48 Monte Carlo Crescent
Kyalami Business Park
Kyalami, Johannesburg, 1684, RSA
Tel: +27 (0)11 463 3260
Fax: + 27 (0)86 557 2232
Email: ThistleQA@LGCgroup.com
www.thistle.co.za

Please read this section first

The HPCSA and the Med Tech Society have confirmed that this clinical case study, plus your routine review of your EQA reports from Thistle QA, should be documented as a "Journal Club" activity. This means that you must record those attending for CEU purposes. Thistle will not issue a certificate to cover these activities, nor send out "correct" answers to the CEU questions at the end of this case study.

The Thistle QA CEU No is: MTS 17/011

Each attendee should claim ONE CEU point for completing this Quality Control Journal Club exercise, and retain a copy of the relevant Thistle QA Participation Certificate as proof of registration on a Thistle QA EQA.

DIFFERENTIAL SLIDES LEGEND

CYCLE 50 SLIDE 3

ACUTE MYELOID LEUKAEMIA

AML occurs in all age groups. It is the common form of acute leukaemia in adults and is increasingly common with age. AML forms only a minor fraction (10-15%) of the leukaemia's in childhood. An important distinction is between primary AML which appears to arise de novo and secondary AML which can develop from Myelodysplasia and other haematological diseases or follow previous treatment with chemotherapy. Both types are associated with distinct genetic markers and have different prognoses. In addition, cytogenetic abnormalities and response to initial treatment have a major influence on prognosis.

Signs and symptoms

Clinical features include pallor, lethargy, dyspnoea, fever, and malaise, features of infections, spontaneous bruises, and purpura, bleeding gums, menorrhagia, tender bones, lymphadenopathy, moderate splenectomy and hepatomegaly. Anaemia, neutropenia and thrombocytopenia are often profound. A bleeding tendency caused by thrombocytopenia and DIC is characteristic of the M3 variant of AML. Tumour cells can infiltrate a variety of tissues. Gum hypertrophy and infiltration, skin involvement and CNS disease are characteristic of the myelomonocytic M_4 and monocytic M_5 types. An isolated mass of leukemic blasts is usually referred to as a granulocytic sarcoma.

Classification

Classification is usually based on the morphological criteria of the FAB scheme. This divides AML into variants: M0, M1, M2, M3, M4, M4eos, M5, M6 and M7. The FAB subtypes are associated with characteristic patterns of Cytochemical stains, immunophenotyping and chromosomal changes. The typical "myeloid immunophenotyping" CD13+, CD33+, TdT- and special antibodies are helpful in the diagnosis of AML M_0, M_6 or M_7. Although the distinct AML subtypes are in fact different genetic diseases, their grouping together is valid as generally their treatment and prognosis is similar. However, differences in treatment according to subtype have been introduced. Cytogenetic abnormalities have a major influence on prognosis.

Investigation and diagnosis

Haematological findings may reveal a normochromic, normocytic anaemia with thrombocytopenia in most cases. The total WBC may be decreased, normal or increased up to 200 x 10^9/l or more. Blood film examination typically shows variable number of blasts. The bone marrow is hypercellular with >30% leukaemic blasts. The blast cells are characterized by morphology, immunological tests and cytogenetic analysis. Cytogenetic analysis

48 Monte Carlo Crescent
Kyalami Business Park
Kyalami, Johannesburg, 1684, RSA
Tel: +27 (0)11 463 3260
Fax: + 27 (0)86 557 2232
Email: ThistleQA@LGCgroup.com
www.thistle.co.za

shows different patterns in infants, children and adults which partly explains the different prognoses of these groups. Tests for DIC are positive in patients with promyelocytic leukaemia (M_3) variant of AML.

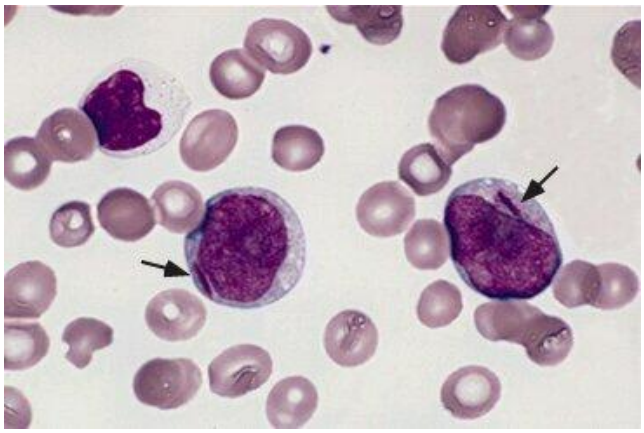

Fig 1: Myoblasts showing few granules with Auer rods in AML

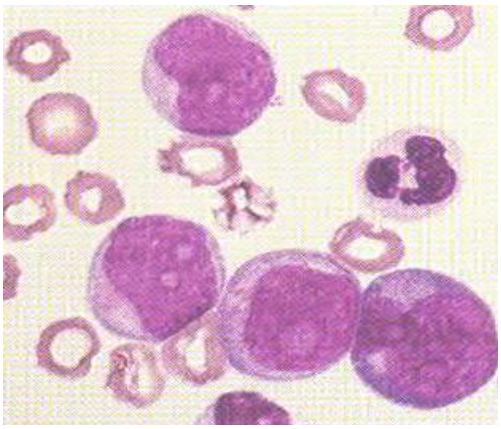

Fig 2: M2 blasts showing multiples cytoplasmic granules.

