How to Use New Biology to Guide Therapy in Multiple Myeloma

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An inconvenient truth about myeloma

The vast majority of patients will relapse
Two patient cases to start

• A 49 y old man
  – Diagnosed in nov 2011 with kappa light chain disease SD stage IIA
  – Treated with 4 x VTD, ASCT, 2 x VTD consolidation
  – He reached a CR
  – In sept 2013 a relapses

• A 64 y old woman
  – Diagnosed in 2000 with IgG kappa, SD stage IIIA
  – Treated with 4xVAD followed by ASCT
  – she reached a PR
  – In sept 2013 he is still in PR
Multiple myeloma: a heterogeneous disease with many faces
Models of myeloma evolution

Linear acquisition of genetic change

Clonal succession and selective sweeps driving homogeneity

Branching evolutionary acquisition of change

* Clones with a distinct pattern of mutations
How can we use biology to optimize myeloma treatment?

1. What are the **prognostic factors** in multiple myeloma?

2. How can we use these **prognostic factors** to optimize treatment (**risk-adapted therapy**)?
Categories of prognostic factors

- **Patient related**
  - age\(^1\)
  - comorbidities\(^2\)

- **Disease related:**
  - **Blood:**
    - albumin, B2 microglobulin
    - LDH
    - circulating plasma cells
  - **Bone marrow:**
    - presence of plasma blasts
    - proliferation index
    - cytogenetics:
      - Karyotyping
      - FISH

1. Ludwig et al, J Clin Oncol 2010;28:1599
The ISS staging for multiple myeloma

< 65 y

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum $\beta_2$-microglobulin &lt; 3.5 mg/L, Serum albumin $\geq$ 3.5 g/dL</td>
<td>62</td>
</tr>
<tr>
<td>II</td>
<td>Not stage I or III*</td>
<td>44</td>
</tr>
<tr>
<td>III</td>
<td>Serum $\beta_2$-microglobulin $\geq$ 5.5 mg/L</td>
<td>29</td>
</tr>
</tbody>
</table>

*There are two categories for stage II: serum $\beta_2$-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum $\beta_2$-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.

Greipp et al, J Clin Oncol 2005;23:3412
Cytogenetics and prognosis in MM

- Nearly all patients have cytogenetic abnormalities in their plasma cells.
- However, abnormal cytogenetics are only found in around 30% of samples because of the poor ex vivo growth of myeloma cells.
- Abnormal cytogenetics can be considered as a surrogate marker for plasma cell proliferation.
- Prognostic value:
  - **Standard risk**: hyperdiploidy
  - **Poor risk**: hypodiploidy, monosomy 13 (del13)
## FISH and prognosis in MM

<table>
<thead>
<tr>
<th>High-risk</th>
<th>Standard-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(4;14)</td>
<td>t(11;14)</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>t(6;14)</td>
</tr>
<tr>
<td>t(14;20)</td>
<td></td>
</tr>
<tr>
<td>amp (1q21)</td>
<td></td>
</tr>
<tr>
<td>del (1p32)</td>
<td></td>
</tr>
<tr>
<td>del(17p13)</td>
<td></td>
</tr>
</tbody>
</table>

Munshi et al. Blood 2011;117:4696  
Chng et al. Leukemia 2013; Aug 26 [Epub]  
Avet-Loiseau et al,Leukemia 2013; 29 SEP [Epub]
Combination of iFISH and ISS

N = 2642 patients
(source = IMWG database)

Avet-Loiseau et al. Leukemia 2013;27:711
Combination of ISS and cytogenetics

Overall survival by ISS and (t(4;14) or FISH 17) in patients whose age >= 65 yrs
P-value: a vs b < 0.0001, b vs c = 0.03, a vs c < 0.0001

N = 2642 patients
(source = IMWG database)

<table>
<thead>
<tr>
<th>Group</th>
<th>Events/N</th>
<th>4-Year Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. ISS I/II &amp; -FISH</td>
<td>159/409</td>
<td>62% (56, 67)</td>
</tr>
<tr>
<td>b. ISS III &amp; -FISH or ISS I &amp; +FISH</td>
<td>136/230</td>
<td>38% (31, 45)</td>
</tr>
<tr>
<td>c. ISS II/III &amp; +FISH</td>
<td>113/160</td>
<td>24% (16, 32)</td>
</tr>
</tbody>
</table>

