CHRONIC LEUKAEMIA

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Chronic myeloid leukaemia:

A myeloprolifrative stem cell disorder resulting in Proliferation of all haematopoietic lineages but manifestation Predominantly in the granulocytic series.
The disease occurs chiefly between 30 and 80 years, with A peak incidence at the 55 years.
***accounts for 15% of all leukaemis.**
***found in all races.**
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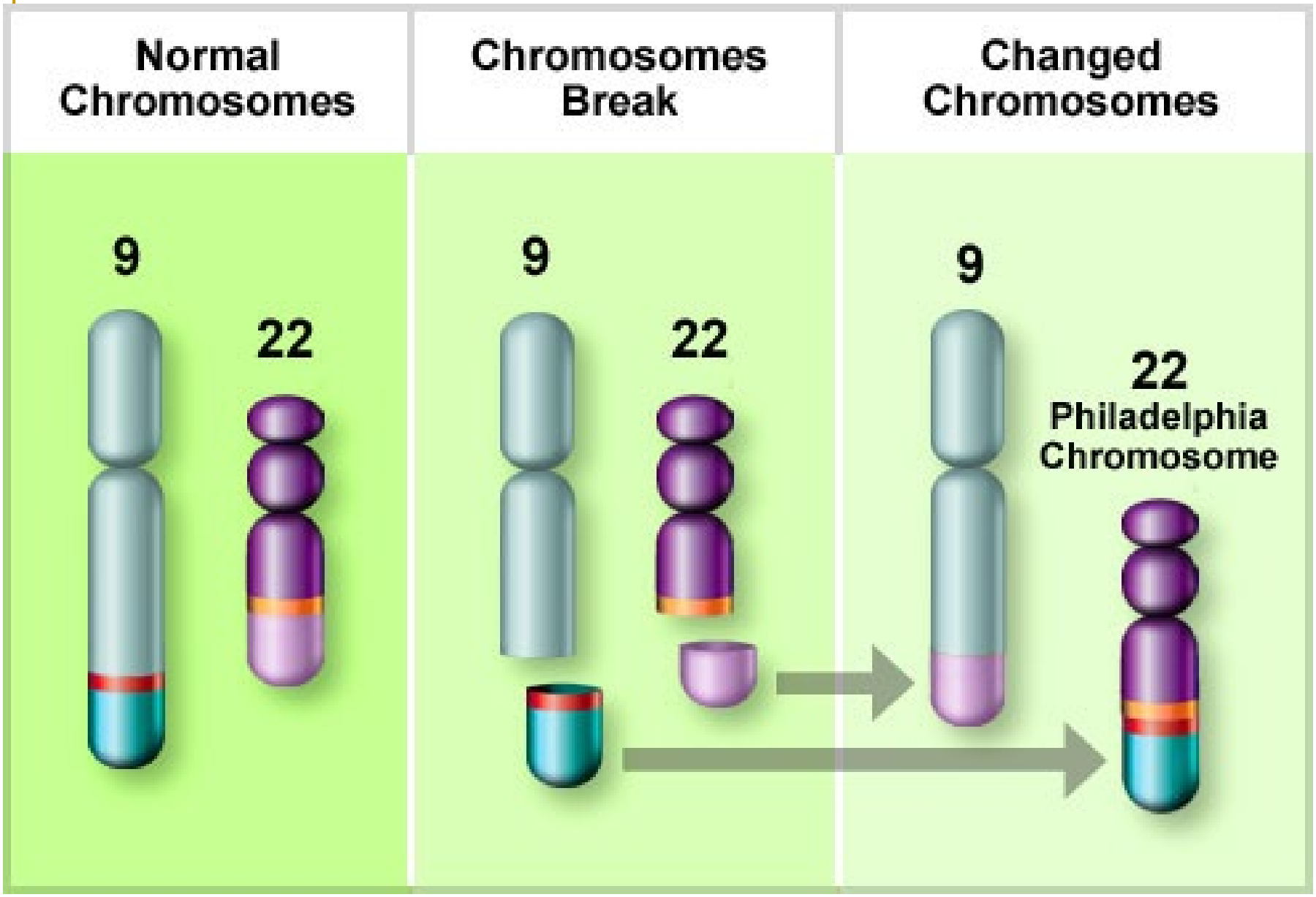
Cytogenetic and molecular aspects :

The defining characteristic of CML is a chromosome abnormality Known as the philadelphia (Ph) chromosome.
This is a shortened chromosome 22 and is the result of
A reciprocal translocation of material with chromosome 9.
The break on chromosome 22 occurs in the breakpoient Cluster region (BCR).the fragment from chromosome 9 that Joins the BCR carries the *abl* oncogene, which form a fusion Gene with the remains of the BCR.


