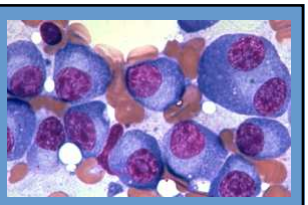

Multiple Myeloma, Amyloidosis, and Other Nephro-Relevant Plasma Cell Diseases

May 2017

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Disclosures

Research support: Takeda, Celgene, Novartis, Merck, Prothena

Consulting: Takeda, Celgene

Speakers' bureau: Takeda, Celgene

I will mention off-label use of bortezomib in amyloidosis

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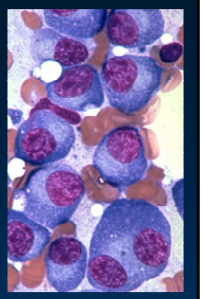
Learning objectives

1) To identify which tests are useful in characterizing plasma cell disorders and to have an understanding of how to interpret them

2) To gain insight into the differences in presentation between different plasma cell cancers

3) To understand the basic framework for treating plasma cell cancers with chemotherapy

Plasma cell diseases



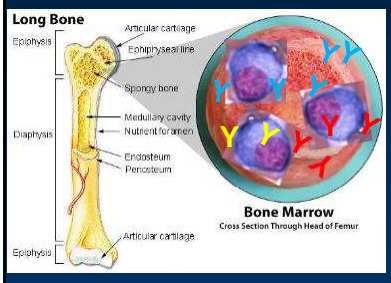
- Background
  - Epidemiology
  - Definitions / Concepts
  - Clinical presentations including MGRS
- Management: How far we've come

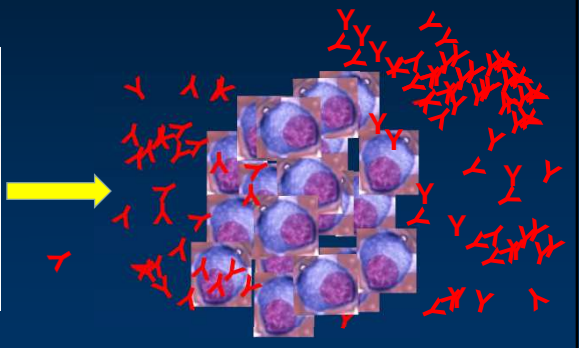
The epidemiology of plasma cell diseases

- Multiple myeloma: 2nd most common hematological malignancy
- ~30,000 new cases and 11,000 deaths yearly in the U.S.
- 1% of cancers, 2% of cancer-related deaths
- Median age of 70 at diagnosis
- Amyloidosis: ~1/10th as common as myeloma
- MGUS: Prevalence of ~1% of all people, 2-3% above 50yo, close to 10% above 80yo

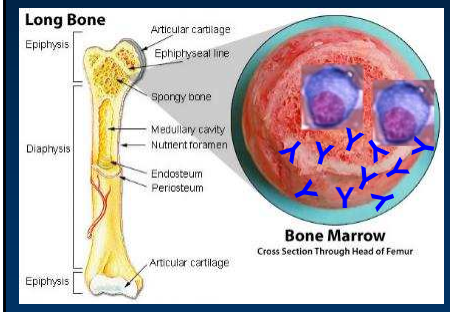
http://seer.cancer.gov/; Kyle R, *Mayo Proc* 2003

Back to basics: When plasma cells go awry

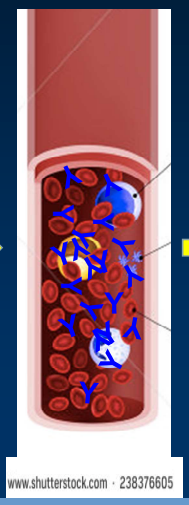




Back to basics: What is a monoclonal gammopathy?



