ADVANCES IN IMMUNOPHENOTYPING OF MULTIPLE MYELOMA

Servicio de Citometría y Servicio de Hematología
Universidad y Hospital Universitario de Salamanca

Centro de Investigación del Cáncer

CiC

Sao Paulo, 18th of April, 2009
<table>
<thead>
<tr>
<th>IMMUNOPHENOTYPING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>- Acute Leukemias &amp; Lymphoproliferative disorders:</strong></td>
</tr>
<tr>
<td>• <em>Mandatory for diagnosis &amp; monitoring</em></td>
</tr>
<tr>
<td><strong>- Multiple Myeloma:</strong></td>
</tr>
<tr>
<td>• <em>Restricted to research</em></td>
</tr>
<tr>
<td>• <em>Differential diagnosis of unusual cases</em></td>
</tr>
</tbody>
</table>
MM PLASMA CELL

cIg^+

PC-associated Ags:
- CD38^{++/+} .... 100%
- CD138 + .......... 98%

HPC-associated Ags:
- CD34^+ .......... 0%
- CD117 + .......... 27%

B-cell-associated Ags:
- CD19^+ ..........3-8%
- CD20^+ ..........2-25%
- CD22^+ ..........20-30%
- CD10^+ ..........6-20%
- HLA-DR^{+het} 10%
- CD23^+ ..........0%
- FMC7^+ ..........0%

Co-stimulatory Ags:
- CD28^{++} ..........30-40%
- CD40 + .......... 100%
- CD27 -/dim .... 40-50%

Adhesion molecules:
- CD56^{++/+} ...... 60-70%
- \beta1/\beta2 integrins 98%

Myeloid-associated Ags:
- CD13^+ .......... 28%
- CD33^{++/+} ..... 24%

Pan-leuc. Ag:
- CD45^+ ...20-40%
Plasma cell quantification (BM infiltration)

• **Morphological PC count:**
  - area of BM smear
  - infiltration pattern

Variability

• **Immunophenotyping:**
  - precise identification by CD38/CD138

- Co-expression of CD38/CD138
- Specific expression
- High-intensity

- but.....diluted sample → lower numbers
Are myelomatosous PC different from normal PC?

MONOCLONAL GAMMOPATHIES: IDENTIFICATION OF CLONAL PLASMA CELLS

CD38-FITC

Transposed SSC

10 10 10 10 10 0 1 2 3 4

CD138 PerCP/Cy5.5

CD38-FITC gated PC

Normal PC

Clonal PC

Perez-Andres, J Biol Reg, 2004

CD38-FITC

T-SSC

CD138-PerCP/Cy5.5

CD38-FITC

Perez-Andres, J Biol Reg, 2004
Frequency of Aberrant Phenotypes

N=195 patients

Infra-expression  Over-expression  Asynchronous expression

CD38  CD56  CD28  CD33  sIg  CD117  CD20

80%  52%  25%  16%  21%  15%  11%

Almeida et al, Br J Haematol, 1999
RESULTS: Immunophenotype of normal vs clonal PC

- **CD56**: p<0.001
- **CD126**: p<0.001
- **CD95**: p=0.72
- **CD86**: p<0.001
- **CD38**: p<0.001
- **HLA-Iα**: p=0.002
- **β2-microglobulin**: p=0.21
- **CD40**: p=0.005
# MOST USEFUL ANTIGENS FOR THE DETECTION OF ABERRANT PC IN MM

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Expression</th>
<th>% MM with altered expression</th>
<th>Requirement for MRD studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Altered</td>
<td></td>
</tr>
<tr>
<td><strong>CD19</strong></td>
<td>+ (&gt;70%)</td>
<td>-</td>
<td>95%</td>
</tr>
<tr>
<td><strong>CD56</strong></td>
<td>- (&gt;85%)</td>
<td>++</td>
<td>75%</td>
</tr>
<tr>
<td><strong>CD20</strong></td>
<td>- (100%)</td>
<td>+</td>
<td>10%</td>
</tr>
<tr>
<td><strong>CD117</strong></td>
<td>- (100%)</td>
<td>+</td>
<td>30%</td>
</tr>
<tr>
<td><strong>CD28</strong></td>
<td>-/dim (100%)</td>
<td>++</td>
<td>15%</td>
</tr>
<tr>
<td><strong>CD81</strong></td>
<td>+</td>
<td>-/dim</td>
<td>N.A.</td>
</tr>
<tr>
<td><strong>CD27</strong></td>
<td>++</td>
<td>-/dim</td>
<td>40-50%</td>
</tr>
</tbody>
</table>

N.A.: not analyzed/not reported.

