

Immunotherapy in myeloma

Horizons Infosheet Clinical trials and novel drugs

This Horizons Infosheet provides information on immunotherapy, a type of treatment 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 novel 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 immunotherapy?

Immunotherapy is a type of cancer treatment which helps the immune system to recognise and kill cancer cells.

What is the immune system?

The immune system is made up of specialised cells, tissues and organs which work together in a process known as an immune response. An immune response protects the body from foreign organisms (such as bacteria or viruses) that enter the body.

The immune system also identifies and kills faulty or abnormal cells in the body.

White blood cells, produced in the bone marrow, are an important part of the immune system. Different types of white blood cell, such as plasma cells and T cells, perform specific immune functions.

Plasma cells

Plasma cells make antibodies (also known as immunoglobulins) and release them into the bloodstream. Antibodies flag foreign or potentially harmful organisms for removal by other cells of the immune system. Myeloma cells are abnormal plasma cells which produce a large amount of a single type of antibody, known as paraprotein, which has no useful function.

T cells

T cells are immune cells that circulate around the body scanning for abnormal or infected cells. T cells can either directly kill and remove abnormal or infected cells, or they can stimulate healthy plasma cells to make antibodies and flag the cell for removal.

How does immunotherapy in myeloma work?

Myeloma cells are able to evade the immune system through a variety

of mechanisms, allowing them to multiply and grow in the body. Immunotherapy stimulates the immune system to work harder or smarter to kill myeloma cells.

The complexity of the immune system means that there are many ways in which it can be harnessed, and many of the different substances produced as part of the immune response can now be made in the laboratory.

Immunotherapy currently in use

There are a number of myeloma treatments already in use that work partly through immunotherapy. Allogeneic (donor) stem cell transplantation works by harnessing the immune system of a healthy donor to attack a patient's myeloma cells. However, the risk of serious side effects is greater with allogeneic stem cell transplantation than autologous (self) stem cell transplantation, meaning that it is only appropriate for a small number of myeloma patients.



For more information see the **Allogeneic stem cell transplantation in myeloma Infoshield** from Myeloma UK

The ‘immunomodulatory drugs’ (IMiDs) thalidomide, lenalidomide (Revlimid®) and pomalidomide (Imnovid®), are widely used in myeloma. They work in several different ways including directly killing myeloma cells. They also stimulate the immune system, which increases their effect.

Daratumumab (Darzalex®) is a drug licensed in the UK to treat myeloma. It is a type of immunotherapy called a monoclonal antibody (see following section for more about this type of drug).

Immunotherapies in development

The main types of immunotherapies now being investigated for the treatment of myeloma are:

- Monoclonal antibody drugs
- CAR-T cell treatments
- Oncolytic viruses

Monoclonal antibody drugs

Foreign organisms such as viruses and bacteria have proteins on their cell surface (known as antigens) that are specific to that organism. Healthy plasma cells produce antibodies which recognise and attach to antigens, flagging the organism for destruction by other immune cells, such as T cells.

Each antibody recognises only one antigen, and so millions of antibodies are produced by the body to defend against a range of foreign organisms or abnormal cells.

Monoclonal antibody drugs exploit the ability of antibodies to recognise specific antigens. They are engineered in the laboratory to recognise antigens specific to myeloma cells so that the immune system can be directed to recognise and kill them. ‘Monoclonal’ means all one type. This means that each monoclonal antibody drug is made up of identical copies of one type of antibody that recognise one specific antigen, for example a protein that is expressed by myeloma cells (Figure 1).

