Myeloma care and proteasome inhibitors

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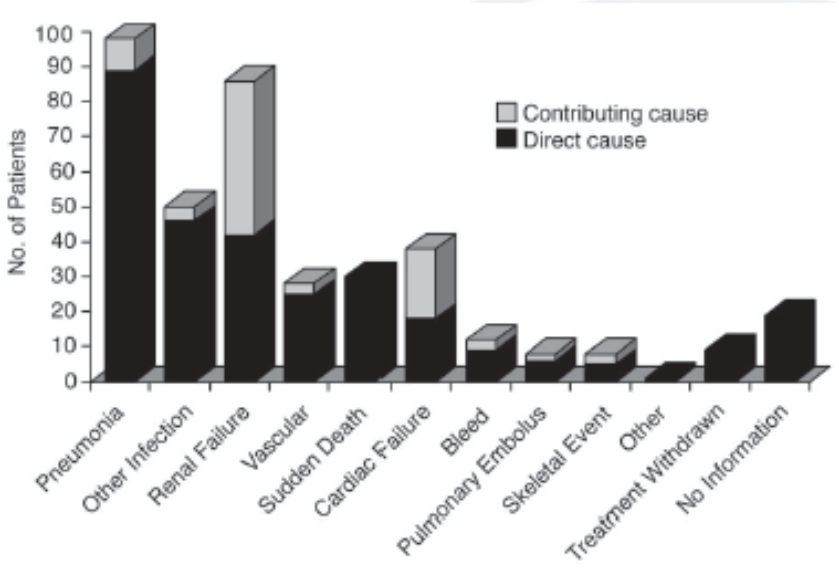
Why care about CV toxicities in MM?

- 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

Causes of early death in UK MRC trials MM 1980-2002



Auguston JCO 2005

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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

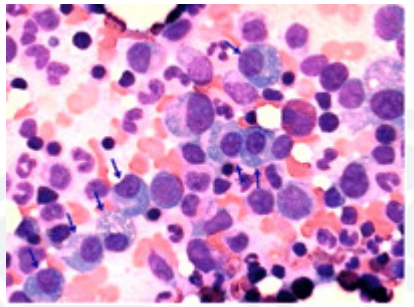
- Hypertension on atenolol - BP 129/75
- Baseline echocardiogram, LVEF 60%, mild diastolic dysfunction
- NTproBNP 414, Troponin T <0.01
- Received carfilzomib 20/27 mg/m2 over 30 min with 500 mL fluid pre and post-infusion in local oncologist's office
- Presented weekly to ED with shortness or breath, 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

