Multiple Myeloma:
A General Practice Review

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Disclosure

- Active/Recent Clinical Trial Sponsorship
  - Abbvie, Celgene, Lundbeck, Onyx, Roche
- Advisory Board/Speaker Honoraria
  - Celgene, Lundbeck, Roche
- The use of therapeutics outside of Health Canada approval will be discussed

Outline

- Epidemiology
- Myeloma Presentation & Initial Investigations
- How to Interpret Protein Studies
- Treatment Considerations
- Supportive Care
- What is Upcoming in Myeloma Management?

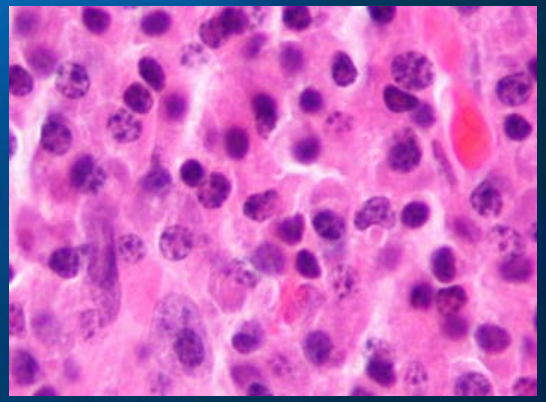


Image from Bonert, 2009, https://commons.wikimedia.org/wiki/User:Nephron

Multiple Myeloma Epidemiology

- ~ 8000 people live with MM in Canada
- 330 people in BC diagnosed with MM per year
- 170 people in BC die from MM per year

Canadian Cancer Society, Statistics, 2015

Multiple Myeloma Epidemiology

- Accounts for:
  - 20% of deaths from hematologic cancers
  - 2% of deaths from all cancers

Canadian Cancer Society, Statistics, 2015

Multiple Myeloma Epidemiology

- Median age at diagnosis of 69 years
- 15% of cases diagnosed before age 55 years
- Slightly more common among males

National Cancer Institute, SEER Cancer Statistics Factsheets: Myeloma, 2016

Multiple Myeloma Presentation

- Bone Pain 60%
- Fatigue >30% (usually due to anemia)
- Weight Loss 20%

Kyle *et al*. Mayo Clin Proc. 2003;78:21-33.

Diagnostic Challenge

- Symptoms of fatigue and pain are non-specific, and variable
- Diagnostic delays relative to other cancers

Diagnostic Challenge

- Study of MM presenting to GPs found:
  - Positive Predictive Value for any individual presenting symptom is low, including bone pain, weight loss, nosebleeds, *etc*
  - With a low threshold for considering MM, standard tests including CBC, Creat, Ca, and X-ray of bone pain dramatically improves predictive ability

Shephard *et al*. Br J Gen Pract. 2015; e106-e113.

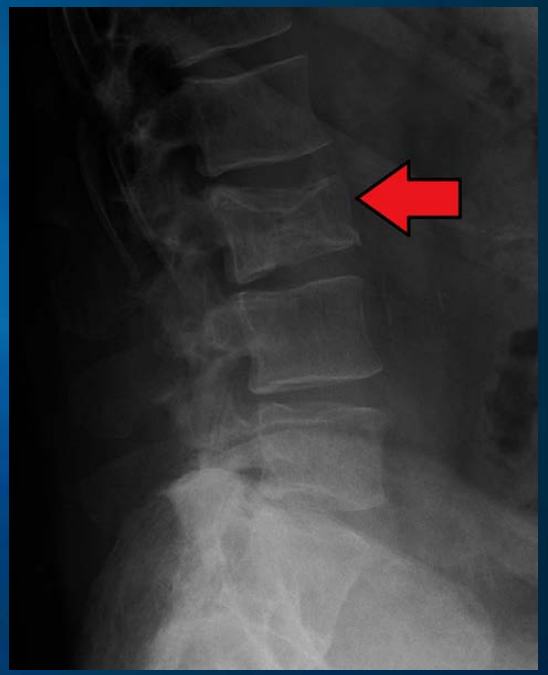
Diagnostic Challenge

- Study of MM presenting to GPs found:
  - Positive Predictive Value >10% for combinations of:
    - hyperCa and bone pain
    - Anemia and bone pain
  - Abnormal results should prompt further investigations directed to MM

Shephard *et al*. Br J Gen Pract. 2015; e106-e113.

