Epidemiology, aetiology and risk factors

A Guide for Nurses

Leukaemia Care
Nurse Academy

In this booklet

If you would like any information on the sources used for this booklet, please email **communications@leukaemiacare.org.uk** for a list of references.

About Leukaemia Care

Leukaemia Care is a national charity dedicated to ensuring that people affected by blood cancer have access to the right information, advice and support.

Our services

Helpline

Our helpline is available 9:00am – 5:00pm Monday - Friday and 7:00pm – 10:00pm on Thursdays and Fridays. If you need someone to talk to, call **08088 010 444**.

Alternatively, you can send a message via WhatsApp on **07500068065** on weekdays 9:00am – 5:00pm.

Nurse service

We have two trained nurses on hand to answer your questions and offer advice and support, whether it be through emailing **nurse@leukaemiacare.org.uk** or over the phone on **08088 010 444**.

Patient Information Booklets

We have a number of patient information booklets like this available to anyone who has been affected by a blood cancer. A full list of titles – both disease specific and general information titles – can be found on our website at **www.leukaemiacare.org.uk/support-and-information/help-and-resources/information-booklets/**

Support Groups

Our nationwide support groups are a chance to meet and talk to other people who are going through a similar experience. For more information about a support group local to your area, go to **www.leukaemiacare.org.uk/support-and-information/support-for-you/find-a-support-group/**

Buddy Support

We offer one-to-one phone support with volunteers who have had blood cancer themselves or been affected by it in some

way. You can speak to someone who knows what you are going through. For more information on how to get a buddy call **08088 010 444** or email **support@leukaemiacare.org.uk**

Online Forum

Our online forum, **www.healthunlocked.com/leukaemia-care**, is a place for people to ask questions anonymously or to join in the discussion with other people in a similar situation.

Webinars

Our webinars provide an opportunity to ask questions and listen to patient speakers and medical professionals who can provide valuable information and support. For information on upcoming webinars, go to **www.leukaemiacare.org.uk/support-and-information/support-for-you/onlinewebinars/**

Website

You can access up-to-date information on our website, **www.leukaemiacare.org.uk**.

Campaigning and Advocacy

Leukaemia Care is involved in campaigning for patient well-being, NHS funding and drug and treatment availability. If you would like an update on any of the work we are currently doing or want to know how to get involved, email **advocacy@leukaemiacare.org.uk**

Patient magazine

Our magazine includes inspirational patient and carer stories as well as informative articles by medical professionals: **www.leukaemiacare.org.uk/communication-preferences/**

Epidemiology

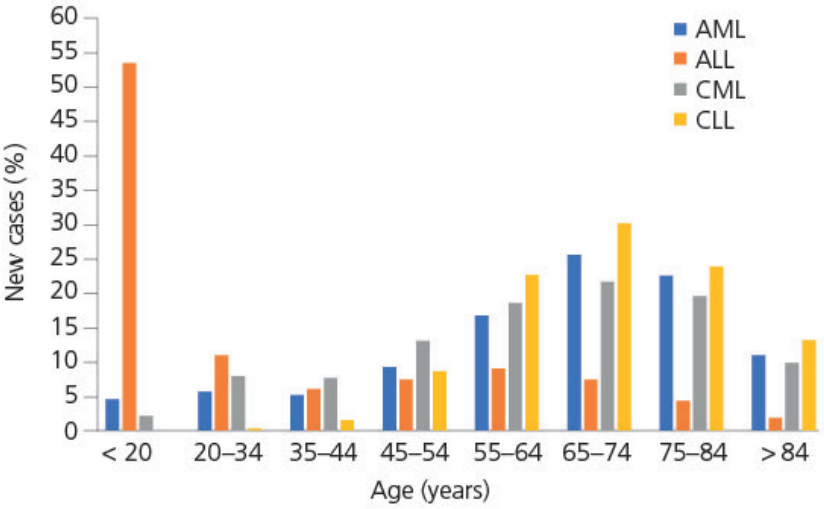

Figure 3.1 Incidence of new cases of AML, ALL, CML and CLL by age group, 2013–2017, in the USA, for all races and both sexes.