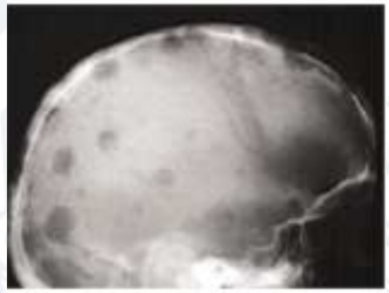
Agenda

- Overview of myeloma and 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





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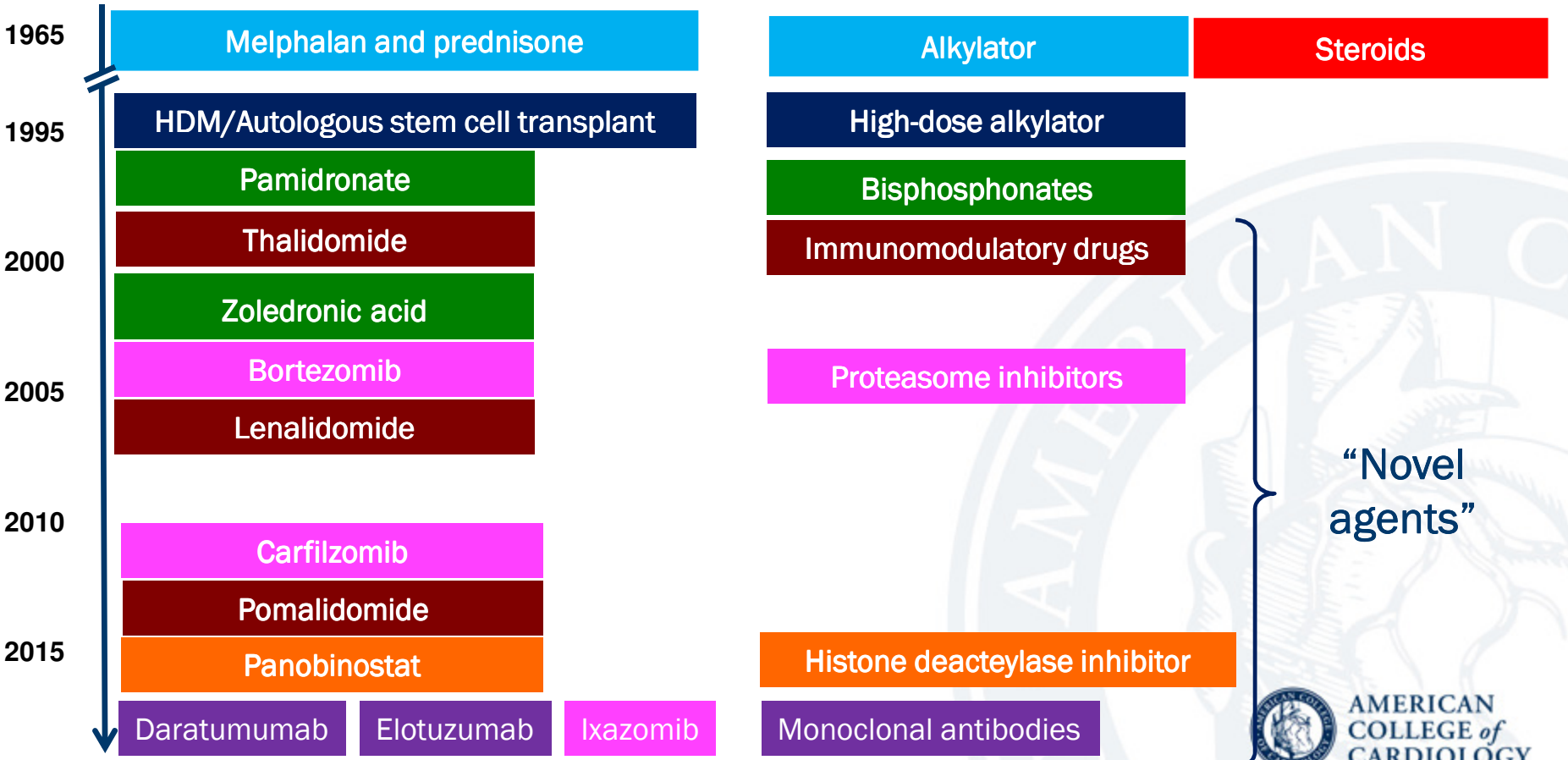
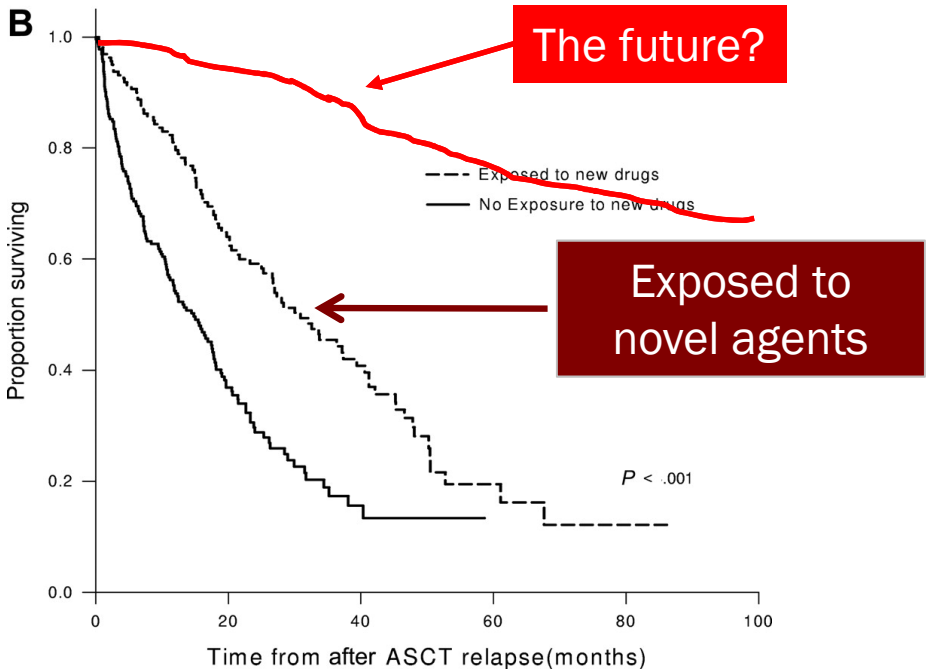
Timeline of progress in MM therapy