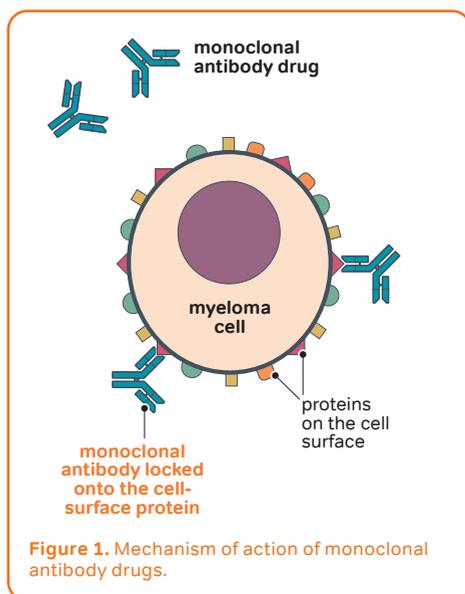


Figure 1. Mechanism of action of monoclonal antibody drugs.

Monoclonal antibodies are an established treatment in many other cancers. Some monoclonal antibodies are starting to show huge promise in the treatment of myeloma. Daratumumab (Darzalex®), the first drug in this group to be licensed in the UK, is available as a monotherapy (given on its own) for patients who have had three previous drug treatments, and as a combination treatment for patients at first relapse.

For more information see the **Daratumumab (Darzalex®) Treatment Guide** from Myeloma UK



Other monoclonal antibody drugs currently being investigated for the treatment of myeloma include siltuximab, isatuximab and elotuzumab.

For more information see the **Elotuzumab (Empliciti®) Horizons Infosheet** and the **Isatuximab (Sarclisa®) Horizons Infosheet** from Myeloma UK



Antibody drug conjugates

Drugs are also being developed which combine a monoclonal antibody with a chemotherapy drug (known as an antibody-drug conjugate) to guide the chemotherapy directly to the myeloma cells. One of these is belantamab mafodotin, which contains the powerful chemotherapy drug mafodotin joined to an antibody. Mafodotin is too toxic to be given on its own, but in the conjugate it only becomes active once the antibody had guided it to a myeloma cell.

For more information see the **Belantamab mafodotin Horizons Infosheet** from Myeloma UK



Bispecific T cell engagers

Antibodies called bispecific T-cell engagers (BiTEs) recognise two antigens, one on the myeloma cells and one on T cells. This brings the T cells and myeloma cells into close contact, and targets the T cell activity to the myeloma cells (see Figure 2). BiTEs are at an early stage of development.

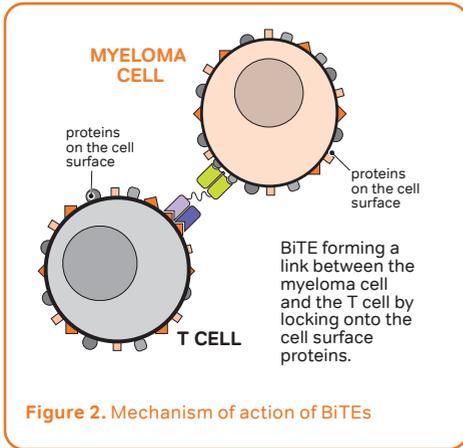


Figure 2. Mechanism of action of BiTEs

CAR-T cell treatments

CAR (chimeric antigen receptor) T cell treatments are a personalised treatment. This means the treatment is tailored to an individual patient. In this case, a patient's own T cells are taken and modified so that they recognise a specific target

on the surface of myeloma cells. The T cells can then target and kill the patient's myeloma cells.

CAR-T cells are used in a process called adoptive T cell transfer. T cells are collected from a patient's blood and genetically modified in a laboratory, forming CAR-T cells. The cells are then multiplied and infused back into the patient (Figure 3). Following the infusion, the CAR-T cells continue to multiply within the patient's body and target and kill myeloma cells.

CAR-T cell treatments have already shown impressive results in certain types of lymphoma and leukaemia. Development of CAR-T treatments for myeloma, however, is at a very early stage.