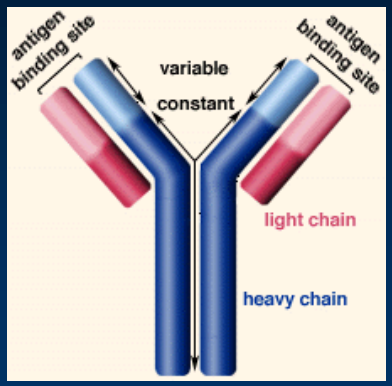
http://www.cybersurgeons.net/resources/?/skeletalsys/177/



www.shutterstock.com · 238376605

http://what-when-how.com

Back to basics: What is a monoclonal gammopathy?



http://www.biology.arizona.edu/immunology/tutorial.00/page3.html

- The tests:
  - SPEP / UPEP
  - Serum/urine immunofixation (IFE)
  - Serum free light chain assay

Measuring monoclonal gammopathies

- SPEP: Best for measuring intact immunoglobulin (“the whole Y”). Insensitive for light chain myeloma. Quantitative.
- Serum IFE: More sensitive than SPEP but non-quantitative
- 24h UPEP/IFE: Sensitive but laborious
- Serum free light chain assay: Only detects unbound light chain. More sensitive than SPEP for light chains

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Takeaway slide #1

- The combination of SPEP + serum immunofixation + serum free light chains detects most monoclonal plasma cell diseases (~97% of myeloma)
- 24h urines are less mandatory than previously for measuring monoclonal gammopathies

