Chronic Lymphocytic Leukemia: New Approaches for a Common Disease

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Chronic Lymphocytic Leukemia

Disclosure

None

Goals Today:

• Distinguish Chronic Lymphocytic Leukemia (CLL) from other B-cell chronic lymphoproliferative disorders
• Understand the definition of the term monoclonal B-cell lymphocytosis (MBL)
• Realize the issues associated with minimal residual disease (MRD) detection in CLL
• Future Hot Topics on CLL: “Risk Stratification in CLL – The Role of the Clinical Laboratory”
CLL: Evolution of Diagnostic Criteria

- **1975 / Rai Staging:**
  - ≥15 x 10^9/L ALC in peripheral blood
  - ≥30% lymphocytes in bone marrow aspirate

- **1988 & 1996 / NCI-WG:**
  - ≥5 x 10^9/L ALC (flow cytometric detection of clonal B cells)
  - 1996: CLL immunophenotype necessary

- **2008 / IWCLL:**
  - B cells >5 x 10^9/L of at least 3 month duration
  - Clonality confirmed by flow cytometry; CLL immunophenotype
  - The presence of a cytopenia caused by a typical marrow infiltrate defines the diagnosis of CLL regardless of the number of B cells or nodal involvement


Chronic B-Cell Lymphoproliferative Disorders: Prototypic Immunophenotype

<table>
<thead>
<tr>
<th>Disorder</th>
<th>sig</th>
<th>CD20</th>
<th>CD5</th>
<th>CD23</th>
<th>CD10</th>
<th>CD193</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL / SLL</td>
<td>Weak</td>
<td>Weak</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lymphoplasmacytic (LPL)</td>
<td>Mod</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Mantle cell (MCL)</td>
<td>Mod</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Marginal zone: Nodal / MALT</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+/</td>
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<td>-</td>
</tr>
<tr>
<td>Splenic marginal zone (MALT)</td>
<td>+</td>
<td>+</td>
<td>+/</td>
<td>+/</td>
<td>-</td>
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</tr>
<tr>
<td>Hairy cell</td>
<td>+</td>
<td>+</td>
<td>-</td>
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</tbody>
</table>

CLL: Dim sIg, dim CD20, CD5+ & CD23+

“Copycat”: MCL with CD5+/partial CD23+

“Copycat”: LPL with CD5+/CD23-
Diagnosis of MBL & SLL: IWCLL

- Monoclonal B-Cell Lymphocytosis (MBL):
  - B cells <5 x 10⁹/L
  - Absence of lymphadenopathy / organomegaly (as defined by physical exam and CT scan)
  - Absence of cytopenias due to marrow involvement
  - Similar expression of genetic risk factors as compared to early stage CLL

- Small Lymphocytic Leukemia (SLL):
  - Lymphadenopathy and the absence of cytopenias caused by a clonal marrow infiltrate
  - B-cells should not exceed 5 x 10⁹/L
  - Confirm by lymph node biopsy whenever possible
Identification of MBL

- General population screening
- Familial CLL
- Routine clinical practice

Need to keep in mind which group of patients we are talking about when we discuss MBL!

How will MBL be Recognized in Routine Clinical Practice?

- Lymphocytosis identified on CBC screening will be the most common way of identifying MBL in routine clinical practice

What is a lymphocytosis?

- Is it an ALC above ~3.0 x 10^9/L?
  - Labs with thorough normal value studies
  - Quantitative lymphocyte subsets
- Is it an ALC above ~5.0 x 10^9/L?
  - Textbooks (historic?): instrument manufacturers

How is MBL Recognized in Routine Clinical Practice?

