CAR-T Therapy

A Guide for Patients

Leukaemia Care
YOUR Blood Cancer Charity

Introduction

Chimeric antigen receptor T-cell (CAR-T) therapy is a new type of cancer treatment that uses the patient's T-lymphocyte white blood cells (T-cells) to target and destroy specific cancer cells. For information on how it works, who can receive this treatment and potential side effects - this booklet covers the basics for you.

The booklet was compiled by our Patient Information Writer Isabelle Leach and peer reviewed by Dr Sara Ghorashian at UCL Great Ormond Street Institute of Child Health and Saskia Burridge, CAR-T Cell Therapy Nurse Specialist at GOSH. We are also grateful to Sophie Wheldon for her valuable comments 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 quarterly magazine includes inspirational patient and carer stories as well as informative articles by medical professionals: **www.leukaemiacare.org.uk/communication-preferences/**

What is CAR-T therapy?

Chimeric antigen receptor T-cell (CAR-T) therapy is a new type of cancer treatment in which the patient's T-lymphocyte white blood cells (T-cells) are removed and genetically altered to make them recognise and target specific cancer cells when re-infused back into the patient.

Your immune system helps to keep you healthy by fighting illnesses and bugs. Lymphocytes are a part of the immune system that help to fight different bugs such as bacteria and viruses.

There are three types of lymphocytes:

1. **B-lymphocyte white blood cells (B-cells)** - B-cells produce antibodies that seek out invading foreign substances or antigens. Antibodies help us to fight infection by labelling bugs which can then be removed efficiently by the body. Sometimes B-cells can mutate and turn into cancer cells, one type is called B-cell acute lymphoblastic leukaemia.
2. **T-lymphocyte white blood cells (T-cells)** – They destroy the foreign substances that have been labelled by the B-cells, such as viruses like the common cold or virally-infected cells.
3. **Natural killer lymphocyte white blood cells (NK-cells)** - NK-cells attack cancer cells and viruses.

How does CAR-T therapy work?

CAR-T therapy contains the patient's own living T-cells that have been modified by adding a special antibody to make the T-cells better at recognising the cancer cells and getting rid of them. CAR T-cells target the antibody CD19 which is present on the surface of nearly all B-cells, but not on other normal cells in the body.

The CAR-T therapy process which modifies the T-cells requires a number of steps over several weeks:

Leukapheresis

The patient's T-cells are collected from the blood by a process called leukapheresis. This is a process where blood is collected from one vein, passed through a machine to filter out the white blood cells, and then the remaining blood is returned to the body. Normally, a large needle is placed in one arm for the blood to flow out of and a cannula is placed into the other for the blood to return into. This process is painless but does take four to five hours and sometimes needs to take place over two days. If access is extremely bad, it will require a central line to be inserted into a big vein, normally in the groin or neck area.

Manufacture and bridging

The T-cells which have been collected are sent to the pharmaceutical manufacturer's laboratory where they are modified. This process normally takes five to six weeks and you may be given some treatment during this period. Your doctor will explain this treatment if necessary.

The modified CAR T-cells are now able to recognise the antigens on the surface of the cancer cells. These antigens are called CD19.

Admission and infusion

Patients will be admitted to a ward to begin their treatment once the CAR T-cells have been delivered back to the treatment centre. Most patients receiving CAR-T therapy are given a course of chemotherapy before they receive the CAR-T therapy to make a space for the CAR T-cells to expand in the blood and bone

marrow. This step, which is called lymphodepletion, depends on the patient's lymphocyte count, but is normally delivered wherever possible. The chemotherapy will be explained in more detail by your doctor, but some of the drugs used may be ones you have had before.

The aim is for CAR T-cells to stay in the body for a long time, recognising and attacking the specific cancer cells to give the patient the best chance of long-term remission. Infusion of CAR-T therapy can be thought of as a one-time treatment, but it must be noted that not all CAR T-cell products will persist and further treatment could be needed.

Who can receive CAR-T therapy?

There are currently two CAR-T therapies that have been approved by the National Institute for Health and Care Excellence (NICE) for use by the National Health Service (NHS) England:

- Tisagenlecleucel (KYMRIAH®, Novartis Europharm Ltd) approved for treating B-cell ALL and DLBCL.
- Axicabtagene ciloleucel (Yescarta®, Gilead Sciences Ltd) approved for treating DLBCL.

