

Childhood ALL

Haematology Association of Ireland
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Sorcha Ní Loingsigh

Acute Lymphoblastic Leukaemia (ALL)

- ALL is the commonest malignancy of childhood, accounting for 30-35% of all paediatric cancers.
- Effective treatment first reported in 1948.
- Remarkable improvement in cure rates over past 30 years with new combinations of old drugs.
- Current focus of research is to maximise cure rates while minimising treatment toxicities.

Clinical Characteristics

- Symptoms usually present for less than 4 weeks before diagnosis.
- Initial symptoms are usually non-specific – lethargy, fatigue, bone pain.
- Specific symptoms of marrow failure such as infection and bleeding usually occur later in course and reflect increasing marrow infiltration.
- Occasionally discovered incidentally on FBC analysis performed for other reasons.

Extramedullary Manifestations

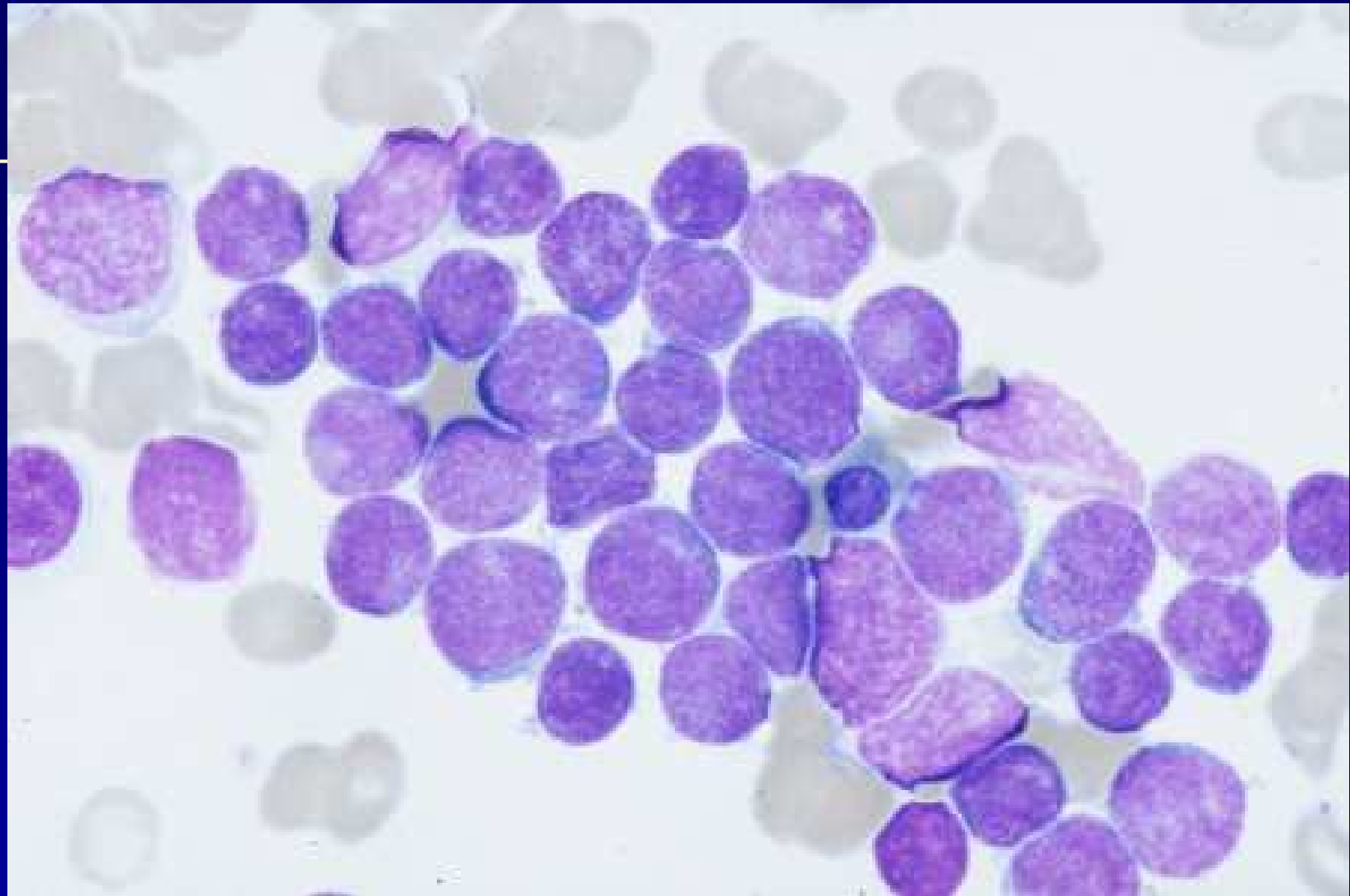
- Any organ can be infiltrated with ALL blasts.
- Hepatosplenomegaly seen in 30-60%.
- CNS involvement is detected by the finding of blast cells in CSF and is seen in 1.5-10%. May present with non-focal signs such as headache, vomiting, or with focal neurological deficits.
- Mediastinal masses occasionally seen, and usually arise from the thymus. Can result in SVC or airway obstruction which is a medical emergency.