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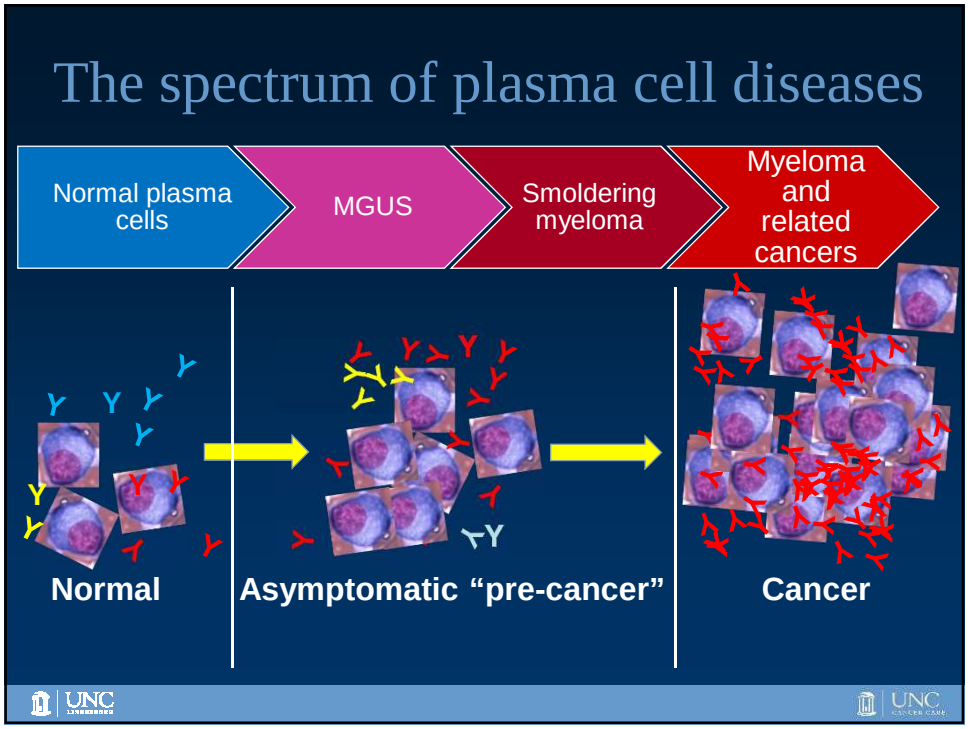
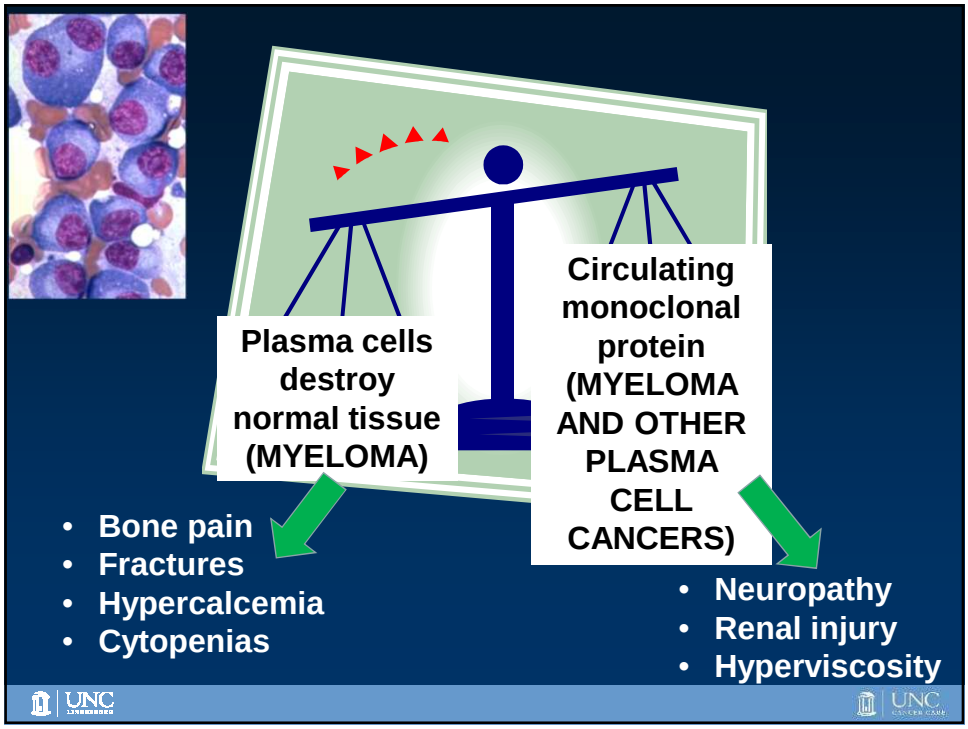
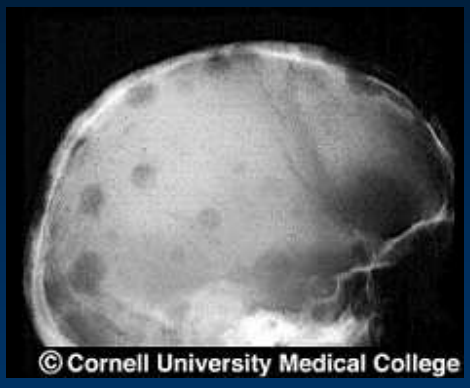
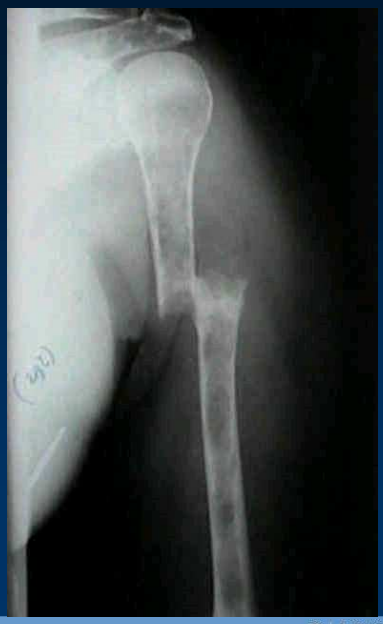

The spectrum of plasma cell diseases
Normal plasma cells
MGUS
Smoldering myeloma
Myeloma and related cancers
Normal
Asymptomatic "pre-cancer"
Cancer


