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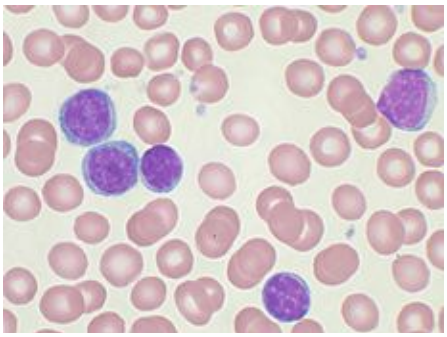
B-cell chronic lymphocytic leukemia



B-cell chronic lymphocytic leukemia (B-CLL), also known as **chronic lymphoid leukemia** (CLL), is the most common type of leukemia. Leukemias are abnormal and malignant neoplastic proliferations ("cancers") of the white blood cells (leukocytes). CLL involves a particular subtype of white blood cells, which is a lymphocyte called a B cell. B cells originate in the bone marrow, develop in the lymph nodes, and normally fight infection. In CLL, the DNA of a B cell is damaged, so that it can't fight infection by producing antibodies. Additionally, they grow out of control and accumulate in the bone marrow and blood, where they crowd out healthy blood cells.

CLL is a disease of adults, but in rare cases it can occur in teenagers and occasionally in children (inherited). Most (>75%) people newly diagnosed with CLL are over the age of 50, and the majority are men.

Most people are diagnosed without symptoms as the result of a routine blood test that returns a high white blood cell count, but as it advances CLL results in swollen lymph nodes, spleen, and liver, and eventually anemia and infections. Early CLL is not treated, and late CLL is treated with chemotherapy and monoclonal antibodies. Survival varies from 5 years to more than 25 years. It is now possible to predict survival length more precisely by examining the DNA mutations; patients with slowly-progressing disease can be reassured and may not need any treatment in their lifetimes. [1]

Although not originally appreciated, CLL is now felt to be identical to a disease called **small lymphocytic lymphoma** (SLL), a type of non-Hodgkin's lymphoma which presents primarily in the lymph nodes. The World Health Organization considers CLL and SLL to be "one disease at different stages, not two separate entities". [2]

Classification and prognosis

Clinical staging

Staging, determining the extent of the disease, is done with the Rai staging system or the Binet classification (see details [3]) and is based primarily on the presence, or not, of a low platelet or red cell count. Early stage disease does not need to be treated.

Gene mutation status

Recent publications suggest that two [4] or three [5] prognostic groups of CLL exist based on the maturational state of the cell. This distinction is based on the maturity of the lymphocytes as discerned by the immunoglobulin variable-region heavy chain (IgV_H) gene mutation status. [6] High risk patients have an immature cell pattern with few mutations in the DNA in the IgV_H antibody gene region whereas low risk patients show considerable mutations of the DNA in the antibody gene region indicating mature lymphocytes. [7]

Since assessment of the IgV_H antibody DNA changes is difficult to perform, the presence of either cluster of differentiation 38 (CD38) or Z-chain–associated protein kinase-70 (ZAP-70) may be surrogate markers of high risk subtype of CLL.[6] Their expression correlates with a more immature cellular state and a more rapid disease course.

Fluorescence in situ hybridization (FISH)

In addition to the maturational state, the prognosis of patients with CLL is dependent on the genetic changes within the neoplastic cell population. These genetic changes can be identified by fluorescent probes to chromosomal parts using a technique referred to as fluorescent in situ hybridization (FISH).[6] Four main genetic aberrations are recognized in CLL cells that have a major impact on disease behavior.[8]

1. Deletions of part of the short arm of chromosome 17 (del 17p) which target the cell cycle regulating protein p53 are particularly deleterious. Patients with this abnormality have significantly short interval before they require therapy and a shorter survival. This abnormality is found in 5-10% of patients with CLL.
2. Deletions of the long arm on chromosome 11 (del 11q) are also unfavorable although not to the degree seen with del 17p. The abnormality targets the ATM gene and occurs infrequently in CLL (5-10%).
3. Trisomy 12, an additional chromosome 12, is a relatively frequent finding occurring in 20-25% of patients and imparts an intermediate prognosis.
4. Deletion of the long arm of chromosome 13 (del 13q) is the most common abnormality in CLL with roughly 50% of patients with cells containing this defect. These patients have the best prognosis and most will live many years, even decades, without the need for therapy. The gene targeted by this deletion is a segment coding for microRNAs miR-15a and miR-16-1.

Array-based Karyotyping

Array-based karyotyping is a cost-effective alternative to FISH for detecting chromosomal abnormalities in CLL. Several clinical validation studies have shown >95% concordance with the standard CLL FISH panel.[9] [10] [11] [12] [13] See also Virtual Karyotype.