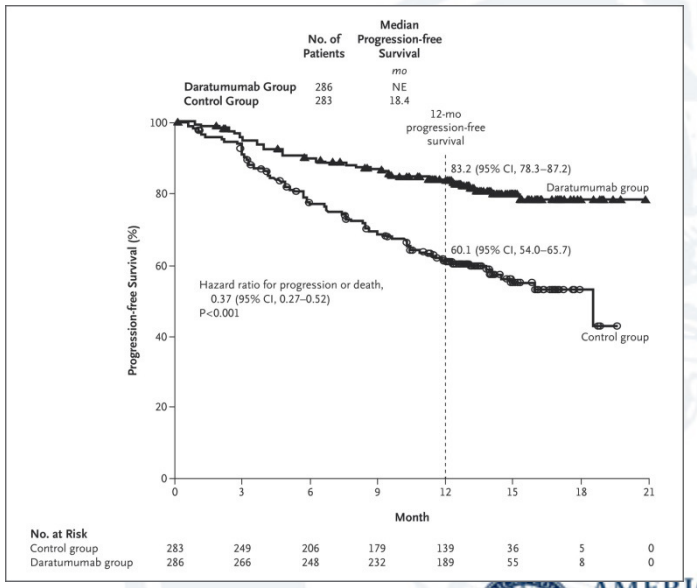


There has been more progress in MM than any other cancer – incurable but controllable

