Leukemias

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Introduction

- Leukaemias are malignant disorders of the haematopoietic stem cell compartment, characteristically associated with increased numbers of white cells in the bone marrow and/or peripheral blood.

- The course of leukaemia may vary from a few days or weeks to many years, depending on the type.

Epidemiology and aetiology

- The incidence of leukaemia of all types in the population is approximately 10/100 000 per annum, of which just under half are cases of acute leukaemia.

- Males are affected more frequently than females.

- Acute leukaemia occurs at all ages.
- Acute lymphoblastic leukaemia shows a peak of incidence in children aged 1–5 years.
- All forms of acute myeloid leukaemia have their lowest incidence in young adult life and there is a striking rise over the age of 50.
- Chronic leukaemias occur mainly in middle and old age.

- The cause of the leukaemia is unknown in the majority of patients.

- Several risk factors, however, have been identified.

24.46 Risk factors for leukaemia

Ionising radiation

- After atomic bombing of Japanese cities (myeloid leukaemia)
- Radiotherapy for ankylosing spondylitis
- Diagnostic X-rays of the fetus in pregnancy

Cytotoxic drugs

- Especially alkylating agents (myeloid leukaemia, usually after a latent period of several years)
- Industrial exposure to benzene

Retroviruses

- One rare form of T-cell leukaemia/lymphoma appears to be associated with a retrovirus similar to the viruses causing leukaemia in cats and cattle

Genetic

- Identical twin of patients with leukaemia
- Down's syndrome and certain other genetic disorders

Immunological

- Immune deficiency states (e.g. hypogammaglobulinaemia)

Terminology and classification

- Leukaemias are traditionally classified into four main groups:
- acute lymphoblastic leukaemia (ALL)
- acute myeloid leukaemia (AML)
- chronic lymphocytic leukaemia (CLL)
- chronic myeloid leukaemia (CML).

- In acute leukaemia, there is proliferation of primitive stem cells, leading to an accumulation of blasts, predominantly in the bone marrow, which causes bone marrow failure.

- In chronic leukaemia, the malignant clone is able to differentiate, resulting in an accumulation of more mature cells.

- The diagnosis of leukaemia is usually suspected from an abnormal blood count, often a raised white count, and is confirmed by examination of the bone marrow.

- This includes the morphology of the abnormal cells, analysis of cell surface markers (immunophenotyping), clone-specific chromosome abnormalities and molecular changes.

- The features in the bone marrow not only provide an accurate diagnosis but also give valuable prognostic information, allowing therapy to be tailored to the patient’s disease.

Acute leukaemia

- There is a failure of cell maturation in acute leukaemia.

- Proliferation of cells which do not mature leads to an accumulation of primitive cells which take up more and more marrow space at the expense of the normal haematopoietic elements. Eventually, this proliferation spills into the blood.

- Acute myeloid leukaemia (AML) is about four times more common than acute lymphoblastic leukaemia (ALL) in adults.

- The clinical features are usually those of bone marrow failure (anaemia, bleeding or infection).

24.47 WHO classification of acute leukaemia

Acute myeloid leukaemia (AML) with recurrent genetic abnormalities

- AML with t(8;21), gene product AML-ETO
- AML with eosinophilia inv(16) or t(16;16), gene product CBFβ-MYH11
- Acute promyelocytic leukaemia t(15;17), gene product PML-RARA
- AML with t(9;11)(p22;q23), gene product MLLT3-MLL
- AML with t(6;9)(p23;q34), gene product DEK-NUP214
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2), gene product RPN1-EVI1

Acute myeloid leukaemia with myelodysplasia-related changes

- e.g. Following a myelodysplastic syndrome

Therapy-related myeloid neoplasms

- e.g. Alkylating agent or topoisomerase II inhibitor

Myeloid sarcoma

Myeloid proliferations related to Down's syndrome

Acute myeloid leukaemia not otherwise specified

- e.g. AML with or without differentiation, acute myelomonocytic leukaemia, erythroleukaemia, megakaryoblastic leukaemia, myeloid sarcoma

Acute lymphoblastic leukaemia (ALL)

- Precursor B ALL
- Precursor T ALL

Investigations

- Blood examination usually shows anaemia with a normal or raised MCV.
- The leucocyte count may vary from as low as 1 × 109/L to as high as 500 × 109/L or more.
- Severe thrombocytopenia is usual but not invariable.
- Frequently, blast cells are seen in the blood film but sometimes blast cells may be infrequent or absent.

