Acute leukaemia

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Abstract

The acute leukaemias consist of acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML). ALL occurs predominantly in children whereas AML occurs mainly in the elderly. These may present as medical emergencies such as neutropenic sepsis, hyperleucocytosis and coagulopathy. Whilst 80% of children with ALL are cured, the outcomes for most AML patients remain poor and treatment strategies to improve this are needed. In both ALL and AML recurrent cytogenetic abnormalities have prognostic significance. A normal karyotype is intermediate risk in AML and ALL but is made up of a heterogeneous group with varied outcomes. Whole exome sequencing of patients with normal karyotype acute myeloid leukaemia reveals recurrent molecular mutations in FLT3, NPM, CEBPα, IDH1 and 2 and DNMT 3a that are of additional prognostic and possible therapeutic value. Whilst the mainstay of treating acute leukaemia remains chemotherapy with additional allogeneic stem cell transplantation as consolidation in high-risk disease, the discovery of novel molecular mutation may result in personalized therapy with drugs that target the abnormal pathways and also offer a marker that can be monitored for minimal residual disease. The ability to detect minimal residual disease enables the possibility of early intervention to prevent relapse. Cumulatively these may improve the outcomes in acute leukaemia.

Keywords acute lymphoblastic leukaemia; acute myeloid leukaemia; acute promyelocytic leukaemia; granulocytic sarcoma; leukaemia cutis

What's new?

- Use of mutations in FLT3-ITD, NPM, IDH1, IDH2 and DNMT 3a to stratify risk in normal karyotype AML
- Treatment of acute promyelocytic leukaemia with triple therapy as a new standard
- Prospective detection of minimal residual disease in ALL to guide optimal timing of therapy

Introduction

Leukaemia is the clonal proliferation of haematopoietic cells, with impaired lineal differentiation, that results in an excess of immature cells at the expense of more mature forms and leads to functional bone marrow failure. Acute leukaemias are broadly classified as acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL). Those that show characteristics of both are termed biphenotypic/bilineal.[1] Historically, these disorders were rapidly and uniformly fatal but treatment with chemotherapy, radiotherapy, and stem cell transplantation underpinned by improved supportive care has resulted in long-term remission and survival in some patients.

Epidemiology and pathogenesis

The incidence of AML is three per 100,000 in children and adults under 50 years of age, but increases to almost 20 per 100,000 in the eighth decade of life, making it a disease of the elderly.[2] By contrast, ALL demonstrates a bimodal peak; it occurs predominantly in children aged between 4 and 14 years of age but has a second peak in adults over 50 years old. In most cases, the occurrence of leukaemia is sporadic but epidemiological studies have identified predisposing conditions. These include exposure to chemicals (benzene), radiation or tobacco smoke, prior chemotherapy (topoisomerase inhibitors, such as etoposide, are associated with 11q23 abnormalities; and alkylating agents, such as melphalan and cyclophosphamide, with deletion of chromosomes 5 and 7), and inherited conditions such as Down's syndrome.

Presentation of ALL and AML

Leukaemia may be discovered by an incidental blood test in an asymptomatic individual. More often, patients present with symptoms, such as fatigue, dyspnoea or angina due to anaemia, with severe sepsis due to neutropenia or with epistaxis and mucosal bleeds due to thrombocytopenia. Acute promyelocytic leukaemia (APL) may present with bleeding due to disseminated intravascular coagulopathy, whereas acute monocytic leukaemia often leads to gum hypertrophy due to infiltration of the gums with monocytic blasts. In ALL lymphadenopathy, splenomegaly or a mediastinal mass (in T-ALL) may be present in half the patients. Leukaemic infiltration of the central nervous system (CNS) at presentation occurs in fewer than 10% of patients with ALL and is rare in AML. However, a few patients present with symptoms of raised intracranial pressure and the diagnosis is made on cytological examination of the cerebrospinal fluid (CSF). A family history of leukaemia may be due to the presence of a chromosome breakage disorder, such as Fanconi's anaemia, or isolated inherited gene defects in myeloid differentiation factors, such as mutation in core epsilon binding protein α (CEBPα) mutations or Runt-related transcription factor 1 (RUNX 1) mutations. Presentation with a white blood cell (WBC) count greater than 100×10^9/litre (hyperleucocytosis) may result in dyspnoea or confusion due to infiltration of the tissues. Both hyperleucocytosis and the coagulopathy of APL are medical emergencies wherein urgent leukapheresis (in non-APL) or expedient administration of all-*trans*-retinoic acid (ATRA) in APL may be life saving.

Classification of leukaemia

The WHO classification of leukaemia 2008, based on morphology, immunophenotyping and cytogenetic characteristics, enables identification and, to an extent, stratification of risk. The classification recognizes acute myeloid leukaemia, acute

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leukaemia of ambiguous lineage (a related neoplasm) and precursor lymphoid neoplasms as broad categories. Each is further stratified on the basis of phenotypic or recurrent cytogenetic abnormalities.

