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Is chronic lymphocytic leukemia one disease?

Chronic lymphocytic leukemia (CLL), the most frequent adult leukemia in the Western world is a neoplastic disease of advancing age, characterized by a progressive accumulation of functionally incompetent, long-lived small mature monoclonal B lymphocytes, with a characteristic phenotype ($CD5^+$,$CD23^+$, low surface immunoglogulins and CD79b).[1] It is far from uniform in presentation and clinical course.[2,3] About one-third of patients never require treatment and have a long survival; in another third an initial indolent phase is followed by progression of the disease; the remaining third of patients have aggressive disease at the ontset and require early treatment.[4] The development of the Rai[2] and Binet[3] staging systems has allowed the division of patients with chronic lymphocytic leukemia into three prognostic groups: good, intermediate and poor prognosis (Table 1). Binet's good prognosis group (stage A, 63% of CLL patients with a 10-year survival of 51%) includes twice as many patients as Rai's stage 0, since it includes all Rai's stage 0, 2/3 of Rai's stage I and 1/3 of Rai's stage II. Rai's stage 0, which includes 31% of CLL patients, display a 10-year survival 59%. Rai's intermediate prognosis group includes 59% of CLL patients compared to 30% in Binet's intermediate group.[4]

The two staging systems have improved the identification of patients who need immediate treatment. Two long-term French trials[4] and a meta-analysis of most randomized trials[5] demonstrated that therapy with chlorambucil, an oral alkylating agent and the standard treatment of chronic lymphocytic leukemia, could be deferred for Binet's stage A patients. This low-risk group, which constitutes almost two-thirds of patients with chronic lymphocytic leukemia, has a median age at diagnosis of 64 years and an expected survival of >10 years, which is close to the life expectancy of a normal population matched for sex and age.[4,5] Moreover, deferring therapy until forced by disease progression does not compromise survival.[4,5] However, as shown in Table 1, over 25 percent of these indolent cases, die of causes related to CLL, 40 percent progress to advanced stages, and 50 percent ultimately require treatment.[4]

Table 2 depicts the long term progression pattern of patients included in the abstention arms from the CLL-80 (308 patients) and CLL-85 (466 patients) trials.[4] As concerns evolution and treatment requirement there is a very good correlation between both trials. With a median follow up of respectively more than 11 and 7 years for the CLL-80 and CLL-85 trials, these results show that about one third of these patients were requiring treatment within 36 months and about 15% were evolving to more advanced stages in this period of time. At seven years, progression to stages B and C was observed for 18% of patients and 40% of these patients were requiring treatment.

Next, we tried to determine whether this evolution could be predicted according to the different clinical and biological data at that time available. Table 3 depicts the differences observed in the group included in the wait and watch policy. Of the 308 patients included in this group, 158 were switched to receive treatment, whereas 150 did not receive any treatment at a median 11-year follow-up. We analyzed the predictive value of lymphocyte counts, spleen enlargement, the number of involved tumoral areas, as well as Rai staging and A'-A'' substagings. Our results demonstrate that an increased initial lymphocyte count, the presence of splenomegaly, an increased number of involved areas, Rai's stage 0 as well as a Binet A' sub-staging, are all able to statistically predict treatment requirement. As shown in the table, although all these parameters display a statistically significant predictive value, there are still important fluctuations. For instance, in the case of spleen enlargement 65% of patients with splenomegaly required treatment, whereas 35% did not.

These results demonstrate that neither the Rai nor the Binet staging system can accurately predict which patients among the good prognosis group will shift into progressive disease. Lympho-

Table 1. Rai and Binet good prognosis patients after 11 years (results from the CLL-80 study).

	% of pts	10-year survival %	% of pts without evolution	% of CLL related deaths	% of pts evolving to B or C	% of pts receiving treatment
Rai stage 0	31	59	57	27	32	43
Binet stage A	65	51	47	31	41	53

cyte doubling time, serum levels of β2-microglobulin,[6] thymidine kinase[7] and soluble CD23,[8] as well as CD38 expression on malignant cells[10] can help predict disease activity, but the presence in the leukemic B-cells of cytogenetic abnormalities like 11q deletions,[9] or somatic mutations in the immunoglobulin heavy chain genes[1,10-12] are better predictors of rapid progression and survival.