Plasma cells destroy normal tissue (MYELOMA)
Circulating monoclonal protein (MYELOMA AND OTHER PLASMA CELL CANCERS)
• Bone pain
• Fractures
• Hypercalcemia
• Cytopenias
• Neuropathy
• Renal injury
• Hyperviscosity

CRAB criteria for multiple myeloma

- HyperCalcemia
  - Lethargy, confusion, constipation
- Renal insufficiency
  - Bence-Jones proteinuria, nephrotic syndrome, renal failure
- Anemia
  - Also other cytopenias or suppression of normal immunity
- Bone lesions
- Not an exclusive list





Monoclonal proteins as nephrotoxins: ETOH or cyanide?

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WH

- Completely healthy 56yo male. New dyspnea and peripheral edema in June 2015
- Presented elsewhere with HTN (SBP 260), hematuria, SCr 3. BP controlled and D/C'd home
- Came to us September 2015. Oliguric ESRD. 10g non-specific proteinuria with active urine sediment (WBC casts + hematuria)
- Started HD.

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WH

- SPEP negative. Serum IFE IgG-kappa. Serum free kappa 16 mg/dL, lambda 4, ratio 4
- Renal biopsy: Membranoproliferative GN with monoclonal IgG-kappa deposition
- Bone marrow biopsy: Normal
- Started pulse steroids, then bortezomib, cyclophosphamide and dex chemotherapy
- Off HD x 2 years, SCr stable at 1.7

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RM

Date	Serum M-spike (g/dL)	Serum free kappa (mg/dL)	Urine M-spike (mg/24h)	SCr
Jan 2015	1.1	unknown	3800	1.6
Feb 2015	unknown	unknown	5100	1.5
June 2015 (first visit with me)	1.1	1070 (high!)	Unknown	1.3
August 2015	1.3	885	4900	1.3
Jan 2016	1.1	962	4000	1.3

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Monoclonal proteins as toxins: ETOH or cyanide?

- Depends on the protein's structure
- Myeloma: Often like ETOH and not nephrotoxic unless high levels
- Amyloid, MIDD (light/heavy chain deposition disease), GN with monoclonal protein: Like cyanide. Can be very toxic even in low concentrations

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MGRS: Recognizing monoclonal proteins when they're cyanide

- Monoclonal Gammopathy of Renal Significance
- Renal diseases mediated by M-proteins that don't meet criteria for myeloma
  - Often look like MGUS until renal biopsy comes back
- Includes AL amyloidosis, MIDD, cryoglobulinemia, proliferative GN with monoclonal Ig deposition, etc.

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UNC Leung, *Blood* 2012 UNC

MGRS: Recognizing monoclonal proteins when they're cyanide

- Not all that appears to be MGUS is really MGUS
- It's not MGUS if there's renal injury due to M-protein
- 30% of cases in some series are left untreated: "not enough to call it myeloma"
- Prognosis is often different from myeloma
  - Excellent survival overall. Just not for the kidneys.

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Leung, *Blood* 2012; Pozzi, *Am J Kidney Dis* 2003

Vice versa: Not all that appears to be myeloma is really myeloma

M-protein + end organ damage can mean either:

1) M-protein is causing the damage (i.e., a real plasma cell cancer), or
2) MGUS + unrelated organ damage

Critical to differentiate:

#1 gets chemotherapy, #2 does not

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Takeaway slide #2

- Figuring out if the plasma cells and/or monoclonal protein are causing damage is critical
- The gold standard for diagnosing end organ damage in plasma cell diseases is biopsy of the involved organ, not the bone marrow
  - (Bone marrow biopsies show the source of M-protein but not whether it's causing damage.)