Avet-Loiseau et al. Leukemia 2013;27:711
Addition of LDH as prognostic factor with t(4;14) and/or del(17p) and ISS III

• Study details:
  • Investigation of prognostic parameters of pts enrolled in IFM2005-01 trial

• Results
  – Multivariate logistic regression analysis: risk of death from PD within 2 years from start of therapy related to:
    • high LDH > normal value ($p = 0.0014$)
    • ISS 3 ($p = 0.0097$)
    • cytogenetic abnormalities (= presence of either t(4;14) or 17p deletion ($p = 0.0002$))
  – Development of scoring system
  – Identification of small group of pts with very high-risk disease and a shortened survival despite use of intensive novel agent-based therapy

Moreau et al. ASH 2012 (Abstract 598), oral presentation
<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
<th>% of overall population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absence of adverse factors (neither high LDH, nor ISS 3, nor t(4;14) and/or del(17p))</td>
<td>57%</td>
<td>3-year OS: 89%</td>
</tr>
<tr>
<td>1</td>
<td>Presence of only 1 adverse factor (either high LDH or ISS 3 or t(4;14) and/or del(17p))</td>
<td>32%</td>
<td>3-year OS: 73%</td>
</tr>
<tr>
<td>2</td>
<td>Presence of high LDH plus ISS 3 in the absence of t(4;14) and/or del(17p)</td>
<td>6%</td>
<td>3-year OS: 68%</td>
</tr>
<tr>
<td>3</td>
<td>Presence of t(4;14) and/or del(17p) in addition to either ISS 3 or high LDH</td>
<td>5%</td>
<td>3-year OS: 24%</td>
</tr>
</tbody>
</table>

Moreau et al. ASH 2012 (Abstract 598), oral presentation
Chromosomal Abnormalities Are Major Prognostic Factors in Elderly Patients With Multiple Myeloma: The Intergroupe Francophone du Myélome Experience

**Patients and Methods**
To answer this important question, we retrospectively analyzed a series of 1,890 patients (median age, 72 years; range, 66 to 94 years), including 1,095 with updated data on treatment modalities and survival.

**Results**
This large study first showed that the incidence of t(4;14) was not uniform over age, with a marked decrease in the oldest patients. Second, it showed that both t(4;14) and del(17p) retained their prognostic value in elderly patients treated with melphalan and prednisone–based chemotherapy.

**Conclusion**
t(4;14) and del(17p) are major prognostic factors in elderly patients with MM, both for progression-free and overall survival, indicating that these two abnormalities should be investigated at diagnosis of MM, regardless of age.
Gene expression profiling

- Aims to take into account biological heterogeneity of MM
- Several groups have identified different high-risk signatures:
  - Arkansas 70 gene model\(^1\) IFM 15-gene model\(^2\)
  - MRC 97-gene and 6-gene signature\(^3\)
  - 7-gene prognostic score\(^4\)
  - HOVON: 10 subgroups\(^5\)
- GEP is not commonly used outside clinical trials
- GEP might be more informative for diagnosis of subgroups than for prognosis
- Further research needed before application in routine clinical practice is feasible

\(^1\)Shaughnessy et al., Blood 2007;109: 2276-2284
\(^2\)Decaux et al. J Clin Oncol 2008;26:4798-4805
\(^3\)Dickens et al. Clin Cancer Res 2010;16(6):1856–64
\(^4\)Moreaux et al. Haematologica 2011;96(4):574-582
GEP: the EMC-92 gene set

Prognostic validation in patient cohorts from other trials

Kuiper et al. Leukemia 2012;26:2406
Prognostic factors: mSMART

mSMART 2.0: Classification of Active MM

<table>
<thead>
<tr>
<th>High-Risk</th>
<th>Intermediate-Risk*</th>
<th>Standard-Risk*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ FISH</td>
<td>▪ FISH</td>
<td>All others including:</td>
</tr>
<tr>
<td>▪ Del 17p</td>
<td>▪ t(4;14)†</td>
<td>▪ Hyperdiploid</td>
</tr>
<tr>
<td>▪ t(14;16)</td>
<td>▪ Cytogenetic</td>
<td>▪ t(11;14)**</td>
</tr>
<tr>
<td>▪ t(14;20)</td>
<td>Deletion 13 or</td>
<td>▪ t(6;14)</td>
</tr>
<tr>
<td>▪ GEP</td>
<td>hypodiploidy</td>
<td></td>
</tr>
<tr>
<td>▪ High risk</td>
<td>▪ PCLI &gt;3%</td>
<td></td>
</tr>
<tr>
<td>signature</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Note that a subset of patients with these factors will be classified as high-risk by GEP
† LDH >ULN and beta-2 M > 5.5 may indicate worse prognosis
‡ Prognosis is worse when associated with high beta-2 M and anemia
**t(11;14) may be associated with plasma cell leukemia

v2 Revised and updated: Jun 2010

mSMART.org and V. Rajkumar, Educational session ASH 2012
Overall survival according to prognostic factors