Overall survival Mayo Clinic 1971-2006



Daratumumab, lenalidomide and dexamethasone v. lenalidomide and dexamethasone



Kumar Blood 2007, Rajkumar N Engl J Med 2016, Dimopoulos N Engl J Med 2016

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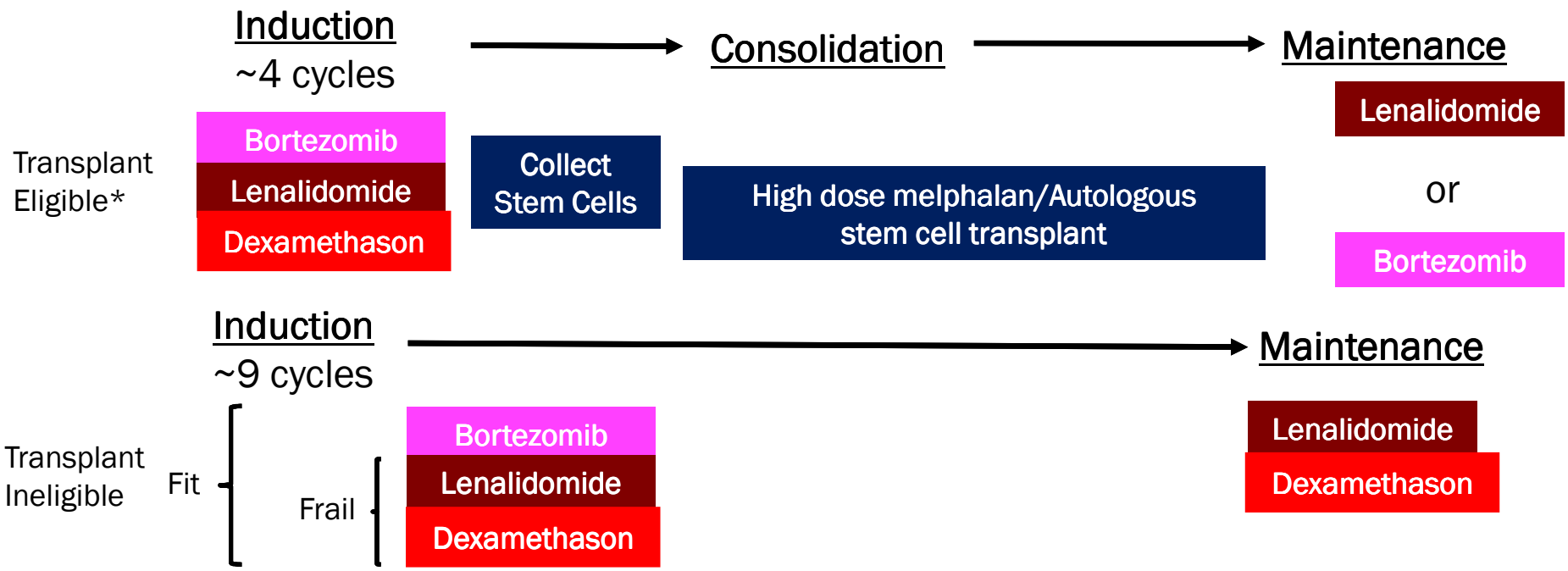
Standard treatment approach to newly diagnosed MM



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

Treatment at relapse

Early relapses
1-3 prior lines of therapy

Clinical trials

Carfilzomib
Lenalidomide
Dexamethasone

Ixazomib
Lenalidomide
Dexamethasone

Elotuzumab
Lenalidomide
Dexamethasone

Daratumumab
Lenalidomide
Dexamethasone

Daratumumab
Bortezomib
Dexamethasone

HDM/Autologous stem cell transplant

Later relapses

Clinical trials

Pomalidomide
Dexamethasone

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?

Corticosteroids **Dexamethasone** **Prednisone**	**Immunomodulatory drugs** **Thalidomide** **Lenalidomide** **Pomalidomide**	**Proteasome inhibitors** **Bortezomib** **Carfilzomib** **Ixazomib**
Hypertension	Autonomic dysfunction	Heart failure
Fluid retention	Fluid retention	Arrhythmias
Adrenergic stimulation	Venous thromboembolism	Pulmonary hypertension
Hyperglycemia/DM	Arterial thromboembolism	Hypertensive urgency
	Pneumonitis	Dyspnea
		Fluid retention/edema
		Venous thromboembolism
		Pneumonitis

Cardiovascular toxicity of myeloma regimens

Clinical trials — Yes — Unknown — No

Early relapses
1-3 prior lines of therapy

- Carfilzomib, Lenalidomide, Dexamethasone
- Ixazomib, Lenalidomide, Dexamethasone
- Elotuzumab, Lenalidomide, Dexamethasone
- Daratumumab, Lenalidomide, Dexamethasone
- Daratumumab, Bortezomib, Dexamethasone
- HDM/Autologous stem cell transplant

