Myeloma: Are We on the Brink of a Cure?

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Survival in Myeloma

Multiple Myeloma (MM)

- 95,874 currently with MM
  - Accounts for 1% of all malignancies and about 10% of hematological cancers
  - Accounts for 2% of deaths from all cancers and 20% of deaths from hematological cancers
- Slightly more common in men than women
- Incidence in African Americans is about twice that of whites
- Median age at diagnosis is 66 years
  - Age <50 years: 10%
  - Age <40 years: 2%

MM is characterized by:

- Excessive numbers of abnormal plasma cells in the bone marrow
- Overproduction of intact monoclonal immunoglobulins (IgG, IgA, IgD) or free antibody light chains
- Concomitant drop in other immunoglobulins
- CRAB Criteria
  - HyperCalcemia
  - Renal
  - Anemia
  - Bone Lesions

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Characteristics of Active Multiple Myeloma and Its Precursors

<table>
<thead>
<tr>
<th>Serum Protein Electrophoresis</th>
<th>MGUS</th>
<th>Smoldering Multiple Myeloma</th>
<th>Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb, α1, α2, β, γ</td>
<td></td>
<td></td>
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<table>
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<tr>
<th>Bone Marrow</th>
<th>&lt;10% Plasma cells</th>
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<tbody>
<tr>
<td>Clinical Picture</td>
<td>Asymptomatic</td>
<td>Asymptomatic</td>
<td>Symptomatic</td>
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<tr>
<td></td>
<td>No end-organ damage</td>
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<td>Therapy</td>
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Historical Criteria for Diagnosis of Myeloma

**MGUS**
- < 3 g/dL M spike
- < 10% plasma cells

**SMM**
- ≥ 3 g/dL M spike
- ≥ 10% plasma cells

**Active MM**
- ≥ 10% plasma cells
- M spike + in serum and/or urine

AND NO CRAB* features
or end-organ damage

AND CRAB* features

*C: Calcium elevation (> 10.5 mg/L or ULN)
R: Renal dysfunction (serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g < normal)
B: Bone disease (lytic lesions)

Smoldering Multiple Myeloma

51% will convert in first 5 yrs
~ 10% per yr

27% more will convert in remaining 15 yrs
~ 2% per yr

Mimics MGUS

Biomarkers to Predict Risk of Progression

- FLC ratio ≥ 100 predicts risk ($P < .0001$)
- Clonal plasma cells in BM predicts risk ($P < .001$)

Pre-existing MGUS
(Monoclonal Gammopathy of Undetermined Significance)
PLCO Study
Landgren, et.al.

- 100% of patients with samples 2 years prior had MGUS
- 82.4% with samples 8 years prior had MGUS
- 97.1% of all patients had MGUS from 2 to 8 or more years prior
Walter Reed Study
Weiss et al.

- Samples available for 30/90
- Median number of samples available 3.5 (1-14)
- PPCD detected in 27/30
  - +SPEP and/or IFE 21
  - + sFLC 6
- First detected
  - sFLC alone 6
  - IFE alone 1
  - SPEP + IFE 5
  - IFE + sFLC 1
  - All three 14
Imaging
Bortezomib +/- Dex: Confirmation of Remission: PET Scan

Pretreatment

After 4 Cycles
Imaging

- Either
  - PET/low dose whole body CT
  - MRI of spine and pelvis
  - New: Combined WB PET/MRI

- Must be used
  - To confirm sCR and MRD neg CR
  - To confirm smoldering myeloma
Measurement of the Disease

- **Measurement of protein**
  - **Immunoelectrophoresis** (IEP) or Immunofixation (IF or IFE)
  - **Serum Protein Electrophoresis** (SPEP) with **M-spike** (**M-protein**)
  - **Quantitative immunoglobulins** (**IgG**, **IgA**, **IgD**, **IgM**)
  - **Free light chain** analysis replacing urine studies, including Bence-Jones and 24 hour total protein
  - **MRD – Flow or NGS**
Measurements of Response

- IMWG Criteria
  - SD = <25% reduction
  - MR = 25% - 49% reduction
  - PR = 50% or greater reduction
  - VGPR = 90% reduction in protein spike (includes nCR)
  - nCR = pos IEP
  - CR = neg IEP
  - sCR = nml free lite and absence of clonal cells in BM

- MRD neg CR
The Iceberg

Getting to Minimal Residual Disease (MRD)

Disease burden

- S.S. Patient
- CR
- Stringent CR
- Molecular/Flow CR
- ?Cure?

