

CAR-T cell treatments

Horizons Infosheet Clinical trials and novel drugs

This Horizons Infosheet contains information on CAR-T cell treatments, which are being investigated in myeloma.

The Horizons Infosheet series provides information relating to novel drugs and treatment strategies that are currently being investigated for the treatment of myeloma. The series also aims to highlight the considerable amount of research currently taking place in the field of myeloma.

The drugs and treatment strategies described in the Horizons Infosheets may not be licensed and/or approved for use in myeloma. You may, however, be able to access them as part of a clinical trial.

What are CAR-T cell treatments?

CAR (chimeric antigen receptor) T cell treatments are in a class of treatments called immunotherapy, which uses the body's own immune system to kill myeloma cells.

A lot of research is focusing on the potential role of the immune system in treating cancer and some myeloma drugs already in use work by affecting the immune system, such as the immunomodulatory drugs (IMiDs) lenalidomide (Revlimid®) and pomalidomide (Imnovid®).

However, CAR-T cell treatments are unlike any other immunotherapy treatments currently used in myeloma. Rather than using a drug to modify the immune system, a patient's own immune cells are collected and genetically modified in a laboratory to enable them to kill myeloma cells.

What is the immune system?

The immune system is made up of specialised cells, tissues and organs which work together to protect the body from infection and disease. This involves protecting the body from foreign organisms such as bacteria or viruses, and from cells within the body if they become infected or abnormal.

What are T cells?

T cells are a type of white blood cell and are one of the key components of the immune system. They are produced in the bone marrow and circulate around the body looking for any potentially harmful, infected or abnormal cells (such as cancer cells). When T cells come into contact with such a cell, they can either kill it or release chemical messengers (cytokines) to recruit other immune cells to kill it.

How do CAR-T cell treatments work?

Myeloma cells can avoid being recognised as abnormal by the immune system, meaning that a patient's own T cells are not able to kill the myeloma cells. CAR-T cell treatments aim to get round this by boosting the ability of a patient's T cells to recognise and kill myeloma cells.

There are several steps in the process of producing and using CAR-T cells:

- The patient's blood is pumped through a machine which filters out the T cells and returns the blood to the body. This is called apheresis (see Figure 1)
- The collected T cells are genetically modified in a laboratory so that they can recognise myeloma cells
- The modified T cells are called CAR-T cells, and have a receptor on their surface that will recognise a specific protein on the surface of myeloma cells
- The modified T cells are multiplied and infused back into the patient. This is called adoptive T cell transfer (see Figure 2)

