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Chronic lymphocytic leukemia: A brief review

ABSTRACT

Chronic lymphocytic leukemia (CLL), the most common type of leukemia, is often discovered incidentally when a complete blood count is performed during a routine examination. This disease varies in its course, eventually requiring treatment in most patients, but remaining indolent without therapy in a lucky minority. This paper reviews the pathology, diagnosis, and treatment of CLL.

KEY POINTS

The diagnosis of CLL is based on three criteria: persistent lymphocytosis, mature appearance of the lymphocytes on a peripheral blood smear examination, and a peripheral blood lymphocyte immunophenotype consistent with B cells.

Supportive treatments include transfusion of packed red blood cells, platelet transfusions for bleeding, and antibiotics.

Specific treatment includes irradiation, antineoplastic drugs, and corticosteroid therapy, but currently available treatments are reserved for patients with disease-related symptoms.

THE WIDE AVAILABILITY of automated instruments to perform complete blood counts has aided the diagnosis of chronic lymphocytic leukemia (CLL); in fact, many cases are now discovered incidentally when a complete blood count is performed during a routine examination. Yet despite improvements in the diagnosis of CLL, research so far has done little either to elucidate its cause or to improve its prognosis or treatment. This article summarizes the diagnosis and current clinical management of CLL, including the use of fludarabine, a major new drug for the treatment of CLL.

PATHOLOGY

CLL, the most common form of leukemia, predominantly affects older adults and is two to three times more common in men than in women. The defining characteristic of CLL is the progressive clonal expansion of small lymphocytes. The most common form of CLL in Western countries is a malignancy of morphologically mature B cells that are immunologically not functional. (T-cell forms of CLL are more common in Japan and other Asian countries but represent only a small fraction of CLL cases in Western patients.)

CLL cells divide very slowly. Their steady accumulation in patients with progressive leukemia is probably a result of a failure of these B cells to fully mature into immunoglobulin-secreting plasma cells. In addition, most CLL cells overexpress the BCL-2 gene, which prevents the normal senescent death of cells. Thus, both an inability to terminally differentiate and prolongation of survival distinguish the B cell in CLL from its normal counterpart.

TABLE 1

Modified Rai staging system for chronic lymphocytic leukemia

STAGE	RAI STAGES	CLINICAL FEATURES
Low risk	0	Lymphocytosis in blood and marrow only
Intermediate risk	I	Lymphocytosis and enlarged nodes
	II	Lymphocytosis and enlarged spleen
High risk	III	Lymphocytosis and anemia Hemoglobin concentration < 11.0 g/dL
	IV	Lymphocytosis and thrombocytopenia Platelet count < 100,000/mm^3

MODIFIED FROM: ROZMAN C, MONTSERRAT M. CHRONIC LYMPHOCYTIC LEUKEMIA. N ENGL J MED 1995; 333:1052–1057.

The genetic events that lead to CLL have not been defined. CLL is not associated in any way with radiation-induced chromosomal damage. No chromosomal abnormalities that are diagnostic of CLL are known. In large studies of CLL, typically up to 50% of patients had a normal karyotype in their malignant B cells. The most common chromosomal abnormality is a trisomy of chromosome 12, which predicts a slightly worse prognosis for CLL. Investigators are now trying to define the mutations that lead to CLL.

Autoimmune complications

CLL is often associated with autoimmune hemolytic anemia, or autoimmune thrombocytopenia. These autoimmune diseases are most likely caused by aberrant immunoregulation secondary to the accumulation of CLL cells.

Autoimmune hemolytic anemia in a patient with CLL is diagnosed on the basis of an elevated reticulocyte count, a positive direct antiglobulin test (Coomb's test), and a bone marrow biopsy that demonstrates adequate erythropoiesis.

Autoimmune thrombocytopenia is diagnosed by the presence of positive antiplatelet antibodies and a bone marrow biopsy that reveals adequate megakaryocytes. Treatment of autoimmune cytopenias with steroids alone can often result in clinical remission and a subsequent improvement in symptoms.

Infectious complications

CLL most often causes death through infectious complications, either the result of bone marrow failure from replacement by the leukemic cells, or marrow aplasia as a result of cytotoxic chemotherapy. Patients with CLL often present with a compromised immune system on the basis of low gamma globulin levels, and this also predisposes them to infectious complications.

