

CME

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Leukaemia update.

Part 1: diagnosis and management

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About 8000 people in the United Kingdom are diagnosed with leukaemia each year, and in 2010, 4504 people died in the UK from this disease.¹ Leukaemia encompasses a clinically and pathologically diverse set of conditions whose incidence and prevalence are rising. In the past, leukaemia was classified on the basis of the morphological characteristics of abnormally proliferating leucocytes in the blood and bone marrow. Emerging genetic data, however, have shown genomic heterogeneity in what were thought to be homogeneous disorders, prompting the World Health Organization to revise the classification.² Despite these advances, the profound immunological and haematological disturbances inherent in most leukaemias and the systemic side effects of chemotherapy remain complex challenges. This is a two part review with the first part focusing on the current diagnosis and management of leukaemia. The second part will consider the types of support patients need in the community.

What is leukaemia?

Leukaemia is a cancer of circulating white blood cells. Leukaemias are divided into acute and chronic types. When immature white blood cells or blasts proliferate, presentation is usually acute, whereas leukaemias arising from mature cells tend to be chronic. Leucocytes are usually of lymphoid origin (T and B cells) or myeloid origin (neutrophils, basophils, eosinophils, and monocytes). Box 1 summarises the four main types of leukaemia: chronic lymphocytic leukaemia (CLL), chronic myeloid leukaemia (CML), acute lymphoblastic leukaemia (ALL), and acute myeloid leukaemia (AML).²

What are the symptoms and signs of leukaemia?

Patients with leukaemia often present with symptoms related to bone marrow failure: recurrent infections as a result of neutropenia, spontaneous bruising or abnormal bleeding secondary to thrombocytopenia, or symptoms of anaemia (box 2). Non-specific symptoms are common. These include somnolence and fatigue, as well as the

SOURCES AND SELECTION CRITERIA

We searched PubMed for clinical trials and the Cochrane Library for meta-analyses. We also sought expert opinion from experienced consultant haematologists. Keywords used were leuk(a)emia, chemotherapy, supportive care, and community care. We also reviewed guidelines from the British Committee for Standards in Haematology and the National Institute for Health and Clinical Excellence.

Box 1 | Classification of leukaemias

Acute leukaemias: proliferation of immature blast cells

Acute lymphoblastic leukaemia: lymphoblasts

Acute myeloid leukaemia: myeloblasts

Chronic leukaemias: proliferation of mature cells

Chronic lymphocytic leukaemia: lymphocytes

Chronic myeloid leukaemia: myelocytes (for example, neutrophils, eosinophils, basophils)

Less common chronic leukaemias: large granular lymphocytic leukaemia, hairy cell leukaemia

classic “B symptoms”—fevers, night sweats, and unexplained weight loss. Signs of leukaemia are usually related to leucocytic infiltration of lymphatic nodes and organs. The resulting lymphadenopathy, hepatomegaly, or splenomegaly can cause symptoms owing to organ bulk. Less commonly, meningeal involvement can result in headache as well as cranial and peripheral nerve defects, particularly in acute leukaemias. Cutaneous infiltration and gum swelling may also occur. Hyperviscosity symptoms from a raised white cell count are rare. Notably, 75% of CLL cases are diagnosed incidentally in asymptomatic patients after a full blood count is performed for other reasons.²

What investigations are needed in suspected leukaemia?

Recognition of abnormal blood count patterns is crucial in instigating specialised investigations. Typically, leucocytosis is present, which may be accompanied by one or more cytopenias. Aggressive leukaemias may present with only a mild increase in the white cell count, whereas some indolent forms are often accompanied by dramatic leucocytosis. Therefore, unlike cytopenia, the degree of leucocytosis is a poor indicator of disease severity. Importantly, the absence of leucocytosis does not exclude a diagnosis of leukaemia. These “aleukaemic” leukaemias can have a normal or low white cell count but are usually accompanied by cytopenias. Leukaemia is unlikely in the presence of a normal full blood cell count.²

In patients with an abnormal blood count, a blood film is essential to help decide whether leucocytosis is likely to be

SUMMARY POINTS

Chronic lymphocytic leukaemia is the most common leukaemia in adults
Patients with acute leukaemia can deteriorate rapidly—urgent discussion with a haematologist is recommended if acute leukaemia is suspected
Risk is best stratified according to the genetic abnormalities of the leukaemia
Diagnosis of leukaemia requires a multidisciplinary approach
Most chronic leukaemias are not curable but can be treated with non-intensive chemotherapy
Acute leukaemias are curable if patients are fit enough for intensive chemotherapy; palliation is indicated for frail patients

caused by malignancy or inflammation. Most accredited UK laboratories perform a blood film automatically when blood count abnormalities are found, but this practice is not universal, and general practitioners may have to request a film after review of blood count results. Communication between the haematologist and the GP is vital at this stage, because clinical and pathological information must be combined to establish whether urgent admission is needed for further investigation and treatment. If the blood film is suggestive of leukaemia, specialist investigations are carried out to confirm the diagnosis. These are performed in a regional haemato-oncology diagnostic unit, which incorporates services dedicated to blood and bone marrow microscopy, the characterisation of cell surface antigens by flow cytometry, cytogenetics, and DNA mutation analysis.

