Journal of Leukemia
ISSN: 2329-6917

Smith, J Leuk 2014, 2:2
DOI: 10.4172/2329-6917.1000133

Short Communication Open Access

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 malignances 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 linage 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 unmuted 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 patient's exhibits an indolent course that does 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 nodule MCL patients that long-term survivors had a mutated IGVH 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 IGVH 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

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Received January 30, 2014; **Accepted** March 20, 2014; **Published** April 07, 2014

Citation: Smith D (2014) Is it Time for CD5+ B-cell Malignancies to have a New Taxonomy? J Leuk 2: 133. doi:10.4172/2329-6917.1000133

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