CAR-T Therapy in Lymphomas Today

Sara Valente, MPharm, Lymphoma Hub
Sylvia Agathou, PhD, Lymphoma Hub
Lorna Warwick, Lymphoma Coalition
Karen Van Rassel, Lymphoma Coalition

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Introduction

Chimeric Antigen Receptor T-cell (CAR-T) therapy has been making headlines as a promising cancer treatment in certain types of lymphoma and leukaemia. It is still a relatively new treatment with only a few drugs approved and many still in clinical trials. To have a better understanding of what this treatment will mean for patients with lymphoma, this article will explain the science behind CAR-T and what patients should expect from the treatment, including both side effects and after care.

Words highlighted in **bold** are defined in the glossary at the end of the article.

It is important to note each individual CAR-T drug has its own unique design and manufacturing process even though they are all based on the same science. Because the products are not exactly the same, they may have differing safety profiles, and have different administration and management strategies.

It is also important to highlight CAR-T therapy is only provided in select specialty cancer centres. This ensures medical staff are properly trained and have the expertise to manage a patient's care through this multifaceted treatment course. CAR-T also has a high cost, complicated supply chain and complex arrangements for setting up the treatment centre.

The Science Behind CAR-T Therapy

CAR-T is a type of therapy, known as **immunotherapy**, that uses a patient's own immune system to treat cancers. A key component of the immune system are T-cells, which are white blood cells that can detect disease-causing **pathogens** in the body. Once the pathogens are detected, the T-cells activate the body's immune system to destroy and remove them. T-cells can detect and destroy lymphoma cells, but their response might not be enough to get rid of all the lymphoma in the body.

CAR-T therapy involves enhancing a patient's T-cells to be more effective at detecting and destroying lymphoma. T-cells are enhanced by being genetically altered to produce a **chimeric antigen receptor (CAR)**. This **receptor** helps T-cells find lymphoma cells by detecting certain proteins on the tumour cells. Once the lymphoma cells are detected, they can then be destroyed by the immune system. CARs are synthetic receptors that reprogram immune cells for therapeutic purposes. See below for a more detailed description of the treatment process.

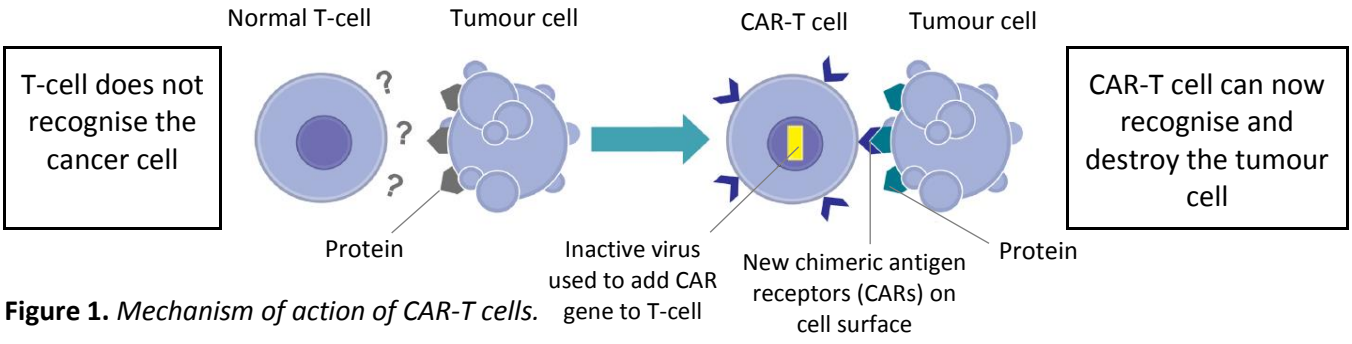

Figure 1. *Mechanism of action of CAR-T cells.*

CAR-T Therapy Protocol

The general CAR-T treatment process contains multiple steps that are outlined below (see Figure 2). It should be noted that variations of this procedure might exist for different CAR-T products developed by different manufacturers.

