

Chronic Lymphocytic Leukemia An Overview

Kanti R. Rai, M.D.

1. Definition of CLL

Thirty years ago, Galton⁽¹⁾ and Dameshek⁽²⁾ defined chronic lymphocytic leukemia (CLL) as a disease characterized by progressively increasing accumulation of functionally inert, long-lived lymphocytes. Caligaris-Cappio⁽³⁾ in a recent review noted three abnormalities which may be considered characteristic of CLL: (i) CD5+ B-CLL cells express low amounts of surface immunoglobulins (sIg); (ii) CLL cells accumulate in G₀ phase of cell-cycle; and (iii) the pathogenic auto-antibodies commonly observed in patients with CLL are polyclonal and target-restricted. In a thesis unifying all these three features, Caligaris-Cappio⁽³⁾ proposed that the cell that leads to CLL is a CD5+ anti-self B lymphocyte which has become anergic. This new definition may technically be more accurate, but for the present the simpler one of Galton and Dameshek seems equally descriptive and perhaps more easy to understand

CLL, relatively uncommon in Asia, is the most common adult leukemia in the Western countries. Unless otherwise stated, any discussion of CLL pertains to the most frequent B-cell phenotype, which accounts for nearly 98% of all cases.

2. B-CLL Lymphocytes Characteristic Immunophenotypic Features

Although numerous features are ascribed to CLL lymphocytes, only a few are considered to be critical for making a diagnosis of this disease. The CLL lymphocyte is a monoclonal B-cell in origin with simultaneous presence of CD5, a T-cell antigen. Surface immunoglobulin is of low density, usually sIgM or sIgM and sIgD. These cells are CD19+, CD20+, CD22+, and form rosettes with mouse erythrocytes.

3. Cytogenetic and Oncogene Abnormalities in CLL

Several chromosomal abnormalities are seen in CLL, but none of these has been demonstrated in more than 15% to 20% of cases; therefore, from a diagnostic point of view, none is considered either a requirement or pathognomonic of the disease. These abnormalities include trisomy-12, aberrations involving the long arm of chromosome 13 at the site of the retinoblastoma gene (RB-1), and abnormalities involving chromosomes 14.⁽⁴⁾ Some investigators have observed that patients with abnormalities of 12, 14 and other chromosomes have a worse prognosis than those with abnormal chromosome 13 and those with normal chromosomes. However, from a clinician's point of view cytogenetic studies are neither easily available nor consistently reproducible enough to be incorporated in the routine care of patients.

Although the bcl-2 gene rearrangement is found infrequently in CLL patients, leukemic cells from virtually all patients express high levels of the bcl-2 protein, perhaps because of hypomethylation of the bcl-2 locus.⁽⁵⁾ Bcl-2 is a known inhibitor of apoptosis

and, therefore, increased levels of bcl-2 protein may to some extent explain the long life span of CLL cells.

Mutations in the p53 gene are observed in 10% of CLL patients.⁽⁶⁾ p53 mutations are associated with advanced stages of disease refractoriness to chemotherapy and Richters transformation. p53 gene functions as a negative regulator of cell growth, and defects or mutations in this gene are considered to have pathogenic role in human malignancies.

The data on expression of aberrant multidrug resistance (MDR) genes in CLL is relatively sparse, but what is available seems to indicate that MDR-1 as well as MDR-3 may play important role in pathogenesis or clonal evolution of this disease.^(7,8)

4. Diagnosis

Absolute lymphocytosis in peripheral blood and lymphocytic infiltration in the bone marrow along with a characteristic phenotypic pattern of monoclonal B-lymphocytes are the criteria required to make a diagnosis of CLL. Morphologically CLL lymphocytes appear as mature, small cells with dense nuclear chromatin. Blood lymphocytosis is not transient, but sustained when rechecked at intervals. The threshold above which CLL was considered as a possible diagnosis used to be $15 \times 10^9/l$. Bone marrow should be hyper- or normo-cellular with $> 30\%$ lymphocytes. The characteristic immunophenotypic profile of lymphocytes required for diagnosis of CLL has been detailed above.

