

METRONOMIC CHEMOTHERAPY IN VETERINARY PATIENTS



What is Metronomic Chemotherapy?

Metronomic chemotherapy uses low doses of oral medication given on a continuous basis. As it is given daily or every other day, this treatment is given at lower doses than 'traditional' chemotherapy, often with reduced side effects such as vomiting or diarrhoea.

This method of chemotherapy administration has been successful for a variety of human tumours, currently, there is only limited veterinary-specific information that has been published. Treatment in animals to date has been largely empirically based on human studies and anecdotal evidence. However, the results of initial and current canine studies are promising and, as more canine and feline-specific dosing and scheduling data becomes available, the applications of this treatment are expected to increase.

Metronomic Chemotherapy vs Traditional Chemotherapy

Conventional chemotherapy is given at high dosages, known as maximum tolerated doses (MTD). The goal of conventional chemotherapy is to kill rapidly dividing cancer cells. But there are normal cells in the body that also replicate quickly which can be temporarily damaged. Most commonly the gastrointestinal tract (stomach and intestines) and the white blood cells in the bone marrow are affected. To allow these cell populations to recover, a break period is allowed into the chemotherapy schedule, usually around one week but this can vary depending on the drug used. The concern is that this break may also allow the tumour cells to recover.

In contrast, the goal of metronomic chemotherapy is not to kill the cancer cells directly. Instead, metronomic chemotherapy targets and inhibits tumour blood vessel growth. Tumour blood vessels are more fragile than

normal blood vessels and are therefore sensitive to metronomic chemotherapy. The aim is to disrupt the nutrient supply to the tumour. Blood vessel growth is technically called angiogenesis, so you might hear metronomic chemotherapy being called "anti-angiogenic." There is also evidence that some low-dose chemotherapy drugs, like cyclophosphamide, have an effect on tumour immunology which seems to contribute to tumour control.

Indications for Metronomic Chemotherapy

Metronomic chemotherapy has been shown to be particularly useful in the management of soft tissue sarcomas and splenic haemangiosarcoma in dogs but may be useful in a wider variety of tumour types than we currently recognize. Especially in splenic haemangiosarcomas can be used as a follow-up treatment after MTD (chemotherapy switch) or less commonly as a sole treatment. Although the idea of metronomic chemotherapy is relatively new, there are cancers for which we have used a low-dose oral approach for years. Examples include low-grade/small cell lymphomas (especially in cats) with chlorambucil and multiple myeloma in dogs with melphalan.

Metronomic chemotherapy can also be used for some patients with metastatic disease — such as the spread of the tumour to the lungs. The treatment may slow the progression of the disease as traditional chemotherapy is often not very effective for dogs in this scenario.

Another use for metronomic chemotherapy is for dogs that have failed the standard of care, meaning their cancer came back or progressed on the recommended first-line drugs. Alternatively, this therapy may be suggested if there is no standard of care for an uncommon cancer.

What does metronomic chemotherapy involve and how frequent are the visits?

Metronomic chemotherapy is given orally at home as tablets or capsules. The most commonly used drugs in veterinary oncology are called cyclophosphamide and chlorambucil. Given the small size of cats and dogs compared to humans, these drugs often need to be re-formulated into smaller capsules to avoid splitting or crushing the tablets. These drugs might need to be ordered specifically for an individual patient.

A number of different anti-cancer drugs may be used, these are given at lower doses (e.g. between 5% and 25% of the standard dose) than used for traditional chemotherapy. Other drugs will often be used in combination with anti-cancer drugs, such as anti-inflammatory drugs which contribute to the overall effect of the treatment. Other concurrent medication might also be needed depending on the pet's general health, but this will be discussed in more in detail with one of the Oncology clinicians.

Prior starting treatment your pet will need a blood and urine test to check if any abnormalities are present and exclude any other underlying health problems that might negatively affect the chemotherapy. Scheduled re-assessments will be required every month or so to assess for side effects. At these visits, we will carry out a physical examination, run some basic blood work, and we will also periodically check tumour response (which might require chest X-rays or ultrasound, depending on the case). If well tolerated, Metronomic chemotherapy is usually given for at least six months unless the tumour progression occurs before that. If any side effects develop, we may also adjust the dose and/or take a treatment break.

How quickly can I expect to see results?

With metronomic chemotherapy, it might take up to six to eight weeks to see an effect. In some cases, tumours that have failed to respond to other therapies, stabilizing the disease (meaning it doesn't progress) can still be considered a success.

Complications

The aim of chemotherapy in pets is quality of life over quantity. The majority of pets undergoing metronomic chemotherapy experience a normal quality of life. Side effects with metronomic chemotherapy are rare (<20%) compared to more traditional protocols, and in very rare occasions may require hospitalisation. Most side effects are managed at home only with symptomatic treatment and usually resolve within a few days. The main side effects of chemotherapy are:

- + Cyclophosphamide in dogs can cause inflammation of the bladder (cystitis) in up to 20% of cases. We minimize the risk as much as possible by checking the urine before each treatment. We will instruct you to monitor your dog's urine at home every one or two weeks by using urine dipsticks to check for any haematuria (microscopic blood in urine).
- + **Gastro-intestinal:** mild vomiting, diarrhoea and inappetence can be seen but this is usually caused by the anti-inflammatory medication. We use anti-nausea medication to prevent this as much as possible
- + **Bone marrow suppression:** chemotherapy can reduce the white cell count, and we perform regular blood tests to monitor for this. However, we very rarely see bone marrow suppression with this type of chemotherapy. A low white cell count can increase the body's susceptibility to infection which in very rare occasions might be life-threatening (sepsis)
- + **Hair loss:** some dog breeds (e.g. Poodle, Old English Sheepdog, Schnauzer, Puli, Lhasa apso) and cats might lose hair after a few months of treatment – this usually causes a thin hair coat rather than complete baldness. Cats may lose their whiskers.
- + Thalidomide in dogs is usually very well tolerated and the most common side effect that we see is transient sleepiness. For this reason, we administer the medication in the evening.

Please monitor your pet closely after each treatment and telephone us if you feel your pet seems ill or if you have any questions or concerns (01268 564664).

How do I give the medication?

The medication is given as a capsule or tablet, generally once a day. It should be given in the morning with or without food. Please remember to wear gloves when handling the medication and do not split/crush the tablets or open the capsules.

If your dog is receiving cyclophosphamide, we will provide you with some urine dipsticks to monitor for blood in the urine, which is an early sign of cystitis. Please check the urine once or twice weekly whilst wearing gloves. If the square on the dipstick turns green or speckled green please contact the hospital for advice.

Both dogs and cats will excrete very small amounts of the chemotherapy medication in their urine and faeces. **Please wear rubber/latex gloves to handle any of their urine and double-bag faeces while they are receiving chemotherapy. Pregnant women or those who are trying to conceive should not be in touch with any waste.**

If you have any further questions, please do not hesitate to contact the hospital.

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