Kyprolis® (carfilzomib)

This Horizons Infosheet contains information on Kyprolis® (also known as carfilzomib), a drug being investigated for the treatment of myeloma.

The Horizons Infosheet series provides information relating to novel drugs 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 drug development.

The drugs 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 Kyprolis?

Kyprolis is a new drug being used to treat myeloma.

Like Velcade® (bortezomib), Kyprolis belongs to a group of drugs known as proteasome inhibitors. Kyprolis works in a

similar way to Velcade, however it has been developed to target a different area of the proteasome from Velcade. This is thought to make Kyprolis more effective and potentially cause fewer side-effects than Velcade.

What are proteasomes?

Proteasomes are large molecules which are present in all cells in the body. They are involved in the removal, breakdown and recycling of damaged proteins or those that are no longer needed by the cell.

How does Kyprolis work?

Kyprolis works by binding to proteasomes and permanently blocking their function which stops them from breaking down unwanted proteins (Figure 1). This causes proteins to build up and become toxic, killing the cell.

Myeloma cells multiply more quickly than normal healthy cells and rely more heavily on proteasomes as they produce unwanted proteins at a faster rate. They are therefore much more sensitive to Kyprolis.

Myeloma cells appear to be even more dependent on the actions of proteasomes than other types of cancer cells. This may be due to the need of the myeloma cells to dispose of the abnormal protein (paraprotein) they produce.

By blocking the function of the proteasome, Kyprolis prevents the myeloma cells from growing and multiplying.

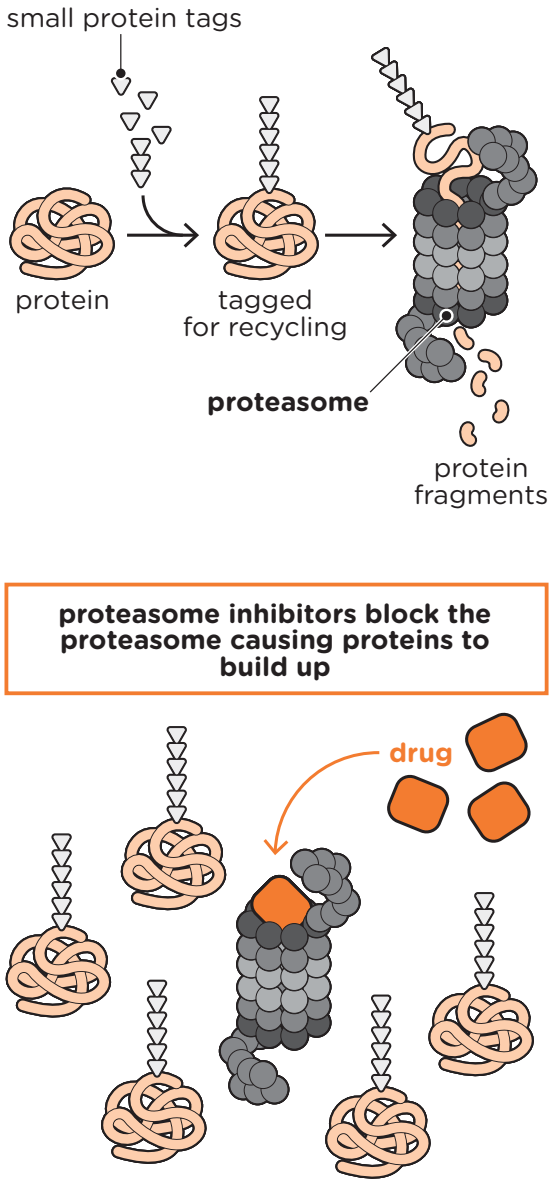

Figure 1. Mechanism of action of proteasome inhibitors

How is Kyprolis given?

Kyprolis is given as an intravenous (into the vein) infusion. It has been shown to be most effective when used in combination with other myeloma treatments such as Revlimid® (lenalidomide) and dexamethasone.

When given in combination with Revlimid and dexamethasone, Kyprolis is administered over a 28-day treatment cycle. Kyprolis is given over 2 consecutive days each week for 3 weeks followed by 12 days off.

It is administered as a 10 minute intravenous infusion which starts at 20mg/m^2 during the first cycle (on days 1 and 2). If this dose is tolerated, the dose is increased to 27mg/m^2 for the remaining cycles. Patients receive Revlimid on days 1 to 21 and dexamethasone on days 1, 8, 15 and 22 of each cycle.