Rawstron et al, EMN consensus, Haematologica, 2008
CLINICAL APPLICATIONS OF IMMUNOPHENOTYPING OF NEOPLASTIC PLASMA CELLS

Diagnostic classification
Prognostic evaluation
Treatment monitoring
Diagnostic classification
(differential diagnosis between MGUS vs MM)

Prognostic evaluation

Treatment monitoring
Are myelomatosous PC different from MGUS PC?
## Inmunophenotype of Polyclonal PC in MGUS vs Controls

<table>
<thead>
<tr>
<th>Antigen</th>
<th>MGUS: Polyclonal PC (n=76)</th>
<th>Controls' PC (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD38*</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>CD19</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>CD138</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>CD9</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>CD13</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>CD33</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>CD40</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>CD56*</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Results expressed as positive cases (> 20% positive PC)

*Strong reactivity
Other Ags explored were constantly negative
INTRATUMOURAL GENETIC HETEROGENEITY IN MM vs OTHER MONOCLONAL GAMMPATHIES

% of cases

MGUS  MM  PCL
N. of pathologic PC clones

Rasillo et al, Cancer, 2003
RESULTS: Immunophenotype of clonal PC in MGUS vs MM and PCL

MM vs Normal BM plasma cells

Abnormal plasma cells

Normal plasma cells
BM plasma cells in MGUS
Differential diagnosis

Only 20% of MM patients showed poly-PC and constantly <5% (median: 0.25%)\(^1\)

>5% poly-PC: 98% MGUS

The most powerful single criteria for differential diagnosis (even in stage I MM)


Risk of MGUS transformation\(^2\)

Cases with predominantly (>95%) CD19\(^{-}\)ve PC.... High risk (26% transformed in 31 months)

2. Rawstron A, Blood 2003, 102, 36 a (Abstr.116)
<table>
<thead>
<tr>
<th>N. of colors</th>
<th>PB</th>
<th>AMCA</th>
<th>FITC</th>
<th>PE</th>
<th>PerCPCy5.5</th>
<th>APC</th>
<th>PE-Cy7</th>
<th>Alexa700</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>CD38</td>
<td>CD56</td>
<td>CD19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>CD38</td>
<td>CD56</td>
<td>CD19</td>
<td>CD45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>cyIgL</td>
<td>cyIgk</td>
<td>CD19</td>
<td>CD45</td>
<td>CD56</td>
<td>CD38</td>
</tr>
<tr>
<td>8</td>
<td>CD19</td>
<td>CD45</td>
<td>cyIgL</td>
<td>cyIgk</td>
<td>CD138</td>
<td>CD28</td>
<td>CD56</td>
<td>CD38</td>
</tr>
</tbody>
</table>
CLINICAL APPLICATIONS OF IMMUNOPHENOTYPING OF NEOPLASTIC PLASMA CELLS

Diagnostic classification

Prognostic evaluation
- Enumeration of myelomatous PC
- Patterns of antigen expression
- Risk of progression of smoldering MM

Treatment monitoring
Correlation between Immunophenotyping & Morphology:

![Graph showing correlation between Immuno-phenotyping and Morphology](image)

- $R^2 = 0.4$

Proportion of plasma cell by flow cytometry vs. Proportion of plasma cell by morphology
• Correlation between Immunophenotyping & Morphology:

![Correlation Graph](image)

• Prognostic influence of the number of BMPC:

![Prognostic Influence Graph](image)
CLINICAL APPLICATIONS OF IMMUNOPHENOTYPING OF NEOPLASTIC PLASMA CELLS

Diagnostic classification

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- Enumeration of myelomatous PC
- Patterns of antigen expression
- Risk of progression of smoldering MM

Treatment monitoring
Prognostic influence of PC antigenic expression (I)

CD56

- CD56⁺ (n=272)
- CD56⁻ (n=355)