These are available for:

- Patients up to 25 years of age with refractory or relapsed B-cell acute lymphoblastic leukaemia (ALL).
- Adult patients with refractory or relapsed diffuse large B-cell lymphoma (DLBCL) in whom two or more previous treatments have failed.

Patients are usually referred to a treatment centre through the national panel, where clinical experts will discuss a patient's individual case and confirm eligibility. Your consultant will be able to give you more information about whether CAR-T therapy may be the right treatment for you and, if so, they can refer to the national panel.

Where is CAR-T therapy available?

A collaboration between NHS England, the Joint Accreditation Committee of the International Society for Cellular Therapy-Europe (JACIE), the European Society for Blood and Marrow Transplantation (EBMT) and the pharmaceutical companies manufacturing the CAR-T therapy has enabled specialised centres to operate across the country. JACIE is Europe's only official accreditation body for haematopoietic stem cell transplantation and cellular therapy.

In England, the referral centres for CAR-T therapy for B-cell ALL are shown below:

- Great Ormond Street Hospital
- University College London Hospital

- King's College London
- Royal Manchester Children's Hospital
- The Christie NHS Foundation Trust
- Manchester Royal Infirmary
- Birmingham Queen Elizabeth Hospital
- University Hospitals Bristol NHS Trust
- Great Northern Children's Hospital Newcastle

At present, many children will have to travel to their nearest CAR-T treatment centre if they are referred. This includes Scotland, Northern Ireland and Wales. Geographical location is considered at the national panel, where possible, for families travelling from afar.

What are the possible side effects of CAR-T therapy?

There are two main side effects seen when being treated with CAR-T therapy. They are normally short lasting; however, you will be monitored in hospital for signs and symptoms so supportive care can be put in place during this time.

Cytokine release syndrome

Cytokines are released as the CAR T-cells work to get rid of the CD19 positive cells. They are a large group of small proteins involved in signalling between cells in the body. Cytokines are important for the immune system, specifically in the immune response and inflammation. When cytokines are released after CAR-T infusion, many can be triggered in a small period of time causing what is called cytokine release syndrome.

Symptoms of the cytokine release syndrome may include high fever and/or chills, headaches, low blood pressure, and difficulty breathing. These symptoms can vary in severity. Very occasionally, cytokine release syndrome may result in more serious side effects such as heart symptoms, poor kidney function and multiple organ failure. These serious side effects require intensive care treatment.

Not all patients have all of these symptoms and therefore they are treated as they arise.

Neurological problems

Patients on CAR-T therapy may suffer from neurological symptoms such as confusion, difficulty speaking and understanding language, and difficulty writing. In more severe cases, patients may have a very reduced response to stimulation and generally a poor level of consciousness. These side effects are reversible in the majority of cases but may take several weeks to return to normal. There does not appear to be any long-term side effects. Nevertheless, some of the side effects can be life-threatening and the cause of these neurological side effects is a topic of research among specialists.

Less common side effects

Infections

Some patients may develop infections during the admission for CAR-T therapy. Serious infections are rare and often due to the additional chemotherapy required prior to the CAR-T therapy. The risk of developing a severe infection is no different to any other form of intensive therapy given to patients who have relapsed a number of times.

The CAR T-cells target all CD19 cells, including normal functioning B-cells that help in producing antibodies called immunoglobulins. Over time, immunoglobulin levels may decrease, causing an increased risk of infection. Your centre will monitor these and may decide that you need replacement therapy.

Tumour lysis syndrome

CAR-T therapy can cause a large number of cancer cells to be killed over a short period of time, releasing their contents (called blood uric acid) into the bloodstream. This increase in blood uric acid, which may cause damage to the kidneys, heart or liver, is called tumour lysis syndrome. It can be managed with standard supportive treatments.

What is the likely future for CAR-T therapy?

CAR T-cells are continually being modified to improve the effect of CAR-T therapy, reduce the number of side effects and, more recently, to avoid relapse.

Relapse

CD19 CAR-T therapy has been shown to achieve remission in up to 90% of patients with B-cell ALL. However, despite this excellent short-term response, relapse is known to occur in a subset of up to 30% of patients.