CLL most often causes death through infectious complications

PROGNOSIS

CLL is clinically heterogeneous, progressing inexorably in most patients, but causing no major morbidity in a small percentage of other patients (although necessitating periodic follow-up visits). Thus, the prognosis varies widely, depending on the stage of the disease. The 5-stage (0 to IV) staging system developed by Rai has largely been replaced by three categories of risk: low, intermediate, and high (TABLE 1).

Low-risk patients, ie, those with lymphocytosis only, survive for a median of more than 10 years. In this category are patients with "smoldering" CLL, characterized by an elevated lymphocyte count, a hemoglobin concentration greater than 13 g/dL, periph-

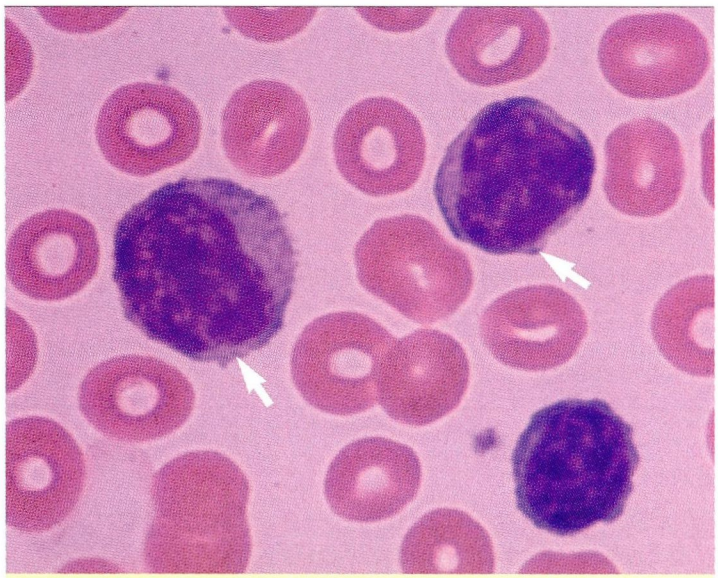

FIGURE 1. Peripheral blood smear from a patient with CLL. Shown are two small lymphocytes, (arrows) which are mature-appearing because the chromatin within the nucleus is clumped. The lymphocyte on the left appears slightly more activated because of its larger size and more irregular nuclear contours.

Suspect CLL in any patient with persistent lymphocytosis and mature-appearing lymphocytes

eral blood lymphocytosis (but less than 30,000 lymphocytes/mm^3), a lymphocyte doubling rate of more than 12 months, and no lymph node or splenic involvement. Patients with this condition do very well and may not need treatment for many years. (Potentially toxic therapy should be avoided in patients who will not benefit from it in terms of either symptom relief or prolonged survival.)

Intermediate-risk patients are those with lymphocytosis and lymphadenopathy, or lymphocytosis and hepatosplenomegaly. These patients are clinically more heterogeneous, with CLL progressing more rapidly in some than in others, but overall median survival is still quite long at approximately 8 years. Because this group is so clinically heterogeneous, their risk is the most difficult to assess; therefore, careful observation is warranted to determine the pace of the progression of disease in individual patients.

High-risk patients are those that present with a significant anemia (hemoglobin <11.0 g/dL) or a significant thrombocytopenia (platelets <100,000/mm^3). These patients have much more aggressive disease and have a median survival of only 2 years.

In its different degrees of severity and aggressiveness, CLL is similar to multiple myeloma, a malignant disease in which there is a monoclonal proliferation of more-mature, immunoglobulin-secreting B cells.

In multiple myeloma, some patients have monoclonal immunoglobulin elevations but no symptoms (ie, "monoclonal gammopathy of undetermined significance"), have a low risk of developing full-blown multiple myeloma, and do not require any initial therapy; some patients have smoldering or indolent myeloma, which requires therapy only after years of observation; and others have rampantly progressive myeloma and disease-related symptoms that require immediate treatment for relief.

In up to 10% of cases, CLL transforms into a high-grade lymphoma, called Richter's syndrome. The median survival time for patients with Richter's syndrome is only 6 months, even with aggressive chemotherapy. CLL only rarely transforms to acute leukemia.

DIAGNOSTIC CRITERIA FOR CHRONIC LYMPHOCYTIC LEUKEMIA

Persistent lymphocytosis

Chronic lymphocytic leukemia should be suspected in any patient with persistent lymphocytosis (more than 5,000 lymphocytes per mm^3), when a concomitant examination of the peripheral blood smear reveals that these are mature-appearing lymphocytes. To confirm the typical B-cell phenotype of CLL, peripheral blood immunophenotyping using a panel of monoclonal antibodies is performed on freshly harvested blood.

