Multiple Myeloma
Making Sense of the Report Forms

Parameswaran Hari
Medical College of Wisconsin
Milwaukee

Indications for Blood and Marrow Transplantation in North America 2003

Objectives

- Myeloma – the disease & its natural history
- Transplantation in Myeloma – Autologous & Allogeneic
- Response Criteria – What is new and what is coming?
- The MYE form – limitations, sources of confusion
- Common Queries
- Questions
Myeloma Disease Biology

- Cancer of Plasma Cells
- Plasma Cells secrete Immune (Monoclonal) Proteins – detected in serum or urine by electrophoresis / IFE
- Rarely nonsecretory type
- New test: Serum Free lite chains
- Organ dysfunction – “CRAB”

Plasma Cells come from B cells circulate all over produce immune globulins

- “Activated B cell”
- Memory B cell
- Plasma Cell

Immunoglobulins

- Major types of Immune Globulins: IgG, IgA, IgM, IgD, IgE
- Light Chains – Kappa or Lambda
- Concept of Monoclonality
- Malignant plasma cell – is monoclonal
- One plasma cell clone = only one type of Ig K or L
- Rare exceptions –
  - 2 different spikes – IgG K and IgA L
**Myeloma Plasma Cells**
- Grow, proliferate and infiltrate
- Secrete – Immunoglobulins or Light chains
- “Create space” - dissolve bone osteolysis
- Immune dysfunction
- Deposition of light chains / amyloid – Renal Impairment, AL amyloid

**Epidemiology of MM**
- >16000 newly diagnosed patients per year
- 45000 Americans living with MM
- In 2005 – 16570 new cases and 11000 deaths
- Similar numbers from the EU
- Median Age at diagnosis
  - 70 yrs (>75% are 70yrs or above)
- Remains Incurable
- Median Survival from diagnosis 33 months
- Higher (almost double) incidence in Americans of African heritage.
- Almost no one under 20 has MM

**“pathological fracture” MRI Scan – do I report?**
- MRI Scan – do I report?
Stepwise Progression to Myeloma

MGUS (Monoclonal Gammopathy of Unknown Significance)

- SOLITARY PLASMACYTOMA
- SMOLDERING MYELOMA
- ACTIVE SYMPTOMATIC MYELOMA
  - EXTRAMEDULLARY MYELOMA
  - PLASMA CELL LEUKEMIA

2. Prior solitary extramedullary plasmacytoma (or absence of bone marrow findings diagnosis for multiple myeloma or plasma cell leukemia)?

3. Date of diagnosis: [ ] [ ] [ ]

3. Date of diagnosis: [ ] [ ] [ ]

3. Plasma cell leukemia at diagnosis (blood plasma cells >10% of WBC differential or absolute blood plasma cells >2.6 [10^9/L; 1.7 [10^9/L]?)

3. Date of diagnosis: [ ] [ ] [ ]

3. Prior monoclonal gammapathy of unknown significance (MGUS)?

3. Date of diagnosis: [ ] [ ] [ ]

3. Prior the Date of diagnosis Of MM

3. Date of diagnosis Of MM
**Plasmacytoma**

**Plasma Cell Leukemia versus Circulating Plasma Cells**
- **Plasma Cell Leukemia**
  - >2000 cells/cu mm or >20% PC in WBC
  - WBC counts & differential count for total plasma cell number
- **Peripheral Smear Report**
  - Circulating Plasma Cells seen – THIS IS NOT PLASMA CELL LEUKEMIA

**Clinical Spectrum of Plasma Cell Dyscrasia**
- Multiple Myeloma
- Solitary plasmacytoma
- MGUS
- Waldenström’s macroglobulinemia
- Lymphoplasmacytic lymphoma
- Primary amyloidosis
- Macroglobulinemia
- AL amyloidosis
- Cryoglobulinemia
- Heavy chain disease
Smoldering MM
- Serum M protein
- Bone marrow plasma cells
- Absence of CRAB
- Not MGUS / MM or plasmacytoma
- Observation, with treatment beginning at disease progression

Solitary Plasmacytoma

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal plasma cells</td>
<td>in marrow (≥10%) or biopsy proven plasmacytoma</td>
</tr>
<tr>
<td>Monoclonal protein in serum / urine</td>
<td>if no monoclonal protein (nonsecretory) – need 30% plasma cells in marrow or plasmacytoma</td>
</tr>
<tr>
<td>Myeloma related organ dysfunction – at least one</td>
<td>“CRAB”</td>
</tr>
<tr>
<td>Calcium (elevated &gt;10.5)</td>
<td>Renal (Kidney Disease)</td>
</tr>
<tr>
<td>Anemia (Hb&lt;10 or 2g/dl below normal)</td>
<td>Bone Disease (lytic lesions / advanced osteoporosis)</td>
</tr>
</tbody>
</table>

