Leukaemia in childhood

Leukaemia is one of the more common childhood cancers.

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Leukaemia means white blood. It is a disease of the white blood cells and was first described by Virchow in 1845.[1] Leukaemia can present as an acute disease, occurring more often in the younger age groups, or as a chronic disease, usually in the older age group. Acute leukaemia is rare, but about 1 in 2 000 people will develop the disease.[2] The two acute forms in children are acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML). The chronic form is chronic myeloid leukaemia (CML).[2,3]

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Acute leukaemia

Acute lymphoblastic leukaemia (ALL)

Prevalence

ALL is the most common childhood cancer and comprises nearly 23.5% of all cancers in the age group 0 - 14 years.[3] The incidence is 3 - 4 children per 100 000.[3,4]

Pathophysiology

Leukaemia is the uncontrolled proliferation of a single immature haematopoietic cell with arrested or aberrant differentiation, resulting in clonal disease.[1-3] Programmed cell death or apoptosis is abnormal.[1] These abnormal blasts accumulate in the bone marrow, suppressing and replacing the normal haematopoietic cells, and circulate to the blood and other haematopoietic tissue.[1,2] Specific syndromes, such as Down syndrome, Fanconi's anaemia, and congenital immunodeficiency syndromes, predispose to leukaemia.[1,3] Chromosome translocations, which occur prenatally, are the initiating events, as shown by retrospective scrutiny of neonatal blood spots on Guthrie cards and ALL in identical twins.[2] This applies to all cases of infant leukaemia (fusion of the MLL gene) and most cases of common ALL (with TEL-AML1).[2] A 'second hit' after birth induces leukaemia and includes infection with the Epstein-Barr virus (associated with B-cell leukaemia) or other RNA retroviruses or ionising radiation.[1,2] Early diagnosis is important, as delay may lead to mutations that induce drug resistance, with a negative impact on outcome.

Clinical presentation

Boys are more commonly affected than girls, with a ratio of 1.2 for 0 - 14 years and 2.2 for 15 - 19 years.[4] The peak incidence is between 2 and 5 years of age.[4] Clinical symptoms and signs reflect bone marrow failure, manifesting as anaemia, pallor, and abnormal bruising (Table I).[1] Children usually present with pallor, abnormal bleeding (Fig.1), or easy bruising, fatigue, fever, lymphadenopathy and hepatosplenomegaly.[4] The lympadenopathy is painless. They may also present with severe bone or joint pains due to lytic lesions (Fig. 2), which should be distinguished from normal 'growth pains' that only occur during the afternoon and do not require pain medication. The child usually limps or refuses to walk. These bone and/or joint pains occur at any time, wake the child at night and necessitate medication. Any pain that wakes a child during the night should be regarded as pathological pain. The bone pain may mimic rheumatoid arthritis or osteomyelitis. The duration of symptoms may vary from days to months.[4]

The majority of children will develop common ALL, which characteristically has CD10 expression on the surface of the leukaemia blasts.[4] Some children may present with a large mediastinal mass and a high initial white blood cell count. This is usually a T-cell ALL, which is also associated with a higher incidence of central nervous system involvement. A good prognosis is associated with being a girl, the age group 2 - 10 years and a low white blood cell count. There are geographical differences – common ALL is the predominant leukaemia in industrialised countries, while T-cell ALL is more common in developing countries.[4]

Table I. Clinical symptoms, signs and diagnostic tests for acute leukaemia

Symptoms
Malaise, fatigue
Weight loss
Bruising
Joint and bone pain
Headache
Signs
Pallor and anaemia
Thrombocytopenia with petechiae, ecchymosis, and/or epistaxis
Fever
Infection
Renal enlargement (infiltration) – rare
Cranial neuropathy – rare

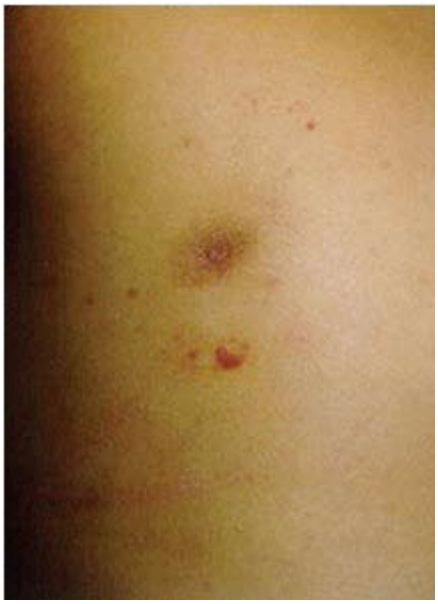

Fig. 1. Petechiae around the nipple.

