Thalidomide in Myeloma

What is thalidomide?

Thalidomide belongs to a group of drugs called immunomodulatory drugs (IMiDs). IMiDs work by modifying the body’s immune system. First prescribed in the 1950s for nausea and insomnia in pregnant women, thalidomide was taken off the market in the 1960s after it was found to cause birth defects. In more recent years scientists discovered that it can be used to treat conditions of the immune system. In 2006 thalidomide was registered in Australia for use in relapsed myeloma and in 2009 it was approved as a first line treatment. Thalidomide can now also be used as maintenance therapy after a stem cell transplant.

How does thalidomide work?

Thalidomide is a more targeted therapy than conventional chemotherapy; however the exact mechanism of action is still not fully understood. There are several theories on how thalidomide works, some or all of which may occur:

- It directly kills or suppresses the growth and survival of myeloma cells.
- It blocks the growth of new blood vessels (angiogenesis) that feed the myeloma cells with nutrients and oxygen.
- It stimulates the natural killer cells in the immune system to attack the myeloma cells.
- It blocks the activity of chemicals involved in the growth and survival of myeloma cells.

How is thalidomide different from chemotherapy?

Unlike the IMiDs, chemotherapy does not appear to act on the mechanisms described above that support disease progression. Rather, chemotherapy targets cells that are dividing to make new cells. Cancer cells divide frequently, as the body cannot regulate them. Some healthy body cells also need to divide frequently and can therefore also be affected by chemotherapy. These cells include hair follicles, cells that line the digestive tract and bone marrow cells. Hence, the effect of chemotherapy can cause hair loss, nausea, vomiting, diarrhoea and falling blood cell counts. Because IMiDs and chemotherapy act in different ways to attack myeloma cells they can be powerful treatments when given in combination.

When is thalidomide prescribed?

As it has more than one anti myeloma action, thalidomide may be used at different stages in the course of myeloma. It may be prescribed alone or in combination with other anti myeloma drugs. Patients may be taking it after diagnosis and/or after a relapse. Thalidomide may also be prescribed as maintenance therapy after a stem cell transplant. If thalidomide cannot be tolerated, there are other treatment options available.
What are the possible side effects from taking thalidomide and how are they managed?

Below is a list of the most common side effects of thalidomide. The patient may experience none or a few of these side effects. It is important to communicate any change noticed to the doctor. This ensures the correct dose is prescribed and any other possible cause of the symptom is eliminated.

Blood Clots
Developing a blood clot in deep veins in the leg is a potentially serious side effect of treatment with thalidomide. This condition is called deep vein thrombosis (DVT). Symptoms include redness, swelling, tenderness and pain in the leg. If patients develop any of these symptoms the doctor must be informed immediately. Sometimes a piece of the clot breaks off and travels to the lung. This can be life threatening and is called pulmonary embolism (PE). Symptoms of PE include anxiety, shortness of breath with or without exertion and chest pain/tightness. Patients must seek medical assistance urgently if these symptoms occur.

What can be done to minimise the risk of getting a blood clot?
Before commencing treatment, the risk of developing a clot will be assessed. The doctor must be informed if the patient has ever had or has been suspected of having a blood clot. Other risk factors include prolonged bed rest (e.g. after surgery) or long periods of sitting, being overweight, smoking and heart disease. Many patients taking thalidomide are prescribed an anticoagulant (blood thinning medication) or aspirin. These are drugs that decrease the blood’s tendency to clot. Other measures to minimise the risk include regular exercise (keeping mobile) and staying well hydrated. If patients would like to wear special stockings to help the blood flow from the feet and up the legs, they must make sure the stockings are the right size and don’t roll down, constricting the leg. These stockings can be fitted by a nurse at the hospital or by an assistant in a pharmacy.

Drowsiness
Drowsiness is a common and expected side effect because thalidomide’s original use was as a sedative. Drowsiness usually decreases over time while on the same dose, but the doctor may reduce the dose if severe drowsiness occurs.

What can be done to reduce the severity?
Thalidomide is best taken in the evening before going to bed (at least one hour after food) to reduce sleepiness and a ‘hangover’ effect the next morning. Patients may need to adopt a trial and error approach but generally take it 2 to 3 hours before bedtime. Avoid alcohol and medications that cause drowsiness unless prescribed by the doctor. If affected by drowsiness patients should not operate machinery or drive a car. Drowsiness can exacerbate problems associated with fatigue, a common symptom for many people with myeloma. A balanced diet, regular exercise and a regular sleep pattern can help minimise the effects of fatigue.

For further information on fatigue see the “Fatigue Fact Sheet” on our website at www.myeloma.org.au or call the Myeloma Support Line 1800 693 566
**Peripheral Neuropathy**

Peripheral neuropathy is a condition of the nervous system that usually begins in the hands and/or feet with symptoms of numbness, tingling, burning and/or weakness. It is caused by damage to the long nerves radiating from the spine to the arms and legs. This side effect varies in severity and may occur at any time while taking thalidomide, or occasionally after the drug has been stopped. The myeloma itself and some other myeloma treatments, such as bortezomib (Velcade®) can also cause peripheral neuropathy. If patients experience symptoms such as numbness, tingling, burning and pain, it is very important to tell the doctor or medical team as soon as possible. The thalidomide may need to be reduced or stopped (sometimes only temporarily) and other options discussed. The symptoms may disappear after stopping treatment or reducing the dose, but effects are sometimes irreversible, which is why it is important to tell the doctor about any symptoms as soon as possible.

**What can be done to help stay comfortable?**

Early recognition of peripheral neuropathy is important. It is a good idea for patients to monitor symptoms using an assessment questionnaire (see table below).