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Case study: WJ

- 62yo male with DM, HTN, CHF, obesity
- SCr 2.5, 24h urine with 9g proteinuria inc 700 mg M-spike
- No serum M-spike. Serum free kappa 71 mg/dL, lambda 2.9, ratio 24
- Marrow with 10-15% plasma cells
- That's enough to call this myeloma…
- But renal biopsy showed DM/HTN nephropathy
- Final diagnosis: Smoldering (asymptomatic) myeloma with unrelated CKD

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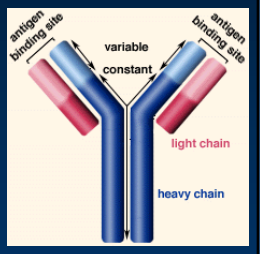
Serum free light chains and CKD

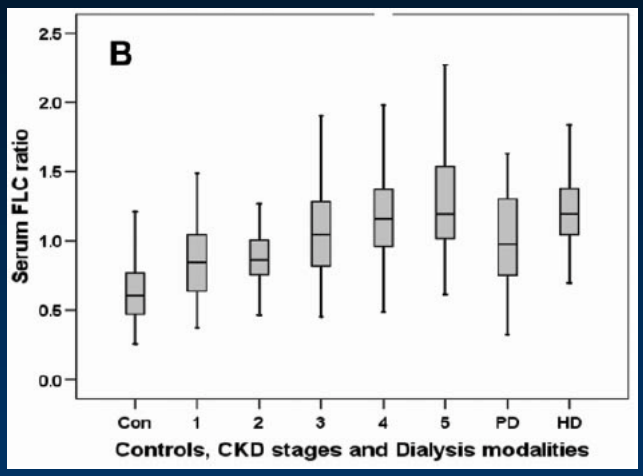
Ig Free Light Chain Kappa	0.33-1.94 mg/dl	64.70 (H)
Ig Free Light Chain Lambda	0.57-2.63 mg/dl	4.05 (H)
Ig FLC Kappa/Lambda Ratio	0.26-1.65	15.98 (H)



Serum free light chains and CKD

- Light chains are renally excreted
- Kappa:lambda (κ:λ) production is usually 2:1
- λ forms dimers, slowing renal clearance
- It balances out: serum κ:λ ratio is normally around 1
- In CKD, reticuloendothelial SFLC clearance is more important and κ:λ clearance rate is similar
- End result: κ rises more than λ, and ratio rises

Hutchison C, *BMC Nephro* 2008; Hutchison C, *Am Soc Nephro* 2008



Normal SFLC ratio in CKD:
0.35 – 3.1

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Hutchison C, *BMC Nephro* 2008; Hutchison C, *Am Soc Nephro* 2008

Takeaway slide #3

When evaluating CKD:

No M-spike on SPEP, serum IFE or 24h urine, AND

SFLC ratio outside normal range but between 0.35 and 3.1

means

SFLC abnormalities due to CKD and generally not a primary plasma cell disorder.

(And pt doesn't need a bone marrow biopsy or an oncologist.)

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Takeaway slide #4

Serum free light chain >150 mg/dL (1500 mg/L)

+

renal insufficiency (especially if new onset or progressive)

=

cast nephropathy until proven otherwise

(don't need a renal biopsy)

Renal patterns of injury in plasma cell diseases: how a lone oncologist acknowledges nephropathology in a room full of nephrologists and nephropathologists

Disease	Usual mechanism of injury	Clinical features
Multiple myeloma	Tubular (cast nephropathy)	Elevated SCr, Bence-Jones proteinuria, minimal albuminuria
Amyloid, MIDD	Glomerular	Nephrotic syndrome with non-specific proteinuria, small Bence-Jones proteinuria, SCr rises later
Cryo, GN, etc.	Various	Various

Disease	Clinical features
Multiple myeloma	Bone pain, fractures, anemia +/- pancytopenia, elevated SCr
Amyloid	**Disproportionate hypoalbuminemia, resting or orthostatic hypotension**, GI symptoms, CHF, arrhythmia, peripheral neuropathy, **peripheral edema**, macroglossia, raccoon eyes
Light / heavy / light + heavy chain deposition disease	Renal injury with associated sequelae but uncommonly involves other organ systems

