Diagnosis and Management of Multiple Myeloma and Related Plasma Cell Disorders: A Primary Care Perspective

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Plasma Cell Disorder Spectrum
Multiple Myeloma (and MGUS)
How Common is Multiple Myeloma?

- Multiple Myeloma is the 2nd most common cancer of the blood.
- 103,463 living with, or in remission.
- Myeloma represents 1.8% of all new cancer cases in the U.S.
- Myeloma is most frequently diagnosed among people aged 65-74.
- Median age at diagnosis is 69.
Definitions

- **Plasma cells**: Terminally differentiated B lymphocytes specialized to produce antibodies

- **Myeloma cells**: Clonal proliferation of malignant plasma cells which produce a monotypic antibody.

- **"M-protein" (paraprotein)**: An immunoglobulin, with light and/or heavy chains, usually secreted from the cells. (2-5% of MM patients are non-secretory)
What is Multiple Myeloma?

Normal plasma cells

Antibodies

M proteins

Light chain

Heavy chains

Multiple myeloma cells

Bone

Bone marrow
Risk Factors for Developing Multiple Myeloma

- Age
- 9/11
- Gender
- Race
- Family History
- Chemicals
- MGUS

Multiple Myeloma
Effects of Myeloma and Common Symptoms

- Low blood counts
  - Weakness
  - Fatigue
  - Infection

- Decreased kidney function
  - Weakness

- Bone damage
  - Bone pain

- Bone turnover
  - Loss of appetite
  - Weight loss

*About 10% to 20% of patients with newly diagnosed myeloma do not have any symptoms.*
Know the Diagnosis
Key Items That Define the Diagnosis

- MGUS
  - 1% risk of progression/year to active myeloma or related conditions

- Smoldering Myeloma
  - 10% risk of progression/year to active myeloma

- Active Multiple Myeloma
MGUS

- Cancers
  - Myeloma
  - Macroglobulinemia
  - Plasmacytoma

- Paraprotein
  - AL Amyloidosis
  - LCDD
  - Cryoglobulinemia

- Associations
  - Proliferative GN
  - Neuropathy
  - Skin Disorders
Knowing the Diagnosis

- Immunoglobulins/ Light Chains
Knowing the Diagnosis

- Protein Electrophoresis ("M-Spike")

Diagram showing the process of protein electrophoresis, including steps such as buffer-saturated strip of filter paper, serum sample, anode, cathode, and light absorption with percentage ranges for albumins, α1, α2, β, and γ-globulins.
Knowing the Diagnosis

- Protein Electrophoresis ("M-Spike") – "The How Much"

Normal

Multiple Myeloma
Knowing the Diagnosis

- Immunofixation – “The What”
Knowing the Diagnosis

• Light Chains – “The Confusing!”

  • Units
  • Absolute Numbers
    • One Increased
    • Other Decreased
    • Both Increased
  • Ratio
Knowing the Diagnosis

- Light Chains – “The Confusing!”
  - Units
  - Absolute Numbers
    - One Increased
    - Other Decreased
    - Both Increased
  - Ratio
Knowing the Diagnosis

- Light Chains – “The Confusing!”

  - Units
  - Absolute Numbers
    - One Increased
    - Other Decreased
    - Both Increased

<table>
<thead>
<tr>
<th>Kappa</th>
<th>Lambda</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>100 (Involved)</td>
<td>1 (Uninvolved)</td>
<td>100</td>
</tr>
<tr>
<td>100 (Involved)</td>
<td>0.5 (Uninvolved)</td>
<td>200</td>
</tr>
<tr>
<td>50</td>
<td>40</td>
<td>1.3</td>
</tr>
</tbody>
</table>
Bone Marrow Biopsy

• “The Necessary!”

• Plasma cell percentage

• Cytogenetics/FISH
  • Risk Category/Prognosis

• Evolving into Genomic testing

• Additional information
  • Any other causes of anemia
  • Iron stores

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### Differential Diagnosis and Diagnostic Criteria for MGUS → Multiple Myeloma

<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>Smoldering Myeloma</th>
<th>Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asymptomatic</strong></td>
<td>M protein &lt;3g/dL</td>
<td>M protein ≥3g/dL</td>
<td>M protein in serum or urine</td>
</tr>
<tr>
<td></td>
<td>Bone marrow plasma cells &lt;10%</td>
<td>Bone marrow plasma cells ≥10%</td>
<td>Bone marrow plasma cells ≥10%</td>
</tr>
<tr>
<td></td>
<td>No related organ or tissue impairment</td>
<td>No related organ or tissue impairment</td>
<td>Related organ or tissue impairment</td>
</tr>
<tr>
<td></td>
<td>No other B cell proliferative disorder</td>
<td></td>
<td>“CRAB”</td>
</tr>
</tbody>
</table>
High risk of progression

Similar to MGUS?