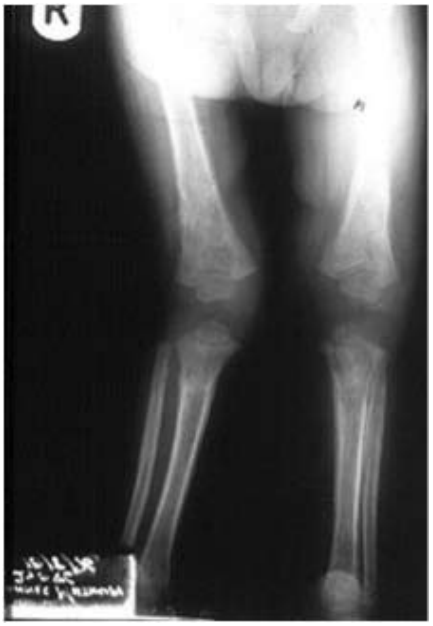

Fig. 2. Lytic bone lesions in the proximal tibia and distal femur.

Diagnosis

A full blood count and differential count will show either pancytopenia or anaemia, and/or thrombocytopenia with a high white blood cell count. The peripheral smear may have lymphoblasts. The diagnosis is made on bone marrow aspiration and/or bone marrow biopsy if there are more than 30% blasts in the bone marrow.[1,4] Morphological classification is according to the French-American-British (FAB) classification and has 3 different types of ALL, based on morphology and cytochemistry (Table II).[1] Flow cytometry for cell surface markers is done on bone marrow to determine immunophenotype, as these are characterised by their surface expression of cell surface glycoproteins, know as clusters of differentiation (CDs) (Table II).[1] A panel of antibodies, directed at these cell surface markers, will identify the maturational status of the blast, which is used to diagnose and stratify the leukaemia according to risk or prognosis for the purpose of treatment. Cytogenetic studies are done to determine ploidy and possible translocations, which are also associated with prognosis, and molecular genetic studies are performed to determine genetic mutations (Table II). As mentioned above, the most common type is common ALL with CD10 surface expression and hyperdiploidy, which is associated with a good prognosis.[1,4]

Leukaemia is the uncontrolled proliferation of a single immature haematopoietic cell with arrested or aberrant differentiation, which results in clonal disease.

Other investigations include serum electrolytes, creatinine, calcium, and especially uric acid to determine breakdown of cells, which can cause tumour lysis syndrome, inducing acute renal failure. A lumbar puncture is performed to exclude central nervous system (CNS) involvement. Radiological studies are done when indicated, using radiography and computed tomography of the chest for a large mediastinal mass (associated with T-cell ALL) or for abdominal lymph nodes. If a patient is diagnosed with high-risk leukaemia, human leucocyte typing is done in younger patients for potential future bone marrow transplantation.

Treatment

During the past 50 years the treatment of childhood ALL has been remarkable, because the cure rate improved from 0% to 80%.[4] The abnormal leukaemia clone is eradicated with the administration of a combination of chemotherapeutic agents. However, the treatment is non-selective and also affects the normal bone marrow precursors. Therefore, aggressive supportive care is needed, especially with regard to the management of infections (discussed in this edition of CME) and blood transfusions, as indicated.[1,4] Haematopoietic growth factors may be added to support bone marrow function.[1,4] The goal is complete remission, defined as less than 5% blasts in the bone marrow. Treatment is divided into different phases, i.e. an induction phase, a consolidation phase, a re-induction-consolidation phase and maintenance with CNS prophylaxis.[1,4] The drugs administered during induction are vincristine, prednisone, an anthracycline and L-aspariginase.[1,4,5] The consolidation drugs are a combination of cytarabine, anthracyclines, epipodophyllotoxins, alkylators or antimetabolites (methotrexate).[1,4,5] Maintenance therapy consists of oral treatment with methotrexate and 6-mercaptopurine.[4]

Acute myeloid leukaemia (AML)

The incidence of AML is about 5 - 7 children per 1 000 000 people per year and it comprises about 15% of childhood leukaemias in white children.[6] The incidence of AML is slightly increased in black children.[6] Children with Down syndrome have a 14-fold increased risk of developing AML, while twins have an increased risk in the first 6 years of life.[6] The frequency remains stable during childhood, with a slight increase in adolescence.[6] The clinical presentation is similar to that of ALL, with fatigue, anaemia, a bleeding tendency and bone pain. Children may present with life-threatening infections, granulocytic

