Acute leukaemia

Anne Mwirigi

Richard Dillon

Kavita Raj

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 elderly individuals. They can present as medical emergencies such as neutropenic sepsis, hyperleucocytosis and coagulopathy. Whereas 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 confers intermediate risk in AML and ALL but comprises a heterogeneous group with varied outcomes. Whole-exome sequencing of patients with normal-karyotype AML reveals recurrent molecular mutations in *FLT3*, *NPM1*, *CEBPA*, *IDH1*, *IDH 2* and *DNMT3A* that are of additional prognostic and possible therapeutic value. Although 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 mutations may result in personalized therapy with drugs that target the abnormal pathways and also offer a marker that can be used to monitor minimal residual disease. The ability to detect minimal residual disease enables the possibility of early intervention to prevent relapse. Cumulatively, these approaches may improve the outcomes in acute leukaemia.

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

Key points

- Both acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) remain high-risk diseases
- Minimal residual disease monitoring is proving to be important in prognostication and may trump traditional risk factors
- Key treatment modalities remain unchanged, but targeted therapies such as ponatinib for Philadelphia chromosome-positive ALL and IDH1/2 inhibitors may improve outcomes. Cellular therapies such as chimeric T-cell therapy cells are promising

Introduction

Leukaemia is a blood cancer characterized by the clonal proliferation of haemopoietic cells with impaired lineal differentiation, resulting in an excess of immature cells at the expense of mature forms, and functional bone marrow failure. Acute leukaemias are broadly classified as acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL). The less common biphenotypic leukaemias exhibit features of both. Historically, these disorders were rapidly and uniformly fatal, but treatment with chemotherapy, radiotherapy, stem cell transplantation and targeted therapies underpinned by improved supportive care has resulted in long-term remission and survival in some patients.

Epidemiology and pathogenesis

The incidence of AML is 3 per 100,000 in children and adults <50 years of age, increasing to almost 20 per 100,000 in the eighth decade of life, with a median age of 70 years at presentation. In contrast, ALL demonstrates a bimodal peak, occurring predominantly in children aged 4–14 years of age, with a second peak in adults >50 years old. Leukaemia usually occurs sporadically; predisposing factors include exposure to chemicals (benzene), radiation or tobacco smoke, previous chemotherapy (topoisomerase inhibitors, e.g. etoposide, being associated with 11q23 abnormalities; alkylating agents, e.g. melphalan and cyclophosphamide, with deletion of chromosomes 5 and 7), and inherited conditions such as Down's syndrome.

Presentation of ALL and AML

Leukaemia can be discovered following an incidental blood test in an asymptomatic individual. More often, patients present with symptoms such as fatigue, dyspnoea or angina caused by anaemia, severe sepsis resulting from neutropenia or bruising, epistaxis and mucosal bleeds owing to thrombocytopenia. Acute promyelocytic leukaemia (APL) can present with bleeding due to disseminated intravascular coagulopathy, whereas acute monocytic leukaemia often leads to gum hypertrophy because of infiltration with monocytic blasts. In ALL, lymphadenopathy, splenomegaly or a mediastinal mass (in T cell − ALL) can be present in half the patients. A high white blood cell count (hyperleucocytosis) at presentation (>100 × 10^9/litre) can result in dyspnoea or confusion because of infiltration of the tissues. Both hyperleucocytosis and the coagulopathy of APL are medical emergencies for which urgent leucapheresis (in non-APL) or expedient administration of all-*trans*-retinoic acid (ATRA) in APL can be lifesaving.

Leukaemic infiltration of the central nervous system (CNS) at presentation occurs in <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. A family history of

Anne Mwirigi *MB ChB MRCP FRCPath is a Locum Consultant Haematologist at Guy's and St Thomas' Hospitals, London, UK. Competing interests: none declared.*

Richard Dillon *MB BS PhD MRCP FRCPath is a Consultant Haematologist at Guy's and St Thomas' Hospitals, London, UK. Competing interests: none declared.*

Kavita Raj *MD PhD FRCP FRCPath is a Consultant Haematologist at Guys and St Thomas' and Kings College Hospitals, London, UK. Research interest: myelodysplastic syndromes, acute myeloid leukaemia, epigenetic therapies and haploidentical stem cell transplantation. Competing interests: none declared.*

Please cite this article in press as: Mwirigi A, et al., Acute leukaemia, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.02.010

leukaemia can result from the presence of a chromosome breakage disorder, such as Fanconi's anaemia, or isolated inherited gene defects in myeloid differentiation factors, such as CCAAT/Enhancer Binding Protein Epsilon (*CEBPA*) mutations or runt related transcription factor 1 (*RUNX1*) mutations.

Classification of leukaemia

The 2008 World Health Organization (WHO) classification of leukaemia recognizes AML, acute leukaemia of ambiguous lineage and precursor lymphoid neoplasms as broad categories. Both AML and ALL are classified according to recurrent genetic abnormalities.

