







#### Outline

- What is Multiple Myeloma?
  - Common Presenting Features
  - Epidemiology and Risk Factors for Multiple Myeloma
  - Diagnosis of Multiple Myeloma
- Disease Course in Multiple Myeloma
  - How to interpret lab results
  - When is imaging ordered? What type?
  - When do I need a bone marrow biopsy?
- Common patient and caregiver questions

#### Multiple Myeloma:

- Malignancy of plasma cells
- Hallmarks:
  - Monoclonal Ig M-spike
  - Anemia
  - Renal failure
  - Destructive bone lesions
  - High blood calcium
  - Increased risk of infection

Munshi, N., et al. (2001). Plasma cell neoplasms. Principles and Practice of Oncology. J. DeVita, VT., S. Hellman and S. Rosenberg. Philadelphia, PA, Lippincott Williams & Wilkons: 2465-2499. \* Images are from Tomer Mark's personal collection





#### Myeloma is Part of a Group of Plasma Cell Disorders

- Multiple Myeloma
- Other Disorders
  - Monoclonal gammopathy of undetermined significance (MGUS)
  - Smoldering multiple myeloma (SMM)
  - Solitary Plasmacytoma
    - Bone
    - Extramedullary
  - Waldenström's Macroglobulinemia
  - Primary Amyloidosis (AL)
  - Heavy chain disease
  - POEMS syndrome
  - Type I and II cryoglobulinemia

Munshi, N., et al. (2001). Plasma cell neoplasms. Principles and Practice of Oncology. J. DeVita, VT., S. Hellman and S. Rosenberg. Philadelphia, PA, Lippincott Williams & Wilkons: 2465-2499.





#### Myeloma Epidemiology and **Risk Factors**







#### "Old" Diagnostic Criteria for MM

- Presence of M protein in serum or urine
- Identification of >10% monoclonal plasma cells in bone marrow and/or plasmacytoma
- Evidence of end-organ damage: CRAB(I) criteria
  - <u>C</u>alcium Elevation: Ca<sup>++</sup> ≥ 11 mg/dL
  - <u>**R</u>enal Failure: SCr ≥ 2 mg/dL**</u>
  - <u>A</u>nemia: Hb < 12 g/dL
  - Bone: lytic lesions, pathologic fracture
  - Infections: Recurrent, due to hypogammaglobulinemia



Image Source: wikimedia commons

Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia 2009; 23: 3–9.











#### How often to do testing?

- Serum protein electrophoresis and immunofixation, Immunoglobulins, CBC, CMP, Free light chains: monthly
- Urine protein electrophoresis and immunofixation : At diagnosis and then varies per patient
- Radiology Imaging: At diagnosis, when clinically indicated, to confirm complete remission.
- Bone marrow biopsy:
  - At diagnosis
  - At relapse
  - To confirm complete remission



#### Example Myeloma Imaging: X-Ray



- Skeletal survey: x-rays of all long bones, pelvis, spine, and skull.
- Quick, easy, but low sensitivity.
- Not very useful to follow disease course

#### Example Myeloma Imaging: MRI



Image source: Tomer Mark

Coronal T2-weighted MRI with plasmacytoma in the L3 vertebral body (large arrowhead) And also a compression fracture of L5 with epidural extension of tumor (small arrow)

- MRI: very sensitive to detect marrow changes; can detect lesions before fractures occur
- Uncomfortable, claustrophobia
- No one has a normal spine

#### Example Myeloma imaging: PET-CT



Image source: Tomer Mark



- PET/CT: most sensitivity, quick, results correlate with tumor activity
- Radiation: equal to about 30 x-rays
- TOO sensitive