The discovery of recurrent cytogenetic abnormalities in acute leukaemias, such as the t(8;21) translocation in AML, has led to changes in the way these diseases are diagnosed and treated. Until recently, a diagnosis of AML required the presence of at least 20% immature undifferentiated myeloid cells, or myeloblasts, in the bone marrow as determined manually. A normal bone marrow should have fewer than 5% myeloblasts. AML can now be diagnosed with fewer blasts if the blasts carry a chromosomal aberration associated with AML.² The reclassification of acute leukaemias on the basis of genetics rather than solely on microscopy has diversified the skill sets required for accurate diagnosis, and biomedical scientists specialising in leukaemia genetics and immunophenotyping now have a vital role in diagnosis. The clinical, morphological, immunophenotypic, and genetic data are integrated at a multidisciplinary team meeting and the leukaemia is assigned to a WHO category.

Figure 1 provides a management algorithm for patients in the community with suspected leukaemia, and the red flags box summarises the clinical features of greatest concern.

How are leukaemias managed?

Chronic lymphocytic leukaemia

CLL is the most common leukaemia in adults, with an incidence of 4.2 per 100 000 population and a median age of 71 years at diagnosis. Because CLL is associated with a long

Box 2 | Presentation of leukaemia

Acute leukaemias

- Short history of feeling unwell
- May present with neutropenic fever or bleeding
- Organ infiltration may occur: skin, gums, testes, meninges
- Peripheral blood usually shows leucocytosis with circulating blasts and cytopenias

Chronic leukaemias

- Often diagnosed incidentally
- Usually long history of non-specific symptoms
- Splenomegaly is common
- Lymphadenopathy is common in chronic lymphocytic leukaemia
- Peripheral blood usually shows leucocytosis with circulating mature lymphocytes or myeloid cells; blasts are rare

overall survival, it has a high prevalence, and most GP practices will probably see patients with this disease. Patients may have chronic fatigue, which can be marked. Stage B symptoms and bone marrow failure are typically less common at presentation but may be seen in more advanced cases, where lymphadenopathy is common, particularly in the cervical, axillary, and inguinal regions. An enlarged spleen may be palpable.

Lymphocytosis is the most common blood abnormality associated with CLL. Malignant lymphocytes in CLL express CD5 and CD23 membrane antigens, so usually have a distinctive immunophenotype.² Recommendations are available that provide a diagnostic approach to an isolated lymphocytosis for GPs.³ If the blood film raises the suspicion of CLL we recommend flow cytometry of the peripheral blood, particularly when unexplained lymphocytosis persists for more than three months. Flow cytometry is usually performed on blood collected into an EDTA tube. Additional investigations for suspected CLL include a direct Coomb's test to exclude autoimmune haemolysis (which is associated with CLL), routine biochemistry, and serum immunoglobulins.

Most patients newly presenting with CLL are classified as stage A (box 3). A meta-analysis of randomised controlled trials with more than 2000 patients showed that chemotherapy does not improve overall survival in patients with stage A disease and can cause serious toxicity. Hence, most newly diagnosed patients with stage A disease are not treated with chemotherapy but are observed on a "watch and wait" programme. Most patients with stage A CLL have a life expectancy similar to that of age matched healthy people, and the mean overall survival is greater than 10 years.⁴

Specialist referral of patients with stage A disease is not clinically mandatory, but some patients may benefit from a discussion about CLL with a specialist. A visit to an oncology unit is potentially stressful, however, and can reinforce the negative connotations of a diagnosis of leukaemia.

It may be preferable for the diagnosis to be given by a specialist, particularly if the diagnosis is in doubt, with the GP resuming management if appropriate. In line with recent guidelines from the British Committee of Standards in Haematology, we recommend a repeat full blood count and clinical review in the community after three months.