Figure 2. *Outline of CAR-T treatment process.*

1. Screening

CAR-T is currently available to a limited subset of patients (see *CAR-T eligibility, pg. 6*). Patients are initially screened to ensure they meet certain criteria.

What should a patient expect during this step?
Patients will have an initial discussion with their doctor to ensure that they meet the criteria for receiving CAR-T therapy and to discuss their medical history. The referring provider or the patient must submit their appropriate medical records (including recent pathology reports, imaging, histology, laboratory results, treatment history and other information) that may be required during the screening process.

2. Blood sampling

CAR-T therapy begins with taking blood from the patient, passing it through an apparatus that isolates the white blood cells that contain T-cells, then the remainder of the blood is transfused back to the patient. This process is called **apheresis** or **leukapheresis**.

What should a patient expect during this step?
During this procedure, a small temporary catheter will be placed intravenously, while patients usually lie in bed or sit in a reclining chair. The patient needs to stay still for 3–6 hours during the procedure. During this time, patients might experience numbness, tingling or muscle spasms due to a decrease in calcium levels. This can be easily treated with calcium, which may be given orally or through the intravenous catheter.

3. Cell manufacturing

Once apheresis is completed, the cells are then shipped to designated laboratories and are genetically modified into CAR-Ts. In the laboratory, with the help of inactive viruses, a **chimeric antigen receptor (CAR)** gene is inserted into the DNA of the patient's T-cells, converting then to CAR T-cells that are better at recognising and attacking cancer cells. These cells are essentially a "living drug" that will be put back into the patient. Since a large number of CAR T-cells needs to be produced for this therapy, this process can take a few weeks. Once the appropriate number of

CAR T-cells has been produced and tested for safety, the cells are frozen and shipped back to the treatment centre. The CAR-T cells can be kept frozen at appropriate freezing facilities for a long time (more than a year). The time from blood sampling to CAR T-cell production and shipment to the treating centre usually takes 2–4 weeks (the exact time will vary, depending on the type of CAR-T product, as manufacturing processes differ between pharmaceutical companies).

What should a patient expect during this step?
While patients wait for the CAR T-cells to be produced, they may have administration of a low-dose chemotherapy regimen (**bridging therapy**) to avoid any tumour growth. Not every patient requires bridging therapy. Bridging chemotherapy regimens are highly variable and depend on the diagnosis, the disease burden and whether patients are children or adults. Therefore, for patients for whom bridging therapy is appropriate, each will receive individualised treatment to control their disease until the CAR-T infusion is ready to be performed. Unlike **haematopoietic stem cell transplant**, it is not necessary for patients to achieve a complete response to bridging therapy before CAR-T infusion.

4. Lymphodepleting chemotherapy

Lymphodepleting chemotherapy is a low-dose chemotherapy, given to reduce the number of other immune cells prior to the infusion of the CAR T-cells. This creates a more favourable environment for the CAR T-cells to expand and activate to fight the cancer. The goal of this chemotherapy is not to eradicate all the cancerous cells as CAR T-cells work best when there are some cancer cells to attack.

What should a patient expect during this step?
Approximately 2–14 days before the CAR-T infusion, patients will receive **lymphodepleting chemotherapy**. The type of chemotherapy and the dose the patient receives will vary depending on their diagnosis, past treatments, and treating physician choice. The patient may experience side effects from this treatment and should discuss this with their physician, as well as how any side effects will be managed.

5. CAR-T infusion

The CAR T cells are thawed at the treatment centre and infused intravenously into the patient.

What should a patient expect during this step?
The patient will be examined by the treating physician to determine any change in clinical status that would increase the risk of side effects or impact treatment success, prior to the CAR-T infusion. The same CAR-T product can be given to patients intravenously in an outpatient or inpatient setting at the discretion of the treating physician and lasts approximately 30 to 60 minutes.

6. Observation

Routine long-term follow-up appointments will be frequently scheduled to monitor patients after CAR-T infusion. Even after the patients have left the hospital, they will be closely monitored for potential side effects. As there are still many unknowns regarding CAR-T therapy, routine follow-up up to 15 years after infusion will be scheduled to monitor patients and disease progression long term.

