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Editorial

Prognostic Analysis of Chronic Lymphocytic Leukemia

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Chronic Lymphocytic Leukemia (CLL) is the most common type of blood cancer to be found in adults. It mostly arises when genetic/epigenetic abnormalities accumulate in those cells of the bone marrow that are destined to become B cells. Though this disease may start in bone marrow, at a later stage it moves to the blood. This disease is not often so lethal as the other types of cancers. Based on the aggressiveness of the disease, CLL patients may be classified into three types: little greater than 33% (of the patients) are non-aggressive (NA-CLL), little less than 57% are partly aggressive (PA-CLL), 10% are aggressive (A-CLL) [4]. A NA-CLL patient of a particular age lives so long as the healthy individual of same age. A PA-CLL patient develops the disease slowly over a period of 5-10 years, after which the PA-CLL patient transforms to the A-CLL patient. The A-CLL patient lives up to a maximum of 3 years. The pathogeneses of the disease and the transcriptional signatures of the CLL cells are different in different compartments [5]. The CLL cells have been found residing in the following three compartments: the bone marrow (BM), the peripheral blood (PB), and the lymph node (LN). This editorial is focused on the prognostic data of paper [5], in the context of CLL. The paper [5] has studied the transcriptional dissimilarities and similarities of CLL cells in only the two compartments, PB and LN.

The CLL Cell States

The CLL cells in the LN exist in either of the three cell states: quiescent, activated, proliferating [5]. The three cell states are non-overlapping. The CLL begins to develop from proliferating cells. These proliferating cells thereafter transform to the activated cells which are identified by the overexpression of following ten genes: HSP90AB1, ENO1, TUBB, RAN, PRDX1, LDHA, NME1, DNPH1, HSPD1, PKM. These ten genes are, hereafter, referred to as Activated CLL Cell Gene Signature (ACCGS). The cell states' transformation dynamics is unidirectional which culminates with the emergence of quiescent cells. The relative proportions of the three cell sates in the LN of the patient with fully developed CLL is given in Table 1. The researchers of the work [5] found that the higher expression of the ACCGS co-relates with poor prognosis of the CLL.

CELL STATE	*RELATIVE PROPORTION*
Proliferating	0.4%-1%
Activated	2.2%-4.3%
Quiescent	Greater than or equal to 94.7%

Table 1: Relative proportions of the different cell states of the CLL cells in the Lymph node.

IGHV Mutation Status

The B cells are uniquely identified by B Cell Receptors (BCRs) which are basically the antibodies or Immunoglobulins (Igs). The task of the Ig expressed on a particular B cell is to recognize a particular epitope on a particular antigen expressed on the surface of other cells and bind to it. The binding of the Igs to their complementary epitopes trigger a number of death mechanisms which are under the control of adaptive immune system [2]. In order that the Igs bind to a million different types of epitopes, the Somatic Hypermutation Molecular Machinery (SHMM) is active in the B cells that can produce a million different types of Immunoglobulin Heavy Chain Variable Region (IGHV). It is the IGHV part of the antibody that attaches to the epitope. In the B cells in the Germinal Center (GC) of the LN (and the other secondary lymphoid organs) the IGHV gene mutations occur at such an exceptionally high rate [1] that innumerable Double-strand DNA breaks (DSBs) occur in the DNA segments corresponding to the hypermutated IGHV gene [3]. Similar DSBs are generated in large numbers in the LN in CLL patients. GCs are the structural centers within the B cell follicles wherein the mature B cells proliferate and differentiate to plasma cells and memory B cells upon appropriate activation. After the generation of DSBs in the CLL cells of the CLL patients two types of repair mechanisms occur: Homology-directed repair in CLL cells that proliferate at high rate, and Nonhomology end-joining (NHEJ) repair in CLL cells that proliferate at low rate [4]. The Homology-directed repair corrects the mutations in the IGHV gene that occurred during SHMM activity. But NHEJ does not do that, on the contrary it may even increase mutations in the IGHV gene. Therefore, in the CLL cells in the LN of CLL patients either the mutated IGHV is found (such a patient is referred to as M-CLL in this article) or the non-mutated IGHV is found (such a patient is referred to as U-CLL in this article). The researchers over the years [4] have found that the IGHV mutational status has effect on the prognosis of CLL; the M-CLL has a better prognosis than U-CLL.

The Analysis

The prognosis of CLL, as a function of the IGHV mutation status and or the ACCGS expression status, in terms of Treatment-Free Survival (TFS) of the CLL patients after their LN biopsy, is given in Table 2 [5].

