Plasma cell neoplasms

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23rd Feb 2017
Topics to be covered

• Multiple myeloma
  – Definitions
    • MGUS
    • Asymptomatic multiple myeloma
    • Active or symptomatic multiple myeloma
  – Pathology
  – Diagnosis
  – Treatment
  – Response assessment

• Plasmacytoma

• Light chain (AL) Amyloidosis

• POEMS syndrome
Indications for Hematopoietic Stem Cell Transplants in the US, 2013

- Allogeneic (Total N=8,197)
- Autologous (Total N=11,258)

Number of Transplants

- Myeloma / PCD
- AML
- ALL
- CML
- NHL
- HD
- MDS / MPD
- CLL
- Aplastic Anemia
- Other Non-Malign Dis
- Other Cancer
Myeloma

- Cancer of plasma cells in the bone marrow
- AKA multiple myeloma, plasma cell myeloma, Kahler’s disease
- Abnormal accumulation of myeloma cells in bone marrow:
  - Disruption of normal bone marrow function (anemia, low white cell count, etc.)
  - Destruction and invasion of bone and surrounding areas of bone marrow involvement
- Production and release of monoclonal protein from myeloma cells into the blood stream and/or into urine
- Reduction of normal immune function, reflected by reduced levels of normal immunoglobulins and increased susceptibility to infection.
Monoclonal protein

- M-protein, M-spike, M-component, Paraprotein, myeloma protein, protein spike
- Immunoglobulin or fragment of an Ig
- Myeloma Ig tend to be abnormal, without normal antibody function
- Can be used in lab to determine myeloma activity
Increased production of abnormal Ig

- Excess monoclonal protein accumulation in blood and/or urine
- Can stick to each other and/or blood components, vessels - reducing blood flow and circulation
- Excess light chains (Bence Jones proteins)
- Abnormal properties:
  - binding to normal blood clotting factors (bleeding, clotting)
  - binding to nerves (peripheral neuropathy)
Definitions

• Monoclonal Gammopathy of Undetermined Significance (MGUS)
  – M-protein present but usually <3 g/dl
  – No CRAB features or other indicators of active myeloma
  – Bone marrow plasma cells <10%

• Asymptomatic or Smoldering Multiple Myeloma
  – M-protein >3 and/or BMPC >10%
  – No CRAB features or other indicators of active myeloma

• Active or Symptomatic Multiple Myeloma
  – 1/> CRAB features and/or indicators of organ damage
CaReALbRCm:

calcium elevation

enal failure

nemia

one disease

ight chain ratio ≥100

maging by MRI or PET >1 focal lesion

asma cells ≥60%
Spectrum of tumor burden and activity

- MM Multiple Myeloma
- Early Active Myeloma
- Ultra-High-Risk Smoldering Myeloma
- High-Risk Smoldering Multiple Myeloma
- Low-Risk Smoldering Multiple Myeloma
- MGUS Monoclonal Gammopathy of Undetermined Significance

CRAB Criteria
- Early Active Myeloma
- Bone marrow plasma cells >60%
- Ratio of monoclonal to normal light chains >100
- >1 focal lesion on MRI

Spanish Criteria
- Mayo Criteria
Clinical features

• Symptoms
  – Persistent or worsening tiredness
  – Sudden and non-remitting pain
  – Recurrent unexplained infections

• Signs
  – Pain with movement and/or at night
  – Tenderness/swelling of bone areas
  – Swelling, shortness of breath or evidence of heart or kidney failure
Diagnosis

- Serum electrophoresis (M spike quantification)
- Serum immunofixation (M spike type)
- Serum free light chains
  - Kappa, Lambda. Look at unit: mg/dl or mg/L
- Urine protein electrophoresis and immunofixation
- Serum LDH (risk status)
- Serum albumin + Serum beta2 microglobulin (staging)
- Bone marrow biopsy (risk status)
  - Percent plasma cells
  - FISH analysis
  - Cytogenetics
Staging at diagnosis

• ISS (2005)
  – Serum $\beta_2$ microglobulin
  – Serum albumin

• R-ISS (2015)
  – ISS
  – FISH
    • del17p +/-
    • t(4;14) +/-
    • t(14;16)
  – LDH >ULN

