

# Leukaemia Section

## Mini Review

# Chronic lymphocytic leukaemia (CLL)

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## Clinics and pathology

### **Disease**

Chronic lymphoproliferation

### **Phenotype/cell stem origin**

B-cell disease; the existence of rare cases of T-CLL has been debated.

### **Epidemiology**

Annual incidence 30/10<sup>6</sup>; represents 70% of lymphoid leukaemias, 1/4 of all leukaemias; median age: 60-80 yrs, 2M/1F.

### **Clinics**

Diagnosis is often delayed, due to the lack of symptoms (therefore, median survival from the beginning of the disease may be much more than median survival from diagnosis).

The patient may present with enlarged lymph nodes, splenomegaly, lymphocytosis  $> 45 \times 10^9/l$ ; hypogammaglobulinemia in 60%.

### **Cytology**

Typically, proliferation of mature small lymphocytes of normal morphology; lymphocytes with more abundant cytoplasm may be present. When prolymphocytes are 10% or greater they are classified as 'chronic lymphocytic leukaemia-prolymphocytic leukaemia'.

The main immunophenotypic features that define B-CLL are: the predominant population shares B-cell markers CD19, CD20, and CD23 with the CD5 antigen, in the absence of other pan-T-cell markers; the B-cell is monoclonal with regard to expression of either kappa or lambda; and surface

immunoglobulin (slg) is of low density. Not only are these characteristics generally adequate for a precise

diagnosis, but, importantly, they distinguish CLL from uncommon disorders such as PLL, hairy-cell leukemia, mantle-cell lymphoma, and other lymphomas. Further, the Matutes score based on the most common marker profile in CLL, CD5+, CD23+, FMC7- and weak expression (+/-) of surface immunoglobulin (SIg) and CD22, can distinguish between typical and atypical CLL by assigning scores that range from 5 (typical of CLL) to 0 (atypical for CLL).

### **Treatment**

Binet staging is used for therapeutic intervention. The treatments options are: watchful waiting for symptoms, radiation therapy, chemotherapy, surgery such as splenectomy. Those being tested in clinical trials are monoclonal antibodies, chemotherapy with stem cell transplant.

### **Prognosis**

Evolution: unrelated causes and disease-related infections are the 2 major causes of death; others: autoimmune hemolytic anaemia and thrombocytopenia; transformation into Richter's disease or into prolymphocytic leukaemia (in 10%). Some patients with CLL survive for many years without therapy with minimal signs and symptoms, during the entire disease course and have a survival time similar to age-matched controls, whereas others have a rapidly deteriorating blood counts and organomegaly. Rai et al and Binet et al devised staging: less than 3 lymph nodes, HGB.

Since more than 80% CLL are diagnosed at early disease stages, many prognostic markers have been identified. One of the most important molecular genetic markers defining pathogenic and prognostic subgroups of CLL is the mutation status of VH gene. Surrogate markers for VH status are CD38 and ZAP-70 and their validity has yielded controversial results. Patients with

few or no VH mutations or many CD38+ or ZAP-70+ B cells have an aggressive usually fatal course, whereas patients with mutated clones or few CD38+ or ZAP-70+ B cells have an indolent course.

Genomic aberrations are the other genetic parameter shown to be of prognostic relevance in CLL.

## Cytogenetics

### *Cytogenetics morphological*

Clonal anomaly is found in about 50% of cases by chromosome analysis and in about 80% of CLL cases by fluorescence in situ hybridization (FISH) of interphase cell nuclei with a disease-specific comprehensive probe set. The disease progression as assessed by the treatment-free interval for 17p deletion (n=23), 11q deletion (n=56), 12q trisomy (n=47), normal (n=57) and 13q deletion (single abnormality: n=117) were 9, 13, 33, 49, and 92 months respectively; and the survival probabilities were 32, 79, 114, 111 and 133 months respectively.

Complex karyotypes are found in 10%; unrelated clones demonstrating the existence of cells subpopulations are frequent findings in this disease.

Trisomy 12, found in 15-20% [cytogenetics] or 16-25% [FISH] of CLL cases has an unresolved pathogenic impact, and intermediate outcome. In other studies, trisomy 12 is an adverse prognostic factor (median survival: 5 yrs); found either as the sole anomaly, as an anomaly accompanied by others, or even as an accompanying (secondary) anomaly; present only in a subset of the malignant cell population; Trisomy 12 is found frequently in atypical lymphocyte morphology and CD5- cases, often with an increased number of prolymphocytes.

The most common deletion, del(13)(q14.3) found in 10-20% [cytogenetics] or 36-64% [FISH] CLL cases includes a nontranscribed gene and two micro-RNA genes. As the sole abnormality, has good prognosis. The disease free interval and overall survival is better than cases with normal karyotype because of slow disease progression.

Deletion 11q22-q23, involving ATM gene, is marked by lymphadenopathy and poor survival and is detected in 11-18% [FISH] of CLL cases.

Deletion 17p13 (p53) occurs in 7-8% [FISH] of CLL cases that are resistant to chemotherapy and have a short survival.

Although, 14q32 involvement was frequent in early CLL studies, currently, t(11;14)(q13;q32) with BCL1 / IgH rearrangement, is considered to be a hallmark of mantle cell lymphoma, similarly other rare 14q32 rearrangements such as CLL; t(14;19)(q32;q13), are associated with leukemic lymphoma. Therefore, translocations involving 14q32 IgH locus are probably diseases other than CLL. Eliminating t(11;14) and t(14;18), 14q32 rearrangements are found in about 4% of cases studied by FISH.

IgH deletion may be hetero- or homozygous. A 14q32 involvement is considered a good prognostic feature (median survival > 15 yrs) in CLL. As in other B-cell chronic leukaemias or lymphomas; t(11;14)(q13;q32), typical of mantle cell lymphoma with BCL1/IgH rearrangement, t(14;19)(q32;q13) with BCL3/IgH rearrangement, may be associated with short survival, t(2;14)(p13;q32), exceptional; and other t(14;var) may occasionally be found in CLL.

Other recurring anomalies are del(6q) [0-6% by FISH], +8q24 [5% by FISH], +3, and +18. Deletion 6q21 has a poor prognosis.

## Genes involved and proteins

### Note

Genes involved as a primary event are still unknown. ATM and P53 are deleted in 11q and 17p deletions, respectively.

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