Normal Chromosomes
Chromosomes Break
Changed Chromosomes
9
22
9
22
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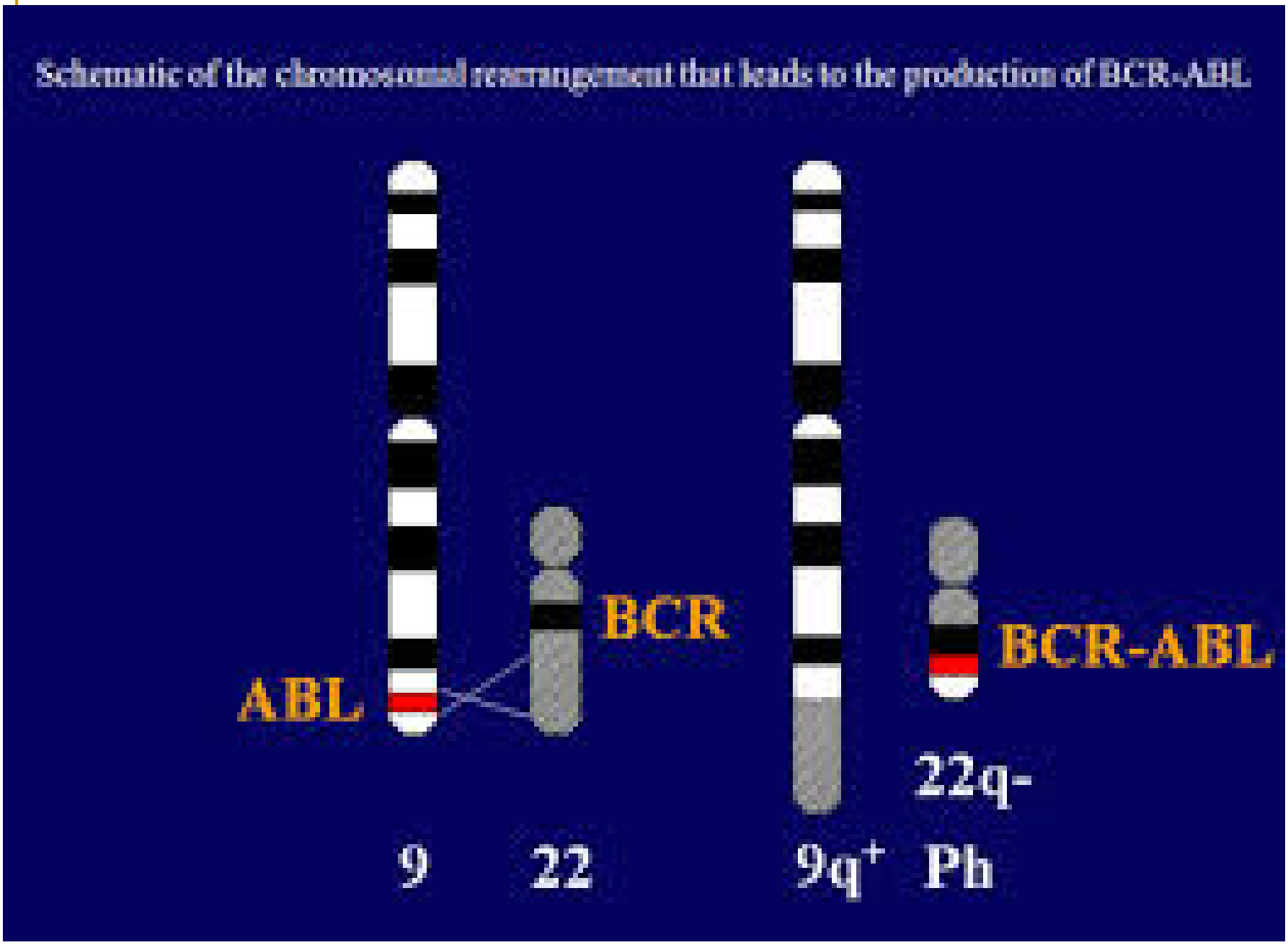
22
Philadelphia Chromosome


Schematic of the chromosomal rearrangement that leads to the production of BCR-ABL
ABL
BCR
BCR-ABL
9
22
9q+
22q-
Ph

This BCR ABL chimeric gene codes for a 210 kDa Protein with tyrosine kinase activity, which plays A causative role in the disease, influencing cellular Proliferation, differentiation and survival and is a target for very effective tyrosine kinase inhibitor (TKI) therapy .

In some apparently Ph chromosome –negative patients The BCR ABL gene product is detectable by molecular Techniques.

Natural history

The disease has three phases:

A chronic phase, *in which the disease is responsive to* treatment and is easily controlled, which used to last 3–5 years. With the introduction of tyrosine kinase inhibitors (TKI)therapy, this phase has been prolonged to encompass a normal life expectancy in many patients

An accelerated phase (not always seen),
in which disease control becomes more difficult.

Blast crisis,
in which the disease transforms into an acute leukaemia, either myeloblastic (70%) or lymphoblastic (30%), which is relatively refractory to treatment. This is the cause of death in the majority of patients; survival is therefore dictated by the timing of blast crisis, which cannot be predicted.

Prior to TKI therapy , approximately 10% of patients per year would transform; the transformation rate has been reduced to 0.5%–2.5% per year with TKI therapy.

Clinical features

Symptoms at presentation may include lethargy, weight loss, abdominal discomfort and sweating, but about 25% of patients are asymptomatic at diagnosis.

Splenomegaly is present in 90%; in about 10%, the enlargement is massive, extending to over 15 cm below the costal margin. A friction rub may be heard in cases of splenic infarction.

Hepatomegaly occurs in about 50%. Lymphadenopathy is unusual.

Approach Considerations

The workup for chronic myelogenous leukemia (CML) consists of a complete blood count with differential, peripheral blood smear, and bone marrow analysis. Although typical hepatomegaly and splenomegaly may be imaged by using a liver/spleen scan, these abnormalities are often so obvious clinically that radiologic imaging is not necessary.