Table II. Leukaemia subtypes (adapted from DeVita *et al.*[1])

Subtype	Bone marrow morphology	Immunophenotype	Genotype	Comments
ALL-L1	Small cells with minimal cytoplasm, no granules and rare nucleoli, TdT+	B-lineage: CD 10; 19; 20; 22; 34; HLA-DR; cytoplasmic Ig T-lineage: CD2; 5; 7; 10; 34	t(9;22), t(4;11), t(1;9) hyperdiploidy	Most common in children
ALL-L2	Larger cells, moderate amount of cytoplasm, prominent nucleoli, TdT+	As for ALL-L1	As for ALL-L1	
ALL-L3	Large round cells, deep basophilic cytoplasm, TdT+	CD10; 19; 20; 21; 22; surface Ig	t(8;14), t(2;8), t(8;22)	Poor prognosis 5% of ALL

granuloma or chloroma (most commonly orbital) and/or gum infiltration (Fig. 3).[1,6] Disseminated intravascular coagulation (DIC) is associated with AML-M3 or acute promyelocytic leukaemia (APL). With intensive post-remission therapy the event-free survival is 50%. Failure to obtain the same cure rate as in ALL is due to the development of drug resistance and treatment-related mortality.[6]

Fig. 3. Chloroma – myeloid blast infiltration in the soft tissue around the eyeball.

Diagnosis

A full blood count and peripheral smear are done and may present, as in ALL, with pancytopenia, and/or anaemia and/or thrombocytopenia. The white blood cell count may be normal, low or elevated, with a few patients presenting with high white blood cell counts of more than 100 000 cells/µl (20%).[1] The FAB morphological classification identifies 7 subtypes of AML (Table III).[1,6] A bone marrow aspiration or biopsy is done and AML is diagnosed if there are more than 20% myeloblasts.[7] Flow cytometry and cytogenetics or molecular genetics are done on bone marrow to determine the immunophenotype and genotype.[6]

Treatment

The treatment goal is similar to that of ALL, i.e. to eradicate the abnormal leukaemic clone in the bone marrow using chemotherapy. The standard induction therapy for AML includes cytarabine, anthracycline, etoposide and dexamethasone.[1,6] Favourable cytogenetics include t(8;21) and inv16, while children with Down syndrome also have a good prognosis.[6] There are various post-remission treatments, ranging from high-dose chemotherapy to autologous or allogeneic stem cell transplants (SCTs).[1,6] Currently, HLA-matched family-related SCTs are offered to patients in first remission if the cytogenetics are unfavourable and a familial donor can be identified. It can increase survival to nearly 60%.[6,8]

APL (AML-M3) is a distinct entity with a good prognosis. If treated with standard induction therapy the disease has a high mortality rate owing to increased coagulopathy.[1,6] Currently all-trans retinoic acid (ATRA) is used to induce

Table III. Leukaemia subtypes (adapted from DeVita *et al.*[1])

Subtype	Bone marrow morphology	Immunophenotype	Genotype	Comments
AML-M0	Type 1 blasts Cytochemistry negative	CD13, 33, 34, HLA-DR	NA	Poorer prognosis; less than 3% of childhood AML[6]
AML-M1 Minimal maturation	Type I & II blasts Sudan black+ or peroxidase+ Occasional Auer rods	CD13, 14, 15, 33, 34, HLA-DR	Occasionally inv(3)	20%[6]
AML-M2 Maturation	Types I, II 7 II blasts and monocytic cells, Sudan black+, peroxidase or chloroacetate esterase; Auer rods possible	CD13, 15, 33, 34, HLA-DR	t(8;21) in 50%	Translocation associated with a favourable prognosis; 30% of all AML cases[6]
AML-M3 Promyelocytic leukaemia	Abnormal promyelocytes; multiple Auer rods	CD13, 33, 15, less CD34, HLA-DR negative	t(15;17)	Best prognosis; 5 - 10% of childhood AML[6]
AML-M4 Myelomonocytic leukaemia	Monocytic lineage >20% and <80%; α-naphtol+	CD13, 14, 15, 33, 34, HLA-DR positive	NA	Extramedullary involvement; increased incidence in children <2 years of age[6]
AML-M5	Large blasts >80% of monocytic lineage; α-naphtol+	CD13, 14, 33, 34, HLA-DR	Abnormal 11q23	Poor prognosis; extramedullary involvement; up to 50% of childhood AML <2 years of age[6]
AML-M6	Erythroid cells >50%; non-erythroid >30%; periodic acid-Schiff +	CD13, 33, 41, 71, HLA-DR, glycoprotein A	Deletion of 5 and 7 – often	Often preceded by myelodysplasia; poor prognosis; secondary AML
AML-M7	>30% blasts of megakaryocytic origin	CD41, 61	Occasional inv(3); t(3;3); trisomy 21; t(9;22); t(1;22	Children <3 years; Down syndrome

complete remission by the differentiation of the blasts into normal neutrophils, which is obtained in 90 - 95% of patients.[1,6] Standard AML induction therapy is then administered to eradicate the abnormal clone.[1,6] The disease now has an excellent prognosis.