27% will convert in 15 yrs
Roughly 2% per yr

Smoldering Myeloma

- M-protein >3 g/dl and/or >10% BM plasma cells
- No “CRAB” criteria
- Evolution into overt MM @ ~3%/year
  - >10% PCs in BM
  - BJ proteinuria detected
  - IgA isotype
- Recently added to “active” MM:
  - BM PCs >60%
  - LC involved/uninvolved >100
  - MRI: ≥1 focal lesion

mSMART 3.0: Classification of Active MM

**High-Risk**
- High Risk genetic Abnormalities
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - Del 17p
  - p53 mutation
  - Gain 1q
- RISS Stage 3
- High Plasma Cell S-phase
- GEP: High risk signature

**Standard-Risk**
- All others including:
  - Trisomies
  - t(11;14)
  - t(6;14)

- Double Hit Myeloma: Any 2 high risk genetic abnormalities
- Triple Hit Myeloma: 3 or more high risk genetic abnormalities

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Trisomies may ameliorate

By FISH or equivalent method

Cut-offs vary

t(11;14) may be associated with plasma cell leukemia

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Management of Multiple Myeloma: Some General Principles
Some General Principles

- Combination regimens are more beneficial
  - “Doublets” vs. “Triplets”

- Longer duration of therapy is beneficial in preventing disease progression

- Depth of response is important, especially in newly diagnosed patients
  - DON’T save the best regimen for later.

- Side effect profile:
  - Need to manage side effects well to stay on beneficial regimens
  - Dosing and schedule may be modified but can affect efficacy.
Clonal Evolution: Implications

• **Multiple clones with variable drug sensitivity**
  – *Combination chemotherapy a necessity*

• **Re-emergence of drug sensitive clones**
  – *Once resistant not always resistant*
  – *Continuous suppressive therapy logical*

• **Minor drug resistance clones lethal**
  – *Need to understand mechanism of resistance as a means to eradicate*
## FDA Approved MM Therapeutics in the U.S.

### The “Big Five”

<table>
<thead>
<tr>
<th>Name</th>
<th>Use</th>
<th>Route</th>
<th>Mode of Action</th>
<th>Plus</th>
<th>Minus</th>
<th>Clinical Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>ND, RR</td>
<td>Oral</td>
<td>IMiD</td>
<td>Safe in kidney dysfunction, Minimal myelo-suppression</td>
<td>Neuropathy, Fatigue, Thrombosis</td>
<td>ORR; especially in combinations even in late disease</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>ND, RR</td>
<td>Oral</td>
<td>IMiD</td>
<td>Little neuropathy, Safe over long durations</td>
<td>Thrombosis, GI side effects, Cytopenias, Fatigue, Secondary malignancies</td>
<td>ORR; especially in combinations in early and late disease, Most extensive maintenance data</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>RR</td>
<td>Oral</td>
<td>IMiD</td>
<td>Little neuropathy, more combination data emerging</td>
<td>All similar to Len. May need lower dose (2 mg) in triplet combinations</td>
<td>ORR</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>ND, RR</td>
<td>SC/IV</td>
<td>Proteasome</td>
<td>Excellent efficacy, use in renal dysfunction, high risk, manageable cytopenias</td>
<td>Peripheral neuropathy (SC and weekly)</td>
<td>ORR, OS benefit, extensive efficacy and safety data including maintenance</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>ND, RR</td>
<td>IV</td>
<td>Proteasome</td>
<td>All benefits as bortezomib, minimal neuropathy</td>
<td>Twice/Once weekly, cardiopulm toxicity</td>
<td>High CR rate, OS benefit</td>
</tr>
</tbody>
</table>

**ND=Newly Diagnosed, RR=Relapsed/Refractory, SC=Subcutaneous, IV=Intravenous, ORR=Overall Response Rate, CR=Complete Response, OS=Overall Survival**
## FDA Approved MM Therapeutics in the U.S.