Lymphocytes in peripheral blood

The total white blood cell count has a wide normal range, from 4,000 to 10,000 cells/mm^3. The numbers of each leukocyte type in the peripheral blood are under relatively autonomous control. For example, a patient may have a lymphopenia or a lymphocytosis with no change in the absolute numbers of other leukocytes.

The leukocyte differential is usually reported as both the percentage of each type of leukocyte and, of greater clinical significance, the absolute concentration of each type of leukocyte in the peripheral blood. *Relative lymphocytosis* is an increase in the percentage of lymphocytes without an increase in the absolute concentration of lymphocytes and is of little clinical significance. *Absolute lymphocytosis* is an increase in the overall concentration of lymphocytes; a diagnostic workup should be performed when the cause of the lymphocytosis is not readily apparent from the clinical presentation. In patients who are not acutely ill, the absolute lymphocyte count varies less from day to day than does the neutrophil count. Most peripheral blood lymphocytes in healthy persons are polyclonal T cells, with only a small number of B cells.

The malignant cell of CLL is a small, mature-appearing lymphocyte that cannot be reliably distinguished from a normal lymphocyte on routine Wright's-Giemsa stained smears of peripheral blood (FIGURE 1).

TABLE 2

Causes of lymphocytosis

Bacterial infections
- Pertussis
- Rickettsia
- Syphilis
- Brucellosis
- Shigella
- Tuberculosis

Viral infections
- Mononucleosis
- Cytomegalovirus
- Herpes virus
- Adenovirus
- Rubella
- Mumps
- Varicella
- Hepatitis A
- Hepatitis B

Malignant diseases
- Chronic lymphocytic leukemia
- Acute lymphocytic leukemia
- Lymphoma

Metabolic diseases
- Thyrotoxicosis
- Adrenal insufficiency

Lymphocyte immunophenotyping in the diagnosis of chronic lymphocytic leukemia

Before flow cytometry for cell phenotyping became widely available, the diagnosis of CLL was based on a persistent increase in the absolute numbers of morphologically normal-appearing lymphocytes and on evidence of tissue infiltration by these lymphocytes on bone marrow biopsy or lymph node biopsy. Today, flow cytometry allows physicians to analyze the characteristics of thousands of cells per second as they pass one-by-one through a beam of laser light. Flow cytometry uses an array of monoclonal antibodies conjugated with a fluorescent tag to rapidly determine the lineage of B cells or T cells in the peripheral blood, a procedure known as "immunophenotyping."

However, there is no standard panel of antibodies absolutely diagnostic of CLL like the one used in routine CD4 T-cell counts, because of more-complex analysis required for the diagnosis of CLL and the need to correlate the immunophenotype of the malignant cell with its morphology.

Cell surface markers. The malignant lymphocyte of CLL typically expresses the cell surface antigens CD5, CD19, and CD20, and cell surface immunoglobulin. This constellation of cell surface markers is found rarely on cells in the peripheral blood of healthy persons, but is found on the majority of lymphocytes in patients with CLL. The monoclonal nature of the CLL cells is demonstrated by the uniform expression of all of these cell surface antigens, as well as the uniform expression of a single isotype of immunoglobulin.

Flow cytometric analysis of abnormal peripheral blood lymphocytes must always be correlated with the morphologic appearance of the lymphocytes, as several other types of low-grade B-cell malignancies can have a phenotype similar to CLL; however, these other low-grade B-cell malignancies have a different morphologic appearance. Occasionally, some low-grade lymphomas that have disseminated to the peripheral blood have an appearance similar to the CLL cell under a light microscope, and in these unusual instances a precise

Perform a diagnostic workup if the cause of lymphocytosis is not apparent

TABLE 3

Indications for bone marrow biopsy in chronic lymphocytic leukemia

To confirm the diagnosis if peripheral blood immunophenotyping is not available or is inconclusive

To evaluate the cause of peripheral blood cytopenias

To determine the prognosis (ie, nodular vs diffuse histology)

To evaluate bone marrow reserve before starting intensive chemotherapy

diagnosis (CLL vs low-grade lymphoma with dissemination to the peripheral blood) is difficult. A biopsy of a lymph node can be helpful in these difficult cases.