Multiple Myeloma Presentation

- X-ray abnormality 80%
  - Lytic lesions, osteoporosis, pathologic fracture, vertebral compression fracture
- Anemia 70%
- Renal Failure 20%
- HyperCalcemia 15%



Presenting features from Kyle *et al*. Mayo Clin Proc. 2003;78:21-33.
Image from Heilman. 2016. https://en.wikipedia.org/wiki/File:PathFracMMPlainMark.png

Initial Investigations

- Patient presentation (fatigue, pain, etc)
- Consider MM on differential diagnosis
- Initial tests:
  - CBC and differential
  - Serum Creatinine
  - Calcium
  - X-ray sites of bone pain (Bone scan not useful)

Initial Investigations

- If MM remains a possible diagnosis
  - Order Protein Studies
  - Bone Marrow Biopsy required for diagnosis
- Consult Specialist

Mono-Clonal Protein Testing

- Normal Plasma Cell Function:
  - Part of Humoral Immunity
  - Variety of plasma cells each producing one type of immunoglobulin/antibody (Ig)
  - Each mature plasma cell produces thousands of identical Ig every second

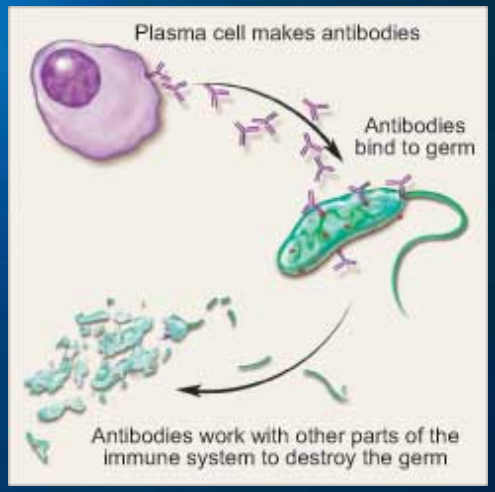


Image from National Cancer Institute, SEER Cancer Statistics Factsheets: Myeloma, 2016

- Myeloma Plasma Cell:
  - Malignant plasma cells from a *single clone* produce one type of Ig
  - *i.e.,* billions of cancer cells each secreting thousands of identical Ig every second

