Multiple Myeloma

• Plasma cell disorder: CRAB
• Estimated 24,050 cases and 11,090 deaths in 2014\textsuperscript{[1]}
• Median age at diagnosis: 69 yrs\textsuperscript{[2]}
• 5-yr survival has improved substantially (45% in 2004-2010 vs 28% in 1987-1989\textsuperscript{[2]}) due to novel agents
• R/O amyloidosis
• Revised ISS—LDH, cytogenetics
• The future: risk-adapted therapy, individualized treatment

Updated IMWG Criteria for Diagnosis of Multiple Myeloma

<table>
<thead>
<tr>
<th>MGUS</th>
<th>Smoldering Myeloma</th>
<th>Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ M protein &lt; 3 g/dL</td>
<td>▪ M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine)</td>
<td>▪ Underlying plasma cell proliferative disorder</td>
</tr>
<tr>
<td>▪ Clonal plasma cells in BM &lt; 10%</td>
<td>▪ Clonal plasma cells in BM ≥ 10% to 60%</td>
<td>▪ AND 1 or more myeloma defining events</td>
</tr>
<tr>
<td>▪ No myeloma defining events</td>
<td>▪ No myeloma defining events</td>
<td>▪ ≥ 1 CRAB* feature</td>
</tr>
</tbody>
</table>

*C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET-CT)

# MM Risk Categories

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Standard Risk (Expected OS: 6-7 Yrs)</th>
<th>High Risk (Expected OS: 2-3 Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISH</td>
<td>t(11;14)</td>
<td>Del(17p)</td>
</tr>
<tr>
<td></td>
<td>t(6;14)</td>
<td>Del(1p)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gain(1q)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t(4;14)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t(14;16)</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Hyperdiploidy</td>
<td>Hypodiploidy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Del(13)</td>
</tr>
<tr>
<td>β₂-microglobulin*</td>
<td>Low (&lt; 3.5 mg/L)</td>
<td>High (≥ 5.5 mg/L)</td>
</tr>
<tr>
<td>Isotype</td>
<td>--</td>
<td>IgA</td>
</tr>
<tr>
<td>Gene expression profile</td>
<td>Good risk</td>
<td>High risk</td>
</tr>
</tbody>
</table>

*Patients with t(4;14), β₂-microglobulin < 4 mg/L, and Hb ≥ 10 g/dL may have intermediate-risk disease.

Clinical Challenges in Treatment Selection

- Renal failure, plasmapheresis
- Aged 70 yrs or older
- Extramedullary MM
- High-risk MM
- Advanced bone disease
- Marrow failure
Factors Affecting Transplantation Eligibility

• Age
  – Older than 65 yrs of age may not be eligible
  – Older patients more sensitive to toxicity; less physical reserve

• Performance score

• Comorbidities
  – Increased risk of infection
  – Decreased tolerability for high-dose therapy
Current Considerations for Initial Treatment of MM

• Induction for younger patients
  – 3-drug induction followed by auto-transplant and consolidation in first response[1]
  – Maintenance therapy post auto-transplant[2]
  – Maximize depth, duration of first response[3,4]
  – Assessing depth of response and understanding implications for patient outcome[5]

Transplantation in the Novel Therapy Era

• Transplantation improves CR/VGPR rate
  – CR/VGPR correlates with improved PFS and OS
  – CR/VGPR pre- and posttransplantation improves PFS and OS
• Tandem transplantation benefits a subgroup of patients
• Novel agents improve induction CR/VGPR rate
• Posttransplantation maintenance may improve CR/VGPR and thereby PFS and OS

Role of MRD Assessment

• Remains a research tool, but indications are that lower levels of MRD predict for better outcomes
  – Can contribute to better definition of response
  – Potential to monitor efficacy of therapy
• Best, easily exportable method and optimal time point is still under investigation
• Even pts who achieve MRD- state can relapse, so all may not be able to stop therapy
• Unsure if changing therapy based on depth of response alters survival outcomes, unsure of next steps for MRD-
Post-ASCT Maintenance in Newly Diagnosed MM

• Does maintenance therapy prolong survival (PFS, OS) and does the choice of maintenance therapy make a difference?
  – If so, who should get treatment, for how long, and at what dose schedule?

• NCCN recommended maintenance therapies
  – Category 1: thalidomide, lenalidomide
  – Category 2A: bortezomib

Why Approach Older Patients Differently?