Amyloid: hypoalbuminemia + CHF + orthostatic hypotension + GI problems = very challenging volume status

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Plasma cell diseases

- Background
  - Epidemiology
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  - Clinical presentations including MGRS
- Management: How far we've come

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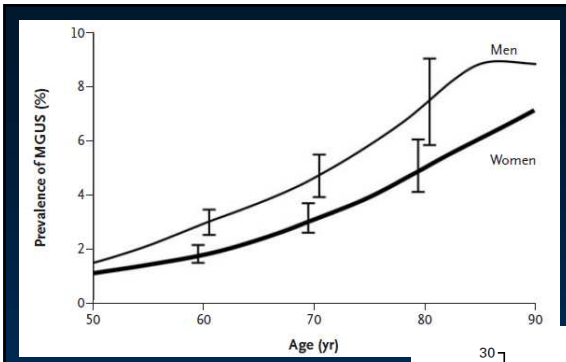
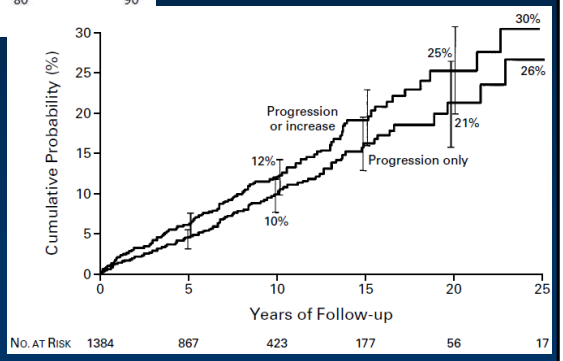


MGUS: Fairly prevalent, usually benign, so we leave it alone



Kyle R, *New Eng J Med* 2002 and 2006

Managing multiple myeloma and other plasma cell cancers

- Incurable
- Chemotherapy extends survival and provides symptom control
  - Most importantly to present company, it protects the kidneys
- Radiation and surgery have limited roles – primarily for symptomatic management of focal issues

- Cytotoxic agents
  - Melphalan (inc. stem cell transplant), cyclophosphamide, vincristine, etc.
- Corticosteroids
- Immunomodulatory agents
  - Thalidomide, lenalidomide, pomalidomide
- Proteasome inhibitors
  - Bortezomib, carfilzomib, ixazomib
- Monoclonal antibodies
  - Daratumumab, elotuzumab
- Histone deacetylase inhibitors
  - Panobinostat

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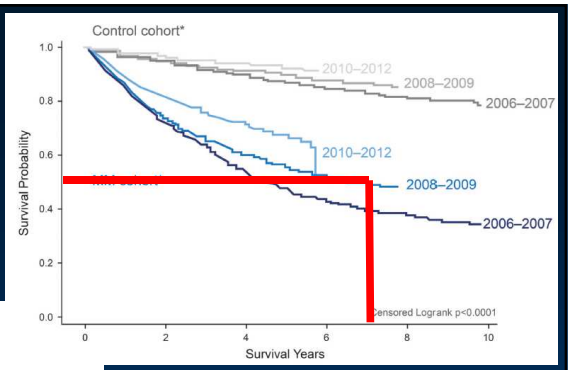
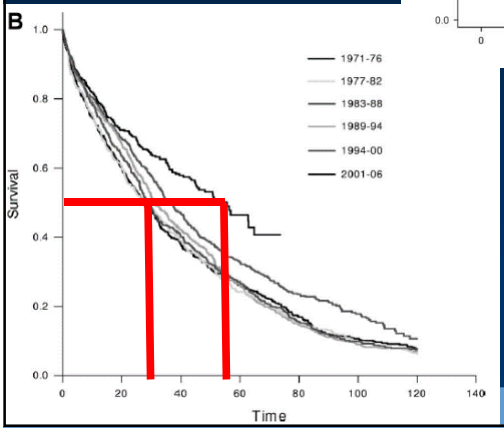
Survival is improving





