Childhood leukaemia

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Abstract

As a group, acute leukaemias are the most common childhood malignancies, and continue to be an important cause of non-accident related childhood mortality. Fortunately, with modern chemotherapy the majority of children and young people with leukaemia can be cured. However, this treatment comes with a significant burden for our young patients and their families. Here, we review the essential and differential diagnostics and the initial management of children with suspected leukaemia, as relevant for secondary paediatric care. We will give a short overview of current treatment protocols for childhood acute lymphoblastic and acute myeloid leukaemia. We will explain how stratification according to certain prognostic factors – most importantly response to therapy – guides treatment intensity. Using modern molecular techniques for minimal residual disease monitoring and molecular disease classification, it is increasingly possible to identify patients with a cure rate well above 90% in whom a reduction in treatment intensity may seem feasible. In addition, these techniques also allow the definition of poor-risk patients who may benefit from more intensive chemotherapy and bone-marrow transplantation. Finally, we discuss long-term follow-up of survivors of childhood leukaemia as a multidisciplinary paediatric team approach, as well as the challenges of transition into adult care.

Keywords acute lymphoblastic leukaemia; acute myeloid leukaemia; chemotherapy; childhood leukaemia; leukaemia diagnosis

Introduction

As a group, leukaemias represent the most common malignant conditions of childhood, with acute lymphoblastic leukaemia (ALL) – the most common single condition – representing approximately 25% of malignant diagnoses in childhood. As such they are an important cause of morbidity and mortality for children in the UK and abroad. Treatment regimens may be lengthy, and success requires enormous dedication from the child, their family, and the family's extended social network.

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Nevertheless, acute leukaemia provides a paradigm for the development of paediatric haematology and oncology over the last 40 years. It highlights the importance and power of nationally and increasingly internationally coordinated clinical trials to improving the outcome for children with rare conditions. Almost universally fatal as recently as the 1960s, ALL now has an overall survival of over 80%. Despite this success story, the twin challenges remain of improving survival for the 15–20% of children who relapse following first-line therapy whilst reducing the burden of therapy on the 50% of children who would previously have been cured by less intensive regimens.

Significant improvements have also been made in the care of children with acute myeloid leukaemia (AML). Whilst progress has been made, improving overall survival in children with myeloid leukaemia, towards the proportion cured in ALL remains a key target. Other, rarer, conditions – including chronic myeloid leukaemia and myelodysplasias – are seen occasionally in children, but will not be discussed further in this review.

Epidemiology

In Europe, the incidence of ALL in children aged 0–14 years is 35 cases per million children per year, representing approximately 370 children diagnosed each year in the UK. Boys are slightly more frequently affected than girls (sex ratio 1.3:1.0). Between 1978 and 1997 the incidence in the UK and Europe rose slowly by approximately 0.8% per year.

AML is rather less common, affecting 6.5 children per million per year, or approximately 90 children per year in the UK. Boys are again slightly more frequently affected than girls (ratio 1.2:1.0).

Aetiology

Pioneering work by Professor Mel Greaves has shown that in many childhood leukaemias the malignant development starts before birth, and the leukaemias originate in a fetal cell. Clones harbouring the most common genetic mutations, *TEL-AML1* and high hyperdiploidy, are identifiable in umbilical cord blood and Guthrie card blood spots following delivery. It has been speculated that the occurrence of these genetic aberrations may be linked to prenatal exposure of ubiquitously present natural DNA-damaging substances. However, no clear causative agent has yet been identified. Reassuringly, both concordance studies in twins and studies looking at the prevalence of these mutations in the background population indicate that only a small minority go on to develop leukaemia, implying a necessary and infrequent (perhaps in one per hundred predisposed children) 'second hit' or hits.

The nature and cause of these additional hits is the focus of ongoing research. In the case of *TEL-AML1*-positive ALL this is often the deletion of the remaining normal TEL allele. In addition, frequent deletions of B-cell transcription factors have recently been described and may play a key role in leukaemic development and progression.

Significant epidemiological data support the theory that a delayed exposure and/or an abnormal response to childhood infection may facilitate the postnatal malignant transformation in ALL. Evidence in support of this shows that regular attendance

at day care in the first year of life, used as a proxy for early exposure to infections, reduces the risk of developing ALL.

Other putative risk factors – including exposure to overhead power lines and intramuscular vitamin K in neonates – have not been demonstrated to relate to the incidence of acute leukaemia.

