A new prognostic score for CLL

Comment on Pflug et al, page 49

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In this issue of Blood, Pflug et al describe the new prognostic score published by the German Chronic Lymphocytic Leukemia Study Group (GCLLSG).1

Accurate prognostication is essential in modern medicine. For nearly 40 years, prognostication for patients with chronic lymphocytic leukemia (CLL) used simple measures of disease bulk and residual normal bone marrow function, such as the Rai2 and Binet stage. In order to provide improved discriminatory power for patients within these traditional disease stages, an expanding and at times bewildering list of novel prognostic markers in CLL has emerged.3 Many of these markers were developed and validated in small, retrospective, and heterogeneously treated cohorts of patients, often without consideration of potential association or interaction with other markers.

The new prognostic score published by the GCLLSG1 took these new developments into account by exploring the relative contributions of disease stage, disease biology, and patient-related factors such as age and fitness in a large cohort of patients enrolled onto 3 prospective studies with mature follow-up. In total, 1223 treatment-naïve patients with complete risk profiles (including immunoglobulin heavy chain [IgHV] mutation status and fluorescent in situ hybridization [FISH] studies4) were selected from 2068 patients enrolled onto an early intervention protocol (CLL1: Binet stage A CLL, in which patients with high-risk features were randomly assigned to observation or fludarabine) and two treatment protocols (CLL4: fludarabine vs fludarabine-cyclophosphamide [FC] or CLL8: FC vs FC-rituximab). A multivariate model identified 8 factors as being independently associated with inferior survival from study entry. The hazard ratio for each of these factors then formed the basis for a new prognostic score (see figure). The authors acknowledged that this score was derived from a mixed population of patients not requiring treatment and those about to embark on initial therapy (CLL4 and CLL8), and they undertook additional analyses to show that the same prognostic factors applied to both populations. Finally, the prognostic score was validated in an independent cohort of newly diagnosed patients managed at the Mayo Clinic.

The elimination of Rai and Binet stage from the prognostic model underscores how far our understanding of CLL biology has evolved. Rather than determining

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Score</th>
<th>Patients (%)</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0 to 2</td>
<td>25</td>
<td>95%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>3 to 5</td>
<td>38</td>
<td>82%</td>
</tr>
<tr>
<td>High</td>
<td>6 to 10</td>
<td>34</td>
<td>68%</td>
</tr>
<tr>
<td>Very high</td>
<td>11 to 14</td>
<td>4</td>
<td>19%</td>
</tr>
</tbody>
</table>

B2m, beta-2-microglobulin; ECOG, Eastern Cooperative Oncology Group performance status; IgHV, immunoglobulin heavy chain variable region; TK, thymidine kinase.
Comment on Mraz et al, page 84

miR in CLL: more than mere markers of prognosis?

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In this issue of Blood, Mraz et al show that microRNA-150 (miR-150) is the most abundantly expressed miR in chronic lymphocytic leukemia (CLL) and affects the threshold for B-cell receptor (BCR) signaling by repressing expression levels of GAB1 and FOXP1. This functional link might explain the described association between expression levels of miR-150 and prognosis.1

In 2002, the first link between small noncoding RNAs, known as miRs, and cancer was made by the observation that in CLL, the most common genetic aberration 13q14 deletion, was associated with downregulation of miR-15a and miR-16-1, which reside in the minimally deleted region within 13q14.2 This seminal observation initiated many studies into the role of miRs in the pathogenesis of cancer in general and especially in CLL. The pioneering work on miR-15a and 16-1, however, also exemplified the complexity of aberrant miR expression and its possible relation with alterations in cancer-specific biological pathways. Although early studies suggested that in CLL, miR-15a/16-1 mediated control of BCL2 expression and survival, it took until 2010 to learn that in fact the function of these miRs in B-cell malignancies is exerted mainly by downregulation of genes controlling cell-cycle entry.3

Because each miR can affect the expression of hundreds of different genes, which not only differs per cell type but also depends on their developmental stage, and because currently available bio-informatic tools are imperfect in predicting targets via sequence similarities, it has been highly challenging to interpret the pathophysiological relevance of aberrations in miR levels measured ex vivo, or after in vitro manipulation.

Despite these challenges, over the years, several miRs could convincingly be mapped to disease-specific relevant pathways, such as the identification of miR-34a as a component of the chemotherapy resistance network in CLL.4

REFERENCES
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