To define these issues better we compared the prognostic value of Ig mutational status within the different stages of the Binet staging system in 146 patients. In addition, since sequencing of IgVH genes is not available in most laboratories and an easily performed surrogate assay is desirable, we examined the ability of sTK, sCD23, β_2-microglobulin and CD38 to predict mutational status of Ig VH genes. Based on the VH gene status, our series consisted of 80 unmutated and 66 mutated cases. The Binet staging system revealed a heterogeneous distribution, with predominance of A patients in the mutated (75%), and B/C in the unmutated (69%) group. The median follow-up of this population was 61 months (range 1-432). Prognostic value was assessed in terms of overall survival and progression-free survival. Unmutated (UM) cases displayed a median overall survival (OS) and a progression-free survival (PFS) of respectively 84 and 68 months, while for mutated (MT) ones the median OS was not achieved (70% 12-year survival, $p < 0.0001$) and PFS was 141 months ($p<0.0001$). Regarding stage A patients, median OS and PFS were significantly shorter for UM than MT cases (97 months vs not achieved, $p=0.0017$; and 42 vs 156 months, $p<0.0001$ respectively). Taking into account these results, it can be reasonably assumed that a majority of the progressions observed in the CLL-80 and 85 trials involved patients displaying an unmutated profile in Ig genes. Interestingly, the mutational status was also able to segregate patients with stages B and C into two groups with different survival patterns (median OS of 78 vs 120 months for UM and MT cases respectively; $p=0.002$). As concerns the ability of sTK, sCD23 and CD38 to predict the mutational status of Ig VH genes, our results demonstrate that serological levels of TK and CD23 and CD38 expression can predict the mutational status of Ig VH genes, for about two thirds of these patients. In addition, our results clearly demonstrate that the mutational status of Ig VH genes is the best prognostic indicator in CLL within all Binet stages (*Y. Vasconcellos et al., ASH meeting, 2002*).

These recent studies on Ig V genes may suggest that there are two types of chronic lymphocytic leukemia according to the mutational pattern of Ig V genes: one arises from relatively less differentiated (immunologically naive) B-cells with unmutated heavy chain genes and has a poor prognosis;

Table 2. Progression to stages B and C or switch to treatment (Tt switch) for stage A patients being initially randomized in the abstention arm of CLL-80 and CLL-85 trials from the French Cooperative Group.

	A to B or C/%	Treatment switch /%	A to B or C/%	Treatment switch /%
12 months	15/4.9%	36/11.7%	23/5.0%	50/10.7%
<24 months	28/9.1%	64/20.8%	53/11.9%	114/24.4%
<36 months	40/13.3%	97/31.6%	63/13.5%	146/31.3%
<48 months	50/16.5%	112/36.5%	69/14.8%	165/35.6%
<60 months	55/18.1%	125/40.7%	79/17.0%	180/38.8%
<72 months	57/18.7%	135/43.9%	82/17.6%	187/40.3%
<84 months	57/18.7%	138/44.9%	83/17.8%	191/41.2%
>84>132mo	61/19.8%	158/54.6%	–	–
Total	61/19.8%	158/54.6%	83/17.8%	191/41.2%

Table 3. CLL-80 - Stage A. Abstension arm. Variables predicting treatment requirement.

	Total 308	Treated 158	Untreated 150	p value
Lymphocytosis <30×10⁹/L	262	52%	48%	–
Lymphocytosis >30×10⁹/L	46	61%	39%	0.001
Splenomegaly Yes	40	65%	35%	0.0095
Involved areas 0	130	42%	58%	–
Involved areas 1	110	55%	45%	–
Involved areas 2	68	70%	30%	0.0001
Rai 0	127	43%	57%	–
Rai 1	129	58%	42%	
Rai 2+3	52	65%	35%	0.0001
A'	246	51%	49%	–
A''	62	60%	40%	0.0001

the other evolves from more differentiated B cells (memory B-cells) with somatically mutated heavy chain genes and has a good prognosis.[10-12] However, recent data derived from gene expression profiling analysis failed to clearly distinguish unmutated and mutated cases and favor the view that all cases of CLL have a common cell origin and/or a common mechanism of malignant transformation.[13,14] A recent study from our group on 18 cases of CLL, compared 9 Binet stage A cases with stable disease (*i.e.* at least 5 years without treatment and any evolution) and mutated Ig genes to 9 cases with stage B or C aggressive disease and unmutated Ig genes. In agreement with previous reports indicating that Ig mutated and unmutated cases have globally the same gene expression pattern, a supervised statistical analysis showed that only 85 genes were differently expressed by a factor >2 between the two groups of CLL. However, in contrast to previous reports, a non supervised hierarchical clustering analysis could clearly separate the stable mutated group from the aggressive unmutated one, except for one case (*Davi et al., ASH meeting 2002*).

These results show that gene expression profiling can distinguish CLL cases with a stable evolution and mutated Ig genes from those with unmutated Ig genes and progressive disease. Thus, monitoring the expression of a very limited number of genes might suffice to identify patients displaying an indolent disease from patients exhibiting an aggressive one.

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Note

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The most obvious reason for thinking that chronic lymphocytic leukemia (CLL) comprises two diseases, similar to each other but distinguishable, is the fact that some patients are killed by it and some are not. Furthermore, this heterogeneity is not a gradual blend from one to the other, but a distinct demarcation. Even more convincing is the fact that the allocation to one camp or the other is predictable from the date of diagnosis. The surest discriminator is the presence or absence of somatic mutations in the immunoglobulin variable region (*IgV*) genes. The very fact that most experts used to think of CLL as a tumor of naïve B-cells reinforces this concept.[1] Experts work in tertiary referral centers. Tertiary referral centers see