To the editor:

Lymphocytes, B lymphocytes, and clonal CLL cells: observations on the impact of the new diagnostic criteria in the 2008 Guidelines for Chronic Lymphocytic Leukemia (CLL)

The diagnostic criteria for CLL have been constant for the past 20 years under the 1988 and 1996 Guidelines. This has now changed with the 2008 Guidelines.

1. The effect of change in definition: Moving early CLL to MBL. The 1988 and 1996 Guidelines established an absolute lymphocyte count (ALC) of $5.0 \times 10^9/L$ or more as the diagnostic criterion for CLL. Over the following decade, increasing numbers of patients with small clonal populations below this level were identified. In 2005, criteria for monoclonal B lymphocytosis (MBL) were proposed that suggested a cutoff of $5.0 \times 10^9/L$. This has now been recommended as the new definition for CLL. The impact of this change is noteworthy.

We analyzed in our laboratory a cohort of 322 patients who fulfilled the criteria for MBL with a typical CLL phenotype (Table 1). We found that only 156 (48%) did not fulfill 1988/1996 criteria for CLL with an ALC less than $5.0 \times 10^9/L$. Hence, 52% previously classified as CLL are now redefined as MBL. Although the natural history of early CLL is well defined, evidence on clinical outcomes and rates of progression of MBL patients with ALC less than $5.0 \times 10^9/L$ is still emerging, based currently on small numbers identified from differently selected populations that are not easily comparable. Further data are needed on patients with low-level clones of uncertain significance.

2. Practical observations with the change in definition. There is now significant variation in the ALC for a diagnosis of CLL. Using a B-lymphocyte definition means the ALC ranges from $0.0 \times 10^9/L$ to more than $10.0 \times 10^9/L$. This results in some additional complexity for patients, clinicians, and reporting laboratories, especially when patients have a prior diagnosis of CLL under earlier Guidelines. During follow-up of some MBL patients with ALC less than $5.0 \times 10^9/L$ but a B-lymphocyte count greater than $5.0 \times 10^9/L$ a change to the guidelines, but we believe changing the diagnostic criteria for CLL to $5.0 \times 10^9/L$ B cells requires further study as the current recommendation will likely create more questions than answers. The real challenge is not to focus on numeric cutoffs, but to devise a classification system that recognizes a common clonal B-cell immunophenotype and reflects today’s genetic and biologic knowledge in a way that will benefit our patients.

Curtis A. Hanson, Paul J. Kurtin, and Ahmet Dogan

Contribution: All authors conceived the letter and approved the final draft of the letter. C.A.H. wrote the letter.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Curtis A. Hanson, MD, Division of Hematopathology, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: cahanson@mayo.edu.

References

4. Shanafelt TD, Kay NE, Call TG, et al. MBL or CLL: which classification best categorizes the clinical course of patients with an absolute lymphocyte count $>5 \times 10^9/L$ but a B-cell lymphocyte count $<5 \times 10^9/L$? Leuk Res. 2008;32:1458-1461.

Table 1. Absolute CD19, CD20, dual CD19/CD5, and total lymphocyte (ALC) counts in a cohort of patients (n = 322) with MBL with a typical “CLL phenotype”

<table>
<thead>
<tr>
<th>Absolute count $\times 10^9/L$</th>
<th>CD19</th>
<th>CD20</th>
<th>CD19/CD5</th>
<th>Lymphocytes (ALC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0-0.99</td>
<td>44 (13.7%)</td>
<td>45 (14.0%)</td>
<td>62 (19.2%)</td>
<td>6 (1.9%)</td>
</tr>
<tr>
<td>1.0-1.99</td>
<td>57 (17.7%)</td>
<td>64 (19.9%)</td>
<td>70 (21.7%)</td>
<td>17 (5.3%)</td>
</tr>
<tr>
<td>2.0-2.99</td>
<td>69 (21.4%)</td>
<td>73 (22.6%)</td>
<td>71 (22.1%)</td>
<td>16 (5.0%)</td>
</tr>
<tr>
<td>3.0-3.99</td>
<td>84 (26.1%)</td>
<td>86 (26.7%)</td>
<td>82 (25.5%)</td>
<td>38 (11.8%)</td>
</tr>
<tr>
<td>4.0-4.99</td>
<td>88 (21.1%)</td>
<td>88 (26.7%)</td>
<td>73 (22.1%)</td>
<td>35 (10.9%)</td>
</tr>
<tr>
<td>5.0-5.99</td>
<td>69 (21.4%)</td>
<td>73 (22.6%)</td>
<td>70 (21.7%)</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>6.0-6.99</td>
<td>63 (19.9%)</td>
<td>63 (20.2%)</td>
<td>69 (21.4%)</td>
<td>10 (3.1%)</td>
</tr>
<tr>
<td>7.0-7.99</td>
<td>69 (21.4%)</td>
<td>69 (21.4%)</td>
<td>69 (21.4%)</td>
<td>10 (3.1%)</td>
</tr>
<tr>
<td>8.0-8.99</td>
<td>69 (21.4%)</td>
<td>69 (21.4%)</td>
<td>69 (21.4%)</td>
<td>10 (3.1%)</td>
</tr>
<tr>
<td>9.0-9.99</td>
<td>69 (21.4%)</td>
<td>69 (21.4%)</td>
<td>69 (21.4%)</td>
<td>10 (3.1%)</td>
</tr>
<tr>
<td>10+</td>
<td>69 (21.4%)</td>
<td>69 (21.4%)</td>
<td>69 (21.4%)</td>
<td>10 (3.1%)</td>
</tr>
</tbody>
</table>

Data show number of patients and percentage (in parentheses).
patients, changes in the ALC may be difficult to interpret without B-cell enumeration. At the MBL/CLL cutoff point, we observed some fluctuation in the level of the clone.

