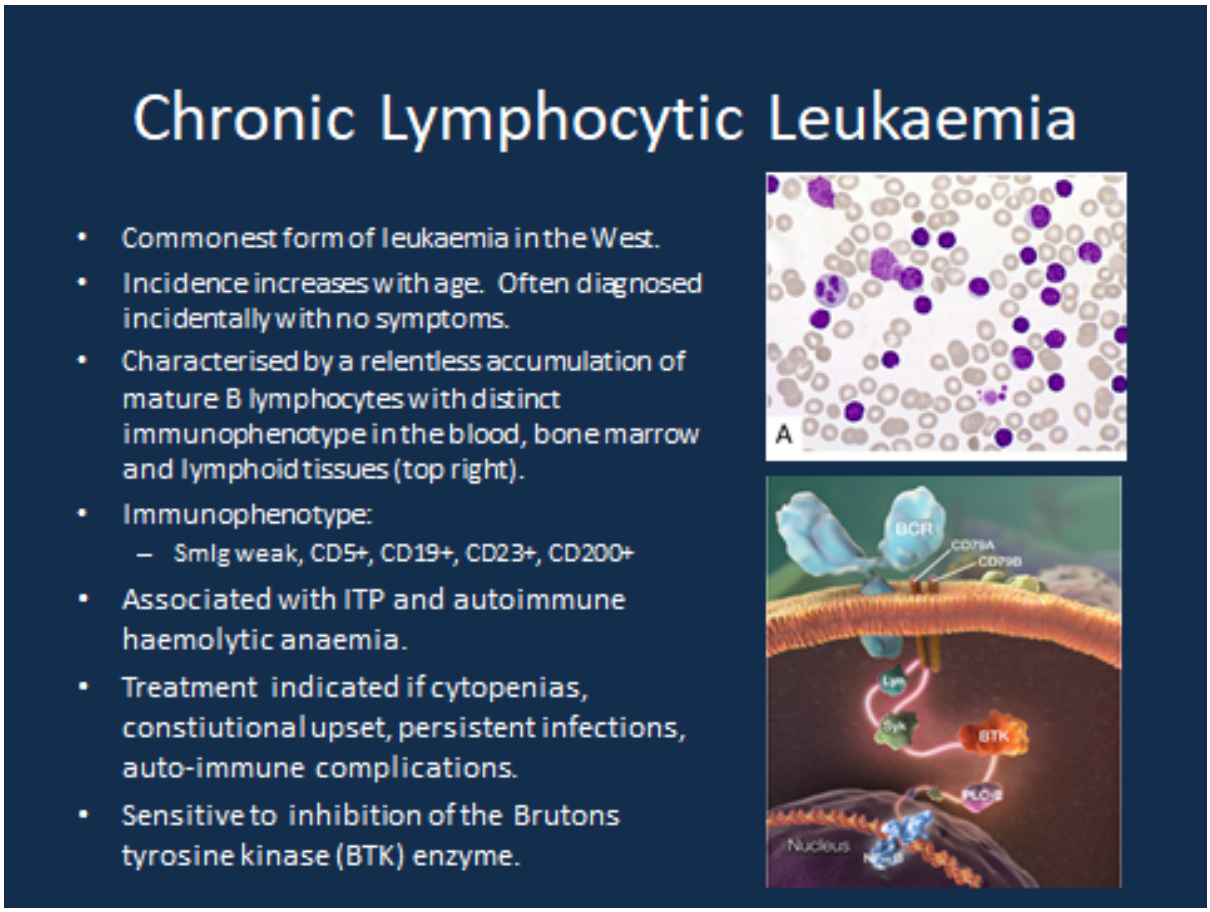

CLL and SLL (small lymphocytic leukaemia / lymphoma) are considered the same mature B-cell lymphoid neoplasm but differ in the extent to which they involve the blood (CLL) and lymphoid tissue (SLL). Most (99%) of CLL cells are not proliferating and are in $G_{0/1}$ phase of cell cycle but are resistant to apoptosis due to BCL-2 overexpression.

Epidemiology: most common form of leukaemia in the West. 4.2/100,000 p.a.; median age 70yrs, incidence dramatically increases with age. In Asia and far East, CLL is a rare disease.

Diagnosis: For CLL - lymphocytes >$5x10^9$/L sustained > 3 months with clonality confirmed (light-chain restriction by flow cytometry). For SLL – lymphadenopathy and absence of cytopenias caused by clonal marrow infiltrate and lymphocytes <$5x10^9$/L in blood. Immunophenotype – positive for CD5, CD19, CD20 (weak), CD23, and kappa or lambda light-chain-restricted (in borderline cases CD42, CD79b (weak), CD81, CD200, CD10 or ROR1 may help. Morphology - cells are mature, monomorphic small lymphocytes with smear cells (see image A).

Molecular genetics – important to exclude 17p deletion (respond poorly to conventional chemotherapy and eligible for a targeted therapy (BTK-inhibitor or bcl-2 inhibitor); most common chromosome abnormalities are 13q deletion, trisomy 12 and 11q deletion.

Immunoglobulin variable heavy chain (IGHV) may or may not be mutated (outcome is inferior if unmutated, particularly with FCR chemotherapy).

Clinical Features: Very heterogeneous clinical course. 80% are asymptomatic at diagnosis and many may not require treatment at all. Painless generalised peripheral lymphadenopathy is common. Auto-immune disorders such as ITP and haemolytic anaemia are relatively common in CLL due to the CLL cells ability to proliferate and produce antibody in response to self-antigens – a perversion of the normal B-cell response, but demonstration of a continued reliance on antigen and the B-cell receptor to proliferate and survive. Median survival is 10yrs but highly variable.

Staging is by the Rai or Binet classification systems based on cytopenias and clinically involved sites.

Treatment is reserved for those with active disease meeting at least 1 of the following criteria (see iWCLL guidelines):

1. Evidence of progressive marrow failure (progressive cytopenias)
2. Massive or progressive or symptomatic splenomegaly
3. Massive, progressive or symptomatic lymphadenopathy
4. Progressive lymphocytosis (>50% increase over 2 months or <6 month lymphocyte doubling time (only reliable once lymphocytes >30x10^9/L)
5. Autoimmune complications poorly responsive to steroids
6. Symptomatic or functional extranodal involvement (e.g. skin, lung, kidney, spine)
7. Disease related symptoms (weight loss, fatigue, fevers, night-sweats)

Treatment has been revolutionised by the recent development of targeted non-cytotoxic therapies such as Brutons tyrosine kinase inhibitors (ibrutinib, acalabrutinib), bcl2 inhibitors (venetoclax) and PI3k inhibitors (idelalisib) although the latter has fallen out of favour recently due to more toxicity than the former 2 agents. They do have some side-effects and are often used as continuous therapies (this may change) but are generally very well tolerated. Currently these agents are not available first-line on the NHS although this may change. Therefore most patients currently receive some immunochemotherapy as first line and then a targeted therapy at relapse (or clinical trial).

References

IWCLL Guidelines on the Diagnosis and Treatment of Chronic Lymphocytic Leukaemia

British Society for Haematology Guidelines on the Management of Chronic Lymphocytic Leukaemia

Author: Dr David Tucker