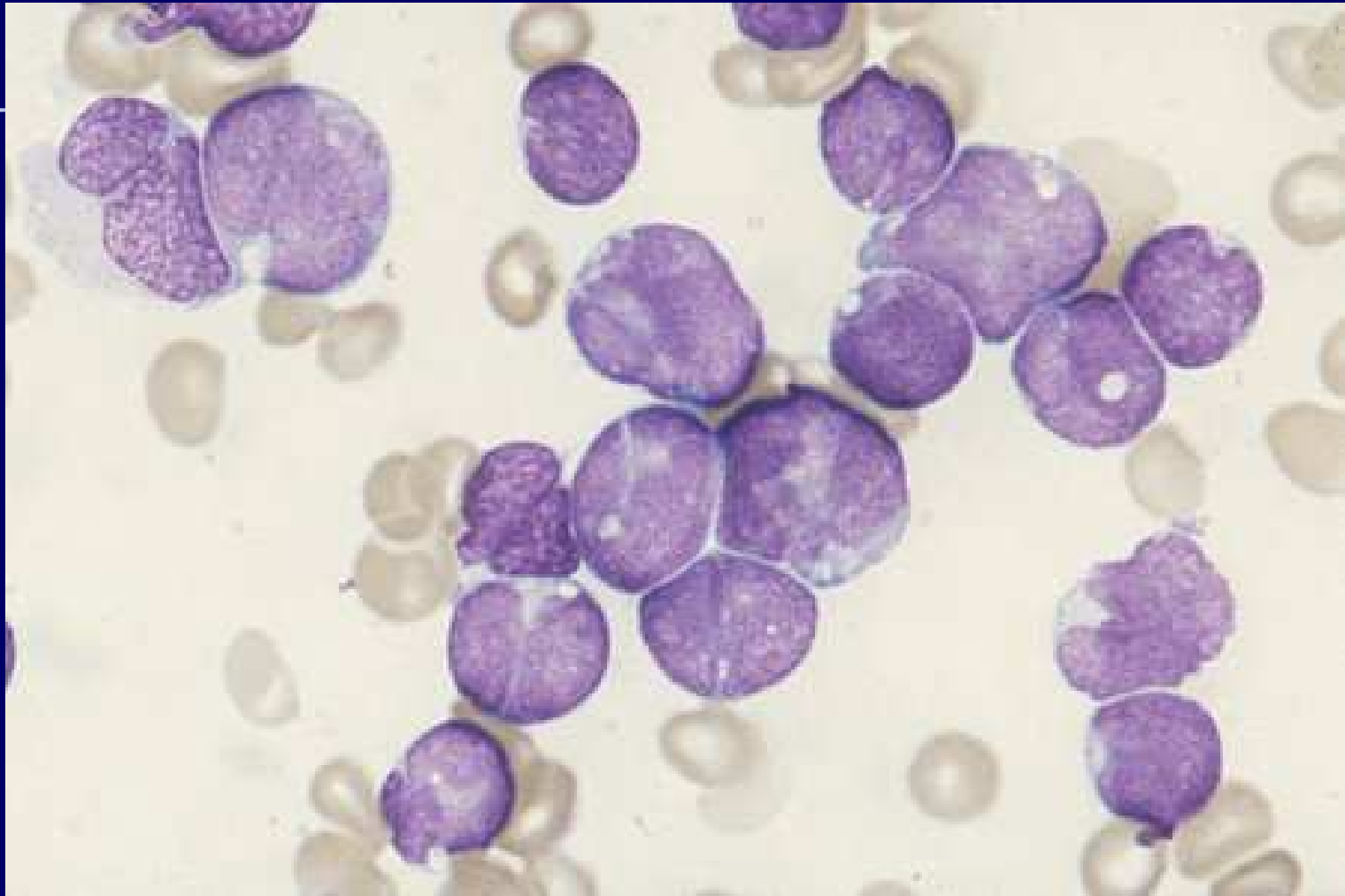
Laboratory Findings.

