

Primer on Chronic Lymphocytic Leukemia: Part I

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ABSTRACT

Chronic lymphocytic leukemia is the most common leukemia in the Western world and is primarily a disease of the aging population. Its typically indolent course lends itself to an often long-term relationship between patients and primary care providers, who must be cognizant of the rapidity of recent developments in diagnostics, prognostic tools and markers, and current and emerging therapies. Primary care providers must be vigilant in the monitoring and managing of acute and chronic complications related to the immune dysfunction that is hallmark of the disease. Collaboration with specialty is key in providing superior, current, and cost-effective care for the patient with chronic lymphocytic leukemia.

Keywords: chronic lymphocytic leukemia, CLL, primary care, targeted therapies, tumor biology

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia diagnosed in the Western world, with an estimated 20,110 new cases in 2017 and accounting for 25% to 30% of all leukemias.¹ It is primarily a disease of the older population, with a median age of 71 at diagnosis.² Incidence is higher in males and among whites as compared with African Americans and Asian Pacific Islanders.² A large percentage of patients are diagnosed at an early, asymptomatic stage of disease (80% to 90%), often incidentally by their primary care providers (PCP).^{3,4} CLL often carries an indolent course with a large number of patients never requiring treatment, and of those that do, many will not require treatment for years.^{5,6} With no proven benefit to early use of therapy, the “watch and wait” approach remains the most appropriate course of action for the sizable proportion of patients with early and intermediate-stage asymptomatic CLL.^{7,8} With the increasing longevity of the population, the frequency of comorbid conditions, and the more widespread availability of sophisticated diagnostics, there are significant implications for the role of the PCP in the diagnosis and management of CLL.⁹ This supports the need for an increasing awareness of,

among other things, the emerging prognostic factors that may help to predict clinical course at outset and complications frequently encountered in this population.

PATHOPHYSIOLOGY

CLL is among the chronic lymphoid disorders characterized by the proliferation and accumulation of a malignant clone of nonfunctional CD5+ B lymphocytes in the bone marrow, peripheral blood, and lymph tissue.¹⁰ The CLL cells are morphologically small, mature lymphocytes, similar to those of CD5+ B-cells found in healthy adults.¹¹ The CLL cells, however, are distinguished by nature of their apparent arrest at an intermediate point in the B-cell differentiation pathway.^{12,13} Multiple studies related to immunoglobulin heavy-chain variable-region gene (IGHV) mutation suggest 2 distinct classes of CLL based on the presence or absence of IGHV mutation: un-mutated IGHV CLL cells are believed to be derived from mature CD5+CD27- B cells with un-mutated IGHVs, while mutated CLL cells are thought to be derived from CD5+CD27+ post-germinal center B cells with mutated IGHVs.¹¹ Of note, small lymphocytic leukemia is the identical disease process, with leukemic cells aggregating

