ABC of clinical haematology

The acute leukaemias

R J Liesner, A H Goldstone

Acute leukaemia is a clonal (that is, derived from a single cell) malignant disorder affecting all age groups from infancy to old age. It is characterised by the accumulation of abnormal white blood cells in the bone marrow which replace normal marrow tissue, including haemopoietic precursor cells. This results in bone marrow failure and peripheral blood involvement. Infiltration of various organs is also a feature of some forms of leukaemia.

In most cases the aetiology is not obvious, but some constitutional and acquired disorders do predispose to acute leukaemia.

In the past 40 years advances in the treatment of acute leukaemia have improved the chance of cure from virtually zero to 20-75%, depending on age and type of leukaemia. This has largely been the result of clinical trials—many of which are still ongoing—and the development and continued improvements in bone marrow transplantation.

Classification

Acute leukaemia is subdivided into (a) acute lymphoblastic leukaemia, in which the abnormal proliferation is in the lymphoid progenitor cells (that is, immature lymphocytes) and (b) acute myeloid leukaemia, which involves the myeloid lineages (that is, cells from which neutrophils, eosinophils, monocytes, basophils, megakaryocytes, etc are derived). The distinction between the two leukaemias is based on morphological, cytochemical, and immunological differences and is of paramount importance as the treatment and prognosis are usually different.

Both acute lymphoblastic leukaemia and acute myeloid leukaemia are further subdivided on the basis of morphological criteria: acute lymphoblastic leukaemia into FAB (French-American-British) subtypes L1, L2, and L3 and acute myeloid leukaemia into FAB subtypes M0 to M7.

On the basis of surface antigen expression acute lymphoblastic leukaemia is divided into T cell lineage and B cell lineage. B cell lineage is further subdivided: early B precursor acute lymphoblastic leukaemia is the most immature and is negative for the common acute lymphoblastic leukaemia antigen (CD10); common acute lymphoblastic leukaemia and pre-B cell acute lymphoblastic leukaemia are more mature and are CD10 positive; and B cell acute lymphoblastic leukaemia is the most mature and is the only one to express surface immunoglobulin. Little correlation exists between morphological subtype and immunophenotype or prognosis in acute lymphoblastic leukaemia, except that L3 morphology is almost exclusively found in B cell acute lymphoblastic leukaemia.

In acute myeloid leukaemia immunophenotyping may not help to distinguish between leukaemias of the myeloid (M0 to M3), the myelomonocytic (M4), and the monocytic (M5) lineages, and special cytochemical stains are usually used to support morphological findings. In erythroleukaemia (M6) and megakaryoblastic leukaemia (M7), however, the surface antigen expression is often diagnostic.

Aetiological factors in acute leukaemia

- Unknown (usually)
- Hereditary
 - Down's syndrome
 - Bloom's syndrome
 - Fanconi's anaemia
 - Ataxia telangiectasia
 - Klinefelter's syndrome
 - Osteogenesis imperfecta
 - Wiskott-Aldrich syndrome
 - Leukaemia in siblings
- Chemicals
 - Chronic benzene exposure
 - Alkylating agents (chlorambucil, melphalan)
- Radiation
- Predisposing haematological diseases (myeloproliferative disorders, myelodysplasia, and aplastic anaemia).
- Viruses (HTLV-I causing adult T cell leukaemia/lymphoma)

FAB* 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
M4	Acute myelomonocytic leukaemia
M5	Acute monocytic/monoblastic leukaemia
M6	Acute erythroleukaemia
M7	Acute megakaryoblastic leukaemia

*French-American-British

Blood film of patient with acute lymphoblastic leukaemia.

Blood film of patient with acute myeloid leukaemia.

Incidence

Acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia is commonest in the age range 2-10 years with a peak at 3-4 years. The incidence then decreases with increasing age, though there is a secondary rise after 40 years. In children it is the most common malignant disease and accounts for 85% of childhood leukaemia.

Acute lymphoblastic leukaemia is slightly more common among males than females

Acute myeloid leukaemia

Acute myeloid leukaemia accounts for 10-15% of childhood leukaemia but is the commonest leukaemia of adulthood, particularly as chronic myeloproliferative disorders and preleukaemic conditions such as myelodysplasia usually progress to acute myeloid leukaemia rather than acute lymphoblastic leukaemia. The incidence increases with age, and the median age at presentation is 60 years.

Acute myeloid leukaemia is equally common among males and females

Presentation

Acute leukaemia is always serious and life threatening, and all patients suspected of having this condition should be immediately referred for urgent assessment.

Common symptoms and signs at presentation result from bone marrow failure or organ infiltration. Anaemia can result in pallor, lethargy, and dyspnoea. Neutropenia results in infections of the mouth, throat, skin, or perianal region. Thrombocytopenia may present as spontaneous bruising, menorrhagia, bleeding from venepuncture sites, gingival bleeding, or prolonged nose bleeds.

