Monoclonal B cell lymphocytosis: Much ado about nothing? A clinical perspective

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Barcelona, 7 September 2012
MBL

• History
• Classification
• Relationship between MBL, CLL and SLL
• Problems of defining diseases by cut-offs
• Clinical aspects of MBL
  – General
  – Management
  – In relationship with BMT
History: Previous names for MBL

• “Bening Monoclonal B Cell Lymphocytosis”
  Han T. Blood 1984
• “Smoldering CLL”
  Montserrat E. Nouv Rev Franç d’H. 1988
• “Monoclonal Lymphocytosis of Unknown Significance”
• “Chronic Lymphocytic Leukemia with Low Lymphocyte Count”
  Batata A & Shen B. Cancer 1993
• “Monoclonal B cell lymphocytosis”
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MBL

- **CLL typical immunophenotype**
  - Clinical MBL: High-count MBL (>2,000/µl)
  - MBL: Low-count MBL (~50/µl)

- **CLL atypical immunophenotype**

- **Non-CLL immunophenotype**
Monoclonal B lymphocytes*

< 5,000/microliter

lymphadenopathy
spleen / liver enlargement
cytopenias related to BM infiltration

No

MBL

Yes

SLL

> 5,000/microliter

CLL

* SmIg weak, CD5+, CD19+, CD23+, CD20 weak

IWCLL Blood 2008; WHO 2008
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< 5,000/microliter

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MBL

Yes

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CLL

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IWCLL Blood 2008; WHO 2008
Processes recapitulated in the xenograft model

MBL phase

CLL phase

Primary event

HSC   CLL-HSC

Polyclonal   Oligoclonal   Monoclonal

Lymphoid priming

Auto-, or Xeno-antigens

ProB

Expansion

Selection

Oncogenic events

Abnormal chromosome etc

Transformation

Kikusighe Y et al. Cancer Cell 20; 246-259, 2011

Courtesy: G. Ferrer
MBL, CLL and SLL
MBL, CLL and SLL

If you do not find this complicated enough, it can complicated a little bit further…
Involvement by CLL/SLL-like cells of uncertain significance

Gibson et al. Haematologica 2011
The problem of defining a disease based on a threshold rather than well defined biologic characteristics
The problem of defining a disease based on a threshold rather than well defined biologic characteristics
Blood lymphocyte count at diagnosis

Hospital Clínic, Barcelona

N = 1146

54% (n = 617)

19% (n = 218)

22% (n = 255)

5% (n = 56)

Lymphocyte count (x10.9/L)

Frequency
How many MBL?

• Not all MBLs are created equal
  – Immunophenotypically
    • CLL
    • Atypical-CLL
    • Non-CLL
  – Numerically
    • High-count MBL (“clinical” MBL)
    • Low-count MBL (“non-clinical” MBL)
  – Clinically
    • Diagnosed in the clinical workup of a patient with moderate lymphocytosis
    • “Research” population

Reflecting difficulties in using thresholds to define diseases

<table>
<thead>
<tr>
<th>MBLs/μL</th>
<th>&gt;2,000</th>
<th>&gt;1,000</th>
<th>&gt;500</th>
<th>&gt;200</th>
<th>&gt; 1% in blood</th>
</tr>
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<tbody>
<tr>
<td></td>
<td><strong>cMBL</strong></td>
<td><strong>Rai 0</strong></td>
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<tr>
<td>Frequency</td>
<td>~ 600/100,000* (prevalence)</td>
<td>3-5/100,000/year** (incidence)</td>
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<tr>
<td>Blood lymphocytes</td>
<td>&lt; 5,000</td>
<td>&gt; 5,000</td>
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<tr>
<td>Phenotype</td>
<td>SmIg, CD5, CD19, CD23</td>
<td>SmIg weak, CD5, CD19, CD23 &amp; others</td>
<td></td>
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<tr>
<td>Transient cases</td>
<td>Infrequent; low-couts</td>
<td>Infrequent; 1% year</td>
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<tr>
<td>Disease progression</td>
<td>1-2% per year</td>
<td>5-10% year</td>
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<tr>
<td>Progression predictor</td>
<td>WBC count (11,000/µl?)</td>
<td>WBC count</td>
<td></td>
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<tr>
<td>Biologic distinctive feat.</td>
<td>No; cMBL=Rai 0</td>
<td>No; Rai0=cMBL</td>
<td></td>
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<tr>
<td>Symptoms</td>
<td>Infections, AIHA</td>
<td>Infections, AIHA</td>
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<tr>
<td>Survival</td>
<td>cMBL=Rai 0</td>
<td>cMBL=Rai 0</td>
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</table>
How to follow subjects with MBL?

• “Clinical” MBL:
  – As early stage CLL

• “Flow” MBL:
  – Leave them alone!

• Atypical CLL/Non-CLL immunophenotype
  – Workup as in NHL (BM, CT, genetics, etc) and behave accordingly
Should bone marrow donors be screened for MBL?

- EBMT survey (Hertestein B et al. Haematologica 2005)
  - 10,489 allogeneic stem cell transplants
    - 7 AML
    - 3 ALL
    - 3 MDS
    - 1 CML
Should bone marrow donors be screened for MBL?

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  - 10,489 allogeneic stem cell transplants
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    - 1 CML

No cases of CLL or indolent lymphoma

No cases of MGUS or myelona, either!
Should bone marrow donors be screened for MBL?

• Anecdotal cases reported
  – 1/19 syngenic SCT (Pavletic et al. Leukemia 2007)
  – Perz et al. (BMT 2008)
  – Nahi et al. (BJH 2008)
  – Del Giudice et al. (Blood 2009)
  – Flandrin-Gresta et al (Blood 2010)
  – Herishanu et al. (BJH 2010)
  – Ferrand et al (EJH 2012) (unrelated donor)
Should bone marrow donors be screened for MBL?

- 13 siblings candidates to be donors to CLL patients
  - 2 cases MBL

Del Giudice et al. Blood 2009
Should bone marrow donors be screened for MBL?

- No consensus

- Given the 2-7 fold higher risk of CLL among family members of patients with CLL, it is advisable to rule out “clinical” MBL (CLL!) in sibling donors.
Should individuals with MBL be discarded as bone marrow donors?

- No consensus
- “Clinical” MBL $\rightarrow$ yes!
- “Flow” MBL $\rightarrow$ no (not necessarily)
MBL screening should be part of the diagnostic workup of...

- Immune cytopenias
- Abnormalities in serum immunoglobulins
- HCV infection
- DLCL – “bone marrow MBL”
- Immune disorders
Thanks to...

Alberto Orfao
CLL Global Foundation

Julio Delgado
Tycho Bauman
Gabi Ghita
Rodrigo A. Santacruz

ERIC
ELN (WP 7)
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Alberto Orfao  
CLL Global Foundation

Julio Delgado  
Andy Rawstron

Tycho Bauman
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