Long-term follow-up of IFM 99 trials

Fig 1. Overall survival according to the number of poor-prognosis factors [i.e., age > 55 years; β2-microglobulin > 5.5 mg/L; t(4;14), del(17p), 1q gains]: zero, one, two, or more than two.

# IMWG risk stratification

<table>
<thead>
<tr>
<th>characteristics</th>
<th>Low-risk</th>
<th>Standard-risk</th>
<th>High-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS I/II and absence of t(4;14), del17p13 and +1q21</td>
<td>others</td>
<td></td>
<td>ISS II/III and t(4;14) or del17p13</td>
</tr>
<tr>
<td>Percentage of patients</td>
<td>20%</td>
<td>60%</td>
<td>20%</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>&gt; 10 y</td>
<td>7 y</td>
<td>2 y</td>
</tr>
</tbody>
</table>

*Cng et al. Leukemia 2013; Aug 26 [Epub]*
In multiple myeloma, focal lesions, as well as diffuse and variegated infiltration patterns, can be detected by magnetic resonance imaging. In the current study, we compared treatment response in 100 myeloma patients with changes in infiltration patterns in whole body magnetic resonance imaging before and after autologous stem cell transplantation. We found an agreement between serological response and changes in imaging \((P<0.001)\). In detail, a significant agreement of treatment response was observed for diffuse \((P=0.004)\) as well as for focal \((P=0.01)\) infiltration patterns. The number of focal lesions at second magnetic resonance imaging was of prognostic significance for overall survival \((P=0.001)\). We conclude that treatment response in myeloma goes along with a decrease in imaging findings. We suggest that residual disease after high-dose chemotherapy detected by magnetic resonance imaging...

Hillengass et al. Haematologica 2012;97:1757
Prognostic value of imaging: 18F-FDG PET/CT after ASCT

- N = 192
- Prognostic parameters at diagnosis:
  - > 3 focal lesions (44%)
  - SUV > 4.2 (46%)
  - EM disease (6%)
- Prognostic parameters at 3 months post ASCT:
  - PET positivity was associated with shorter PFS and OS

Zamagni et al. Blood 2011;118:5989

SUV: Standardized Uptake Value
EM: Extra Medullary
Which prognostic parameters should be assessed in routine clinical practice?

Standard examination should take into account:

- age
- presence of co-morbidities
- ISS stage
- LDH
- presence of t(4;14), del17p or del1q using FISH
- evaluation for extramedullary disease
How should prognostic information be incorporated in current treatment regimens?

What is the evidence to tailor treatment according to risk-category?

Or

Should we treat high-risk patients differently?
High-risk patients: maintaining remission is the biggest challenge

Barlogie et al, Cancer 2008;113:355
The best news about myeloma treatment

- More drugs for relapsed MM have become available
  - Currently:
    - bortezomib
    - thalidomide
    - lenalidomide
    - pomalidomide
  - In the near future:
    - second generation proteasome inhibitors: e.g. carfilzomib
    - monoclonal antibodies
    - .....
Bortezomib-dex vs VAD

benefit for patients with t(4;14)

<table>
<thead>
<tr>
<th></th>
<th>Overall results (n=240)</th>
<th></th>
<th>t(4;14) (n=106)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median PFS / EFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vel/dex</td>
<td>36 months</td>
<td>0.064</td>
<td>28 months</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VAD</td>
<td>29.7 months</td>
<td></td>
<td>16 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>0.508</td>
<td>63% (@ 4 yrs)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vel/dex</td>
<td>81.4% (@ 3 yrs)</td>
<td></td>
<td>32% (@ 4 yrs)</td>
<td></td>
</tr>
<tr>
<td>VAD</td>
<td>77.4% (@ 3 yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HOVON 65/GMMG-HD4: study design

