Monoclonal B-cell Lymphocytosis: Much Ado About Nothing? NO!

Andy C. Rawstron
HMDS, Leeds Teaching Hospitals, UK

Disclosures:
Honorarium / Ad Board: Celgene, Genzyme, GSK, Mundipharma, Roche Consultancy: Biogen Idec. Royalties: BD Biosciences
Monoclonal B-cell Lymphocytosis: Much Ado About Nothing? NO!

“Friendly” nickname from my boss:

Professor of Insignificant Disease
Changes in the diagnostic criteria for CLL over time

1975
At clinical stage 0, the findings at diagnosis were lymphocytosis only, in blood as well as in bone marrow (absolute lymphocytes, 15,000/cu mm or more in blood, with 40% or more lymphocytes in the marrow). At clinical stage I, the findings at diagnosis were lymphocytosis with enlarged lymph nodes. At clinical stage II, the findings at diagnosis were lymphocytosis with

1996
Table 1. Comparison of NCI-Working Group and IWCLL Guidelines for CLL

<table>
<thead>
<tr>
<th>Variable</th>
<th>NCI</th>
<th>IWCLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (×10⁹/L)</td>
<td>&gt;5; ≥1 B-cell marker (CD19, CD20, CD23) + CD5</td>
<td>≥10 + B-phenotype or bone marrow involved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;10 + both of above</td>
</tr>
</tbody>
</table>

2008
The diagnosis of CLL requires the presence of at least 5 × 10⁹ B lymphocytes/L (5000/μL) in the peripheral blood. The clonality of the circulating B lymphocytes needs to be confirmed by flow cytometry. The leukemia cells found in the blood smear are symptoms, the presence of fewer than 5 × 10⁹ B lymphocytes per liter of blood is defined as “monoclonal B-lymphocytosis.”
Why was there any need to change from 1996 criteria?

Late 1990s onwards:
• Haematology analysers flag cases with a lymphocyte count above 3.5 x 10⁹/L or with some atypical lymphs as being “abnormal”
• Increasing referrals for flow cytometry in individuals with a lymphocyte count below 5 x 10⁹/L
• Increasingly common to detect “CLL” cells in these individuals

T-cells = 5.5 x 10⁹/L with CLL cells = 0.2 x 10⁹/L
1 colour flow cytometry = Normal
3 colour flow cytometry = CLL
Why not just call it CLL??

Progression is rare and people requiring Rx for CLL have a similar overall survival to those with a stable condition.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population (n=1060)</td>
<td>19.4</td>
<td>20.5</td>
</tr>
<tr>
<td>Cancer patient (n=2235)</td>
<td>18.7</td>
<td>18.6</td>
</tr>
<tr>
<td>CLL patients (n=1482)</td>
<td>16.8</td>
<td>17.8</td>
</tr>
</tbody>
</table>

Telling people that they have leukemia that does not require treatment causes disproportionate stress.

Emotional QOL Using FACT-G significantly (P<0.001) worse for CLL vs. other cancers.

Shanafelt, BJH 139:255

Approximately 1% of MBL cases develop progressive CLL per year.

Rawstron A, NEJM 2008, 359:575-83
Treatment-free survival for “clinic” MBL

“While this difference appears subtle it equates to a 10-year risk of requiring treatment of 7–14% for individuals with MBL compared to 50–70% for patients with Rai stage 0 CLL.”

Shanafelt, J Clin Oncol 2009; 27: 3959-3963
Much ado about not very much??

