Role of Genomics in Multiple Myeloma

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Genomics: Definition

Analysis of tumor genomes on μarrays

New paradigm:
- usually: many patients, one biological target
- genomics: many patients, thousands of targets

Requirements:
- tumor cell purity (> 80%)
- bio-informatics
Genomics: Definition

Gene Expression Profiling (GEP)   SNP-array
Gene Expression Profiling (GEP): Tumor RNA

Malignant plasma cell sorting

Tumor RNA Extraction

Hybridization on expression chips
Gene Expression Profiling (GEP): Arkansas model

13% of pts

Shaughnessy et al., Blood 2007
Gene Expression Profiling (GEP): IFM model

→ High-risk population (25%)

Decaux et al., JCO 2008
CGH or SNPArray: Tumor DNA

Malignant plasma cell sorting

Tumor DNA Extraction

Hybridization on chips 500,000/2 M SNPs
Avet-Loiseau et al., JCO 2009
SNP-array

Avet-Loiseau et al., JCO 2009
Hyperdiploidy/Gains chromosome 5

Avet-Loiseau et al., JCO 2009
Chromosome 1 abnormalities

1q gain: observed in 1/3 of the patients

Avet-Loiseau H et al., JCO 2012
Chromosome 1 abnormalities

Combination del(17p), t(4;14), 1q gain, and β2M

Avet-Loiseau H et al., JCO 2012
Chromosome 1 abnormalities

Hebraud B et al., submitted
### Chromosome 1 abnormalities

FISH analysis of 1195 pts treated with HDM for 1p22 et 1p32

- 15% deletion 1p22
- 7% deletion 1p32

<table>
<thead>
<tr>
<th></th>
<th>Del(1p22)</th>
<th>No del(1p22)</th>
<th>Del(1p32)</th>
<th>No del(1p32)</th>
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</thead>
<tbody>
<tr>
<td>PFS</td>
<td>22 months</td>
<td>35 months</td>
<td>14 months</td>
<td>35 months</td>
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<tr>
<td>OS</td>
<td>70 months</td>
<td>108 months</td>
<td>26 months</td>
<td>109 months</td>
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</tbody>
</table>

Hebraud B et al., submitted
Chromosome 1 abnormalities

Hebraud B et al., submitted
# Chromosome 1 abnormalities

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>IC[95%]</th>
<th>p</th>
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<tbody>
<tr>
<td>Bortezomib induction</td>
<td>0.50</td>
<td>0.26-0.95</td>
<td>0.04</td>
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<tr>
<td>Beta2 microglobulin</td>
<td>1.03</td>
<td>1.01-1.05</td>
<td>0.01</td>
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<tr>
<td>Deletion 1p32</td>
<td>4.14</td>
<td>2.67-6.44</td>
<td>&lt;0.001</td>
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<tr>
<td>t(4;14)</td>
<td>2.02</td>
<td>1.42-2.87</td>
<td>&lt;0.001</td>
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<tr>
<td>Deletion 17p (&gt; 60%)</td>
<td>3.07</td>
<td>2.17-4.33</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Hebraud B et al., submitted
Role of SNP-array in progression analysis
Oncogenetic progression

Most (all?) patients present relapse

Is the relapse due to the same clone?

Or does chemotherapy select subclones?

Is there any difference between « old » CT and novel drugs?
Oncogenetic progression

Analysis of 24 patient pairs (diagnosis/relapse)

12 patients treated with VAD + HDMEL

12 patients treated with Vel/Dex + HDMEL

Analysis on Affymetrix SNP 6.0 array (1.8 M markers)
Oncogenetic progression

Evolutionary relationship map

MGUS

Primary MM

Relapse MM

Gain and loss of lesions: 37.5%
8/12 Vel/D
1/12 VAD

Gain of lesions: 54.2%
4/12 Vel/D
9/12 VAD

No change: 8.3%
0/12 Vel/D
2/12 VAD
Oncogenetic progression
Oncogenetic progression
Oncogenetic progression

[Diagram showing genetic progression and copy number changes over diagnosis and relapse stages.]
Oncogenetic progression
Oncogenetic progression
Oncogenetic progression

Evolutionary relationship map

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Conclusion

SNP-array enables to detect recurrent abnormalities
Enables identification of high risk CNAs
Enables analysis of events leading to relapse
Favor drug combination as soon as diagnosis