
Juvenile Myelomonocytic Leukaemia (JMML)

**A Guide for
Patients**

Introduction

Being told your child has juvenile myelomonocytic leukaemia (JMML) can be a shock, particularly when you may never have heard of it. If you have questions about JMML – what causes it, who gets it, how it affects your body, what symptoms to expect and likely treatments – this booklet covers the basics for you.

You will also find useful advice about how to get the best advice from your child's haematologist, plus practical advice on how to help important people in your child's life understand such a rare condition. For more information, talk to your child's haematologist or clinical nurse specialist.

This booklet was originally written, and has since been updated, by our Patient Information Writer, Isabelle Leach. It has been peer reviewed by Professor Mary Frances McMullin. We are also grateful to Jazzmyn Saunders, whose son has JMML, for her contribution as a reviewer.

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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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/online-webinars/**

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 is juvenile myelomonocytic leukaemia?

Juvenile myelomonocytic leukaemia (JMML) is classed as an overlapping condition between myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs) in the 2016 World Health Organisation classification of blood and bone marrow cancers.

- In MDS, bone marrow cells of all types reproduce uncontrollably and show abnormal (dysplastic) changes. MDS are identified by a poorly functioning bone marrow and an increased likelihood of developing acute myeloid leukaemia (AML).
- MPNs are chronic disorders where the myeloid stem cells in the bone marrow make too many abnormal red blood cells, white blood cells, or platelets which do not function properly.

The term JMML replaces all

the leukaemia conditions previously named as:

- Juvenile chronic myeloid leukaemia
- Chronic myelomonocytic leukaemia of infancy
- Infantile monosomy 7 syndrome

JMML is identified by an excessive production of the monocyte white blood cells in the bone marrow, leading to increased numbers of monocytes in the blood, bone marrow and other organs. Some of these cells develop into immature monocytes called blasts or leukaemia cells, which are unable to do their job properly. These extra monocytes can interfere with the production of the other healthy blood cells such as the red blood cells, platelets and the other white blood cells in the bone marrow.

White blood cells are one of the types of cells found

in the blood and bone marrow, along with red blood cells and platelets. White blood cells play an important part in the protection of the body against infectious disease and foreign invaders. White blood cells and their functions are:

- Neutrophils protect against bacterial infections and inflammation.
- Eosinophils protect against parasites and allergens.
- Basophils create the inflammatory reactions during an immune response.
- Monocytes remove infection products from the body.
- Lymphocytes recognise bacteria, viruses and toxins, to which they produce antibodies.

Monocytes are the largest type of white blood cell,

and, with the other white blood cells, they play an important part in the protection of the body against infectious disease and foreign invaders. Specifically, monocytes multiply in response to infection and injury, and migrate to the site of injury where they transform into macrophages and dendritic cells.

- Macrophages can swallow up and dispose of the foreign bodies or toxins, and also recruit other immune cells by secreting chemokines, which are chemical messengers.
- Dendritic cells take up the foreign substances, like bacteria or viruses, and present them to other cells, and then those other cells make antibodies against it.

In a standard functioning bone marrow, the blood forming stem cells divide either to produce more

What is juvenile myelomonocytic leukaemia? (cont.)

stem cells, or mature into either red cells, white cells or platelets. The production of new blood cells is very closely controlled so that it is balanced with the loss of worn-out cells or cells lost by bleeding or damage.

Who is affected by JMML?

JMML is a very rare disease with an incidence of between 0.6 and 1.2 per million per year for children aged 0 to 14 years. JMML represents 2% to 3% of all childhood leukaemias. Around 75% of patients are diagnosed below three years of age. Around 40% of JMML cases present before one year of age.

Boys are affected more often than girls by a ratio of 2.5 to 1.

What causes JMML?

In 10% of children with JMML, there are no identifiable gene

mutations. However, in approximately 90% of children with JMML, there is a mutation in at least one of the following genes:

PTPN 11 (Protein Tyrosine Phosphatase, Non-receptor type 11) gene mutation:

- Occurs in around 35% of children with JMML.
- Mutation in this gene can lead to the Noonan syndrome, which is characterised by unusual facial features, short stature, skeletal anomalies, heart defects, learning difficulties, and bleeding disorders.
- Deletion of chromosome 7 is also seen in around 25% of these children.

K-RAS or N-RAS gene mutation:

- Occurs in 20% to 25% of children with JMML.
- These genes are part of the RAS signalling pathway.

NF1 (Neurofibromatosis type 1) gene mutation:

- Occurs in 15% to 20% of children with JMML.
- This gene functions as a tumour suppressor, and in some patients with a mutation in the NF1 gene, the condition neurofibromatosis type 1 is also present. Patients with this gene have benign or malignant tumours, larger than average head, learning and behavioural problems, fold freckling (freckles in areas not exposed to the sun) and multiple café-au-lait (milky coffee) coloured spots.

CBL (Casitas B-lineage Lymphoma) gene mutation:

- Occurs in 10% to 15% of children with JMML.
- The CBL gene functions as a tumour suppressor and is also known to prevent normal immune

responses turning into autoimmune diseases. In children with CBL mutations, there is a high rate of the JMML resolving spontaneously.

- These children also have diminished growth, developmental delays, undescended testes and inflammation of the blood vessels.