PFS

0 6 12 18 24 30 36 42 48 54 60

OS

0 6 12 18 24 30 36 42 48 54 60

CD117

- CD117⁺ (n=195)
- CD117⁻ (n=388)

p=0.05

p=0.01

p=0.03

p=0.1

Months from diagnosis

Mateos et al, JCO, 2008
Prognostic influence of PC antigenic expression (II)

**CD19**

- **PFS**
  - CD19 + (n=47)
  - CD19 -ve (n=580)
  - 28 m, 36 m
  - p=0.2

- **OS**
  - CD19 + (n=47)
  - CD19 -ve (n=580)
  - 54 m, 62 m
  - p=0.06

**CD28**

- **PFS**
  - CD28 + (n=235)
  - CD28 -ve (n=368)
  - 31 m, 37 m
  - p=0.05

- **OS**
  - CD28 + (n=235)
  - CD28 -ve (n=368)
  - 54 m, 66 m
  - p=0.1

Mateos et al, JCO, 2008
Prognostic influence of phenotypic profiles

CD56 & CD117
- CD56+CD117+ n=130 45 m
- +/- or +/- n=267 36 m
- CD56-CD117- n=186 31 m

CD56 & CD28
- CD56+CD28- n=1116 41 m
- +/- or +/- n=327 37 m
- CD56-CD28+ n=116 29 m

CD28 & CD117
- CD28-CD117+ n=142 45 m
- +/- or +/- n=327 37 m
- CD28+CD117- n=114 29 m

PFS
- Mateos et al, J Clin Oncol, 2008
### Multivariate analysis for RFS and OS

<table>
<thead>
<tr>
<th></th>
<th>RFS $P$</th>
<th>OS $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>% BMPC by FCM $&gt;20%$</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>% BMPC in S-phase $\geq 2.5%$</td>
<td>0.03</td>
<td>0.004</td>
</tr>
<tr>
<td>Non-hyperdiploidy DNA</td>
<td>0.05</td>
<td>NS</td>
</tr>
<tr>
<td>ISS stage 3</td>
<td>0.003</td>
<td>0.0001</td>
</tr>
<tr>
<td>Calcium $\geq 11$ mg/dl</td>
<td>0.005</td>
<td>NS</td>
</tr>
<tr>
<td>Platelets $\leq 130 \cdot 10^9$/L</td>
<td>0.017</td>
<td>0.04</td>
</tr>
</tbody>
</table>
CLINICAL APPLICATIONS OF IMMUNOPHENOTYPING OF NEOPLASTIC PLASMA CELLS

Diagnostic classification

Prognostic evaluation
- Enumeration of myelomatous PC
- Patterns of antigen expression
- Risk of progression of smoldering MM

Treatment monitoring
Introduction
Smoldering Multiple Myeloma

- Kyle & Alexanian 1980\textsuperscript{a}.
- Estimated incidence: 15\% of newly diagnosed MM\textsuperscript{b}.
- Estimated Risk of progression: 10\% per year\textsuperscript{c} vs. 1\% on MGUS

\textsuperscript{a} Kyle 1980, Alexanian 1980; \textsuperscript{b} Rajkumar 05; \textsuperscript{c} Kyle 05
Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the

Table 3  Smoldering or indolent myeloma* Diagnostic criteria: all three required

1  Monoclonal protein present in the serum and/or urine
2  Monoclonal plasma cells present in the bone marrow and/or a tissue biopsy
3  Not meeting criteria for MGUS, multiple myeloma, or solitary plasmacytoma of bone or soft tissue

*Note: These criteria identify Stage IA myeloma by Durie/Salmon

BMPC + High MC (>3 IgG or >2g/dl IgA)

> 10% of BMPC + MC

> 10% BMPC + High MC
## Parameters Associated with Disease Progression

<table>
<thead>
<tr>
<th>Predictive factors</th>
<th>Alexanian</th>
<th>Facon</th>
<th>Weber</th>
<th>Cesana</th>
<th>Rosiñol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BJ &gt;200 mg/24 h</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MC &gt;3 g/dl</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hb &lt;12 g/dl</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PC &gt;25%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MC &gt;3 g/dl</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IgA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Evolving type*</td>
</tr>
<tr>
<td><strong>BJ &gt;50 mg/24 h</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pathological MRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>% BMPC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*IgA + SMM with constant increase of MC*
## Characteristics of the Series

