Down's Syndrome and Leukaemia

A Guide for Patients

Leukaemia Care
YOUR Blood Cancer Charity

Introduction

Adults and children with Down's syndrome prefer to be referred to as "a person with Down's syndrome" rather than "a Down's person" or "a Down's" as they are individuals first and foremost.

Down's syndrome (DS) can increase the risk of a wide range of medical problems, including leukaemia. If you have any questions about Down's syndrome and leukaemia – the risk of developing leukaemia, symptoms, diagnosis and possible treatments - this booklet covers the basics for you.

This booklet was written by our Patient Information Writer, Isabelle Leach and reviewed by Professor Irene Roberts, Professor of Paediatric Haematology in the Department of Paediatrics at the University of Oxford, and the Down's Syndrome Association, as well as the Down's Syndrome Medical Interest Group. We are also grateful to Leanne Tennant, whose daughter has Down's syndrome and leukaemia, for her contribution as a patient reviewer.

For more tailored information, talk to your haematologist, clinical nurse specialist or hospital pharmacist.

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

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In this booklet

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 8:30am – 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.

Patient and carer conferences

Our nationwide conferences provide an opportunity to ask questions and listen to patient speakers and medical professionals who can provide valuable information and support.

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/**

What types of leukaemia affect people with Down's syndrome?

A person with DS may have any of the same kinds of leukaemia that are seen in the wider population. However, these occur more frequently, especially in childhood. In addition, babies and young children with DS are particularly susceptible to a type of acute leukaemia which is very rarely seen in children without DS. Overall, it is estimated that around 2% of young people with DS will have had leukaemia by the time they are 16 years old.

The main subtypes of leukaemia in children with DS are as follows:

- **Neonatal leukaemia of Down's syndrome (NL-DS)** - this is seen in between 5-30% of all new borns with DS. In the laboratory it looks exactly like a normal leukaemia, but most babies look very well, have no symptoms and get better without any treatment. Some babies with NL-DS may be very unwell and will need treatment. It is associated with a gene change called a GATA1 mutation and around 1 in 5 babies who have had NL-DS will develop another leukaemia in early childhood. It was previously called transient myeloproliferative disorder or transient abnormal myelopoiesis. As it is important to know whether or not babies have NL-DS, the 2018 British Society of Haematology guidelines strongly recommend that all babies with DS should have a blood test within three days of birth to assess their risk.
- **Myeloid leukaemia of Down's syndrome (ML-DS)** - there are two kinds of acute myeloid leukaemia: ML-DS arising in association with a GATA1 mutation or sporadic AML. Overall, about 1 in 100 children with DS will develop some kind of ML-DS.
- **Acute Lymphoblastic Leukaemia (ALL)** - this affects about 1 in 100 children with DS.

The different types of leukaemia are named after the cell line in which the leukaemia has

developed. The different blood cells come from haemopoietic stem cells in the bone marrow. The stem cells might go down a myeloid or a lymphoid pathway.

Cells in the myeloid pathway may then differentiate further to become either white blood cells, red blood cells or platelets. The white blood cells in the myeloid line will eventually become neutrophils, monocytes, basophils or eosinophils.

Cells in the lymphoid pathway become different kinds of white blood cells, known as lymphocytes. These may be B-cells, T-cells or NK-cells.

All the blood cells have multiple different roles. These are usually thought of like this:

- The red blood cells carry oxygen
- The white blood cells fight infection
- The platelets help clotting to prevent bleeding and bruising

The relationship between neonatal leukaemia of Down's syndrome and myeloid leukaemia of Down's syndrome (ML-DS)

Acute myeloid leukaemia is a form of blood cancer and occurs when cells in the myeloid pathway become malignant. In children with DS this kind of leukaemia is particularly seen in those who previously had neonatal leukaemia of Down's syndrome (NL-DS). In most cases of NL-DS there is complete resolution, either spontaneously, or as a result of treatment with chemotherapy. In both groups around 1 in 5 will develop ML-DS before the age of five years old. The ML-DS in this situation is a very characteristic kind of leukaemia. It is associated with mutations in the GATA binding protein 1 (GATA1) gene which is also seen in NL-DS. The function of the GATA1 gene is to create the instructions for producing the