What should a patient expect during this step?
Patients and their carers are advised to stay within two hours of the treatment centre for at least a few weeks after the CAR-T infusion. Side effects may develop rapidly, and the symptoms of the side effects can mimic other health issues *(see CAR-T Side Effects and Management)*. The carer should be someone who knows the patient well and is able to recognise any out-of-character behaviours that may be indicative of a serious side effect. If a patient experiences health concerns during this period, to ensure they receive the correct diagnosis and treatment, it is important they return to the cancer centre where they received their CAR-T infusion and make sure admitting staff know they have received CAR-T therapy. Patients might be hospitalised, depending on the severity of their side effects, and may stay in hospital until their symptoms are alleviated with appropriate treatment, which generally lasts around two weeks.

CAR-T Side Effects and Management

The short-term side effects of CAR-T therapy can be serious and potentially life-threatening (*see Safety Profiles, pg. 8, for information on the incidence of reported side effects in clinical trials*).

After infusion, the CAR T-cells multiply in the patient's body. This highly activates the patient's immune system and causes a massive release of proteins called **cytokines** from immune cells into the blood. This causes one of the most common side effects associated with CAR-T, the **cytokine release syndrome (CRS)**. CRS may occur within the first week after infusion but can also occur later in some cases. It causes very high fevers, hypoxia (oxygen deficiency), low blood pressure and/or multi-organ toxicity. The intensity and duration of CRS varies. CRS can be severe and require treatment in an intensive care unit (ICU).

Another very common side effect of CAR-T infusion is **neurotoxicity**. Neurotoxicity results from the effects of the CAR-T cells on your brain and it can occur together with CRS or on its own. Patients experiencing neurotoxicity might feel confused, unaware, agitated and might present with headaches, difficulties with language (written or spoken), anxiety and occasional seizures[6].

Because of the severity of these side effects, patients (and their family/carers) need to know how to identify potential symptoms and to immediately inform their cancer care team.

Other CAR-T related side effects that have been reported include infections and haematological-related issues, such as prolonged or **febrile neutropenia**, **anaemia** and **thrombocytopenia**. In rare cases, **macrophage-activation syndrome** that leads to severe immune activation and multi-organ failure might also occur.

In most cases, however, CAR-T-related side effects are mild enough that they can be managed with standard supportive therapies.

Severe side effects of CAR-T are often the result of a highly active immune system. In such severe cases, symptom management involves the use of an immunosuppressive drug called tocilizumab and/or corticosteroids. The goal of this immunosuppressive treatment is to deplete the immune system enough to curtail the side effects but not enough to get rid of the CAR T-cells.

Due to the fact CAR-T is a relatively new therapy, long-term side effects or late-effects are unknown. Some patients who have received CAR-T therapy are experiencing ongoing **B-cell aplasia**. This is a result of CAR T-cells destroying normal B-cells as well as cancerous B-cells. B-cell aplasia causes hypogammaglobulinemia where the body does not make enough antibodies, leaving patients susceptible to infections that may be life-threatening. This is managed through immunoglobulin replacement, administered either intravenously (IVIG) or subcutaneously (SCIG).

Potential Costs of CAR-T to Consider

There are additional potential non-medical costs that patients should be aware of in addition to any medical costs, including: long distance travel to centres that provide CAR-T therapy; living expenses for the patient and carer during and after treatment for the weeks they are required to live within two hours of the treatment centre; potential lost income for the patient and the carer.

CAR-T is currently approved for use in some aggressive lymphoma in the USA (*see CAR-T eligibility*), with the costs of the products alone varying, but starting at approximately $370,000 USD and up. In addition to the cost of the product itself would be other services associated with the treatment. Certain manufacturers have been known to create outcomes-based pricing arrangements, where the company only receives payment if the patients responded to treatment at one month.