A small proportion of acute leukaemia develops in children with an identifiable constitutional genetic disorder. By far the most common of these is Down syndrome, which confers a 200-fold increase in the risk of megakaryoblastic (M7) AML in infants and a 20-fold increase in ALL at all age groups. Myelodysplastic syndrome and AML may be preceded by a condition peculiar to newborn children with Down syndrome called transient myeloproliferative disorder (TMD). Seen in approximately 10% of newborns with Down syndrome, TMD is characterized by the presence of a clonal proliferation of megakaryoblasts in their peripheral blood. Whilst the majority recover spontaneously, some 20% will subsequently develop AML.

Pathophysiology

ALL and AML are defined by the uncontrolled proliferation of immature cells of lymphoid (B or T) or myeloid lineages respectively. The cell of origin in which the different leukaemias arise is still subject to scientific debate. The most common form of childhood leukaemia, B-cell-precursor ALL, appears to originate in a fetal B-cell precursor; however, the evidence is indirect, as it is difficult to model and study the first steps of human leukaemogenesis. Related to the cell of origin is the question of which cells maintain the leukaemia, the so-called leukaemic stem cells. Until recently it was thought that, as in normal haematopoiesis, all types of leukaemias are maintained by a small population of highly specialized stem cells. More recently, evidence is accumulating – in particular for childhood B-cell-precursor ALL – that many blasts at different stages of maturation may be able to propagate the leukaemia. Therefore, leukaemic stem cells may be more frequent than previously thought. It is crucial for future drug development to understand the mechanisms by which a population of cells maintains the leukaemic clone in our patients, and this is currently the focus of intense research.

Presentation

In practical terms, the pathophysiology and thus the clinical symptoms and signs can be explained by proliferation of the leukaemic cells within the bone marrow and other organs of the children (Table 1).

Whilst many children are not critically unwell at presentation, certain findings require prompt action. Significant respiratory compromise may result from profound anaemia with or without cardiac failure, mediastinal obstruction, or respiratory infection. These patients are often critically ill and need careful interdisciplinary management. The same is true of the small number of children with very high white cell counts (much greater than 100×10^9/litre) who are at risk of leukostasis and resultant neurological and cardiorespiratory events.

Children presenting with leukaemia are conventionally considered to be immunocompromised, whatever the results of their full blood count. Febrile illness should be managed as for febrile neutropenia. The presence of headaches, meningism, or cranial nerve dysfunction raises the concern of central nervous system (CNS) involvement. In boys, testicular involvement results in painless enlargement of a testis.

Presenting features in acute leukaemia

Bone-marrow failure syndrome	
Anaemia	Weakness, lethargy, pallor, shortness of breath
Thrombocytopenia	Easy bruising, bleeding (e.g. nose and gums), petechiae, CNS bleeds causing spinal cord infarcts or other CNS infarcts (rare)
Neutropenia	Febrile illness, often with prolonged or unusual course
Direct infiltration	
Hepatic/splenic	Hepatosplenomegaly may cause pain from capsule stretch
Medullary	Bone pain (may also have peri-osteal infiltration)
CNS	Headache, meningism, cranial nerve palsies, numbness of the chin Cord compression in AML (from chloromas) (rare)
Testicular	Painless hard enlarged testis
Thymus	Superior vena cava syndrome with distended veins and facial/neck swelling, dyspnoea, cough (typical in T-ALL)
Gum	Classical of monocytic AML
Skin	Leukaemia cutis (typical in babies with monocytic AML)
Soft tissues	Chloroma formation in AML
Other	
Leukostasis: WCC $>100 \times 10^9$/litre (very rare)	Poor perfusion of vital organs, pain from infarcts, priapism, visual disturbance
Coagulopathy	Classically seen in acute promyelocytic leukaemia, but also in other types of AML (e.g. monocytic leukaemias with a high cell count), potentially severe CNS bleeds causing spinal cord infarcts or other CNS infarcts

CNS, central nervous system; T-ALL, T-cell acute lymphoblastic leukaemia; AML, acute myeloid leukaemia.

Table 1

Immediate management

Essential diagnostics

Essential diagnostic investigations are aimed at confirming the diagnosis of acute leukaemia and investigating for the complications, which may exist at presentation. These are:

- full blood count and peripheral blood film: malignant blasts may be present in peripheral blood and may even be immunologically assessed by flow cytometry