Advances in the Clinical Staging of Chronic Lymphocytic Leukemia

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Featured Article: Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46:219–34.[3]

Before publication of this article, clinicians treating chronic lymphocytic leukemia (CLL) experienced a high level of frustration because of the vast heterogeneity in the clinical courses of patients with CLL. After their initial diagnosis, some patients had an extremely aggressive course and would die in about 2 to 3 years despite therapy, whereas some CLL patients would live for years and sometimes die decades later from causes unrelated to CLL.

CLL remained a relatively less investigated disease for more than 60 years of the 20th century. The publication of this article in 1975 provided an extremely practical, clinically usable, and reliable method of assigning CLL patients at the time of initial diagnosis into 3 broad prognostic groups: Those with evidence of significant compromise to bone marrow function had the worst prognosis, those who barely fulfilled the minimum diagnostic requirement and had no other stigmata of disease had the best prognosis, and the rest of the patients belonged to an intermediate-prognosis group. In 1977, Binet et al. (1) developed a 3-stage staging system for CLL that was similar to the Rai 5-stage system. In 1987, the Rai system was also modified into 3 stages by assigning separate risk groups: low risk (stage 0), intermediate risk (stages I and II), and high risk (stages III and IV). Once clinicians and basic-science researchers became aware of this method of prospectively identifying patients in distinct prognostic groups, the pace of research in CLL took off. Investigations of the leukemic B lymphocytes of CLL, their clinical implications, and their immunologic abnormalities rapidly became possible.

These subsequent advances in our understanding of the biology of the disease became possible because the clinical-staging system rendered CLL as a disease entity more amenable to rational approaches for investigating its underlying pathology.

In the late 1990s, various groups reported a correlation between clinical outcome and Rai stage with respect to the morphology of CLL lymphocytes, the pattern of bone marrow infiltration, lymphocyte doubling time, and the percentage of prolymphocytes.

A major breakthrough in understanding the molecular biology of CLL came in 1999, when 2 laboratories (2, 3) independently reported stratification of CLL into 2 patient groups according to the mutational status of genes for immunoglobulin heavy chain variable regions. This stratification was able to successfully predict disease progression in patients in an early Rai stage. Other markers of CLL B cells, such as the status of expression of CD38 and ZAP70, were then identified and correlated significantly with the Rai stages.

Cytogenetic abnormalities observed in 80% of CLL patients were later reported to be capable of stratifying CLL patients into good-risk cytogenetics [del(13q)] and poor-risk cytogenetics [(del(17p), *TP53*[4] (tumor protein p53), and del(11q)] (4). Use of these cytogenetic abnormalities further enhanced the prognostic power of clinical staging. In addition, the serum concentrations of thymidine kinase, β_2-microglobulin, and soluble CD23 have also been reported to help improve prognostication in CLL (5). More recently, in 2010, investigators proposed a molecular-scoring system based on a combination of tests for the expression of the *ZAP70*, *LPL* (lipoprotein lipase), *CLLU1* (chronic lymphocytic leukemia up-regulated 1), *MIR29C* (microRNA 29c), and *MIR223* (microRNA 223) genes that seemed to predict patient outcomes (6).

It is noteworthy that despite all the advances, which only became possible because of the development of the Rai staging system, this system still maintains its influence in the risk stratification of patients with CLL.

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[3] This article has been cited more than 1730 times since publication.

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[4] Human genes: *TP53*, tumor protein p53; *ZAP70*, zeta-chain (TCR) associated protein kinase 70kDa; *LPL*, lipoprotein lipase; *CLLU1*, chronic lymphocytic leukemia up-regulated 1; *MIR29C*, microRNA 29c; *MIR223*, microRNA 223.

Citation Classic

References

1. Binet JL, Lepoprier M, Dighiero G, Charron D, D'Athis P, Vaugier G, et al. A clinical staging system for chronic lymphocytic leukemia: prognostic significance. Cancer 1977;40:855–64.

2. Damle RN, Wasil T, Fais F, Ghiotto F, Valetto A, Allen SL, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood 1999;94:1840–7.

3. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V_H genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood 1999;94:1848–54.

4. Döhner H, Stilgenbauer S, Benner A, Leupolt E, Kröber A, Bullinger L, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 2000;343:1910–6.

5. Cramer P, Hallek M. Prognostic factors in chronic lymphocytic leukemia—What do we need to know? Nat Rev Clin Oncol 2011;8:38–47.

6. Stamatopoulos B, Meuleman N, De Bruyn C, Pieters K, Anthoine G, Mineur P, et al. A molecular score by quantitative PCR as a new prognostic tool at diagnosis for chronic lymphocytic leukemia patients. PLoS One 2010;5: e12780.