What types of leukaemia affect people with Down's syndrome? (cont.)

proteins that bind to specific regions of DNA, thereby helping regulate many other genes. It also predominantly affects platelets and red blood cells making parts of the myeloid pathway. This means that the leukaemia cells, also known as blasts, have a typical pattern in the laboratory - under the microscope and in flow cytometry tests. In most of these cases it is the platelet pathway that is involved and the blasts are known as megakaryoblasts. The subtype of leukaemia is sometimes referred to as megakaryoblastic leukaemia. This kind of leukaemia occurs 500-fold more often in DS and is rare in those without DS.

At present, it is not possible to predict which children with NL-DS are going to develop ML-DS. However, ML-DS is very responsive to treatment. As it appears that this kind of leukaemia develops before the age of five years old, with a median age of around two years old, surveillance is recommended. It is advised that all those who have had NL-DS have a clinical review with a full blood count and blood film check every three months up to the age of two years and then every six months up to the age of four years old. If there is any cytopenia or finding of myelodysplastic changes on the blood film, then a bone marrow aspirate and trephine is recommended. In addition to the usual tests, the samples should be sent for GATA1 mutation analysis.

Myeloid leukaemia of Down's syndrome

In addition to the kind of leukaemia previously described which is associated with NL-DS and has a GATA1 mutation, children with DS can get a sporadic kind of acute myeloid leukemia, which is more similar to that seen in children without DS. Both kinds of leukaemia may have similar symptoms, and they are treated in the same way.

Signs and symptoms

Patients with ML-DS may have one or more of the following symptoms:

- **Paleness and tiredness** - this is due to low levels of red blood cells, also known as anaemia.
- **Bruising and bleeding** - this is due to low levels of platelets, also known as thrombocytopenia.
- **Enlarged liver and spleen** - these may cause abdominal discomfort and distension.
- **Enlarged lymph nodes** - these can sometimes be felt in the neck, under the arms or in the groin.
- **Bone pain** - this may cause a limp.
- **Infections** - particularly chest infections as the white blood cells are not working as well.
- **Weakness and fatigue** - due to fibrosis in the bone marrow which impairs the production of normal blood cells; infants may be listless, showing little or no interest in things.

Diagnosis

A bone marrow biopsy is usually needed to establish a diagnosis of ML-DS. This may be an aspirate alone or a trephine sample may also be taken. These are usually performed under general anaesthetic.

Treatment

Children with ML-DS have better results with chemotherapy than children with AML who do not have DS. However, they are more susceptible to the side effects of the chemotherapy. For both these reasons ML-DS is treated with a specific protocol designed to offer the best chance of cure whilst trying to minimise side effects.

There are usually four blocks of chemotherapy. The first block is called induction, and the second consolidation. The aim

What types of leukaemia affect people with Down's syndrome? (cont.)

is to have achieved remission after these. If remission has been achieved then two further blocks of chemotherapy are given. If remission has not been reached, or if there are features that suggest relapse is likely, then an allogeneic stem cell transplant will be considered. A combination of chemotherapy drugs are given at the start of each block. The blood counts then fall and the patient is supported until the counts recover. This may take five to six weeks. Another bone marrow test is done at the end of each block to assess the response. Chemotherapy is also given directly via a lumbar puncture into the fluid that bathes the brain in order to treat that area directly. Immunotherapies, such as the monoclonal antibody drug gemtuzumab, are being used in children without DS and are likely to be added to the ML-DS protocol in future regimens as they appear to improve treatment, both in children overall, and in infants specifically.

Once the response to a block has been assessed and the count has recovered the next block will start. Altogether, for a child having four blocks of chemotherapy this usually means around six months in hospital with just short breaks at home between courses if well.