Later relapses

Clinical trials

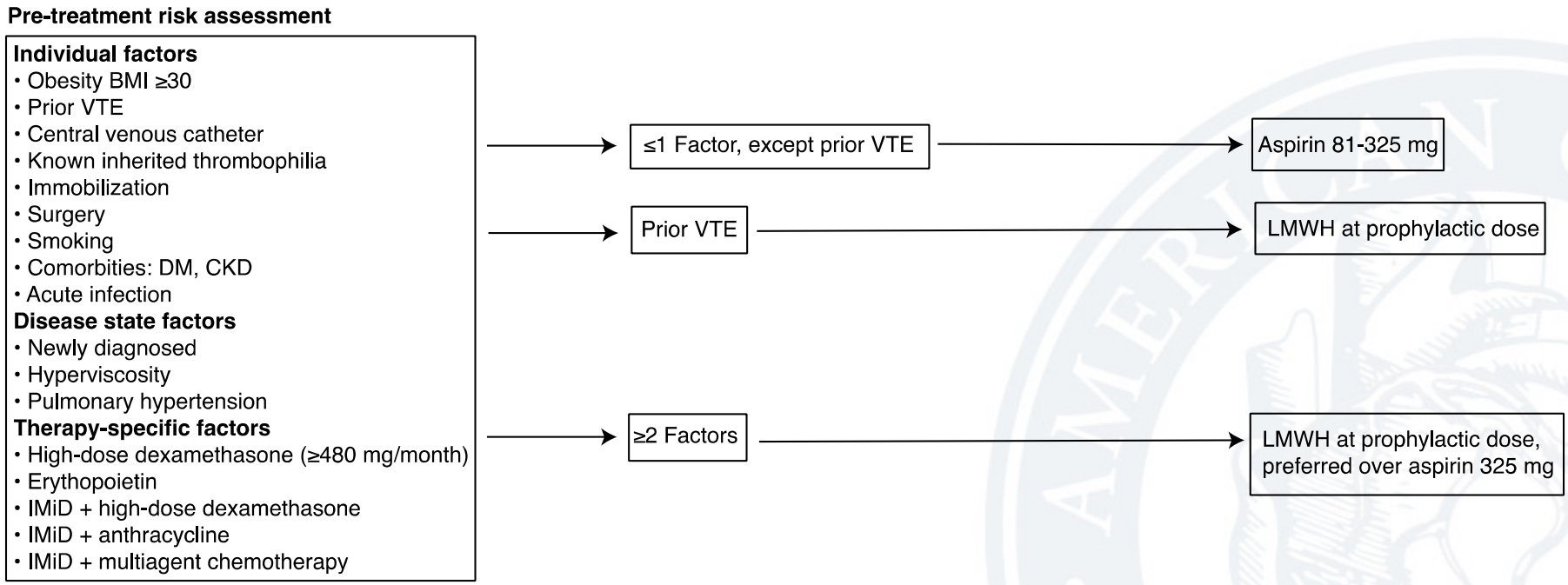
- Pomalidomide, Dexamethasone
- Panobinostat, Bortezomib, Dexamethasone
- Carfilzomib, Dexamethasone
- Dexamethasone, Thalidomide, Cisplatin, Adriamycin, Cyclophosphamide, Etoposide
- HDM/Autologous stem cell transplant

VTE and immunomodulatory drugs

	VTE Incidence (%)	
Regimen	**NDMM**	**RRMM**
Thalidomide		
Alone	4	3-4
+ Dexamethasone	12-26	4-9
+ Melphalan	18-20	11-13
+ Doxorubicin	26-27	58
+ Multiagent chemotherapy	26	16-31
Lenalidomide		
Alone	NA	0-13
+ dexamethasone	19-75	11-15

Modifed from Li JAMA Onc 2016

Algorithm for thromboprophylaxis in multiple myeloma



Modified from Palumbo Leukemia 2007, Li JAMA Onc 2016

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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

Drug (Approval Year)	Mechanism	Use	CV toxicities (%)
Bortezomib (2003)	Reversible	Newly diagnosed Relapsed	2-3%
Carfilzomib (2012)	Irreversible	Relapsed ≥1 prior line Relapsed 1-3 priors with lenalidomide, dexamethasone	15-20%
Ixazomib (2015)	Reversible	Relapsed 1-3 priors with lenalidomide, dexamethasone	No clear signal