In addition to the genetic mutations, the RAS signalling pathway may show somatic mutations, which are mutations in an individual's body that are not related to the individual's genetic mutations, and therefore cannot be passed on to their offspring. These somatic mutations can be linked to progression of JMML. These somatic mutations include the SETBP1 (SET binding protein 1) gene, the JAK3 (Janus Kinase 3) gene and ASXL1 (Additional Sex combs like 1) gene.

What are the signs and symptoms of JMML?

JMML generally progresses slowly, so there may only be a few symptoms at the onset. The most common symptoms of JMML are listed below; however, children with JMML can show any combination of these symptoms:

- Pale appearance
- General fatigue or weakness
- Decrease in appetite and/or weight loss
- Irritability
- Developmental delays
- Fever
- Rash
- Recurrent infections
- Bruising easily or bleeding
- Enlarged liver, spleen or lymph nodes
- Abdominal pain, bone and joint pain (due to overcrowding with

monocytes)

Symptoms can appear over weeks or months.

Children who have neurofibromatosis type 1 or Noonan's syndrome will also display the symptoms specific to those conditions as previously described.

How is JMML diagnosed?

The haematologist may suspect your child has a type of leukaemia, either following the results of a blood test or symptoms that you have reported to them. Further tests are required to reach and confirm a diagnosis. These test results can take a little while, which may be a worrying time for you and your child, but it is worth remembering that they are essential so your child's haematologist can reach the correct diagnosis.

Tests used to make a diagnosis

JMML is diagnosed by the use of blood tests, bone marrow aspiration/biopsy, analysis of chromosomes and gene mutations. The tests that your child may have include:

- **Full blood count:** This is a routine blood test which measures the number of red cells,

the different types of white cells, and the platelets in the blood. The blood is smeared onto a microscope slide, allowing the blood cells to be examined under the microscope.

- **Bone marrow aspiration/biopsy:** The bone marrow sample can be taken from the hip bone under local anaesthetic, using special biopsy needles. In an aspirate, liquid bone marrow is taken and/or a tiny core of bone marrow tissue using a trephine (a surgical instrument with a cylindrical blade).
- **Chromosome abnormalities or gene mutations tests:** Blood or bone marrow may be tested to check for chromosome abnormalities or gene mutations of the leukaemia cells.

How is JMML diagnosed?

(cont.)

- **Immunophenotyping:**
A process that analyses the types of antigens or markers on the surface of the leukaemia cells based on antibodies to them that are present in the patient's blood. According to which antibodies are present, it is possible to identify the type of leukaemia.
- **Minimal residual testing (MRD) testing:**
This test measures the presence of leukaemia at a molecular level rather than at a cell level. Biomarkers (a specific characteristic that helps to identify something) linked to the leukaemia cells are measured using molecular techniques such as flow cytometry to determine the very small level of leukaemia cells which are still remaining in the bone marrow of patients, but may not be seen under a microscope.

MRD testing is important in planning the next phase of your treatment.

- **Imaging investigations:**
X-rays, ultrasounds or scans, including computer tomography (CT) and magnetic resonance imaging (MRI) can be done to assess the impact of the JMML on the body's organs.
- **Measurement of hypersensitivity to GM-CSF (Granulocyte macrophage colony-stimulating factor):**
GM-CSF is a growth factor which stimulates the growth of living cells. Increased amounts of GM-CSF are added to samples of blood or bone marrow in which healthy cells will not grow, but JMML cells will grow. However, this test takes weeks to complete, and is neither standardised nor widely available.

- **Human leukocyte antigen (HLA) typing:**
Also called tissue typing, this process is used to find a suitable donor for a stem cell transplant. For children with aggressive JMML, the search for a donor is started soon after diagnosis. The proteins on the surface of the child's blood cells are matched with those of a potential donor. The greater the number of HLA markers that are shared by the patient and donor, the better the chance of a successful transplant.

Blood tests, bone marrow samples and scans will be repeated throughout treatment to monitor your child's response to treatment.

Diagnosis of JMML

JMML is a rare type of leukaemia with unusual symptoms and signs which may lead to a

misdiagnosis. Prior to reaching a diagnosis of JMML, other diagnoses are generally excluded, particularly if the child is older than the average age of two years at diagnosis. Conditions which can be similar to JMML are chronic myeloid leukaemia, acute myeloid leukaemia or other MPNs.

A definite diagnosis of JMML can be reached if the criteria set out in the 2016 World Health Classification of blood and bone marrow cancers are met. They are as follows:

Presence of all four of the following clinical and haematologic features:

- Number of monocytes in the blood equal to or greater than $1 \times 10^9/l$
- Percentage of leukaemia cells in the blood and bone marrow less than 20%
- Enlarged spleen

How is JMML diagnosed?

(cont.)

- No presence of the Philadelphia chromosome, which is an abnormal chromosome seen in all patients with chronic myeloid leukaemia and some patients with acute lymphoblastic leukaemia. Therefore, if there is no Philadelphia chromosome, the doctors know it is not ALL or AML instead. This abnormal chromosome results from the swapping over and fusion of sections of DNA between chromosomes 9 (ABL1) and 22 (BCR), resulting in a new fusion gene BCR-ABL1.