Acute myeloid leukaemia

Acute myeloid leukaemia is the most common acute leukaemia in adults, with an incidence of 4.3 new cases per 100,000 men and women per year in the USA between 2013 and 2017, and around 3200 new cases in the UK between 2015 and 2017. As such, this is a relatively uncommon cancer in comparison to many more common solid organ tumours: it accounts for 1.1% and less than 1% of all new cases of cancer in the USA and UK, respectively.

The incidence of AML increases with age (Figure 3.1). Although AML affects all age groups, according to the US-based Surveillance, Epidemiology, and End Results

Program (SEER) AML is most frequently diagnosed among people aged 65–74 years; the median age of diagnosis is 68 years, with a slight predominance in men. The fact that AML predominantly affects elderly patients, who may not be tolerant of intensive treatment, has major implications for the management of these patients. AML diagnosis is more likely in developed than developing countries and is more common in whites than in other ethnic groups.

In the USA, age-adjusted mortality for AML was 2.8 per 100,000 men and women per year in 2014–2018, with the highest mortality among people aged 75–84 years. In the UK, there were around 2600 AML-related deaths per year in 2016–2018, with the highest mortality in people aged 85–89 years. In the UK in 2018, AML accounted for 2% of all cancer deaths.

Acute lymphoblastic leukaemia

The number of new cases of ALL was 1.7 per 100,000 men and women per year in the USA between 2013 and 2017, and there were 803 new cases in the UK between 2015 and 2017.

ALL commonly affects younger people, with over 50% of patients with ALL being under the age of 20 (see Figure 3.1). The median age of diagnosis is 17 years. The management and prognosis of patients with ALL differs greatly between adults and children. There is a slight predominance in males (58% of cases in the UK). In the USA, ALL is most common in Hispanic and white populations.

In the USA, deaths from ALL are highest among people aged 65–74 years. In the UK, mortality for ALL is highest in people over 90 years old and have remained stable over the past decade.

Chronic myeloid leukaemia

The number of new cases of CML was 1.9 per 100,000 men and women per year in the USA between 2013 and 2017, and there were 788 new cases in the UK between 2015 and 2017. The incidence of CML increases with age (see Figure 3.1), with the

Epidemiology (cont.)

median age at diagnosis being 65 years. Slight predominance exists in men (54% in the UK).

CML mortality is strongly related to age, with rates being highest among people over 75 years old in both the USA and the UK. However, since the discovery of TKIs, the survival rates with this leukaemia have increased dramatically.

Chronic lymphocytic leukaemia

The number of new cases of CLL was 5 per 100,000 men and women per year in the USA between 2013 and 2017, and there were 3824 new cases in the UK between 2015 and 2017.

The incidence of CLL increases with age (see Figure 3.1), and the median age at diagnosis is 70 years. However, because of this leukaemia's indolent nature, the 5-year survival rate is high: in Europe, the average 5-year survival rate is 68% (42–80%) for men and 74% (50–82%) for women.

There is a slight predominance in white men. People who have relatives with CLL also appear to have an increased risk of developing CLL and other lymphoid malignancies; studies have shown a 6- and 8.5-fold increased risk of developing CLL if a relative also has CLL in Norway and Sweden, respectively.

Aetiology and risk factors

Genetic mutations

Like most cancers, the main risk factor for AML, CML and CLL is age, and so with an ageing population the prevalence of these conditions increases. Despite certain aetiological factors, the major reason for the development of most leukaemias is the accumulation of genetic mutations as a person ages. Many different gene mutations can lead to leukaemia. Both AML and B-cell ALL can be subtyped based on recurrent genetic mutations. CML is one of the few cancers in which a single, specific genetic mutation causes most cases: chromosome translocation t(9;22), a cytogenetic abnormality known as the Philadelphia chromosome.

The presence of pre-existing populations of cells that place individuals at risk for developing leukaemia has long been recognised. A classic example is the identification of the RUNX1-ETO fusion protein in the blood of neonates, as identified by Guthrie cards. This suggests that RUNX1-ETO fusion occurs in utero in some patients and pre-dates the development of frank leukaemia.