The diagnosis of CML is based on the histopathologic findings in the peripheral blood and the Philadelphia (Ph1) chromosome in bone marrow cells. Findings from the workup—in particular, the percentage of blasts in peripheral blood or bone marrow—are used to determine the phase of CML: chronic, accelerated, or blast

Investigations:

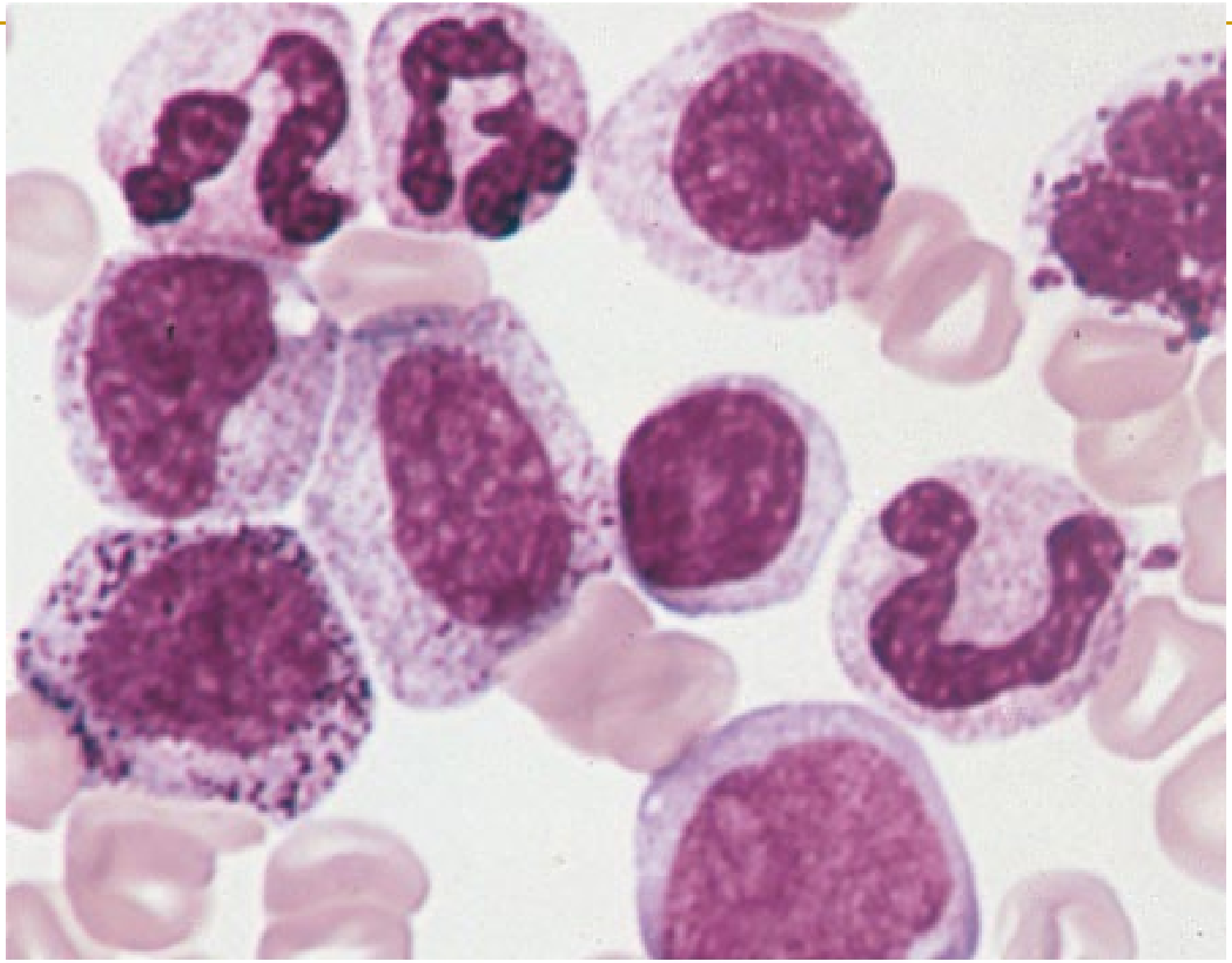
FBC results are variable between patients.
There is usually a normocytic, normochromic anaemia.
The leucocyte count can vary from 10 to 600 × 10^9/L. In about one-third of patients there is a very high platelet count, sometimes as high as 2000 × 10^9/L.

In the blood film the full range of granulocyte precursors from myeloblasts to mature neutrophils is seen but the predominant cells are neutrophils and myelocytes . Myeloblasts usually constitute less than 10% of all white cells.