Presence of one of these genetic findings:

- PTPN11, K-RAS or N-RAS mutation, except for Noonan syndrome
- NF1 mutation or clinical diagnosis of neurofibromatosis
- CBL mutation and loss of a gene contribution from one parent

For patients with no genetic mutations, the four clinical and haematologic features listed above must be present and they must be accompanied by:

- Monosomy 7 (one copy of a chromosome pair, instead of two) or any other chromosomal abnormality
- Or at least two of the following criteria:
 - Haemoglobin F (foetal haemoglobin or HbF) must be increased for the child's age
 - Immature bone marrow cells or red blood cells seen in the blood
 - Hypersensitivity to GM-CSF

What is the treatment for JMML?

Overview of treatment

At present, the only potential cure for JMML is an allogeneic stem cell transplant (Allo-SCT), which is a stem cell transplant from a matching donor. Without an Allo-SCT, the median time of survival from diagnosis is often less than two years. Chemotherapy may lessen the symptoms of JMML, but it cannot offer a cure. Combinations of chemotherapies are regularly used to keep the disease under control while arrangements for the child to have an Allo-SCT are made.

Chemotherapy can improve the symptoms of JMML in patients who do not suffer from an aggressive form of the disease or those with no matching donor.

However, for some children, particularly those with genetic PTPN-11

mutations, CBL mutations and some somatic N-RAS mutations, their JMML resolves spontaneously for no apparent reason (spontaneous remission). These children are generally in good health and have a low level of HbF. The best treatment approach for these patients is a 'Watch and Wait' strategy, where the child is closely monitored but treatment is not started until symptoms appear or worsen.

The treatment pathway chosen for your child will be explained to you by the medical team.

Allogeneic stem cell transplantation

An Allo-SCT is the most effective treatment currently available for children with JMML. An Allo-SCT has been shown to achieve a cure in 52% to 63% of children. An early Allo-SCT following diagnosis improves the

What is the treatment for JMML? (cont.)

prognosis of children with JMML substantially. Moreover, the younger the child when the Allo-SCT is performed, the better the outcome.

During an Allo-SCT, healthy bone marrow stem cells from a matched relative or a matched unrelated donor are infused in the child's blood. These healthy stem cells migrate to the bone marrow to restore the bone marrow and start forming new blood cells. The procedure requires a hospital stay for four to six weeks, while the stem cells multiply and make new blood cells, a process which is called engraftment. After the Allo-SCT, your child will receive drugs to help prevent rejection of the donated stem cells.

To prepare the child's bone marrow to receive the healthy donor stem cells, high dose chemotherapy is given to the child to kill the leukaemia cells in the

bone marrow. This process is called conditioning of the bone marrow to prevent the donor's immune system rejecting the newly donated stem cells. In the United Kingdom, the conditioning chemotherapy regimen used in children with JMML is busulphan, cyclophosphamide and melphalan. Whole body radiation can be given with the high dose chemotherapy, but it is still controversial due to possible side effects later in life, such as small height, learning difficulties and sterility. Your child's doctor will explain why they feel it is necessary.

The main side effect with an Allo-SCT is called graft-versus-host disease. This occurs when the T-lymphocyte cells in the donated stem cells attack and destroy the child's cells which they view as foreign. Symptoms of graft-versus-host

disease include skin rashes, diarrhoea and liver damage. Graft-versus-host disease can be treated with immunosuppressants such as steroids or other immunosuppressants such as ciclosporin, sirolimus or ruxolitinib. Graft-versus-host disease tends to be more common with matched unrelated donors, mostly due to infection. Other side effects with an Allo-SCT include infections or bleeding.

Despite the negative effects of graft-versus-host disease, it also has a positive effect, known as graft-versus-leukaemia, where the donated cells not only attack the body by accident, but may attack any remaining leukaemia cells. This results in a lower relapse rate for these patients. The graft-versus-leukaemia effect is particularly useful for children who receive reduced intensity conditioning of the bone

marrow, which, because it is less toxic, may not be able to completely destroy all the leukaemia cells.

Despite any side effects, an Allo-SCT is the treatment of choice for long-term survival if a donor is available.

If you would like more information, you can get a copy of our booklet on Allo-SCT by downloading it at www.leukaemiacare.org.uk, emailing us at support@leukaemiacare.org.uk or calling 08088 010 444.

Relapse and second Allo-SCT

A relapse, where a child initially responds to treatment, but after a period of time, the response stops, is a major problem with an Allo-SCT. The rate of relapse with Allo-SCTs can range from 26% to

What is the treatment for JMML? (cont.)

58%. In approximately 35% to 40% of relapsed patients, the relapse occurs within the first year. In these cases, a second stem cell transplant can be performed and be beneficial in many individuals.

Factors that predict an increased risk of relapse are:

- Allo-SCT patient over four years of age
- Having more than 20% of leukaemia cells in the bone marrow before transplant

However, Allo-SCTs using matched family donors have similar relapse rates as matched unrelated donors, which means that a lack of a matched family donor does not prevent good Allo-SCT outcomes.

Second Allo-SCTs are not generally successful in other types of leukaemia, but they have been reported to be effective to treat relapse in over 50%

of children with JMML. A second Allo-SCT can still achieve a cure in children with JMML, particularly when combined with reduced intensity conditioning of the bone marrow, as this produces a stronger graft-versus-leukaemia effect and is more appropriate for very young children.