Differential diagnosis of CLL

Chronic increases in mature-appearing lymphocytes in the peripheral blood are the hallmark of CLL, but persistent lymphocytosis can have other causes (TABLE 2).

Infectious mononucleosis can cause an acute rise in lymphocytes, but these are usually morphologically atypical forms.

If infections occur, measure the serum immunoglobulin level

Other infections. Less common causes of benign lymphocytosis include pertussis infections, rickettsial infections, and several viral infections. In each of these instances, the clinical manifestation of the underlying disease is usually apparent. But in cases where the cause is not apparent, if the cause is benign, immunophenotyping of the peripheral blood will demonstrate a polyclonal population of lymphocytes. In CLL, the finding is a monoclonal population of lymphocytes.

Other malignant diseases. Acute lymphoblastic leukemia and various lymphomas can also cause absolute lymphocytosis. Review of the morphology of the lymphocytes by a pathologist can usually distinguish CLL from these other malignant disorders. In the lymph node, CLL is called small lymphocytic lymphoma. Other advanced-stage, low-grade lymphomas can also cause monoclonal peripheral blood lymphocytosis, but the morphology of these other low-grade lymphoma cells is usually distinct from that of CLL. Prolymphocytic leukemia, arbitrarily defined as more than 55% prolymphocytic forms in the peripheral blood, is generally more aggressive clinically than CLL.

THE STAGING WORKUP

Once CLL is diagnosed, a staging workup is necessary to determine its extent. Staging consists of a physical exam, a complete blood count, and possibly a computed tomographic (CT) scan and bone marrow aspiration and biopsy.

Physical examination

The physical examination consists of careful palpation of the neck, axilla, and inguinal regions for any evidence of adenopathy, and of the abdomen for evidence of hepatosplenomegaly. Palpable lymph nodes larger than 1 to 1.5 cm that persist for more than 6 weeks are considered pathologic. Most involved lymph nodes in CLL grow very slowly, although they can exhibit an exaggerated response to infection. If a lymph node is enlarging rapidly, a biopsy should be performed, because CLL transforms to a more-aggressive malignant disease in up to 10% of patients. The spleen and liver can be moderately enlarged in CLL.

Role of computed tomography uncertain

There is no universal agreement yet on the need for a CT scan to determine the stage of newly diagnosed CLL. A CT scan is most helpful to investigate abdominal signs and symptoms that might be due to an enlarged spleen (such as feelings of fullness and weight loss), or if the patient has persistent fever or is morbidly obese. On the other hand, most patients would not be subjected to treatment on the basis of CT findings in the absence of symptoms; therefore, abdominal CT evaluation is probably not warranted in an asymptomatic patient.

Complete blood count

A complete blood count is performed to test for any significant anemia (defined as a hemoglobin concentration less than 11.0 g/dL) or thrombocytopenia (platelet counts less than 100,000/mm^3). If the patient has any recurrent infections, then serum immunoglobulin levels should measured, as these are often

depressed in late-stage CLL, and replacement therapy with immunoglobulin is available.

Bone marrow aspiration and biopsy

Bone marrow aspiration and biopsy are not required to diagnose CLL, but they can be helpful in certain situations (TABLE 3). For example, bone marrow aspiration and biopsy are required in evaluating anemia or thrombocytopenia, as either of these can occur through an autoimmune mechanism or through generalized bone marrow replacement with malignant lymphocytes. Patients who have anemia or thrombocytopenia of autoimmune etiology are candidates for treatment with steroids only, rather than cytoreductive chemotherapy.

Bone marrow biopsy can also help determine the prognosis: patients with a nodular pattern of bone marrow involvement have a more favorable prognosis than patients with a diffuse pattern of involvement. Occasionally a bone marrow biopsy is helpful in confirming a diagnosis of CLL when peripheral blood immunophenotyping is inconclusive. Culture of the bone marrow aspirate may help in defining an occult source of infection in patients with fever and night sweats but no apparent source of infection.

TREATMENT IS PALLIATIVE

The treatment of CLL remains palliative, as no approach has yet proven curative. Enlarged nodal masses can be dramatically reduced with chemotherapy. In patients with more advanced disease, the requirements for transfusions can be reduced or eliminated if there is sufficient cytoreduction with chemotherapy. Most patients can be followed for a period of time without any treatment, to determine the pace of their disease.