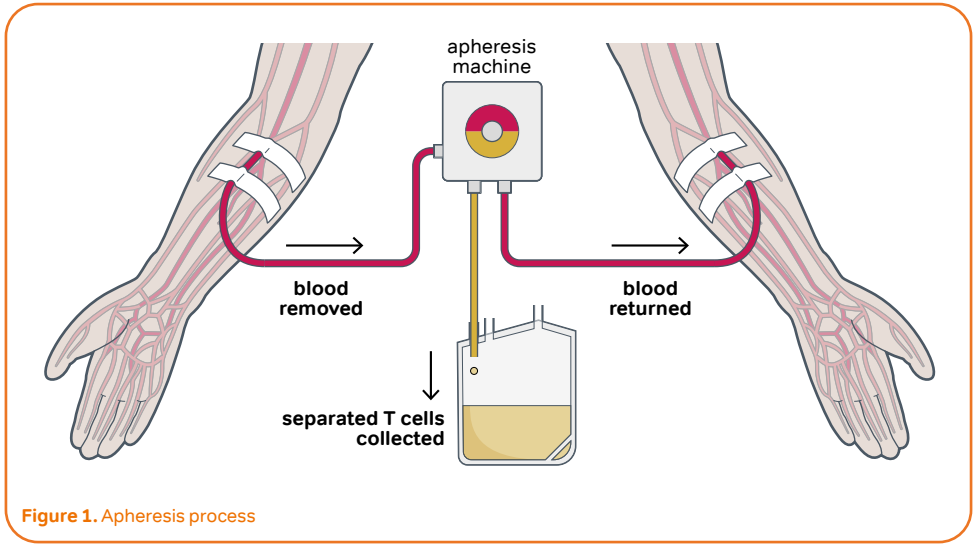


Figure 1. Apheresis process

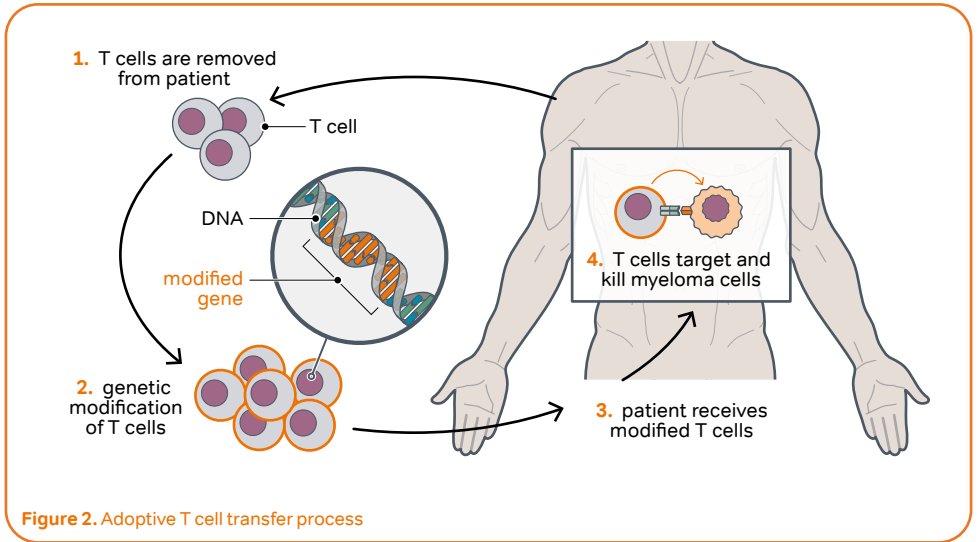


Figure 2. Adoptive T cell transfer process

Unlike drugs, CAR-T cells can persist in the body for a long time and can also multiply to give rise to new cells. This means CAR-T cells have the potential to provide long-term control, and are designed to be a one-off therapy, in contrast with standard drug treatments in myeloma which have to be given repeatedly to achieve control. However, it has been found that CAR-T cells can get 'exhausted' and stop working after a while. There is a lot of research currently ongoing to look at ways to keep the cells active within the patient to provide long-term control.

What evidence exists to support the use of CAR-T cell treatments?

CAR-T cell treatments have already shown impressive results in other blood cancers, and two CAR-T cell treatments have been approved in the UK for use in specific types of leukaemia and lymphoma.

Development of CAR-T cell treatments for myeloma is at an early stage. Early results have been promising with good remission rates in relapsed and/or refractory patients, but the studies have been small with limited follow-up. Larger trials are needed to generate more

robust results and to compare CAR-T cell treatments with other available myeloma treatments.

A number of different CAR-T cell treatments are being developed for myeloma. They are different from those in lymphoma and leukaemia, because the cancer cells being targeted are different. The depth of response with myeloma CAR-T cell treatments, and how long the response lasts, have so far been more limited than that in lymphoma and leukaemia.

Two CAR-T cell treatments being investigated for treatment of myeloma are bb2121 (also called ide-cel) and JNJ-4528. Both of these recognise a protein called BCMA on the surface of myeloma cells.

One trial of bb2121 included 128 patients with relapsed and refractory myeloma (RRMM). The overall response rate (that is, the number of patients who had a partial response or better) was 94 of the 128 patients (73%). The median progression-free survival (average time before the myeloma came back) was 8.6 months.

In another trial of bb2121, results for 33 RRMM patients have been reported so far. Overall response

rate was 28 of these 33 patients (85%), and median progression-free survival was 12 months.

A trial of the CAR-T cell treatment JNJ-4528 has also recently been published. This trial included 29 patients with RRMM. Overall response rate was 100% (i.e. all the patients had a partial response or better).

What are the possible known side effects of CAR-T cell treatments?

CAR-T cell treatments carry a risk of serious side effects that need expert care, including cytokine release syndrome and neurotoxic effects. Patients will be monitored frequently for early indications of side effects, and given rapid intensive care treatment if needed.

Cytokine release syndrome (CRS), also called infusion reaction, happens when the modified T cells cause an excessive amount of cytokine to be released. This results in symptoms in the period after the infusion, such as fever, rapid heart rate and drops in blood pressure, which can range from mild to very severe.

Neurotoxic effects can include headache, confusion and decreased alertness (stupor) and can range from mild to very severe.

Other possible side effects: reductions in blood cells (white cells, red cells and platelets) can be severe. This can lead to anaemia, increased risk of infections, or bleeding/bruising. It is possible for an allergic reaction to CAR-T cells to occur, or for the CAR-T cells to cause damage to normal, healthy cells. Because CAR-T cell treatments for myeloma are not yet in widespread use, it is possible that new side effects will emerge.

Some CAR-T treatments have been designed with a 'safety switch'. This switch can be triggered to kill the CAR-T cells in a patient if they are causing extreme problems.

Are CAR-T cell treatments currently available in any UK clinical trials?