Related diseases

In the past, cases with similar microscopic appearance in the blood but with a T cell phenotype were referred to as T-cell CLL. However, it is now recognized that these so-called T-cell CLLs are in fact a separate disease group and are currently classified as T-cell prolymphocytic leukemias.[14][15]

CLL should not be confused with acute lymphoblastic leukemia, (ALL) a highly aggressive and highly treatable leukemia most commonly diagnosed in children.

Symptoms and signs

Most people are diagnosed without symptoms as the result of a routine blood test that returns a high white blood cell count. Uncommonly, CLL presents as enlargement of the lymph nodes without a high white blood cell count or no evidence of the disease in the blood. This is referred to as small lymphocytic lymphoma. In some individuals the disease comes to light only after the neoplastic cells overwhelm the bone marrow resulting in anemia producing tiredness or weakness.

Diagnosis

The disease is easily diagnosed. CLL is usually first suspected by the presence of a lymphocytosis, an increase in one type of the white blood cell, on a complete blood count (CBC) test. This frequently is an incidental finding on a routine physician visit. Most often the lymphocyte count is greater than 4000 cells per microlitre (µl) of blood but can be much higher. The presence of a lymphocytosis in an elderly individual should raise strong suspicion for CLL and a confirmatory diagnostic test, in particular flow cytometry, should be performed unless clinically unnecessary.

The diagnosis of CLL is based on the demonstration of an abnormal population of B lymphocytes in the blood, bone marrow, or tissues that display an unusual but characteristic pattern of molecules on the cell surface. This atypical molecular pattern includes the co-expression of cells surface markers cluster of differentiation 5 (CD5) and cluster of differentiation 23 (CD23). In addition, all the CLL cells within one individual are clonal, that is genetically identical. In practice, this is inferred by the detection of only one of the mutually exclusive antibody light chains, kappa or lambda, on the entire population of the abnormal B cells. Normal B lymphocytes consist of a stew of different antibody producing cells resulting in a mixture of both kappa and lambda expressing cells. The lack of the normal distribution of kappa and lambda producing B cells is one basis for demonstrating clonality, the key element for establishing a diagnosis of any B cell malignancy (B cell Non-Hodgkin lymphoma).

The combination of the microscopic examination of the peripheral blood and analysis of the lymphocytes by flow cytometry to confirm clonality and marker molecule expression is needed to establish the diagnosis of CLL. Both are easily accomplished on a small amount of blood. A flow cytometer is an instrument that can examine the expression of molecules on individual cells in fluids. This requires the use of specific antibodies to marker molecules with fluorescent tags recognized by the instrument. In CLL, the lymphocytes are genetically clonal, of the B cell lineage (express marker molecules cluster of differentiation 19 (CD19) and CD20), and characteristically express the marker molecules CD5 and CD23. Morphologically, the cells resemble normal lymphocytes under the microscope, although slightly smaller, and are fragile when smeared onto a glass slide giving rise to many broken cells (smudge cells).

Differential diagnosis

Hematologic disorders that may resemble CLL in their clinical presentation, behavior, and microscopic appearance include mantle cell lymphoma, marginal zone lymphoma, B cell prolymphocytic leukemia, and lymphoplasmacytic lymphoma.

B cell prolymphocytic leukemia (B PLL), is a related but more aggressive disorder, has cells with similar phenotype but that are significantly larger than normal lymphocytes and have a prominent nucleolus. The distinction is important as the prognosis and therapy differs from CLL.

Hairy cell leukemia is also a neoplasm of B lymphocytes but the neoplastic cells have a distinct morphology under the microscope (hairy cell leukemia cells have delicate, hair-like projections on their surface) and unique marker molecule expression.

All the B cell malignancies of the blood and bone marrow can be differentiated from one another by the combination of cellular microscopic morphology, marker molecule expression, and specific tumor-associated gene defects. This is best accomplished by evaluation of the patient's blood, bone marrow and occasionally lymph node cells by a pathologist with specific training in blood disorders. A flow cytometer is necessary for cell marker analysis and the detection of genetic problems in the cells may require visualizing the DNA changes with fluorescent probes by fluorescent in situ hybridization (FISH).

Treatment

CLL treatment focuses on controlling the disease and its symptoms rather than on an outright cure. CLL is treated by chemotherapy, radiation therapy, biological therapy, or bone marrow transplantation. Symptoms are sometimes treated surgically (splenectomy removal of enlarged spleen) or by radiation therapy ("de-bulking" swollen lymph nodes).

Initial CLL treatments vary depending on the exact diagnosis and the progression of the disease, and even with the preference and experience of the health care practitioner. There are dozens of agents used for CLL therapy, and there is considerable research activity studying them individually or in combination with each other.[16]

Decision to treat

While generally considered incurable, CLL progresses slowly in most cases. Many people with CLL lead normal and active lives for many years - in some cases for decades. Because of its slow onset, early-stage CLL is generally not treated since it is believed that early CLL intervention does not improve survival time or quality of life. Instead, the condition is monitored over time to detect any change in the disease pattern.