Prognosis

Overall, children with ML-DS can look forward to an excellent prognosis with an overall survival rate of around 90%. This response rate is much higher than for a similar leukaemia in children without DS. It is thought that the same mutations in chromosome 21 and the GATA1 gene that predispose children with DS to ML-DS also enable them to respond better to certain types of chemotherapy. However, if children with ML-DS relapse after treatment, the overall survival rate decreases and they have a poorer prognosis.

Acute Lymphoblastic Leukaemia (ALL)

ALL is seen in children with DS throughout childhood with a median age greater than four years, which is older than that for ALL in children without DS. Additionally, there is a virtual absence of ALL in children with DS under the age of one.

Over 90% of ALL in children with DS involves lymphocytes which have gone down the B-cell pathway and the leukaemia is known as B-cell ALL (B-ALL). The incidence of acute B-ALL is around 33 times higher in children with DS than in those without DS. T-cell ALL (T-ALL) does occur, but is much less common.

Lymphocytes are the white blood cells that are involved in the immune response. There are three types of lymphocytes:

1. **B-lymphocytes (B-cells)** - made in the bone marrow; B-cells produce antibodies that immobilise and label the bacteria, viruses, and toxins which invade the body.
2. **T-lymphocytes (T-cells)** - made in the thymus gland behind the sternum; T-cells destroy the invading organisms that have been labelled by the B-cells, as well as any cells that have become cancerous.
3. **Natural killer lymphocytes (NK-cells)** - made in the bone marrow, lymph nodes, spleen, tonsils, and thymus; NK-cells attack viruses and all types of cancer cells. NK-cells are unique because they recognise cells under attack without needing antibodies to label them and therefore produce a much faster immune response.

Causes

The reason for an increased incidence of ALL in children with DS compared with the general population is not yet

What types of leukaemia affect people with Down's syndrome? (cont.)

known. A number of good-quality population-based studies have explored whether there might be environmental risk factors, but have not identified a link.

Signs and symptoms

Children with DS and ALL may experience any of the typical signs and symptoms of leukaemia, including weakness, bruising or bleeding and increased susceptibility to infections. Bone pain appears to be more common in ALL, while an enlarged liver or spleen or enlarged lymph nodes may be less common than in AML. This is probably because ALL tends to develop very rapidly and at a faster rate than AML.

Diagnosis

In children with DS and ALL, there is no single genetic abnormality which defines the leukaemia as seen with NL-DS and GATA1. Instead, there is a wide variety of genetic changes seen and the implications of these are not yet clear in most cases.

Treatment

Children with DS and ALL do not have as good a response to chemotherapy as children without DS. When this has been studied in detail, it has become clear that this is largely because children with DS and ALL are much more susceptible to the serious side effects of the chemotherapy, but without the apparent increase in leukaemia response seen in ML-DS. This understanding led to revised guidelines for looking after children with DS and ALL focusing on reducing the risks of infectious complications in particular, as well as reducing cardiac toxicity. In the most recent UK study, UKALL 2011, it has been shown that these guidelines have reduced the number of deaths of children with DS from toxicity and so have improved the outcomes of children with DS and

ALL.

Treatment for ALL currently consists of five blocks. The first four blocks are considered to be intense and take around six to nine months to complete depending on how quickly counts recover and on what complications occur. The fifth block is called maintenance and takes just under two years. Chemotherapy for ALL is given differently to treatment for ML-DS. In most of the blocks, chemotherapy is given continuously through a block, rather than just at the start. It is also mostly delivered as an outpatient. There are some similarities. For example, response to treatment is also assessed with bone marrow tests, and chemotherapy will also be given directly to the central nervous system via lumbar punctures.

Different chemotherapy combinations are given depending on the child's risk factors, with the more intensive regimens for those with more aggressive disease. Those with more low-risk features can be given less intensive chemotherapy regimens and spared the more toxic effects. Other than infectious complications, drugs and side effects that are a particular concern in children with DS on ALL therapy include the following:

- **Dexamethasome** - this is a steroid which is an important part of ALL therapy. High blood sugar, also referred to as hyperglycaemia, can be a particular problem.
- **Daunorubicin or doxorubicin** - these both belong to a group of drugs called anthracyclines and can affect the heart. A cardiac ultrasound, called an echocardiogram, will be used to monitor the heart function and the drugs are only used if their benefit is thought to outweigh

What types of leukaemia affect people with Down's syndrome? (cont.)

the risk.