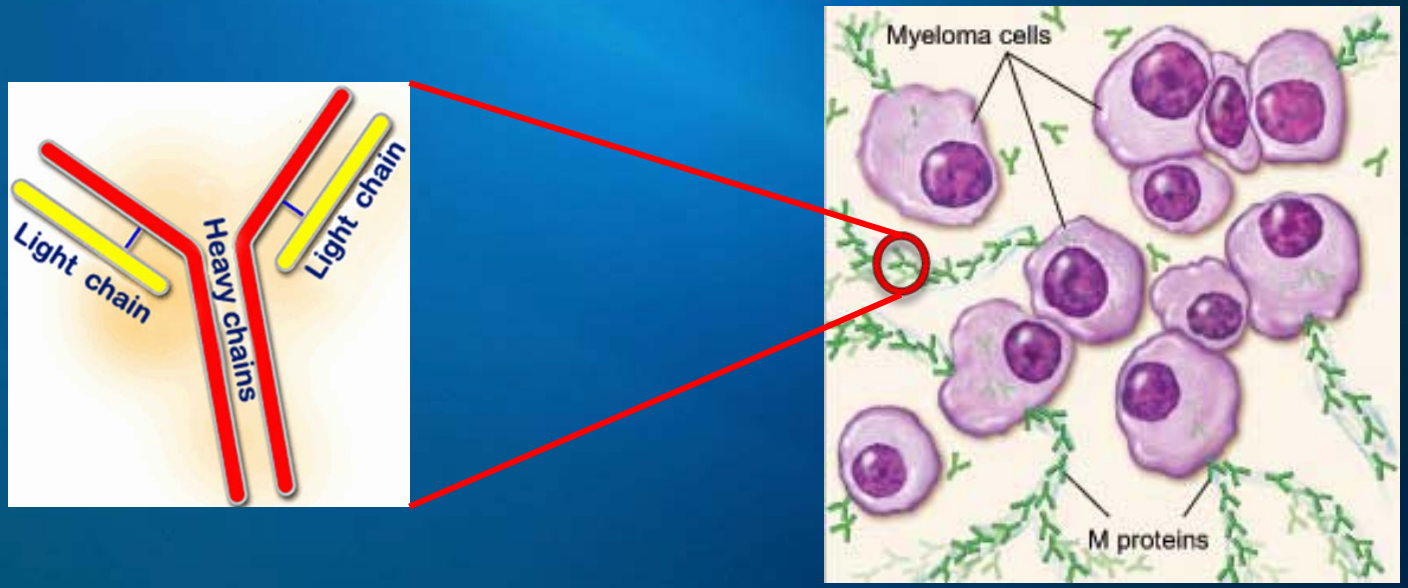
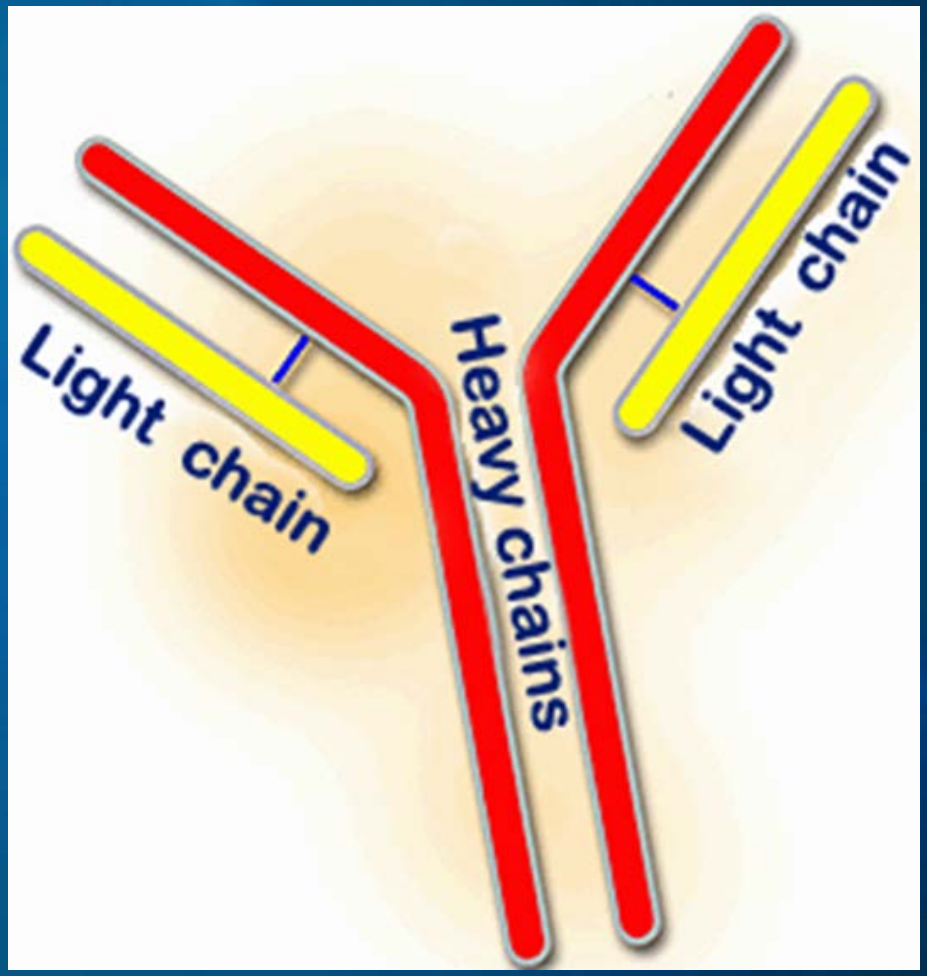


Image from National Cancer Institute, SEER Cancer Statistics Factsheets: Myeloma, 2016

Mono-Clonal Protein



Mono-Clonal Protein Testing

- Monoclonal Protein also called:
  - M-protein
  - Para-protein
  - M-spike
  - Bence Jones Proteins (urine light chains)