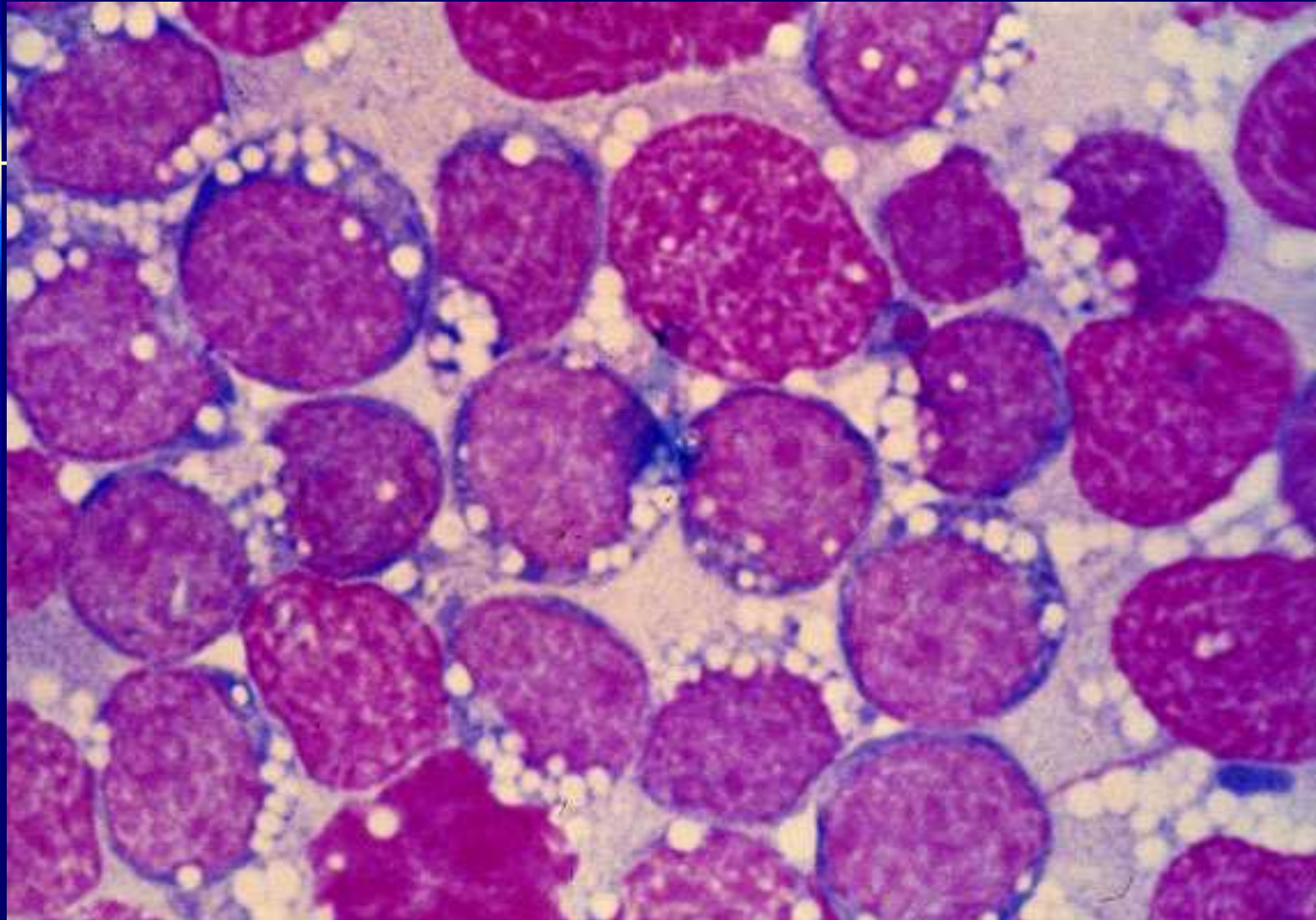
- Various degree of anaemia and thrombocytopenia may be apparent, reflecting marrow failure.
- WCC is elevated >10 in 50%, due to the proliferation of ALL blasts.
- However, in approx 5% of children, the WCC will be <2 , and blasts may not be apparent in peripheral blood.
- Occasionally, ALL presents initially with marrow aplasia. This prodrome is followed by marrow recovery, with subsequent development of overt leukaemia.

