Chronic lymphocytic leukaemia

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Abstract

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in developed countries. It is a disease of the elderly, usually incurable and characterized by significant clinical and biological heterogeneity. Many patients are diagnosed after the incidental finding of a sustained lymphocytosis, while others present with symptomatic disease requiring treatment. Clinical features arise from immune dysfunction and tissue infiltration, and include fatigue, infections, lymphadenopathy, hepatosplenomegaly and cytopenias. Key diagnostic tests are peripheral blood morphology and immunophenotyping. Clinical staging, lymphocyte doubling time and biomarkers are useful in assessing prognosis. Overall, median survival is 10 years. Patients with CLL undergo regular monitoring, and therapy is reserved for those with symptomatic or rapidly progressive disease. Early intervention has no impact on outcome and can encourage drug resistance. Consideration must be given to the patient's fitness for treatment and the management of co-morbidities. Supportive care includes prevention and treatment of infection, transfusion support and treatment of autoimmune cytopenias. Chemo-immunotherapy continues to be the mainstay of front-line treatment for standard-risk disease. However, treatment of CLL has rapidly evolved over recent years with the introduction of targeted therapies that inhibit signalling downstream of the B cell receptor, second-generation monoclonal antibodies and BCL2B Cell Lymphoma 2 (*BCL2*) antagonists.

Keywords Aetiology; B cell chronic lymphocytic leukaemia; biomarkers; blood; diagnosis; drug therapy; epidemiology; genetics; pathology; prognosis

Key points

- Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the developed countries and is a disease of the elderly
- Clinical features arise from infiltration of the lymph nodes, liver, spleen and bone marrow compartments and from disruption of the normal immune system
- CLL is highly heterogeneous, and biomarkers are useful in prognostication
- Treatment is reserved for patients who have symptoms of progressive disease
- CLL harbouring *TP53* deletions or mutations respond poorly to conventional therapy and should be treated accordingly
- The introduction of targeted therapies is improving clinical outcomes, particularly in patients with poor prognosis relapsed or refractory disease

Introduction

Chronic lymphocytic leukaemia (CLL) is a common and highly heterogeneous tumour caused by the expansion of a clone of mature B lymphocytes. It is the most common leukaemia in developed countries, with an incidence rising from 0.7 to 21 per 100,000 per year between the ages of 40 and 70 years. There is a male predominance (1.7:1), and both a genetic and ethnic predisposition, with a 5.7-fold risk in first-degree relatives and a lower incidence in Far-Eastern populations.

A pre-leukaemic disorder, termed monoclonal B lymphocytosis (MBL), affecting 5% of healthy individuals aged >60 years, has been described. Patients with MBL are estimated to have a 1% chance per year of developing symptomatic CLL.

Pathogenesis

As with other cancers, CLL arises because of an imbalance between the proliferation and death of the malignant clone. Proliferation takes place in the lymph node compartment, where CLL cells interact with components of the tumour microenvironment including activated CD4 T cells, stromal cells and endothelial cells. Within the lymph node compartment, signalling through the B cell receptor (BCR) plays a major role in the survival and proliferation of tumour cells and has recently been found to be a highly effective therapeutic target (Figure 1c). Disease progression is associated with clonal evolution that renders the disease more aggressive and resistant to therapy. Whole-genome sequencing studies have identified a number of mutations in the tumour cells that can become therapeutic targets.[1]

Clinical and diagnostic features

In many patients, CLL is diagnosed following the incidental detection of an isolated lymphocytosis. A diagnosis of CLL requires the presence of a clonal B lymphocytosis of $\geq 5 \times 10^9$/litre sustained over 3 months. Small lymphocytic lymphoma is a

