Plasma cell Neoplasms

Pei Lin, M. D.

Disclosures

I have nothing to disclose.

Outlines

• Updated diagnostic criteria (DD)
• Myeloma phenotype and MRD detection by MFC
• Identifying high risk patients
  – MRD, FISH, NGS, GEP
  – Updated staging system R-ISS
• Differential diagnosis from LPL and other CD138+ lymphomas

Plasma Cell Neoplasms

• MGUS (Non-IgM )
• Multiple myeloma
  – Smoldering myeloma
  – Plasma cell leukemia
• Primary Amyloidosis
• Ig deposition disease
• Solitary Plasmacytoma
  – Plasmacytoma with minimal bone marrow involvement (<10%)
• POEMS syndrome
  – Polyneuropathy
  – Organomegaly
  – Endocrinopathy
  – M component
  – skin changes
• TEMPI syndrome (provisional)
  – Telangiectasias,
  – ↑Epo + erythrocytosis
  – M component
  – Perinephric fluid collections
  – Intrapulmonary shunting
• Solitary Plasmacytoma
  – Plasmacytoma with minimal bone marrow involvement (<10%)
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  – Polyneuropathy
  – Organomegaly
  – Endocrinopathy
  – M component
  – skin changes
• TEMPI syndrome (provisional)
  – Telangiectasias,
  – ↑Epo + erythrocytosis
  – M component
  – Perinephric fluid collections
  – Intrapulmonary shunting
Common Types of Cancer

<table>
<thead>
<tr>
<th>Estimated New Cases 2017</th>
<th>Estimated Deaths 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breast Cancer (Female)</td>
<td>252,710</td>
</tr>
<tr>
<td>2. Lung/Bronchus</td>
<td>222,500</td>
</tr>
<tr>
<td>3. Prostate Cancer</td>
<td>181,860</td>
</tr>
<tr>
<td>4. Colon/Rectum</td>
<td>155,430</td>
</tr>
<tr>
<td>5. Melanoma, skin</td>
<td>81,110</td>
</tr>
<tr>
<td>6. Bladder Cancer</td>
<td>79,030</td>
</tr>
<tr>
<td>7. NHL</td>
<td>71,240</td>
</tr>
<tr>
<td>8. Kidney/Renal Pelvis</td>
<td>63,990</td>
</tr>
<tr>
<td>9. Leukemia</td>
<td>62,130</td>
</tr>
<tr>
<td>10. Endometrial Cancer</td>
<td>61,380</td>
</tr>
<tr>
<td>11. Myeloma</td>
<td>30,280</td>
</tr>
</tbody>
</table>

Median age at dx: 69 years old

https://seer.cancer.gov/statfacts

Therapeutics against myeloma

<table>
<thead>
<tr>
<th>Therapeutic category</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMiDs</td>
<td>Thalidomide, Lenalidomide, Pomalidomide</td>
</tr>
<tr>
<td>Proteasome inhibitors</td>
<td>Bortezomib, Carfilzomib, Ixazomib</td>
</tr>
<tr>
<td>Chemoagents</td>
<td>Doxorubicin, cyclophosphamide, melphalan</td>
</tr>
<tr>
<td>Steroid</td>
<td>Dexamethasone, prednisone</td>
</tr>
<tr>
<td>Stem cell Transplant</td>
<td>Auto- or allo-</td>
</tr>
<tr>
<td>Monoclonal antibody</td>
<td>Daratumumab (CD38), elotumumab (CS1)</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>HDAC inhibitor Panobinostat</td>
</tr>
<tr>
<td></td>
<td>BCL2 inhibitor Venetoclax</td>
</tr>
<tr>
<td></td>
<td>PD-1 inhibitor Pembrolizumab, Nivolumab</td>
</tr>
<tr>
<td>CAR-T and vaccine</td>
<td>CD19, BCMA (B cell maturation antigen), SLAMF7</td>
</tr>
</tbody>
</table>

1962: Oral melphalan and prednisone
RD, VD, VRD, VCD, VTD, KRD, VRD+Dara +/- SCT

Therapeutic category Agents

Thalidomide, Lenalidomide, Pomalidomide

Bortezomib, Carfilzomib, Ixazomib

Doxorubicin, cyclophosphamide, melphalan

Dexamethasone, prednisone

Auto- or allo-

Daratumumab (CD38), elotumumab (CS1)

