Haematology

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Chronic lymphocytic leukaemia

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Chronic lymphocytic leukaemia (CLL) is the most common of the neoplastic conditions associated with peripheral blood lymphocytosis. They include prolymphocytic leukaemia, lymphoma with blood involvement, hairy cell leukaemia and Sézary syndrome. The morphological classification of CLL has been improved by cell surface antigen analysis, cytogenetics and molecular biology. In 95% of patients with a morphological diagnosis of CLL the cells are of B lymphocyte origin.

Epidemiology

B-CLL is the most common adult leukaemia in developed countries and accounts for 30–40% of all leukaemias[1]. The annual incidence is 2.5 per 100,000, the male to female ratio is 2:1, and the median age at diagnosis 65–70 years (only 6% <50 years). There is a sevenfold excess of leukaemia in first-degree relatives of CLL patients[1].

Occupational factors include:

- farming (high levels of soya bean production, cattle breeding, dairy production and herbicide use)[2]
- rubber manufacture (benzene, xylene), asbestos and tyre repair workers
- exposure to carbon tetrachloride.

CLL has not been linked to exposure to radiation, other known carcinogens or viruses.

A low incidence among people of Japanese origin, including migrants to Hawaii, suggests that genetics has a stronger influence than environment.

Cytogenetics and molecular biology

There is a strong correlation between karyotype and prognosis, but no indisputable pathogenetic relationship has been established for the chromosome abnormalities found. Any clonal abnormality is associated with poor prognosis compared to a normal karyotype. A high proportion of abnormal metaphases indicates poor prognosis[3].

Conventional cytogenetics detects clonal abnormalities in 50% of patients, while fluorescence *in situ* hybridisation (FISH) demonstrates abnormalities in over 80%[4]. Up to 75% may display 13q14 deletion[5], which as a solitary abnormality (36%) has a favourable prognosis (median survival >15 years). Other common abnormalities and associations are:

- del(11q23): bulky disease and poor prognosis (6.6 years) in 17%
- trisomy 12: atypical morphology and poor prognosis (10.9 years) in 15%
- del(17p): drug resistance, very poor prognosis (3.6 years) in 8%
- del(6q): bulky disease (11 years) in 7%.

Complex abnormalities occur in 10–15% of cases.

The mutation status of the immunoglobulin (Ig) genes correlates with morphology, genotype, phenotype, stage, response to chemotherapy and survival[6,7]. CLL with unmutated Ig V genes responds poorly to chemotherapy and confers shorter survival than CLL with mutated Ig V genes, which requires minimal/no chemotherapy and confers prolonged survival.

Clinical presentation

CLL usually follows an indolent course. Lymphocytes gradually accumulate in blood, marrow, lymph nodes, spleen and liver until marrow failure occurs. Early CLL is generally asymptomatic and isolated peripheral blood lymphocytosis is frequent. Lymphadenopathy, anaemia, bacterial infection, herpes zoster, autoimmune haemolysis or autoimmune thrombocytopenia may prompt presentation. Later, symptoms due to pancytopenia or immune-paresis develop insidiously and gross lymphadenopathy (usually symmetrical) and organomegaly become evident. Night sweats, fever, weight loss or lethargy usually occur only in advanced disease. Splenomegaly is

Key Points

- **Persistent lymphocytosis in an adult usually, but not always, indicates chronic lymphocytic leukaemia (CLL)**
- **Cytogenetic analysis of blood or bone marrow provides useful prognostic information**
- **Treatment should be administered for specific clinical indications, not just to normalise the lymphocyte count, and should be delayed if possible**
- **Chlorambucil remains first choice for initial therapy for most patients with CLL, but should be administered in an intermittent regimen**
- **Bone marrow transplantation should be discussed as a possibility with patients under 55 years with progressive CLL and a compatible sibling donor**

Table 1. National Cancer Institute Working Group revised criteria for diagnosis of chronic lymphocytic leukaemia[8].

Peripheral blood lymphocytosis	Absolute lymphocyte count >5 x 10^9/l Morphologically mature appearing cells
Characteristic phenotype	Predominance of CD19+, CD20+ CD23+ & CD5+ B cells Light chain restriction (ie monoclonal κ or λ expression) Low density surface immunoglobulin expression
Bone marrow examination	±30% lymphocytes in bone marrow if peripheral blood lymphocytosis is relatively low (ie close to 5 x 10^9/l)

found in 66% of patients at presentation, while hepatomegaly is more common in advanced CLL.