- A bone marrow examination will confirm the diagnosis.

- The bone marrow is usually hypercellular, with replacement of normal elements by leukaemic blast cells in varying degrees (but more than 20% of the cells).

- Classification and prognosis are determined by immunophenotyping, chromosome and molecular analysis.

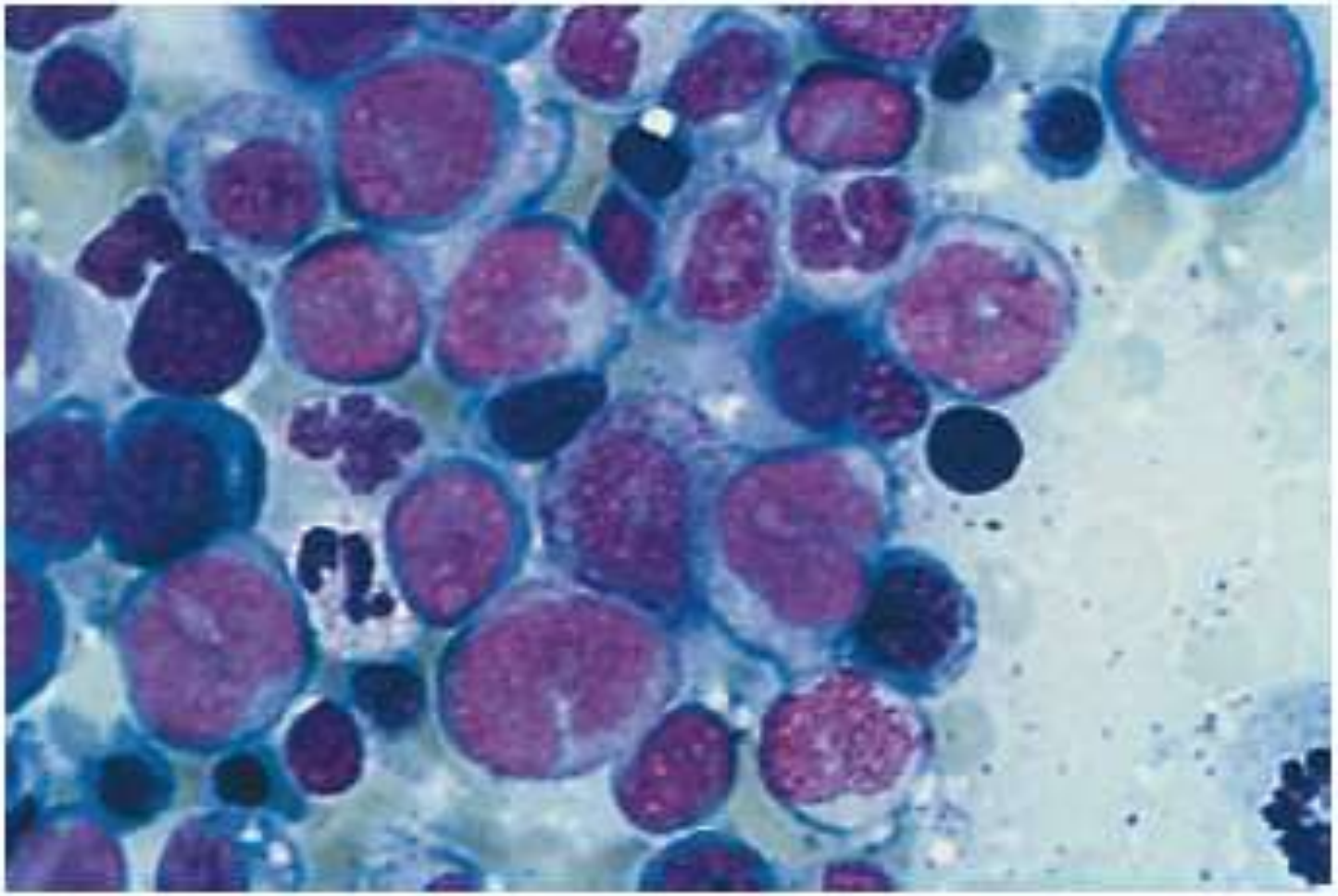

Fig. 24.25 Acute myeloid leukaemia. Bone marrow aspirate showing infiltration with large blast cells which display nuclear folding and prominent nucleoli.