For AML, this includes balanced translocations and inversions such as AML with t(8; 21) (q22; q22.1), inv(16) (p13.1q22) and APL with t(15; 17) (q22; q12) (Table 1). It also includes AML with gene mutations, of which mutated *NPM1* (nucleophosmin) and *CEBPA* are of particular prognostic significance. Understanding of the significance of mutations in AML is evolving. As some early founder mutations, such as in *DNMT3A* (DNA methyltransferase 3α), *IDH1* and *IDH2* (isocitrate dehydrogenase 1 and 2) and *TET2* (tet methylcytosine dioxygenase 2), also frequently occur in elderly people without manifest disease, the presence of these mutations should be interpreted within the clinical context.

Investigations to diagnose and classify leukaemia, and stratify risk

Acute leukaemia is suspected when circulating blasts (cells with scanty basophilic cytoplasm, open chromatin and prominent nucleoli) are identified in the peripheral blood film. Myeloid blasts often have cytoplasmic granules or Auer rods (Figure 1), whereas lymphoid blasts are agranular. APL blasts are densely granulated with multiple Auer rods (faggot cells). Rarely, patients have pancytopenia with no circulating blasts (aleukaemic leukaemia).

The distinction between AML and ALL is sometimes difficult using morphology alone but can usually be made definitively by identifying cell surface antigens through immunophenotyping. A bone marrow trephine sample is particularly useful in patients with inaspirable marrows and can identify any associated fibrosis. Analysis of chromosomes in metaphase and interphase fluorescent *in situ* hybridization identifies associated cytogenetic abnormalities, which can provide important diagnostic and prognostic information (Table 1). A greater understanding of the role of key driver mutations and oncogenic enhancers and their prognostic impact has led to their incorporation into the diagnostic work-up; polymerase chain reaction (PCR) analysis for molecular mutations can provide vital prognostic information, particularly in normal-karyotype AML (Table 1). Monitoring mutant transcripts before and after therapy to detect minimal residual disease (MRD) and inform therapy is increasingly useful to detect early relapse and guide the best response to therapy.

Current stratification of molecular genetic and cytogenetic alterations according to European Leukaemia Network (ELN) Recommendations

Risk profile	Subsets
Favourable	t(8; 21) (q22; q22); *RUNX1-RUNX1T1*
	inv(16) (p13.1q22) or t(16; 16) (p13.1q22); *CBFB-MYH11*
	Mutated NPM1 without *FLT3-ITD* (normal karyotype)
	Biallelic mutated *CEBPA* (normal karyotype)
Intermediate I	Mutated *NPM1* and *FLT3-ITD* (normal karyotype)
	Wild-type *NPM1* and *FLT3-ITD* (normal karyotype)
	Wild type *NPM1* without *FLT3-ITD* (normal karyotype)
Intermediate II	t(9; 11) (p22; q23); *MLLT3-KMT2A*
	Cytogenetic abnormalities not classified as favourable or adverse
Adverse	inv(3) (q21q26.2) or t(3; 3) (q21; q26.2); *GATA2-MECOM (EV1)*
	t(6; 9) (p23; q34); *DEK-NUP214*
	t(v; 11) (v; q23); *KMT2A* rearranged
	−5 or del(5q); −7; abn(17p); complex karyotype

Table 1

Predictors of response in leukaemia

Certain factors can help to predict how well a patient will respond to chemotherapy, and how long the response will last (Table 2). These include age, gender, white cell count, circulating blasts, cytogenetic abnormalities, molecular mutations, response to induction therapy, presence of extramedullary disease, and primary or secondary leukaemia.

Cytogenetic abnormalities can guide treatment strategies; for example, t(15; 17), which results in a fusion gene *PML/RARA* (promyelocytic leukaemia/retinoic acid receptor-α) and the APL subtype of AML, predicts response to treatment with ATRA. The presence of core-binding factor (*CBF*) translocations, i.e. inv16 t(16; 16)or t(8; 21), predicts the response to high-dose cytarabine and benefit from additional therapy with gemtuzumab ozogamicin (Mylotarg) which is currently available in clinical trials. The 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 (TKI) such as imatinib (Glivec®) targets the fusion transcript BCR-ABL.

The most powerful prognostic factor currently is cytogenetic abnormalities; a large proportion of patients have a normal karyotype, with an intermediate risk of relapse. Although the presence or absence of certain mutations (such as *FLT3* (fms related tyrosine kinase 3)) can be used to further refine prognosis in these patients, the presence or absence of MRD (assessed by flow cytometry or real-time PCR) is emerging as the factor most strongly predictive of relapse.

Treatment of acute leukaemia

Basic principles of chemotherapy

The aim of treating leukaemia with combination chemotherapy is to achieve a complete morphological remission (CR), defined as $<5\%$ blasts in the bone marrow with neutrophils $>1 \times 10^9$/litre and platelets $>100 \times 10^9$/litre. Induction chemotherapy is

Please cite this article in press as: Mwirigi A, et al., Acute leukaemia, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.02.010