

Patient information sheet for Kymriah CAR-T cell Therapy

T Cells are cells which naturally fight viral infections in the body, and are key players in the immune system, providing ongoing immunological memory which in some cases can protect us against certain infections for the rest of our lives.

It is possible to modify T cells so they become capable of recognising a marker (called CD19) on the surface of leukaemia cells and normal B cells (immune cells). We call these cells CD19 CAR-T Cells or Kymriah. These modified cells will 'see' the CD19 marker on the leukaemia and will target and attack them. While many patients with acute lymphoblastic leukaemia (ALL) can be cured with chemotherapy, there are still patients who relapse and for whom the outcome with existing treatments like chemotherapy or bone marrow transplant aren't effective or are poor.

Studies have shown that CAR-T cell therapy can be very effective in treating such patients and have resulted in long term remission in 40-50% of patients. The reasons for therapy failure include failure of CAR T cell persistence, in which case the leukaemia usually still has CD19 on its surface. This was a rarer form of treatment failure in the ELIANA study but is being seen in about 40% of patients being treated with the licensed CAR T cell treatment for ALL. The other cause of treatment failure is when the leukaemia evolves to escape recognition by the CAR T cells (CD19 negative relapse). Other than treatment failure, the main risks of treatment are short term side effects which can be severe, and longer term side effects. The latter are rarer than equivalent therapies such as bone marrow transplantation. As a result, CAR-T cell therapy has been considered a successful form of novel therapy in children with advanced ALL which is why this treatment has now been licensed in the US and Europe for these patients.

Your consultant and nurse specialist will go through all of the information with you and then you will have the opportunity to take this information away and read it carefully before deciding if you wish to consent to the treatment.

If you decide to go ahead with this therapy, we will ask you to some consent forms for the treatment as well as storage of the T cells.

What happens next?

We need to assess if it is appropriate for your child to receive the treatment. This will include a medical assessment and some tests which your child may have had before.

These include a review of your child's medical history, physical examination, weight, blood tests (including screening for viruses), computerised tomography (CT) scan, an echocardiogram (ECHO), audiology test, bone marrow aspirate and lumbar puncture to assess disease as well as a pregnancy test (if applicable).

Most of these tests can be done at your referring hospital however, some blood and bone marrow samples will be sent to specialist laboratories at Great Ormond Street Hospital for a more detailed analysis of their disease.

What does the treatment involve?

1. Leucapheresis

Your child will undergo a leucapheresis which involves removal of some white blood cells from his/her blood whilst returning the remaining blood cells to him/her. These will be used to make the CAR-T Cells. This can normally be done within one day, but we may need a second day of collection if more cells are needed.

A special central line will be fitted for this procedure, it is inserted into a large vein in the top of their leg. Your child will have to have a general anaesthetic for this, normally the day before the leucapheresis. The line can be taken out without an anaesthetic by your specialist nurse or a nurse on the ward once we know we have collected enough cells.

Sometimes, we may not be able to make the modified CAR-T cells due to technical problems. In this care, your doctor will discuss the next step.

2. Lymphodepletion

This week before we return the CAR-T cells, back to your child, he/she will be admitted to hospital to receive some low dose chemotherapy. This will make space in the bone marrow for the CAR-T Cells to grow once infused. The chemotherapy used is:

- Fludarabine – given as an intravenous infusion (over 30 minutes). It is usually given one a day for four days. Sometimes this schedule is adapted.
- Cyclophosphamide – given as an intravenous infusion (about 1 hour) once a day, usually for two days. This treatment can sometimes cause bladder irritation and therefore your child will have fluids and a drug called Mesna to protect the bladder.

During this time we will also give your child medications to keep him/her feeling well. These will include anti-sickness.

3. Infusion of the CAR-T Cells

Before your child receives the modified CAR-T Cells, he/she will have the following tests done to check he/she is well enough to receive them:

- Physical examination
- Oxygen levels
- Blood tests
- Bone marrow assessment (this may be done before the admission)

Your child will have some piriton and paracetamol before the infusion. The CAR-T cells will then be infused over 5-10 minutes. Your nurse will monitor your child closely during and after the infusion and for four hours after the infusion. The CAR-T cells are preserved in a special formula called DMSO. This can give a funny smell once infused, some say it smells like sweetcorn. This will last approximately 24 hours and does no harm to your child.

4. In-patient monitoring

Your child will remain in hospital for at least two weeks. This allows us to check that he/she is well after the infusion. During this time, we will monitor your child closely with examinations and blood tests.

5. Outpatient monitoring

Your child will continue to be regularly monitored for at least one year after the infusion, and thereafter will continue to be followed up at least annually long term.

During these visits your child will need to have the following assessments performed:

- Physical examination
- Blood tests
- Bone marrow aspirates to assess how the disease has responded. We aim to do this at 1, 3, 6, 12 months following the CAR-T cell infusion

It is important that your child attends all scheduled appointments for clinic visits, blood tests and treatments so his/her progress can be closely monitored.

If at any time after the CAR-T Cell infusion has been given your child develops any of the following signs:

- Fever
- Breathing difficulties
- Light Headedness
- Confusion or difficulty with speech
- Any other unusual symptoms

YOU MUST ATTEND YOUR CHILD'S LOCAL HOSPITAL IMMEDIATELY

The local hospital should contact the **CAR-T Consultant on call**.

Your child will be given a patient card, which will give details of who to contact.