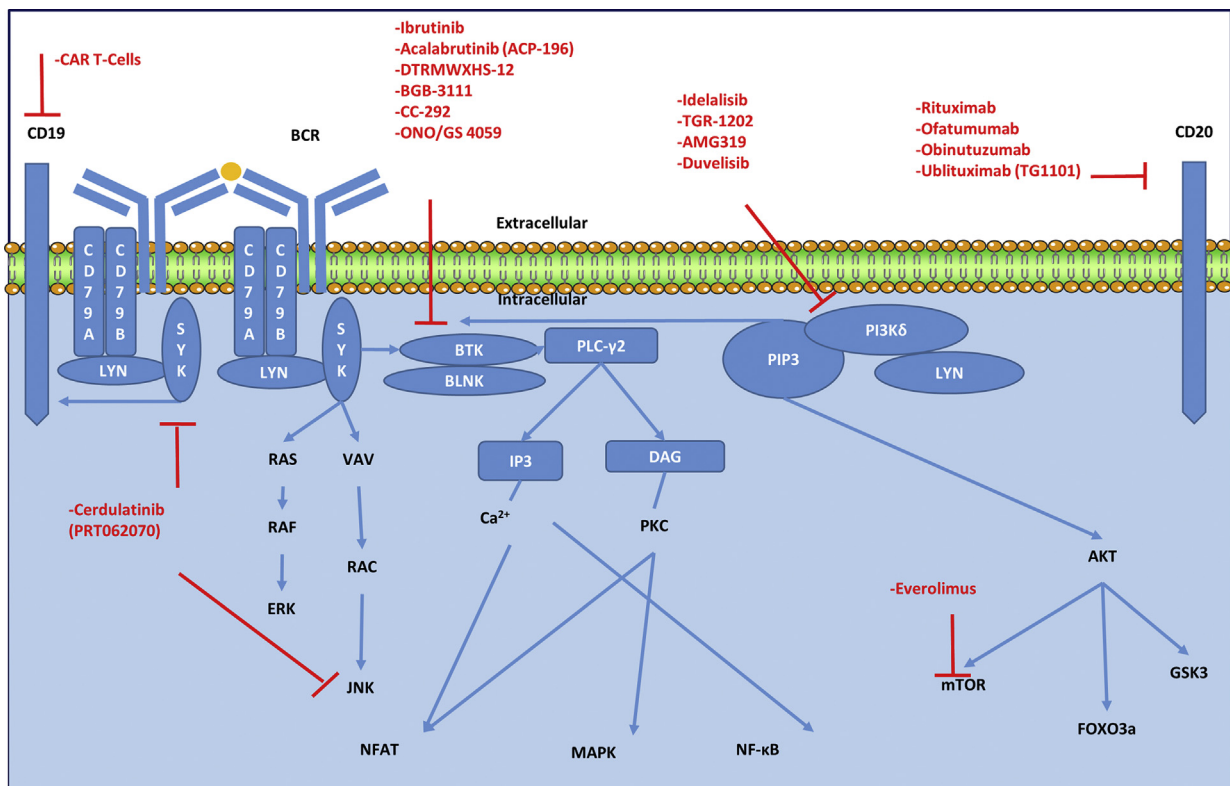
primarily in the lymph nodes, as opposed to CLL, where the cells are found primarily in blood and marrow; there is no distinction in prognosis or treatment.

B-cell receptor (BCR) signaling and the tissue microenvironment are of critical importance in the pathogenesis of CLL.¹⁴ CLL cells express BCRs that, when activated, result in a signaling cascade that promotes growth and survival. This process, while strictly regulated in normal B cells, is aberrant in malignant cells. BCR activation results in the mobilization of kinases such as Bruton's tyrosine kinase (BTK), spleen tyrosine kinase (SYK), Lyn tyrosine kinase (LYN), and phosphatidylinositol 3-kinase (PI3K), and downstream activation of mammalian target of rapamycin (AKT/mTOR), nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB), and extracellular signal-regulated kinase (ERK), which promote cell growth and survival. Correspondingly, the microenvironment, in particular stromal cells and T

lymphocytes, contributes to the survival of CLL cells.¹⁵ These factors cause a disruption in the normal balance of proliferation and apoptosis.¹⁵ Significantly, this understanding of CLL biology has formed the backbone of newer therapies that focus on the BCR as a therapeutic target (Figure).

A non-malignant, asymptomatic precursor entity known as monoclonal B-cell lymphocytosis (MBL) is now thought to predate the occurrence of CLL, akin to the way in which MGUS (monoclonal gammopathy of undetermined significance) precedes multiple myeloma.¹⁶ MBL is defined as the presence of CLL-phenotypic clonal B cells in the peripheral blood with $< 5 \times 10^9/L$ and absent any other signs of a lymphoproliferative disorder.¹⁷ Notably, MBL can be detected in up to 15% of the general population over age 60; the rate of progression to CLL/small lymphocytic leukemia is approximately 1% annually.^{18,19} Thus, the multistage process of CLL occurs via the development of MBL, which results in the formation of a clone of B cells bearing the

Figure. B-cell signaling pathways and their pharmacotherapeutic targets.



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