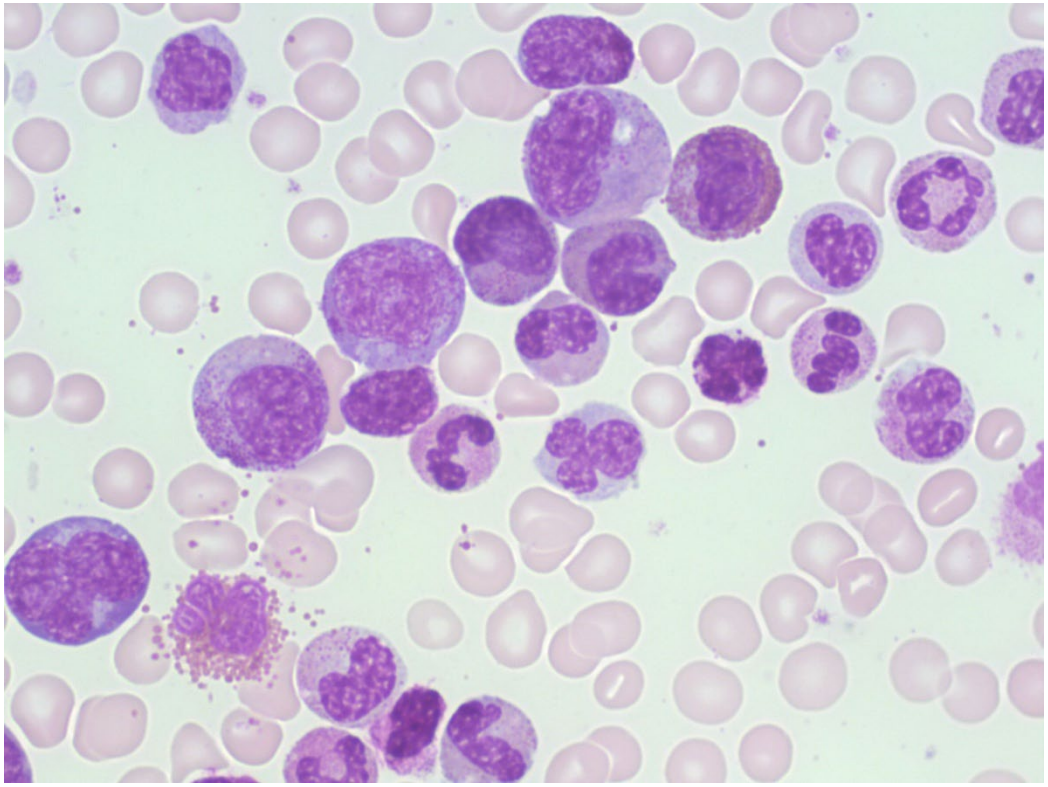
There is often an absolute increase in eosinophils and basophils, and nucleated red cells are common.

If the disease progresses through an accelerated phase, the percentage of more primitive cells increases.

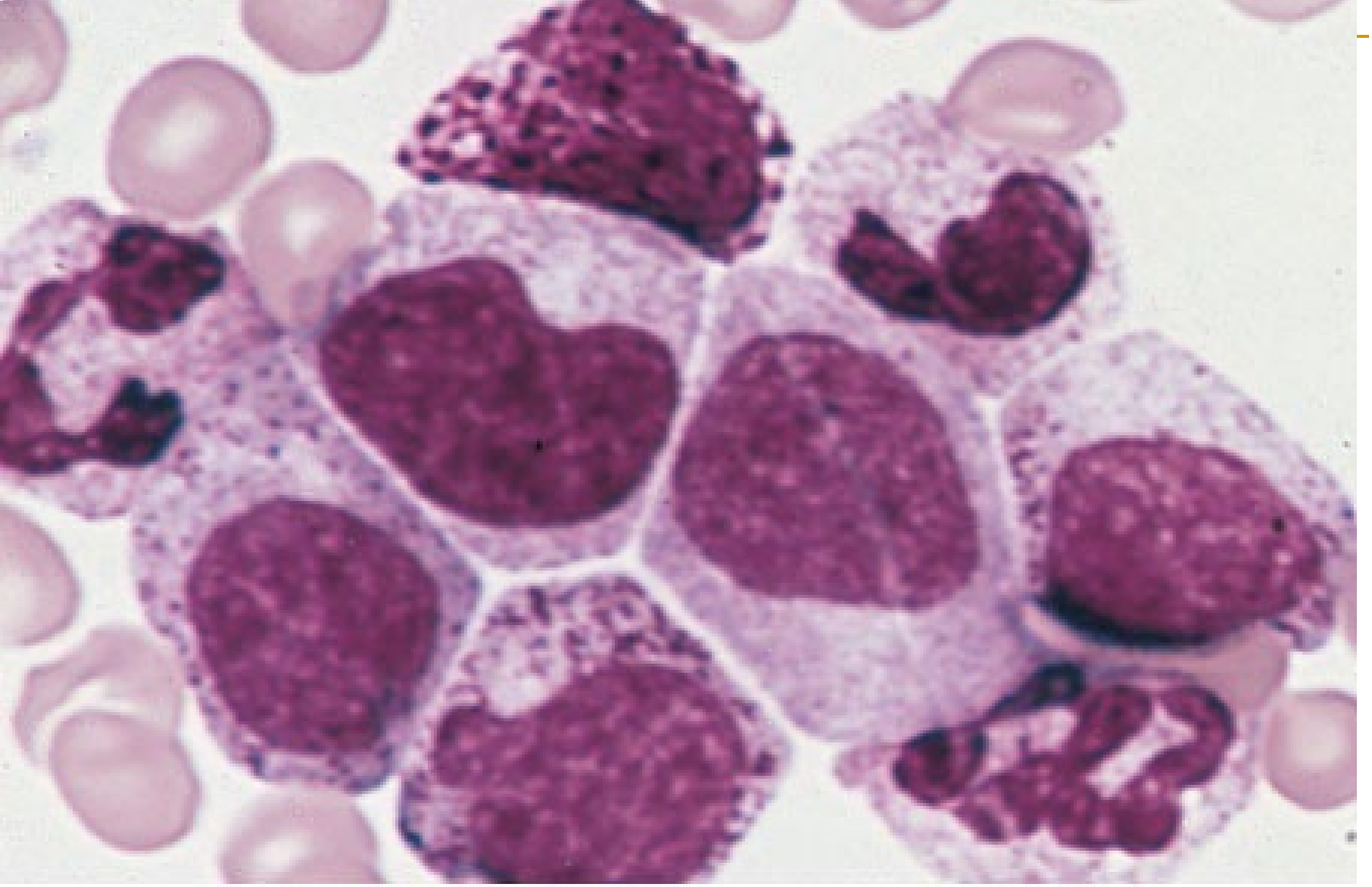
Blast transformation is characterised by a dramatic increase in the number of circulating blasts.