- MBL vs. CLL - arbitrary threshold is inherently problematic (? incorrect)
- Threshold debatable:
  - $5 \times 10^9/L \Rightarrow$ CLL incidence stable, MBL = very low risk
  - $10 \times 10^9/L \Rightarrow$ CLL incidence changes, MBL = intermediate risk
  - MGUS / Myeloma situation is generally practical for patients and clinicians so some equivalent is likely to remain
- The risk of progression in MBL can be very troubling for people with the disorder but perhaps should not be the primary concern
- ? Debate should be about the level of CLL cells begins to have an impact on health (lower threshold) ?
CLL-phenotype cells detectable in a high proportion of the general population

• All cases (even <0.001 x 10^9/L) have CLL phenotype and genotype (13q14, predisposition polymorphisms)

CLL-like B-cells (low-count / population MBL) vs. CLL-like MBL (clinic MBL)

2CLR Flow
MBL in 0.6%

MRD-flow
MBL in 3-5%

Ultra-sensitive
MBL in 10-90%


Rawstron, Blood 2002; 100(2): 635-39
Ghia, Blood 2004; 103(6): 2337-42

Dagklis, Blood 2009; 114:26-32
Nieto Blood. 2009; 114(1):33-7

NHS

2CLR Flow
MBL in 0.6%

MRD-flow
MBL in 3-5%

Ultra-sensitive
MBL in 10-90%


Rawstron, Blood 2002; 100(2): 635-39
Ghia, Blood 2004; 103(6): 2337-42

Dagklis, Blood 2009; 114:26-32
Nieto Blood. 2009; 114(1):33-7

NHS
CLL-like B-cells: no increase in infection risk
CLL-like MBL: 5x risk of severe infection

CLL-like B-cells typically $<0.01 \times 10^9/L$

CLL-type B-cells detected

B-cells polyclonal

P=0.32

Leeds ASH 2009

Moreira/Shanafelt Leukemia ePub
CLL-like B-cells: no impact on survival
CLL-like MBL: 20% reduction in 10yr OS

CLL-like MBL: 5/48 oncology, 3/5 MBL
Controls: 0/88 oncology referrals

P=0.430

Ten-year relative survival for CLL-type MBL Diagnosed 1995-2000, updated series n=361, median follow-up 8.7 years
CLL-like MBL 10-year relative survival is similar to Stage A CLL

Abrisqueta, Blood 2009; 114: 2044-2050

Shanafelt, Leukemia 2012; 26: 373-6
Normal B-cell numbers are suppressed if the CLL cell count is $> 0.5 \times 10^9$/L.
B-cell suppression in CLL-type disorders

Hauswirth, Am J Hematol 2012; 87(7):721
Different impact according to the neoplastic B-cell count

MBL: May develop progressive CLL &/or immune suppression

CLL-like B-cells: No known progressive disease or health issue

NHS

HMD OUTREACH
CLL-like MBL progressively impairs normal B-cell production

- Significance of CLL-like MBL (clinic MBL / cMBL):
  - 10-20% reduction in 10yr overall survival
  - 5-fold increase in risk of hospitalised infections
  - Similar outcome to stage A CLL but progressive lymphocytosis is rare.
- ? CLL-like MBL should be defined by replacement of B-cell compartment (typically >0.5 x 10^9/L or >500/µL)
  - if the total B-cell Kappa:Lambda ratio is normal, there is no impact on 10yr health outcomes
- No debate (!?) about whether CLL-like MBL has a significant healthcare issue but what is the optimal management??
- Is the presence of CLL-like B-cells without suppression of normal B-cell compartment (low-count MBL, population MBL, flow MBL) “much ado about nothing”?
  - Clinically NO but scientifically YES!
Geographical Variation in Leukaemia

GLOBOCAN 2008 (IARC) - 12.9.2011
Population MBL study in rural Uganda

The graph shows the percentage of people with a CD19+CD5+CD20+(wk) monoclonal B-cell population in the UK and Uganda. The absolute numbers of CLL-phenotype cells are indicated by different color shades:

- Red: > 100/μL
- Brown: 10 - 100/μL
- Orange: 1 - 10/μL
- Yellow: < 1/μL
Population MBL study in rural Uganda

CD5- MBL with >95% replacement of B-cell compartment: **Uganda 8% vs. UK 2.4%**
CD5- MBL with <95% replacement of B-cell compartement: **Uganda 35% vs. UK 6.5%**
Infectious agents or inherited predisposition?