Investigations to diagnose and classify leukaemia, and to stratify risk

The diagnosis may be made on examining a blood film that demonstrates circulating blasts. Both AML and ALL have blasts with nuclei with an open chromatin and nucleoli. Additionally myeloid blasts may have cytoplasmic granules or Auer rods (see Figure 1). The blasts of APL are densely granulated with multiple Auer rods (faggot cells). Rarely, patients may have pancytopenia with no circulating blasts (aleukaemic leukaemia). The distinction between AML and ALL is sometimes difficult on morphology alone but can be made definitively on immunophenotyping the antigens expressed on the leukaemic cells. A bone marrow trephine is particularly useful in patients with inaspirable marrows and can clarify whether there is associated marrow fibrosis. Metaphase cytogenetics from the bone marrow and interphase fluorescent *in situ* hybridization provide evidence of associated cytogenetic abnormalities, which are very important from both diagnostic and prognostic points of view (recurrent translocations with APML, good-risk AML or high-risk AML).[3] In some instances where cytogenetics either fail or are uninformative, polymerase chain reaction analysis for molecular mutations may be useful, particularly in normal karyotype AML (Table 1). Monitoring mutant transcripts pre- and post-therapy to detect minimal residual disease (MRD) and inform therapy is increasingly useful to detect early relapse and guide the best response to therapy.

Predictors of response in leukaemia

At diagnosis, certain key variables are predictive of rates of complete response and likely duration of remission (Table 1). These include age, gender, white cell count, circulating blasts, cytogenetic abnormalities, molecular mutations, response to induction therapy, presence of extramedullary disease, primary or secondary leukaemia and whether it is related to previous chemotherapy. Cytogenetic abnormalities may suggest treatment strategies; for example, t(15;17), which results in a fusion gene PML/RARA (promyelocyte and retinoic acid receptor-α) predicts response to treatment with ATRA. The presence of core binding factor (CBF), characterized by the presence of either inv16 t(16;16)or t(8;21), predicts response to high-dose cytarabine and benefit from additional therapy with gemtuzumab ozogamicin (Mylotarg®).[4] Presence of the Philadelphia chromosome with t(9;22), in AML or ALL, predicts a high rate of relapse and justifies stem cell transplantation as soon as this is feasible. Additional therapy with a tyrosine kinase inhibitor such as imatinib (Glivec®) targets the fusion transcript bcr-abl. The presence of molecular mutations is prognostic of response and relapse; for example, fms-like tyrosine kinase-3 internal tandem duplication (FLT3-ITD) in AML predicts early relapse. Integrated analysis of the common molecular mutations in genes such as nucleophosmin (NPM), CEBPα, FLT3-ITD, DNA methyltransferase 3a (DNMT 3a) and isocitrate dehydrogenase 1 and 2 (IDH 1 and 2) help further to stratify risk.[5]

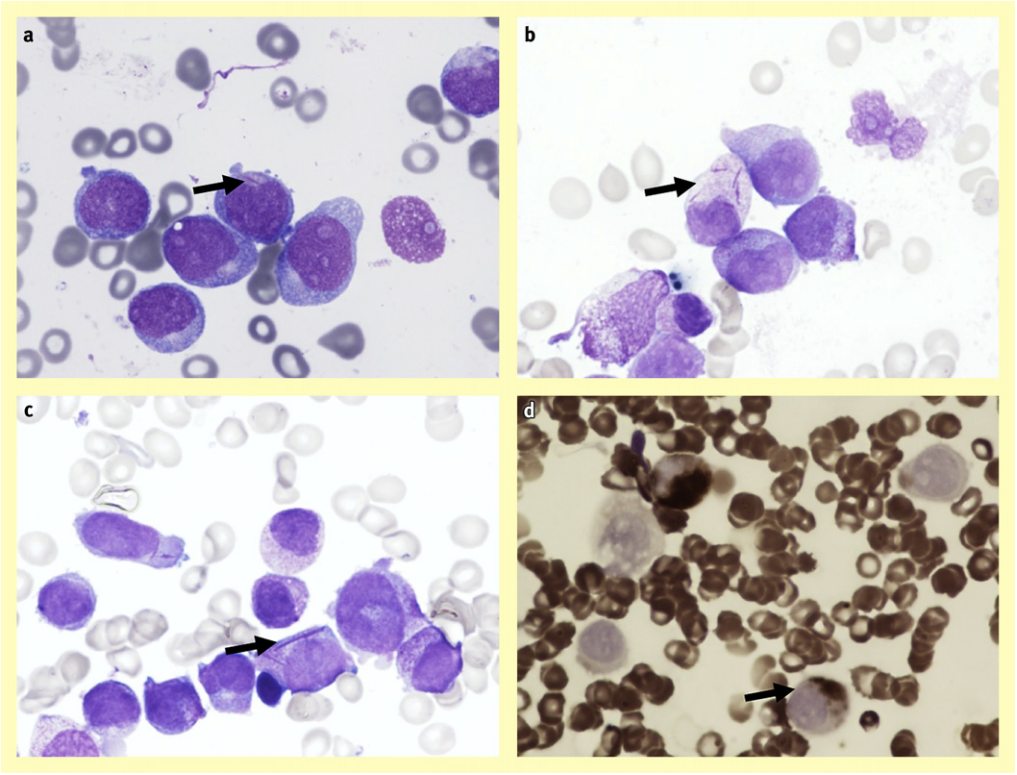

Figure 1 Acute myeloid leukaemia showing (**a**) Auer rods in a myeloid blast, (**b**) multiple Auer rods in granulated blasts in acute promyelocytic leukaemia (APML), (**c**) multiple APML blasts with Auer rods and granulation and (**d**) myeloperoxidase stain-positive myeloid blasts.