Source: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT: *Williams Hematology*, 7th Edition: http://www.accessmedicine.com



An image from a peripheral blood smear demonstrating a neutrophilia and myeloid precursors seen in CML. 500x oil immersion.



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Bone marrow should be obtained to:
1-confirm the diagnosis and phase of disease by morphology.
2- chromosome analysis to demonstrate the presence of the Ph chromosome.
3-and RNA analysis to demonstrate the presence of the BCR ABL gene product.
Blood LDH levels are elevated and the uric acid level may be high due to increased cell breakdown

Management

Chronic phase

There are now five available tyrosine kinase inhibitors (TKIs) for the treatment of CML .

These specifically inhibit BCR ABL tyrosine kinase activity. Imatinib, nilotinib and dasatinib are recommended as first-line therapy in chronic phase CML; they usually normalise the blood count within a month and within 3–6 months produce complete cytogenetic response (disappearance of the Ph chromosome) in some 90% of patients.

A sample of bone marrow is taken at 6 months to confirm complete cytogenetic response, and patients are subsequently monitored by 3-monthly real-time quantitative polymerase chain reaction (PCR) for BCR ABL mRNA transcripts in blood.

The aim is to reduce the BCR ABL transcript levels by 3–5 logs from baseline and this is called major molecular response (MR3–MR5).

A proportion of patients achieve a complete molecular response where the transcripts are not detectable by PCR.

It may be possible for patients with a complete or a major molecular response to stop TKI therapy and this is being investigated in clinical trials. For those failing to respond or who lose their response and progress on first-line therapy, options include switching to a different TKI . Some patients develop detectable mutations in the *BCR ABL gene, which renders them resistant to* one or more of the TKIs.

The T315I mutation has been particularly problematic, as this provides wide-ranging resistance.

The third-generation TKI ponatinib is effective.

Allogeneic HSCT is now reserved for patients who fail TKI therapy.

Hydroxycarbamide and interferon were previously used for control of disease. Hydroxycarbamide is still useful in palliative situations and interferon is used in women planning pregnancy.

Tyrosine kinase inhibition in chronic myeloid leukaemia

Agents

First-line

- Imatinib
- Dasatinib
- Nilotinib

Second-line

- Imatinib
- Bosutinib
- Nilotinib
- Ponatinib*
- Dasatinib

Outcomes

- 90% achieve complete cytogenetic response
- Responses faster with nilotinib and dasatinib
- Median survival comparable to normal population

*For patients with T315I kinase domain mutations use ponatinib

Accelerated phase and blast crisis

Management is more difficult. For patients in accelerated phase, TKI therapy is indicated, most commonly with nilotinib or dasatinib. When blast transformation occurs, the type of blast cell should be determined. Response to appropriate acute leukaemia treatment is better if disease is lymphoblastic than if myeloblastic.

Second- or third-generation TKIs such as dasatinib are used in combination with chemotherapy to try and achieve remission. In younger and fitter patients an allogeneic HSCT is appropriate therapy if a return to chronic phase is achieved. Hydroxycarbamide can be an effective single agent and low-dose cytarabine can also be used palliatively in older patients.

Chronic lymphocytic leukaemia (CLL)

-is the most common variety of leukaemia, accounting for 30% of cases.

- The male-to-female ratio is 2:1

-the median age at presentation is 65–70 years.

CLL is characterised by the clonal expansion of small mature-looking B cells. Failure to apoptose because of overexpression of BCL-2 and in some cases mutations in TP53 leads to an ever-increasing accumulation of immuno-incompetent leukaemic B cells.

This is to the detriment of immune function and normal bone marrow haematopoiesis. CLL cells are dependent on abnormal and persistent signalling through the B-cell receptor (BCR) pathway. Drugs that can inhibit these pathways are now available and show great promise .

Clinical features :

The onset is very insidious.
In around 70% of patients the diagnosis is made
Incidentally on a routine full blood count.
Presenting problems may be anaemia, infections,
Painless Lymphadenopathy and systemic symptoms
Such as night sweats or weight loss.
those more often occur later in the progress of
Disease or in disease that is advanced at presentation.