Diagnostic Criteria – Symptomatic Multiple Myeloma
- Monoclonal Plasma Cells in Marrow (≥10%) or biopsy proven plasmacytoma
- Monoclonal protein in serum / urine
  - If no monoclonal protein (nonsecretory) – need 30% plasma cells in marrow or plasmacytoma
- Myeloma related organ dysfunction – at least one
  - “CRAB” (Calcium, elevated >10.5) Renal (Kidney Disease) Anemia (Hb<10 or 2g/dl below normal) Bone Disease (lytic lesions / advanced osteoporosis)
MGUS and Plasma Cell Leukemia

- Monoclonal Gammopathy of Undetermined Significance (MGUS)
  - Presence of monoclonal protein at concentration of ≤ 3g/dl in serum or urine without evidence of MM, Waldenström’s macroglobulinemia, amyloidosis, or other lymphoproliferative disorder
  - Incidence: up to 2% individuals ≥ 50 yr old
  - <3 g/L monoclonal lg, little or no proteinuria
  - <10% monoclonal bone marrow plasma cells if done
  - Absence of anemia, renal failure, hypercalcemia, and lytic bone lesions
  - No suppression of uninvolved immunoglobulins
  - Observation with treatment beginning at progression

Myeloma with Amyloid – not AL amyloid on its own

Techniques for measuring myeloma burden

- Immune Electrophoresis (SPEP, PEP)
- Immunofixation (IFE)
- Bone Marrow Aspirate or Biopsy

- Serum Free Light chains
  (How do we report it ?)
  No box in current MYE form
  Write in:
  Kappa Light Chains
  Lambda Light Chains
Sometimes the subtype may not have been known at diagnosis but identified later in the course of disease – ok to put it in if known at the time of filling the form.


distribution of monoclonal proteins in mm

- M protein found in serum or urine or both at time of diagnosis in 97% of patients
  - - Serum M spike: 80%
  - - Immunofixation positive: >90%
  - - Urine presence: 75%
  - - Ig G: 50%-54%
  - - Ig A: 20%
  - - Monoclonal light chain: 16%-<20%
  - - Ig D: 2%

Conventional Staging: Durie Salmon

- Stage I:
  - All of the following must be present:
    - Marrow plasmacytosis >10%.
    - Serum lambda <2 mg/dL.
    - Services bone or radiograph, or solitary plasmacytoma:
      - @<5 cm.
      - Uric light chains <4 g/L.
  - Filling either Stage I or II.

- Stage II:
  - One of the following must be present:
    - Marrow plasmacytosis >10%.
    - Serum lambda >2 mg/dL.
    - Services bone or radiograph, or solitary plasmacytoma:
      - @>5 cm.
      - Uric light chains >6 g/L.

- Stage III:
  - Uric light chains >3 g/L.

International Staging System for MM

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum $\beta_2$M &lt;3.5 mg/L, Serum albumin &gt;3.5 g/dl</td>
<td>62 mo</td>
</tr>
<tr>
<td>II</td>
<td>Serum $\beta_2$M &lt;3.5 mg/L, Serum albumin &gt;3.5 g/dl OR Serum $\beta_2$M 3.5 to &lt;5.5 mg/L, Respective of serum albumin</td>
<td>44 mo</td>
</tr>
<tr>
<td>III</td>
<td>Serum $\beta_2$M 5.5 mg/L</td>
<td>29 mo</td>
</tr>
</tbody>
</table>


Primary Source: Initial Marrow Biopsy
- Not Flow Cytometry
- Uses Aspirate differential count or Biopsy estimate

24 hr Urine Light chain result:
- Not 24 hr urine protein excretion

Immunofixation results on the 24 hr urine sample
- Reported as xxx mg in 24hr of k or l light chains
- Or mg/dl in which case multiply by volume of urine e.g. 145 mg/dl of lambda light chains & Total urine vol = 1500 ml. So 24hr value = 145 * 150 mg.
Chromosomal Abnormalites in Myeloma

- Specific chromosome changes in MM
- Ig translocations
  - 11q13: most common (Cyclin D1, 15-20%)
  - 4p16.3 (FGFR3, MMSET, 12%)
  - 8q24 (c-myc, <10%)
  - 16q23 (c-maf, 5-10%)
  - 6p25 (IRF4, 5%)
- 13 deletion (Rb, ~50%)

Kuehl WM, Bergsagel P. Nat Rev Cancer. 2002;2:175

Initial Therapy for MM – prior to transplant

Usual Sequence of therapy

Key when transplant is upfront therapy – interval? <6m
### Usual Sequence of Therapy

