Immunoglobulin heavy variable somatic hyper mutation status in chronic lymphocytic leukaemia: on the threshold of a new era?

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Since the introduction of the IGHV gene somatic hypermutation (SHM) status as prognostic marker in chronic lymphocytic leukaemia (CLL) patients in the two 1999 landmark publications from the Stevenson and Chiorazzi groups (Damle et al., 1999; Hamblin et al., 1999), its value has been consistently confirmed in virtually all CLL cohorts analysed thus far. To distinguish good from poor prognostic CLL subgroups, a threshold of 98% identity to the closest germline (unrearranged) immunoglobulin heavy variable (IGHV) gene was introduced. CLL cases showing a clonally rearranged IGHV gene with <98% identity to the closest IGHV gene (classified as Ig-mutated CLL, M-CLL) constitute the more favourable group, while those with ≥98% identity (un-mutated CLL, U-CLL) represent the adverse group.

Notably, the 98% threshold is purely mathematical rather than biological, considering that even a single SHM (representing far less than the 2% deviation from germline) could have a major impact on antigen specificity and affinity. Nevertheless, from a haematological perspective, the 98% threshold is useful to define CLL subgroups with statistically distinct outcomes. That said, the 98% threshold has been challenged, although the published data are somewhat conflicting (Davis et al., 2016; Jain et al., 2018; Morabito et al., 2018). In particular, the group of so-called borderline CLL cases (i.e. 97–97.9% IGHV identity) has raised interpretation issues as to whether these would be bona fide M-CLL cases or not (Davis et al., 2016). Reflecting this uncertainty, the most recent ERIC (European Research Initiative on CLL) guidelines on IGHV gene SHM status interpretation consider this borderline group as a category that should be reported with caution (Rosenquist et al., 2017).

In this issue of the British Journal of Haematology, a retrospective analysis from the Italian CLL group addresses the prognostic impact of borderline IGHV SHM status (Raponi et al., 2020). IGHV data from two large cohorts of untreated CLL patients were updated in line with current ERIC guidelines (i.e. repeat analysis with an IGHV leader protocol, if required) and using the latest IMGT (ImMunoGeneTics) version for annotation. In doing so, the most accurate definition of percentage of IGHV gene identity and SHM determination for the prognostic evaluation could be achieved, still resulting in almost 10% shifts in categories (borderline vs. M-CLL vs. U-CLL), highlighting the critical importance of robust analytical standards. Subsequent evaluation showed that the time-to-first treatment (TFT) of borderline cases appeared very similar to M-CLL but was clearly different from U-CLL, while the same held true even in newly diagnosed and Binet stage A CLL, leading the authors to conclude that borderline cases can be considered favourable-prognostic, albeit with a single striking exception represented by stereotyped subset #2. The latter is very relevant, given that the subset #2 is renowned for its adverse prognosis and is known to be enriched in borderline CLL cases (Baliakas, 2015). Moreover, it raises the question as to whether this is restricted to subset #2 or whether other, as of now non-disclosed, stereotyped subsets with adverse prognosis might also be over-represented in this borderline group, which is especially relevant considering emerging evidence for the existence of ‘satellites’ to subset #2, i.e. subgroups of cases with similar immunogenetic and clinicobiological features [Gemenetzi et al. iwCLL (International Workshop on CLL) 2019]. Hence, arguably, a ‘compartmentalised’ approach may assist in cleaning up the borderline group to enrich for truly indolent cases, eventually refining risk stratification. Multi-centre studies from collaborative groups collecting enough CLL borderline cases should reveal the impact of more stereotypic subsets being present in the borderline group. More broadly, these findings emphasise the importance of accurate IGHV gene

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sequence analysis and interpretation in CLL, a fact acknowledged by the inclusion of IGHV gene SHM-testing in the list of mandatory tests for all CLL patients requiring frontline treatment (Hallek et al., 2018); as well as the recent decisions/proposals by national CLL study groups [e.g., FILO (French Innovative Leukemia Organisation), GCCLLSG (German CLL Study Group)] that subset #2 membership should be used for risk stratification of patients in clinical trials (Fischer et al., 2016).

Raponi et al. also made another intriguing observation that perhaps not only the borderline group (97.0–97.9% IGHV identity) is relevant for further consideration, but equally so the 98.0–98.9% IGHV identity group, which is sometimes also referred to as a borderline group by some authors. In their experience, this CLL group appears indistinguishable from the true borderline group, yet shows a better TTF than the 99–100% group (Raponi et al., 2020). Even though this seems to conflict with other published data (Davis et al., 2016), the observation is interesting and highlights the need for further investigation.

Taken together, these considerations elicit the question as to whether the IGHV gene SHM status should be considered as a binary or a continuous marker – in other words, whether using one threshold (98%) is accurate for all situations or whether, perhaps in context-dependent fashion, this parameter should be interpreted as a continuous variable (Jain et al., 2018). This is a most relevant question for CLL today, for at least two important reasons: i) IGHV gene SHM status is not only a prognostic factor any more, but also predictive of responses to individual treatments, and so the required accuracy for the individual patient is more demanding; ii) with the introduction of NGS-based strategies for IGHV SHM analysis, it remains to be determined if current thresholds for non-NGS strategies are still valid. Twenty years after the first description, IGHV SHM analysis is thus still highly valid, and perhaps more relevant than ever before.

References


