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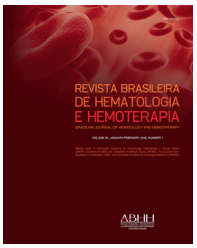

Special article

Diagnosis and treatment of chronic lymphocytic leukemia: recommendations from the Brazilian Group of Chronic Lymphocytic Leukemia

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ABSTRACT

Chronic lymphocytic leukemia is characterized by clonal proliferation and progressive accumulation of B-cell lymphocytes that typically express $CD19^+$, $CD5^+$ and $CD23^+$. The lymphocytes usually infiltrate the bone marrow, peripheral blood, lymph nodes, and spleen. The diagnosis is established by immunophenotyping circulating B-lymphocytes, and prognosis is defined by two staging systems (Rai and Binet) established by physical examination and blood counts, as well as by several biological and genetic markers. In this update, we present the recommendations from the Brazilian Group of Chronic Lymphocytic Leukemia for the

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diagnosis and treatment of chronic lymphocytic leukemia. The following recommendations are based on an extensive literature review with the aim of contributing to more uniform patient care in Brazil and possibly in other countries with a similar social–economic profile.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults and accounts for approximately 30% of all leukemias in this population group. The annual incidence of CLL in the United States is approximately 4.6 cases/100,000 persons per year. The median age at diagnosis is 71 years, and over 95% of patients are older than 50 years.[1] CLL is less frequent in individuals with Asian and Middle Eastern ancestry.[2] It is slightly more common in males, with a 1.25:1 male:female ratio.[3]

The etiology of CLL is still unknown. Genetic and environmental factors may have an important role. The low frequency of CLL in individuals with Eastern ethnicity and the higher incidence in family members (5–10%) than other mature B-cell neoplasms reflect the potential importance of a genetic factor.[4] CLL used to be considered a disease of naïve B-cell lymphocytes however recent studies suggest there is a post-germinal center origin.[5]

The clinical presentation at diagnosis is extremely variable. Approximately 60% of patients are asymptomatic, and the disease may be suspected after a routine blood count. When symptomatic, patients present with vague symptoms of fatigue or weakness.[6]

Patients usually have a good performance status at diagnosis. Lymphadenopathy may be observed in approximately 80% of cases often with cervical and axillary lymph nodes bilaterally and symmetrically being affected. Splenomegaly is usually mild to moderate and is observed in approximately 50% of cases; hepatomegaly is less frequent.[7,8] Although rare at diagnosis, as the disease progresses patients can have B symptoms, which are defined as unintentional weight loss of 10% or more within six month, fever above 38 °C for two or more weeks without other evidence of infection, and night sweats for more than a month without evidence of infection.

Anemia and thrombocytopenia may be observed in 15–30% of patients. They generally result from bone marrow infiltration, although they can also be related to an autoimmune phenomenon [autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), and immune neutropenia].[7,8] Lymphocytosis is always present, but the absolute number of lymphocytes is extremely variable. In a recent analysis by the Brazilian CLL Registry (unpublished data), the median hemoglobin level was 13 g/dL, platelet count was 180×10^9/L, white blood cell count was 35×10^9/L (range: 7–900×10^9/L), and lymphocyte count was 27×10^9/L (range: 5.4–891.0×10^9/L) among 1612 Brazilian patients with CLL.

Richter Syndrome, which is defined as the transformation of CLL into an aggressive lymphoma (most commonly diffuse large B-cell lymphoma) occurs in 5–10% of all cases. The syndrome may be suspected if there are signs of aggressive disease, such as impairment of performance status, presence of B symptoms, and rapid increase in the size of lymph nodes.[1]

Infections are common complications of CLL due to the deficiency of both the cellular and humoral immune system. T cells, natural killer cells, neutrophils, and monocytes/macrophages may be significantly compromised.[9,10] Furthermore, hypogammaglobulinemia is not rare and can become more intense after CLL treatment.[11] Although preventive use of intravenous immunoglobulin is controversial, it may be necessary if there are severe recurrent infections.[12,13] Bacterial infections are common even prior to the treatment of CLL. The most common agents are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*. Response to immunization is variable, and vaccination should be carried out early in the disease to obtain the best results. Live virus vaccines should be avoided.[14] Viral infections can also occur, and special attention should be paid to herpes zoster reactivation. Fungal infections or opportunistic bacteria, however, are rare in untreated CLL. The introduction of immunosuppressive drugs significantly increases the risk for cytomegalovirus infections, as well as *Pneumocystis jiroveci*, *Listeria monocytogenes*, and fungal infections.[14]

Autoimmune complications can occur during the disease course,[15–17] and the most common complication is AIHA (occurs in approximately 3% of patients with stable disease). The incidence of AIHA increases with disease progression (up to 11% in late-stage Binet B and C), and up to 15% of CLL patients may have positive direct antiglobulin (DAT) or Coombs tests during the disease course, including non-anemic patients.[18] The diagnosis of AIHA may be difficult because the reticulocyte count can be low due to erythroid hypoplasia when bone marrow is extensively infiltrated by CLL. Increased Lactate dehydrogenase (LDH) levels may occur as the disease progresses, and other associated factors, such as impaired hepatic function and bilirubin, may be preserved with normal liver function. Measurement of serum haptoglobin may be useful in this setting.[17] Other immune cytopenias can occur less frequently. Clinically significant immune thrombocytopenia (2% of CLL patients) should be suspected when there is a rapid drop in platelets and no evidence of bone marrow failure.[18] Approximately one third of cases can evolve to Evans syndrome. There is usually a good response to first-line therapy (steroids or intravenous immunoglobulin), but approximately 20% of cases are refractory. These patients may benefit from rituximab alone or in association with cyclophosphamide and dexamethasone. Splenectomy should be reserved for select refractory cases.[19] Pure red cell aplasia and autoimmune neutropenia can also occur, but these conditions are extremely rare.[18]

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