In a large JMML study, where a second Allo-SCT was performed adding total body irradiation to the conditioning regimen of busulfan, cyclophosphamide and melphalan, remission was seen in 46% of the children (7/15 patients), but a high rate of graft-versus-host disease was reported as a result of using total body irradiation. Remission is said to have occurred when the blood cell counts have returned to normal and less than 5% of abnormal, leukaemia cells are still present in the bone marrow.

In two later studies where

children with JMML received a second Allo-SCT, remission was seen in 100% of children (5/5 patients) who received conditioning of high-dose cytarabine and mitoxantrone in one study, and 50% of children (4/8 patients) who received conditioning of busulfan, cyclophosphamide and melphalan in the other study.

Despite the number of patients receiving a second Allo-SCT in these studies being relatively small, these findings suggest that relapse does not inevitably mean a poor prognosis and that a second Allo-SCT is a valid option for patients in good physical condition.

Chemotherapy

Despite not being able to achieve a cure for JMML, chemotherapies are still beneficial for minimising the symptoms of JMML, while arrangements for an Allo-SCT are being

made. Chemotherapy is also used to improve the symptoms of JMML in patients who do not suffer from an aggressive form of the disease. Patients with JMML may be given 6-mercaptopurine or low-dose cytarabine intravenously to control their symptoms; however, responses are usually temporary.

Without chemotherapy treatment, around one third of children with JMML normally progress rapidly. Nevertheless, there have been reports of some patients remaining in a stable condition without treatment for up to 12 years.

DNA hypomethylating agents

The use of DNA hypomethylating agents such as azacitidine or decitabine for JMML was introduced following the discovery of the presence of an abnormal DNA methylation process in

What is the treatment for JMML? (cont.)

various cancer cells.

DNA methylation is a normal chemical change to the DNA which allows cells to change from one cell type to another. Abnormal DNA methylation seen in cancer cells results in activation of the cancer genes that produce cells and suppression of the genes whose function is to prevent cancer. DNA-hypomethylating agents inhibit abnormal DNA methylation and have been successful in the treatment of adults with MDS. In newly diagnosed children with JMML, azacitidine has been shown to be effective in JMML and well tolerated, providing clinical benefit to these children.

Azacitidine is approved in the UK for the treatment of MDS, chronic myelomonocytic leukaemia and AML in adults. Encouraging results of azacitidine in children have prompted the setting up of a

Paediatric Investigation Plan for its use in children with MDS, JMML and AML. This is an agreed drug development plan between the European Medicines Agency and the pharmaceutical company so that the drug may be used for children, and the pharmaceutical company can collect the data which will be required to apply for approval of the medicine in children.

Despite the fact that DNA-hypomethylating agents cannot cure JMML, they may have a useful part to play in reducing the number of leukaemia cells before an Allo-SCT. In addition, azacitidine has been reported to achieve complete remission in some cases of JMML.

In Europe, the efficacy of azacitidine is being investigated in clinical trials for newly diagnosed or relapsed JMML patients who can't receive it under a Paediatric Investigation Plan.

New treatments

Investigations into other treatments for JMML have focussed on targeted therapies which are drugs that specifically interrupt the ability of the leukaemia cells to grow and reproduce in the body.

Following the positive results with azacitidine and decitabine, the search for more effective hypomethylating drugs is ongoing. Currently being investigated are drugs such as zebularine which is similar in action to decitabine and azacitidine, and CP-4200 that is related to azacitidine.

Another major area of research is for drugs that can block compounds further down the RAS pathway. One of these compounds is MEK (Mitogen-activated protein kinase/Extracellular signal-regulated kinase), which is particularly important in promoting cancer growth. Trametinib

is a MEK inhibitor that has shown efficacy against a number of cancers, particularly melanoma and lung cancer. A trial of trametinib for the treatment of children with relapsed and refractory JMML is ongoing (NCT03190915). The study is due to be completed in December 2021.

Farnesyl transferase inhibitors, such as tipifarnib, block some of the enzymes necessary for cancer cell growth. Tipifarnib in patients with newly diagnosed JMML was safe and yielded a 51% initial response rate as a single agent but failed to reduce relapse rates or improve long-term overall survival.

Other targeted treatments for use in JMML, still in the early stages of investigation, include:

- RAS mimetics, which disrupt the link between RAS with RAF

What is the treatment for JMML? (cont.)

- SHP-2 (Src homology phosphotyrosine phosphatase 2) inhibitors which prevents mutated SHP 2 producing too many leukaemia cells
- Chimeric antigen receptor (CAR) T-cell therapy is a targeted immunotherapy that uses the body's own immune system to fight the cancer. CAR T-cell therapy will involve genetically engineering the child's T-cells to target and kill the JMML leukaemia cells

It is likely that, in the future, JMML treatment will include the use of some of these new targeted chemotherapies in addition to an Allo-SCT.

Splenectomy

Splenectomy (removal of the spleen) prior to an Allo-SCT for the purpose of avoiding a relapse has been tried in several patients with JMML. The reasoning for

a splenectomy is that the numerous white blood cells in the enlarged spleen will prevent dormant JMML cells from being eliminated by irradiation therapy or chemotherapy, thus leading to relapse. However, it has been shown that the size of the spleen at the time of the Allo-SCT, and performing a splenectomy prior to the Allo-SCT, did not influence the risk of relapse or the probability of survival.