Newly diagnosed: $1 \times 10^{12}$

$1 \times 10^{8}$

$1 \times 10^{4}$

0.0
Evidence that CR Matters
APEX Trial: OS (Velcade vs Dex)
CR vs nCR / VGPR / PR vs Less

Prognostic effect of CR patients vs those in nCR or VGPR or PR vs patients with SD or PD after HDT/ASCT

**PFS**

\[ P = 0.00001 \]

**OS**

\[ P = 0.00001 \]

Minimal Residual Disease (MRD)

Flow

Next Generation Sequencing
Measurement of MRD

- Black Swan (Spanish) Flow
  - 8-12 color

- Characteristics
  - $10^5$
  - No need for ID specimen
  - Must do it on fresh specimen

- Clonoseq (Adaptive)
  - NGS

- Characteristics
  - $10^6$
  - Requires ID specimen
  - 8% failure to identify clone
Time to progression for patients achieving conventional complete remission (CR), according to minimal residual disease (MRD) status as determined by deep sequencing.

MRD at post-maintenance for patients in CR

Patients without progression (%)

Months since randomization

N at risk (events)

<table>
<thead>
<tr>
<th>MRD neg (&lt;10(^{-6}))</th>
<th>80 (0)</th>
<th>80 (0)</th>
<th>80 (0)</th>
<th>80 (0)</th>
<th>80 (0)</th>
<th>80 (3)</th>
<th>73 (3)</th>
<th>57 (5)</th>
<th>33 (0)</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD positive</td>
<td>51 (0)</td>
<td>51 (0)</td>
<td>51 (0)</td>
<td>51 (3)</td>
<td>47 (9)</td>
<td>36 (5)</td>
<td>26 (9)</td>
<td>6 (0)</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

P-value: p<0.0001
Why are we Failing to Obtain Long Periods of Disease Control in 25% of Patients?
Evolution of Myeloma Therapy
Patient Case:

39 y.o. female with months of severe back pain, right leg pain, and lower extremity weakness. Subsequently she developed clavicular fractures and spine and lower extremity deformities.

Admitted to her local hospital, April 15, 1844

Solly, Med Chirur Trans London 1844
Treatment

• wine
  • arrow-root
  • a mutton chop
  • a pint of porter daily
  • an infusion of orange peel
  • a rhubarb pill when necessary
  • opiates
Conclusion

“earthy matter of the bone is absorbed and thrown out by the kidneys”
Myeloma Therapy (1961-1970)
Myeloma Therapy (1971-1990)

- Steroids
- Alkylators
  - Cyclophosphamide (Cytoxan)
  - Melphalan (low dose)
- OS = 2 years
Myeloma Therapy (1991-2000)

- VAD (Vincristine, adriamycin, decadron)
- Autologous PSC-T (peripheral stem cell transplant) (use of high dose melphalan)
- +/- Allogeneic PSC-T
- +/- Interferon

- OS = 3-4 years for good risk, lower stages
  = 2 years for everyone else
Myeloma Therapy (2001-2010)

- Thalidomide
- Bortezomib (Velcade) (5/2003)
- Lenalidomide (Revlimid) (12/27/05)
- Pegylated liposomal doxorubicin (Doxil) (2007) (in combo with bortezomib)

- Continued auto PSC-T
- Began combinations with new agents and old
  - RVd
  - CyBorD
Myeloma Therapy (2011 – 2013)

- Carfilzomib (Kyprolis) (7/20/12)
- Pomalidomide (Pomalyst) (2/8/13)

- Role of “Maintenance” Therapy defined
- Develop combinations for induction followed by transplantation
- OS = 8-10 years for standard risk
Myeloma Therapy (2014-2016)

- Panobinostat (Farydak) (2/23/15)
- Daratumumab (Darzalex) (11/16/15)
- Ixazomib (Ninlaro) (11/20/15)
- Elotuzumab (Empliciti) (11/30/15)

- Concept of post transplant consolidation
- Adding in newer agents (Carfilzomib) to induction
- Doublets and triplets for “High Risk” maintenance
- Use of Minimal Residual Disease testing
- Further confirmation of the role of auto PSC-T
Decisions at Diagnosis

- Does this patient need treatment at all? Smoldering?
  - Use of PET/CT
  - Studies of Revlimid and other agents in smoldering

- Transplant candidate vs not (Melphalan issue)
  - Not necessarily still true
    - Nobody (except in Europe) uses frontline melphalan
    - There are combinations that work for both groups
    - We now have Plerixafor
Initial Induction Therapy for Patients Eligible for Transplant

NO MELPHALAN
Improving Response Rates with Combination Therapies
Carfilzomib (Kyprolis)
KRd (? Improvement over RVd?)