Circle one number per line to indicate how true each symptom has been during the last 7 days

<table>
<thead>
<tr>
<th>Symptom</th>
<th>None</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbness or tingling in hands and feet</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Numbness or tingling in feet</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Discomfort in hands</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Discomfort in feet</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Joint or muscle cramps</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Weakness all over</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Trouble hearing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Ringing or buzzing in ears</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Trouble doing up buttons</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Trouble feeling the shape of small objects</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Trouble walking</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>


Keeping active helps maintain good blood flow to the hands and feet, so patients should try to walk and exercise within individual limits. Pain and discomfort can be helped by gentle massage with cocoa butter moisturiser, taking warm baths, using heat or cold packs and paying attention to posture. Neuropathy related pain may be improved by medications, such as pregabalin and gabapentin, prescribed and monitored by the doctor. Other things that may help symptoms of neuropathy include nutritional supplements such as vitamin B, folic acid and various amino acid supplements. However, anything patients wish to take should be discussed with their doctor first.

For further information on peripheral neuropathy see the Peripheral Neuropathy Guide on our website at www.myeloma.org.au or call the Myeloma Helpline 1800 693 566
Skin Rashes
In some people, thalidomide can cause a rash, which appears on the trunk and may spread to the arms and legs. It usually starts 2 to 6 weeks after commencing thalidomide and often clears up spontaneously. If the rash is itchy, antihistamines or steroid cream may be prescribed. If severe, the thalidomide may be stopped for a short time and restarted at a lower dose. A rare side effect is the skin turning red and peeling. If this occurs, thalidomide should be stopped immediately, as the condition can become more serious if it is continued. Many drugs cause rashes as a side effect. If a rash occurs, patients must contact their doctor without delay to determine the cause and treat where necessary.

Dizziness
Sometimes dizziness occurs just after standing up. Sitting upright for a minute or two before standing will help the blood pressure adjust, especially if patients have been lying down for a while. If patients are also taking blood pressure, fluid or heart medication, their doctor must be informed.

Constipation
A decrease in the normal frequency of bowel movements may occur while taking thalidomide. It may be accompanied by gas, pain, or pressure in the stomach. Constipation is usually easier to prevent than to treat.

What can be done to reduce the chance of constipation being a problem?
Patients should eat a healthy diet that is high in fibre. Fibre absorbs water, making stools softer, bulkier and easier to eliminate. Drinking plenty of fluids (aim for about 8 glasses of water a day) helps the fibre work. Pear or prune juice may also help. Regular gentle exercise keeps the bowels more active to help move things along. Gentle laxatives (consult a nurse or pharmacist) may be needed but if constipation continues to be a problem, consult the doctor.

Low white cell count
Thalidomide very rarely causes a low white blood cell count, which places the patient at increased risk of infection. Blood cell counts can be monitored with regular blood tests. If the white blood cell count gets too low, patients should avoid being in crowded places and ask anyone who is unwell not to visit. A fever, which is a temperature of 38°C or above is a sign of infection. It is recommended that patients have a thermometer at home and check their temperature if they feel excessively warm or hot, or develop the shakes (rigors). If the white cell count is consistently low, the dose of thalidomide may have to be changed or the treatment may need to be interrupted.

If a patient’s temperature is 38°C or above medical attention must be sought immediately.

Birth defects
Patients taking thalidomide must not plan to conceive. This is because thalidomide can adversely affect sperm and eggs and therefore can also affect the foetus. Patients must always use at least one method of appropriate contraception for at least four weeks before commencing thalidomide, during treatment and for at least four weeks after completion.

Prescribing and taking thalidomide
In Australia thalidomide is dispensed under the trade name Thalomid® and supplied by Celgene Pty Ltd. To ensure the risk of birth defects is minimised, it is dispensed using a restricted distribution program called the ‘i-access™ thalidomide risk management program’. Only physicians and pharmacists registered with this program can prescribe and dispense thalidomide. In addition, thalidomide will only be given to patients who are registered by their doctor and meet all the conditions of the program.
Specific information regarding this will be given to patients when they start thalidomide. Thalomid® is available as 50mg capsules in blister packs containing 28 capsules. The typical dose is 100mg to 200mg per day but patients may be prescribed doses of 50mg up to 400mg daily depending on their specific needs, tolerance of the drug, height and weight.

**How to tell if thalidomide is working**

Patients may observe a reduction in the symptoms caused by the myeloma associated with an improved quality of life. The doctor will order regular blood tests, urine collections, radiology scans or bone marrow tests to measure the biological response to treatment. How the disease is monitored will be determined by the patient’s doctor and the type of myeloma.

Adequate response to treatment may show:
- A reduction in the paraprotein or serum free light chain level in the blood and/or Bence Jones protein/light chains in the urine
- A reduction in the percentage of myeloma plasma cells in the bone marrow
- A reduction in size or absence of plasmacytoma or lytic lesion
- An improvement in kidney function
- Increased haemoglobin levels
- Decreased calcium levels

Thalidomide has been used successfully by many patients since it was introduced for treating myeloma. In most cases the benefits of taking the drug outweigh the side effects experienced by the patient. It is important that patients tell their doctor if they experience any symptoms of side effects. Early recognition and careful monitoring and treatment of side effect symptoms usually allow a patient to get maximum benefit from taking thalidomide.

For further myeloma information please see our website, www.myeloma.org.au or call the Myeloma Helpline 1800 693 566

**References**

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Update:
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Editor:
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Publication Date:
March 2013 (review due March 2015)

The information in this fact sheet is not intended to replace medical care or the advice of a physician. Your doctor should always be consulted regarding diagnosis and treatment.

For further information please contact one of our Myeloma Support Nurses on our Support Line:
1800 MYELOMA (1800 693 566)
or visit our website: www.myeloma.org.au