Many economic models look at the cost per quality-adjusted life year (QALY) to determine cost-effectiveness of a therapy. As the current data available for CAR-T is limited, with many unknowns regarding long-term side effects and duration of effect, this has been difficult to determine and agree upon amongst economists. Uncertainty in the evidence has raised questions around the long-term value for the money.

There is no available information yet about the costs of CAR-T therapies in Europe and the rest of the world.

CAR-T Eligibility

There are many CAR-T products in clinical trials for various haematologic malignancies, including lymphoma, chronic lymphocytic leukaemia, acute lymphoblastic leukaemia and multiple myeloma, among others. Regarding lymphoma, all CAR-T products that are currently being investigated in clinical trials are considered for the treatment of relapsed or refractory (R/R) adult patients with lymphoma.

The only CAR-Ts approved for lymphoma at this time are YESCARTA (axicabtagene ciloleucel) and KYMRIAH (tisagenlecleucel), in the US. Both are also under consideration for similar use in Europe. These CAR-T products have been targeted at specific subtypes as described below. JCAR017 is also described as it is anticipated this will be the next CAR-T approved.

- YESCARTA is approved for adult patients with diffuse large B-cell lymphoma (DLBCL), transformed follicular lymphoma (TFL) or primary mediastinal B-cell lymphoma (PMBCL) who do not respond to chemotherapy (one or multiple therapy lines) and who are ineligible for, or relapse after, autologous stem cell transplant (ASCT)[1]. This CAR-T is still in clinical trials for other lymphoma subtypes (mantle cell lymphoma [MCL], indolent lymphomas), for R/R transplant-ineligible aggressive lymphoma or for R/R DLBCL in combination with a checkpoint inhibitor.

- KYMRIAH is being developed for adult patients with DLBCL who do not respond to chemotherapy (one or multiple therapy lines) and who are ineligible for, or relapse after, ASCT[2].

- JCAR017 is being investigated in clinical trials for R/R patients with DLBCL not otherwise specified (*de novo* or transformed from indolent lymphoma), high-grade B-cell lymphoma, PMBCL or Grade 3B FL, after two prior lines of chemotherapy or failed ASCT. This CAR-T product is also in clinical trial for patients with MCL who are R/R to one prior line of chemotherapy[3].

Treatment Outcomes

It is important to understand the patient outcomes after the treatment with CAR-T, because while initial results for some patients are positive, CAR-T therapy is not considered a cure.

Complete response rate (CR) means the percentage of patients that experienced a disappearance of all signs of cancer in response to treatment. Even if patients do not achieve CR, they could experience a PR (**partial response**).

Median overall survival (mOS) is the median length of time from either the date of diagnosis or start of treatment that patients are still alive.

Clinical trials are currently underway to continue to monitor the outcomes of patients on these treatments, but it is not possible to compare the outcomes from the various trials due to the varying factors involved in the study design and treatment, and mainly because there is no trial comparing these three CAR-T products. Each trial of these CAR-T products is different in terms of trial phase, number of patients, CAR-T formulation and dosing and follow-up time.

A summary of each trial outcome is below:

- YESCARTA – with a longer follow-up, the ZUMA-1 phase II trial analysed 101 patients with refractory DLBCL, PMBCL and TFL treated with a target dose of 2×10^6 anti-CD19 CAR T-cells per kilogram of body weight. The CR was 40% and mOS was not reached after approximately two years. The objective response rate was 82% and at 18 months, the overall survival rate was 52%.[6]

- KYMRIAH – JULIET phase II trial analysed 81 patients with R/R DLBCL treated with a single dose of CTL019 (0.1–6.0x10^8 cells). At a follow-up of 3 months, 43% achieved CR with 30% of these patients achieving CR at 6 months. The best overall response at 3 months was 53.1%. The probability of overall survival at 6 months was 64.5% however, the mOS was not yet reached at 6 months. This means that more than 50% of the patients are still alive, so the mOS could not yet be calculated[4].

