Leukaemia

Leukaemia encompasses a group of malignant disorders of haemopoietic tissues associated with increased numbers of primitive white cells, initially within the bone marrow and then spilling into the peripheral circulation.[1] This review will cover the incidence, presentation, diagnosis and a brief overview of management of the most common acute and chronic leukaemias seen in primary and non-specialist secondary care.

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The incidence of all leukaemias is 10 per 100 000 per annum[1] and leukaemia accounts for 2.5% of all cancers.[2] Leukaemia can be divided into acute and chronic forms, which relates to the speed of onset of symptoms and treatments available. The acute and chronic forms can be divided into myeloid and lymphoid subtypes.

In all forms of leukaemia symptoms are due to white cell and bone marrow dysfunction. Accurate diagnosis is crucial in order to start appropriate treatment and helps with prognosis. Confirmation of the type of leukaemia is with blood tests, blood film, bone marrow aspirate and trephine, cytogenetics (presence of gene mutations) and immunotyping (identifying specific cell surface markers). Management should be multi-disciplinary.

Acute leukaemia

Acute leukaemias encompass acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML) and a subset of AML, acute promyelocytic leukaemia (APML). Acute leukaemias present with symptoms over days and weeks with signs of systemic upset, weight loss, fever, malaise, bruising and bleeding. The underlying leukaemia cannot be diagnosed on clinical examination alone. At presentation white count can be less than $1x10^9$/L but also greater than $500x10^9$/L.[1] Acute leukaemias are aggressive and rapidly progressive without intervention. In patients under the age of 60 years, 80% will be able to achieve remission, however, prognosis is poorer in older patients, with high relapse rates.[1,3]

Acute lymphoblastic leukaemia (ALL)

Less than 1% of leukaemias are due to ALL, and 550 new cases are diagnosed per year[2,4] with an incidence of 1.7 per 100,000 per annum.[5] There is a bimodal presentation of ALL, first in childhood and then in people over the age of 60 years. In the older age group ALL occurs as a result of acute transformation of a chronic haematological disease process, usually chronic myeloid leukaemia (CML).[3] Men are affected slightly more frequently than women in a 1.5:1 ratio and ALL occurs more frequently in people of northern European origin. Trisomy 21 and Fanconi's disease are also associated more commonly with ALL. At presentation, frequently there is bone marrow failure and central nervous system involvement in 10% of patients, which is diagnosed by cerebrospinal fluid (CSF) analysis.

Diagnosis is made on routine blood tests, blood film and confirmed with a bone marrow biopsy, trephine, cytogenetics and immunotyping. CSF may also be obtained, which may confirm spread to the central

Box 1: Sub-division of the main leukaemias

	Lymphoid	Myeloid
Acute	Acute lymphoblastic leukaemia	Acute myeloid leukaemia
Chronic	Chronic lymphocytic leukaemia	Chronic myeloid leukaemia

Box 2: French-American-British classification of Acute Myeloid Leukaemia

M0 = Acute myeloid leukaemia with minimal evidence of myeloid differentiation

M1 = Acute myeloblastic leukaemia without maturation

M2 = Acute myeloblastic leukaemia with maturation

M3 = Acute promyelocytic leukaemia (APML)

M4 = Acute myelomonocytic leukaemia

M5 = Acute monocytic/ monoblastic leukaemia

M6 = Acute erythroleukaemia

M7 = Acute megakaryoblastic leukaemia

nervous system by the presence of lymphoblastic cells in the CSF. Based on these results, ALL can be further sub-divided with immunotyping into an abnormality of B cells, T cell, pre B cells or undifferentiated cells. Additionally, the presence of the Philadelphia chromosome (detected with cytogenetics) also affects treatment options. Philadelphia chromosome is the name given to a genetic translocation between chromosome 9 and 22. The fusion gene created leads to an activation of the enzyme tyrosine kinase, and this can be targeted by some chemotherapeutic agents. Philadelphia chromosome is only present in 20% ALL cases,[2] but is found in most cases of chronic myeloid leukaemia.

Treatment in all forms of ALL is with supportive measures (treating anaemia, infections, coagulopathies) and is aimed at inducing remission with chemotherapy—some drugs used include vincristine (Oncovin), corticosteroids, cyclophosphamide, etoposide, or asparaginase. In Philadelphia positive disease, treatment is with monoclonal antibodies—imatinib (Glivec).[1,3] Cure can also be achieved with bone marrow transplantation. Radiotherapy is used usually pre-bone marrow transplantation. However, in B cell ALL, despite standard chemotherapy or autologous bone marrow transplant, long term survival may not be achieved.[4] Cure rates are 80% in children and 45–60% in adults.[2]

Acute myeloid leukaemia

AML has an incidence of three per 100 000 per annum,[3] increasing to 20 per 100 000 in those over the age of 80 years. Peak age of incidence is over 50 years of age and it affects both genders equally. Underlying myelodysplasia is a risk factor for the development of AML. It is the most common acute leukaemia in adults.

