  - Myocardial injury
  - Impact of other drugs in regimen

- Answer: unknown
Factors that may impact CV toxicity of carfilzomib

- 30 min infusions may be safer than 10 min
- Excess hydration may increase risk
- Increased dose is associated with increased CV toxicity
- Unclear if weekly versus bi-weekly schedule impacts toxicity
- Unclear if baseline CV factors impact risk
Cardiovascular risk assessment and management for myeloma patients
A proposed algorithm

Pre-treatment risk assessment

**Cardiovascular factors**
- Age > 65
- History of MI/CAD/PVD
- History of CHF
- Diabetes
- Hypertension
- Smoking
- Hyperlipidemia
- Family history of CAD

**Pulmonary factors**
- History of PE
- COPD/Asthma
- Pulmonary hypertension

**Myeloma-specific factors**
- History of mediastinal radiation
- Prior anthracycline
- Severe kyphosis
- Cardiac amyloidosis

- None
- Any Risk Factor

**Low risk patient**
- Echocardiogram
- Pulmonary function tests
- Biomarkers

**High risk patient**
- Low risk regimen
- High risk regimen

**Consider cardio-oncology consultation**
- CV risk factor management
- Thromboprophylaxis

**Expediting cardio-oncology consultation prior to chemotherapy**
- CV risk factor management
- Thromboprophylaxis

Adapted from Li, JAMA Onc 2016
Monitoring for cardiovascular and pulmonary toxicities during therapy

• Maintain high suspicion for CV toxicity
• Be vigilant about changes in blood pressure and volume status
• Partner with a cardiologist
  – Plan for regular follow-up with a cardiologist during chemotherapy for high risk patients
  – Communication is key – between specialists and between patient and physicians
• Approaching dyspnea
  – Consider broad differential
  – Cardiac v. pulmonary?
  – Myeloma related causes: anemia, kyphosis, plasmacytomas, pleural effusions
Case

- Admitted for blood pressure control and diuresis
- Myeloma was aggressively progressing with pancytopenia
- Repeat echocardiogram 5 weeks later showed LVEF 55%, diastolic dysfunction
- Began therapy with infusional adriamycin, cyclophosphamide and etoposide
- No cardiac issues 1 month after therapy
- Myeloma is refractory
• MM patients are at high risk of CV events
• Are living longer and being exposed to multiple cardiotoxic regimens
• Proteasome inhibitors, in particular, carfilzomib are associated with high rates of diverse CV events
• Prevention and monitoring strategies have not been formally tested in clinical trials
• Vigilance and partnering with cardiology are critical to safe delivery of these regimens