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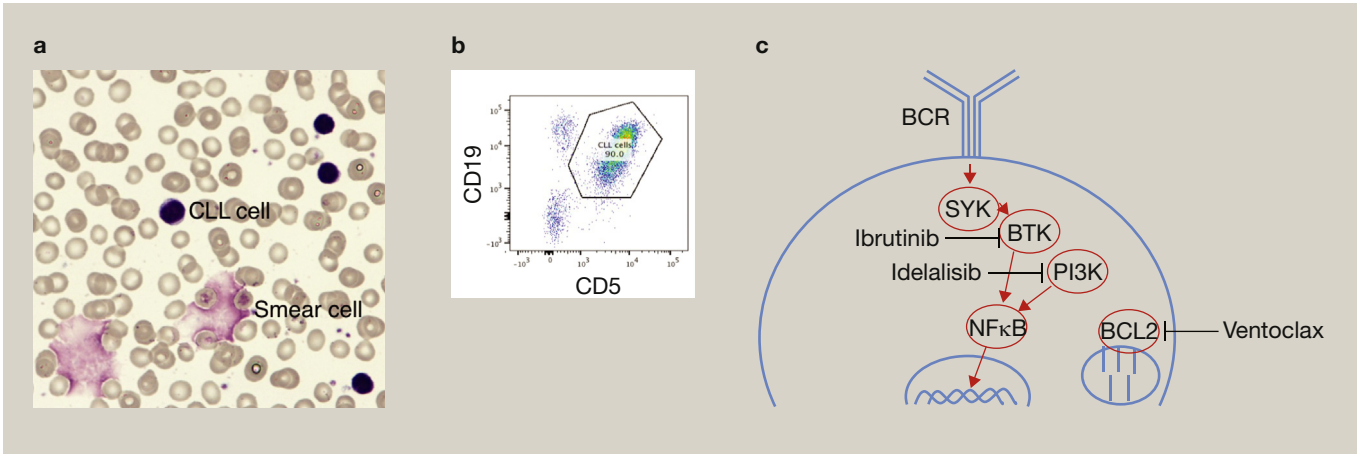

Figure 1 (**a**) Blood film demonstrating small, round mature lymphocytes with clumped chromatin and scanty cytoplasm and smear cells. (**b**) Flow cytometry plot demonstrating CLL cells that co-express CD5 and CD19. (**c**) Schema of drug targets downstream of the BCR in CLL cells.

lymphoid tumour with the morphology and immunophenotype of CLL without a leukaemic component.

When symptoms are present, they arise as a consequence of immune dysfunction and tissue infiltration, as outlined in Table 1.

The differential diagnosis includes other types of low-grade B lymphoproliferative disorder and reactive and leukaemic T cell disorders.

The diagnosis of CLL is made on the basis of a typical blood film appearance and a characteristic immunophenotype (Figure 1a, b).

Prognostic factors

Clinical stage

Clinical staging systems (Table 2) reflect disease bulk and the degree of bone marrow failure. They can be used to estimate prognosis.

Biomarkers

The following biomarkers have been shown to correlate with clinical outcome:

- **Mutational status of immunoglobulin heavy chain variable genes** – in normal lymph node germinal centres, the variable portion of the immunoglobulin heavy chain genes (*IgVH*) undergoes mutation to generate high-affinity antibody. Approximately half of patients with CLL have mutated *IgVH* genes, and this correlates with a good prognosis.
- **CD38 expression:** increased tumour expression of this activation marker is associated with faster disease progression and reduced overall survival (OS).
- **Fluorescence *in situ* hybridization (FISH)/cytogenetics:** *TP53* (tumour protein p53) abnormalities (deletions, mutations) and 11q deletion are poor prognostic markers. Patients with an isolated 13q deletion have a favourable prognosis.[2]

With the exception of *TP53* abnormalities (chromosome 17p), which predict resistance to chemotherapy, these markers are not currently used to guide patient management. *TP53* status should be assessed by FISH and/or sequencing before commencing chemotherapy.

Management

CLL has traditionally been considered to be incurable with chemotherapy, so the goals of therapy are to prolong survival and manage symptoms. The diagnosis of CLL can have profound effects on quality of life even in the earliest stages of the disease, and accurate information and appropriate support are essential. Many patients with CLL are elderly with multiple comorbidities that limit the feasibility of myelosuppressive chemotherapy.

The recent introduction of targeted therapies, including idelalisib[3] and ibrutinib,[4] that inhibit signalling downstream of the BCR has revolutionized the treatment of particularly challenging groups of patients; these include patients with *TP53* abnormalities and those who relapse quickly after front-line therapy. Idelalisib (a phosphatidylinositol 3-kinase) inhibitor and ibrutinib (a Bruton's tyrosine kinase antagonist) are oral, potent, small-molecule inhibitors of BCR signalling that inhibit the activation, proliferation and homing of CLL cells (Figure 1c). They are associated with higher response rates and are generally well tolerated; however, long-term safety data are not yet available and unexpected toxicities may emerge.

Stage A disease

The use of alkylating agents in this setting does not prolong survival. These patients should be monitored for disease progression and educated regarding immunizations and the measures to reduce the risk of secondary malignancy.

Stage B/C disease

Treatment should be reserved for those with symptomatic or rapidly progressive disease as outlined below:

- progressive bone marrow failure, manifest as anaemia, neutropenia or thrombocytopaenia not resulting from autoimmunity
- massive, progressive or symptomatic splenomegaly or lymphadenopathy
- rapidly progressive lymphocytosis (e.g. doubling in <6 months)
- autoimmune cytopenias, which are poorly responsive to corticosteroids

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