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>89</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>jan96- sep04</td>
</tr>
<tr>
<td>Age* (range)</td>
<td>69 (43-88)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>44/45</td>
</tr>
<tr>
<td>Follow-up*(range)</td>
<td>50 (24-107)</td>
</tr>
<tr>
<td>Progression (%)</td>
<td>38 (42)</td>
</tr>
</tbody>
</table>

*median (in months)

---

**Patients (%)**

- BMPC + High MC (>3 IgG or >2g/dl IgA) | 21 (24)
- >10% of BMPC + MC                    | 45 (50)
- >10% BMPC + High MC                  | 23 (26)

---

Perez-Persona et al, Blood, 2007
### Flow Cytometry Results

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Total PC in BM*</td>
<td>2.8 (0.9-22.0)</td>
</tr>
<tr>
<td>% of aPC / BMPC compartment</td>
<td>97 (35-100)</td>
</tr>
<tr>
<td>&lt; 95% aPC / BMPC</td>
<td>36 (40%)</td>
</tr>
<tr>
<td>&gt; 95% aPC / BMPC</td>
<td>53 (60%)</td>
</tr>
</tbody>
</table>

* Median (range)
Proportion of aPC referred to the total-PC (aPC/BMPC)

1st step
Total cellularity

% PC within BM cellularity

2nd step
PC compartment

% aPC/BMPC

% nPC/BMPC

Proportion of aPC referred to the total-PC (aPC/BMPC)
Impact of % aPC/BMPC by FC on Progression Free Survival

<95% aPC/BMPC n= 36 (4 progressions)

>95% aPC/BMPC n= 53 (34 progressions)

p=0.0000
Multivariate analysis for PFS

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>% a PC / BMPC</td>
<td>0.004</td>
<td>4.9</td>
</tr>
<tr>
<td>Immunoparesis</td>
<td>0.007</td>
<td>2.6</td>
</tr>
</tbody>
</table>
## Impact of prognostic index on PFS

<table>
<thead>
<tr>
<th>Immunoparesis</th>
<th>&gt;95% aPC/BMPC</th>
<th>Score (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>0 (n=32)</td>
</tr>
<tr>
<td>+ / -</td>
<td>-/+</td>
<td>1 (n=27)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>2 (n=27)</td>
</tr>
</tbody>
</table>
Impact of prognostic index on PFS

- No adverse factors
  - n = 32 (3 progressions)
  - Median not reached
  - 91%

- >95% aPC/BMPC or paresis
  - n = 27 (12 progressions)
  - Median 72 months
  - 58%

- >95% aPC/BMPC + paresis
  - n = 27 (22 progressions)
  - Median 20 months
  - 18%

p = 0.003

5 years
CLINICAL APPLICATIONS OF IMMUNOPHENOTYPING OF NEOPLASTIC PLASMA CELLS

Diagnostic classification

Prognostic evaluation

Treatment monitoring
Changes in PC distribution following ASCT

Diagnosis

Post-Trx

Gate CD38
### Minimal Number of PC Required to Be Analyzed in a MRD Assay for MM

<table>
<thead>
<tr>
<th>N. of tests in the MRD assay</th>
<th>N. of total nucleated cells/test</th>
<th>N. of events/test to define a PC population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,000,000</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>500,000</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>333,334</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>250,000</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>200,000</td>
<td>20</td>
</tr>
</tbody>
</table>
## Comparison between ASCT & Chemotherapy
### (changes in PC compartment)

<table>
<thead>
<tr>
<th></th>
<th>Chemo. After 12 cycles n=40</th>
<th>ASCT 3 m post-Trx n=47</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM-PC</td>
<td>0.17 (0-3.7)</td>
<td>0.04 (0-3.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>n-PC</td>
<td>0.12 (0-0.9)</td>
<td>0.21 (0-1.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>% n-PC/TPC</td>
<td>35 (0-100)</td>
<td>86 (0-100)</td>
<td>0.01</td>
</tr>
<tr>
<td>MRD−ve cases</td>
<td>15%</td>
<td>36%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Results expressed as median (range)

MRD−ve: <10⁻⁵ MM-PC with only normal PC being detected

San Miguel et al, Blood, 2002

Diagnosis

VBCMP/VBAD (x4) → Non-responding
  Stem cell collection
VBCMP/VBAD (x2) → Double-Trx

Complete remission (negative electrophoresis)* → ASCT (1º)
  3m post-ASCT
  Maintenance
  Relapse