- Incidental finding
  - Flow analysis of PB or BM for unrelated reasons
  - BM biopsy with a lymphoid infiltrate without PB lymphocytosis; followed by PB flow study
  - SLL identified at surgery in lymph node/tissue biopsy without associated lymphadenopathy, organomegaly, or PB lymphocytosis; followed by PB flow study
MBL: Prevalence and Progression

- Normal population
  - 3.5% will have a CLL phenotype
  - Another 1% will have a non-CLL phenotype
- Prevalence increases with age:
  - 2.1% (40-60 y.o.) to 8.0% (>70 y.o.)
- Low risk genetic factors (e.g., mutated IgVH; 13q-)
- Progression rate to CLL uncertain
  - MBL identified via population studies: 1 to 3% per year
  - MBL identified in clinical practice: up to 40% per year

MBL: Summary

- MBL identified through population screening may exhibit a different behavior than those identified through routine clinical practice.
- ~40% of new cases currently diagnosed as Rai Stage 0 CLL will be reclassified as MBL using IWCLL
- There is no standard method to measure MBL/CLL B-cell counts in the clinical flow cytometry laboratory
- Molecular prognostic factors will likely contribute to the risk of disease progression better than an arbitrary lymphocyte or B-cell count
Familial CLL

- Families with known CLL patients have an increased risk of having MBL or CLL identified in other family members
- 12% to 18% of CLL patients have an extended family member with CLL or some other type of lymphoproliferative disorder
- Genetic factors remain uncertain

MBL Case: Clinical History

- 66 y.o. female
- Normal CBC; absolute lymphs = 1.2 x 10^9/L
- Normal blood smear
- No adenopathy or organomegaly
- “Only God knows why the flow study was ordered.”
- Evaluated in Hematology; bone marrow performed

MBL Case: Peripheral Blood Immunophenotype
MBL Case: Bone Marrow Biopsy

Diagnosis

- CLL
- MBL
- Other B-CLPD

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CLL and Minimal Residual Disease (MRD)

- MRD eradication is goal of current therapies.
- Does absence of MRD improve overall survival?
- Does MRD detection predict early relapse?
- These questions have not been definitively answered. But laboratories are being asked to detect MRD in CLL patients.
CLL and Minimal Residual Disease (MRD)

- Flow immunophenotyping studies: PB or BM?
  - PB is the preferred specimen

- To what detection level: 1% to 0.01%?
  - 0.01%; need to collect 200,000 to 500,000 events

- CD5/CD19 vs. 4-color vs. 6-color?
  - Multicolor adds specificity – not necessarily sensitivity.
  - Sensitivity is dependent on the cell mix and how many polyclonal B cells are present. Challenges arise when there is a mixture of monoclonal and polyclonal B-cells.

- Does immunohistochemistry (IHC) have a role in bone marrow specimens?
  - Stains are often complementary to flow studies in BM, but are often hard to interpret in isolation.
  - T-cell nodules depleted of B cells may be identified post-Rituxan therapy and can be confused with CLL.

- What antibodies should be used for IHC?
  - No specific and easy answer. PAX-5, CD19, CD79b may all be used. CD20 has a minimal role (usually post-Rituxan). A pan-T cell marker (eg, CD3) is also necessary. However, CD5 may be hard to interpret.

CLL MRD Case: Clinical History

- Female; 58 y.o.
- July 1999
  - WBC: 38.1 / Lymphs: 81%
  - Flow: sIg k (d), CD19, CD5, CD20 (d), CD23
  - Dx: CLL
  - No organomegaly
  - No cytopenias
  - Rai Stage 0
  - Observation; no Rx
CLL MRD Case: Clinical History

- 1999 to 2008: Steady progression of disease
- 2007: Chemo – Pentostatin, Cytoxan, Rituxan
- Jan. 2008: minimal clinical disease
  - Anterior node (~1 cm); no organomegaly
  - WBC: 6.9 / Lymphs: 11%
  - Hgb: 12.5 / MCV: 75.6
  - Plt: 346
- June 2008
  - No radiologic evidence of disease
  - Normal CBC (9% lymphs)

CLL MRD Case: Bone Marrow Biopsy

CLL MRD Case: Bone Marrow Biopsy

CD3  PAX-5  CD3
Chronic Lymphocytic Leukemia (CLL) MRD

Case: PB Flow

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