HDAC inhibitor Panobinostat

BCL2 inhibitor Venetoclax

PD-1 inhibitor Pembrolizumab, Nivolumab

CD19, BCMA (B cell maturation antigen), SLAMF7

Tailored therapy based on risk stratification
Drug Resistance
### Myeloma diagnosis

- **Bone scan**
- **CT**
- **MRI**
- **PET-CT**
- **sFLC ratio**
- **SPEP and IFE**
- **Lytic bone lesions**
- **Peripheral blood**
- **Bone marrow**

### Diagnostic criteria: symptomatic (active) myeloma

**CRAB + 10% of PCs**

- **Hypercalcemia**
  - Serum Ca > 2.75 mmol/L (>11 mg/dL)
- **Renal failure**
  - Serum creatinine ≥ 2 mg/dL or creatinine clearance < 40 mL/min
- **Anemia**
  - Hb > 2 g/dL below the lower limit of normal or < 10g/dL
- **Bone**
  - Lytic lesions, pathological fractures or severe osteopenia

**New myeloma defining events (MDEs)**

- ≥ 60% clonal BM plasma cells
- Serum involved/uninvolved FLC ratio ≥ 100 (kappa) or ≤ 0.01
- > 1 focal bone lesion (≥ 5mm) on MRI

**IMWG:** Br J Haematol. 2003;121:749-757
Lancet Oncol 2014 by Rajkumar SV et al

### Smoldering (s) Myeloma vs. MGUS

<table>
<thead>
<tr>
<th></th>
<th>SMM</th>
<th>MGUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCs</td>
<td>10 - 59%</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>M-spike</td>
<td>And/or &gt; 3g/dL</td>
<td>&lt; 3g/dL</td>
</tr>
<tr>
<td>sFLC</td>
<td>&lt;0.26 or &gt; 1.65</td>
<td></td>
</tr>
<tr>
<td>CRAB or MDEs</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

**Treatment not required**

**IMWG:** Br J Haematol. 2003;121:749-757
Rajkumar Lancet Oncol 2014

### Myeloma is not one disease: Spectrum of Myeloma cells

- **Low grade**
- **Intermediate**
- **High**
- **Small cell**
- **Polymorphic**
- **Blastic**
- **Marshalko**
- **Asynchronous**
- **Anaplastic**
Key Issues

- High risk myeloma
- Risk of low grade disease to active ones
- Relapse and refractory myeloma (RRMM)
- Risk stratification for personalized medicine

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Disease Stages and Timing of Oncogenic Events

Modified from Bergsagel PL. J Clin Oncol; 2005; 23:6333-6338

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Common Recurrent IgH Translocations

(Primary)

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11q13</td>
<td>CYCLIN D1</td>
<td>15</td>
</tr>
<tr>
<td>4p16.3</td>
<td>FGFR3 &amp; MMSET</td>
<td>15</td>
</tr>
<tr>
<td>16q23</td>
<td>C-MAF (CYCLIN D2)</td>
<td>5</td>
</tr>
<tr>
<td>6p21</td>
<td>CYCLIN D3</td>
<td>3</td>
</tr>
<tr>
<td>20q11</td>
<td>MAFB (CYCLIN D2)</td>
<td>2</td>
</tr>
</tbody>
</table>

MMSET: AKA: NSD2
MM Risk Groups

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Standard Risk (80%) (OS: 6-7 Yrs)</th>
<th>Adverse Risk (20%) (OS: 2-3Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISH</td>
<td>t(11;14) t(6;14)</td>
<td>Del(17p) t(4;14) t(14;16) +1q21/-1p32 8q24 MYC</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Hyperdiploidy (48-74 chromosomes)</td>
<td>Hypodiploidy Complex del(13q)</td>
</tr>
<tr>
<td>β₂M*</td>
<td>Low (&lt;3.5 mg/L)</td>
<td>High (≥ 5.5 mg/L)</td>
</tr>
<tr>
<td>GEP</td>
<td>Good risk</td>
<td>High risk</td>
</tr>
</tbody>
</table>