## Multiple Myeloma Is a Classification and Prognostic Challenge



27

#### Several Prognostic Factors Have Been Identified in MM

#### **Select Negative Prognostic Factors**

Prognostic Factors	Findings
β <sub>2</sub> -microglobulin <sup>1</sup>	igtharpoonup levels associated with decreased survival
Albumin <sup>2</sup>	igstarrow levels correlate with decreased survival
Lactate dehydrogenase (LDH) <sup>1</sup>	igtharpoonup levels associated with decreased survival
lg isotype <sup>3</sup>	IgA associated with decreased survival
Plasma cell labeling index (PCLI) <sup>1</sup>	igtharpoonup levels associated with decreased survival
Bone marrow plasmacytosis <sup>4</sup>	igtharpoonup level (>20%) associated with decreased survival
Chromosome abnormalities <sup>5</sup>	High-risk abnormalities associated with decreased survival

 Kyle RA. Stem Cells. 1995;13(suppl 2):56-53. 2. Greipp PR, et al. J Clin Oncol. 2005;23(15):3412-3420. 3. Munshi NC, et al. Plasma cell neoplasms. In: DeVita VT, et al, eds. Cancer. Principles & Practice of Oncodegy. 7th ed. 2005;2155-2188. 4. Smadja NV, et al. Blood. 2001;98(7):2229-2238. 5. Fonseca R, et al. Cancer Res. 2004;64(1):1561-1555.









## Multiple Myeloma Is Characterized by Periods of Relapse and Remission







#### The Importance of Continuous Therapy<sup>1</sup>

Continuous therapy may be associated with significant improvement in patient outcomes<sup>1</sup>



Pooled analysis of 3 phase 3 trials analyzing continuous therapy vs fixed-duration therapy in 1218 patients with newly diagnosed multiple myeloma. Primary endpoints were PFS1, PFS2, and OS. Median follow-up was 52 months.





#### How do I know how I am doing?

- We can measure the myeloma directly through bone marrow biopsy....
- We can use the protein secreted by the malignant plasma cell to follow disease activity. Paraprotein ≈ tumor burden.
- Different paraproteins:
  - M-spike: i.e. IgG-lambda, IgA-kappa. Most common. Follow by SPEP.
  - Free light chains: present in serum or urine. When in urine, called Bence Jones Protein.
  - Plasmacytomas: size of masses, used when the myeloma is NONsecretory.
- Achievement of deeper response generally leads to improved remission time and overall survival.

MM	Response Criteria are complicated	
Stringe	nt Complete Response (sCR) requires all of the following:	
	All of the criteria of complete response plus Normal serum free light chain ratio Absence of monoclonal cells on bone marrow aspirate by IHC of IF	
Comple	ete Response (CR) requires all of the following:	
	Absence of M-protein in the serum and urine by IFE. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR. (* post-transplant) <5% plasma cells in bone marrow aspirate	
Very G	ood Partial Response (VGPR) requires all of the following:	
	All of the criteria of complete response plus Normal serum free light chain ratio Absence of monoclonal cells on bone marrow aspirate by IHC of IF	
Partial	Response (PR) requires all of the following:	
	>50% reduction in the level of the serum monoclonal paraprotein Reduction in 24 hour urine light chain excretion by >90% or to < 200mg > 50% reduction in size of soft tissue plasmacytoma (by radiography or physical examination)	
Stable	Disease (SD) requires all of the following:	
	Not meeting the above criteria nor the criteria for progression of disease	
Durie et	t al. <i>Leukemia</i> . 2006. 20,1467-1473	

#### Examples of Follow Labs for Response: M-spike (M-protein)

Flowsheet		
	SPEP MONOCLONAL PROTEIN	
Ref. Range	Latest Ref Range: None Detected g/dL	
6/22/2017 0623	2	2.0 ^
7/21/2017 1136	1	1.1 ^
8/11/2017 0857	(	).9 📤
9/8/2017 0834	C	).5 📤
10/6/2017 0857	(	).4 🔦
11/3/2017 1318	(	).3 🔺
12/1/2017 1258	(	).2 📤
12/15/2017 1144	(	).3 📤
1/26/2018 0808	(	).1 📤
3/13/2018 1315	(	J.2 🔺