• More sensitive to toxicity
• Less physical reserve
• Effective therapy should:
  – Induce high response rates
  – Not have severe toxicity
  – Improve survival compared with standard comparator
FIRST Trial: Efficacy Analysis of Len/Dex vs MPT in SCT-Ineligible Patients With MM

- Median PFS, Mos
  - Rd (n = 535): 25.5
  - Rd18 (n = 541): 20.7
  - MPT (n = 547): 21.2
  - Rd vs MPT: 0.72 (0.00006)

- 4-Yr OS, %
  - Rd (n = 535): 59.4
  - Rd18 (n = 541): 55.7
  - MPT (n = 547): 51.4
  - Rd vs MPT: 0.78 (0.0168)

- Overall response (continuous Rd vs MTP): 75% vs 62% (P < .00001)
- Similar, tolerable safety profiles between treatment groups; incidence of secondary primary malignancies 0.4% in Rd arm vs. 2.2% in MPT

Summary of Recent Therapies

• What is the optimal therapy for newly diagnosed MM?
  – Transplantation ineligible (NCCN recommendations)
    • Category 1 combinations of lenalidomide/low-dose dexamethasone, MPV, MPR, or MPT
    • Category 2A combinations of VD or MP

• Does choice of initial therapy matter? Yes
  – Age, high-risk patients, renal impairment
  – SWOG trial

Salvage Therapy for Relapsed/Refractory MM

• NCCN Category 1
  – Bortezomib
  – Bortezomib/liposomal doxorubicin
  – Lenalidomide/dexamethasone (Rd)

• Large number of other choices if initial iMiD and proteasome inhibitor resistant
  – Carfilzomib—Endeavor, Aspire trials
  – Pomalidomide combinations
  – Panobinostat

NCCN. Clinical practice guidelines in oncology: multiple myeloma. v.1.2013
Salvage Auto Transplant in the Relapsed Setting: Reasonable Option?

- Recent data from Mayo Clinic Transplant Center suggests that auto SCT2 appears safe and effective treatment for relapsed MM (N = 98)
  - ORR: 86%; median PFS: 10.3 mos; median OS: 33 mos
  - Rate of TRM: 4%, suggesting a favorable benefit-to-risk ratio
- Shorter TTP after auto SCT1 predicts shorter OS post auto SCT2

New agents

- Daratumumab, antiCD38, combos
- Oral prot inhibitors—Ixazomib, combos
- Elotuzumab and SLAMF7, combos

Exciting agents in trial
- Checkpoint inhibitors
- CAR T—BCMA, CD19
- filanesib
Phase II SIRIUS: Daratumumab Shows Activity in Heavily Pretreated MM

- Median PFS: 3.7 mos (95% CI: 2.8-4.6); 1-yr OS: 65% (95% CI: 51.2-75.2%)
- Most common grade 3/4 AEs: thrombocytopenia (25%), anemia (24%), neutropenia (14%); infusion-related reactions occurred in 43% (most grade 1/2)

Phase III TOURMALINE-MM1: Statistically Significant Improvement in PFS

- Most common AEs: thrombocytopenia (78%), diarrhea (42%), constipation (34%), PN (28%), nausea (26%), peripheral edema (25%), vomiting (22%), and back pain (21%)

**ELOQUENT-2: Significant Increase in PFS with Elotuzumab in Relapsed MM**

- Significant PFS improvement and higher response rates with elotuzumab + RD vs RD alone in relapsed MM
  - ORR: 79% vs 66% ($P = .0002$), respectively

### PFS, Mos (95% CI) vs Median PFS, Mos (95% CI) – 19.4 (16.6-22.2) vs 14.9 (12.1-17.2)

- HR (95% CI) – 0.70 (0.57-0.85)

- Similar PFS benefit across subgroups, including older pts and pts with high-risk cytogenetics del(17p), t(4;14)

Relapsed/Refractory Disease

• All MM patients relapse
• Factors affecting choice of treatment for relapsed patients
  – Patient comorbidities
    • Presence of significant neuropathy may preclude bortezomib
    • History of DVT may prevent lenalidomide use
  – Time from previous therapy
    • Same regimen may be considered if a sizable amount of time has passed
  – Response to previous therapy
• Consider clinical trial (if available)
Risk Factors for Thrombosis

- Age
- Obesity
- Cardiovascular disease
- Chronic renal disease
- Acute infection
- Immobilization
- General surgery
- Central venous catheter use
- Trauma
- Anesthesia
- Erythropoietin
- Hypercoagulable disorder

Current Treatment of Myeloma Bone Disease

• Bisphosphonates\textsuperscript{[1]}
  – Pamidronate
  – Zoledronic acid

• Surgical procedures\textsuperscript{[1]}
  – Vertebroplasty
  – Balloon kyphoplasty

• Radiotherapy\textsuperscript{[1]}

• RANKL inhibitor denosumab (investigational in this setting)\textsuperscript{[2]}

1. NCCN. Clinical practice guidelines in oncology: multiple myeloma. v.2.2014.
2. ClinicalTrials.gov. NCT01345019.
Management of Multiple Myeloma: Conclusions

• Doublet or triplet combination approaches should be used in both transplantation-eligible and -ineligible patients
  – Maintenance therapy can prolong response
  – MRD is achievable with current combination therapies

• Optimal management approaches should emphasize improving QoL by identifying potential complications of therapy and minimizing long-term toxicity

• New classes of agents and second-generation agents have activity and are of considerable interest