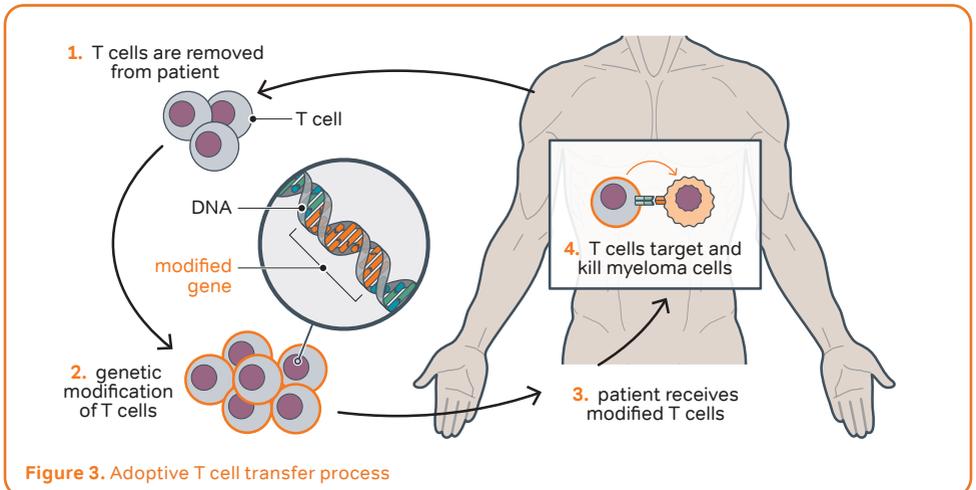


Figure 3. Adoptive T cell transfer process

Results so far have been promising with good remission rates in relapsed and/or refractory patients. However, the depth of response, and how long it lasts, have so far been more limited in myeloma. A CAR-T treatment currently in clinical trial for myeloma in the UK is bb2121.

For more information see the **CAR-T cell treatments Infosheet** from Myeloma UK

Oncolytic viruses

Oncolytic viruses infect and kill cancer cells, while having only a limited effect on normal cells. When an oncolytic virus infects a myeloma cell, it continues to

multiply within the myeloma cell until the cell bursts. This causes the myeloma cell to die and release the virus into the surrounding area (Figure 4). The virus then goes on to infect other myeloma cells, causing them to also die.

At the same time, the virus causes the immune system to mount an immune response against the the myeloma cell. As such, the effects against the myeloma cells are doubled.

Oncolytic viruses currently being investigated for the treatment of myeloma include pelareorep (Reolysin®).

For more information see the **Reolysin® Infosheet** from Myeloma UK

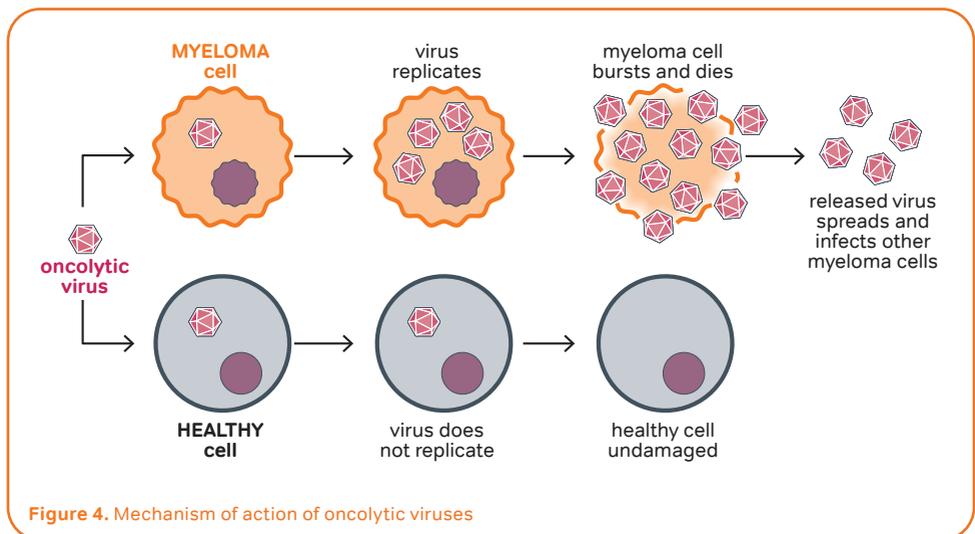


Figure 4. Mechanism of action of oncolytic viruses

What are the potential side effects of immunotherapy?