Jakubowiak, 2015

Response Rates Over the Course Treatment

KRd w/o ASCT

- After 4 cycles (n=49):
  - ≥VGPR: 69%
  - ≥nCR: 43%
  - ≥CR: 18%
  - sCR: 8%

- After 8 cycles (n=44):
  - ≥VGPR: 89%
  - ≥nCR: 66%
  - ≥CR: 34%
  - sCR: 30%

- After 18 cycles (n=41):
  - ≥VGPR: 90%
  - ≥nCR: 80%
  - ≥CR: 59%
  - sCR: 51%

nCR, near complete response; VGPR, very good partial response
Frontline Therapy for Patients Ineligible for Transplant

Melphalan OK
Improving Response Rates with Combination Therapies

Induction Regimen

Percent Response

- VAD
- TD
- RD
- PAD
- VTD
- RVD
- CVRD
- CyBorD
- CarRD*

Colors:
- ORR
- VGPR
- CR/nCR
Stem Cell Transplantation

There is still a role!!!
The Debate... ASCT: Up-Front or at Relapse
DFCI/IFM 2009 Trial

Len-Bz-Dex ×3

Stem collection

ASCT

Len-Bz-Dex ×2

Len ×12m (IFM)

Len until relapse (US)

Len-Bz-Dex ×3

Stem collection

Len-Bz-Dex ×5

Len ×12m (IFM)

Len until relapse (US)

ASCT at relapse

NCI Clinical Trial Identifier NCT01191060.
Transplant improved PFS

N at risk

<table>
<thead>
<tr>
<th></th>
<th>HDT</th>
<th>no HDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N at risk</td>
<td>350</td>
<td>350</td>
</tr>
<tr>
<td>Patients (%)</td>
<td>350</td>
<td>350</td>
</tr>
<tr>
<td>309</td>
<td>296</td>
<td></td>
</tr>
<tr>
<td>261</td>
<td>228</td>
<td></td>
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<tr>
<td>153</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>24</td>
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Further Evidence for Role of Auto ASCT
KRd (? Improvement over RVd?)
Jakubowiak, 2015

Response Rates Over the Course Treatment

KRd w/o ASCT

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<tr>
<td>≥VGPR</td>
<td>69</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>≥nCR</td>
<td>43</td>
<td>66</td>
<td>80</td>
</tr>
<tr>
<td>≥CR</td>
<td>18</td>
<td>34</td>
<td>59</td>
</tr>
<tr>
<td>sCR</td>
<td>8</td>
<td>30</td>
<td>51</td>
</tr>
</tbody>
</table>

nCR, near complete response; VGPR, very good partial response
KRd + ASCT
Zimmerman, 2016

Response Rates Over the Course of Treatment

KRd + ASCT

Rate after ASCT
(n=50)

<table>
<thead>
<tr>
<th>Rate</th>
<th>98%</th>
<th>48%</th>
<th>26%</th>
<th>20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>nCR</td>
<td>20</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>≥VGPR</td>
<td>77</td>
<td>85</td>
<td>73</td>
<td>82</td>
</tr>
<tr>
<td>≥nCR</td>
<td>20</td>
<td>12</td>
<td>8</td>
<td></td>
</tr>
<tr>
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<td>100</td>
<td>100</td>
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<td>sCR</td>
<td>82</td>
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nCR, near complete response; VGPR, very good partial response
Maintenance Therapy
(continuation therapy)
CALGB 100104:
A Phase III Randomized, Double-Blind Study of LEN vs. PBO Maintenance Therapy Following ASCT for MM

McCarthy P., et al

CALGB 100104: Study Design and Endpoints

- Primary endpoint: TTP (time from ASCT to PD/death)
- Secondary endpoints: OS, post-ASCT response, long-term LEN feasibility

- All patients received thromboprophylaxis; † LEN dose adjustments between 5-15 mg permitted.

ASCT: autologous stem cell transplant; β2-M: β2-microglobulin; CALGB: Cancer and Leukemia Group B; CR: complete response; LEN: lenalidomide; MEL200: melphalan 200 mg/m²; MR: minimal response; OS: overall survival; PD: progressive disease; PR: partial response; R: randomization; SD: stable disease; THAL: thalidomide; TTP: time to progression; Tx: treatment.