Diagnosis and staging

Diagnostic criteria are shown in Table 1[8]. The blood film reveals a population of homogeneous small lymphocytes of mature appearance with 'smear cells', a consistent artefactual finding due to cell rupture while the film is being made. Bone marrow aspiration is essential only when the lymphocytosis is modest, but the trephine biopsy provides prognostic information about the extent of marrow involvement and may influence treatment decisions.

Phenotyping of cells from blood or bone marrow is essential to exclude reactive lymphocytosis and other lymphoid neoplasms (Table 2). The characteristic pattern is strong expression of pan-B cell antigens in association with the T cell antigen CD5, but poor expression of surface Ig and CD20. Mantle cell lymphoma, which also expresses CD5 and B cell antigens and may be associated with lymphocytosis, can be distinguished by strong surface Ig and absent CD23.

The reticulocyte count and direct antiglobulin test are useful to exclude haemolysis, as is Ig quantification to screen for hypogammaglobulinaemia. Radiology is not generally indicated unless infection is suspected, nor are computed tomography, magnetic resonance imaging examination, lymphangiography or gallium scanning.

Clinical staging and prognostic criteria

The Binet clinical staging system[9] divides patients into three groups, A, B and C (Table 3). Stage C comprises the 20% of patients with the poorest prognosis. Prognosis for the other 80% depends on the number of lymph node sites involved. Several other poor prognostic factors have been defined, the most important of which are:

- male sex
- advanced stage disease
- initial lymphocyte count above 50 × 10^9/l
- more than 5% prolymphocytes in film
- lymphocyte doubling time less than 12 months
- diffuse bone marrow infiltration on biopsy
- cytogenetic abnormalities
- poor response to therapy.

The diagnosis 'smouldering CLL' is applied to about 30% of patients who have stage A CLL with non-diffuse bone marrow involvement, haemoglobin above 13 g/dl, lymphocytosis below 30 × 10^9/l and lymphocyte doubling time less than 12 months. They have a life expectancy without treatment equal to that of matched controls without CLL.

Table 2. Immunophenotype of B cell chronic lymphoid leukaemias (CLL).

	CLL	PLL	HCL	SLVL	FL	MCL
Surface Ig	–/+	++	++	++	++	++
MHC Class II	++	++	+	+	+	+
CD5	+	–/+	–	–/+	–/+	+
CD10	–	–/+	–	–/+	+/–	–/+
CD11c	–/+	–	+	+/–	–	–
CD19	++	++	++	++	++	++
CD20	–/+	+	+	+	+	++
CD22	–/+	+	+	+	+/–	+/–
CD23	+	–/+	–	+/–	–/+	–
CD24	+	+	–/+	+	+	+
CD25	+/–	–	+	–/+	–	–
FMC7	–/+	+	+	+	+	+/–
CD103	–	–	+	–/+	–	–

FL = follicular lymphoma; HCL = hairy cell leukaemia; MCL = mantle cell lymphoma; MHC = major histocompatibility complex; PLL = prolymphocytic leukaemia; SLVL = splenic lymphoma with villous lymphocytes.

Treatment

Treatment is not always indicated. At diagnosis, a decision needs to be taken whether to initiate therapy immediately or to defer it. Therapy is palliative rather than curative and should be introduced only when it may prolong survival or alleviate symptoms. Over-enthusiastic treatment may compromise haematopoiesis or immune competence.

There is no evidence that therapeutic intervention in patients with lymphocytosis or uncomplicated lymphadenopathy prolongs survival. If possible, patients with Binet stage A or B disease should be 'watched'. When lymph node enlargement causes symptoms, local or systemic therapy is often helpful. Criteria for treatment are shown in Table 4[8].

Chlorambucil

First-line therapy remains chlorambucil because of convenience, efficacy and absence of gastrointestinal upset or alopecia, but there is cumulative haemopoietic toxicity and eventually CLL develops resistance. Chlorambucil

Table 3. Binet clinical staging system for chronic lymphocytic leukaemia[9].

Stage	Lymphoid involvement*	Haemoglobin (g/dl)		Platelets ($x10^9$/l)	Survival (years)
A	0, 1 or 2 areas	>10		>100	12
B	3, 4 or 5 areas	>10		>100	5
C		<10	and/or	<100	2

* Lymphoid areas include cervical, axillary or inguinal lymph nodes, spleen or liver.

is administered orally, usually for 7–10 days in a 28-day cycle. It reduces lymphocytosis, improves haemoglobin and platelets, shrinks lymphadenopathy and splenomegaly, and improves constitutional symptoms in over 50% of patients. Complete response is rare. In a study of stage A patients, those with delayed therapy survived longer than those treated at diagnosis[10]. Patients treated with continuous chlorambucil had shorter survival due to a high incidence of epithelial cancers.