Kumar, *Blood* 2008 and Fonseca, *Leukemia* 2016

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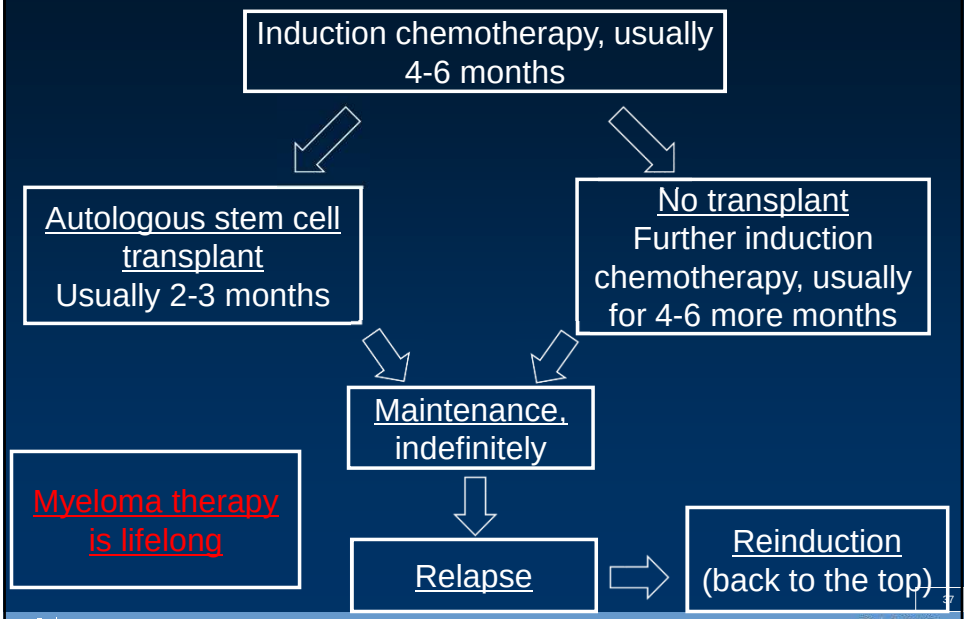
Framework for myeloma treatment



Other renal aspects of plasma cell cancers

- Renal insufficiency at diagnosis of myeloma has been a poor prognosis marker but decreasingly so
- Renal insufficiency from myeloma and amyloid kidney improves in 50-75% of cases
- Bortezomib is a drug of choice – not renally cleared and improves prognosis in high-risk myeloma

Knudsen LM, *Eur J Haem* 2000; Ludwig H, *Haem* 2007

Treating AKI from myeloma

- High cutoff dialysis to remove light chains – under testing in Europe
- Plasma exchange for cast nephropathy – single underpowered study didn't show benefit. We occasionally do it. More important is starting effective chemotherapy.

Summary

- SPEP, serum IFE and SFLC are ~97% sensitive for diagnosing myeloma
- A plasma cell disease isn't MGUS if there's renal injury (i.e., MGRS)
- Normal SFLC ratio in CKD is 0.35-3.1
- Serum free light chain of >150 mg/dL is generally diagnostic of myeloma. Don't usually need renal biopsy
- Chemotherapy prolongs survival and reduces morbidity in in plasma cell cancers
- Renal considerations are critical in these diseases

The UNC Amyloidosis (Virtual) Multidisciplinary Clinic

- Hematology/Medical oncology: B. Reeves, S. Tuchman
- Hematopoietic stem cell transplantation: W. Long
- Cardiology: B. Jensen, P. Chang
- Neurology: R. Traub
- Nephrology: K. Jain, P. Nachman, W. Pendergraft
- Pulmonary: H. Ford
- GI: S. Arora, Y. Scarlett

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