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.

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](http://myeloma.org.uk) from Myeloma UK

Some of the newer and more widely used anti-myeloma treatments, such as the ‘immunomodulatory drugs’ or IMiDs e.g. thalidomide, lenalidomide (Revlimid®) and pomalidomide (Imnovid®), are also known to
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).
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 in England, Wales, Scotland and N. Ireland for patients who have had three previous drug treatments, and in England, Wales and N. Ireland 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.

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.

Antibodies called bispecific T-cell engagers (BiTE therapies) recognise two antigens, one on the myeloma cells and one on T cells. This targets

the T cell activity to the myeloma cells. BiTE therapies are at an early stage of development.

**Immune checkpoint inhibitors**

The immune system uses a checkpoint system to avoid harming healthy cells. Immune cells carry checkpoint receptors that recognise checkpoint molecules on healthy cells – this acts like a traffic light ‘stop-go’ system, preventing the immune system from reacting when it comes into contact with a healthy cell. Myeloma cells manipulate this system by expressing checkpoint molecules alongside antigens which would normally trigger the immune system to respond.

For example, myeloma cells express the checkpoint molecule PD-L1, which binds to the checkpoint receptor PD-1 found on immune cells. When an immune cell expressing PD-1 comes into contact with the checkpoint molecule PD-L1 on a myeloma cell, the immune system’s response to the myeloma cell is switched off.
Immune checkpoint inhibitors are drugs which reduce the ability of myeloma cells to exploit the checkpoint system. They prevent checkpoint molecules on myeloma cells from binding to checkpoint receptors on immune cells such as T cells (Figure 2). The immune system is then more likely to recognise the antigens expressed by the myeloma cell and start an immune response to kill the cell.

Immune checkpoint inhibitors are in an earlier phase of development than monoclonal antibodies but some are showing promise in early phase trials.

Checkpoint inhibitors currently being investigated for the treatment of myeloma include nivolumab (Opdivo®) and durvalumab (Imfinzi®).

Figure 2. Mechanism of action of checkpoint inhibitor drugs
**Adoptive T cell transfer**

Adoptive T cell transfer involves collecting T cells from a patient’s blood and genetically modifying them in a laboratory so they will recognise and kill myeloma cells. They are then multiplied and infused back into the patient (Figure 3).

Following the infusion, the T cells continue to multiply within the patient’s body and target and kill myeloma cells.

The adoptive T cell transfer technology showing the most promise is known as chimeric antigen receptor (CAR) T cells. CAR-T cells have already shown impressive results in other blood cancers, such as acute lymphoblastic leukaemia. Results from treatment of myeloma patients are showing promise so far. This includes AUTO2, which is being investigated in the APRIL trial in the UK, and another called bb2121.

For more information see the **Adoptive T cell transfer and CAR-T cells Infosheet** from Myeloma UK

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**Figure 3. Adoptive T cell transfer process**

1. T cells are removed from patient
2. Genetic modification of T cells
3. Patient receives modified T cells
4. T cells target and kill myeloma cells
**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 myeloma cell. As such, the effects against the myeloma cells are doubled.

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

For more information see the Reolysin® Infosheet from Myeloma UK

**Figure 4. Mechanism of action of oncolytic viruses**

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What are the potential side effects of immunotherapy?

Some people think of immunotherapy as a more ‘natural’ type of treatment, as it works by enhancing the body’s natural defence system. However, there are still side effects associated with immunotherapy, some of which are potentially serious.

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 which can occur with both adoptive T cell transfer and monoclonal antibody drugs is cytokine release syndrome. This is often called an infusion reaction. It can occur immediately or soon after receiving the treatment. Infusion reactions occur 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.

If an infusion reaction occurs, it requires emergency management.

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

As discussed, allogeneic stem cell transplantation, IMiDs such as lenalidomide, and the monoclonal antibody drug daratumumab are currently available to selected groups of patients.

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.
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. Therefore, it is likely that a combination of immunotherapies with different but synergistic mechanisms of action may be particularly effective in treating myeloma. Similarly, immunotherapies may enhance the effect of established treatment combinations.

For more information on open clinical trials in the UK see the Myeloma Trial Finder at trials.myeloma.org.uk

Key points

- Myeloma cells evade 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, immune checkpoint inhibitors, CAR-T cells, and cancer-targeting (oncolytic) viruses.
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.
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We’re here for everything a diagnosis of myeloma brings

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