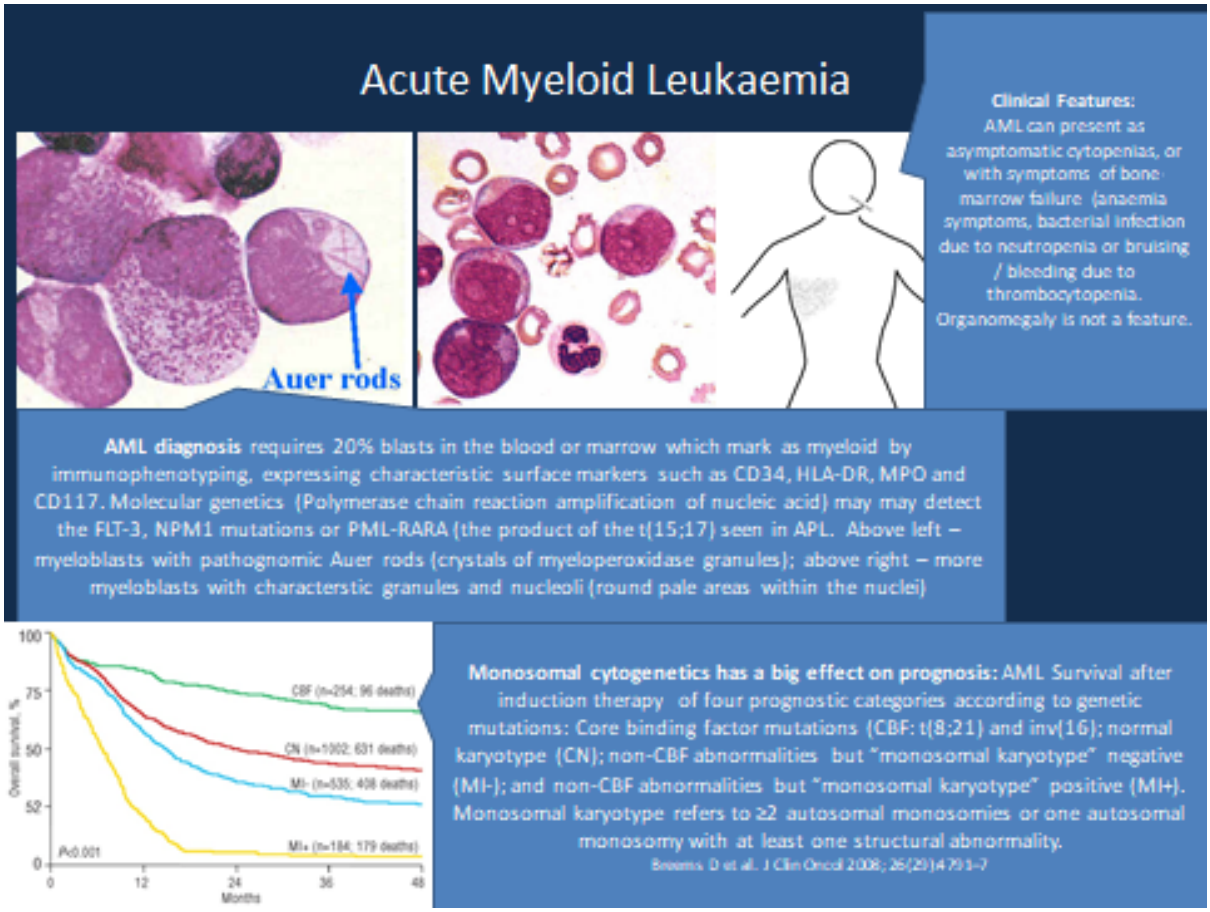
AN INTRODUCTION TO AML



Definition: AML is a heterogenous disease characterised by signs and symptoms of acute bone marrow failure caused by the accumulation of an excess of primitive "blast" cells in the bone marrow, often spilling over into the peripheral blood. Myeloid blasts making up ≥20% of all nucleated cells in the bone marrow or blood is required to make the diagnosis.

Epidemiology: incidence is 2-3 per 100,000 per annum in children rising to 15 per 100,000 in older adults. Can occur at any age but peaks in 7th decade.

Pathophysiology and clinical features: Caused by the acquisition of genetic mutations (often a balanced translocation) in early bone marrow haematopoeitic stem/progenitor cells generating oncoproteins which induce leukaemic transformation with the accumulation of additional cooperating mutations.

Signs / symptoms of bone marrow failure are common presenting features. Adenopathy / organomegaly is rare. Disseminated intravascular coagulopathy (DIC) usually accompanied by skin / mucosal haemorrhage due to consumption of platelets and clotting factors is a presenting feature of acute promyelocytic leukaemia (APL).

Aetiology is usually unknown although chemo-radiotherapy can be implicated (therapy-related AML)

Classification: 20% myeloblasts in BM or peripheral blood is diagnostic (except t(15;17), t(8;21) inv(16)or t(16;16) where just the markers are diagnostic. Classification is by the WHO System of Myeloid Neoplasms 2016.

Diagnosis requires a full blood count, a blood film, a bone marrow aspirate for morphology, immunophenotyping ("flow cytometry"), cytogenetics, molecular genetics and more recently, whole genome sequencing.

Immunophenotyping:

- Precursors: CD34, CD117, CD33, CD13, HLA-DR
- Granulocytic markers: CD65, cytoplasmic MPO
- Monocytic markers: CD14, CD36, CD64
- Megakaryocytic markers: CD41 (glycoprotein IIb/IIIa), CD61 (glycoprotein IIIa)
- Erythroid markers: CD235a (glycophorin A), CD36

AML-related genetic prognostic factors:

- Favourable: core-binding factor mutations [t(8;21); RUNX1-RUNX1T1 inv(16) or t(16;16); CBFB-MYH11]. Mutated NPM-1 without FLT3-ITD ro with FLT3-ITD$^{low\ allelic\ ratio}$. Biallelic CEPPA mutation
- Intermediate: mutated NPM1 and FLT3-ITD^{high}; wtNPM1 without FLT3-ITD or with FLT3-ITD^{low}; t(9;11); MLLT3-KMT2A; other Cytogenetic abnormalities not classified
- Adverse – there are lots but include -5, -7, t(9;22) GATA2, complex karyotype, wtNPM1 and FLT3-ITD^{high}; RUNX1, ASXL1, TP53 mutations.

Treatment can be with curative or palliative intent depending on the age and frailty / comorbidities of the patient. Intensive curative chemotherapy requires reasonable baseline fitness and is generally reserved for patients under 75yrs due to toxicity. Combinations of an anthracycline antibiiotic (e.g. daunorubicin) and cytarabine for 2 to 4 monthly cycles is often used. Arsenic trioxide and all-trans-retinoic acid (ATRA) are used in the rare APL subtype.

Allogeneic bone marrow transplantation for younger fitter patients with adverse prognostic genetics or after relapse in second remission is sometimes performed.

For frailer patients where palliative care is more appropriate, supportive care with infection treatment / prevention, blood products for symptomatic anaemia / bleeding with or without low dose cytoreductive chemotherapy or azacitidine is commonly employed.

Prognosis: Regardless of approach, prognosis is better in children and young adults but remains unsatisfactory in older adults and determined by age and genetic mutations

(described as favourable, intermediate or adverse) with 5 year overall survival in the over 60yr group of 34% with favourable, 13% with intermediate and 4% for adverse genetics.

References:

Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel Hartmut D et al. (Blood. 2017; 129(4):424-447)

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