What is the prognosis of JMML?

The prognosis of a medical condition is its likely course based on the traits of the condition, the patient's individual characteristics and how well the patient responds to initial treatment. The prognosis of children with JMML can vary.

Seeking help early, having a proactive medical approach at diagnosis and using aggressive therapy are important

for the best prognosis. In general, the prognosis for JMML is modest because the disease has a variable course, and it is also notoriously difficult to treat given current chemotherapies are not being particularly effective. However, an Allo-SCT has been shown to achieve a cure in 52% to 63% of children.

Research has shown that patients who have additional somatic mutations in genes such as SETBP1 and JAK3 are less likely to achieve a cure compared with those with only one of the genetic mutations being PTPN 11, K-RAS, N-RAS, NF1 or CBL.

New targeted treatments, however, are continually being discovered to improve chemotherapy treatment prior to the Allo-SCT, with the aim of decreasing the side effects both from the Allo-SCT and the conditioning regimen. At present, busulphan, cyclophosphamide and

melphalan is the best conditioning used in the UK.

Being aware of your child's gene mutations and risk factors prior to the Allo-SCT can facilitate the treatment approaches. Children with PTPN 11 and CBL gene mutations often get better spontaneously, and therefore treatment is rarely needed. On the other hand, children with the mutations NF1, PTPN 11, KRAS, and the majority of those with NRAS mutations have a type of JMML that progresses rapidly, and these children require an early Allo-SCT.

The current strategy for the best prognosis in children with JMML is targeted chemotherapy alongside an Allo-SCT.

Living with JMML

After your child's diagnosis of JMML, you may find that it affects you emotionally. This chapter will talk about how receiving this news can impact you and your child.

Emotional impact of JMML

Being told your child has cancer can be very upsetting. Seeing your child with some of the symptoms of JMML can be hard to cope with and, because of this, you both may need emotional, as well as practical, support. Your child's diagnosis with a rare disease can affect you emotionally at any point of your child's journey. It is likely that you and your child will experience a range of complex thoughts and emotions, some of which may feel strange or unfamiliar. It is important to know that these feelings are all valid and a normal response to your situation.

If your child has a less aggressive type of JMML, the haematologist might advise the best course of action is the Watch and Wait approach, where your child is closely monitored, but treatment is not started until symptoms appear or worsen.

The Watch and Wait approach can be a worrying time, especially for parents. The uncertainty about whether your child's condition will progress can make you anxious and feel out of control. These are common feelings that you will ultimately need to learn to live with as the Watch and Wait approach is the best treatment strategy for your child. However, human beings are actually incredibly resilient and good at coping with adversity. It is a good idea to learn some coping strategies to help you feel less overwhelmed.

If you are worried about delaying treatment, there are some things you can do to help your child. More details are available in our booklet, Watch and Wait. Download it from our website at www.leukaemiacare.org.uk or request a copy by calling the helpline on **08088 010 444** or emailing support@leukaemiacare.org.uk.

Looking after your child and your family

Following a diagnosis of JMML you may want to make changes to your child's routine to ensure the best health of your child after the diagnosis and during treatment. Do not try to change too much at once. Adopting a healthy routine for your child is about making small, manageable changes.

A healthy lifestyle includes

a well-balanced diet and remaining active. With some of the side effects your child may be experiencing, the idea of going out to play and being active may be the last thing your child wants to do, but it is important to try and stay as active as possible to make your child feel better and distract them from some of the symptoms or side effects.

One of the most commonly experienced side effects of the treatment of JMML is fatigue. This is not normal tiredness and does not improve with sleep.

Some general tips on how to deal with your child's fatigue include:

- Having a regular lifestyle – going to bed and waking up at approximately the same time every day
- Taking part in regular, gentle play to maintain

Living with JMML (cont.)

your child's fitness level as much as possible

- Building rest periods in your child's day to preserve their energy for what is important
- Avoiding stimulating activities before going to bed, such as television, or using laptops, tablets or mobile phones, if applicable
- Keeping your child's bedroom quiet and at a comfortable temperature
- Talking to your child about their worries
- Discussing your child's symptoms with their doctor or nurse

Practical support

Work and finances

If your child is diagnosed with JMML, it can sometimes lead to difficulties relating to your work life. You may want to reduce working hours, but it can also mean that

you have to stop work altogether. You may need to make an arrangement with your employer for times when you need to accompany your child into hospital.

It is often worth taking time to explain your child's JMML to your employer, as it is likely they will never have heard of the disease. Your child's consultant or your GP can arrange letters to confirm your child's diagnosis to help you explain your situation to your employer.

If you would like more information about speaking to your employer or about some of the things you may be entitled to, you can speak to our Patient Advocacy team by emailing advocacy@leukaemiacare.org.uk or by calling 08088 010 444.



Talking about JMML

Talking to the haematologist

JMML is a rare condition. It is important for you to develop a good working relationship with the haematologist and/or clinical nurse specialist, so your child is given the best treatment possible.

The following gives advice on working well with your child's haematologist:

- If it is an initial consultation, take along a list of your child's current medications and doses, and a list of any allergies your child may have.
- If your child has a complicated medical history, take a list of diagnoses, previous procedures and/or complications.
- Make a list of questions to take to the appointment. This will help the discussion with your child's

haematologist.

