Adoptive T cell transfer and CAR-T cells

Horizons Infosheet
Clinical trials and novel drugs

This Horizons Infosheet contains information on adoptive T cell transfer, a type of treatment being investigated in myeloma, and in particular, treatment involving CAR-T cells.

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 is adoptive T cell transfer?

Adoptive T cell transfer is a new type of treatment that uses the body's own immune system to kill myeloma cells.

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

However, adoptive T cell transfer is 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 chemicals (cytokines) to recruit other immune cells to kill it.

How does adoptive T cell transfer 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. Adoptive T cell transfer aims to get round this by boosting the ability of a patient's T cells to recognise and kill myeloma cells.

Adoptive T cell transfer starts with collecting T cells from the patient's blood by a process called apheresis. This is where the patient's blood is pumped through a machine which filters out the T cells and returns the blood to the body (Figure 1).

The collected T cells are genetically modified in a laboratory so that they can recognise myeloma cells. They are then multiplied and infused back into the patient. The modified T cells continue to multiply within the patient's body where they target and kill myeloma cells (Figure 2).

CAR-T cells

The type of adoptive T cell transfer showing the most promise is known as chimeric antigen receptor (CAR) T cells. CAR-T cells are T cells that have been modified to express a

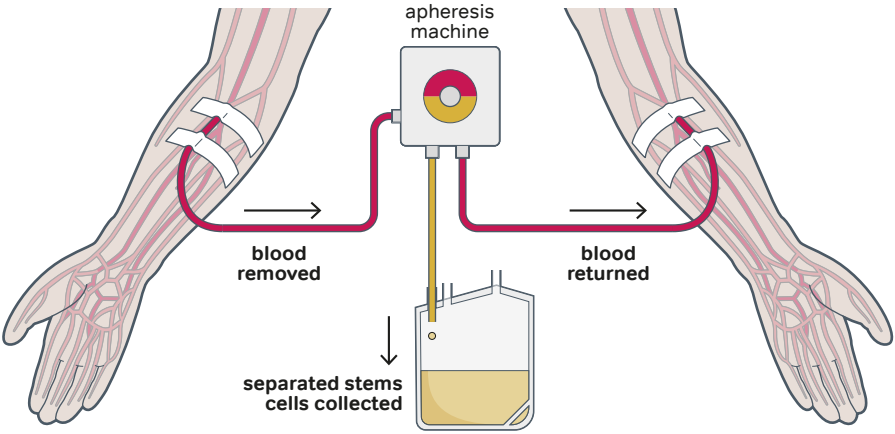

Figure 1. Apheresis process

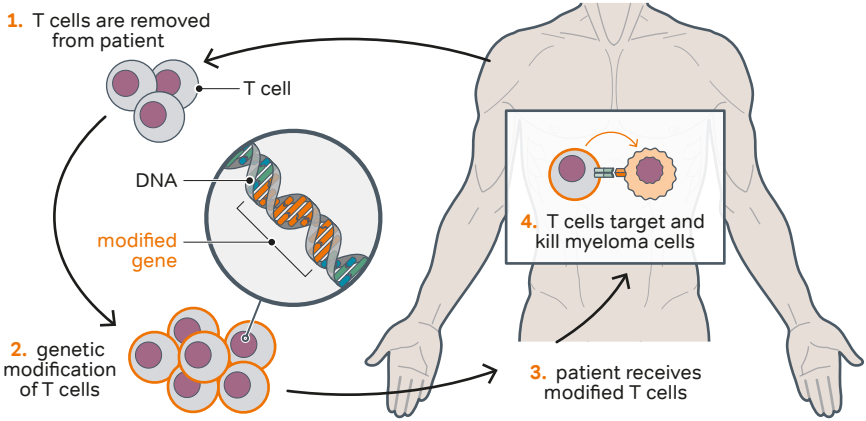

Figure 2. Adoptive T cell transfer process

receptor that will recognise a specific target on the surface of myeloma cells. In some cases, the T cells are engineered to recognise two targets on the myeloma cells. This increases the chance of the CAR-T cells being able to recognise myeloma cells, and decreases the chance of the myeloma cells evolving to escape the CAR-T cells by removing one of the targets from their surface.

Unlike drugs, CAR-T cells can persist in the body for years and can also multiply to give rise to new cells. This means CAR-T cells have the potential to provide long-term control, which distinguishes it from standard treatment approaches in myeloma where a drug needs to be taken continuously 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 adoptive T cell transfer?

Adoptive T cell transfer, and in particular CAR-T cells, have already shown impressive results in other blood cancers, such as acute lymphoblastic leukaemia.

In myeloma patients, clinical trials are in very early stages but early results have been promising. CAR-T cells have been used to treat relapsed and/or refractory patients in a few international early phase trials. Of the small number of patients taking part, many have had at least a partial response after treatment, with some reaching complete remission (after limited follow-up).

The published data are very preliminary and much larger trials are needed to generate more robust results.

What are the possible known side effects of adoptive T cell transfer?

Adoptive T cell transfer has two particularly serious side effects – cytokine release syndrome (CRS) and neurotoxicity (damage to the brain).

CRS, also known as an infusion reaction, occurs when the modified T cells release an excessive amount of cytokines (a type of chemical involved in normal immune reactions) into the blood, resulting in symptoms such as fever, nausea, rapid heart rate and abnormally low blood pressure. This can occur

immediately or soon after receiving the treatment.

Neurotoxicity, also known as CAR-T-cell-related encephalopathy syndrome (CRES), occurs when the modified T cells cause swelling in the brain.

Both CRS and CRES can range from relatively mild to life-threatening but can normally be successfully managed if caught early. Patients will be monitored closely for signs of CRS and CRES after adoptive T cell transfer and given any treatment necessary.

It is also possible to have an allergic reaction to the treatment resulting in anaphylaxis (difficulty breathing due to the swelling of the tongue and throat).

Although the CAR-T cells are engineered to target myeloma cells, they can sometimes damage normal, healthy cells in the body which also express the target or a similar target. This can cause a variety of side effects, depending on which other cells are damaged.

To prevent life-threatening side effects, some CAR-T cells have been designed with a "safety switch", which can be triggered to kill the CAR-T cells if they cause significant problems in a patient.

Is adoptive T cell transfer currently available in any UK clinical trials?

For an up-to-date list of UK clinical trials involving adoptive T cell transfer, 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.

Availability of adoptive T cell transfer in the UK

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 compares how effective the newly-licensed treatment is to existing treatments already in use on the NHS and decides whether it 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

Adoptive T cell transfer is not currently licensed for use in myeloma in the UK and is only accessible to patients as part of a clinical trial.

Future directions

Modified T cells can persist in the body for years, so it is hoped that patients will only need a single adoptive T cell transfer to produce a continuing and long-term response to myeloma cells. This is unlike most other myeloma treatments which require a drug to be taken regularly.

However, adoptive T cell transfer is still in the early stages of clinical trials in myeloma and the long-term effect of this treatment approach is not yet known. Current and future trials will provide information about the safest and most effective way to use adoptive T cell transfer in myeloma.

CAR-T cells with different targets on myeloma cells are being investigated.

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

Another limitation of this treatment at the moment is that collecting and modifying T cells from each individual patient is a very time-consuming and expensive process, and requires highly specialised skills. This may exclude some patients from receiving this treatment, such as those requiring urgent treatment.

More research is needed to address these limitations before adoptive T cell transfer can be approved for use in myeloma patients, but it offers the prospect of a highly effective new treatment for myeloma in the future.

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

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Myeloma UK has a range of publications available covering all areas of myeloma, its treatment and management.

To order your free copies or 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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