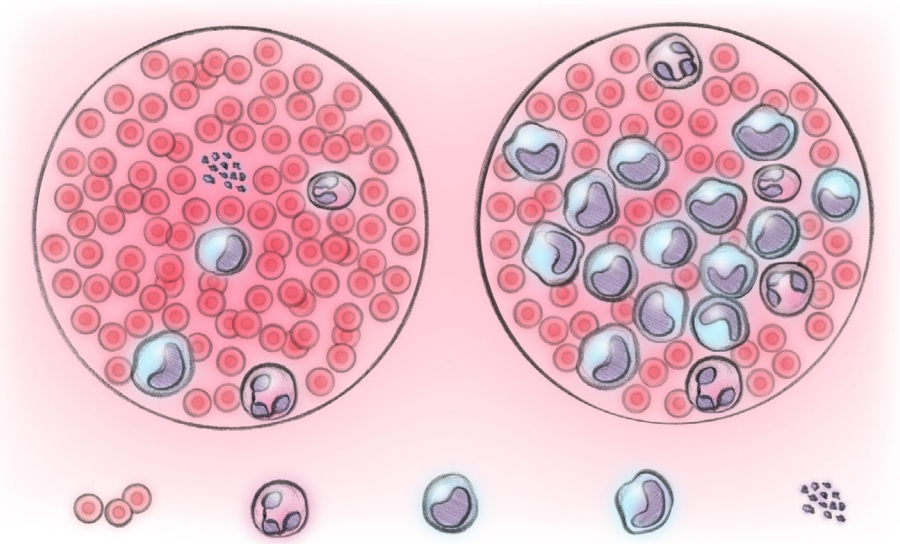
- **Methotrexate** - this may be given as a high dose treatment in the earlier part of treatment. It is also given into the central nervous system via lumbar puncture and forms part of the maintenance chemotherapy recommended for all children. Children with DS are very sensitive to methotrexate as they process it differently and so are at much higher risk of side effects from it, especially painful inflammation and ulceration of the mucous membranes lining the digestive tract, known as mucositis. This can affect any part from mouth to the perianal area.

There is ongoing work at an international level to help determine the best drug combination for particular patients and investigate the most effective new drugs.

Prognosis

The outcomes for children with DS and ALL are getting better. For children with DS and ALL, the outcomes are slightly poorer than for children without DS and ALL. In the latest published analysis of children with DS and ALL in the UK, overall survival was 70%, but unpublished data on the reduction in treatment related deaths since then means that this should have increased further.

Children with DS who have ALL are particularly sensitive to the side effects of chemotherapy. Not only should the chemotherapy regimens be adapted for children with DS and ALL, increasing the intensity of treatment to try and improve cure rates is likely to be counterproductive.



Outcomes for people with Down's syndrome and leukaemia

Today, people with Down's syndrome are living into their 50s and 60s, with some individuals living into their 70s and 80s.

While this is an encouraging reduction in mortality rates, improving the provision of supportive care for children with Down's syndrome and leukaemia remains extremely important. It is well recognised that children with Down's syndrome are more prone to infections and sensitive to the side effects of chemotherapy.

To improve outcomes for children with Down's syndrome and leukaemia, future aims should include early diagnosis, improved supportive care with antibiotic and antifungal medications, as well as respiratory support throughout therapy. In addition, to reduce the side effects of chemotherapy, treatment can be reduced in those patients with good prognoses and the search for new, less toxic drugs must continue.

Glossary

Allogeneic Stem Cell Transplantation

A transplant of stem cells from a matching donor.