Predisposing conditions

Myelodysplasia or MDS is a heterogeneous group of haematopoietic clonal disorders of the bone marrow that results in one or more cytopenias. MDS is classically diagnosed by characteristic morphological features that affect myeloid, erythroid or megakaryocytic cells on a peripheral blood film or bone marrow aspirate. The risk of developing AML from MDS is highly variable: prediction can be based on several scoring systems. One of the most widely used is the revised International Prognostic Scoring System, which takes into account several factors, including the severity of cytopenias, bone marrow blast count and cytogenetic risk. The risk of developing AML affects the overall survival of patients with MDS.

Monoclonal B-cell lymphocytosis (MBL) is another example of a condition that pre-dates the onset of leukaemia. It is defined by a clonal B-cell population of less than 5×10^9/L. Patients with MBL are asymptomatic and have no lymphadenopathy

Aetiology and risk factors (cont.)

or hepatosplenomegaly. In a prospective study of over 77,000 apparently healthy people over 60 years old, 45 eventually developed CLL. In virtually all cases, a preceding diagnosis of MBL was identified. MBL has a prevalence of approximately 5% in individuals over the age of 60 years, with an annual rate of transformation to CLL of 1%.

Clonal haematopoiesis of indeterminate potential (CHIP). A surprising finding in recent years has been the high prevalence of mutations associated with myeloid neoplasms (for example, recurrent mutations in the epigenetic regulators DNMT3A, TET2 and ASXL1) in otherwise healthy individuals, the frequency of which increases with age. In one study in which exome sequencing was performed in over 12,000 patients without haematological malignancies, 10% of patients over the age of 65 years had at least one mutation suggesting clonal haematopoiesis. Patients with CHIP have an increased risk of haematological malignancies, but it is important to emphasise that most individuals with CHIP do not develop a haematological disorder.

Mutations in normal HSCs from otherwise healthy individuals accumulate over time. It has been postulated that the clones of HSCs with mutations have a competitive advantage over otherwise normal HSCs. For example, 'preleukaemic' HSCs with mutant DNMT3A from patients with AML in remission had a repopulation advantage compared with normal HSCs in an immunodeficient mouse (a xenotransplantation model).

These findings have many implications, including how they are explained to patients and how they should be monitored. Furthermore, if mutations are to be used as a marker of measurable (minimal) residual disease (MRD) it may be unclear whether the persistence of these mutated cells truly represents the presence of continuing disease.

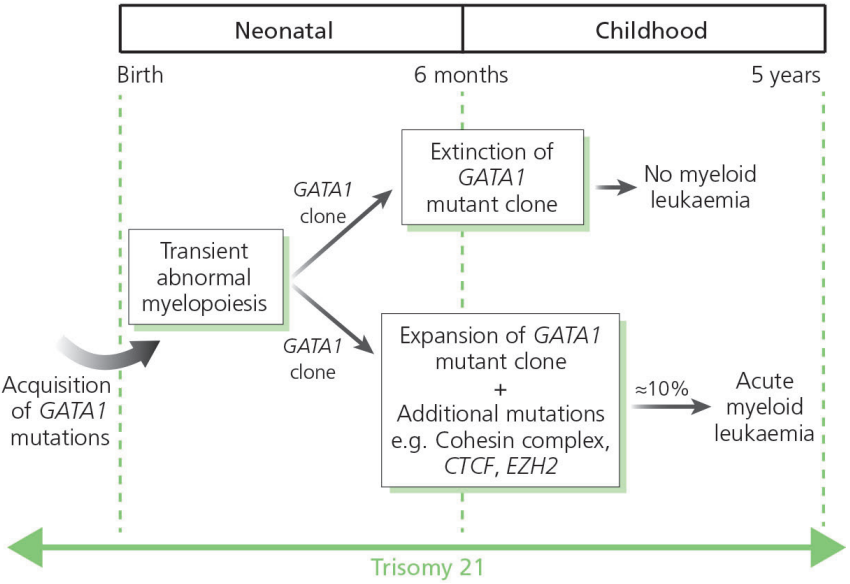

Figure 3.2 Natural history and pathogenesis of TAM and AML associated with Down's syndrome. HSCs and progenitors with trisomy of chromosome 21 acquire N-terminal-truncating GATA1 mutations resulting in TAM in early neonatal life. Most cases of TAM spontaneously remit by the age of 6 months, but in about 10% of cases additional mutations in other genes lead to further clonal expansion, resulting in AML before the age of 5 years. Adapted from Bhatnagar et al. 2016.