Complications caused by chemotherapy include tumour lysis syndrome, DIC and life-threatening infections. Supportive care is therefore very aggressive, with allopurinol and hyperhydration for tumour lysis syndrome, plasma and low-dose heparin for DIC, and combination broad-spectrum intravenous antibiotics[6] (see article on febrile neutropenia in this edition of *CME*).

Chronic leukaemia

Chronic myeloid leukaemia (CML)

Prevalence

Chronic leukaemia is very rare in childhood and comprises only 5% of childhood leukaemias.[9,10] The majority of children diagnosed with CML are older than 6 years.

Pathophysiology

CML has the phenotype of more mature cells.[9] It is a clonal disease, involving a pluripotent stem cell. On clinical presentation, it is in an indolent chronic or a stable phase with excessive numbers of myeloid cells in both the peripheral blood and bone marrow.[9,10] Philadelphia chromosome or t(9;22) is characteristic of CML as the cytogenetic marker, which is found in myeloid, erythroid and megakaryocytic lineages. This marker is also found in B cells and a small proportion of T cells, confirming the clonality of the disease originating from a pluripotent haematopoietic stem cell. About 5 - 10% of patients with CML may be Philadelphia chromosome negative.[9] The translocation between chromosomes 9 and 22 leads to the development of the BCR-ABL fusion protein with tyrosine kinase activity, which activates several signalling pathways that decrease apoptosis, enhance proliferation of haematopoietic stem cells, and increase the number of myeloid cells with early release from the bone marrow into the peripheral blood.[9,10]

Clinical presentation

Patients with CML usually present in the chronic or stable phase with an elevated white blood cell count and few or no symptoms.[9,10] Symptoms include night sweats, fever, bone pain, weakness and discomfort due to an enlarged spleen.[9] After 4 - 6 years the disease progresses into an accelerated phase or a blastic phase, when the blasts can no longer terminally differentiate.[10] These children will present with fatigue, anaemia, weight loss, abdominal distension and splenomegaly, where the size correlates with the leukocytosis. Patients rarely present with hyperviscosity resulting in stroke or priapism.[10]

Boys are more commonly affected than girls, with a ratio of 1.2 for 0 - 14 years and 2.2 for 15 - 19 years.

Diagnosis

The white blood cell count is high (>50×10^9/l), while the white blood cell function is normal during the chronic phase.[10] Basophilia, eosinophilia and thrombocytosis are often present.[10] During the blast crisis the majority of blasts are myeloblasts, but one-third may have a lymphoid morphology, usually early B-cell markers.[9]

Treatment

Treatment options for CML include various chemotherapy drugs and allogeneic SCTs.[10] The drugs used in CML include busulfan, hydroxyurea and interferon alfa. Imatinib mesylate (Gleevec), an oral drug, is currently the drug of choice.[9] Imatinib is a small 2-phenylaminopyrimidine, which inhibits the BCR-ABL protein binding of ATP and suppresses the malignant clone.[9,11] The majority of patients (96%) achieve complete haematological remission, with a 99% 24-month survival if a major cytogenetic response is obtained.[11] The only permanent curative therapy is allogeneic SCT, resulting in a 10-year disease-free survival rate of 50 - 60%. This is obtained if the SCT is done in the chronic phase of the disease.[10] There is currently a debate around which of the two therapies, i.e. imatinib or SCT, is the preferred treatment, as children have a survival rate of 65 - 75% with SCT.[9,12]

Brief guidelines for referral to a paediatric oncologist

- Refer a child who presents with the following:
  - abnormal bleeding tendency
  - lymphadenopathy with/without hepatosplenomegaly
  - weight loss in the presence of abnormal haematological findings
  - bone pain, arthralgia or arthritis in the presence of abnormal haematological findings
  - an unexplained high white blood cell count, pancytopenia, bicytopenia or monocytopenia of unknown origin.

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