

Is it Time for CD5+ B-cell Malignancies to have a New Taxonomy?

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The major challenge of 21 century medicine is risk stratification, not diagnosis.

Virtually everything has a name. With names, we hope to succinctly convey a set of qualities allowing for the rapid communication of ideas. In regards to neoplastic diseases of the blood we have re-categorized and re-named illnesses for years: the Rappaport Classification (1966), along with the Lukes Collins modifications (1974), the Kiel Classification (1974), the Working Formulation (1982), REAL/WHO classifications (2008). In these classification systems, cellular phenotypes dominate designation and grouping. However, phenotype often does not convey the most critical information about malignancy, risk stratification: the "...statistical process to determine detectable characteristics associated with an increased chance of experiencing unwanted outcome with the goal to develop targeted interventions to mitigate their impact [1]. We hold that for low grade B cell malignancies co-expressing CD5 a new taxonomy is warranted, which discriminates by risk stratification rather than by phenotype.

CD5 is a pan T cell marker expressed at various developmental and activation stages on human B cells [1]. Two hematologic malignancies that commonly co-express CD5 and the B cell lineage markers are Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) and Mantle Cell Lymphoma (MCL). Interestingly, both of these malignancies exhibit heterogeneous survival rates [2].

Current clinical CLL grading systems poorly predict overall survival and disease aggressiveness, especially in early stage patients [3-5]. Among the independent molecularly-based CLL prognostic markers, interphase fluorescence *in-situ* hybridization (FISH) DNA analysis [6] and immunoglobulin variable region heavy chain (IGHV) mutational status [7-11] appear to be the most predictive. There is growing evidence that when compared to FISH analysis that the IGHV mutational sequence status better discriminates for overall survival. We have recently shown poor clinical outcomes in those harboring both the good prognostic FISH finding of del(13q) and an unmutated IGHV sequence [12] and we have also shown superior clinical outcomes with those harboring the poor prognostic FISH findings of del(11q)/del(17p) if a mutated IGHV sequence was present [13], also concluded in CLL patients that IGHV mutational status was the most important predictor to time to first treatment [14]. Additionally in 2013, Rossi et al, found "IGHV mutation status, not BCR stereotypy distinguishes different clinical and biologic subgroups of CLL" [15].

As in CLL, MCL patients have variable survival rates. Frequently, MCL patients are treated aggressively at diagnosis [16,17]. However, a clinically significant subset of MCL patients exhibits an indolent course that does not require oncologic intervention for long periods [18]. Importantly, early identification of such patients could impact their clinical management. As in CLL, IGHV mutational is predictive of clinical outcome in MCL. Orchard et al, reported in small, non-randomized population of no nodular MCL patients that long-term survivors had a mutated IGHV sequence [19]. And in another small series, Fernandez found that highly mutated IGHV patients more frequently experienced an indolent MCL clinical course [20].

Why should IGHV mutational status predict clinical outcome?

Somatic hyper mutation of the immunoglobulin heavy chain variable region genesis the process by which a naïve B cell turns into a high-affinity antibody producer. This often T-cell dependent process occurs in a germinal lymph node center after antigen stimulation. Therefore, a mutated IGHV sequence, defined by an IGHV non-homologous sequence of >2% compared to germline, [21] suggests that the malignant clone was established late in B cell development. Accordingly, unmutated clones are derived from an early B cell precursor. In fact, our preliminary data support that in unmutated CLL, oncologic changes are present in the CD34+ cells. It is plausible that unmutated B cell neoplasms retain resistance mechanisms to chemotherapy often encountered in stem cells.