Patients who relapse after CD19 CAR-T therapy have been shown to be either:

- **CD19-positive** - CD19 target antigens are still present on the surface of cancerous B-cells, and the relapses are thought to be linked to poor T-cell function or early CAR T-cell disappearance.
- **CD19-negative** - the CD19 target antigen on the surface of cancerous B-cells can no longer be detected by the CAR T-cells. This phenomenon is called tumour antigen escape. Relapse due to tumour antigen escape is known to occur in 7% to 33% of children and adults who respond to CAR T-cells for the treatment of B-cell ALL.

The reasons behind these relapse mechanisms are still unknown, but they are the subject of intense research. The possible solutions to these types of relapse are still at the early stage of research, but include:

- In **CD19-positive** patients, placing additional doses of CD19 CAR-T therapy into their body may re-establish remission.
- For **CD19-negative** patients, researchers are looking at using different antigens to CD19, or targeting multiple antigens when engineering the T-cells with the hope of improving the rate of patients responding and length of response. Early trials of CD19-CD22, CD19-CD123 and CD19-CD20 CAR-T therapy are ongoing.

Manufacturing of CAR-T therapy

If CAR-T therapy is to reach as many patients as possible, both

the time-consuming nature of the procedure and the cost to generate an individual CAR-T product need to be addressed.

Currently, CAR-T therapy is autologous which means the patient's own T-cells are collected, modified genetically and returned to patients on a case-by-case basis. Autologous is a term which refers to cells or tissues derived from part of the same individual and are genetically the same. In contrast, allogeneic refers to cells or tissues which have come from a matched donor and are genetically dissimilar.

Allogeneic CAR-T therapy would address both the painstaking procedure required for manufacturing CAR-T therapy as well as its cost; however, the immune responses to allogeneic CAR T-cells which could lead to their rejection still need to be overcome.

Solid tumours

Given the success of CAR-T therapy in some blood cancers, researchers are investigating the treatment with CAR-T therapy in solid tumours such as breast, pancreatic and lung cancer. However, CAR-T therapy for solid tumours is still in the early stage of development.

What CAR-T therapy clinical trials are happening in the UK?

In the UK, there are clinical trials looking at CAR-T therapy for a number of different cancers including:

- Leukaemias (mainly B-cell ALL)
- Lymphomas (Hodgkin, Non-Hodgkin, Burkitt and DLBC lymphomas)
- Myelomas (cancer of the plasma cells in the marrow)
- Colorectal cancers (cancer of the bowel and/or colon)
- Neuroblastoma (a rare cancer of the nerve cells called neuroblasts affecting mainly young children)

The details for these trials are available on the **ClinicalTrials.gov** website.

Clinical trials in leukaemia

Three clinical trials in the UK are currently recruiting patients with ALL to investigate the new CD19CAT-41BBZ T-cells in ALL, CD19/22 CAR T-cells in ALL and CD19 CAR T-cells in ALL and Burkitt lymphoma.

All these trials are open label, which means that all the patients are getting CAR-T therapy. The trials are conducted at centres in London and Manchester.

To date, clinical trials of CAR-T therapy have shown outstanding results in patients with B-cell ALL. In studies of children and adults with B-cell ALL who had previously relapsed several times or been refractory, up to 90% of patients managed to achieve remission with CAR-T therapy.

Studies of CAR-T therapy for other blood cancers such as CLL and multiple myeloma are ongoing and show great promise.

The studies that have been conducted so far have only followed patients for a relatively short period of time. However, with further long-term data, researchers will be able to determine the duration of the responses with CAR-T therapy.

Further clinical trials with greater numbers of children and adult

patients and longer treatment periods are also essential to allow researchers to better evaluate and refine CAR-T therapy, in addition to improving the management of its side effects.

Taking part in a clinical trial

Clinical trials are essential to make sure that new medicines are safe and effective. The results of these clinical trials are part of the evidence submitted by pharmaceutical companies to the authorities that grant a marketing authorisation for the drug. Following marketing authorisation and NICE approval, these drugs can be made available for patients.

From the point of view of the patients, a clinical trial is an opportunity to receive a new groundbreaking treatment or one that is unavailable to them in their area.

- If the design of the trial is open label, patients will know they are getting the trial treatment as both patient and doctor are aware of the study treatment.
- Where the trial is comparing a new drug to a placebo or an existing treatment, the treatment that patients receive will usually be decided using a random code generated by a computer. Neither the patients nor the doctors conducting the trial will know which treatment patients are on in order to prevent any bias by either party. This is called a double-blind design, and there is a chance that patients are not receiving the drug being investigated.