HOVON 65/GMMG-HD4
impact of cytogenetics

<table>
<thead>
<tr>
<th>Aberration, yes vs no</th>
<th>Patients analyzed, n</th>
<th>Incidence, %</th>
<th>PFS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median, mo</td>
<td>HR [95% CI]</td>
</tr>
<tr>
<td>del(8p21)</td>
<td>80 of 344</td>
<td>23.3</td>
<td>27 vs 35</td>
<td>1.3 [1.0-1.8]</td>
<td>.096</td>
</tr>
<tr>
<td>del(13q14)</td>
<td>171 of 354</td>
<td>48.3</td>
<td>27 vs 39</td>
<td>1.5 [1.2-2.0]</td>
<td>.0023†</td>
</tr>
<tr>
<td>del(13q14) only*</td>
<td>106 of 272</td>
<td>39.0</td>
<td>31 vs 40</td>
<td>1.3 [0.9-1.8]</td>
<td>.13</td>
</tr>
<tr>
<td>del(17p13)</td>
<td>37 of 350</td>
<td>10.6</td>
<td>18 vs 36</td>
<td>2.5 [1.7-3.7]</td>
<td>&lt; .0001†</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>50 of 352</td>
<td>14.2</td>
<td>22 vs 36</td>
<td>2.0 [1.4-2.8]</td>
<td>.0002†</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>68 of 354</td>
<td>19.2</td>
<td>39 vs 32</td>
<td>1.0 [0.7-1.3]</td>
<td>.8</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>6 of 339</td>
<td>1.8</td>
<td>29 vs 35</td>
<td>1.6 [0.7-4.0]</td>
<td>.30</td>
</tr>
<tr>
<td>+1q21</td>
<td>111 of 344</td>
<td>32.3</td>
<td>27 vs 39</td>
<td>1.7 [1.3-2.3]</td>
<td>.00002†</td>
</tr>
<tr>
<td>+11q23</td>
<td>172 of 344</td>
<td>48.6</td>
<td>36 vs 31</td>
<td>0.9 [0.7-1.2]</td>
<td>.45</td>
</tr>
<tr>
<td>+19q13</td>
<td>182 of 350</td>
<td>52.0</td>
<td>36 vs 31</td>
<td>0.8 [0.6-1.1]</td>
<td>.19</td>
</tr>
<tr>
<td>Hyperdiploidy</td>
<td>175 of 354</td>
<td>49.4</td>
<td>35 vs 32</td>
<td>0.9 [0.7-1.2]</td>
<td>.54</td>
</tr>
</tbody>
</table>

Bortezomib-based induction benefit for patients with del(17p)

- PFS: 12% vs 26% for bortezomib arm (p = 0.024)
- 3y OS: 17% vs 69% (p = 0.028)

Neben et al, Blood 2012;119:940
VTD vs VD: GIMEMA

Randomisation

Allocated to receive induction therapy (three 21-day cycles) with VTD
- 1.3 mg/m² bortezomib on days 1, 4, 8, and 11
- 100 mg thalidomide daily for the first 14 days and 200 mg thalidomide daily thereafter
- 40 mg dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12

Allocated to receive induction therapy (three 21-day cycles) with VD
- 100 mg thalidomide daily for the first 14 days and 200 mg thalidomide daily thereafter
- 40 mg dexamethasone on days 1-4 and 9-12

Mobilisation of autologous peripheral blood stem cells
- 4 g/m² cyclophosphamide
- 10 µg/kg G-CSF daily starting on day 2 after cyclophosphamide

First autologous stem-cell transplantation
- 200 mg/m² melphalan
- 5 µg/kg G-CSF daily starting on day 5 after melphalan

100 mg thalidomide daily and 40 mg dexamethasone on days 1-4, every 28 days

Second autologous stem-cell transplantation
- 200 mg/m² melphalan
- 5 µg/kg G-CSF daily starting on day 5 after melphalan

Consolidation therapy (two 35-day cycles) with VTD
- 1.3 mg/m² bortezomib on days 1, 8, 15, and 22
- 100 mg thalidomide daily
- 40 mg dexamethasone on days 1, 2, 8, 9, 15, 16, 22, and 23

Consolidation therapy (two 35-day cycles) with VD
- 100 mg thalidomide daily
- 40 mg dexamethasone on days 1-4 and 20-23