41

## Examples of Follow Labs for Response: serum free light chains

Flowsheet			
-	KAPPA ONT FREE LIGHT CHAINS		
Ref. Range	Latest Ref Range: 0.69 - 2.34 mg/dL		
1/27/2017 0734	117.00 ^		
3/1/2017 0842	65.80 🔦		
3/29/2017 1111	39.90 🔦		
4/26/2017 1114	15.70 🔦		
5/24/2017 1051	17.00 ^		
6/15/2017 0933	19.20 🔦		
8/24/2017 0838	1.87		
10/18/2017 1323	1.57		
11/10/2017 0738	2.06		
12/13/2017 0944	2.26		
1/10/2018 1011	2.24		
2/7/2018 1050	3.57 🔦		
2/21/2018 0934	5.98 ^		
3/21/2018 0924	10.30 🔷		



#### Examples of Follow Labs for Response: Bence Jones Protein: urine free light chains

Flowsheet			
	UPEP MONOCLONAL PROTEIN Latest Ref Range: None Detected mg/Day		
Ref. Range			
8/4/2017 1041	1,926 ^		
12/12/2017 0600	812 ^		
12/19/2017 0826	854 🔷		
2/12/2018 0800	667 ^		
3/10/2018 0900	485 * ^		



43

## Responses now are deeper than we can find in blood and urine:

	IMWG Criteria for Minimal Residual Disease (MRD)					
Sustained MRD-negative	Flow MRD-negative	Sequencing MRD-negative	Imaging Plus MRD-negative			
MRD negativity in the marrow NGF, NGS, or both, and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years.	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using a validated equivalent method with a minimum sensitivity of 1 in 10 <sup>5</sup> nucleated cells or higher.	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue.			

### Achievement of Complete Response Does Not Eliminate All Myeloma Clones



Median OS increases by ~1 year for each log reduction in MRD<sup>3</sup>: MRD > 10%: 1 yr MRD 1-10%: 4 yr MRD 0.1-1%: 5.9 yr MRD: 0.01 - 0.1%: 6.8 yr MRD < 0.01%: > 7.5 yrs

References: 1. Dingli D et al. Cuncer Sci. 2007;98(7):1035-1040. 2. Dingli D et al. J Clin Oncol. 2007;25(31):4933-4937. 3. Munshi NC et al. J Clin Oncol. 2013;31(20):2523-2526. 3. Andy C. Rawstron et al. Blood 2015;125:1932-1935

45



# Common patient and caregiver questions

#### Should I take any supplements?

- OK to take calcium 500-1500mg/day + vitamin D 1000-2000 i.u./d
- OK to take a centrum silver (or similar multivitamin) daily
- AVOID:
  - Antioxidants: Green tea, acai berries, etc.
  - Excess vitamin C (extra supplements; vit C in food is ok).
- Best supplement is water:
  - Adequate hydration flushes chemotherapy and excess light chains through the kidneys

#### Are there any medications to avoid?

- Never take NSAIDS:
  - Ibuprofen, alleve, motrin, advil, naproxen, etc... → can lead to kidney damage
- Avoid IV contrast (iodine) for CT scan:
  - Can also cause kidney damage
  - Includes CT angiograms
  - MRI / PET-CT generally ok
- Ask your myeloma doctor about safety before starting IV antibiotics:
  - Certain antibiotics that are IV (like gentamycin) can also lead to renal failure in multiple myeloma

49

## Are there any lifestyle changes that I should make?

- Try to get 20 minutes of cardiovascular exercise most days of the week
  - · Reduces inflammation in the body
  - · Better control of blood sugar
  - · Get rid of excess weight
  - Tolerate chemo better
- Take care of your teeth!
  - See the dentist regularly to avoid osteonecrosis of the jaw

#### Things to ask your doctor:

- Define: What type of myeloma do I have?
- Action Plan: What treatment is best for me? How are we going to follow my response to treatment? How are we going to maintain my response?
- Review Progress: What is my response now? i.e. What is my M-spike and free light chain level?