Plasma cell leukemia, Extramedullary disease, Plasmablastic morphology
Patients with t(4;14), +1q21 and -1p32: Intermediate risk

Revised International Staging System (ISS)

<table>
<thead>
<tr>
<th>ISS (2005)</th>
<th>BrM &lt;3.5 Albumin ≥3.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS (2015)</td>
<td>Low LDH No high risk factors</td>
</tr>
<tr>
<td>Revised ISS (2015)</td>
<td>ISS I/II Not R- ISS I or III</td>
</tr>
<tr>
<td>Frequency</td>
<td>20% 60% 20%</td>
</tr>
<tr>
<td>Survival</td>
<td>&gt;10 yrs 7 yrs 2 yrs</td>
</tr>
</tbody>
</table>

β₂ microglobulin in mg/L
Albumin in g/dL

FISH panel at MDACC
- t(4;14) FGFR3-IGH
- 13q RB
- 1p/1q CDKN2C/CKS1B
- 17p TP53
- t(14;16) MAF-IGH
- t(11;14) CCND1-IGH
- 8q24 MYC

CDKN2C/CKS1B probe by Cytocell

Greipp PR. J Clin Oncol 2005;23:3412-20
GEP to distinguish risk groups

Subgroups

- PR: Proliferation
- MF: MAF/MAFB
- MS: FGFR3/MMSET
- HY: Hyperdiploidy
- LB: Low bone disease
- CD1: CCND1
- CD2: CCND3


Intratumor genetic heterogeneity

NCI-MATCH Trial
(Molecular Analysis for Therapy Choice)

BRAF nonV600 or BRAF fusion: Trametinib
BRAFV600 Dabrafenib + trametinib

Lehr JG. et al., Cancer Cell, 2014; 25:91-101

Relapse and refractory diseases

Intratumor Tumor heterogeneity

EMD: Extramedullary disease
FL: Focal lesions

Clonal dynamics in a patient with high-risk MM

Implication for FISH testing for TP53


Treatment Response

Conventional CR:
Serum/Urine IFE negative
BM PCs< 5%

Stringent CR (sCR):
Normal serum FLC ratio
No clonal PCs in BM

MRD negative
Flow (8 color)
NGS
Imaging

TTP and OS stratified according to different MRD levels >10−3 vs 10−3 to 10−5 vs <10−5.

Rawstron AC et al: J Clin Oncol. 2013:2540-7

(A) TTP and (B) OS
Deep sequencing


MRD+ in adverse risk myeloma has more profound effect on PFS and OS

(A) Progression-Free Survival
(B) Overall Survival

Rawstron AC at al: J Clin Oncol. 2013:2540-7
MRD (Measurable or Minimal)

- Surrogate marker of tumor biology and drug efficacy
- Define depth of response
- Correlate with clinical outcomes, esp. for HR patients
- Sensitivity of MRD testing matters
- Guide therapy

Kumar Lancet Oncol. 2016;17(8)

Comparison of NPC and APC

<table>
<thead>
<tr>
<th>Marker</th>
<th>NPC</th>
<th>APC</th>
<th>% of myeloma cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19</td>
<td>+/-dim</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>CD45</td>
<td>+/-dim</td>
<td>75-90% (ref 1 &amp; 2)</td>
<td></td>
</tr>
<tr>
<td>CD27</td>
<td>+/bright/-dim</td>
<td>40-68%</td>
<td></td>
</tr>
<tr>
<td>CD81</td>
<td>+/bright/-dim</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>CD38</td>
<td>+++/+</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>CD56</td>
<td>-/+dim</td>
<td>60-75%</td>
<td></td>
</tr>
<tr>
<td>CD117</td>
<td>+/-dim</td>
<td>20-30%</td>
<td></td>
</tr>
<tr>
<td>CD20</td>
<td>-/+dim</td>
<td>20-30%</td>
<td></td>
</tr>
<tr>
<td>CD28</td>
<td>-/+dim</td>
<td>15-45%</td>
<td></td>
</tr>
<tr>
<td>CD200</td>
<td>Dim/+/-dim</td>
<td>65-86%</td>
<td></td>
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</table>

Comparison of normal and aberrant PCs

Abnormal/Normal PC ratio may predict progression.