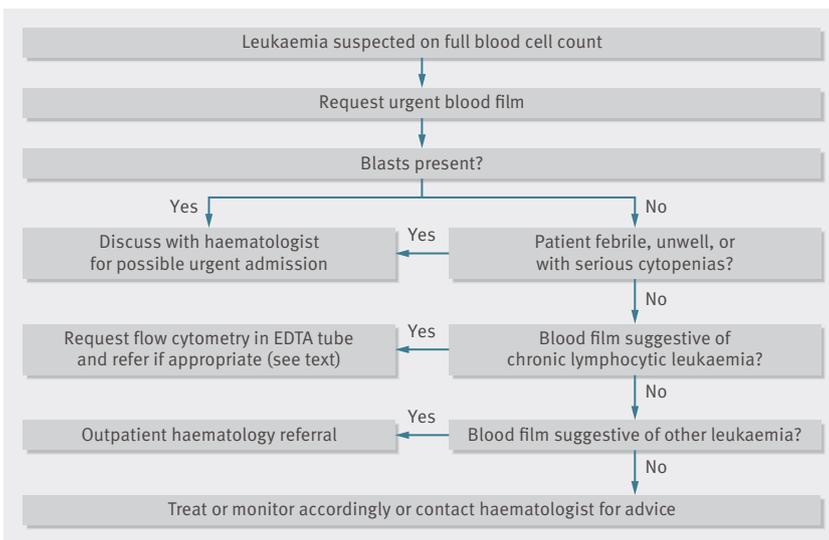


Fig 1 | Proposed management algorithm for suspected leukaemia in the community

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- ▶ Outpatient parenteral antimicrobial therapy (*BMJ* 2013;346:f15852)
- ▶ Diagnosis and management of carotid atherosclerosis (*BMJ* 2013;346:f1485)
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- ▶ Malignant and premalignant lesions of the penis (*BMJ* 2013;346:f1149)
- ▶ Postpartum management of hypertension (*BMJ* 2013;346:f894)
- ▶ Diagnosis and management of pulmonary embolism (*BMJ* 2013;346:f757)

At the first visit, advise patients to report any stage B symptoms that develop and to check their temperature if they are unwell. Most patients will have stable disease and can be reviewed every six months, then every 12 months if the disease remains stable after a year. Clinical deterioration, recurrent infections, new or worsening cytopenias, and an estimated lymphocyte doubling time of less than 12 months usually prompt specialist referral.⁵

Although most patients are initially assigned to a watch and wait strategy, this is not without its problems. A quality of life substudy of the large randomised CLL4 trial has reported that patients on such a programme often report fatigue and anxiety, particularly in relation to the lack of treatment.⁶ Patients may benefit from interaction with a support association such as the UK CLL Support Association (www.clisupport.org.uk), which works closely with the UK CLL Forum (www.ukcllforum.org), a collaborative network of CLL patients and doctors.

Patients who present with stage B or C disease as well as those with symptoms require specialist referral to assess the need for treatment. In the UK, cytogenetic analysis is performed at this time because patients with certain abnormalities, such as *TP53* deletion, have a much worse prognosis and need to be treated differently.⁷ Treatments recently approved by the National Institute for Health and Clinical Excellence (NICE) range from less intensive oral chemotherapy with chlorambucil to combination regimens that require intravenous infusions, such as bendamustine or the anti-CD20 monoclonal antibody, rituximab, combined with fludarabine and cyclophosphamide.⁸

Chronic myeloid leukaemia

Chronic myeloid leukaemia is rare, with an incidence of 1 per 100 000 population. Symptoms are usually chronic and non-specific, but splenomegaly is common and may extend beyond the umbilicus. Lymphadenopathy is not usually prominent. Neutrophilia is common and may be accompanied by thrombocytosis, basophilia, monocytosis, or eosinophilia. Blood film appearances are typical, often showing neutrophilia, thrombocytosis, basophilia, and eosinophilia. The t(9;22) translocation, also known as the Philadelphia chromosome, is the genetic hallmark of this disease; it results in fusion of the BCR and ABL proteins and leads to uncontrolled myeloid proliferation.²

Until recently, this condition progressed inexorably through acute transformation after a chronic phase of variable duration and was universally fatal without stem cell transplantation. The development of the targeted tyrosine

Box 3 | Staging of chronic lymphocytic leukaemia

Stage A: Lymphocytosis with fewer than three groups of enlarged lymph nodes

Stage B: Lymphocytosis with three or more groups of enlarged lymph nodes

Stage C: Lymphocytosis with anaemia (haemoglobin <100 g/L), thrombocytopenia (platelets <100×10⁹/L), or both

kinase inhibitor, imatinib, has revolutionised the management of these patients. Lifelong treatment with this drug remains the standard of care. The pivotal IRIS trial showed that more than 80% of patients achieve a durable remission and require only outpatient follow-up.⁹ In other patients remission is less durable, often because the leukaemic cells acquire mutations that confer resistance to imatinib.¹⁰ NICE has recently approved second generation tyrosine kinase inhibitors to treat patients who acquire imatinib resistance and those who cannot tolerate imatinib.¹¹ However, acquisition of a mutation that results in the substitution of tyrosine for isoleucine in amino acid position 315 (T315I) in the BCR-ABL fusion protein causes resistance to all currently available tyrosine kinase inhibitors, leaving intensive cytotoxic chemotherapy with transplantation as the only treatment option. Novel third generation tyrosine kinase inhibitors that can target T315I mutants are in development.¹²