Bone Marrow

- The diagnosis of ALL rests on bone marrow biopsy demonstrating infiltration of blasts accounting for >25% of marrow elements.
- Morphological classification (L1/L2/L3) can be used to describe appearance of ALL cells, but only L3 subtype has clinical significance.







ALL subtypes

- Further characterisation of cells can be obtained by immunophenotyping, cytogenetic analysis and molecular studies.
- Using these criteria, several subtypes of ALL can be identified which will provide further prognostic information.

Common Subtypes

- Infant ALL
- ALL associated with t(12;21) – TEL/AML1
- Burkitt's like ALL – associated with t(8;14) and L3 blasts.
- ALL associated with t(1;19) – E2A/PBX1.
- T-ALL.

Infant Leukaemia

- Occurring in children under 12 months. Usually associated with higher WCC, larger disease bulk and higher incidence of CNS involvement.
- Genetic abnormality 11q23 often found, affecting the MLL gene.
- Associated with a poorer prognosis.

ALL with t(12;21)

- First reported in 1994 and now recognised as the commonest type of ALL, seen in approx 25% of patients.
- This finding is associated with a better prognosis.

ALL with t(8;14)

- Associated with Burkitt-like ALL.
- Results in an aggressive, rapidly progressive form of leukaemia.
- Previously associated with a worse prognosis, but more shorter, more intensive chemotherapy regimens have improved outcomes.

T Cell ALL

- T-ALL accounts for 12% of childhood ALL and is more commonly seen in older boys.
- Associated with bulky disease, e.g. mediastinal masses, hepatosplenomegaly and high WCC.
- Associated with poorer prognosis.

Diagnostic Work-Up

- Bloods FBC, U&E, LDH, LFTs, coagulation screen, virology (EBV, CMV, Measles)
- Bone Marrow Morphology, Immunophenotyping, cytogenetics, molecular studies.
- CNS LP for cell count, morphology, protein, glucose, c+s.
- Echocardiogram, CXR, Abdominal ultrasound.

Prognostic Features

- Important to identify these features to allow risk stratification of each patient.
- Can allow tailored treatment regimens, reserving more intensive protocols for those with poor prognostic features to maximise cure rates, while using less toxic regimens for good risk patients, reducing toxicity.
- Now for the bad news! – results in complicated treatment protocols.