S. No.	*Type of patients according to IGHV mutation status*	*Type of patients according to ACCGS expression status*	*Median TFS from the time of diagnosis to first treatment or death (months)*	*Symbol to denote median TFS for this class*
1.	M-CLL, U-CLL	Activated	29	$T_{MU,A}$
2.	M-CLL, U-CLL	Non-Activated	124.6	$T_{MU,N}$
3.	M-CLL	Activated	76.5	$T_{M,A}$
4.	M-CLL	Non-Activated	186.5	$T_{M,N}$
5.	U-CLL	Activated	16.1	$T_{U,A}$
6.	U-CLL	Non-Activated	37.4	$T_{U,N}$

Table 2: The Prognosis of CLL.

As expected the class of patients corresponding to $T_{U,A}$ has the least median TFS, and hence these patients have the most aggressive disease. Also as expected the class of patients corresponding to $T_{M,N}$ has the greatest median TFS, and hence these patients have the least aggressive disease. Consistent with this observation, I define here a term “Degree of Aggressiveness of the Disease (D)” as.

$D_{Class} = 186.5 / T_{Class}$

The D_{Class} for various classes is given in Table 3 in ascending order.

S. No.	*Class*	D_{Class}
1.	$D_{M,N}$	1.0
2.	$D_{MU,N}$	1.5
3.	$D_{M,A}$	2.44
4.	$D_{U,N}$	5.0
5.	$D_{MU,A}$	6.43
6.	$D_{U,A}$	11.6

Table 3: The "Degree of Aggressiveness of the Disease" for various classes of CLL patients.

As observed from Table 3 the least aggressive disease has the value of D as 1, and aggressiveness of the disease increases with the increase in the value of D.

If the class of CLL patients with ACCGS expression status as Non-Activated had the pre-dominant effect on prognosis over whether the patients were M-CLL or U-CLL, in the Table 3 above $D_{U,N}$ would have followed $D_{MU,N}$ as Serial No. 3 data. Hence the conclusion follows that the IGHV mutation status has a greater effect on the prognosis of CLL than the ACCGS expression status.

From Figure 1 it is clear that for the class of CLL patients with ACCGS expression status as Non-Activated, there is near exponential rise in the value of D as the IGHV mutation status changes from mutated to non-mutated. Also from Figure 2 it is clear that for the class of CLL patients with ACCGS expression status as Activated, there is near linear rise in the value of D as the IGHV mutation status changes from mutated to non-mutated. This observation again proves that as a prognostic factor (in CLL) IGHV mutation status is dominant over the ACCGS expression status.

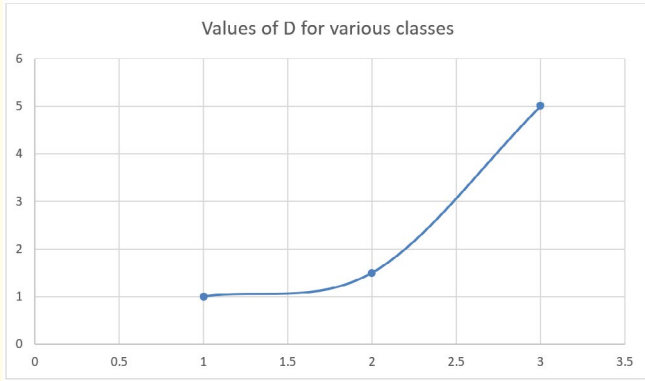

Figure 1: Values of D for all the classes of CLL patients for the ACCGS expression status as Non-Activated only. The 1 on x-axis corresponds to M-CLL class, 2 corresponds to both M-CLL and U-CLL class, and 3 corresponds to U-CLL class.

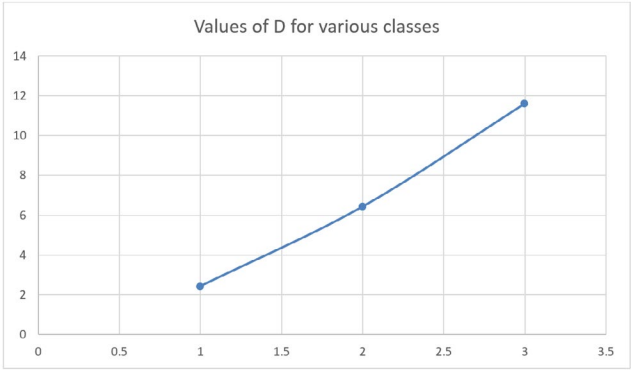

Figure 2: Values of D for all the classes of CLL patients for the ACCGS expression status as Activated only. The 1 on x-axis corresponds to M-CLL class, 2 corresponds to both M-CLL and U-CLL class, and 3 corresponds to U-CLL class.

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