Inherited syndromes

Down's syndrome is associated with an increased risk of both ALL and AML. The risk differs according to age, and is greatest in early childhood. Myeloid disorders associated with Down's syndrome, including transient abnormal myelopoiesis (TAM) and AML, are characterised by a proliferation of megakaryocytes. Neonates and infants with TAM typically have excess blasts in the peripheral circulation, with varying clinical sequelae. In most patients with TAM, blasts are cleared from the peripheral bloodstream and blood counts are normal within a few months. However, a subset of patients with TAM subsequently develop AML. All patients with TAM have an N-terminal-truncating mutation in the transcription factor gene GATA1. The accumulation of other gene mutations, including those that encode the Cohesin complex, results in the development of AML (Figure 3.2).

Inherited predisposition to AML.

Aetiology and risk factors (cont.)

TABLE 3.1

2016 WHO classification of myeloid neoplasms with germline predisposition
Without a pre-existing disorder or organ dysfunction • AML with germline CEBPA mutation • Myeloid neoplasms with germline DDX41 mutation*
With pre-existing platelet disorders • Myeloid neoplasms with germline RUNX1 mutation* • Myeloid neoplasms with germline ANKRD26 mutation* • Myeloid neoplasms with germline ETV6 mutation*
With other organ dysfunction • Myeloid neoplasms with germline GATA2 mutation • Myeloid neoplasms associated with bone marrow failure syndromes • Myeloid neoplasms associated with telomere biology disorders • Juvenile myelomonocytic leukaemia associated with neurofibromatosis, Noonan syndrome or Noonan syndrome-like disorders • Myeloid neoplasms associated with Down's syndrome*

*Lymphoid neoplasms also reported.

Adapted from Arber et al. 2016.

As described above, most cases of AML are sporadic, arising as a result of the steady accumulation of mutations in somatic cells. However, a small but increasingly well-recognised subset of patients with AML have a germline inherited genetic predisposition to AML. In the 2016 WHO classification of haematopoietic diseases, 'myeloid neoplasms with germline predisposition' are classified as a separate subset of the disease (Table 3.1).

The implications of diagnosing such cases are far reaching. They include the need for genetic counselling for the patient's family and the selection of donors for allogeneic HSCT. Patients with an inherited predisposition to AML present in a variety of ways: some have no other symptoms, some have other cytopenias and some may have other organ dysfunction.

An example of one such group of disorders encompasses patients with mutations in the transcription factor GATA2 gene. In these patients, germline heterozygous mutations in GATA2 result in a predisposition to MDS and AML. There are associations with a highly variable number of presentations, including cytopenias (for example, monocytopenia) and deficiencies of other immune system components, such as dendritic cells and lymphocyte subsets, resulting in an immune deficiency and predisposition to serious and atypical infections. Other patients commonly have lymphoedema and congenital deafness as part of Emberger's syndrome (Figure 3.3).

Environmental risk factors. Exposure to benzene, high-dose ionising radiation and chemotherapeutics are all known risk factors for leukaemia to varying degrees. Patients may develop secondary AML after chemotherapy or radiotherapy for other malignancies. Those with previous exposure to alkylating agents, with or without radiation, often have a myelodysplastic phase before the development of AML, whereas those exposed to topoisomerase II inhibitors do not. These forms of AML are known as therapy-associated AML and are associated with adverse-risk cytogenetics.

Aetiology and risk factors (cont.)