A common presenting feature resulting from organ infiltration in childhood acute lymphoblastic leukaemia is bone pain, but acute lymphoblastic leukaemia can also present with superficial lymphadenopathy, abdominal distension due to abdominal lymphadenopathy and hepatosplenomegaly, respiratory embarrassment due to a large mediastinal mass, testicular enlargement, or a meningeal syndrome. Gum hypertrophy and skin infiltration are more commonly seen in acute myeloid than in acute lymphoblastic leukaemia.

Infiltration of optic fundus by acute lymphoblastic leukaemia.

Severe gum swelling at presentation in acute myeloid leukaemia M5.

Investigations

Full blood count usually but not invariably shows reduced haemoglobin concentration and platelet count. The white cell count can vary from $<1.0 \times 10^9/l$ to $>200 \times 10^9/l$, and the differential white cell count is often abnormal, with neutropenia and the presence of blast cells. The anaemia is a normochromic, normocytic anaemia, and the thrombocytopenia may be severe (platelet count $<10 \times 10^9/l$).

Coagulation screening may yield abnormal results, particularly in promyelocytic leukaemia (acute myeloid leukaemia M3) when granules from the leukaemic blasts can have procoagulant activity and trigger a consumptive coagulopathy.

Biochemical screening is particularly important if the leucocyte count is very high, when there may be evidence of renal impairment and hyperuricaemia.

Chest radiography is mandatory to exclude the presence of a mediastinal mass, which is present in up to 70% of patients with T cell acute lymphoblastic leukaemia. In childhood acute lymphoblastic leukaemia lytic bone lesions may also be seen.

Bone marrow aspiration with or without trephination is essential to confirm acute leukaemia. It is usually hypercellular with a predominance of immature (blast) cells.

Differential diagnosis of acute leukaemia

- If lymphadenopathy—Infections such as infectious mononucleosis or lymphoma
- If hepatosplenomegaly—Myeloproliferative or lymphoproliferative disorder, myelodysplasia, metabolic, storage or autoimmune disorders (rarely, tropical disease—eg visceral leishmaniasis)
- If no peripheral leukaemic blasts but pancytopenia—Aplastic anaemia or infiltrated bone marrow involvement from non-haemopoietic small round cell tumour
- Myelodysplasia
- Lymphoblastic lymphoma—Lymphomatous presentation with $<25\%$ of blasts in the marrow (distinction may be arbitrary as treatment may be the same)

Immunophenotyping of the antigens present on the bone marrow or peripheral blasts is the most reliable method of determining whether the leukaemia is lymphoid or myeloid, and cytochemistry helps to confirm myeloid or monocytic origin.

Cytogenetics and molecular studies often detect abnormalities within the leukaemic clone that can have diagnostic or prognostic value—for example, the Philadelphia chromosome, which is the product of a translocation between chromosomes 9 and 22, the presence of which confers a very poor prognosis in cases of acute lymphoblastic leukaemia.

Lumbar puncture with cerebrospinal fluid cytospin is an important initial staging investigation to detect leukaemic cells in the cerebrospinal fluid, indicating involvement of the central nervous system.

Management

All patients who have either suspected or confirmed acute leukaemia should be referred for specialist advice, assessment, and treatment. Where a patient is referred to and the type of treatment given will depend on the patient's age and condition. Children and young adults should always be treated in recognised specialist centres to maximise the chance of cure with minimal toxicity. On admission to a specialist unit the patient will need chemotherapy to treat the leukaemia and supportive care to ameliorate or correct the effects of the leukaemia and to facilitate treatment.

Supportive care

Supportive care includes regular transfusions of platelet concentrate for bleeding episodes or if the platelet count is $< 15\text{--}20 \times 10^9/l$; infusions of fresh frozen plasma if the coagulation screen results are abnormal; and packed red cell transfusions for anaemia, though these are contraindicated if the white cell count is extremely high.

In most patients a central venous catheter has to be inserted to facilitate blood product support, administration of chemotherapy and antibiotics, and frequent blood sampling.

Serious infection is a common cause of death in patients with acute leukaemia as bone marrow failure due to the leukaemia and to chemotherapy often results in profound neutropenia for two weeks or more. Patients should therefore be reverse-barrier nursed, and intravenous antimicrobial agents should be started as soon as there is a fever or other sign of infection.

Chemotherapy

The aim of chemotherapy for leukaemia is initially to induce a remission ($< 5\%$ blasts in the bone marrow) and then to eradicate the residual leukaemic cell population by further courses of consolidation therapy. The drugs damage the capacity of the leukaemic cells to divide and replicate, and using cyclical combinations of three or more drugs increases the cytotoxic effect, improves the chance of remission after the initial "induction" period, and reduces the emergence of drug resistance. In Britain acute myeloid leukaemia is currently treated with four courses of intensive chemotherapy, each of which entails five to 10 days of chemotherapy and then a period of three to five weeks before the next course. During this interval the patient is severely myelosuppressed and needs inpatient blood product support and antimicrobial drugs. In acute myeloid leukaemia M3 the drug ATRA (all-*trans*-retinoic acid) has been used as an adjunct to chemotherapy as it causes differentiation of the malignant clone.

