

FAQ about metronomic chemotherapy

Your veterinarian just recommended this form of therapy to treat your pet's cancer. But what is it and how does it work? Here are some facts from Dr. Sue Ettinger, (aka Dr Sue Cancer Vet), a veterinary oncologist.

What is metronomic chemotherapy?

Metronomic chemotherapy is a new way of administering old chemotherapy drugs but targets tumor cells in a completely different way. It involves low-dose oral, or pulse, chemotherapy given on a continuous treatment schedule. Since it is given daily or every other day, the chemotherapy is given at lower doses than typical chemotherapy and often has fewer negative side effects.

How is it different than traditional chemotherapy?

Conventional chemotherapy is given at high dosages known as the maximum tolerated dose, or MTD. The goal is to kill the rapidly dividing cancer cells. But some normal cells—most commonly the gastrointestinal (GI) tract cells and the white blood cells—that also turnover often can be temporarily damaged by MTD chemotherapy. As a result there is a break period to allow these cell populations to recover. MTD is typically given weekly to every three weeks.

Instead of killing the cancer cells directly, metronomic chemotherapy targets and inhibits tumor blood vessels growth, which is called angiogenesis. So you will hear that this type of chemotherapy is “anti-angiogenic.” Tumor blood vessel cells are more active than normal blood vessel cells and

are the targets of this type of low-dose oral chemotherapy.

There is also some evidence that some low-dose chemotherapy drugs (such as cyclophosphamide) have effects on the way the pet's immune system attacks cancer cells.

When is metronomic chemotherapy used?

We are truly still at an early stage in understanding the mechanisms and the efficacy of this approach. I use this approach for some patients with metastatic disease, such as the spread of the tumor to the lungs, in an attempt to slow progression of the nodules on the lungs. Traditional chemotherapy does not work well for dogs and cats with metastasis.

Another use is for dogs and cats that have failed standard of care, meaning their cancer came back or progressed on the recommended drugs. Additionally, sometimes there is no standard of care for uncommon cancers, and metronomic approach may be considered.

Metronomic chemotherapy has been evaluated recently for splenic hemangiosarcoma and incompletely removed soft tissue sarcomas. Metronomic chemotherapy has been shown to help delay the recurrence of incompletely removed soft tissue sarcoma. Traditionally, a second surgery or radiation is recommended to prevent tumor regrowth but this gives us another option.



Although the idea of metronomic chemotherapy is relatively new, we have used a low-dose oral approach for years for some cancers. Examples include low-grade/small cell lymphomas (especially in cats) with chlorambucil and multiple myeloma in dogs with melphalan.

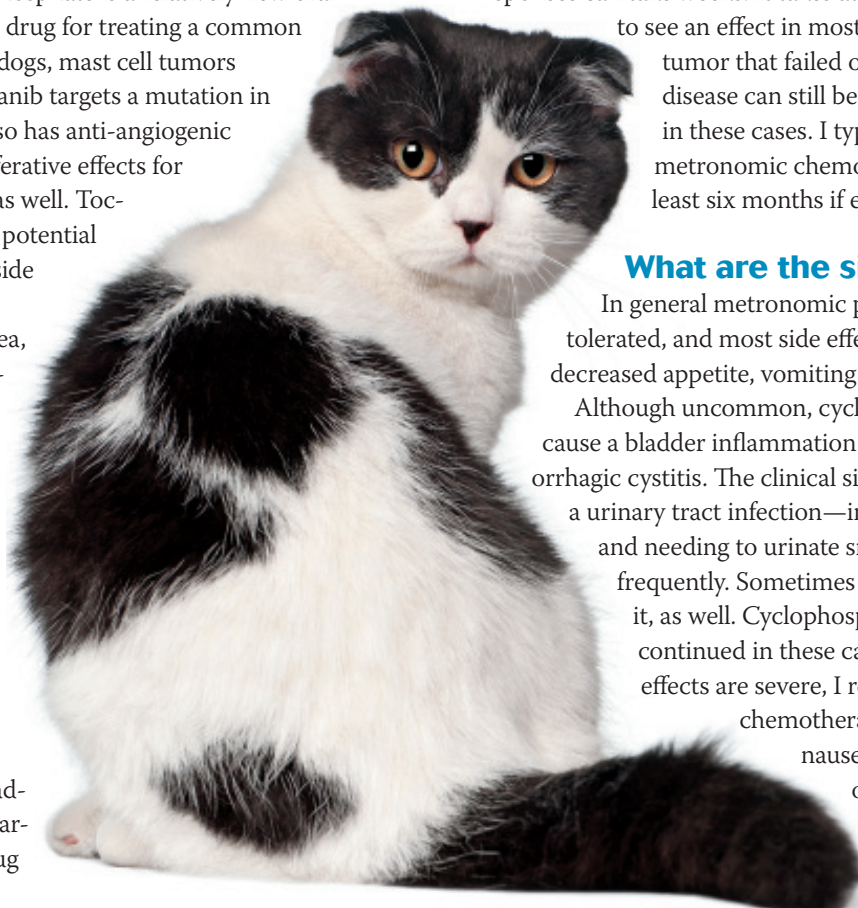
What drugs are usually given?