- It can be useful to repeat back what you have heard so that you can be sure that you fully understand what the next steps are for your child.
- Note information down to help you remember what was said.
- Be open when you discuss your child's symptoms and how you and your child are coping. Good patient-doctor communication tends to improve outcomes for patients.

Other tips:

- Bring someone else along with you to your child's appointment – they can provide support, ask questions and take notes if you are focussing on your child in the appointment.
- Do not be afraid to ask for a second opinion – most haematologists are

happy for you to ask.

You need to tell the haematologist if...

Your child is having any medical treatment or taking any products such as prescribed medicines, over the counter treatments or vitamins. It is important to understand that treatments, including complementary therapies, which are perfectly safe for most children, may not be safe if your child is receiving treatment for JMML.

If you choose to start your child on any form of complementary treatment outside of their medical treatment, discuss this with their haematology consultant or clinical nurse specialist, prior to beginning it.

It is important to understand the difference between complementary therapies, used alongside standard treatment, and alternative therapies,

used instead of standard treatment. There is no evidence that any form of alternative therapy can treat JMML.

Talking to other people

Telling people that your child has a rare condition like JMML can be hard to explain. You might find it useful to let your close family and friends, as well as your employer, know about your child's health condition. It might be easier to provide people with basic information and give them information leaflets or a booklet like this one about JMML if they want to know more in-depth details.

It is probably best to focus conversations on the symptoms that your child is experiencing, how the condition affects them and how they feel about it. Often people misunderstand and, unfortunately, it will mostly fall to you to

Talking about JMML (cont.)

educate them as best as you can. Where possible, it's advisable to let people know what you find helpful and unhelpful, in terms of what others say and do.

Often people make assumptions and do what they think helps. For example, saying your child looks well, recounting stories of others they know with a similar diagnosis, encouraging you to look ahead and stay positive is not always what people really want to hear. In many ways, the more you communicate with them, the better.

These points may help you:

- Explain that your child has a condition that means their bone marrow does not function properly, and that this affects the number of blood cells it produces
- Explain your child's symptoms (maybe tiredness or a lot of pain)

You could also consider the following when telling people about your child's diagnosis:

- **Find out more** - Try to find out as much as you can about your child's condition, from reliable internet sources, charitable organisations or your child's consultant haematologist. The more you know, the more you can share.
- **Have a print-out to hand** - It may help to have some information to hand to share with family and friends. This will take the pressure off you having to remember everything they may want to know.
- **Explain yours and your child's needs** - Try and be clear about what your needs may be. Perhaps you need help with the weekly food shop, help with cooking dinner, or someone to drive you to and from your child's appointments. You may

find that friends and family are pleased that they can do something to help you.

- **Be open about how you feel** - Don't be afraid of opening up about how you feel, as people who care will want to help you as best they can. Talk as and when you feel comfortable, so those around you will know when you need them most.

If you're struggling to come to terms with your child's diagnosis and prognosis, you can speak to us on our helpline. Call us on **08088 010 444**.

Glossary

Acute Leukaemias

Leukaemias which progress rapidly and are generally aggressive. There are two main types: acute lymphoblastic leukaemia and acute myeloid leukaemia.

Acute Lymphoblastic Leukaemia (ALL)

A leukaemia in which lymphocytes start multiplying uncontrollably in the bone marrow, resulting in high numbers of abnormal, immature lymphocytes. Lymphocytes are a type of white blood cell involved in the immune response.

Acute Myeloid Leukaemia (AML)

A rapid and aggressive cancer of the myeloid cells in the bone marrow.

Allogeneic Stem Cell Transplant (allo-SCT)

A transplant of stem cells from a matching donor.

Antigen

A toxin or other foreign substance which induces an immune response in the body, especially the production of antibodies.

Blast Cells (Blasts)

Immature cells found in the bone marrow which are not fully developed. Up to 5% of the cells found in the bone marrow are blast cells. Patients with leukaemia have a much higher number of immature, abnormal cells called blast cells.

Blood Cancer

Cancer of blood cells from the bone marrow or lymphatic system. There are three main types of blood cancer:

- Leukaemia begins in the bone marrow and is classified according to the type of blood cell it affects (either myeloid or lymphoid) and whether it grows quickly (acute) or slowly (chronic).
- Lymphoma starts in the lymphocyte white blood cells within the lymphatic system.
- Myeloma is a cancer of the plasma cells and starts in the bone marrow. Plasma cells are a type of white blood cell that makes antibodies.

Blood Cells

Cells present in the blood and bone marrow which include red blood cells, white blood cells and platelets. These three types of blood cell make up 45% of the blood volume, with the remaining 55% being plasma, the liquid component of blood.

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

A bone marrow aspirate consists 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 one to two-centimetre core of bone marrow in one piece.

Café-au-lait Spots

Milky coffee (in French) coloured spots typically seen in patients with neurofibromatosis type 1.

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.

Chimeric

The description given to an organism that contains cells from two or more different species.

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.

Glossary (cont.)

Chronic Leukaemias

Leukaemias which progress slowly and are less aggressive than acute leukaemia. There are two main types: chronic lymphocytic leukaemia and chronic myeloid leukaemia.

