

Mitoxantrone

Fact Sheet

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This factsheet is written for anyone affected by multiple sclerosis who needs basic information about mitoxantrone. It is not intended as a full guide, and should be used only to support discussion with a neurologist or MS nurse.

1. What is mitoxantrone?

Mitoxantrone is a chemotherapy drug that was developed in the 1970s. It is used to treat a variety of cancers, including non-Hodgkin's lymphoma, metastatic breast cancer and acute myeloid leukaemia¹.

Since the late 1990s it has been used in some specialist MS centres to treat aggressive forms of relapsing remitting MS. Mitoxantrone might be used for someone who experiences very frequent and severe relapses that leave residual disability, or it may be used for people who have not responded to either beta interferon or glatiramer acetate. It might also be used to stabilise someone with severe, frequent relapses so that they can subsequently start on beta interferon or glatiramer acetate. It is also used in secondary progressive MS where relapses are still a significant feature. There is no robust evidence to support the use of mitoxantrone in primary progressive MS, or in secondary progressive MS where there are rare or no relapses (Expanded Disability Scale Score >6.0)².

2. How does mitoxantrone work?

Mitoxantrone acts in two ways. Firstly, it causes damage to the DNA of some cells in the immune system, particularly T-cells and B-cells (types of white blood cells), which means the cells can't divide and proliferate, effectively suppressing the body's immune system. Secondly, it inhibits the secretion of some molecules that promote inflammation in the body. One of the molecules inhibited by mitoxantrone is the protein gamma interferon, which is thought to induce the symptoms of MS³. In both cancer and MS, this suppression of the immune system during treatment gives the body a chance to effectively 'restart' and sort out what has gone wrong with the immune system.

3. Trials of mitoxantrone in MS

There have been three key clinical trials of mitoxantrone in MS:

- In 1997, an Italian group published results of their trial which compared mitoxantrone against placebo in 51 people with relapsing remitting MS⁴. Participants were randomised to receive either an intravenous (iv) infusion of mitoxantrone at a dose of 8mg/m² of body area every month for one year, or a monthly infusion of saline (placebo). The trial found that mitoxantrone had a significantly beneficial effect on the number of relapses. It also seemed to slow the rate of long-term accumulation of disability when compared with people who received no treatment. However, criticisms were levelled at this trial. Some neurologists argued that the trial involved a relatively small number of patients, that the potential clinical benefits of mitoxantrone were small, and that the long-term side effects were sufficiently serious to warrant more research before the treatment was widely recommended.
- A second trial also reported in 1997 from a French-British collaboration⁵. 42 people with relapsing remitting or secondary progressive MS were randomised to receive either a combination of mitoxantrone (20mg iv monthly) and the steroid methylprednisolone (1g iv monthly), or methylprednisolone only for six months. In the mitoxantrone group there was a significant reduction in the number of relapses and an improvement on the Expanded Disability Status Score (EDSS).

- A larger phase III study known as the MIMS study (Mitoxantrone in MS) reported in 2002⁶. 194 people with worsening relapsing remitting or secondary progressive MS received placebo, or 5mg/m² of mitoxantrone, or 12mg/m² of mitoxantrone administered intravenously every three months for 24 months. The higher dose of mitoxantrone was shown to be effective and generally well tolerated, reducing the progression of disability and the number of relapses compared to placebo. The benefits for those assigned the 5mg/m² dose were less convincing.

More recently, a number of clinical reports of long-term results from observational studies using mitoxantrone have been published. Comparison between the reports is difficult since treatment length, strength of dosage and length of follow-up varies. Best results were reported in a French study of aggressive relapsing remitting MS where people experienced several relapses a year. This observational study of 100 people looked at mitoxantrone for six months, followed in 73 cases by some form of maintenance therapy such as beta interferon. One year after treatment, 78 people were relapse-free and over five years the average time to the first relapse was 2.8 years. Disability remained stable up to five years following treatment. Some significant side effects were seen, including one case of leukaemia which was in remission five years after treatment⁷.