Dr Henry Bence Jones
1813-1873

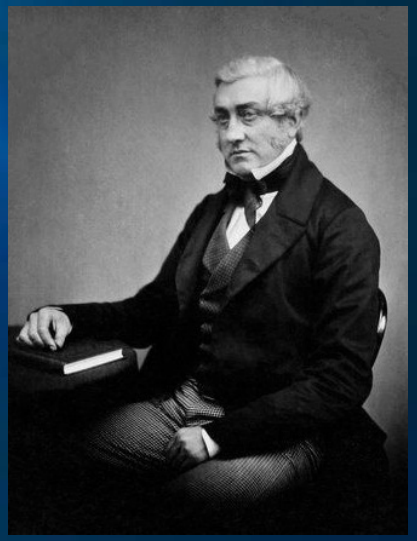


Image public domain

Mono-Clonal Protein Testing

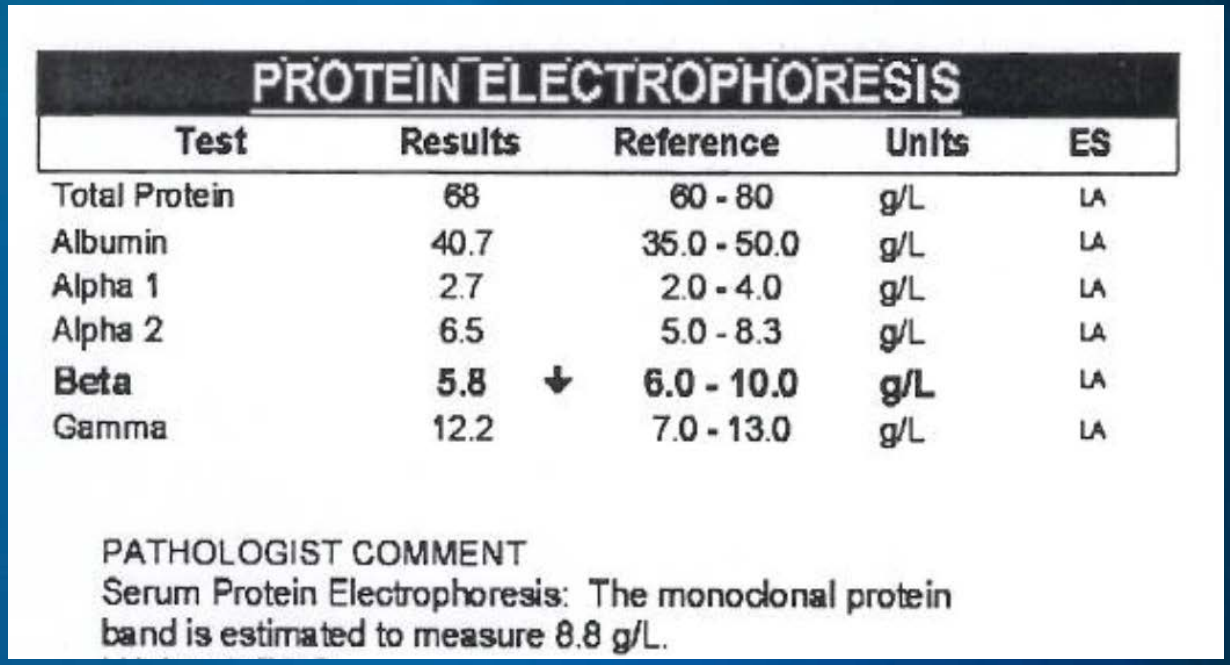
- M-protein is assessed to:
  - Confirm diagnosis
  - Monitor disease
  - Assess response to therapy

Mono-Clonal Protein Testing

- Protein tests include:
  - Serum Protein Electrophoresis & Immunofixation
  - Serum Free Light Chain Assay
  - 24hr Urine Protein Electrophoresis

Mono-Clonal Protein Testing

- Serum Protein Electrophoresis Example



PROTEIN ELECTROPHORESIS

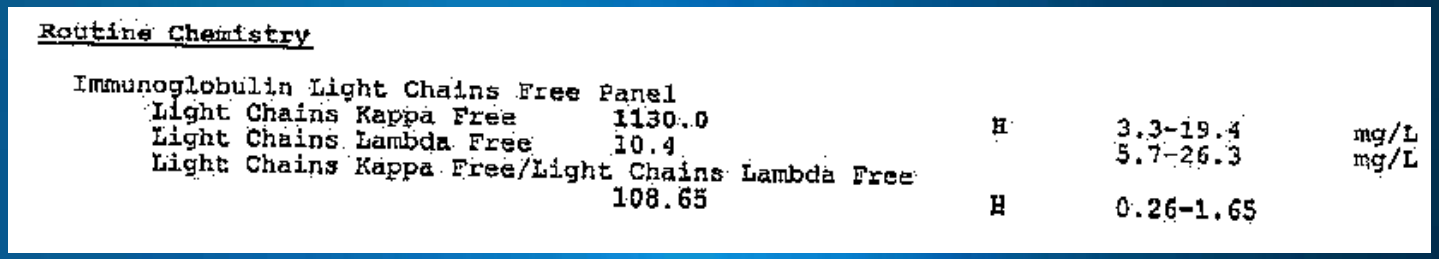
Test	Results		Reference	Units	ES
Total Protein	68		60 - 80	g/L	LA
Albumin	40.7		35.0 - 50.0	g/L	LA
Alpha 1	2.7		2.0 - 4.0	g/L	LA
Alpha 2	6.5		5.0 - 8.3	g/L	LA
Beta	**5.8**	↓	**6.0 - 10.0**	**g/L**	LA
Gamma	12.2		7.0 - 13.0	g/L	LA

PATHOLOGIST COMMENT
Serum Protein Electrophoresis: The monoclonal protein band is estimated to measure 8.8 g/L.