Investigations

the diagnosis is based on the peripheral blood finding of

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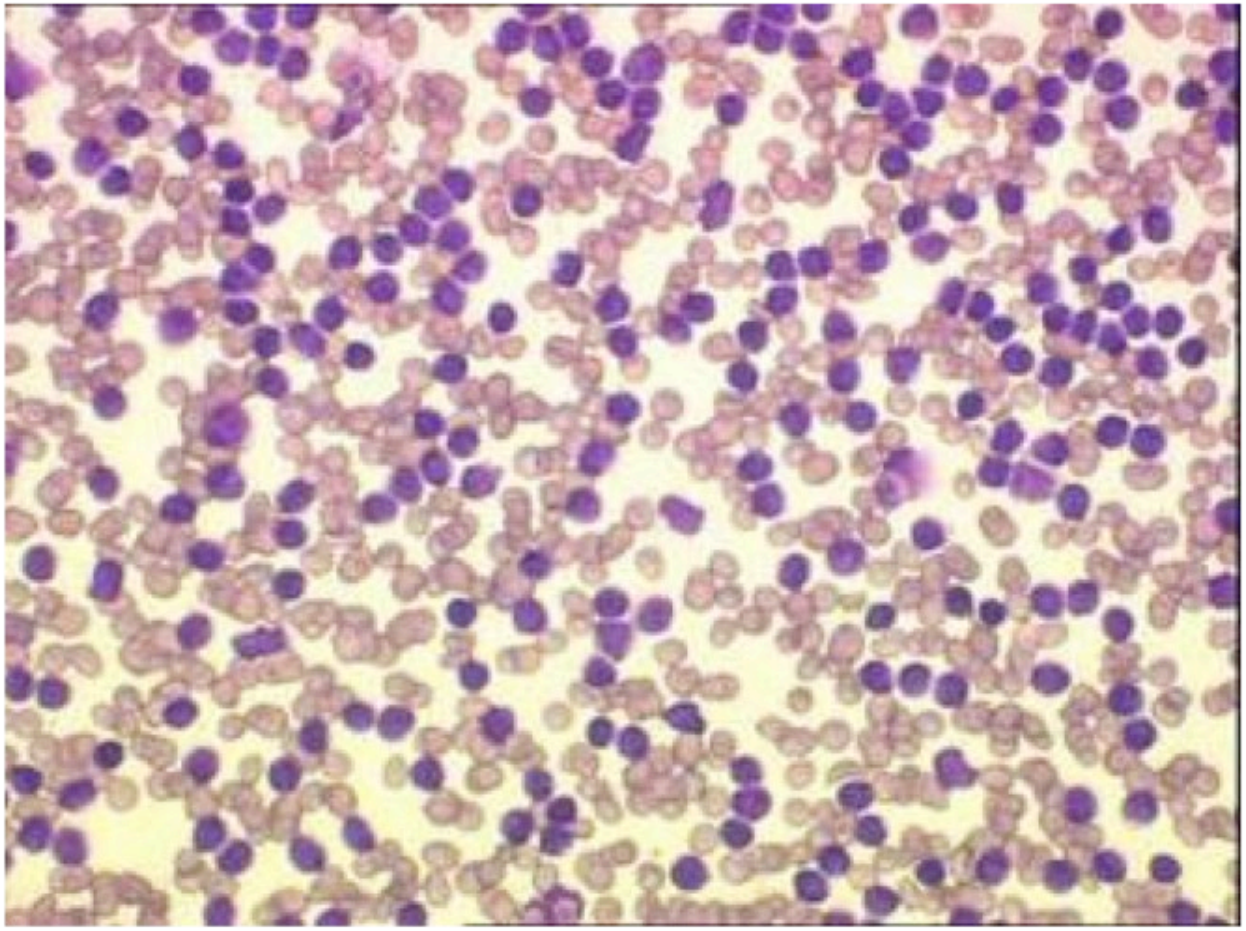
A mature lymphocytosis(more than 5x10/l)with
Characteristic morphology and cell surface markers.
Immunophenotyping reveals the lymphocytes to be
Monoclonal B –cells expressing the b-cell antigens CD19
And CD23 with either kappa or lambda immunoglobulin
Light chains and, characteristically , T-cell antigen, CD5 .

On flowcytometry, some people are shown to have circulating CLL cells at a level less than 5 × 109/L.
This is knownas monoclonal B lymphocytosis of uncertain significance (MBL). Such patients progress to CLL at a rate of 1% per year.



CLL blood film morphology

OTHER TEST :

Reticulocytosis and positive direct coombs test as autoimmune Haemolytic anaemia may occur.

Serum immunoglobulin level should be estimated to establish the Degree of immunosuppression.

***bone marrow examination by aspirate and trephine is not essential For the diagnosis of CLL , but may be helpful in difficult cases, for Prognosis(diffuse marrow involvement tend to do worse) and to Monitor response to therapy.**

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The main prognostic factor is a stage of the disease

however, loss of chromosome 17p or mutation in the TP53 gene, which resides at this genetic locus, is a powerful prognostic marker and predictor of response to therapy.

A mutation in TP53 is present in < 10% of patients at presentation but rises to 30% of cases at relapse. This test should be performed in all patients prior to the initiation of therapy

Staging of CLL :

Clinical stage A (60% of patients)

*no anaemia or thrombocytopenia and less than three areas of Lymphoid enlargement.

Clinical stage B (30% of patients)

*no anemia or thrombocytopenia, with three or more involved areas of Lymphoid enlargement.

Clinical stage C (10% of patients)

*anaemia and /or thrombocytopenia, regardless of the number of areas of Lymphoid enlargement.

Management

No specific treatment is required for most clinical stage A patients, unless progression occurs. Life expectancy is usually normal in older patients. The patient should be offered clear information about CLL and be reassured about the indolent nature of the disease, as the diagnosis of leukaemia inevitably causes anxiety.