Cyclophosphamide is the drug most commonly used in metronomic protocols in people and pets. It can be combined with a nonsteroidal anti-inflammatory drug (NSAID), such as piroxicam or carprofen, for its potential anti-cancer effect on certain cancers. Remember, even though NSAIDs are not chemotherapy drugs they can also cause side effects (GI, liver, kidney), so discuss with your oncologist or veterinarian if it is appropriate to use in your dog or cats.

Other chemotherapy drugs that can be given low dose and continuous are chlorambucil and lomustine.

Cyclophosphamide can also be combined with some of the new targeted chemotherapeutic drugs, such as the receptor tyrosine kinase inhibitors. In fact, my preferred metronomic approach combines toceranib phosphate (Palladia—Zoetis) with low-dose cyclophosphamide.

Toceranib phosphate is a relatively new oral chemotherapy drug for treating a common skin tumor in dogs, mast cell tumors (MCT). Toceranib targets a mutation in MCT but it also has anti-angiogenic and anti-proliferative effects for other tumors as well. Toceranib has the potential to have more side effects. These include diarrhea, vomiting, lethargy, GI ulcers and weight loss. In my opinion, most toceranib side effects are manageable with early recognition, and early recognition is critical. That means I adjust or temporarily stop the drug



if needed. GI side effects are most common, and most are mild to moderate in intensity. That's why I monitor my patients carefully with physical examinations, monitoring weight closely and blood work throughout therapy. Most of my clients are very happy with their pets' quality of life during treatment.

How frequent are visits?

Personally, when I start these protocols, I recheck every two weeks typically for two to three visits. And then I spread out to every four to six weeks depending on the case. At the visits, I am doing my examination, comparing weight, running some basic blood work and periodically checking response to treatment (often requires chest radiographs or an ultrasonographic examination, depending on the case). If the patient is having side effects, I may adjust the dose adjustments or take a treatment break.

How quickly can I expect to see results? How long will my pet be on a metronomic protocol?

Since we are targeting the tumor blood vessels, responses can take weeks. It takes at least six to eight weeks to see an effect in most cases. Remember in a tumor that failed other therapies, stable disease can still be considered a success in these cases. I typically recommend metronomic chemotherapy be given for at least six months if effective.

What are the side effects?

In general metronomic protocols are well-tolerated, and most side effects are mild—mildly decreased appetite, vomiting and diarrhea.

Although uncommon, cyclophosphamide can cause a bladder inflammation called sterile hemorrhagic cystitis. The clinical signs are similar to a urinary tract infection—increased straining and needing to urinate small amounts more frequently. Sometimes the urine has blood in it, as well. Cyclophosphamide should be discontinued in these cases. If any of the side effects are severe, I recommend we stop the chemotherapy, give prescribed nausea and vomiting and/or diarrhea medications, and contact the veterinary clinic.