Management

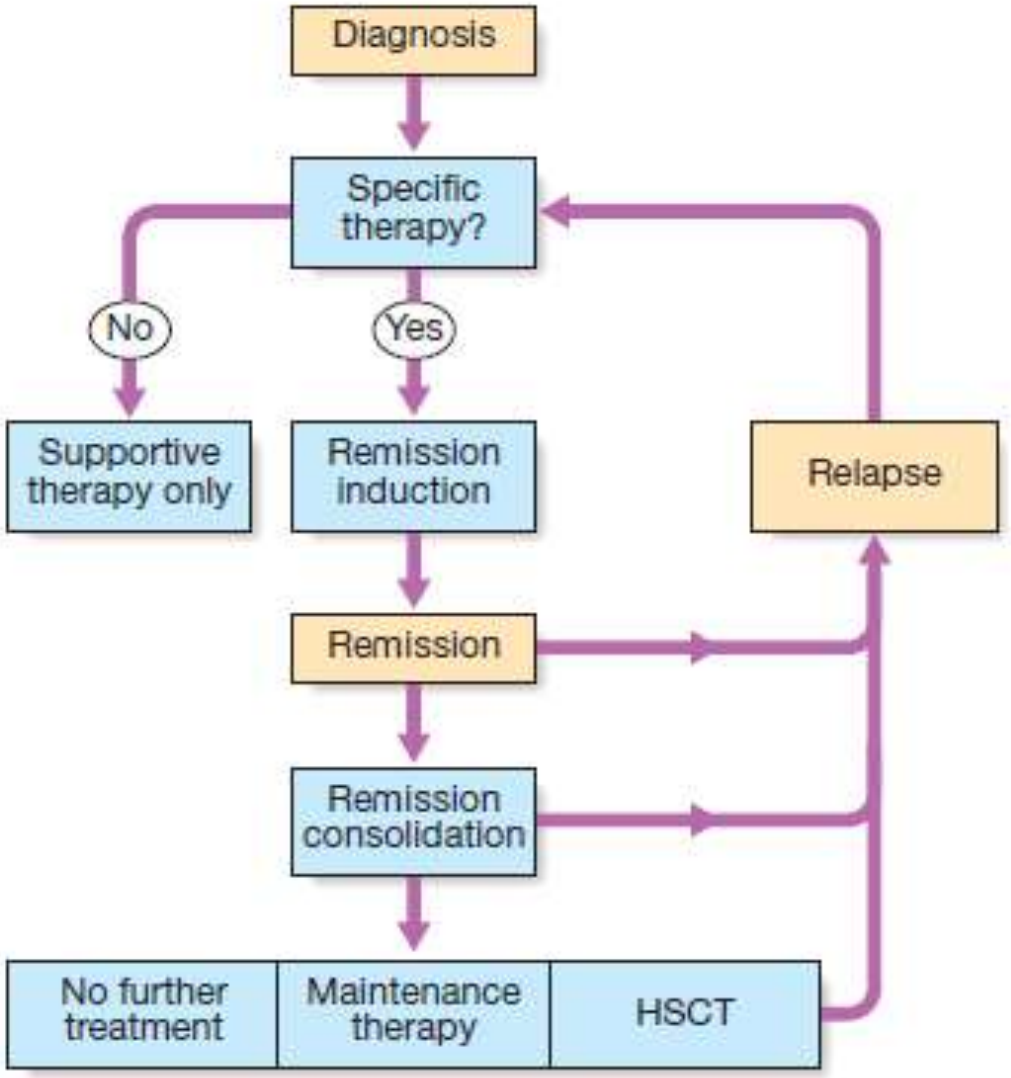

Fig. 24.27 Treatment strategy in acute leukaemia. (HSCT = haematopoietic stem cell transplantation)

Specific therapy

- If a decision to embark on specific therapy has been taken, the patient should be prepared.

24.48 Preparation for specific therapy in acute leukaemia

- Existing infections identified and treated (e.g. urinary tract infection, oral candidiasis, dental, gingival and skin infections)
- Anaemia corrected by red cell concentrate transfusion
- Thrombocytopenic bleeding controlled by platelet transfusions
- If possible, central venous catheter (e.g. Hickman line) inserted to facilitate access to the circulation for delivery of chemotherapy, fluids, blood products and other supportive drugs
- Tumour lysis risk assessed and prevention started: fluids with allopurinol or rasburicase
- Therapeutic regimen carefully explained to the patient and informed consent obtained
- Consideration of entry into clinical trial

- The aim of treatment is to destroy the leukaemic clone of cells without destroying the residual normal stem cell compartment from which repopulation of the haematopoietic tissues will occur.