- **M-protein is 8.8 g/L**
- **No immunofixation done so we don't know the type of M-protein**
- **Note M-protein does not correspond with any of the other protein levels in the SPEP**

Mono-Clonal Protein Testing

- Serum Free Light Chain Example



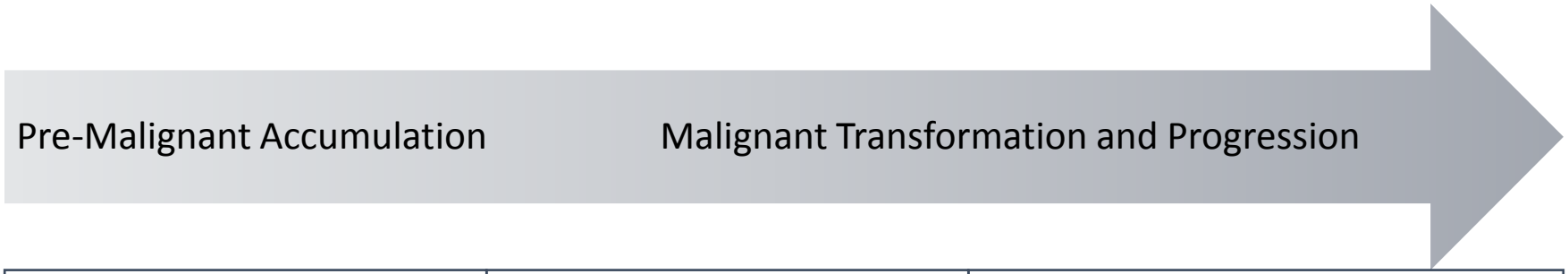
Routine Chemistry

Immunoglobulin Light Chains Free Panel

Light Chains Kappa Free	1130.0	H	3.3-19.4	mg/L
Light Chains Lambda Free	10.4		5.7-26.3	mg/L
Light Chains Kappa Free/Light Chains Lambda Free	108.65	H	0.26-1.65	

- **Free light chain level is 1130mg/L (normal = 3-19mg/L)**
- **Free light chain type is Kappa**
- **Ratio of Kappa to Lambda is 108 (normal ≈ 1)**

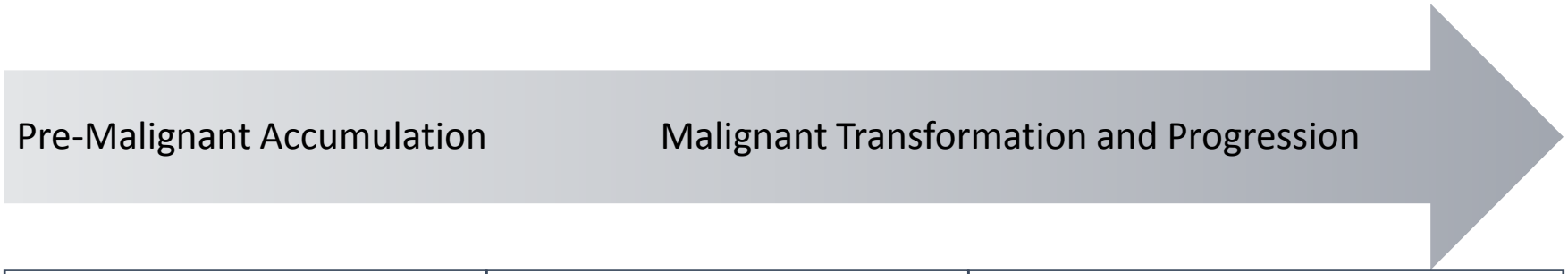
- Monoclonal Proteins may be found in:
  - Multiple Myeloma
  - Monoclonal Gammopathy of Undetermined Significance
  - Plasmacytoma
  - Waldenströms Macroglobulinemia/Lymphoplasmacytic Lymphoma
  - Chronic Lymphocytic Leukemia
  - Other B cell Lymphomas



MGUS	Smoldering Myeloma	Myeloma
• M-protein <30g/L, and • BMPC <10%, and • No myeloma related end organ damage • 1%/yr risk of progression to Myeloma • Observation only	• M-protein ≥30g/L, and • BMPC ≥10%, and • No myeloma related end organ damage • 10%/yr risk of progression to Myeloma in the first 5 years • Observation only	• Any M-protein, and • BMPC ≥10%, and • ≥1 CRAB feature of myeloma related end organ damage, or • New criteria including at least one "myeloma defining event": BMPC ≥60%, involved/uninvolved SFLC ratio >100, 2 or more focal bone lesions on MRI

Abbreviations: MGUS: monoclonal gammopathy of undetermined significance; BMPC: bone marrow plasma cells; CRAB: calcium >2.75mmol/L, renal dysfunction with CrCl <40ml/min or serum creatinine > 177umol/L, anemia with Hb < 100g/L or 20g/L < normal, bone disease including lytic lesions or osteoporosis: SFLC: serum free light chain.