Biochemical tests may reveal a raised serum uric acid, serum LDH and less commonly hypercalcaemia. Liver and renal functions are performed as a baseline before treatment begins. X-rays may reveal lytic bone lesions. Blood and urinary lysozyme may be raised in monocytic leukaemia.

Treatment

First-line treatment of AML consists primarily of chemotherapy, and is divided into two phases: induction and post remission (or consolidation) therapy. The goal of induction therapy is to achieve a complete remission by reducing the amount of leukemic cells to an undetectable level; the goal of consolidation therapy is to eliminate any residual undetectable disease and achieve a cure. Hematopoietic stem cell transplantation is usually considered if induction chemotherapy fails or after a patient relapses, although transplantation is also sometimes used as front-line therapy for patients with high-risk disease.

Management is both supportive and specific.

- Problems unique to AML include the haemorrhagic syndrome associated with the AML M_3 variant. The disease may present with catastrophic haemorrhage or this may develop in the first few days of treatment. It is treated as for DIC with replacement of clotting factors with FFP and multiple platelet transfusions.In addition all-transretinoic acid (ATTRA) therapy is given in conjunction with chemotherapy.
- Specific therapy of AML is primarily with the use of intensive chemotherapy. This is usually given in four or five blocks each approximately 1 week and the most commonly used drugs include cytosine arabinoside, daunorubicin, idarubicin, 6-thioguanine, mitoxantrone or etoposide. All the AML subtypes (FAB M_0 – M_7) are treated similarly except for the promyelocytic (M_3) variant associated with the t(15;17) translocation in which ATRA is added to the initial chemotherapy. The drugs are myelotoxic with limited selectivity between leukaemic and normal marrow cells and so marrow failure is severe, and prolonged and intensive supportive care is required. Maintenance therapy is not needed and CNS prophylaxis is not usually given in AML.
- An important concept developing in AML therapy is that of basing the treatment schedule of individual patients on their risk group. Remission after one course of chemotherapy is also favourable. In contrast, monosomy 5 or 7 abnormalities, blasts cells with Flt-3 mutations or poorly responsive disease places patients into poor risk groups which may need more intensive treatments. Radiolabelled monoclonal antibodies targeted against CD33 or CD45 are being developed as a possible addition to AML therapy.

48 Monte Carlo Crescent
Kyalami Business Park
Kyalami, Johannesburg, 1684, RSA
Tel: +27 (0)11 463 3260
Fax: + 27 (0)86 557 2232
Email: ThistleQA@LGCgroup.com
www.thistle.co.za

Stem cell transplantation (SCT)

Autologous transplantation reduces the rate of relapse but adds further toxicity to the treatment regime. Its role in treatment is the subject of continuing debate but it tends to be reserved until relapse for good risk groups and children. Allogeneic SCT is used in some centres in patients under 45 years old with an HLA matching sibling donor with standard or poor risk AML in first remission although some groups save it as an option for relapse disease. Patients with t(8;21) and t(15;17) and inv16 who go into remission after the first course do not have a SCT unless they subsequently relapse.

Epidemiology

Results of AML therapy in patients over 60 years are poor because of primary disease resistance and poor tolerability of intensive treatment protocols. Death from haemorrhage, infection or failure of the heart, kidneys or other organs is more frequent than in younger patients. In elderly patients with serious disease of other organs, the decision may be made to use supportive care with or without gentle, single drug chemotherapy. However, in those otherwise well, combination chemotherapy similar to that used in younger patients may produce long-term remission.

Prognosis

The prognosis for patients with AML has been improving steadily, particularly for younger patients. Perhaps 50% of children and young adults may expect a long term "cure". Cytogenetic abnormalities and initial response to treatment are major predictors of prognosis. For the elderly the situation is poor and only 5% of those over 65 years of age can expect long-term remission.

Table 12.7 Prognosis in acute myeloid leukaemia (AML)

	Favourable	Unfavourable*
Cytogenetics	t(15; 17) t(8; 21) inv(16)	Deletions of chromosome 5 or 7 Flt-3 mutation 11q23 t(6; 9) abn(3q) Complex rearrangements
Bone marrow response to remission induction	< 5% blasts after first course	> 20% blasts after first course
Age	< 60 years	> 60 years

References

1. Essential Haematology – Hoffbrand, Pettit and Moss 4th Edition
2. http://en.wikipedia.org/wiki/Acute_myeloid_leukemia

Questions

1. Discuss the laboratory finding in AML.
2. What is the prognosis for patients with AML?
3. Discuss the treatment regimen of patients diagnosed with AML?