Remission induction.

- In this phase, the bulk of the tumour is destroyed by combination chemotherapy.

- The patient goes through a period of severe bone marrow hypoplasia, requiring intensive support and inpatient care from a specially trained multidisciplinary team.

Remission consolidation.

- If remission has been achieved, residual disease is attacked by therapy during the consolidation phase.

- This consists of a number of courses of chemotherapy, again resulting in periods of marrow hypoplasia.

Remission maintenance.

- If the patient is still in remission after the consolidation phase for ALL, a period of maintenance therapy is given, with the individual as an outpatient and treatment consisting of a repeating cycle of drug administration.

- In patients with ALL, it is necessary to give prophylactic treatment to the central nervous system, as this is a sanctuary site where standard therapy does not penetrate.

24.49 Drugs commonly used in the treatment of acute leukaemia

Phase	ALL	AML
Induction	Vincristine (IV) Prednisolone (oral) L-asparaginase (IM) Daunorubicin (IV) Methotrexate (intrathecal) Imatinib (oral)*	Daunorubicin (IV) Cytarabine (IV) Etoposide (IV and oral)
Consolidation	Daunorubicin (IV) Cytarabine (IV) Etoposide (IV) Methotrexate (IV) Imatinib (oral)*	Cytarabine (IV) Amsacrine (IV) Mitoxantrone (IV)
Maintenance	Prednisolone (oral) Vincristine (IV) Mercaptopurine (oral) Methotrexate (oral) Imatinib (oral)*	

*If Philadelphia chromosome-positive.

Supportive therapy

- Aggressive and potentially curative therapy, which involves periods of severe bone marrow failure, would not be possible without appropriate supportive care.

- ***Anaemia.*** Anaemia is treated with red cell concentrate transfusions.

- ***Bleeding.*** Thrombocytopenic bleeding requires platelet transfusions. Coagulation abnormalities occur and need accurate diagnosis and treatment.

- ***Infection.***
- Fever (> 38°C) lasting over 1 hour in a neutropenic patient indicates possible septicaemia.

- Parenteral broad-spectrum antibiotic therapy is essential.

- Empirical therapy is given according to local bacteriological resistance patterns: for example, with a combination of an aminoglycoside (e.g. gentamicin) and a broad-spectrum penicillin (e.g. piperacillin/tazobactam) or a single-agent beta-lactam (e.g. meropenem).

- Gram-positive infection may require vancomycin therapy.

- If fever has not resolved after 3–5 days, empirical antifungal therapy is added.

- Patients with ALL are susceptible to infection with *Pneumocystis jirovecii* , which causes a severe pneumonia.

- Prophylaxis with co-trimoxazole is given during chemotherapy.

- Isolation facilities and barrier nursing practices are used to guard against infections.

- ***Metabolic problems.***
- Frequent monitoring of fluid balance and renal, hepatic and haemostatic function is necessary.

- Patients are often severely anorexic and diarrhoea is common as a consequence of the side-effects of therapy; they may find drinking difficult and hence require intravenous fluids and electrolytes.

- Cellular breakdown during induction therapy (tumour lysis syndrome) releases intracellular ions and nucleic acid breakdown products, causing hyperkalaemia, hyperuricaemia, hyperphosphataemia and hypocalcaemia. This may cause renal failure.

- Allopurinol and intravenous hydration are given to try to prevent this.

- ***Psychological problems.***
- Psychological support is a key aspect of care.

- Patients should be kept informed, and their questions answered and fears allayed as far as possible.

Haematopoietic stem cell transplantation

- In patients with high-risk acute leukaemia, allogeneic HSCT can improve 5-year survival from 20% to around 50%.

Prognosis

- Without treatment, the median survival of patients with acute leukaemia is about 5 weeks.

- This may be extended to a number of months with supportive treatment.

24.50 Outcome in adult acute leukaemia

Disease/risk	Risk factors	5-yr overall survival
Acute myeloid leukaemia		
Good risk	Promyelocytic leukaemia t(15;17) t(8;21) inv 16 or t(16;16)	76%
Poor risk	Cytogenetic abnormalities –5, –7, del 5q, abn(3q), complex (> 5)	21%
Intermediate risk	AML with none of the above	48%
Acute lymphoblastic leukaemia		
Poor risk	Philadelphia chromosome High white count > 100×10^9/L Abnormal short arm of chromosome 11 t(1;19)	20%
Standard	ALL with none of the above	37%

- Patients who achieve remission with specific therapy have a better outlook. Around 80% of adult patients under 60 years of age with ALL or AML achieve remission.