Rajkumar *et al.* Lancet Oncol. 2014. e538-e548.



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Smoldering Myeloma

- M-protein ≥30g/L, and
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Pre-Malignant Accumulation → Malignant Transformation and Progression

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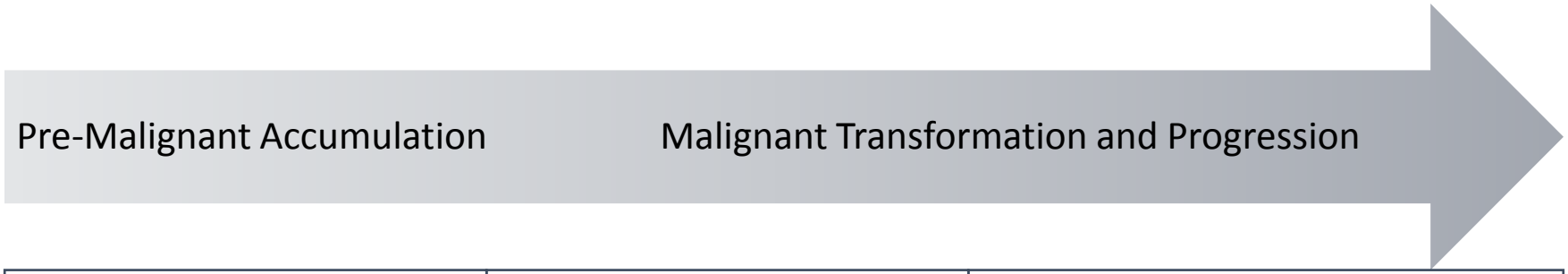

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Treatment Considerations

- MM remains incurable with current treatments
- Survival is variable, based on:
  - Cytogenetics*
  - LDH*
  - Albumin*
  - Beta-2 microglobulin*
  - Age
  - Gene expression profiling

*Revised International Staging System - Palumbo *et al*. J Clinic Oncol. 2015; 33(26):2863-2869

Treatment Considerations

- Factors influencing treatment choice include:
  - Patient comorbidities
  - Functional status
  - Cytogenetics
  - Response to therapy (relapsed setting)
  - Toxicity of therapy (relapsed setting)
  - Drug access

Dimopoulos, *et al*. Nat Rev Clin Oncol. 2015;42-54.

Active Myeloma

Previously Untreated

Transplant Candidate
- Age < 70 years
- Otherwise healthy

Non-Transplant Candidate
- Age ≥ 70 years
- Comorbidities

Relapsed Disease

Active Myeloma

Previously Untreated

Transplant Candidate
- Age < 70 years
- Otherwise healthy

Non-Transplant Candidate
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Relapsed Disease

Active Myeloma

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- Age < 70 years
- Otherwise healthy

Non-Transplant Candidate
- Age ≥ 70 years
- Comorbidities

Relapsed Disease

Case 1

- 54 yr man presents with:
  - 2 - 3 months progressive low back pain
  - Fatigue
  - PMH: hypertension, 2 years renal dysfunction

Case 1

- After initial visits to GP, pain worsened, patient presented to local ER
  - CT thoracic and lumbar spine identified
    - T10 wedge compression fracture
    - lytic disease L spine
    - decreased bone density
    - “mottled” bone marrow
- Prompted MM directed investigations

Case 1

- Bone Marrow Biopsy
  - Up to 90% plasma cellularity
- Protein Studies
  - SPEP: 1.5g/L kappa free light chains
  - 24 hr UPEP: 12.9g kappa free light chains
  - Serum FLC Assay: 18,200 mg/L kappa free light chains
- Imaging
  - Skeletal Survey (plain x-ray): T10 compression fracture

Case 1

- Labs:
  - CBC normal
  - Ca normal
  - Creat 151 (GFR ~ 40ml/min)

  - Other labs relevant to MM staging/prognosis:
    - LDH, albumin, beta 2 microglobulin, cytogenetics

Active Myeloma

Previously Untreated

Transplant Candidate
- Age < 70 years
- Otherwise healthy

Non-Transplant Candidate
- Age ≥ 70 years
- Comorbidities

Relapsed Disease

Case 1

- Treated with triplet Bortezomib-Cyclophosphamide-Dexamethasone
- Discussed T10 kyphoplasty with neurosurgeon
- Monthly Pamidronate