Most CAR-T cell treatment clinical trials are in patients who have relapsed/refractory myeloma, and for whom existing treatment options are limited, rather than patients at earlier stages of their treatment pathway.

For an up-to-date list of UK clinical trials involving CAR-T cell treatments, visit the Myeloma Trial Finder on myeloma.org.uk

To be enrolled on a clinical trial, patients have to meet certain conditions known as eligibility

criteria. You should speak to your doctor in the first instance if you are interested in taking part in a trial.

If you are considering taking part in a clinical trial your doctor will discuss in detail the risks and benefits for you. They will give you detailed information to enable you to make an informed decision about whether to take part.

Availability of CAR-T cell treatments in the UK

CAR-T cell treatments are not currently available for use in myeloma in the UK, and are only accessible to patients as part of a clinical trial.

Before a drug or treatment strategy can be widely used, it must first be licensed as a safe and effective treatment. This is usually done by the regulatory authorities at a European level and involves a review of evidence from large-scale clinical studies.

Normally, the licensed treatment must then be approved by a UK drug appraisal body before it can be routinely prescribed by NHS doctors. The treatment appraisal process differs from licensing – it looks at how effective the newly-licensed treatment is compared with existing treatments already in use on the

NHS, and decides whether the treatment offers the NHS good value for money.

The main body responsible for carrying out appraisals in England and Wales is the National Institute for Health and Care Excellence (NICE). NICE recommendations are usually adopted in Northern Ireland. Scotland's appraisal body is the Scottish Medicines Consortium (SMC).

For more information see the [Health Technology Assessment \(HTA\) Infosheet](#) from Myeloma UK

Future directions

There has been some very exciting news published about CAR-T cell treatments, but there are limitations of these treatments currently, such as serious potential side effects and the possibility of the T cells becoming 'exhausted'.

Another limitation is that collecting and modifying T cells from each individual patient is a very time-consuming and expensive process, and requires highly specialised skills.

Current and future trials will provide information about the safest and most effective ways to use these treatments in myeloma.

The CAR-T cell treatments most advanced in development target the BCMA protein on myeloma cells (like bb2121 and JNJ-4528). Larger-scale trials comparing these treatments with established myeloma drugs are underway.

CAR-T cells targeting various other antigens on myeloma cells are also being developed.

There are a number of other areas of research currently.

Researchers are looking for markers on patients' myeloma cells which may identify those patients most likely to respond to CAR-T cell treatments, and those at high risk of having serious reactions to the infusions.

Research is also being done on 'exhaustion' of CAR-T cell populations, how this happens and how to keep the CAR-T cells active for as long as possible.

Some CAR-T treatments are being developed which recognise two different targets. It is hoped that this will increase the chance of the CAR-T cells being able to recognise myeloma cells, and decrease the chance of the myeloma cells evolving to escape the CAR-T cells by removing one of the targets from their surface.

Key points

- CAR-T cell treatments are a new type of myeloma treatment that uses the body's own immune system to kill myeloma cells
- Some of the patient's own blood cells called T cells are taken out of the blood and modified in a laboratory
- The modified cells, called CAR-T cells, have a receptor that can recognise myeloma cells. The CAR-T cells are infused back into the patient
- CAR-T cell treatments in myeloma are not as well developed as in other blood cancers, and only early-stage trials have been done so far
- Side effects of CAR-T treatments can be severe and can include infusion reactions, effects on the nervous system and reductions in blood cells (causing anaemia, increased risk of infections, or bleeding/bruising)
- CAR-T cell treatments are not yet widely available, because none have been licensed and approved for use in myeloma. However, patients may be treated with them as part of a clinical trial

About this Horizons Infosheet

The information in this Horizons Infosheet is not meant to replace the advice of your medical team. They are the people to ask if you have questions about your individual situation.

For a list of references used to develop our resources, visit myeloma.org.uk/references

We value your feedback about our patient information.

For a short online survey go to myeloma.org.uk/pifedback or email comments to myelomauk@myeloma.org.uk

Other information available from Myeloma UK

Myeloma UK has a range of publications available covering all aspects of myeloma, its treatment and management. Download or order them from myeloma.org.uk/publications

To talk to one of our Myeloma Information Specialists about any aspect of myeloma, call our Myeloma Infoline on **0800 980 3332** or **1800 937 773** from Ireland.

The Infoline is open from Monday to Friday, 9am to 5pm and is free to phone from anywhere in the UK and Ireland.

Information and support about myeloma is also available around the clock at myeloma.org.uk

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We're here for everything a diagnosis of myeloma brings

Get in touch to find out more about how we can support you

Call the Myeloma Infoline on

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