As important, since we are better able to predict clinical outcomes of our CLL and MCL patients based on IGHV mutational status, future clinical trials should stratify for this parameter. Additionally, future research is required to determine if risk stratification by IGHV mutational status is applicable to all low grade B-cell lymphomas and not limited to those co-expressing CD5+. Nonetheless, at this time, we support a new taxonomy for CD5+ B-cell malignancies based on IGHV

References

1. Dalloul A (2009) CD5: a safeguard against autoimmunity and a shield for cancer cells. *Autoimmun Rev*: 349-353.
2. Dighiero G (2003) Unsolved issues in CLL biology and management. *Leukemia* 17: 2385-2391.
3. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, et al. (1975) Clinical staging of chronic lymphocytic leukemia. *Blood* 46: 219-234.
4. Montserrat E, Sanchez-Bisoso J, Viñolas N, Rozman C (1986) Lymphocyte doubling time in chronic lymphocytic leukaemia: analysis of its prognostic significance. *Br J Haematol* 62: 567-575.
5. Codony C, Crespo M, Abrisqueta P, Montserrat E, Bosch F (2009) Gene expression profiling in chronic lymphocytic leukaemia. *Best Pract Res Clin Haematol* 22: 211-222.
6. Döhner H, Stilgenbauer S, Benner A, Leupolt E, Kröber A, et al. (2000) Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med* 343: 1910-1916.
7. Kharfan-Dabaja MA, Chavez JC, Khorfan KA, Pinilla-Ibarz J (2008) Clinical and therapeutic implications of the mutational status of IgVH in patients with chronic lymphocytic leukemia. *Cancer* 113: 897-906.
8. Dewald GW, Brockman SR, Paternoster SF, Bone ND, O'Fallon JR, et al. (2003) Chromosome anomalies detected by interphase fluorescence in situ hybridization: correlation with significant biological features of B-cell chronic lymphocytic leukaemia. *Br J Haematol* 121: 287-295.

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9. Trojani A, Montillo M, Nichelatti M, Tedeschi A, Colombo C, et al. (2010) ZAP-70, IgVh, and cytogenetics for assessing prognosis in chronic lymphocytic leukemia. *Cancer Biomark* 6: 1-9.
10. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK (1999) Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. *Blood* 94: 1848-1854.
11. Damle RN, Wasil T, Fais F, Ghiotto F, Valetto A, et al. (1999) Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. *Blood* 94: 1840-1847.
12. Gladstone DE, Swinnen L, Kasamon Y, Blackford A, Gocke CD, et al. (2011) Importance of immunoglobulin heavy chain variable region mutational status in del(13q) chronic lymphocytic leukemia. *Leuk Lymphoma* 52: 1873-1881.
13. Gladstone DE, Blackford A, Cho E, Swinnen L, Kasamon Y, et al. (2012) The importance of IGHV mutational status in del(11q) and del(17p) chronic lymphocytic leukemia. *Clin Lymphoma Myeloma Leuk* 12: 132-137.
14. Bulian P, Rossi D, Forconi F (2012) IGHV gene mutational status and 17p deletion are independent molecular predictors in a comprehensive clinical-biological prognostic model for overall survival prediction in chronic lymphocytic leukemia. *J Transl Med*:10:18.
15. Rossi D, Spina V, Bomben R, Rasi S, Dal-Bo M, et al. (2013) Association between molecular lesions and specific B-cell receptor subsets in chronic lymphocytic leukemia. *Blood* 121: 4902-4905.
16. Gianni AM, Magni M, Martelli M, Di Nicola M, Carlo-Stella C, et al. (2003) Long-term remission in mantle cell lymphoma following high-dose sequential chemotherapy and in vivo rituximab-purged stem cell autografting (R-HDS regimen). *Blood* 102: 749-755.
17. Romaguera JE, Fayad L, Rodriguez MA, Broglio KR, Hagemester FB, et al. (2005) High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. *J Clin Oncol* 23: 7013-7023.
18. Martin P, Chadburn A, Christos P, Weil K, Furman RR, et al. (2009) Outcome of deferred initial therapy in mantle-cell lymphoma. *J Clin Oncol* 27: 1209-1213.
19. Orchard J, Garand R, Davis Z, Babbage G, Sahota S, et al. (2003) A subset of t(11;14) lymphoma with mantle cell features displays mutated IgVH genes and includes patients with good prognosis, nonnodal disease. *Blood* 101: 4975-4981.
20. Fernández V, Salamero O, Espinet B, Solé F, Royo C, et al. (2010) Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. *Cancer Res* 70: 1408-1418.
21. Teng G, Papavasiliou FN (2007) Immunoglobulin somatic hypermutation. *Annu Rev Genet* 41: 107-120