Clinical Trials

Trials designed and planned to determine a specific answer or aim; for example, whether treatment A is better than treatment B. The study will be conducted in patients who meet particular inclusion criteria, and the results are collected and analysed to provide an answer.

Complete Molecular Remission

Complete remission with no leukaemia cells anywhere else in the body (i.e., no minimal residual disease).

Complete Remission

Complete remission has occurred when:

- Blood cell counts have returned to normal
- Less than 5% of

abnormal, leukaemia cells are still present in the bone marrow

Conditioning Regimen

This consists of chemotherapy or total body irradiation to eliminate the cancer cells and prevent the immune system rejecting the new stem cells prior to an allogeneic stem cell transplant.

Corticosteroids (Steroids)

Hormones normally produced by the adrenal glands which are two small glands found above the kidneys. Corticosteroids reduce inflammation (redness and swelling) and the activity of the immune system. They are used for inflammatory conditions such as asthma and eczema and autoimmune diseases such as rheumatoid arthritis.

Cytarabine

An antimetabolite drug which works by disrupting the DNA of cancer cells, thereby slowing or stopping their growth.

Dendritic Cells

Dendritic cells are white blood cells that capture toxins or other foreign substances and present them to the T-cell lymphocytes for destruction. A dendritic cell has a branched appearance resembling a tree, hence its name.

DNA (Deoxyribonucleic Acid)

A thread-like chain of amino acids found in the nucleus of each cell in the body which carries genetic instructions used in the growth, development and functioning of the individual's cells.

Engraftment

The process by which stem cells from a donor multiply and make new blood cells.

Eosinophil

A type of white blood cell which protects against parasites and allergens.

Farnesyltransferase

The enzyme involved in activating the RAS protein to transfer growth signals to normal cells of the body.

Farnesyltransferase Inhibitor

If there is a mutation in the RAS protein, inhibiting farnesyltransferase will prevent activation of the mutated RAS protein.

Flow Cytometry

The technology used to analyse the physical and chemical characteristics of particles in a fluid as it passes through at least one laser. A flow cytometer can rapidly measure the size and structures of thousands of cells.

Genes

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

Graft-versus-Host Disease (GvHD)

A serious complication that occurs with allogeneic stem cell transplants. It happens when the graft (donated marrow or stem cells) reacts against the host (patient receiving the stem cells).

Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)

A growth factor required

Glossary (cont.)

to stimulate the growth of living cells.

Granulocytes

Group of white blood cells, which have granular bodies in their cytoplasm. They include the neutrophils, eosinophils and basophils white blood cells, all of which protect the body from bacteria, allergens and inflammation.

Haemoglobin

A red protein contained within the red blood cells and responsible for transporting oxygen to the tissues of the body.

Haemoglobin F

Foetal haemoglobin. Normal range: 0.3% to 4.4% of haemoglobin.

Human Leukocyte Antigen (HLA) Typing

Also called tissue typing, this process is used to find a suitable donor for stem cell transplantation. The proteins on the surface of the patient's blood cells are matched with those of a potential donor. The greater the number of HLA markers that are shared

by the patient and donor, the better the chance of a successful transplant.

Hypomethylating Agents

Drug that inhibits the DNA methyltransferase enzyme, which prevents DNA from producing the proteins required for the normal development of JMML cells.

Immunophenotyping

The process that uses antibodies to identify cells based on the types of antigens or markers on the surface of the cells. This process is used to diagnose specific types of leukaemia and lymphoma by comparing the cancer cells to normal cells of the immune system.

JAK Gene

The Janus Kinase gene manages signals from cytokines.

JAK3 Gene

The specific Janus Kinase 3 gene.

Lymph Nodes

A component of the lymphatic system (part of the body's immune system) that contain

lymphocytes which produce antibodies and macrophage cells which digest dead cells. Lymph nodes are swollen with cell fragments in the event of infection or cancer. They are located mainly in the spleen but also in the neck, armpit and groin.

Lymphocytes

Type of white blood cell that is vitally important to the immune response. There are three types of lymphocytes: B-cells, T-cells and natural killer (NK)-cells. B-cells produce antibodies that seek out invading organisms. T-cells destroy the organisms that have been labelled by the B-cells, as well as internal cells that have become cancerous. NK-cells attack cancer cells and viruses.

Macrophage

A type of white blood cell that submerges and digests cellular debris, foreign substances, microbes, cancer cells, and anything else that does not have the type of proteins specific to healthy body cells on its surface.

Megakaryocyte

A large cell in the bone marrow which produces the platelets in the blood to prevent bleeding.

Melanoma

Cancer of the pigment-producing cells in the skin known as melanocytes.

Minimal Residual Disease (MRD)

A measure of the presence of leukaemia at a molecular level rather than at a cell level. It is measured using molecular techniques such as flow cytometry and polymerase chain reaction analysis.

Mitogen-activated protein kinase extracellular signal-regulated kinase (MEK)

The enzyme involved in the communication of a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell.

Monoclonal antibody

Man-made antibodies created from identical cloned immune cells so that they all bind to the same protein commonly found on the leukaemia

Glossary (cont.)

cells such as CD20.

Monocyte

A white blood cell that attacks invading organisms and helps combat infections.

Mutation (Gene)

The permanent alteration in the DNA sequence of a gene, so that it differs from what is found in most people.