5. Differential Diagnosis

There are several lympho-proliferative conditions which may be confused with CLL; certain clinical and pathological features are

Prolymphocytic leukemia: Lymphocytes are large cells with open chromatin and many reveal prominent nucleoli. sIg is high density. CD5 may or may not be positive. Rosetting with mouse erythrocytes is absent.

Hairy cell leukemia: Lymphocytes have characteristic morphological features, positive staining for tartrate resistant acid phosphatase and bone marrow biopsy lymphocytic infiltration pattern is distinct from that in CLL. Lymphocytes in HCL are CD11c+ and CD25+.

Mantle cell lymphoma: Although similar to CLL, these monoclonal B-lymphocytes are CD5+, their sIg is high density and CD23- (while CLL cells are CD23+). Lymph node histology shows characteristic expansion of the mantle zone with intermediate sized lymphocytes, while in CLL there is a diffuse infiltration with small lymphocytes.

6. Clinical Features

Patients with CLL may have a wide range in abnormalities in symptoms, physical findings and laboratory tests at the time of initial diagnosis. Patients may be completely free of symptoms, ostensibly feeling quite well; on the other extreme, they may have profound weakness, night sweats, fever and weight loss. Upon physical examination there

may not be abnormality at one end of the spectrum, while at the other end, large bulky palpable and generalized adenopathy or enlarged spleen and liver may be noted. Laboratory findings also may range from no abnormalities to a marked reduction in platelets, hemoglobin and neutrophil levels, and elevations of serum lactic dehydrogenase and beta-2-microglobulin levels. A majority of patients, however, present with symptoms and abnormalities in physical examination and laboratory findings which are somewhere in between the extremes listed above.

7. Staging and Other Prognostic Features

Clinical staging methods of Rai et al(11,12) and Binet et al(13) are the ones used most often, and the measurement of total tumor mass as devised by Jaksic and Vitale⁽¹⁴⁾ has been used in some studies. The high-risk group of the modified Rai method and Stage C of Binet consists of CLL patients with anemia and/or thrombocytopenia. The Rai classification then considers all other patients intermediate risk if there is any palpably enlarged adenopathy or hepatosplenomegaly and low risk if there are none of the above. The Binet classification divides all non-C stage patients into Stage A if there are fewer than three, and stage B if there are three or more palpably enlarged sites among five lymphoid sites, which include three lymph node groups and spleen and liver. The median survival time of the low-risk group is greater than 12 years, intermediate-risk group eight years and high-risk group about three years

In CLL patients who are not receiving any cytotoxic therapy, the rate of increase in blood lymphocyte level has been found to be an additional prognostic indicator^(15,16)—when the absolute lymphocyte count doubles in less than 12 months it predicts a worse clinical course as compared to the patients with doubling time 12 months or longer. If the pattern of lymphocytic infiltration in the bone marrow biopsy specimen is diffuse, the prognosis is worse as compared to the patients with non-diffuse (interstitial or nodular) infiltration.^(15,17)

A certain subset of patients with CLL may have no progression of their disease for a long time or ever and may die eventually of causes unrelated to CLL. These patients may have smoldering CLL as defined by early stage (Binet's A or Rai's low-risk) with non-diffuse pattern of lymphocytic infiltration in the bone marrow biopsy specimen, a long lymphocyte doubling time, a normal (130 gm/l) hemoglobin, and a relatively low ($< 30 \times 10^9/l$) absolute lymphocyte count in the blood.⁽¹⁸⁾

8. Indications for Instituting Cytotoxic Therapy in CLL(19)

Patients with CLL do not have to be started on any cytotoxic therapy immediately after diagnosis. In most cases it is possible (and advisable) to observe the natural course of the disease in an individual patient for several months or even longer. Treatment should be initiated when any of the following evidences of increased activity of disease develops: (i) any of the following disease-related symptoms—night sweats, weight loss, fever, profound weakness; (ii) progressively increasing or painful enlargement of lymphoid masses or spleen; (iii) progressive decrease in hemoglobin level or platelet count; (iv) absolute lymphocyte counts exceeding 150 or 200 $\times 10^9/l$ (the risk of

hyperviscosity-related complications tends to increase); (v) auto-immune complications such as Coombs' positive hemolytic anemia or immune thrombocytopenia.