### The “New Three”

<table>
<thead>
<tr>
<th></th>
<th>Use</th>
<th>Route</th>
<th>Mode of Action</th>
<th>Plus</th>
<th>Minus</th>
<th>Clinical Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ixazomib</strong></td>
<td>RR</td>
<td>Oral</td>
<td>Proteasome</td>
<td>All benefits as bortezomib, minimal neuropathy</td>
<td>Specialty medication, GI side effects, thrombocytopenia</td>
<td>ORR; being studied wherever bortezomib used, maintenance</td>
</tr>
<tr>
<td><strong>Daratumumab</strong></td>
<td>ND, RR</td>
<td>IV</td>
<td>Anti-CD38</td>
<td>Less overlapping toxicities with other agents, well-tolerated,</td>
<td>Long infusion time, infusion reactions, some safety data in renal failure</td>
<td>ORR; Extensive triplet data emerging. Deepest MRD negativity with lenalidomide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>significant efficacy even as a single-agent</td>
<td></td>
<td>among all regimens</td>
</tr>
<tr>
<td><strong>Elotuzumab</strong></td>
<td>RR</td>
<td>IV</td>
<td>Anti-CS1</td>
<td>Less overlapping toxicities with other agents, well-tolerated</td>
<td>Not much efficacy as single agent, no reported efficacy in patients who are IMiD</td>
<td>ORR, better MRD than doublet. Consider when planning lenalidomide+dexamethasone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>refractory (even patients progressing on lenalidomide maintenance)</td>
<td></td>
</tr>
</tbody>
</table>
Autologous Transplantation

Disease control

Stem Cell Harvest

Transplant

Cytokines

Pheresis

Cryopreserve

High-dose chemo
Myeloma Treatment

Early therapy
- Prevention
- Curative Approach

Risk-adapted Therapy
- Response and MRD directed
- Overcome high risk features
Improved Survival in Myeloma

Waldenstrom’s Macroglobulinemia
What is Waldenstrom’s Macroglobulinemia?

• WM is a rare plasma cell cancer with ~1,400 cases diagnosed each year

• IgM-MGUS is precursor condition, conferring a 46-fold higher relative risk for developing WM

• WM cells arise from B-lymphocytes

• Diagnosis of WM made by increased serum IgM and lymphoplasmacytic cell invasion of bone marrow (and organs) in conjunction with clinical symptoms
Waldenstrom’s Macroglobulinemia

Prevalence and Patients

- WM is more common in men than it is in women

The median age at diagnosis is

63 - 68 years of age

Incidence rates among men and women in Europe are approximately

7.3 and 4.2 per million persons, respectively

Median overall survival rate

5 - 11 years
Diagnostic Entities

- Asymptomatic WM: Watch and wait
  - Absence of any of the symptoms below
- Symptomatic WM: Candidates for therapy
  - Disease-related hemoglobin < 10 g/dL
  - Platelets < 100 x 10^9/L
  - Bulky lymphadenopathy or organomegaly
  - Symptomatic hyperviscosity
  - Moderate/severe or advancing disease-related neuropathy
  - Symptomatic amyloidosis
  - Cryoglobulinemia or cold-agglutininin disease
### WM or MM?

<table>
<thead>
<tr>
<th></th>
<th>MM</th>
<th>WM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatosplenomagaly</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Hyperviscosity</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Bence Jones Proteins in Urine</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Coomb’s Test Positive</td>
<td>Less common</td>
<td>More common</td>
</tr>
<tr>
<td>Bone Lesions</td>
<td>More common</td>
<td>Rare</td>
</tr>
<tr>
<td>Immunoglobulin Subtype</td>
<td>Any, IgG and IgA more common</td>
<td>IgM</td>
</tr>
<tr>
<td>Light Chain Only Disease</td>
<td>In ~15% cases</td>
<td>Not seen</td>
</tr>
</tbody>
</table>
# Treatment for WM: Hybrid Between Myeloma and Lymphoma