Case 1

- Biochemical response based on serum FLC:
  - 18,200mg/L pre treatment
  - 623mg/L after 4 cycles Bort-Cyclo-Dex
  - *i.e.,* 97% reduction in m-protein level
- Patient has now gone to autologous stem cell transplant to deepen response

Case 2

- 74 yr man presents with:
  - Worsening low back pain, radiculopathy
  - Fatigue
  - PMH: chronic low back pain, depression

Case 2

- X-ray L-spine and pelvis:
  - Lytic disease pelvis, compression fracture L-spine
- Lab:
  - Hgb 102
  - Creat 110
  - Ca_{corr} 2.9

Case 2

- Protein Studies
  - SPEP: 42 g/L IgG kappa
- Bone Marrow Biopsy
  - 40% plasma cellularity
- Imaging:
  - MR L spine: no cord compression
  - Skeletal survey: lytic lesions skull, pelvis, and L spine compression fracture

Active Myeloma

Previously Untreated

Transplant Candidate
- Age < 70 years
- Otherwise healthy

Non-Transplant Candidate
- Age ≥ 70 years
- Comorbidities

Relapsed Disease

Case 2

- L-spine compression fracture:
  - No kyphoplasty available at the time
  - Pain responded quickly to analgesics, bisphosphonate, and MM treatment
  - Did not require radiation therapy for pain

Case 2

- MM treated on clinical trial:
  - Lenalidomide Dexamethasone
  - Complete Response
    - No detectable m-protein
    - No detectable MM cells in repeat bone marrow biopsy
  - Remains alive, well, on treatment

Drug Classes

- For a more complete review of mechanism of action, toxicity, renal dosing, etc., please refer to BC Cancer Agency Drug Manual available on line or other resources:

http://www.bccancer.bc.ca/health-professionals/professional-resources/cancer-drug-manual/drug-index

Drug Classes

- Systemic Steroids
  - Oral
  - Dexamethasone (*e.g.*, 40mg once weekly)
  - Prednisone
  - Combined with other drugs
  - Induce a response as a single agent
  - Synergistic with many other MM treatments

Drug Classes

- Alkylators
  - Oral or IV
  - Melphalan
  - Cyclophosphamide
  - Often combined with steroid and other drug class
  - Myelosuppressive

Drug Classes

- Immunomodulatory Drugs
  - Oral
  - Thalidomide
  - Lenalidomide
  - Pomalidomide
  - Regulated by Health Canada b/c Teratogen
  - Increase risk of DVT/PE – require prophylaxis
  - Other prominent side effects:
    - Immunosuppression & Cytopenias
    - Constipation
    - Rash

Drug Classes

- Proteasome Inhibitors
  - Bortezomib (IV or subQ)
  - Carfilzomib (IV), Ixazomib (oral) – not BCCA funded
  - A preferred drug class in renal failure
  - Increase risk of shingles – require prophylaxis
  - Other prominent side effects:
    - Immunosuppresion and cytopenias
    - Peripheral neuropathy
    - Diarrhea