The definition of a B cell is also of interest. The 2 antigens most commonly used for B-cell identification are CD19 and CD20, but a specific definition is not given in either the CLL Guidelines or the MBL criteria. In CLL, CD20 is typically expressed at lower copy number compared with normal B cells. In theory, a B-cell count increases laboratory measurement uncertainty, as 2 measurands (ALC and percentage B cells) are required. In practice, this effect is minor. Furthermore, we observed that using CD19 or CD20 made a negligible difference in the definition of MBL versus CLL in our patient cohort (Table 1). CD19 appears more accurate for normal B-cell enumeration, but the weakened expression of CD20 facilitates detection of small clones.

Finally, a definition that is consistent and complementary between CLL and MBL is essential. The new Guidelines eliminate the overlap that had developed and provide uniformity for future study.

Christopher S. Mulligan, Miriam E. Thomas, and Stephen P. Mulligan

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Stephen P. Mulligan, Departments of Haematology and Flow Cytometry, Symbion Pathology and CLL Australian Research Consortium, 60 Waterloo Rd, Macquarie Park, Sydney 2113, Australia; e-mail: mulligan@staff.usyd.edu.au.

Response

Letters regarding Blood. 2008;111:5446-5456 by Hanson et al and Mulligan et al

We are grateful to both Hanson and colleagues and Mulligan and his colleagues for welcoming our recent revision of the 1996 NCICLL Guidelines and for raising several issues surrounding the diagnostic criteria of CLL and monoclonal B lymphocytosis (MBL). They particularly referred to the change in the criteria for CLL from an absolute lymphocyte count (ALC) greater than $5 \times 10^9/L$ (in the 1996 NCI criteria) to a circulating B-cell count greater than $5 \times 10^9/L$. There are several recent developments that have made this change necessary.

The development of multiparameter flow cytometry has enhanced the ability to detect and accurately quantitate low levels of CLL cells. This has led to increasing numbers of patients with minimal lymphocytosis being found to have low levels of circulating CLL cells. Individuals with less than $5 \times 10^9/L$ B cells have recently been defined as having MBL, as many of these did not fulfill the old criteria for a diagnosis of CLL. In contrast to the comments made by both Mulligan et al. and Hanson et al., we believe that the technique to identify CLL cells has been standardized and validated sufficiently and should be reproducible in laboratories throughout the world.

A major component in interlaboratory variation for absolute lymphocyte subset enumeration is the hematology analyzer result when the ALC is used to calculate the absolute B-cell count from a FACS percentage. The most reproducible results are instead provided by single platform technology, using just quantitative flow cytometry beads to directly measure B-cell concentration. We recognize that this is the “gold standard,” but it is unlikely to be widely adopted due to the additional complexity of the test. Thus, there will continue to be variation among laboratories for lymphocyte counts close to the $5000/\mu L$ cutoff if hematology analyzer lymphocyte count is used. However, the change in criteria for the diagnosis of CLL will have no impact on this variation. We believe that the statement by Hanson et al. that “moving . . . to a B-cell count using a flow cytometry–based procedure will also have unintended consequences affecting cost and access” is incorrect. The use of the B-cell count instead of absolute lymphocyte count should have no financial or access implications as a diagnosis of CLL according to the 1996 criteria already requires basic immunophenotyping, which includes assessment of CD19 expression.

The change in diagnostic criteria for CLL will have an impact on epidemiologic studies, but this will be positive in terms of including patients who are better defined and therefore results will be easier to interpret. It is important to remember that even with potential interlaboratory variations, the changes to the diagnostic criteria will have no impact on clinical management of CLL, as both MBL and Rai stage 0 CLL cases will continue to be approached with watchful waiting.

Furthermore, Mulligan et al. make a strong case for redefining the diagnosis of CLL to complement the current definition of MBL, as has been done in the recent Guidelines. In their cohort of 322 patients who fulfilled the criteria for MBL with a typical CLL phenotype they found that 166 (52%) patients also fulfilled the 1988/1996 criteria for CLL, thus creating confusion. We believe that patients should fall only into one of the 2 diagnostic groups to give clarity to future studies. Both Mulligan et al. and Hanson et al. indicate that further information on the natural history of MBL is required before such a change in classification is merited. One of the problems with the current classification systems is that they are insensitive in defining whether patients within the large group of early-stage CLL (Rai 0 or Binet A) will or will not progress over time. Recent evidence indicates that the CLL count of an individual patient is the most important predictor of the likelihood of progression.

References


Lymphocytes, B lymphocytes, and clonal CLL cells: observations on the impact of the new diagnostic criteria in the 2008 Guidelines for Chronic Lymphocytic Leukemia (CLL)

Christopher S. Mulligan, Miriam E. Thomas and Stephen P. Mulligan