Before clinical trials can go ahead, the Medicines and Healthcare products Regulatory Agency (MHRA) will review the trial design and give authorisation for the trial to proceed if it is appropriate. Clinical trials in the UK must also be approved by an independent research ethics committee who protects the rights and interests of patients.

What CAR-T therapy clinical trials are happening in the UK? (cont.)

If you are interested in participating in a clinical trial, you will be given a document summarising all aspects of the trial including the aim of the trial, who is funding the trial, how long the trial is expected to last, how much of your time will be needed, when and how you will receive treatment, what the possible side effects of the treatment are, and who you can contact if there is a problem.

In addition, a clinical trial nurse or doctor will go through this information with you to make sure that everything is clear before you sign an informed consent form. In some trials, you will receive payment, while for others, just your expenses will be covered depending on what the trial involves.

Points to consider before entering a trial

- Even if you get the trial treatment, you cannot be sure if the outcome will be helpful for you.
- You may have unexpected side effects as you could be on a new treatment.
- You should also be sure of how much time you need to commit to the trial, including if you need to visit the trial centre more often, or have a greater number of tests than you would if you were receiving the standard treatment.
- It is possible that the trial has some restrictions in terms of certain medications or foods that could interact with the treatment.
- At any point during the trial you may choose to stop taking part without giving a reason and without it affecting the care you receive.

Once the trial is over and the results are published, they will be made available to anyone who took part in the trial.

Glossary

Acute Lymphoblastic Leukaemia (ALL)

A leukaemia in which lymphocytes start multiplying uncontrollably in the bone marrow resulting in high numbers of abnormal, immature lymphocytes called blasts.

Antibody

A large Y-shaped protein produced by B-cell lymphocytes in response to a specific antigen, such as a bacteria, virus, or a foreign substance in the blood.

Antigen

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

Bone marrow

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.

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.

Chronic Lymphocytic Leukaemia (CLL)

A leukaemia in which the B-lymphocytes in the bone marrow start multiplying uncontrollably leading to large numbers of abnormal, immature cells called 'blasts', which prevent the bone marrow from producing enough healthy blood cells of all types.

Complete remission

Complete remission has occurred when:

- Blood cell counts have returned to normal
- Less than 5% of blasts (abnormal, immature leukaemia cells) are still present in the bone marrow

Cytokine

Small proteins, such as interferon, interleukin, and growth factors, which are secreted by certain cells in the immune system and have an effect on the signalling between cells in the body.

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.

Leukapheresis

A process that involves collecting blood from a vein in one arm, passing it through a machine to remove the excess of white blood cells, and then re-inserting the blood back through a vein in the other arm.

Lymph nodes

Components of the lymphatic system (part of the body's immune system) that contain the lymphocytes which produce antibodies and macrophages to 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. They are commonly called 'swollen glands'.

Lymphocytes

Lymphocytes are a type of white blood cell that are vitally important to the immune response.

Lymphodepletion

The destruction of lymphocytes prior to immunotherapy to make space for the CAR-T cells in the peripheral blood and bone marrow.

Lymphoma

A cancer of the lymphocytes which are a type of white blood cell that are vitally important to the immune response.

Minimal residual disease

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 which can detect if there is any trace of leukaemia left in the body.

Monoclonal antibody drugs

Antibodies created in the laboratory from the same original cell and which target specific proteins on the cancerous cells.

Plasma cell

A type of white blood cell that produces antibodies and is

Glossary (cont.)

derived from a B-cell lymphocyte. It has a distinct appearance being ovoid (egg-shaped) with an off-centre nucleus.

Refractory condition

A condition for which treatment does not result in a remission.

Relapse condition

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 clear the body of toxins, waste and other unwanted materials. The spleen is located under the ribs on the left of the abdomen.

Standard of care

Treatment accepted by medical experts as the most appropriate treatment for a certain disease and that is widely used by healthcare professionals.

Thymus

The main organ of the lymphatic system, located behind the sternum and between the lungs, where the T-cell lymphocytes develop and mature.

Tumour lysis syndrome

The rapid destruction of a large numbers of white blood cells that can increase blood uric acid levels which may cause damage to the kidneys, heart or liver.

Tell us what you think!

If you would like to give us some feedback about this patient information booklet, please hover over the code to the right using your phone or tablet's camera. Click the link as it appears and this will take you to a short web form to fill in.

Suitable for Android, iPhone 7 and above.

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

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YOUR Blood Cancer Charity