A: ≥ 95% Aberrant PCs,
B: Immunoparesis (decreased normal Ig)

No A or B: Not reached


MRD Detection Consensus panel (8 antibodies): CD138, CD38, CD19, CD45, CD27, CD56, CD81, CD117

Normal PCs have subset of CD19-, CD45- or CD56+

Patient treated with Daratumumab (anti-CD38 antibody)

Daratumumab also causes DAT +

IMWG definition of MRD- by FCM
- 1 to $10^5$ or higher level of sensitivity 0.001% (1 cell in 100,000)
- Euroflow panel (2 tubes, bulk lyse):
  - CD138, CD38, CD19, CD45, CD27, CD56, CD41, CD117
  - CD138, CD19, CD38, CD45, CD27, CD56, vs9, vs38c, vs38a, vs38b

Estimated LOD and LLOQ According to the Total Number of Events Acquired

<table>
<thead>
<tr>
<th>Total number of cells analyzed</th>
<th>LOD (%)</th>
<th>LLOQ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100,000</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>200,000</td>
<td>0.015</td>
<td>0.025</td>
</tr>
<tr>
<td>500,000</td>
<td>0.006</td>
<td>0.01</td>
</tr>
<tr>
<td>1,000,000</td>
<td>0.003</td>
<td>0.005</td>
</tr>
<tr>
<td>2,000,000</td>
<td>0.0015</td>
<td>0.0025</td>
</tr>
<tr>
<td>3,000,000</td>
<td>0.001</td>
<td>0.0017</td>
</tr>
<tr>
<td>5,000,000</td>
<td>0.0006</td>
<td>0.001</td>
</tr>
</tbody>
</table>

LOD = (30/Total cells) x 100%; LOQ = (50/Total cells) x 100.
New Checklist Items

College of American Pathologists

Comparison of MRD Assessment Techniques

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ASO-PCR</th>
<th>NGS</th>
<th>Flow Cytometry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Universal assay</td>
<td>No (pt-specific primers)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sensitivity*</td>
<td>1 in 10^3</td>
<td>1 in 10^4</td>
<td>1 in 10^5</td>
</tr>
<tr>
<td>Applicability</td>
<td>70-80%</td>
<td>92%</td>
<td>100%</td>
</tr>
<tr>
<td>Sample source</td>
<td>BMA</td>
<td>BMA or PB</td>
<td>Fresh BM aspirate</td>
</tr>
<tr>
<td>Sample quality check</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Sampling error</td>
<td>Likely</td>
<td>PB sample can overcome</td>
<td>Likely</td>
</tr>
<tr>
<td>Clonal evolution</td>
<td>Not detected</td>
<td>Limited /detectable</td>
<td>Not detected</td>
</tr>
<tr>
<td>Turnaround time</td>
<td>Days</td>
<td>Days to wks</td>
<td>Hrs</td>
</tr>
<tr>
<td>Cost</td>
<td>$-$-$-$-$&lt;=$</td>
<td>$-$&lt;=$&lt;=$&lt;=$</td>
<td>$&lt;=$</td>
</tr>
</tbody>
</table>


ClonoSeq (NGS)

http://www.adaptivebiotech.com/

Differential diagnosis of IgM M spike

MYD88 L265P mutation can also be detected in LPL with IgA and IgG M protein
PCs in LPL often express CD19 and CD45 but lack CD56 and CD117

DD of plasmablastic or CD138+ neoplasms

- Plasmablastic Myeloma
- Plasmablastic lymphoma (EBV)
- Primary effusion lymphoma (EBV, HHV8)
- Multicentric Castleman disease (HHV8+)
- ALK+ large B cell lymphoma
- Non-hematopoietic tumor

Summary

- High risk MM remains challenging despite novel therapy
- Risk stratification based on clinical and genetic/molecular genetic features
- MRD detection by FCM and NGS can guide therapy
- Intraclonal heterogeneity is the biological basis of clonal evolution and drug resistance

Personalized and Precision Medicine