Interphase fluorescence in situ hybridisation using probes for BCR and ABL genes. Left: Normal cell showing two red dots (two normal copies of BCR) and two yellow dots (two normal copies of ABL). Right: Cell from child with Ph chromosome positive acute lymphoblastic leukaemia with translocation of chromosomes 9 and 22.

Management of acute leukaemia

- Immediate (same day) referral to specialist
- Prompt diagnosis
- Early treatment
- Intensive supportive care
- Systemic chemotherapy
- Treatment directed at central nervous system (in children and in adult acute lymphoblastic leukaemia)
- Minimising early and late toxicity of treatment

Adequate hydration and allopurinol are essential at the start of treatment to reduce the risk of hyperkalaemia, hyperuricaemia, and renal damage

Psychological and social support to patients and families of patients with leukaemia is important, and specialist centres have networks to provide this

Pseudomonas infection of skin and nail bed in patient having treatment for acute myeloid leukaemia

In acute lymphoblastic leukaemia the induction course is followed by two or more consolidation periods and by treatment directed at the central nervous system (see below), followed by long term maintenance or continuation treatment for up to two years. This has been shown to improve long term cure rates in acute lymphoblastic leukaemia, though not in acute myeloid leukaemia.

Treatment directed at central nervous system

Treatment directed at the central nervous system is necessary to treat or prevent leukaemic cells in the central nervous system. Such treatment is part of all treatment protocols in childhood leukaemia and adult acute lymphoblastic leukaemia but not in adults with acute myeloid leukaemia unless they have symptoms or blasts are present in the cerebrospinal fluid. Treatment directed at the central nervous system generally comprises regular intrathecal chemotherapy (usually methotrexate), high dose intravenous methotrexate, or cranial irradiation.

Bone marrow transplantation

Allogeneic bone marrow transplantation may be curative in poor risk acute lymphoblastic leukaemia, acute myeloid leukaemia in first remission, or in relapsed leukaemia in which a second remission has been achieved. Transplantation is not available to all patients, however, owing to lack of compatible donors. Bone marrow transplantation is discussed in a later article.

Ongoing Medical Research Council clinical trials

- Acute lymphoblastic leukaemia in both children and adults
- Relapsed acute lymphoblastic leukaemia in children
- Acute myeloid leukaemia in patients aged < 60 years
- Acute myeloid leukaemia in patients aged > 55 years

Survival with acute leukaemia

Type	At five years
Childhood acute lymphoblastic leukaemia	65-75%
Adult acute lymphoblastic leukaemia	20-35%
Acute myeloid leukaemia, aged < 55 years	40-60%
Acute myeloid leukaemia, aged > 55 years	20%

Poor prognosis in acute leukaemia

Factors	Acute lymphoblastic leukaemia	Acute myeloid leukaemia
Age	< 1 Year or > 10 years	> 60 Years
Sex	Male	Male or female
Presenting white blood cells	> 50 × 10 ⁹ /l	> 50 × 10 ⁹ /l
Central nervous system disease	Presence of blasts in cerebrospinal fluid at presentation	Presence of blasts in cerebrospinal fluid at presentation (rare)
Remission problems	Failure to remit after first induction treatment	> 20% Blasts in bone marrow after first course of treatment
Cytogenetics	Philadelphia positive—that is, t(9;22)—or t(4;11) acute lymphoblastic leukaemia	Deletions or monosomy of chromosome 5 or 7 or complex chromosomal abnormalities

Toxicity of therapy

Early side effects

Most chemotherapeutic agents have pronounced side effects, such as nausea and vomiting, mucositis, hair loss, neuropathy, and renal and hepatic dysfunction. Many also cause myelosuppression, resulting in profound neutropenia for two or more weeks. Recurrent febrile neutropenic episodes require prompt and intensive antibiotics, and many patients also develop fungal infection requiring treatment with systemic antifungal drugs.

Late effects

All treatments for acute leukaemia can result in long term side effects that may bring appreciable morbidity—particularly in children—or even lead to death. All patients therefore need to be followed up for at least 10 years. In particular, the long term problems with growth and endocrine function in children need expert attention.

Late effects of treatment for acute leukaemia

Cardiac—Arrhythmias, cardiomyopathy
Pulmonary—Fibrosis
Endocrine—Growth delay, hypothyroidism, gonadal dysfunction or failure, infertility
Renal—Reduced glomerular filtration rate
Psychological—Intellectual dysfunction, long term anxiety about relapse
Second malignancy—Secondary leukaemias or solid tumours
Cataracts

R J Liesner is senior registrar and A H Goldstone is consultant in the department of haematology, University College London Hospitals NHS Trust, London.

The ABC of clinical haematology is edited by Drew Provan, consultant haematologist and honorary senior lecturer at the Southampton University Hospitals NHS Trust, and Andrew Henson, clinical research fellow, university department of primary care, Royal South Hants Hospital, Southampton.

The interphase fluorescence in situ hybridisation was provided by Brian Reeves and Helen Kempster, department of haematology, Great Ormond Street Hospital for Children NHS Trust, London.