Carfilzomib's cardiovascular toxicities are diverse

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

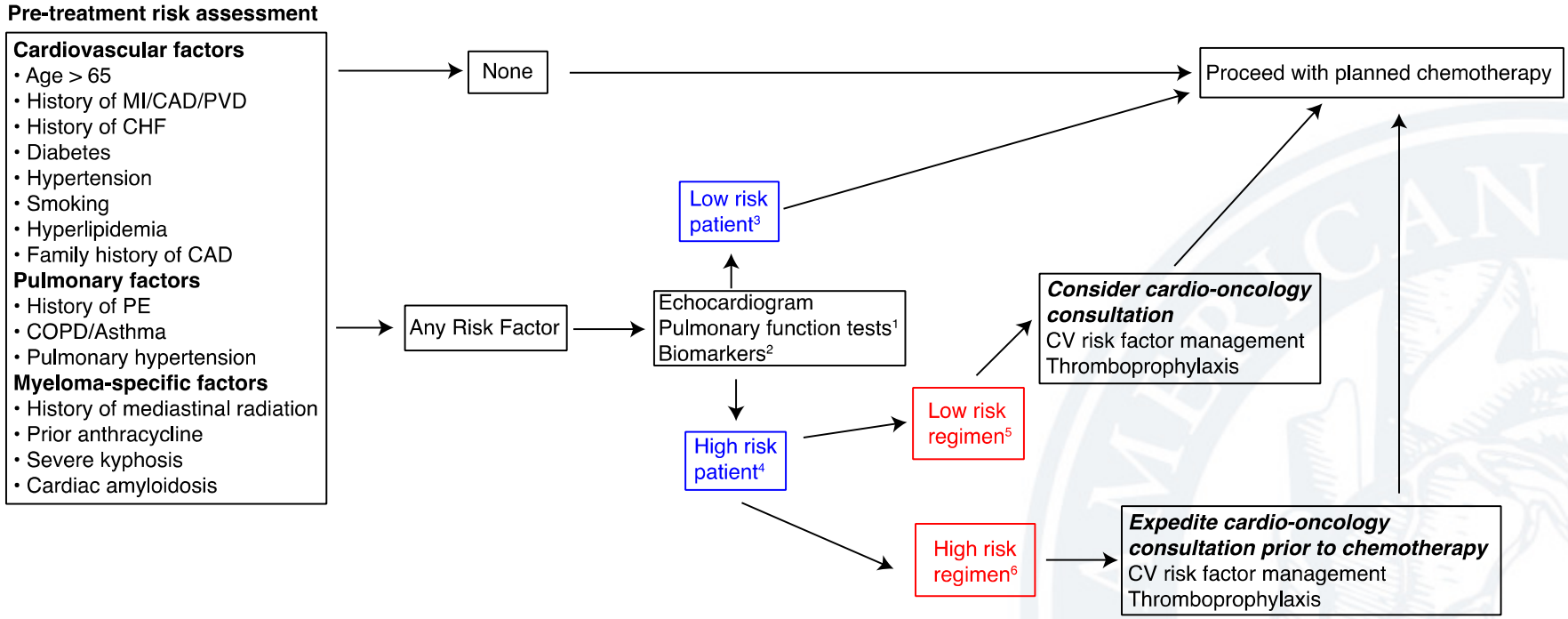
- Why?
  - Multiple mechanisms
  - Endothelial injury
  - Myocardial injury
  - Impact of other drugs in regimen
- Answer: unknown

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



[1]If known COPD/Asthma or severe kyphosis.
[2]Utility unknown, interpret with caution.
[3]Controlled CV factors and normal objective testing.
[4]Uncontrolled CV factors, recent MI, CVA, or PE and/or abnormal results on objective testing

[5]Regimens that do not contain anthracycline, carfilzomib or carfilzomib + IMiD
[6]Regimens that contain anthracycline, carfilzomib or carfilzomib + IMiD

Adapted from Li JAMA Onc 2016

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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

Summary

- 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

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