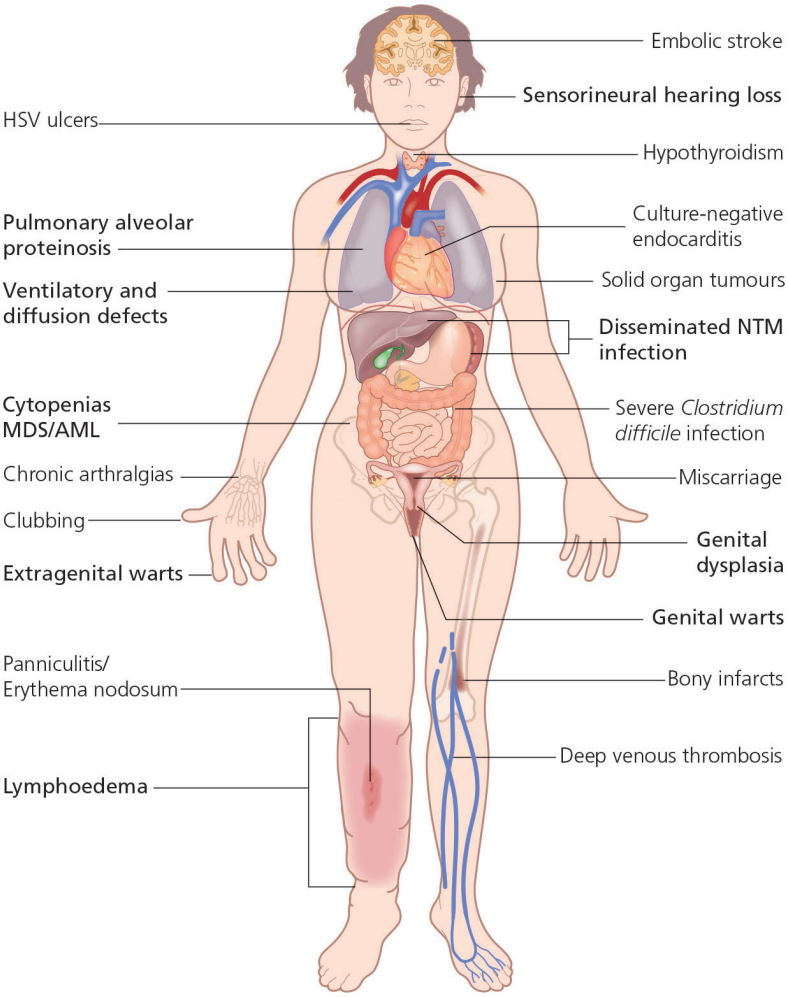

Figure 3.3 Common clinical findings in an individual with GATA2 deficiency, including MDS/AML, immunodeficiency, pulmonary disease and vascular/lymphatic dysfunction. HSV, herpes simplex virus; NTM, non-tuberculous mycobacterial. Key features are shown in bold. Adapted from Spinner et al. 2014

Key points – epidemiology, aetiology and risk factors

- AML is the most common acute leukaemia in adults.
- Age is the main risk factor for AML, CML and CLL; the prevalence of these leukaemias increases with age.
- ALL most commonly affects younger people; over 50% of patients with ALL are under 20 years of age.
- The main risk factor for AML, CML and CLL is the accumulation of recurrent genetic mutations over time.
- Predisposing conditions such as MDS and MBL increase the risk of AML and CLL, respectively.
- CHIP is present in up to 10% of the population aged over 65 years. Although this increases the risk of haematological malignancies, most individuals with CHIP do not develop a haematological disorder.
- Down's syndrome is associated with an increased risk of AML and ALL. The risk is greatest in early childhood, when TAM develops. However, TAM spontaneously remits in most cases; only about 10% of cases, with additional genetic mutations, go on to develop AML.
- Although most cases of AML are sporadic, arising from the steady accumulation of genetic mutations with age, some individuals have a germline inherited genetic predisposition to the disease.
- Environmental exposures to chemicals such as benzene, high-dose ionising radiation and previous chemotherapy increase the risk of leukaemia to varying degrees.

Leukaemia Care is a national charity dedicated to providing information, advice and support to anyone affected by a blood cancer.

Around 34,000 new cases of blood cancer are diagnosed in the UK each year. We are here to support you, whether you're a patient, carer or family member.

Want to talk?

Helpline: **08088 010 444**
(free from landlines and all major mobile networks)

Office Line: **01905 755977**

www.leukaemiacare.org.uk

support@leukaemiacare.org.uk

Leukaemia Care,
One Birch Court,
Blackpole East,
Worcester,
WR3 8SG

Leukaemia Care is registered as a charity in England and Wales (no.1183890) and Scotland (no. SC049802).
Company number: 11911752 (England and Wales).
Registered office address: One Birch Court, Blackpole East, Worcester, WR3 8SG

Leukaemia Care
YOUR Blood Cancer Charity