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. Many myeloma treatments are immunotherapies.

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 Infosheet** 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
- Antibody drug conjugates
- Bispecific antibodies
- CAR-T cell treatments

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.

Cells in the body (including abnormal ones like myeloma cells) all have antigens on their surface as well. Antigens on abnormal cells can also be targeted by antibodies.

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, in this case a protein that is expressed by myeloma cells (Figure 1).

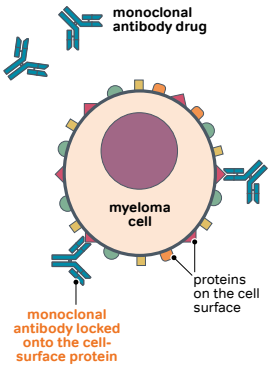

Figure 1. Mechanism of action of monoclonal antibody drugs.

Monoclonal antibodies are an established treatment in myeloma and in many other cancers, with some showing huge promise in the treatment of myeloma. Daratumumab (Darzalex®), was the first drug in this group to be approved for myeloma in the UK. It 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.

A second monoclonal antibody, called isatuximab (Sarclisa®), has now been approved for patients in the UK. It is available in combination with pomalidomide and dexamethasone for patients who have had three previous treatments.

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

Another monoclonal antibody drug currently being investigated for the treatment of myeloma is elotuzumab.

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

Antibody drug conjugates

Drugs are also being developed that 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, belantamab mafodotin (Blenrep®), was recently licensed for use in Europe. It 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 has guided it to a myeloma cell.

Clinical trials comparing belantamab mafodotin with other myeloma treatments are currently underway.

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

Bispecific antibodies

Bispecific antibodies (also called T cell engagers) 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). Bispecific antibodies currently in clinical trials include two called AMG 701 and teclistamab.

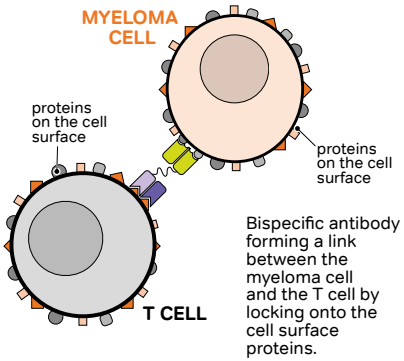

Figure 2. Mechanism of action of bispecific antibodies

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 currently in development include idecabtagene vicleucel (Abecma®, also called ide-cel), and ciltacabtagene autoleucel (also called cilta-cel). Ide-cel was recently approved for use in Europe.

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

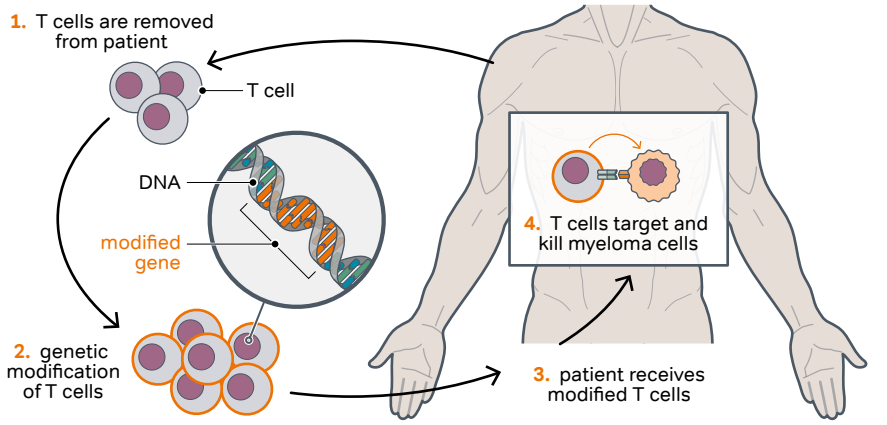

Figure 3. Adoptive T cell transfer process

What are the potential side effects of immunotherapy?

The term "immunotherapies" covers a wide range of treatments that work in different ways. Their side effects vary depending on the particular treatment and how it works, and also depending on the individual patient's reaction to the treatment.

Some side effects of newer immunotherapies can be serious and may need expert care.

One reason side effects can happen is if the immunotherapy makes the person's immune system over-react. An example is cytokine release syndrome (CRS), also called infusion reaction. CRS can happen if the white blood cells are triggered to release excessive amounts of chemicals called cytokines into the blood. This causes side effects including fever, nausea, fast heart rate and low blood pressure. Often these side effects will be short-lived and mild, but they can be serious. You will be given drugs (such as steroids and antihistamines) before and after infusions of drugs such as daratumumab, to lower the chance of infusion reactions. In severe cases, such as during CAR-T treatment, a specific drug may be given to damp down the CRS.

Some immunotherapies such as CAR-T treatments can also cause effects on the nervous system such as confusion and stupor (becoming less alert). These can range from mild to very severe, and may need expert care.

Many immunotherapies can cause reduced numbers of blood cells, which can lead to infections, bruising/bleeding, or anaemia. Other possible side effects include diarrhoea and fatigue. Belantamab mafodotin can cause effects on the eyes. Allogeneic stem cell transplantation can cause adverse effects when the donated (allogeneic) stem cells attack the patient's own body (called graft-versus-host-disease).

As immunotherapies are still in development, new side effects may be discovered that are not yet known about.

For more information about side effects of immunotherapies, see the **Treatment Guides** and the **Allogeneic stem cell transplantation in myeloma Infosheet**, and for newer treatments see the **Horizons Infosheets**, from Myeloma UK.

UK availability of immunotherapy treatments

Allogeneic stem cell transplantation, IMiDs such as lenalidomide, and the monoclonal antibody drugs daratumumab and isatuximab are currently available to selected groups of patients. Elotuzumab, belantamab mafodotin and ide-cel are licensed for use in Europe, but are not approved for use on the NHS in the UK. Some patients may be treated with belantamab mafodotin as part of an expanded access scheme for the drug.

For more information about drug licensing and approval, see the **Health Technology Assessment (HTA) Infosheet** from Myeloma UK

The other immunotherapy treatments for myeloma discussed in this Infosheet are at an earlier stage of development, but patients may be given them as part of a clinical trial.

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

Researchers are also looking at how in future immunotherapies could be combined with existing treatments or other immunotherapies to maximise their effect on the myeloma.

Another important research area is the reasons why myeloma becomes resistant to different treatments, and how this can be overcome or delayed.

In future, immunotherapies may be given at earlier stages in the myeloma treatment pathway. Researchers are looking at how best to use them. This includes how to use them in older and non-transplant eligible patients. The aim is always to maximise effectiveness and length of response, while minimising side effects.

Immunotherapy is a fast-moving and exciting research area, with the potential to provide new and powerful treatment options for myeloma patients.

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 antibody combinations
- The newer immunotherapies now being developed are proving effective in treating myeloma. They 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 patientinfo@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

MyelomaUK

We're here for everything a diagnosis of myeloma brings

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

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0800 980 3332

Email Ask the Nurse at
AskTheNurse@myeloma.org.uk

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Myeloma UK
22 Logie Mill, Beaverbank Business Park,
Edinburgh EH7 4HG
0131 557 3332
myelomauk@myeloma.org.uk
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