To the editor:

Prognostic relevance of MYD88 mutations in CLL: the jury is still out

Genome surveys have offered a comprehensive view of the genetic landscape of chronic lymphocytic leukemia (CLL), identifying several recurrently mutated genes, including myeloid differentiation primary response 88 (MYD88). The predominant mutation concerns a p.L265P substitution within exon 5,1,2 which leads to constitutive nuclear factor κB stimulation, thus conferring a proliferation and survival advantage to the mutant cells.3 MYD88 mutations reach up to 2% to 5% in CLL and are strikingly enriched among patients expressing mutant vs wild-type patients.3-5 To gain further insight into this MYD88 with previous studies reporting no differences in TTFT or OS for mutant cases with wild-type M-CLL patients (supplemental Table 2). The median age of both groups was similar (64.4 years [range, 43-82 years] vs 64.3 years [range, 32-92 years]; P = .66); hence, we cannot confirm the recently reported association between MYD88 mutations and a younger age at diagnosis. This discrepancy could be a result of the combined effect of the differential composition of the evaluated cohorts and the overall rarity of MYD88 mutations.

Regarding the genetic aberrations, the 2 groups were highly similar; that is, both had a high frequency of isolated deletion of chromosome 13q and a complete absence or low frequency of both intermediate/poor prognostic cytogenetic abnormalities and mutations in the TP53, SF3B1, and NOTCH1 genes. A trend was noted in favor of Binet stage B/C at diagnosis (P = .08) and IGHV3-23 gene usage (P = .08) in MYD88 mutant vs wild-type cases (supplemental Table 2). None of the MYD88 mutant cases was assigned to any of the major subsets with stereotyped B-cell receptors.9

Regarding prognostic implications, mutant MYD88 M-CLL cases showed a tendency (P = .06) for shorter median TTFT compared with wild-type MYD88 M-CLL cases (6.6 years [95% confidence interval, 0.5-9 years] vs 14.8 years [95% confidence interval, 0.2-16 years]) (Figure 1). However, this difference could be attributed to the enrichment for advanced clinical stage among mutant MYD88 cases. Indeed, when restricting the analysis to Binet stage A cases, no difference in TTFT or OS was observed between MYD88 mutated vs wild-type M-CLL patients (supplemental Figure 1).

To our knowledge, no other published study has evaluated the prognostic significance of MYD88 mutations within M-CLL, which

Figure 1. Kaplan-Meier curves for MYD88 mutant (m-MYD88) and MYD88 wild-type (wt-MYD88) cases. (A) Time to first treatment, and (B) overall survival. All cases carry mutated IGHV genes (M-CLL).
is the relevant group to consider, given the strong bias for \textit{MYD88} mutations to M-CLL, as evidenced by this and previous studies. The distinction between M-CLL and CLL expressing unmutated IGHV genes is fundamental not only for understanding the biology of the disease but also in the context of prognostication and prediction.\textsuperscript{10} Along these lines, we argue that conclusions regarding the clinical implications of any biomarker should always be adjusted to IGHV gene mutational status.

In conclusion, our findings question the recent proposal that \textit{MYD88} mutant cases may display a distinct clinical behavior attributed solely to the mutations themselves. That said, the possibility of a distinct biological profile linked to constitutional nuclear factor \textk \textit{B} activation remains, which could prove to be of therapeutic relevance in the future. Larger collaborative studies in CLL are imperative to study the prognostic and predictive relevance of \textit{MYD88} mutations, if any.

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