ISS I: B2MG <3.5, alb $\geq$3.5
ISS II: everything else
ISS III: B2MG $\geq$5.5

R-ISS I: ISS I, no FISH abn, nl LDH
R-ISS II: everything else
R-ISS III: ISS III + (↑LDH or FISH abn)
Treatment

• Induction chemotherapy
• Autologous transplant
• Allogeneic transplant
• Tandem transplant
Induction therapies

• Lines of treatment (1 line = a particular combination).
• A line may be used for 1/> cycles
• Priming is not line of treatment (Cytoxan, Etoposide)
• Chemotherapy lines include combinations such as
  – Bortezomib, Lenalidomide, Dexamethasone (VRD)
  – Cytoxan, Bortezomib, Dexamethasone (CyBorD, VCD)
  – Bortezomib, Dexamethasone (VD)
  – Lenalidomide, Dexamethasone (RD)
  – Other drugs: carfilzomib (K), pomalidomide, thalidomide, elotuzumab, daratumumab, bendamustine, melphalan
## Response assessment (IMWG Response Criteria)

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>Stringent complete response</td>
<td>CR + normal FLC ratio and absence of clonal cells in BM by IHC</td>
</tr>
<tr>
<td>CR</td>
<td>(-) IF on sr/ur + disappearance of any soft tissue plasmacytomas and &lt;5% PC in BM</td>
</tr>
<tr>
<td>VGPR</td>
<td>Sr/Ur M-protein on IF but not on EP or ≥90% ↓ in sr M + ur M &lt;100 mg/24 h</td>
</tr>
<tr>
<td>PR</td>
<td>≥50% ↓ Sr M-protein + ↓ 24 h ur M-protein by ≥90% or to &lt;200 mg per 24 h</td>
</tr>
<tr>
<td>MR</td>
<td>≥25% but ≤49% ↓ Sr M-protein and ↓ Ur M-protein by 50-89%</td>
</tr>
<tr>
<td>Progressive ds</td>
<td>↑ of 25% from lowest confirmed response in 1/&gt; Sr M-protein (absolute increase ≥0.5)</td>
</tr>
<tr>
<td>Clinical relapse</td>
<td>CRAB, new plasmacytomas or bone lesions, hyperviscosity</td>
</tr>
<tr>
<td>Relapse from CR</td>
<td>Reappearance of sr/ur M-protein by IF/EP or ≥5% of plasma cells in BM, appearance of any sign of progression</td>
</tr>
</tbody>
</table>

Kumar S et al. Lancet Oncol. 2016 Aug
Prognosis

• Incurable, but controllable
• Outcomes have continued to improve for MM
• Median survival
  – ISS I ~12-15 years
  – High risk ds ~2 years
• Multiple relapses and remissions
• Majority of patients die of myeloma
Plasmacytoma

- Plasma cell neoplasm presenting as a single lesion
- Solitary Bone Plasmacytoma
- Solitary Extramedullary Plasmacytoma
Solitary Bone Plasmacytoma

- 5% of plasma cell neoplasms
- ~450 new patients/year
- Men, median age 55-65 years, B>W
- Axial skeleton
- No anemia, hypercalcemia, or renal insufficiency
Evaluation

- CBC, chemistries
- SPEP with immunofixation
- Free light chain assay
- 24 h UPEP with immunofixation
- Bone marrow biopsy
- Skeletal survey
- PET/CT or MRI of spine/pelvis
SBP plus MGUS

- <10% clonal plasma cells in bone marrow
- Treated as SBP but have a higher risk of progression to symptomatic myeloma
Treatment

• Localized radiation to the tumor site
• Multiple plasmacytomas- treat as multiple myeloma
• Follow up
  – Highest risk of recurrence in first 4 years
  – Devpt of multiple myeloma, local recurrence of new plasmacytomomas
Solitary Extramedullary Plasmacytoma

• 80% occur in head & neck region (upper aerodigestive tract)

• GI tract, Urinary bladder, CNS, Thyroid, Breast, testes, Parotid glands, Lymph nodes, Skin
Systemic light chain (AL) amyloidosis

underlying clone
excess production of unstable FLC
misfolded light chains allowing exposure of hidden epitopes which allow aggregation
pre-fibrillar aggregates

amyloid fibrils formation in an ordered β-pleated sheet structure in tissues
organ damage due to fibril deposition
direct tissue toxicity (mainly affecting the heart)

renal periorbital purpura macroglossia nail dystrophy soft tissue heart

Merlini G. Haematologica 2014;99:209-21
Organ involvement in AL amyloidosis

Merlini G. Blood 2012
Prognosis and Staging

• AL staging (2012)
  – dFLC (iFLC-uFLC) ≥ 180 mg/L
  – NT-proBNP ≥ 1800 pg/ml
  – cTnT ≥ 0.025 ng/ml