CALGB 100104: Time to Progression

Cutoff: Dec 2009

<table>
<thead>
<tr>
<th>Median TTP</th>
<th>LEN 39 months</th>
<th>PBO 21 months</th>
</tr>
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</table>

HR=0.37; \( P < 0.001 \)

Cutoff: Oct 2011

<table>
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<tr>
<th>Median TTP</th>
<th>LEN 46 months</th>
<th>PBO 27 months</th>
</tr>
</thead>
</table>

HR= 0.48; \( P < 0.001 \)

ASCT: autologous stem cell transplant; CALGB: Cancer and Leukemia Group B; HR: hazard ratio; LEN: lenalidomide; N/A: not applicable; PBO: placebo; TTP: time to progression.

CALGB 100104: Overall Survival

Cut-off: Dec 2009

- Jun 2009
  - $P = 0.4$

- Sep 2009
  - $P = 0.14$

<table>
<thead>
<tr>
<th>Events</th>
<th>HR ($P$ Value)</th>
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<tr>
<td>LEN</td>
<td>13</td>
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ASCT: autologous stem cell transplant; CALGB: Cancer and Leukemia Group B; HR: hazard ratio; LEN: lenalidomide; N/A: not applicable; OS: overall survival; PBO: placebo.

New Drugs/New Studies

Ixazomib (Ninlaro)
Panobinostat (Farydak)
Elotuzumab (Impliciti)
Daratumumab (Darzalex)
Daratumumab

Anti CD 38
Castor: Vd vs Dara Vd

Time to Progression

- Median: not reached for Vd
- Median: 7.3 months for Dvd
- 1-year TTP*: 65.4% for Dvd
- 28.8% for Vd

HR: 0.30 (95% CI, 0.21-0.43); P<0.0001

70% reduction in the risk of disease progression for Dvd vs Vd

*KM estimate
Pollux: Rd vs Dara Rd

Progression-free Survival

HR: 0.37 (95% CI, 0.27-0.52; P <0.0001)

63% reduction in the risk of disease progression or death for DRd vs Rd
Immunotherapies

Antibodies
Vaccines
Checkpoint Inhibitors
BiTEs
CAR-Ts
Vaccine approaches: DC fusion

Courtesy of David Avigan
BiTe Therapy
Chimeric Antigen Receptor Effector Cells (CAR-T)
Treatment of High Risk Smoldering Myeloma

Is there a rationale for treating?
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Free Light is Useful for Risk Assessment in SMM

Table 3. Multivariate analysis of prognostic factors for progression of SMM to myeloma and related disorders

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow plasma cells more than 10%</td>
<td>3.1 (1.6-6.3)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Abnormal FLC ratio less than 0.125 or more than 8</td>
<td>1.9 (1.3-2.7)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Serum M protein size, more than 30 g/L</td>
<td>1.9 (1.4-2.6)</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>
**Schedule of therapy (N = 126 pts)**

**Spanish Myeloma Group**

<table>
<thead>
<tr>
<th>Treatment arm (n = 60)</th>
<th>Control arm (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong>&lt;br&gt;Nine 4-week cycles</td>
<td>Therapeutic abstention</td>
</tr>
<tr>
<td>Lenalidomide&lt;br&gt;25 mg/daily during 21d every 28 d</td>
<td>Lenalidomide&lt;br&gt;10 mg/daily during 21 d every month*</td>
</tr>
<tr>
<td>Dexamethasone&lt;br&gt;20 mg D1-D4 and D12-D15 every 28 d</td>
<td>Therapeutic abstention</td>
</tr>
</tbody>
</table>

Ammendment on August 2011: Stop treatment at 2 years of treatment

*Low-dose Dex will be added at the moment of biological progression*
Len-Dex vs. No Treatment: TTP to Active Disease
(N = 119)
ITT analysis

Median follow-up: 32 months (range 12–49)

**Lenalidomide + dex**
Median TTP: NR
9 Progressions (15%)
- 5 pts: early disc followed by DP
- 4 pts: symptomatic DP

**No treatment**
Median TTP: 23m
37 Progressions (59%)
- 20 patients: bone disease
- 7 patients: renal failure

HR: 6.0; 95% IC (2.9–12.6); p < 0.0001
Len-dex vs no treatment: OS from diagnosis (n = 119)

Median follow-up: 38 months (range 14–96)

Lenalidomide + Dex: 94% at 5 yrs
No treatment: 79% at 5 yrs

HR: 5.01; 95% IC (1–22); p=0.03
Thank you