Maintenance therapy
- 40 mg dexamethasone on days 1-4, every 28 days

Cavo et al. Lancet Oncol 2010;376:2075
Meta-analysis: role of bortezomib induction

<table>
<thead>
<tr>
<th>Group</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Non-bortezomib based</th>
<th>Bortezomib based</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>2.05</td>
<td>1.64 to 2.56</td>
<td>n: 772, Response %: 182, 24</td>
<td>n: 775, Response %: 298, 38</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 55</td>
<td>2.23</td>
<td>1.55 to 3.22</td>
<td>n: 302, Response %: 65, 22</td>
<td>n: 296, Response %: 111, 38</td>
</tr>
<tr>
<td>≥ 55</td>
<td>1.94</td>
<td>1.47 to 2.58</td>
<td>n: 470, Response %: 117, 25</td>
<td>n: 479, Response %: 187, 39</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.97</td>
<td>1.46 to 2.64</td>
<td>n: 438, Response %: 105, 24</td>
<td>n: 462, Response %: 175, 38</td>
</tr>
<tr>
<td>Female</td>
<td>2.17</td>
<td>1.54 to 3.05</td>
<td>n: 334, Response %: 77, 23</td>
<td>n: 313, Response %: 123, 39</td>
</tr>
<tr>
<td>ISS staging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1.58</td>
<td>1.12 to 2.23</td>
<td>n: 289, Response %: 92, 32</td>
<td>n: 288, Response %: 121, 42</td>
</tr>
<tr>
<td>II</td>
<td>2.85</td>
<td>1.90 to 4.28</td>
<td>n: 252, Response %: 47, 19</td>
<td>n: 283, Response %: 109, 39</td>
</tr>
<tr>
<td>III</td>
<td>2.28</td>
<td>1.40 to 3.69</td>
<td>n: 191, Response %: 36, 19</td>
<td>n: 168, Response %: 58, 35</td>
</tr>
<tr>
<td>Cytogenetics classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>2.44</td>
<td>1.72 to 3.46</td>
<td>n: 319, Response %: 70, 22</td>
<td>n: 308, Response %: 126, 41</td>
</tr>
<tr>
<td>Standard risk</td>
<td>1.67</td>
<td>1.20 to 2.31</td>
<td>n: 378, Response %: 89, 24</td>
<td>n: 372, Response %: 124, 33</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>2.01</td>
<td>1.22 to 3.31</td>
<td>n: 160, Response %: 37, 23</td>
<td>n: 153, Response %: 58, 38</td>
</tr>
<tr>
<td>≥ 60</td>
<td>2.08</td>
<td>1.62 to 2.67</td>
<td>n: 602, Response %: 142, 24</td>
<td>n: 605, Response %: 235, 39</td>
</tr>
</tbody>
</table>

N = 1572 (787 bz; 785: no bz)

Sonneveld et al. J Clin Oncol 2013;31:3279
## Thalidomide in high-risk patients studies with thalidomide maintenance

<table>
<thead>
<tr>
<th>Study</th>
<th>Significant improvement in PFS with maintenance therapy</th>
<th>Significant improvement in OS with maintenance therapy</th>
<th>Survival after relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer</td>
<td>Yes</td>
<td>Yes (3 years follow up)</td>
<td>Similar in all groups</td>
</tr>
<tr>
<td>Attal</td>
<td>Yes</td>
<td>Yes (@ 39 m), but OS advantage disappeared with longer follow-up (5.7 years)</td>
<td>Similar in all groups</td>
</tr>
<tr>
<td>Barlogie</td>
<td>Yes</td>
<td>Yes (7.2 years follow-up)</td>
<td>Reduced OS after thal exposure</td>
</tr>
<tr>
<td>Lokhorst</td>
<td>Yes</td>
<td>No</td>
<td>Reduced OS after thal exposure</td>
</tr>
<tr>
<td>Morgan</td>
<td>Yes</td>
<td>No</td>
<td>Reduced OS after thal exposure</td>
</tr>
<tr>
<td>Stewart</td>
<td>Yes</td>
<td>No</td>
<td>Reduced OS after thal exposure</td>
</tr>
</tbody>
</table>

Role of thalidomide maintenance

adverse prognosis in high-risk cytogenetics

Adverse cytogenetics defined as:
- amp (1q)
- t(4;14)
- t(14;16)
- t(14;20)
- del(17p)