Anaemia

A condition where the number of red blood cells, which contain haemoglobin and transport oxygen to body cells, are reduced. This may be due to a lack of iron, leukaemia, or sickle cell disease.

Blast Cells

Immature cells found in the bone marrow. They are not fully developed and therefore do not carry any particular function within the body. In normal humans, up to 5% of the cells found in the bone marrow are blast cells.

Bone Marrow

The soft blood-forming tissue that fills the cavities of bones and contains fat, immature and mature blood cells, including white blood cells, red blood cells and platelets.

Bone Marrow Aspirate

Bone marrow aspirates consist of taking a sample of the liquid part of the soft tissue bone marrow inside your bones using a syringe. They are crucial to establish a diagnosis of leukaemia and may be performed at stages during treatment to monitor progress.

Bone Marrow Biopsy

A bone marrow biopsy involves the collection of a sample of bone marrow from the hip bone, generally under local anaesthesia. A bone marrow surgical instrument with a cylindrical blade, called trephine, is used to remove a 1 or 2cm core of bone marrow in one piece.

Chemotherapy

Drugs that work in different ways to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing.

Chromosomes

Thread-like structures which carry the genes, and are located in the nuclei of every cell in the body. There are 46 chromosomes (23 pairs) in humans.

Fatigue

Tiredness and weakness rendering the patient unable to work or perform usual activities.

Glossary (cont.)

Genes

Genes are made up of DNA which stores the genetic information required to make human proteins.

Leukaemia

A group of cancers that usually begin in the bone marrow and result in high numbers of abnormal white blood cells. These white blood cells are not fully developed and are called blasts or leukaemia cells. Depending on the type of white blood cell involved, the leukaemia will have varying characteristics, such as being acute (develops quickly) or chronic (develops slowly).

Megakaryoblasts

Precursor cells for megakaryocyte cells that produce the platelets in the blood to prevent bleeding.

Myeloid Cell

One of the most basic cells in the bone marrow which give rise to white blood cells, red blood cells or platelets.

Platelets

Small blood cells that help the body form clots to stop bleeding.

Prognosis

An indication of how well a patient is expected to respond to treatment based on their individual characteristics at the time of diagnosis or other timepoints in the disease.

Relapse

A relapse occurs when a patient initially responds to treatment, but after six months or more, the response stops. This is also sometimes called a recurrence.

Spleen

The largest organ of the lymphatic system whose function is to help rid the body of toxins, waste and other unwanted materials. The spleen is located under the ribs on the left of the abdomen.

Thrombocytopenia

Low levels of platelets.

Useful contacts and further support

There are a number of helpful sources to support you during your diagnosis, treatment and beyond, including:

- Your haematologist and healthcare team
- Your family and friends
- Your psychologist (ask your haematologist or CNS for a referral)
- Reliable online sources, such as Leukaemia Care
- Charitable organisations

There are a number of organisations, including ourselves, who provide expert advice and information.

Leukaemia Care

We are a charity dedicated to supporting anyone affected by the diagnosis of any blood cancer. We provide emotional support through a range of support services including a helpline, patient and carer conferences, support group, informative website, one-to-one buddy service and high-quality patient information. We also have a nurse on our help line for any medical queries relating to your diagnosis.

Helpline: **08088 010 444**
www.leukaemiacare.org.uk
support@leukaemiacare.org.uk

Bloodwise

Bloodwise is the leading charity into the research of blood cancers. They offer support to patients, their family and friends through patient services.

020 7504 2200
www.bloodwise.org.uk

Cancer Research UK

Cancer Research UK is a leading charity dedicated to cancer research.

0808 800 4040
www.cancerresearchuk.org

Macmillan

Macmillan provides free practical, medical and financial support for people facing cancer.

0808 808 0000
www.macmillan.org.uk

Maggie's Centres

Maggie's offers free practical, emotional and social support to people with cancer and their families and friends.

0300 123 1801
www.maggiescentres.org

Citizens Advice Bureau (CAB)

Offers advice on benefits and financial assistance.

08444 111 444
www.adviceguide.org.uk

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

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