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial therapy</td>
<td>HSCT</td>
</tr>
<tr>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>

### Myeloma Management – Recent History

- 1962 Melphalan
- 1964 Cyclophosphamide
- 1967 Corticosteroids
- 1969 MP
- 1975 Durie-Salmon staging
- 1976 First trials of complex chemotherapy combinations
- 1983 High-dose melphalan; serum β2-microglobulin for prognosis
- 1986 High-dose Dex; HDT with ACST
- 1988 Twin transplants for MM
- 1984 First allogeneic transplants; VAD
- 1985 IFN alfa
- 1996 Bisphosphonates
- 1999 Thalidomide; Nonmyeloablative transplants
- 2000 Bortezomib; lenalidomide
- 2005 IMiDs - Lenalidomide; antiangiogenic: arsenic

### Usual Agents for Initial Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combinations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please use this to report: Thalidomide, Lenalidomide, Bortezomib or combinations.
Autologous Stem Cell Transplantation

- Mobilization and Leukapheresis of Patient Stem Cells
- Cryopreservation of Patient Stem Cells
- Thawing and infusion of patient stem cells

Tandem Autologous Stem Cell Transplantation

- Patient has two planned autologous SCT within six months of each other
- Peripheral Blood Stem Cells -- Collected once before the initial transplant
- Half of the stem cells are used for each procedure
- This is considered one treatment -- pre transplant baseline for calculating response is prior to Transplant #1.

- M spike – 5g/dl at diagnosis → initial therapy & 4 months later
- M spike – 1 g/dl i.e 80% decline PR, chemosensitive disease
- After Tx #1 → done 5 m from diagnosis
- M spike – 0.6 g/dl (response is still 5-0.6 NOT 1-0.6)
- After Tx #2 → done 8 m from diagnosis
- M spike – 0.1 g/dl (response still 5-0.1 i.e 98%)

So unless the second transplant is a late Tx for relapse – use initial pre Tx #1 levels for response assessment.
Continuing CR from before

Last disease status: cross check with qn 88 & 89

Patients may not have had immediate pre Tx staging:
Chemo within 6 months and consolidative transplant use the last status post chemo
Chemo >6 months ago and unknown status thereafter did the patient PROG or REL?
If no progression and later transplant – Very Unusual
Unknown / NE / Other, specify

Probability of Survival after Autologous Transplants for Multiple Myeloma

<table>
<thead>
<tr>
<th></th>
<th>N eval</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>1,304</td>
<td>1-yr 91 ± 9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-yr 70 ± 2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-yr 56 ± 3%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>5,016</td>
<td>1-yr 90 ± 1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-yr 66 ± 1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-yr 51 ± 2%</td>
</tr>
<tr>
<td>Minimal Response</td>
<td>511</td>
<td>1-yr 86 ± 2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-yr 66 ± 3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-yr 47 ± 5%</td>
</tr>
</tbody>
</table>

Bladé Criteria for Complete and Partial Response

COMPLETE RESPONSE (CR) requires all of the following
- No serum/urine M protein by IFE for ≥ 6 wk
- <5% plasma cells in bone marrow aspirate
- No increase in size of lytic bone lesions
- Disappearance of soft tissue plasmacytomas

PARTIAL RESPONSE (PR) requires all of the following
- ≥ 50% reduction in serum M protein ≥ 6 wk
- ≥ 90% reduction in 24-hr urinary light chain excretion ≥ 6wk
- ≥ 50% reduction in soft tissue plasmacytomas
- No increase in size or number of lytic bone lesions

• EBMT, IMBTR, and ABMTR criteria
RESPONSE CRITERIA: Ground Rules

- Stability of Response - maintained for minimum 6 weeks
- Immunofixation – needed for CR
- Bone disease – check to ensure stability
- Nonsecretory disease and plasma cell leukemia – need marrow aspirate
- At any response level: if some but not all criteria met – downgrade to next lower level of response. E.g. CR criteria met except for immunofixation – response is PR

Oligoclonal Reconstitution

- Classic confounder.
- His IgA became IgG?
- Can lambda change to kappa after transplant?
Recovery

CR = Complete Response requires all of the following:
- Absence of the original monoclonal protein on serum and urine by routine electrophoresis and by immunofixation maintained for a period of 6 weeks
- The presence of normal immunoglobulin isotypes by immunoelectrophoresis
- Absence of plasma cells in a bone marrow aspirate and also on bone marrow biopsy, if biopsy is performed. If absence of monoclonal protein is established for 6 weeks, it is not necessary to biopsy the bone marrow unless the patient had non-secretory myeloma.
- No increase in size or number of non bone lesions on radiological imaging, if performed development of a complication feature was not excluded before CR
- Disappearance of soft tissue paraprotein.
- For plasma cell leukaemia, absence of plasma cells in blood
- Criteria in which some but not all, the criteria for CR is fulfilled are classified as PR, providing the remaining criteria satisfy the requirements for PR. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