Role of upfront treatment with lenalidomide in high-risk MM patients

Brief report

Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone

Prashant Kapoor,1 Shaji Kumar,1 Rafael Fonseca,2 Martha Q. Lacy,1 Thomas E. Witzig,1 Suzanne R. Hayman,1 Angela Dispenzieri,1 Francis Buadi,1 P. Leif Bergsagel,2 Morie A. Gertz,1 Robert J. Dalton,3 Joseph R. Mikhael,2 David Dingli,1 Craig B. Reeder,2 John A. Lust,1 Stephen J. Russell,1 Vivek Roy,4 Steven R. Zeldenrust,1 A. Keith Stewart,2 Robert A. Kyle,1 Philip R. Greipp,1 and S. Vincent Rajkumar1

The outcome of patients with multiple myeloma is dictated primarily by cytogenetic abnormalities and proliferative capacity of plasma cells. We studied the outcome after initial therapy with lenalidomide-dexamethasone among 100 newly diagnosed patients, risk-stratified by genetic abnormalities and plasma cell labeling index. A total of 16% had high-risk multiple myeloma, defined by the presence of hypodiploidy, del(13q) by metaphase cytogenetics, del(17p), IGH translocations [t(4;14), or t(14;16)] or plasma cell labeling index more than or equal to 3%. Response rates were 81% vs 89% in the high-risk and standard-risk groups, respectively. The median progression-free survival was shorter in the high-risk group (18.5 vs 36.5 months, \( P < .001 \)), but overall survival was comparable. Because of unavailability of all tests for every patient, we separately analyzed 55 stringently classified patients, and the results were similar. In conclusion, high-risk patients achieve less durable responses with lenalidomide-dexamethasone compared with standard-risk patients; no significant differences in overall survival are apparent so far. These results need confirmation in larger, prospectively designed studies. (Blood. 2009;114:518-521)
## Lenalidomide maintenance therapy

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<thead>
<tr>
<th>Study details</th>
<th>n</th>
<th>Treatment</th>
<th>Outcome</th>
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<td>307</td>
<td>Lenalidomide</td>
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<td>Placebo</td>
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IFM/DFCI 2009 Study
Newly Diagnosed MM Pts (SCT candidates)

Randomize

RVDx3

CY (3g/m²) MOBILIZATION
Goal: 5 x 10^6 cells/kg

Mobilization

Goal: 5 x 10^6 cells/kg

Melphalan
200mg/m² +
ASCT

Stratification ISS, FISH
Systematic GEP, CGH → risk-adapted strategy

RVD x 2

Lenalidomide 12 mos

RVDx3

CY (3g/m²) MOBILIZATION
Goal: 5 x 10^6 cells/kg

SCT at relapse
MEL 200 mg/m² if <65 yrs,
≥65 yrs 140mg/m²

Lenalidomide 12 mos

RVD x 5
Novel Agents Alone versus Intensive Therapy + Novel Agents: European Intergroup Trial

**Registration**
- Induction
- Stem cell mobilization in all pts

**Consolidation**
- Maintenance until relapse

**Maintenance until relapse**

**HDM/ASCT at relapse**

**Induction**

**3 x CVD + Stem cell apheresis**

- **R1**
  - 4 x VMP
  - HDM 1/2

- **R2**
  - 2 x VRD
  - None

**Lenalidomide**

MPT vs Rd in Patients With Newly Diagnosed MM >65 Years Old

CC5013-MM-020, IFM 2007-01, FIRST study

**FIRST study / Trial Design**

**MPT**
- 12 cycles MP at 6-week interval + Thal at 100 or 200 mg/day, no maintenance

**Rd**
- Rev 25mg/day, days 1-21; Dex 20 or 40 mg/day, days 1,8,15, 22
- 18 cycles at 4-week interval

**Primary objective: PFS**

**Newly diagnosed MM patients; age >65 years (N = 1590)**

Some outstanding questions

• What about patients with ‘good’ or ‘standard’ risk myeloma?
  – What is their optimal treatment approach?

• How to integrate minimal residual disease in treatment optimization?

• How to integrate predictive factors for response e.g. Cereblon
Conclusions

• Risk-adapted treatment should replace the ‘one size fits all’ treatment strategy in multiple myeloma
  – this incorporates patient-, disease, -and treatment related factors

• Measurement of the following prognostic factors is recommended at diagnosis:
  – ISS
  – LDH
  – iFISH

• High-risk patients will benefit most from a bortezomib-based induction treatment