Diagnostic findings are the presence of Auer rods (rod shaped granules found within the cytoplasm of the granulocyte cell) on bone marrow trephine and evidence of hypercellular activity due to the presence of the immature cells within the bone marrow. The presence of Auer rods can help differentiate AML from ALL. AML is divided into types using the French-American-British (FAB) classification.[1]

The goal of treatment, as in ALL, is to induce remission, but supportive measures may be required. Patients are encouraged to enrol into specialist chemotherapy trials and

Box 3: Poor prognostic indicators in acute leukaemia:

Advanced age

Male gender

High WCC at presentation

Prior haematological malignancy

Relapsed disease

Central nervous system involvement

Multiple genetic abnormalities

agents such as anthracyclines, hydroxyurea and monoclonal antibiodies may be used such as gemtuzumab ozogamicin (Mylotarg) or imatinib.[5] Without treatment mortality is high, with a life expectancy of five weeks.[1] With treatment, remission can increase survival to 30 months. If age of presentation is under 55 years, there is a 40% survival.[1]

Acute promyelocytic leukaemia

APML is a subset of AML. It can occur in adults of any age. Treatment is with all-trans-retinoic-acid (ATRA) which promotes cell differentiation. Gemtuzmab ozogamicin can also be used. Cure rate is 70%.

Chronic leukaemia

Unlike acute leukaemia, symptoms in chronic leukaemia present insidiously over weeks, months and sometimes even years. Patients may be asymptomatic or have symptoms of malaise, fatigue, weight loss, night sweats, patients may also have tender lymph nodes and abdominal distension from splenic enlargement.

Box 4: Adapted from the Binet staging system[9]

Stage	High white cell count	Anaemia or thrombocytopenia	Lymph node involvement	Frequency	Survival
A	Yes	No	Less than 3 areas	63%	Greater than 10 yrs
B	Yes	No	More than 3 areas	30%	5 years
C	Yes	Yes	Extensive	7%	1.5–3 years

Chronic myeloid leukaemia (CML)

CML has an annual incidence of one per 100 000 per annum[6] with 700 new cases per year[2] and is slightly more common in men than women (1.3:1). Peak incidence is at age 55 years, but can affect people from the age of 30–80 years. CML is associated with prior exposure to a high dose of ionising radiation treatment given for treatment of a previous cancer.

Symptoms are of systemic upset, fatigue, weight loss and sweating. On examination the most consistent sign is that 90% of patients have splenomegaly.

Diagnosis is confirmed with bone marrow aspirate and trephine. However, on routine blood film thrombocytosis, anaemia, granulocytes and myeloblasts may be detected. White cell count is usually $20\text{-}30 \times 10^9$/L. 90–95% of patients have the Philadelphia chromosome.

Philadelphia chromosome (Ph)

As mentioned earlier in the review, Ph is a genetic abnormality due to a translocation between chromosome 9 and 22, this results in activation of a gene at the site of fusion—the BCR-ABL1 gene (break cluster region and Ableson gene). BCR-ABL1 is involved in tyrosine kinase activation.[6] Tyrosine kinase is an enzyme which, unchecked, allows genetic mutations to be propagated and increases the overall number of abnormal cells surviving.

Treatment in CML is aimed at the chronic phase of the disease, when the cells are most chemosensitive. This phase can last 10–20 years and treatment is with imatinib, which is a tyrosine kinase inhibitor. Response to treatment is evaluated by repeat bone marrow and measurement of BCR-ABL1 levels. After 10–20 years the disease progresses to an accelerated phase and then the blast phase when there is transformation to an acute leukaemia—30% ALL and 70% AML. Death usually occurs from a crisis due to acute transformation.