The newer types of immunotherapy such as CAR-T cells can be associated with serious side effects. Some of these can be potentially life-threatening and need expert management.

The side effects of immunotherapy occur when the treatment causes the immune system to behave in an undesired way. As each person's immune system is unique, the side effects of immunotherapy may vary from person to person.

A possible side effect of some types of immunotherapy is autoimmunity. This is when the immune system attacks healthy cells and tissues, failing to recognise them as 'self'. This can occur if the immune system is too active or if the antigen targeted by the immunotherapy is present on healthy cells as well as myeloma cells.

Autoimmune complications can result in symptoms such as nausea, fatigue, fever and skin rashes as well as more serious effects such as pneumonitis (inflammation of the air sacs in the lungs) and certain endocrine (hormonal) disorders.

Another side effect that can occur with immunotherapy drugs is cytokine release syndrome (CRS). This is often called an infusion reaction. It can occur immediately or soon after receiving the treatment. It occurs when white blood cells activated by the treatment release an excessive amount of chemicals into the blood, resulting in a type of allergic reaction.

The symptoms of an infusion reaction include fever, nausea, rapid heart rate and abnormally low blood pressure.

Some immunotherapy treatments can cause neurotoxic effects (effects on the nervous system) such as confusion and decreased alertness (stupor). These can range from mild to very severe.

Infusion reactions and severe neurotoxic effects are serious and need emergency management. In some cases, patients are given a drug to damp down the excessive immune reaction.

Other side effects can occur with immunotherapies, such as reductions in blood cell counts.

As immunotherapy is still the subject of research, some of the treatments may have side effects that we do not know about yet.

UK availability of immunotherapy treatments

Allogeneic stem cell transplantation, IMiDs such as lenalidomide, and the monoclonal antibody drug daratumumab are currently available to selected groups of patients. Elotuzumab and isatuximab are licensed for use in Europe, but are not yet approved for use on the NHS in the UK.

The other immunotherapy treatments for myeloma discussed in this Infosheet are either in very early-stage development or only available in the UK as part of a clinical trial.

For an up-to-date list of UK clinical trials involving immunotherapies, visit the Myeloma Trial Finder at 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.

Future directions

As our understanding of myeloma and the immune system has grown, research into immunotherapy has advanced and some promising clinical trial results have been generated.

The complexity of the immune system means there are many different ways in which it can be triggered to kill myeloma cells.

Different immunotherapies are being studied which recognise different proteins on myeloma cells.

It is also likely that combinations of immunotherapies with different mechanisms of action may be particularly effective in treating myeloma. Similarly, immunotherapies may enhance the effect of established treatment combinations.

Key points

- Myeloma cells are able to escape the body's immune system in a variety of ways. The aim of immunotherapies is to stimulate the immune system to work harder or smarter to kill myeloma cells
- Some myeloma drugs already in use are immunotherapies, for example thalidomide and daratumumab
- A number of types of immunotherapy are now being developed to treat myeloma. These include monoclonal antibodies, CAR-T cell treatments, and cancer-targeting (oncolytic) viruses
- The newer immunotherapies now being developed can trigger side effects that can be serious and need expert care
- Clinical trials and other research are helping scientists to understand better how the immune system works and ways to harness it to treat myeloma

About this Infosheet

The information in this 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/pifeedback 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

Notes

Notes



Horizons Infosheet – Clinical trials and novel drugs:
Immunotherapy in myeloma



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

 **0800 980 3332**

Email Ask the Nurse at

 **AskTheNurse@myeloma.org.uk**

Visit our website at

 **myeloma.org.uk**

Myeloma UK

22 Logie Mill, Beaverbank Business Park,
Edinburgh EH7 4HG

 0131 557 3332

 myelomauk@myeloma.org.uk

Registered Charity No: SC026116

Published by:	Myeloma UK
Publication date:	November 2016
Last updated:	June 2020
Review date:	November 2020