Stereotyped B-cell receptors → ? specific pathogens required to develop CLL

IRF4 risk allele is rare in Africa

10 most common IGHV genes in CLL
Identifying features associated with oncogenesis vs. disease progression

<table>
<thead>
<tr>
<th></th>
<th>CLL-like MBL (clinic MBL)</th>
<th>CLL-like B-cells (low-count MBL, population MBL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-cell suppression</strong></td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Clonality</strong></td>
<td>Clonally related, intraclonal heterogeneity similar to CLL</td>
<td>Frequently bi- or oligoclonal</td>
</tr>
<tr>
<td><strong>Inherited predisposition SNP (e.g. IRF4)</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Chromosomal abnormalities</strong></td>
<td>13q14 deletion common; 11q23 and 17p deletions very rare</td>
<td>13q14 deletion in some cases; 11q23 and 17p deletions very rare</td>
</tr>
<tr>
<td><strong>IGHV repertoire</strong></td>
<td>Similar to CLL (IGHV 3-07, 1-69, 4-34, 3-23 most common)</td>
<td>Different to CLL</td>
</tr>
</tbody>
</table>

Constitutive AKT phosphorylation
Effect on normal T-cells
Responsiveness to BCR stimulation and inhibition
What phenotype / clinical entities arise from specific abnormalities

Marie Lia, Blood 2012, 119: 2981-2990
MBL - Much Ado About Nothing? NO!

- CLL-like B-cells occur frequently in elderly adults from EU/US but are significantly different to CLL cells. These differences may be key to understanding and eradicating disease.

- CLL-like MBL (partial or total replacement of B-cell compartment) similar to Stage A CLL with 10-20% reduction in 10yr OS and 5x increase severe infection risk but little “disease progression”.
Acknowledgements

Al Ssemaganda
Katie Wakeham
Chi Doughty
Gershim Asiki
Eve Roman
Pontiano Kaleebu
Rob Newton

Peter Hillmen
Andrew Jack
Chi Doughty
Fiona Bennett
Jane Shingles
Marieth Plummer
Ruth de Tute
Matt Cullen
Mick Green
Paul Evans
Sheila O'Connor
Stephen Richards
Abraham Varghese
Ben Kennedy
Paul Moreton

Richard Houlston
Dale Crowther
Gabrielle Sellick
Daniel Catovsky
David Gonzales
Should we test stem cell donors for MBL?

- MBL in 10-20% of CLL relatives

- MBL in 15.4% (2/13) HLA-matched siblings
  - Del Guidice, *Blood* 2009: 114(13); 2848-9

- 3 MBL cases from potential sibling donors (2 for CLL, 1 solid tumour)
  - Hardy, *Brit J Haem* 2007: 139; 824-31

- Donor MBL detected on day of transplant; host-derived relapse 7yrs treated with DLI
  - Herishanu, *Brit J Haem* 2010: 149; 905-6

- The presence of CLL-like B-cells is not an issue – high-sensitivity screening not indicated

- If the donor B-cell compartment is replaced by monoclonal B-cells, this could be a consideration in the choice of donor. CD19/Kappa/Lambda assessment as part of a donor evaluation.

Ferrand et al, 2012
*Eur J Haematol* 88, 269
What is in a name?

- **SLL vs. CLL vs. MBL:**
  - Small node (<1cm) replaced with CLL, no organomegaly, no cytopenia, 1 x 10^9/L CLL cells in blood
  - SLL ➔ community oncologist: lymphoma Rx for SLL (? EU)
  - CLL ➔ psychological impact, can be difficult to get life/travel insurance, mortgages/loans
  - MBL ➔ difficult to get follow-up with a haematologist
  - 2 years increase in OS for patients treated by a CLL specialist, largely due to longer TTFT for early stage disease: “Physician’s disease-specific expertise remained an independent predictor of OS after adjusting for age, sex, stage, and lymphocyte count at diagnosis.” (Shanafelt, Cancer 2012; 118(7) 1827)

- **CLL-like B-cells in an individual with a reactive T-cell lymphocytosis**
  - Defensive medicine ➔ immunophenotyping at first sign of a lymphocytosis