Treatment is only required if :

***there is evidence of bone marrow failure**
***massive or progressive Lymphadenopathy or splenomegaly .**
***systemic symptoms such as weight loss or night sweats.**
***a rapidly increasing lymphocyte count.**
***autoimmune haemolytic anaemia or thrombocytopenia .**

Initial therapy for those requiring treatment (progressive stage A and stages B and C) is based on:
1-the age
2-fitness of the patient
3-the *TP53 mutation status.*
For patients who are under 70 years, fit and *TP53 mutation negative,* fludarabine in combination with the alkylating agent cyclophosphamide and the anti-CD20 monoclonal antibody rituximab (FCR) is standard care.

For older, less fit patients, rituximab is combined with gentler chemotherapy: bendamustine or oral chlorambucil. Recently, a more potent type 2 anti-CD20 antibody, obinutuzumab, has become available and produces better responses in combination with chlorambucil than rituximab.

Ibrutinib inhibits Bruton's tyrosine kinase and idelalisib inhibits PI3 kinase, both components of the BCR pathway .

Ibrutinib and idelalisib are licensed for relapsed CLL, but are effective in TP53 mutated disease at all stages

Ibrutinib is first-line standard of care in TP53-mutated CLL. CLL cells are resistant to apoptosis and express increased levels of anti-apoptotic proteins, including BCL-2.

Venetoclax is an inhibitor of BCL-2 and is so effective at killing CLL cells that it frequently causes tumour lysis syndrome when first administered.

Venetoclax is licensed in combination with obinutuzumab for the treatment of adult patients with previously untreated CLL and is attractive as it is given for a fixed period of two years.

Venetoclax can also be used for patients with TP53 mutation or who have failed previous therapy.

Bone marrow failure or autoimmune cytopenias may respond to glucocorticoid treatment or rituximab.

Supportive care is required in:

***progressive disease, e.g. transfusion for symptomatic Anaemia or thrombocytopenia.**
***prompt treatment of infections and for some patients With hypogammaglobulinaemia, immunoglobulin Replacement.**
Radiotherapy may be used for lymph nodes causing Discomfort or local obstruction , and for symptomatic Splenomegaly.
Splenectomy may be required to improve low blood Counts due to autoimmune destruction or to Hypersplenism, and can relieve massive splenomegaly.

Prognosis

The majority of clinical stage A patients have a normal life expectancy but patients with advanced CLL are more likely to die from their disease or infectious complications. Survival is influenced by prognostic features of the leukaemia, particularly *TP53 mutation status, and whether patients can tolerate and* respond to fludarabine-based treatment. In those able to be treated with chemotherapy and rituximab, 90% are alive 4 years later. Rarely, CLL transforms to an aggressive high-grade lymphoma, called Richter's transformation.

Prolymphocytic leukaemia

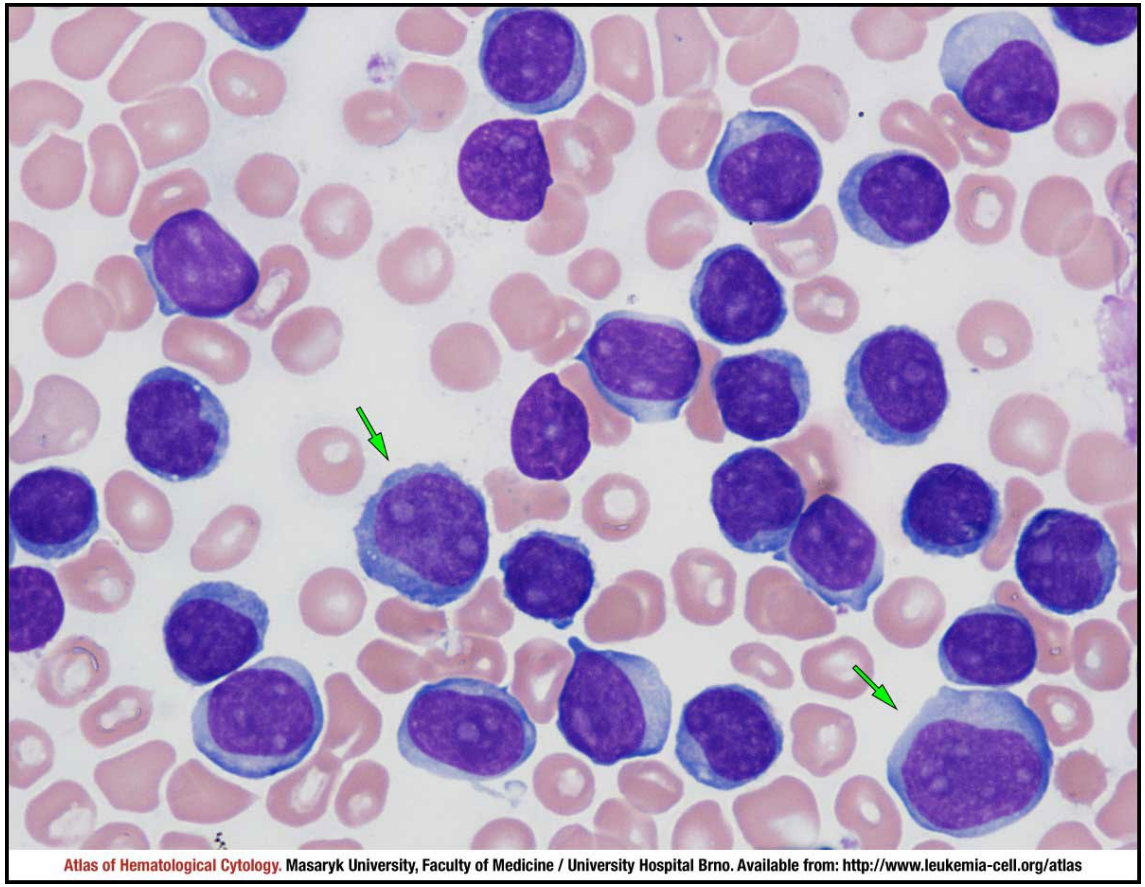
Prolymphocytic leukaemia (PLL) is a form of chronic leukaemia found mainly in males over the age of 60 years; 25% of cases are of T cell origin.