The decision to start CLL treatment is taken when the patient's clinical symptoms or blood counts indicate that the disease has progressed to a point where it may affect the patient's quality of life.

Clinical "staging systems" such as the Rai 4-stage system and the Binet classification can help to determine when and how to treat the patient.[3]

Determining when to start treatment and by what means is often difficult; studies have shown there is no survival advantage to treating the disease too early. The National Cancer Institute Working Group has issued guidelines for treatment, with specific markers that should be met before it is initiated.[17]

Chemotherapy

Combination chemotherapy regimens are effective in both newly-diagnosed and relapsed CLL. Recently, randomized trials have shown that combinations of purine analogues (fludarabine) with alkylating agents (cyclophosphamide) produce higher response rates and a longer progression-free survival than single agents:

FC (fludarabine with cyclophosphamide) [18]

FR (fludarabine with rituximab) [19]

FCR (fludarabine, cyclophosphamide, and rituximab) [20]

CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone)

Although the purine analogue fludarabine was shown to give superior response rates than chlorambucil as primary therapy, [21][22] there is no evidence that early use of fludarabine improves overall survival, and some clinicians prefer to reserve fludarabine for relapsed disease.

Alkylating agents approved for CLL include bendamustine and cyclophosphamide.

Monoclonal antibodies such as alemtuzumab (directed against CD52), rituximab (directed against CD20), and Arzerra (ofatumumab)(directed against CD20).

Stem cell transplantation

Allogeneic bone marrow (stem cell) transplantation is rarely used as a first-line treatment for CLL due to its risk. There is increasing interest in the use of reduced intensity allogeneic stem cell transplantation, which offers the prospect of cure for selected patients with a suitable donor. [23]

Current research is comparing different forms of bone marrow transplants to determine which patients are the best candidates and which approach is best in different situations. [24] Younger patients that are at high risk for dying from CLL might consider hematopoietic stem cell transplantation (HSCT). Autologous stem cell transplantation, a lower-risk form of treatment using the patient's own blood cells, is not curative. Myeloablative (bone marrow killing) forms of allogeneic stem cell transplantation, a high-risk treatment using blood cells from a healthy donor, may be curative for some patients, but most patients cannot tolerate the treatment. An intermediate level, called *reduced-intensity conditioning allogeneic stem cell transplantation*, may be better tolerated by older or frail patients. [24]

Refractory CLL

"Refractory" CLL is a disease that no longer responds favorably to treatment. In this case more aggressive therapies, including lenalidomide, flavopiridol, and bone marrow (stem cell) transplantation, are considered. [25] The monoclonal antibody, alemtuzumab (directed against CD52), may be used in patients with refractory, bone marrow-based disease. [26]

Complications

Chronic lymphocytic leukemia may transform into Richter's syndrome, a term used to describe the development of fast-growing diffuse large B cell lymphoma, prolymphocytic leukemia, Hodgkin disease, or acute leukemia in a patient who has chronic lymphocytic leukemia. Its incidence is estimated to be around 5%. [27]

Epidemiology

CLL is a disease of older adults and is rarely encountered in individuals under the age of 40. Thereafter the disease incidence increases with age.

In the United States during 2009, about 16,000 new cases are expected to be diagnosed, and 4,400 patients are expected to die from CLL.[3] Because of the prolonged survival, which was typically about ten years in past decades, but which can extend to a normal life expectancy,[3] the prevalence (number of people living with the disease) is much higher than the incidence (new diagnoses).
Subclinical "disease" can be identified in 3.5% of normal adults[28], and in up to 8% of individuals over the age of 70.

That is, small clones of B cells with the characteristic CLL phenotype can be identified in many healthy elderly persons. The clinical significance of these cells is unknown.
Of all cancers involving the same class of blood cell, 7% of cases are CLL/SLL.[29]

Complications: hypogammaglobulinemia leading to recurrent infection, warm auto immune haemolytic anaemia in 10-15% of patients, transformation to high grade lymphoma, Richter's transformation.

Rates of CLL are somewhat elevated in people who have been exposed to certain chemicals. Under U.S. Department of Veterans' Affairs regulations,[30] Vietnam veterans who served in-country or in the inland waterways of Vietnam and who later develop CLL are presumed to have contracted it from exposure to Agent Orange and may be entitled to compensation.

See also

- Monoclonal B-cell lymphocytosis
- Virtual Karyotype

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External links

Chronic Lymphocytic Leukemia at American Cancer Society

CLL booklet from Leukemia & Lymphoma Society

General information about CLL from the US National Cancer Institute