Partial response (positive electrophoresis) → ASCT (2º) → Mini-ALO-Trx

MRD investigation

*Immunofixation either –ve or +ve
Correlation between immunophenotyping & electrophoretic responses at three months post-ASCT (n=200)

<table>
<thead>
<tr>
<th>MRD evaluation</th>
<th>Partial response</th>
<th>Complete remission</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EF-positive</td>
<td>IFx-positive</td>
<td>IFx-negative</td>
</tr>
<tr>
<td></td>
<td>n=74 cases</td>
<td>n=27 cases (21%)</td>
<td>n=99 cases (79%)</td>
</tr>
<tr>
<td>MM-PC</td>
<td>0.76 ± 0.9 #</td>
<td>0.28 ± 0.4</td>
<td>0.1 ± 0.3</td>
</tr>
<tr>
<td>MRD-negative cases</td>
<td>8% #</td>
<td>33%</td>
<td>64%</td>
</tr>
<tr>
<td>% n-PC/TPC</td>
<td>42 ± 33 #</td>
<td>69 ± 34</td>
<td>86 ± 25</td>
</tr>
</tbody>
</table>

Results expressed as mean ± SD

# p significance between EF-positive (PR) and CR IFE-positive cases: p=0.005; p= 0.0001; p=0.0001
RFS of MM: Impact of immunophenotyping at 3 months post-ASCT (n=200 patients)

Relapse-free survival

- <0.01% MM-PC
- 0.01% to 1% MM-PC
- ≥ 1% MM-PC

Paiva et al, Blood, 2008
RFS: Impact of immunophenotyping at 3 months post-ASCT in 99 CR (IF-) patients

%MM-PC

%N-PC / total PC

p=0.02

p=0.01

NR

NR

≤ 0.01% MM-PC

≥ 0.01% MM-PC

≥ 75 % N-PC/total PC

< 75 % N-PC/total PC
MRD IN MM: CORRELATION BETWEEN RQ-PCR AND FCM

\[ R = 0.861 \]

Sarrasquete et al, Haematologica, 2005
MRD IN MULTIPLE MYELOMA: APPLICABILITY OF FCM VS RQ-PCR

Patients in CR (N=53)

Cases with aberrant phenotypes (N=48)

Problems associated with the sample (N=16)
  Very low infiltration (N=9) infiltración muy baja
  Degraded DNA (N=4)
  Insufficient DNA (N=3)

Problems associated with the method (RQ-PCR) (N= 8)
  No clonal rearrangement detected (N=3)
  Very short N-region (N=3)
  Cases with mutations in the target sequence (N=2)

APPLICABILITY OF FCM: 90%
APPLICABILITY OF RQ-PCR: 75%

Sarrasquete et al, Haematologica, 2005
## Consensus medical indications of multiparameter flow cytometry immunophenotyping in the study of MM and other MG

<table>
<thead>
<tr>
<th>Clinical utility</th>
<th>Useful flow cytometry parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Differential diagnosis of MM vs MGUS</strong></td>
<td>% aberrant BMPC from total BMPC</td>
</tr>
<tr>
<td><strong>Identification of aberrant phenotypes</strong></td>
<td>Decreased expression (CD19, CD27, CD38, CD45, CD81) Overexpression (CD28, CD33, CD56) Asynchronous expression (CD20, CD117, sIg)</td>
</tr>
<tr>
<td><strong>Diagnosis of unusual cases</strong></td>
<td>PC-associated markers (e.g. CD138, cIg, CD38hi) &amp; aberrant PC markers (see above)</td>
</tr>
<tr>
<td><strong>Patient monitoring</strong></td>
<td>% of aberrant BMPC/total BM cells % normal BMPC/ all BMPC</td>
</tr>
</tbody>
</table>

MM: multiple myeloma; MGUS: monoclonal gammopathy of undetermined significance; BM: bone marrow; PC: plasma cells.

*Rawstron et al, EMN consensus, Haematologica, 2008*
CONCLUSIONS

Inmunophenotypic studies have high clinical value:

- Differential diagnosis MGUS/MM
- Prognostic influence of FCM number of myelomatous PC
- Prognostic influence of the patterns of antigen expression
- Prediction of the risk of transformation in SMM
- Investigation of MRD (immunophenotypic remission)
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