Indications for chemotherapy

Indications for immediate treatment with cytotoxic drugs are cytopenia related to bone marrow involvement, massive adenopathy, and massive splenomegaly (TABLE 4). Disease-related symptoms (fever in the absence of infection, night sweats) also respond to cytoreductive therapy, but a careful search for occult infection should be done before starting therapy for these symptoms.

TABLE 4

Indications for treatment of chronic lymphocytic leukemia

Disease-related symptoms

- Weight loss
- Extensive fatigue
- Fever
- Night sweats without infection

Evidence of progressive marrow failure

- Worsening of anemia
- Thrombocytopenia

Autoimmune anemia or thrombocytopenia or both, poorly responsive to corticosteroids

Splenomegaly

- Massive (> 6 cm below costal margin)
- Progressive

Progressive lymphocytosis with an increase of 50% over a 2-month period, or an anticipated doubling time of less than 6 months

A high absolute lymphocyte count is not an indication for treatment. Very high lymphocyte counts, in excess of 100,000 cells/mm^3, can be almost without symptoms. The pace of progression of the lymphocytosis and the degree of infiltration as manifested by lymphadenopathy, organomegaly, or bone marrow failure are better indications of when to treat a particular patient.

Lymphocytosis alone is not an indication for treatment

Antineoplastic therapy

Chlorambucil, with or without prednisone, is the classic therapy for CLL. However, despite years of experience with this drug, the optimum schedule of administration and the optimum duration of treatment have not been adequately defined. A pulsed-dosing schedule, ie, every 2 weeks, is most commonly used in the United States; however, some investigators have made a strong case for a continuous-dosing schedule. Because chlorambucil's absorption and metabolism varies, doses should be individualized on the basis of nadir complete blood counts.

Fludarabine, the major new drug for CLL, produces response rates of up to 60% in

patients previously treated with chlorambucil. A recent study (as yet published only in abstract form) reported that initial treatment with fludarabine was superior to initial treatment with chlorambucil for obtaining remission, but no overall survival benefit in the fludarabine arm has yet been observed. A third arm of this study, which combined fludarabine and chlorambucil, was closed early due to excessive toxicity without added clinical benefit.

Many physicians recommend fludarabine for younger patients (age < 60), but start with an alkylating agent, most commonly chlorambucil, in older patients. Concern about life-threatening infection in patients with other debilitating illnesses is the major reason for limiting fludarabine therapy in older patients. The overall status of the patient, including any other comorbid conditions, should be considered when assessing which drug may be better for initial therapy.

Hairy cell leukemia: A glimmer of hope

CLL remains incurable with chemotherapy. However, a disease very similar to CLL, hairy cell leukemia, may be curable with the chemotherapeutic agent cladribine, raising hopes that drug therapy may eventually be curative in CLL.

Hairy cell leukemia is distinguished from CLL primarily by the typical morphology of the hairy cell in the peripheral blood. The hairy cell also has unique cytochemical characteristics and a unique immunophenotype characterized by high CD11c expression. Patients with hairy cell leukemia tend to have a much greater degree of splenomegaly than typical CLL patients, and hairy cell leukemia has an even higher male-dominated prevalence than does CLL.

Almost all patients with hairy cell leukemia experience a complete remission after a single course of cladribine. While it remains to be determined if all these patients are cured, a substantial portion have no evidence of disease for several years without any further therapy. This dramatic response to a single course of single-agent therapy is gratifying and raises hope that someday an agent with similar activity in CLL will be discovered.

SUGGESTED READING

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CORRECTION

In "A 34-year-old woman with odynophagia and weight loss" by Kavita R. Kolluri, MD and Darwin L. Conwell, MD (*Cleveland Clinic Journal of Medicine* May 1997; 64:245–248), the headings in the TABLE were reversed. The corrected table is as follows.

TABLE

PREDNISONE THERAPY FOR IDIOPATHIC HIV-RELATED ESOPHAGEAL ULCERS

Variable	4 weeks	2 weeks
No. of patients	12	24
Response, N (%)	11 (92)	23 (96)
None	1	1
Partial	1	5
Complete	10	18
Relapse, N (%)	2 (22)	12 (52)
Median time to relapse, weeks	6	7
Range of follow-up, months	1 to 30	1 to 28
No. lost to follow-up	1	0

None of the differences were statistically significant
From Wilcox, reference 5