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?

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%

Symptoms of fatigue and pain are non-specific, and variable

Diagnostic delays relative to other cancers
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.

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

Multiple Myeloma Presentation

- X-ray abnormality 80%
  - Lytic lesions, osteoporosis, pathologic fracture, vertebral compression fracture

- Anemia 70%

- Renal Failure 20%

- HyperCalcemia 15%

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

Light chain

Heavy chains

Light chain
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
M-protein is assessed to:

- Confirm diagnosis
- Monitor disease
- Assess response to therapy
Protein tests include:

- Serum Protein Electrophoresis & Immunofixation
- Serum Free Light Chain Assay
- 24hr Urine Protein Electrophoresis
Serum Protein Electrophoresis Example

**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

• 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
- Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma
- Chronic Lymphocytic Leukemia
- Other B cell Lymphomas
<table>
<thead>
<tr>
<th>Pre-Malignant Accumulation</th>
<th>Malignant Transformation and Progression</th>
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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.

### MGUS
- M-protein <30g/L, and
- BMPC <10%, and
- No myeloma related end organ damage
- 1%/yr risk of progression to Myeloma
- Observation only

### Smoldering Myeloma
- 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

### Myeloma
- 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

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**Rajkumar et al.** Lancet Oncol. 2014. e538-e548.
### Pre-Malignant Accumulation

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- SFLC: serum free light chain

Treating Considerations

MM remains incurable with current treatments

Survival is variable, based on:
- Cytogenetics*
- LDH*
- Albumin*
- Beta-2 microglobulin*
- Age
- Gene expression profiling

Factors influencing treatment choice include:

- Patient comorbidities
- Functional status
- Cytogenetics
- Response to therapy (relapsed setting)
- Toxicity of therapy (relapsed setting)
- Drug access

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

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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
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
- $\text{Ca}_{\text{corr}}$ 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
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
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
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
Supportive Care in Primary Practice

Pain Management

Analgesics
- Acetaminophen
- Opioids
- Systemic Steroids
- Others for Neuropathic Pain (Gabapentin, etc)

Avoid NSAID
- Risk of renal dysfunction
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.
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)

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
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)
Renal Failure

- Avoid Nephrotoxins;
  - NSAID, CT contrast, etc
- Refer to Nephrology as needed
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.
Systemic Steroids

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