Kumar, S et al. J Clin Oncol 2012
Organ involvement

- Heart: echo: mean wall thickness >12 mm, no other cardiac cause
- Kidney: 24-h ur pr >0.5 g/day, predominantly albumin
- Liver: total liver span >15 cm in the absence of heart failure or alkaline phosphatase >1.5 times ULN
- Peripheral nerve: clinical symmetric lower extremity sensorimotor peripheral neuropathy
Treatment

• Ideal treatment would be 2-pronged
  – Therapy directed to lower concentration of precursor protein
  – Therapy directed toward amyloid fibrils
Treatment if transplant eligible

• Chemotherapy followed by autologous stem cell transplant
• Direct autologous stem cell transplant
• Careful selection of patients as AL patients are more fragile (high early mortality)
• High response rates and long term survivors (selection bias)
• Multidisciplinary supportive care
Transplant outcomes (N=1536)

Early Mortality
- 1995-2000: 30 days: 11%, 100 days: 20%
- 2001-2006: 30 days: 5%, 100 days: 11%
- 2007-2012: 30 days: 3%, 100 days: 5%

Overall Survival
- P-value < 0.001
- 1995-2000, 5y OS = 55%
- 2001-2006, 5y OS = 61%
- 2007-2012, 5y OS = 77%

### Hematologic response and progression criteria

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<th>Response category</th>
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<tr>
<td>Complete</td>
<td>Normalization of the free light chain levels and ratio, negative sr and ur immunofixation</td>
</tr>
<tr>
<td>Very good partial</td>
<td>Reduction in the dFLC to &lt;40 mg/L</td>
</tr>
<tr>
<td>Partial</td>
<td>A &gt;50% reduction in dFLC</td>
</tr>
<tr>
<td>No response</td>
<td>Less than PR</td>
</tr>
<tr>
<td>Progression</td>
<td>From CR, any detectable monoclonal protein or abnormal FLC ratio (light chain must double)</td>
</tr>
<tr>
<td></td>
<td>From PR, 50% ↑ in sr M protein &gt;0.5 or 50% ↑ in ur M protein to &gt;200 mg/day</td>
</tr>
<tr>
<td></td>
<td>Free light chain increase of 50% to &gt;100 mg/l</td>
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<td>Heart</td>
<td>NT-proBNP &gt;30% and &gt;300 ng/l ↓ in patients with baseline NT-proBNP ≥ 650 or NYHA class response</td>
<td>NT-proBNP progression &gt;30% and &gt;300 ng/l increase or cTn progression ≥33% ↑ or ejection fraction progression (≥ 10% decrease)</td>
</tr>
<tr>
<td>Kidney</td>
<td>50% ↓ (at least 0.5 g/day) of 24-h ur pr (ur pr &gt;0.5 g/d pretreatment). Creatinine and Cr clearance must not worsen by 25% over baseline</td>
<td>50% ↑ (at least 1 g/day) of 24-h ur pr to &gt;1 g/day or 25% worsening of sr creatinine or cr clearance</td>
</tr>
<tr>
<td>Liver</td>
<td>50% ↓ in abn alkaline phosphatase value ↓ in liver size radiologically at least 2 cm</td>
<td>50% ↑ of alkaline phosphatase above the lowest value</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>Improvement in electromyogram nerve conduction velocity</td>
<td>Progressive neuropathy by EMG or NCV</td>
</tr>
</tbody>
</table>

POEMS Syndrome

- Very rare disease
- Median age 51
- M > F (3:1)

- Periph neuropathy
- Organomegaly
- Endocrinopathy
- M-spike
- Skin

- Papilledema, polycythemia
- Edema
- Sclerotic bone lesions
- Thrombocytosis
Osteosclerotic lesions
• VEGF level 1250 pg/ml (31-89)
Treatment

- Radiation
- Steroids
- Melphalan
- Lenalidomide
- Bortezomib
- Autologous stem cell transplant
• Questions?