Prognostic Features

Factor	Favourable	Unfavourable
Age	>1 - <6 years	<1 year
WCC	<20	>100
Marrow response on day 14	<5% blasts	>5% blasts
Genetic Features	t(12;21)	t(9;22), t(4,11)
5 year EFS	>80%	10-60%

Treatment

- Cornerstone of treatment depends on use of combinations of drugs used to achieve elimination of malignant cells and restoration of normal haematopoiesis.
- Recent advances in supportive care have allowed use of more toxic combinations while reducing mortality.
- Current protocols follow a standard course:-
 - Induction
 - Intensification
 - CNS treatment
 - Maintenance.

Induction

- Induction treatment is initiated once the patient has been stabilised.
- Relies on combination of steroids, vincristine and an anthracycline to achieve rapid cell kill.
- Current regimens are effective at inducing remission in >95% of patients.
- Failure to achieve remission is split equally between those who develop progressive leukaemia and those who die from toxic complications.

Intensification

- Early trials showed high early relapse rate in those treated with induction regimens alone.
- Intensification blocks of chemotherapeutic agents similar to those used in induction were added designed to maximise cell kill and improve long term remission rates.
- UKALL 2003 regimen is currently evaluating role of 1 vs. 2 blocks in risk stratified patients.

CNS Treatment

- The blood-brain barrier acts as an effective shield, protecting leukaemic cells in the brain and spinal cord from chemotherapy agents.
- Early trials showed high rates of CNS relapse, particularly in those with poor prognostic features.
- Specific modalities targeting the CNS have been developed to counteract this.
- Mainstay of CNS treatment is use of chemotherapy drugs injected directly into the CSF via a lumbar puncture needle. Agents used are methotrexate, cytarabine and hydrocortisone.
- Role of total brain irradiation is controversial.

Maintenance

- Maintenance therapy with oral methotrexate and mercaptopurine is continued for 24-36 months to prevent early relapse.
- Large variation of effectiveness of these agents between patients – for this reason doses are titrated against blood counts for individual patients. ANC <1.5 indicates toxicity while >2.5 indicates insufficient activity.
- Conflicting evidence regarding role of pulses of vincristine and dexamethasone during this period.

Relapse

- Despite improvement in cure rates, 15-20% of patients will relapse.
- Aim of treatment is to re-achieve remission using combination chemotherapy and to provide long term disease control.
- Duration of first remission will impact on effectiveness of re-induction therapy – durations of less than 6-12 months are associated with poor longer term survival.

Role of BMT

- Bone marrow transplantation is an effective method of controlling disease.
- However, it is associated with high levels of mortality and morbidity, with treatment related mortality as high as 30% in some series.
- Limited by availability of suitable source of donor stem cells – ideally from matched family member. Matched unrelated donor transplants are associated with higher mortality and morbidity rates.

Role of BMT

- 1st CR: Those with poor prognostic features, e.g. Philadelphia chromosome +, and those with poor initial response to treatment.
- 2nd CR: Early (<6 months) relapse. Late relapse with poor prognostic features, T-ALL.
- 3rd CR: All patients.

Long Term Complications

- Improved survival now means that more patients are living with the effects of their leukaemia treatment.
- CNS: Reduced neurocognitive function
- Growth: Slowing of growth usually followed by catch up growth
- Cardiac: Anthracyclines found to have greater long term toxicities in younger patients
- Avascular necrosis: Seen in those receiving high dose steroids
- Gonadal function: usually maintained
- Second malignancies: risk appears low

Summary

- ALL is commonest childhood malignancy
- Childhood ALL is not equivalent to Adult ALL.
- New combinations of old drugs have greatly improved outcomes. Role of clinical trials in identifying effective regimens has been pivotal.
- Improved long term survival has increased importance of long term complications of therapy.
- Focus of new research is to identify those who have low risk, to allow de-escalation of therapy in these patients and so reduce toxicities.

Thank You!