There is typically massive splenomegaly with little lymphadenopathy and a very high leucocyte count, often in excess of 400 × 109/L.

Effusions and involvement of skin are well recognized.

The characteristic cell is a large lymphocyte with a prominent nucleolus.

Treatment is generally unsuccessful and the prognosis very poor



Peripheral blood smear with marked leukocytosis. The majority of cells are medium-sized lymphoid elements with round nuclei, visible nucleoli and relatively abundant and basophilic cytoplasm. Green arrows mark larger atypical prolymphocytes.

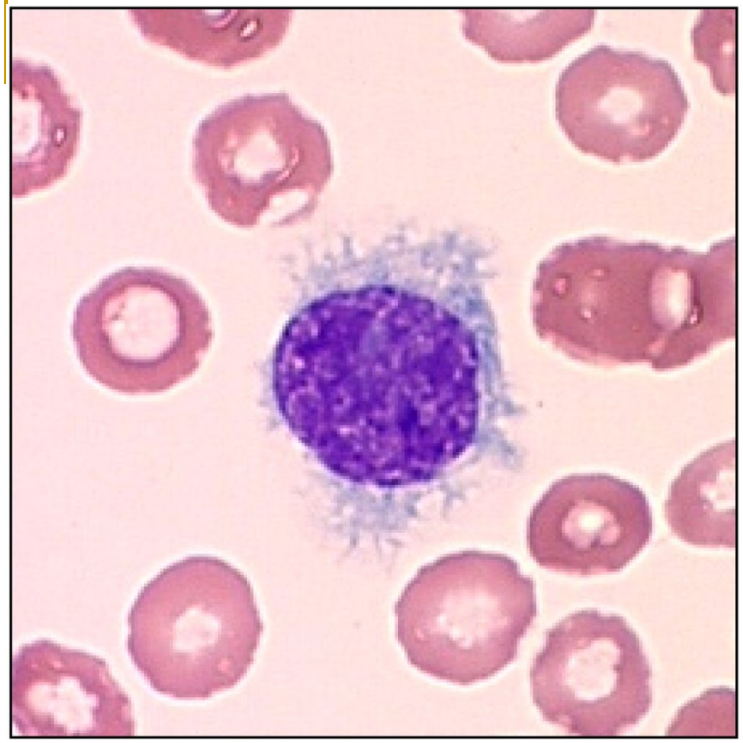
Leukapharesis, splenectomy and chemotherapy may be tried. The anti-CD52 antibody alemtuzumab, when given intravenously, has produced responses in some 90% of patients with T-PLL. Younger patients who respond to treatment may be considered for allogeneic HSCT.

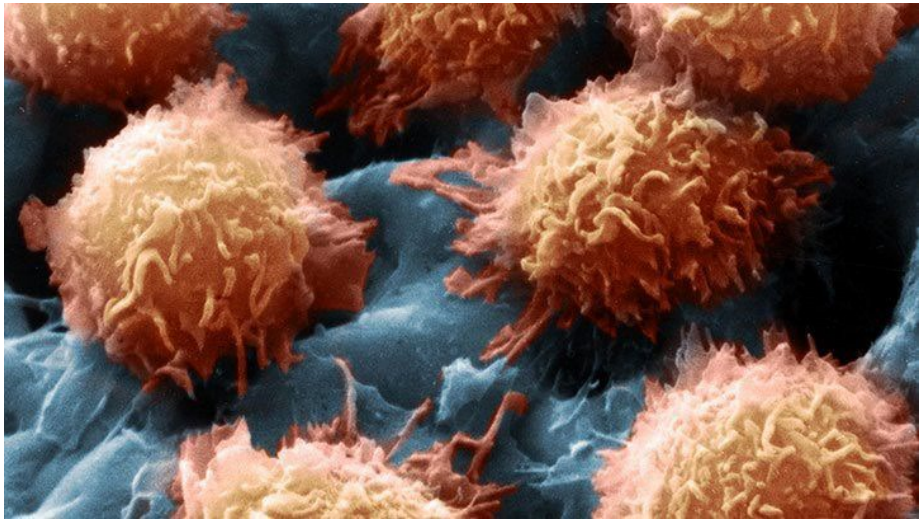
Hairy cell leukaemia

This is a rare chronic B-cell lymphoproliferative disorder. The maleto- female ratio is 6:1 and the median age at diagnosis is 50 years.

Presenting symptoms are general ill health and recurrent infections.

Splenomegaly occurs in 90% but lymph node enlargement is unusual.





Hairy cell leukaemia

Severe neutropenia, monocytopenia and the characteristic hairy cells in the blood and bone marrow are typical. These cells usually have a B-lymphocyte immunotype, but they also characteristically express
CD25 and CD103. Recently, all patients with hairy cell leukaemia have been found to have a mutation in the BRAF gene and this may become a therapeutic target. Chemotherapy treatments such as cladribine and deoxycoformycin can produce long-lasting remissions.

THANK YOU