Kyprolis is given for a maximum of 18 cycles.

When given in combination with dexamethasone only, Kyprolis is administered as a 30-minute infusion starting at 20mg/m^2 on days 1 and 2 of the first cycle. If this dose is tolerated it is increased to 56mg/m^2 for the remaining cycles. Low-dose dexamethasone (20mg/m^2) is given on Days 1, 2, 8, 9, 15 and 16 of a cycle. The treatment is continuous until disease progression.

What evidence exists to support the use of Kyprolis?

In the Phase III ASPIRE clinical trial, Kyprolis, when combined with Revlimid and dexamethasone, significantly extended progression free survival (the length of time following treatment before the myeloma returns) compared to Revlimid and dexamethasone alone.

Further evidence from the Phase III ENDEAVOR clinical trial found that progression free survival was also increased in patients treated with Kyprolis and dexamethasone compared to Velcade and dexamethasone.

Kyprolis is currently being investigated in combination with other myeloma treatments. For example, the MUK *five* trial is investigating the use of Kyprolis with cyclophosphamide and dexamethasone. However, there is no trial data available yet on the effectiveness of this treatment combination.

In ongoing trials, Kyprolis is proving to be an effective initial

treatment for newly diagnosed myeloma patients.

Research into Kyprolis as a monotherapy (on its own and not in combination with other drugs) has found that it is not as effective as when it is given in combination with other drugs.

What are the known possible side-effects of Kyprolis?

The most commonly reported side-effects of Kyprolis include: fatigue, low platelet counts (thrombocytopenia), low red blood cell counts (anaemia), nausea, difficulty breathing, diarrhoea and fever.

Kyprolis has also been found to cause heart problems or worsen pre-existing heart conditions. Therefore, patients being treated with Kyprolis will be monitored carefully during treatment.

Unlike Velcade, which can cause peripheral neuropathy (damage to the nerves that make up the peripheral nervous system causing pain, tingling and altered sensation) in some patients, Kyprolis is thought to cause very low rates of peripheral neuropathy.

Is Kyprolis currently available in any UK clinical trials?

For an up-to-date list of UK clinical trials involving Kyprolis, visit the **Myeloma Trial Finder** on **www.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.

UK availability of Kyprolis

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

Normally, the licensed drug must then be approved by a UK drug appraisal body before it can be routinely prescribed by NHS doctors. The drug appraisal process differs from licensing – it compares how effective the newly-licensed drug is to existing drugs already in use on the NHS and decides whether it offers the NHS good value for money. The main body responsible for carrying out drug 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 drug appraisal body is the Scottish Medicines Consortium (SMC).

Kyprolis has been approved by the European licensing body, the European Medicines Agency (EMA) for relapsed myeloma patients who have received at least one previous treatment.

In England and Wales, Kyprolis has received a draft no from NICE for use in combination with Revlimid and dexamethasone and for use in combination with dexamethasone only for relapsed myeloma patients who have had at least one previous treatment. Negative guidance was issued because of the uncertainty of the clinical benefits justifying the cost of the treatment to the NHS. This draft response will be appealed and more evidence submitted for consideration before the final guidance is issued, which is expected to be in early 2017.

In Scotland, the SMC also turned down Kyprolis for the final time for use in combination with Revlimid and dexamethasone for relapsed myeloma patients who have had at least one previous treatment. This is because the submission did not justify the cost of the treatment to the NHS.

This means that although Kyprolis is now licensed and available to patients in the EU, it is only accessible to UK myeloma patients as part of a clinical trial.

Future directions

Although Kyprolis has been turned down by the SMC for use in combination with Revlimid and dexamethasone, it will be submitted to the SMC for consideration for use in combination with dexamethasone only for relapsed myeloma patients.

Kyprolis continues to be studied in different patient groups and in different treatment combinations. These trials will provide information about the safest and most effective way to use Kyprolis in myeloma.

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. All Myeloma UK publications are extensively reviewed by patients and healthcare professionals prior to publication.

Other information available from Myeloma UK

Myeloma UK has a range of Essential Guides, Infoguides and Infosheets available covering many 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 the **Myeloma Infoline: 0800 980 3332** or **1800 937 773** from Ireland.

The Myeloma 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 **www.myeloma.org.uk**

Notes

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