## The “Big Five”

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Route</th>
<th>Mode of Action</th>
<th>Plus</th>
<th>Minus</th>
<th>Clinical Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>ND, RR</td>
<td>Oral</td>
<td>BTK-inhibitor</td>
<td>Convenient, Long-term, FDA-approved</td>
<td>No deep responses, QoL issues, Bleeding/bruising</td>
<td>ORR; single-agent or with rituximab</td>
</tr>
<tr>
<td>Rituximab</td>
<td>ND, RR</td>
<td>IV</td>
<td>MoAb</td>
<td>Well-tolerated</td>
<td>IgM flare, infusion-related reactions, limited single-agent activity</td>
<td>ORR; combined with other agents, maintenance</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>ND, RR</td>
<td>SC/IV</td>
<td>Proteasome</td>
<td>Use in renal dysfunction, manageable cytopenias</td>
<td>Peripheral neuropathy (SC and weekly)</td>
<td>ORR, Combined with other agents</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>ND, RR</td>
<td>IV</td>
<td>Proteasome</td>
<td>All benefits as bortezomib, no neuropathy</td>
<td>Twice/Once weekly</td>
<td>ORR, Combined with other agents</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>ND, RR</td>
<td>IV</td>
<td>Alkylator</td>
<td>Fast effect, fairly well-tolerated</td>
<td>Myelosuppressive</td>
<td>ORR, Combined with other agents</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>ND, RR</td>
<td>IV</td>
<td>Alkylator</td>
<td>Fast effect, fairly well-tolerated</td>
<td>Myelosuppressive</td>
<td>ORR, Combined with other agents</td>
</tr>
</tbody>
</table>
Gaps in Our Understanding of WM Treatment

- Lack of comparative trials.
- Lack of overall survival advantage data.
- Depth vs. duration of response.
- Need for maintenance therapy and choice of agent.
- Appropriate sequencing of agents.
- Duration of induction therapy – desired response/tolerability vs. fixed duration.
- How much intensity is enough?
Amyloidosis
Diagnosis – In the Correct Clinical Setting

Diagnosis of amyloidosis by Congo Red

Tissue typing by mass spectrometry

AL/AH amyloidosis
(immunoglobulin light or heavy chain)

Other amyloidosis

ATTR amyloidosis
(transthyretin)

ATTR full gene analysis

Disease-causing mutation diagnostic for ATTR familial amyloidosis

Variant of uncertain Significance (VUS)

Wild-type (senile) amyloidosis
Diagnosis – All Criteria Required

AL Amyloidosis

- The diagnosis of systemic amyloidosis requires the presence of all of the following:
  - Presence of amyloid-related systemic syndrome (such as renal, liver, heart, gastrointestinal tract or peripheral nerve involvement)
  - Positive amyloid staining by Congo Red or EM in any tissue
  - Clear evidence that amyloid is immunoglobulin related by direct sub-typing of amyloid deposits (Mass spectroscopy is standard approach at our institution)
  - Evidence of a monoclonal plasma cell proliferative disorder (any or all of the following: serum or urine M protein, abnormal free light chain ratio or clonal plasma cells in bone marrow)

- Localized forms of amyloidosis (such as tracheobronchial, genitourinary, isolated carpal tunnel and non-purpuric cutaneous lesions) do not require systemic therapy

- The recommendations presented herein are a general approach. However, clinical trials are preferred at every step.
Mayo Prognostic System

<table>
<thead>
<tr>
<th>Troponin T</th>
<th>NT-ProBNP</th>
<th>dFLC</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>mcg/L</td>
<td>ng/L</td>
<td>mg/L</td>
<td></td>
</tr>
<tr>
<td>&lt;0.025</td>
<td>&lt;1800</td>
<td>&lt;180</td>
<td><strong>I=All low</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>II=One elevated</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>III=Two elevated</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>IV=All three elevated</strong></td>
</tr>
</tbody>
</table>
AL Amyloidosis Management

Transplant Eligibility Criteria

- “Physiologic” Age ≤ 70 years
- Performance Score ≤ 2
- Systolic BP ≥ 90 mmHg\(^a\)
- TnT < 0.06 ng/ml
- CrCl ≥ 30 ml/min \(^b\) (unless on chronic dialysis)
- NYHA Class I/II
- No more than 2 organs significantly involved

\(^a\) Caution as well for patients with BP <100 mmHg as well
\(^b\) Selected patients may become eligible for ASCT with cardiac and renal transplantation
AL Amyloidosis Management

Newly Diagnosed AL Amyloidosis

Transplant Eligible

- BM PC ≥ 10% or CRAB
  - Yes: Induction 2-4 cycles
    - Mel 200 HSCT
  - No: Transplant Ineligible

- Not wanting transplant
  - BMel-Dex or CyBorD

Transplant Ineligible

- ≥ Hematologic VGPR
  - Yes: Observation
  - No: More chemotherapy

1 Induction also used if delay in proceeding to ASCT, or as clinically indicated
2 If < PR at 2 months consider changing therapy
3 For Age >70 or CrCl <30, use Mel 140 mg/m2
4 Day 100 ASCT or after 4-6 cycles of chemo
Consult or Call Your Friendly Neighborhood Hematologist!
Questions & Discussion

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