- JCAR017 – the phase I TRANSCEND trial analysed 91 lymphoma patients. There were 3 different dosing schedules of JCAR017 during this study (DL1=5x10^7 cells single dose, DL1=5x10^7 cells double dose and DL2=1x10^8 cells). At a follow-up of 6 months the CR was 37% and mOS was not reached. Best overall response at 6 months at all dose levels was 74%[5].

From these three trials, it is apparent that there is more long-term data available from some of the trials, for example, ZUMA-1 has data available up to 2 years whereas the JULIET and TRANSCEND study has data available from 6 months. It should also be noted that the number of patients that respond to treatment varies within each study and not all respond. It is not yet known if patients who do not respond to the first CAR-T infusion can receive further CAR-T treatment. These studies are ongoing, and more conclusive data is expected in the future. Currently, CAR-T therapy is indicated for patients who do not respond to any other available aggressive lymphoma treatment.

Safety Profiles

Due to the different side effect management protocols used between the different clinical trials, it is also difficult to compare the safety profile of each CAR-T product. Nevertheless, the proportion of patients presenting with any grade of CRS or neurotoxicity and with severe enough symptoms to be treated are presented below.

During the clinical trial for YESCARTA (ZUMA-1, with 101 patients enrolled), 93% of the patients developed CRS and 64% neurotoxicity, with 43% further treated with tocilizumab and 27% with corticosteroids[6].

In the clinical trial for KYMRIAH (JULIET, which enrolled 81 patients), 58% of the patients developed CRS and 21% neurotoxicity. To manage the side effects, 15% of patients were treated with tocilizumab and 11% with corticosteroids[4].

In the clinical trial for JCAR017 (TRANSCEND, which had a patient enrolment of 91 patients), 35% of the patients developed CRS and 19% neurotoxicity. In this study, the proportion of patients who had their symptoms treated with tocilizumab or corticosteroids was 12% and 16%, respectively[5].

Almost all severe symptoms were managed with additional treatment. Despite the fact most severe side effects are managed, the potential life-threatening risk of CAR T-cell therapy should not be underestimated. One treatment-related death (1/91) has been reported for JCAR017, two treatment-related deaths (2/101) for YESCARTA[6] and no deaths for KYMRIAH (0/81)[5].

Approval Status of CAR-T

CAR-T is currently in many clinical trials across the globe including Europe, the US and Asia in lymphoma and leukaemia and other types of cancer. There are only two approved drugs for lymphoma in the US, with others still awaiting approval.

This article will focus on FDA/EMA due to recent filings in CAR-T. In the US, drugs are licensed by the Food and Drug Administration and in Europe by the European Medicines Agency. If a drug is approved, also sometimes referred to as licensed, it is available for doctors to prescribe. Doctors can only prescribe for the exact indications (uses) that the drug has been approved for (see Table 1 for example).

Table 1: Approval status of the three CAR-T therapies for lymphoma in the US and Europe, 31 May 2018

Trade name (chemical name) CAR-T therapies and manufacturers	USA–FDA[7]	Europe–EMA[8]
KYMRIAH (tisagenlecleucel) Novartis[2]	Approved 1 May 2018: R/R adult DLBCL, high-grade B-cell lymphoma, TFL	Marketing authorization application submitted: adult R/R DLBCL
YESCARTA (axicabtagene ciloleucil) Kite/Gilead[1]	Approved 18 October 2017: R/R adult DLBCL, PMBCL, TFL	Marketing authorization application submitted: R/R DLBCL, TFL, PMBCL
JCAR017 (lisocabtagene maraleucel) Juno/Celgene[3]	Breakthrough therapy designation: R/R DLBCL not otherwise specified (*de novo* or transformed from indolent lymphoma), high-grade B-cell lymphoma, PMBCL, Grade 3B FL or MCL	Priority medicines scheme (PRIME): R/R DLBCL

Abbreviations: DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; MCL: mantle cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma; PRIME: priority medicines scheme; R/R: relapsed or refractory; TFL: transformed follicular lymphoma

Drug licensing does not mean that the treatment is provided to patients at no cost. In the US, private insurers determine which treatments they will cover for their members. In Europe, individual countries would still need to decide what treatments will be added to publicly-funded drug lists.