Intermittent chlorambucil causes less haematological toxicity and should be continued as long as the patient is responding. When a normal lymphocyte count is achieved, usually after 6–12 months, it should be discontinued because continuous maintenance therapy with chlorambucil causes haematological toxicity. Further responses are often achieved when CLL progresses. A median duration of survival of approximately four years can be expected in responding patients[11]. Chlorambucil slows disease progression but does not improve survival. Addition of prednisolone improves the response rate but has no effect on survival.

Prednisolone

Prednisolone as a single agent reduces bone marrow infiltration and can significantly improve cytopenia and symptoms. It may be useful given for 1–2 weeks prior to chemotherapy in advanced disease with severe cytopenia at diagnosis.

Combination chemotherapy

Higher response rates are achieved with combination therapy with cyclophosphamide, vincristine (Oncovin) and prednisolone (COP) or with CHOP (same drugs plus adriamycin), but there is no survival advantage.

Purine analogues

High response rates are produced with purine analogues. Consistent unwanted effects are profound depletion of normal lymphocytes and predisposition to opportunistic infection by *Pneumocystis carinii, Listeria monocytogenes, Mycobacterium tuberculosis,* nocardia and herpes viruses.

Fludarabine. Given as a single agent, fludarabine produces responses in 78% of previously untreated patients, with 33% complete responses[12]. In previously treated patients, fludarabine achieves responses in up to 57%[13]. Fludarabine as initial treatment shows a higher complete remission rate (27% vs 3%), overall response rate (70% vs 40%) and disease-free survival (33 months vs 17 months) than chlorambucil[14], but with no significant improvement in survival.

Fludarabine may be administered intravenously or orally for five days every four weeks either until maximum response has been reached or for six cycles. Myelosuppression, prolonged and profound T lymphocytopenia and infection are major complications. Routine prophylaxis of *P. carinii* pneumonia with co-trimoxazole is essential, and should continue for one year after treatment. Patients with a history of shingles should receive prophylactic aciclovir, while isoniazid prophylaxis should be considered for patients exposed to *M. tuberculosis*. Cellular blood products should be irradiated for two years after treatment.

Autoimmune haemolytic anaemia occurs in 5–10% of patients treated with fludarabine, and is associated with advanced CLL and previous treatment with chlorambucil or prednisolone. It may occur after one course or many, without a history of haemolysis, with a negative direct antiglobulin test and during therapeutic response. Fludarabine should be discontinued and steroids commenced. Response may be prompt. Haemolysis recurs in most patients if further purine analogues are administered and may be fatal. Care should therefore be exercised using fludarabine in patients with a previous history of haemolysis.

Fludarabine is an option for initial therapy in patients who require treatment, but survival is not improved and chlorambucil offers many patients prolonged disease control. Fludarabine is effective in patients with chlorambucil-resistant CLL, and has a clear role as a second-line therapy.

2-Chloro-deoxy-adenosine. Another purine analogue, 2-chloro-deoxy-adeno-

Table 4. National Cancer Institute criteria for systemic therapy in chronic lymphocytic leukaemia (CLL)[8].

- Constitutional symptoms referable to CLL:
  - weight loss >10% in 6 months
  - fatigue or performance score 2 or worse
  - fever without overt infection
  - night sweats
- Symptomatic lymphadenopathy
- Symptomatic hepatosplenomegaly
- Progressive anaemia with haemoglobin <10 g/dl
- Progressive thrombocytopenia with platelets <100 x 10^9/l
- Progressive lymphocytosis with a rapid rate of increase or an anticipated doubling time of less than 6 months
- Autoimmune disease refractory to prednisolone
- Repeated infections with or without hypogammaglobulinaemia

sine, is effective in alkylator-resistant CLL. No comparative studies have yet been performed with fludarabine.

Allogeneic bone marrow transplantation

A number of patients can achieve durable disease-free survival following an allogeneic bone marrow transplant (BMT), with no molecular evidence of disease[15]. Response to donor lymphocyte infusion after relapse demonstrates the presence of a graft versus leukaemia effect. BMT should be considered in any patient below 55 years with progressive CLL and a histocompatible sibling donor. Follow-up is too brief and the number of cases too few to assess curative potential.

Conclusion

A strategic approach of timely but judicious chemotherapy to prevent or treat symptoms, but also to preserve haematopoiesis, remains the best policy for most patients with CLL.

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Erratum

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Management of alcoholic hepatitis

The author's address was incorrect, and should have read: Centre for Hepatology, Royal Free & University Medical School, Rowland Hill Street, London NW3 2PF. We would like to apologise to Dr Kevin Moore.