CR + Controlling Complete Response requires all of the following:
- CR continuing from CR prior to conditioning

Some Key Features of Response

Criteria

- Immunofixation essential to call CR
- Bone Marrow needed only to confirm a CR
- Upfront Transplant – Baseline comparison for paraprotein level is from before initial therapy (as long as transplant followed such treatment within 6 months)
- Assessment of Transplant response:
  - What is the baseline to assess response?
  - Case #1: Chemo given ≤ 6m prior to transplant? Transplant could then be a consolidation of chemo response.
  - Baseline – pre chemotherapy levels
  - Case #2: Chemo non-response (e.g. progressed on chemo) OR no chemo within 6 months of transplant.
    - Baseline here is immediate pretransplant levels.

Clinical Scenario – CR issue

- Protein Electrophoresis –
  - No suspicion for paraprotein – is this CR?
  - Immunofixation also has to be done to confirm this is CR.
  - No IF – no CR (it is only a PR if an SPEP has shown no paraprotein)
- Remember 6 week stability issue
- Marrow aspirate to confirm? – needed before CR confirmed – Can be omitted if 6 weeks stability criterion met.
- Non secretory MM:
  - Only way to check a response is through serial marrow performed 6 weeks apart
  - Free light chains not accepted currently on our forms
- Skeletal Survey – needed but if done should not show new lesions.
- MRI – not included
- Compression fracture – ok – does not preclude CR
- Plasmacytomas need to have regressed
**Response scenarios**

- PR — >50% decline if serum electrophoresis
- >90% decline in urine 24h light chains or if <200mg/24h
  - E.g. 1500mg/day of Urine light chains at baseline and 180 mg24h post treatment. — Still PR
- Needs to be sustained for 6 weeks
- Our forms D100 – will capture the best response in most patients but if a better response happened later – will need to be captured in the 1 year follow-up report

**REFERENCE POINT: for response assessment**

- Upfront therapy (incl transplant)– baseline at start of initial Rx
- Later transplants (untreated relapse or >6months from therapy) – pretransplant M spike is the reference point
- Transplant Consolidation of chemotherapy- if within 6 months of chemo – use pre chemo level as reference.

**Ongoing Response**

- D100 – will capture the best response in most patients but if a better response happened later – will need to be captured in the 1 year follow-up report.

**SCENARIO:**

- Best Response happening at 8 mo after Tx
  - PR at Day 100 but CR at 1 year
Ongoing Response

- Scenario:
  - PR after transplant Day 100
  - Planned Maintenance with drugs
  - CR at 1 yr post transplant
    - Qn 1 and its date should update the best response as CR and document the date.
  - Patient relapses @ 3 yrs post transplant – Best Response since last report - QN1 is CR
    - Qn 43 – 46 current disease determination
  - REL from CR

The New Response Criteria - 2006

Major Changes in the new schema
Post Transplant Maintenance Therapy

- Interferon
- Prednisone
- Thalidomide
- Dexamethasone
- Revlimid (Lenalidomide)
- Velcade

Issues:
- Any survival benefit?
- Quality of Life affected?
- Delaying of Relapse versus QOL

Newer Drugs for MM

- Thalidomide (Thalomid, Celgene)
  - PO drug, Used in all stages of treatment
- Bortezomib (Velcade, Millennium)
  - IV drug, Used in all stages of therapy
- Lenalidomide (Revlimid, Celgene)
  - PO drug, In relapsed / upfront disease

Common Queries

- When was myeloma diagnosed?
  - Preceding MGUS?
  - Preceding plasmacytoma

- Non-secretory MM?
  - Do not report a light chain or Ig subtype if nonsecretory
Common Queries

- How do I calculate response?
  - Reference points
  - M spike baseline
  - "M spike = M protein = Paraprotein = Myeloma spike"

- Can MM change subtypes?

- Free Lite chains

  - Not being captured now

Common Queries

- Some Scenarios
  - Discordant Responses or Relapses in different organs
    - Hyposeretary Relapse
    - Renal Escape
  - Timeline of response for upfront transplanted patients
  - Pre transplant Response → post transplant response
    - CR → CCR continuing CR
    - PR → CR or continuing PR
    - MR/SD → PR or CR or MR or SD

Thank You

- All of you who sent in questions

- Please keep the questions coming