Myelodysplastic syndromes (MDS), also called myelodysplasia

Myelodysplastic disorders occur when the bone marrow does not make enough normal blood cells. The blood cells made are not fully developed and not able to work normally. These blood cells include red blood cells which supply oxygen to the body's tissues, white blood cells which fight infection and platelets which help blood clot.

Myeloproliferative Neoplasms (MPN)

A group of diseases of the bone marrow in which excess cells are produced.

Neoplasm

Medical term for cancer, meaning literally a new and abnormal growth of tissue anywhere in the body.

NeuroFibromatosis Type 1 (NF1) Gene

NF1 gene is present in a genetic condition characterised primarily by changes in skin colour and the growth of benign (non-cancerous) tumours along the nerves of the skin, brain, and other parts of the body.

Neutrophils

A white blood cell involved in fighting inflammation and infection specifically bacterial infections.

Noonan Syndrome

Syndrome characterized by unusual facial features, short stature, skeletal anomalies, heart defects, mild intellectual handicap, and bleeding disorders. The syndrome is caused by a mutation in the PTPN 11 gene. Up to 35% of patients with JMML have a mutation in the PTPN 11 gene. In JMML occurring in patients with

Noonan syndrome, the cancer is often benign and transitory.

Philadelphia chromosome, also called Breakpoint Cluster Region-Abelson Murine Leukaemia Viral proto-oncogene 1 (BCR-ABL1)

An abnormal chromosome fusion gene due to a swapping over and fusion of sections of DNA between chromosomes 9 (ABL1) and 22 (BCR), resulting in a new fusion gene BCR-ABL1. This gene causes overproduction of myeloid cells. It is found in all patients with chronic myeloid leukaemia and some patients with acute lymphoblastic leukaemia.

Plasma Cell

A type of white blood cell that produces antibodies and is derived from B-cells. It is an ovoid (egg-shaped) cell with an off-centre nucleus.

Platelets

One of the types of blood cells which help 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 timepoint in the disease.

Proliferation

Rapid increase, for example in the number of cells.

Protein Kinase Inhibitor

Protein kinase inhibitors block the protein kinase enzymes that are involved with cell growth, thereby preventing the growth of the cancer cells.

Protein Tyrosine Phosphatase Non-Receptor Type 11 (PTPN 11) Gene

PTPN 11 is a gene involved in regulating a variety of cellular processes including cell growth, cell division and cancer transformation.

RAS Gene

The Rat Sarcoma Virus gene which acts as an on/off switch in cell signalling.

Red Blood Cells

Small blood cells that contain haemoglobin and carry oxygen and other substances to all tissues

Glossary (cont.)

of the body.

Refractory Condition

A condition for which treatment does not result in a remission. However, the condition may be stable.

Relapse

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.

SET Binding Protein 1 (SETBP1) Gene

SETBP1 gene involved in DNA replication. Mutations in this gene are associated with severe mental retardation, distinctive facial features, and multiple congenital malformations.

Signal Transducer and Activator of Transcription (STAT) Gene

The gene that is involved in cell signalling.

Signal Transducer and Activator of Transcription 5 (STAT5) Gene

STAT5 genes are involved

in signalling and mediating how specific genes provide instructions for making proteins.

Skin Fold Freckling

Freckles in areas not exposed to the sun.

Spleen

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

Src Homology Region 2 (SH-2) Tyrosine Phosphatase (SHP2)

The protein involved in the signalling processes of numerous cells and has been noted to have a role in several cancers.

Stem Cell

Most basic cell in the body that has the ability to develop into any of the body's specialised cell types, from muscle cells to brain cells. However, what makes these stem cells reproduce uncontrollably, as in cancer, is thought to be linked to chromosome

abnormalities.

Stem Cell Transplant

The transplant of stem cells derived from part of the same individual or a donor.

Targeted Therapy

Drugs that specifically interrupt the leukaemia cells from growing in the body. However, these drugs do not also harm the body's healthy cells the way conventional drugs do.

Total Body Radiation

Radiation treatment to the whole body to prepare a patient for a stem cell transplant. Total body radiation is used to destroy or suppress the patient's immune system in order to prevent rejection of the donor's stem cells. In addition, it can eliminate any residual cancer cells in the patient's body to increase the chances of a successful transplant.

Watch and Wait

A management approach for slow growing blood cancers. Also called active monitoring, the Watch and Wait approach is the

current standard of care for patients with slow growing blood cancers who do not have any symptoms. Treatment is usually started either once symptoms appear or when test results suggest the blood cancer is progressing.

White Blood Cells

White blood cells are one of the types of cells found in the blood and bone marrow, along with red blood cells and platelets. White blood cells create an immune response against both infectious disease and foreign invaders. Granulocyte white blood cells include the neutrophils (protect against bacterial infections and inflammation), eosinophils (protect against parasites and allergens) and basophils (create the inflammatory reactions during an immune response). Other white blood cells include the lymphocytes (recognise bacteria, viruses and toxins, to which they produce antibodies) and monocytes (clear infection products from the body).



Leukaemia Care is a national blood cancer charity supporting anybody affected by a blood cancer. This includes patients, family, friends and the healthcare professionals that support them.

To make a donation or become a regular giver, please visit www.leukaemiacare.org.uk/donate

Thank you!

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

Blood Cancer UK

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

0808 2080 888
www.bloodcancer.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

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