Acute leukaemias

Patients with acute leukaemia typically deteriorate quickly. They may initially present with generalised fatigue and malaise but usually develop bone marrow failure. Patients may have B symptoms and coagulopathy, with mucocutaneous bleeding or bruising. Untreated acute leukaemias are among the most rapidly fatal cancers.²

ALL is the most common cancer in children. Global incidence is about three per 100 000 population, with around three of four cases occurring in children under 6 years.² It is often difficult to elicit a comprehensive history, and parents may describe the child as being somnolent or performing poorly at school over recent weeks. Timely recognition of the disease is paramount because childhood ALL is one of the most curable cancers, with intensive chemotherapy regimens yielding a long term survival rate of 85%.^{13 14}

ALL is much less common in adults but has a poor prognosis. This is because a higher proportion of adults than children have unfavourable cytogenetic abnormalities, such as the t(9;22) translocation, and many cases present in patients over 60 years, who are unlikely to tolerate intensive chemotherapy. In the recent Medical Research Council trial of intensive chemotherapy in adults with ALL, just under half of those without t(9;22) were considered cured, whereas less than a third with the translocation were alive at two years. In suitable adults, allogeneic transplantation offers the best chance of survival. This involves administration of high doses of chemotherapy followed by rescue of the bone marrow with stem cell infusions from a matched donor. Because of the intensity of this treatment, about one in three patients does not survive owing to toxicity.¹⁵

AML is the most common acute leukaemia in adults, with about 2000 new cases each year in the UK and a median age at presentation of 67 years. Patients typically present

RED FLAGS

Symptoms of leukaemia include unexplained fevers, night sweats, weight loss, and fatigue

Symptoms of bone marrow failure include infections, bleeding, bruising, and anaemia

A rapid onset of symptoms is suggestive of acute leukaemia and usually requires urgent investigation

A febrile patient with suspected leukaemia should be treated as a medical emergency

Circulating blasts often indicate acute leukaemia, which requires prompt management

TIPS FOR NON-SPECIALISTS

A blood film is crucial for investigating suspected leukaemia: acute leukaemias typically have circulating blasts at presentation

The white blood cell count is not always a good indicator of disease severity—the presence of cytopenias is more reliable

Symptomatic cytopenias usually indicate clinical urgency
Childhood leukaemias can present non-specifically

ADDITIONAL EDUCATIONAL RESOURCES**Resources for healthcare professionals**

National Institute for Health and Clinical Excellence (www.nice.org.uk)—Guidelines on the management of all types of leukaemia

British Committee for Standards in Haematology (www.bcsghguidelines.com)—Free guidelines; no registration required

Resources for patients

Macmillan (www.macmillan.org.uk)—Information on treatment

Leukaemia and Lymphoma Research (www.leukaemia-lymphoma.org.uk)—General information on leukaemia

with complications of bone marrow failure. Many patients present with infections and bleeding, and the diagnosis is usually suspected from the blood count and film.² Most patients are admitted acutely to a specialist unit for further management. For patients who are fit enough, the standard management is intensive inpatient chemotherapy. For specific patients allogeneic transplantation may be indicated, as described in a recent review.¹⁶

Curative chemotherapy regimens for AML and ALL are very intensive. Treatment is usually delivered in hospital. Most patients will have severe side effects that require hospital admission. Hospital stays can last several weeks and intensive care may be needed. Older patients are unlikely to tolerate curative regimens and often have unfavourable cytogenetics. Palliative treatment is usually offered to these patients, and the median survival is less than one year.²

Subclassification of AML on the basis of cytogenetics has largely superseded classifications based solely on morphology. For example, patients with the t(15;17) translocation are likely to have a promyelocytic morphology, and cure rates of over 80% were achieved in a large trial using a combination of idarubicin and the vitamin A analogue, all-trans retinoic acid, which is much less toxic than standard chemotherapy.¹⁷ Patients with low risk cytogenetics often respond well to standard chemotherapy and are least likely to benefit from allogeneic transplantation. Furthermore, according to the recent AML15 trial, addition of the anti-CD33 monoclonal antibody, gemtuzumab ozogamycin, may improve survival in this group.¹⁸

Summary

Advances in our understanding of the genetics of leukaemia have led to the first wave of targeted cancer treatments. Intensive cytotoxic chemotherapy combined with targeted treatments and potentially allogeneic transplantation offer a

realistic chance of cure in acute leukaemias, but for selected patients only, because of the morbidity and mortality associated with these regimens. Chronic leukaemias are usually treated non-intensively. Treatment options for patients not deemed fit for intensive chemotherapy, which include blood product transfusions and low dose chemotherapy, aim to minimise hospital admissions. Regardless of treatment intensity, many patients could benefit from community based services, recommendations for which are provided in the second part of this review.

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