The FDA has different review processes for drug licensing depending on the circumstance. ***Priority Review*** means that the FDA will try to review the drug more quickly as it might provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. ***Breakthrough Therapy Designation*** means that the FDA review of a drug will be accelerated if it is intended to treat a serious condition and it has sufficient clinical evidence demonstrating that it could improve patient treatment over currently available therapies.

Similarly, for the EMA, ***priority medicines scheme (PRIME)*** means they will enhance the support for the development of medicines that target an unmet medical need.

CAR-T: Unknowns and Current Challenges

CAR-T is a new therapy with many unknown factors and is associated with potentially serious side effects.

The effects of CAR-T in terms of safety and efficacy in the long-term are still under investigation and it is unknown whether patients receiving this treatment will keep on benefitting from it in the future. It is anticipated that more information will become available later this year, once more clinical trial results are published, and more CAR-T drugs are successfully filed and approved.

It should be noted that currently CAR-T therapy in lymphoma is only for patients with specific B-cell lymphoma subtypes that do not respond to any other available treatment, including chemotherapy and stem cell transplantation.

There are currently no head-to-head trials of YESCARTA and KYMRIAH for patients with R/R B-cell lymphoma or between CAR-T and alternative chemotherapy/stem cell transplantation.

Additionally, a challenge of CAR-T therapy is that only a few centres of excellence have the protocol to deliver this treatment, so patients and their carers may need to travel to a certified centre, resulting in more costs to the patient.

While CAR-T shows promise for lymphoma patients, there is still a long way to go until this therapy is considered the standard of care.

References and Further Reading

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Glossary of Terms

Anaemia: a condition in which the number of red blood cells is below normal.

Apheresis: a technique by which a particular substance (e.g. white blood cells) is removed from the blood

Autologous stem cell transplant (ASCT): a procedure that replaces the patients' own blood stem cells (cells that make new blood cells). The blood stem cells are removed, and the patients are treated with high doses of chemotherapy to kill the cancer cells and the remaining blood-producing cells. The patients' own blood stem cells are then given back to them.

B-cell aplasia: the body does not make enough antibodies, leaving patients susceptible to infections

Bridging therapy: low-dose chemotherapy regimen to avoid any growth and to control disease until the CAR-T infusion

Chimeric antigen receptor: receptors that are specific for detecting a defined type of cell (e.g. lymphoma)

Cytokines: proteins secreted from immune cells into the bloodstream that affect many different processes in the body

Cytokine release syndrome: a type of systemic inflammatory response syndrome

Complete response (CR) rate: the percentage of patients that experienced a disappearance of all signs of cancer in response to treatment

Febrile neutropenia: development of fever, alongside an abnormal decrease in the number of certain white blood cells in the blood.

Haematopoietic stem cell transplant: a procedure in which a person receives blood-forming stem cells (cells from which all blood cells develop) from a genetically similar, but not identical, donor

Immunotherapy: therapy that stimulates the immune system to fight disease

Leukapheresis: a technique by which white blood cells are removed from the blood

Lymphodepleting chemotherapy: a type of therapy that lowers the number of immune cells

Macrophage: a type of white blood cell which work by destroying/ingesting infectious cells (e.g. viruses and bacteria) and they can also control other cells in the immune system to help fight infection

Macrophage-activation syndrome: a severe inflammation of the immune system; multi-organ failure might result

Median overall survival (mOS): is the median length of time from either the date of diagnosis or start of treatment that patients are still alive

Neurotoxicity: a type of toxicity in which a biological, chemical or physical agent produces an adverse effect on the structure or function of the central and/or peripheral nervous system

Partial response (PR): when patients experience a partial disappearance of the signs of cancer in response to treatment

Pathogen: a bacterium, virus or other microorganism that can cause disease

Receptor: a region on a cell membrane that responds specifically to a particular substance

Thrombocytopenia: a decrease in the number of platelets in the blood

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