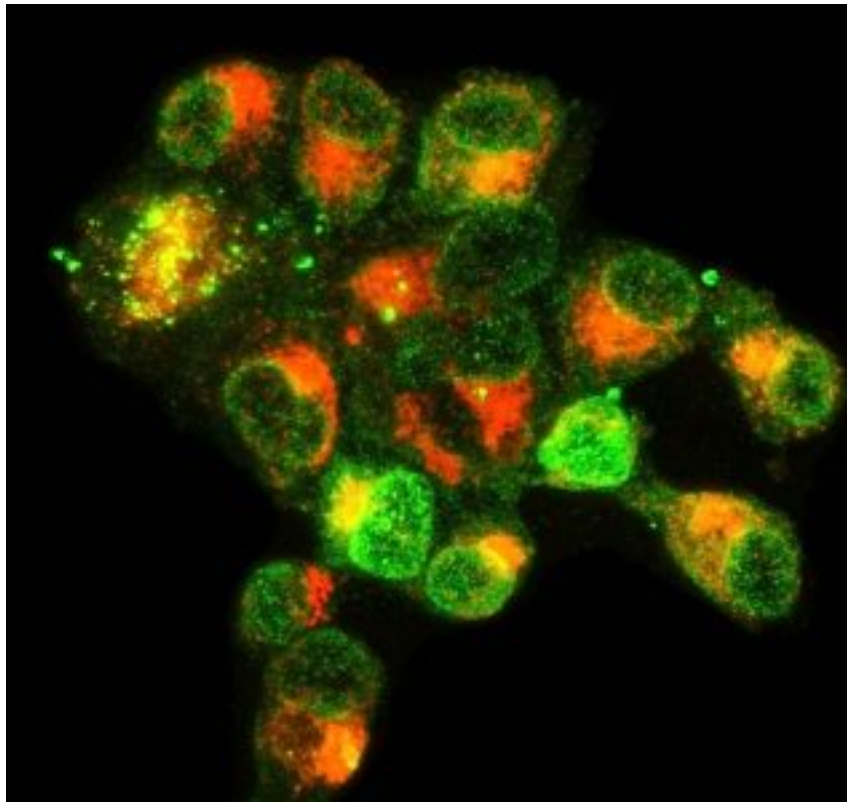
CML resistant to imatinib can be treated with second line therapies such as busalfan, hydroxyurea and alpha interferon. In selected cases patients may also be suitable for bone marrow transplant (aged under 60 years). Poor prognostic factors are male gender, BCR negative disease and low platelets. The survival of patients with CML sensitive to imatinib is 70% at 10–15 years.[1]

Chronic lymphocytic leukaemia (CLL)

CLL is the most common leukaemia with an incidence of 3 per 100,000[7] and 2750 new cases diagnosed per year[2] and affects both genders equally. There is a familial and genetic predisposition, although the causative genes are still unknown. It is an abnormality of B cell expansion, and results in an increase in lamda and kappa chain production (proteins involved in antibody production). CLL is most often (in 25% of patients) diagnosed incidentally[7] on routine blood tests and a diagnosis of CLL can be made when white cell count is greater than 5×10^9/L[4] for more than three months. Patients may be asymptomatic or have constitutional symptoms of weight loss, sweats, lymphadenopathy and abdominal pain. On examination depending on the stage of the disease, there may be no signs, evidence of palpable lymph nodes or splenomegaly.

Diagnosis is made on blood film by the presence of smear or smudge cells and the morphology of the white cell is confirmed. It is rare to proceed to bone marrow aspirate or trephine as blood film is diagnostic. Additionally on blood film there may be evidence of autoimmune haemolysis (anaemia due to the abnormal white cells attacking the red cells in the body) and raised beta-2-microglobulin levels (from lamda and kappa production by the lymphocytes) on immunophoresis.

Treatment depends on the stage of the disease and symptoms. Two different staging systems are used Binet (UK and Europe) and



Rai (USA) to determine the stage of the disease.

Medications used are oral chlorambucil (Leukeran), steroids and pain relief for splenomegaly and lymph node enlargement. There can be a role for surgery for massive and painful splenomegaly. Patients under the age of 65 years are most often enrolled into clinical trials to assess treatment. [7]

However, early treatment is indicated if there are features of autoimmune haemolysis present, but often CLL is a slowly progressing disease and no treatment is required. If autoimmune features are present steroid therapy can be started. Occasionally CLL can transform to hairy leukaemia or a diffuse large B cell lymphoma.[7] Poor prognosis is found in patients with high beta-2-microglobulin levels and un-mutated disease. Overall five year survival for all stages of CLL is 50%.[1]

Hairy cell leukaemia

This is a rare leukaemia compromising 2% of all B cell leukaemias.[7] It most commonly affects people in their 50s and has a male to female ration of 6:1. Symptoms are of left upper quadrant pain, evidence of immunocompromise, vasculitis and evidence of splenomegaly on examination.

Blood film typically shows reduction in neutrophils, monocytes and the presence of hairy cells and the B cells express surface antigens CD25 and FMC7. Treatment is with cladridine (purine analogue), deoxycoformycin (anti-metabolite), Beta interferon, pentostalin (Nipent) and in second line therapy rituximab (MabThera) or other anti CD22/25 specific monoclonal antibodies. Unfortunately due to the rarity of the disease, no consistent cytogenetic abnormalities have been found. There is 90% survival at 10 years.[7,8]

Summary

Leukaemia is rare cause of cancer in older people, but should be considered when patients present with non-specific symptoms or persistently abnormal blood tests. Mortality is high in the acute leukaemias thus underpinning the need for early and accurate diagnosis. AML is the most common acute leukaemia and CLL the most common chronic leukaemia. Management of leukaemia is multi-disciplinary but primarily lead by haematologists. Prognosis is dependent on age and type of leukaemia, but with poor prognosis in older people.

Conflict of interest: none declared

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