- Advances in treatment have led to steady improvement in survival from leukaemia.

Chronic myeloid leukaemia

- Chronic myeloid leukaemia (CML) is a myeloproliferative stem cell disorder resulting in proliferation of all haematopoietic lineages but manifesting predominantly in the granulocytic series. Maturation of cells proceeds fairly normally.

- The disease occurs chiefly between the ages of 30 and 80 years, with a peak incidence at 55 years.

- The defining characteristic of CML is the chromosome abnormality known as the Philadelphia (Ph) chromosome.

- The fragment from chromosome 9 that joins the BCR carries the *abl* oncogene, which forms a fusion gene with the remains of the BCR.

- This *BCR ABL* fusion gene codes for a protein with tyrosine kinase activity, which plays a causative role in the disease as an oncogene influencing cellular proliferation, differentiation and survival.

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 imatinib therapy, this phase has been prolonged to longer than 8 years 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, which is relatively refractory to treatment. This is the cause of death in the majority of patients.

Clinical features

- Symptoms at presentation may include lethargy, weight loss, abdominal discomfort and sweating, may be asymptomatic.
- Splenomegaly is present in 90%; in about 10%, the enlargement is massive.
- Hepatomegaly occurs in about 50%.
- Lymphadenopathy is unusual.

Investigations

- There is usually a normocytic, normochromic anaemia.
- The leucocyte count can vary from 10 to 600 × 10^9/L.
- In the blood film, the full range of granulocyte precursors is seen.

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

- Bone marrow should be obtained to confirm the diagnosis and phase of disease by morphology, chromosome analysis to demonstrate the presence of the Ph chromosome, 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*
- Imatinib specifically inhibits BCR ABL tyrosine kinase activity and reduce the uncontrolled proliferation of white cells. It is recommended as first-line therapy in chronic-phase CML.

- *Accelerated phase and blast crisis*
- For patients presenting in accelerated phase, imatinib is indicated if the patient has not already received it.
- Hydroxycarbamide can be an effective single agent.
- When blast transformation occurs, the type of blast cell should be determined.

- Patients progressing to advanced-phase disease on imatinib may respond to a second-generation tyrosine kinase inhibitor and may be considered for allogeneic HSCT

Chronic lymphocytic leukaemia

- Chronic lymphocytic leukaemia (CLL) is the most common variety of leukaemia, accounting for 30% of cases.

- In this disease, B lymphocytes, which would normally respond to antigens by transformation and antibody formation, fail to do so.

Clinical features

- The onset is usually insidious and diagnosis may be incidental on a FBC.

- Presenting problems may be anaemia, infections, painless lymphadenopathy, and systemic symptoms such as night sweats or weight loss.

Investigations

- The diagnosis is based on the peripheral blood findings of a mature lymphocytosis (> 5 × 109/L) with characteristic morphology and cell surface markers.

- Other useful investigations in CLL include a reticulocyte count and a direct Coombs test, as autoimmune haemolytic anaemia may occur.

- Serum immunoglobulin levels should be estimated.

- Bone marrow examination by aspirate and trephine is not essential for the diagnosis of CLL, but may be helpful in difficult cases, for prognosis and to monitor response to therapy.

24.52 Staging of chronic lymphocytic leukaemia

Clinical stage A (60% patients)

- No anaemia or thrombocytopenia and fewer than three areas of lymphoid enlargement

Clinical stage B (30% patients)

- No anaemia or thrombocytopenia, with three or more involved areas of lymphoid enlargement

Clinical stage C (10% 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.

- Treatment is only required if there is evidence of bone marrow failure, massive or progressive lymphadenopathy or splenomegaly, systemic symptoms, a rapidly increasing lymphocyte count or autoimmune haemolytic anaemia or thrombocytopenia.

- Initial therapy for those requiring treatment (stages B and C) may consist of oral chemotherapy with the alkylating agent chlorambucil.

- Supportive care is increasingly required in progressive disease.

- Radiotherapy may be used for lymphadenopathy which is causing discomfort or local obstruction, and for symptomatic splenomegaly.

Thank you!