What are the possible side effects of the therapy?

Side effects vary for each patient from mild to severe and sometimes can be life-threatening.

Many of the side effects from leucapheresis and lymphodepletion are well known and explained below. The side effects for the CAR-T cells are based on studies and other patients using the same form of CAR-T cells manufactured by Novartis, the pharmaceutical company.

Some of these side effects can be severe and occasionally can cause death. However this is rare, with rates of <3% in the most recent study, which is similar or better than would be the case with any other form of curative therapy in this patient population.

We do not expect that your child will have all or even most of the side effects summarised in this section, but we cannot predict which ones he/she may experience or how serious they may be.

Your child will be closely monitored for any side effects and should report anything that is troubling him/her to their parents, ward staff or their Nurse Specialist/Consultant.

- Possible side effects from leucapheresis

Leucapheresis is well tolerated by most patients. Your child may feel light-headed. In some people calcium levels in the blood may go down and this can cause tingling in the hands, feet and mouth. It can also sometimes cause muscle spasms. The doctor will give your child calcium treatment if this is experienced.

- Possible side effects from lymphodepletion

Cyclophosphamide and fludarabine are both chemotherapy drugs used to treat blood cancers and lymphoma. These drugs will help the CAR-T Cells to grow and survive in patients. These drugs can suppress your child's immune system and make him/her more prone to infection. Your child may develop a fever and may need antibiotics intravenously.

The chemotherapy may also cause anaemia and a drop in platelet counts for a few days so that he/she may need additional blood and/or platelet transfusions.

Other side effects of these chemotherapy drugs include nausea and vomiting (we will give anti-sickness medication to prevent this), lack of appetite, diarrhoea, and hair loss.

Cyclophosphamide can cause bladder irritation and blood in the urine, we will give your child extra fluids and other medication to help.

Fludarabine can cause symptoms affecting the nervous system causing confusion, difficulty with speaking or writing, decreased alertness or fits.

- Possible side effects from infusion of the CAR-T Cells

Allergic Reactions

Administration of the CAR-T cells may cause an allergic reaction and your child may experience fever, shivers, difficulty breathing, low blood pressure, rash and vomiting. We will give your child medicines to prevent this from happening. His/her doctors and nurses will monitor him/her closely during and after the infusion of the cells. If such a reaction occurs, your child will be given appropriate medication and will be monitored until the symptoms resolve. The CAR-T cells are stored in a preservative known as DMSO. This can cause a sweet smell to be produced from your child's bodily fluids. This will disappear after 24-48 hours.

Cytokine Release Syndrome (CRS)

The CAR-T cells may stimulate the release of chemicals called 'cytokines' that can cause severe reactions. Side effects associated with CRS can range from mild (such as fever) to severe (such as low blood pressure and difficulty breathing) and rarely can be life threatening. Your child's medical team will monitor him/her closely for side effects and give appropriate support and medication if such a reaction occurs. We have highly effective treatment for CRS and we work closely with our intensive care department as about a third of patient may need monitoring or supportive care in this setting.

Nervous System Complications

Some patients may develop temporary symptoms affecting their nervous system causing confusion, difficulty with speaking or writing, decreased alertness or fits. These symptoms usually resolve on their own though they can take several weeks to fully resolve. Your child will receive supportive care if needed, again in an intensive care setting if necessary.

Reduced immunity

The CAR-T cells target all CD19 positive cells, including normal B cells that help to fight infections. Decreased numbers of normal B cells may lead to low levels of antibodies, called immunoglobulins, produced by the B cells. Persistently low levels of immunoglobulins may cause an increased risk of infection.

We will monitor your child's immunoglobulin levels monthly and we may decide that he/she needs replacement intravenous immunoglobulin.

Will my child's data be kept confidential?

Details about your child, his/her treatment, any side effects and how the disease responds will be recorded in your child's medical notes. Information which is required for regulatory and quality assessments or our service will be collected on an anonymous basis and may be reported nationally and internationally.

We will let your Shared Care Team and GP know about your child's treatment in order for them to support you following the treatment.

In order to send your child's cells to Novartis for manufacture, you will need to sign a consent form to give permission for the manufacture itself and the transfer of certain information such as your child's name and date of birth so they can ensure the cells come back to your child safely.

What happens to the samples my child provides?

The leucapheresis will be at Great Ormond Street Hospital (GOSH) until they are transported to the manufacturer (Novartis) where the CAR-T cells will be made. The cells will later be stored at GOSH until he/she are ready to receive them.

With your permission, we would like to store and use any surplus cells, if available for future ethically approved research. If you accept, your Consultant will ask you to sign a consent form and explain this further.

What if there is a problem?

Every care will be taken in the course of treating your child, however if you are unhappy with their care, please do raise this with their Nurse Specialist or Consultant at the earliest opportunity.

If you wish to comment or complain about the care your child has received you can contact the Patient Advice and Liaison Service (PALS) within the hospital or your referring centre.

GOSH PALS CONTACT DETAILS

Phone: 020 7829 7862

By Email: pals@gosh.nhs.uk

In person: You are welcome to visit the office during opening times to discuss any issues that you may have. The PALS office is located near the main office reception, on the left as you come through the main entrance.

For more information about GOSH PALS please see our website

<https://www.gosh.nhs.uk/parents-and-visitors/clinical-support-services/about-patient-advice-and-liaisonservice-pals>