Based on the results of the MIMS trial⁶ and supportive data from the study by Edan et al⁵, in October 2000, the US Food and Drug Administration (FDA) licensed mitoxantrone for use in MS. Mitoxantrone is also licensed for use in some European countries including France and Germany. It is not licensed in the UK, although it is used off-licence in some specialist centres. Different treatment regimens are used in different countries according to the different regulatory demands, but the two most common regimes used are:

- 12mg/m² mitoxantrone iv every three months for two years (based on the MIMS study⁶)
- 20mg mitoxantrone iv and 1g methylprednisolone every four weeks for six months (based on the French-British study⁵)

As mitoxantrone is not licensed for use in MS in the UK, there are no hard-and-fast prescribing guidelines, and use of the drug is wholly at the discretion of the neurologist.

4. How is mitoxantrone given?

Mitoxantrone, a dark blue fluid, is administered via an intravenous drip. The actual dose given varies depending on the patient's weight. As explained previously, treatment programmes vary between specialist centres; mitoxantrone may be given every three months, or it may be given monthly for the first three months and then once every three months. Each treatment must be given in hospital, often as a day patient.

As mitoxantrone suppresses the immune system, the white blood cell count of people receiving it is likely to fall, making them more prone to infections. Therefore, regular blood tests are carried out for the duration of the treatment. Mitoxantrone is rapidly distributed throughout the body, and then passes out of the body through bile and urine.

5. Side effects and contraindications

5.1. Temporary side effects

Many people experience some, or all, of these common side effects:

- changes in menstruation pattern and/or temporary cessation of periods, in some women this can be permanent (see 5.2)
- nausea
- temporary hair thinning (in common with other anti-cancer drugs)
- blue-green urine for 24 hours after infusion.

There is a range of other temporary side effects, so if anything unusual is experienced this should be reported to the neurologist as soon as possible.

5.2. Long-term side effects and contraindications

- **cardiotoxicity** - mitoxantrone may damage the heart, and can cause congestive heart disease if taken over a long period of time. To reduce this risk, the total amount any one person may take in their lifetime is limited to 140mg/m² of body surface area, roughly 8-12 doses taken over two to three years. This dose should not be exceeded because of the risk of developing lifelong, and life threatening, heart damage. Regular

echocardiograms (an ultrasound scan of the heart) before each dose are required to monitor for this

- **therapy-related acute leukaemia (TRAL)** - in rare cases, treatment with mitoxantrone can cause some people to develop leukaemia. The risk is low, and is currently estimated at around 1 in 333 people, or 0.3%¹. This compares with a risk of 1:33,333 (0.003%) of developing acute myeloblastic leukaemia in the general population. Over 80% of patients who developed TRAL were exposed to a dose higher than 60mg/m². Research in this area is continuing, and concerns about this risk should be discussed with a neurologist
- **liver damage** - mitoxantrone can cause changes to liver enzyme levels and harm the way the liver works. This normally only lasts for the duration of treatment and is monitored through blood tests
- **infertility** - in around 1 in 10 women, mainly those over 35 years old, mitoxantrone can make periods stop permanently, causing infertility³. Mitoxantrone can also cause infertility in men⁸. Concerns about this risk should be discussed with a neurologist
- **pregnancy** - mitoxantrone may cause birth defects if either the mother or father is receiving it when a baby is conceived. The manufacturers suggest effective contraception should be used whilst on treatment and for up to six months after treatment stops. Women may be asked to provide a urine sample for a pregnancy test prior to each infusion of mitoxantrone
- **breastfeeding** - mitoxantrone may be passed on through breast milk so should not be taken whilst a woman is breastfeeding
- **interactions with other medicines** - mitoxantrone can interact with a range of medicines so it is important that the neurologist is aware of the full range of medications being taken, including any herbal or complementary medicines.

6. Current research: mitoxantrone and glatiramer acetate

Recent studies have suggested that mitoxantrone is most beneficial if followed by some type of maintenance therapy, such as glatiramer acetate (Copaxone) or beta interferon (Avonex, Betaferon or Rebif), but this is not conclusive.

In the UK, promising results have been reported from a small observational study of mitoxantrone followed by glatiramer acetate as a treatment for people with active, aggressive, relapsing remitting MS (two or more relapses a year). Individuals received mitoxantrone for six months followed by glatiramer acetate. The combination therapy reduced relapse rates by 90% and disease was stable or improved between one and three years following treatment. One person on the trial developed leukaemia nine months after mitoxantrone treatment⁹.

A larger research trial investigating this combination, known as the United Kingdom early Mitoxantrone Copaxone trial, has recently completed and the results are currently being prepared for publication.

7. References

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Please contact the MS Trust Information Team if you would like any further information about reference sources used in the production of this publication.

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