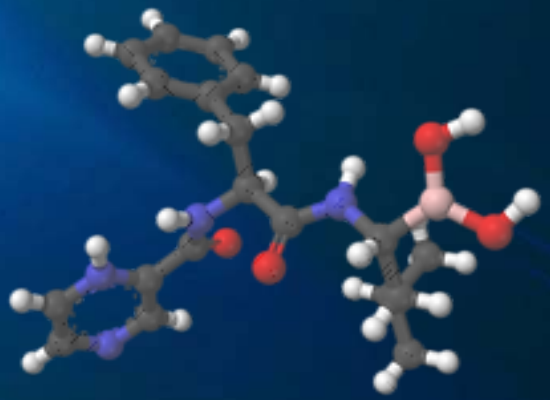


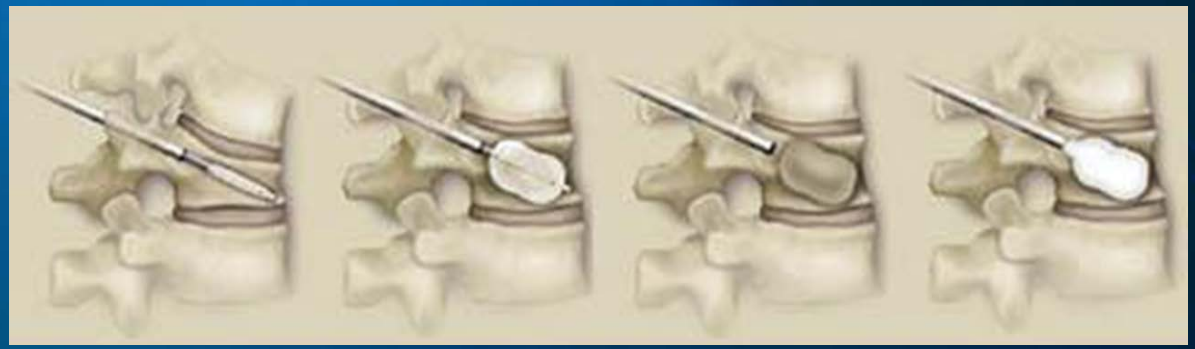
Image by Ben Mills, public domain

Supportive Care in Primary Practice

- Pain Management
  - Analgesics
    - Acetaminophen
    - Opioids
    - Systemic Steroids
    - Others for Neuropathic Pain (Gabapentin, *etc*)
  - Avoid NSAID
    - Risk of renal dysfunction

Supportive Care in Primary Practice

- Managing Painful Bone Disease
  - Radiation Therapy
    - Minimized to areas of active bone marrow
  - Kyphoplasty/Vertebroplasty
    - Treat acute compression fractures



Kyphoplasty image from Kochan *et al*. eMedicine, 2015.

Supportive Care in Primary Practice

- Bisphosphonate
  - Treat bone pain
  - Reduce risk of future bone disease
  - BCCA funds Pamidronate IV for active MM patients
  - Duration of therapy 1-2 years
  - 1% risk of Osteonecrosis of Jaw
    - Preventative dental work prior to bisphosphonate
    - Stop bisphosphonate 2-3 months prior and restart 2-3 months post invasive dental work (Lack of evidence)
    - Prevalence increases with prolonged duration of therapy (*i.e.*, >2 years)

Ruggierro *et al.* Position Paper. American Association of Oral and Maxillofacial Surgeons. Medication Related Osteonecrosis of the Jaw – 2014 Update.

Supportive Care in Primary Practice

- Managing Fatigue
  - Consider Cause
  - Anemia
    - Disease Related
    - Treatment Related
    - Transfuse PRBC
    - Erythropoeisis Stimulating Agents*
  - Anemia often responds to MM therapy
  - Depression, Medications, Other

Supportive Care in Primary Practice

- Infectious Risk
  - Infection is common cause of death in MM
  - Immunosuppressed due to disease and therapy
  - Low threshold for work-up and treatment

  - BCCA recommends immunizations:
    - Annual flu
    - Pneumococcal at diagnosis (≥2 weeks pre chemo)

Supportive Care in Primary Practice

- Renal Failure
  - Avoid Nephrotoxins;
    - NSAID, CT contrast, etc
  - Refer to Nephrology as needed

Supportive Care in Primary Practice

- Thrombosis
  - MM increases risk of thrombosis
  - Immunomodulatory drugs (IMID) and systemic steroids increase risk further
  - MM therapy with IMID requires DVT prophylaxis
  - Low threshold to consider DVT/PE in MM patients
  - LMWH is treatment of choice for DVT/PE

Supportive Care in Primary Practice

- HyperCalcemia
  - Bisphosphonate
  - Hydration, Steroids, etc.

Supportive Care in Primary Practice

- Systemic Steroids
  - Relatively high doses part of MM therapy
  - New onset hyperglycemia, or exacerbation of DM
  - Psychiatric problems including insomnia, and mood change
  - Dyspepsia

What's Upcoming in Myeloma Management?

- Recently approved drugs in Canada for relapsed MM
  - Proteasome Inhibitors:
    - Carfilzomib (IV) in combo with Lenalidomide-Dex
    - Ixazomib (oral) in combo with Lenalidomide-Dex
  - Monoclonal Antibodies:
    - Daratumumab (MoAb vs CD38) single agent
    - Elotuzumab (MoAb vs SLAMF7) in combo with Len-Dex

What's Upcoming in Myeloma Management?

- Other drug classes not approved by Health Canada for MM
  - Panobinostat - histone deacetylase (HDAC) inhibitor (approved for MM by FDA 2015)
  - Selinexor – oral, Selective Inhibitor of Nuclear Export
  - Venetoclax – oral, Bcl2 Inhibitor
  - Pembrolizumab – anti-PD1 MoAb, checkpoint inhibitor (approved for met NSCLC and met melanoma by Health Canada)
  - Many other treatments under investigation…

Outcomes for Myeloma Patients Improving

- Untreated active MM survival ~6 months
- Survival did not improve 1970s to mid 1990's
  - Survival with treatment 2.5 years
- In the following decade with novel therapy:
  - Patients <65, survival improved from 33 months to 60 months
  - Patients >65, survival improved from 26 months to 32 months

Kumar *et al*. Blood 2008 111:2516-2520

Discussion/Questions?