References

1. Galton DAG: The pathogenesis of chronic lymphocytic leukemia. *Canad Med Assoc. J.* 94: 1005, 1966.
2. Dameshek W: Chronic lymphocytic leukemia—an accumulative disease of immunologically incompetent lymphocytes. *Blood* 29: 566, 1967.
3. Caligaris-Cappio F: B-chronic lymphocytic leukemia: a malignancy of anti-self B cells. *Blood* 87: 2615, 1996.
4. Juliusson G, Gahrton G: Cytogenetics in CLL and related disorders. *Baillière's Clin-Haematol.* 6: 821, 1993.
5. Hanada M, Delia D, Aiello A et al: Bcl-2 hypomethylation and high-level expression in B-cell chronic lymphocytic leukemia. *Blood* 82: 1820, 1993.
6. Gaidano G, Newcomb EW, Gong JZ, et al: Analysis of alterations of oncogenes and tumor suppressor genes in chronic lymphocytic leukemia. *Am J. Path.* 144: 1312, 1994.
7. Sparrow RL, Hall FJ, Siregar H, Van der Weyden MB: Common expression of the multi-drug resistance marker P-glycoprotein in B-cell chronic lymphocytic leukemia and correlation with in vitro drug resistance. *Leuk. Res.* 17: 941, 1993.
8. Sonneveld P, Nooter K, Burhhouts JT et al: High expression of the MDR-3 multi-drug resistance gene in advanced stage chronic lymphocytic leukemia. *Blood* 79: 1496, 1992.
9. Cheson BD, Bennett JM, Rai KR et al: Guidelines for clinical protocols for chronic lymphocytic leukemia: report of the NCI-sponsored Working Group. *Am J Hematol* 29: 152, 1988.
10. International Workshop on Chronic lymphocytic leukemia: recommendations for diagnosis, staging, and response criteria. *Ann Intern Med* 100: 236, 1989.
11. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. *Blood* 46: 219, 1975.
12. Rai KR: A critical analysis of staging in CLL. In Gale RP, Rai KR (eds): *Chronic Lymphocytic Leukemia. Recent Progress and Future Direction.* Alan R. Liss, New York, p 253, 1987.
13. Binet JL, Auguier A, Dighiero G, et al: A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer* 48: 198, 1981.
14. Jaksic B, Vitale B: Total tumor mass score (TTM): A new parameter in chronic lymphocytic leukaemia. *Br J Haematol* 49: 405, 1981.
15. Rozman C, Montserrat E: Chronic lymphocytic leukemia. *N Engl J Med.* 333: 1052, 1995.
16. Molica S, DeRossi G, Luciani M, Levato D: Prognostic features and therapeutic approaches in B-cell chronic lymphocytic leukemia: an update. *Haematologica* 80: 176, 1995.

17. Pangalis GA, Roussou PA, Kittas C, et al: B-chronic lymphocytic leukemias. Prognostic implications of bone marrow histology in 120 patients. Experience from a single hematology unit. *Cancer* 59: 767, 1987.
18. Montserrat E, Finolas N, Reverter JC, et al. Natural history of chronic lymphocytic leukaemia: On the progression and prognosis of early clinical stages. *Nouv Rev Fr Hematol* 30: 359, 1988.
19. Rai, KR: An outline of clinical management of chronic lymphocytic leukemia. In BD Cheson (ed): *Chronic Lymphocytic Leukemia*, Marcel Dekker, New York, p. 241-251, 1992.