Cancer, even advanced metastatic disease, is not a death sentence in pets. Chemotherapy is well tolerated in the majority of dogs and cats undergoing treatment. With treatment, many cancer patients with metastasis can live longer and living well.

**CONVENTIONAL CHEMOTHERAPY**

Conventional chemotherapy is typically given at high dosages, known as maximum tolerated dose, or MTD. The goal is to kill the rapidly dividing cancer cells. But some normal cells that also have high turnover often can be temporarily damaged by MTD chemo. Most commonly, it is the GI tract cells and the neutrophils that are temporarily damaged. As a result there is a break period to allow these cell populations to recover. MTD is typically given weekly to every 3 weeks.

Chemotherapy drugs given at MTD attack rapidly dividing cells. The normal tissues that typically are most sensitive to MTD chemotherapy are the bone marrow, hair follicles (alopecia), and the gastrointestinal lining. This is often referred to as “BAG”.

Bone marrow suppression most commonly results in a neutropenia. Neutrophils and platelets are at greatest risk due to the shorter circulating lifespan, and shorter bone marrow transit times. Neutropenia is the dose-limiting toxicity in veterinary oncology. Cats seem to be more tolerant than dogs.

Alopecia (hair loss) is due to damaging the rapidly dividing hair follicle. In dogs, potentially affected breeds have continuously growing coats and include Poodles, Scottish Terriers, and Westies. In cats, alopecia is rare, but shaved areas tend to grow back more slowly (limb catheters, abdominal ultrasounds). Cats more commonly lose their whiskers. The good news is that hair and whiskers will re-grow once the treatments have completed. Occasionally, hair will grow back a different texture or color. In cats it is typically softer, aka the “chemo coat”. It is important to remember pets do not care about this cosmetic side effect, and it does not impact the quality of life. However, pet owners like to be advised about the whiskers and hair coat so they are not surprised.

Gastrointestinal (GI) toxicity includes vomiting, diarrhea, decreased appetite, nausea. It typically 1 to 5 days after chemotherapy and is self-limiting – lasting on average 2-3 days. These side effects are less common in feline chemotherapy patients than dogs. I often will use Cerenia or mirtazapine as needed.

The overall toxicity rate is very low in veterinary chemotherapy patients treated at MTD. In my experience, only 15-20% experience side effects, and this is even less common in cats than dogs. The primary goal is to provide the best quality of life possible for as long as possible. As I say, live longer, live well. Most side effects are mild and medically manageable. If there are side effects, I also typically will add prophylactic medications to prevent side effects like nausea, vomiting or diarrhea as indicated. It is important to be proactive and educate clients.

In my experience, there is less than a 5% chance that a patient will need hospitalization. If this does occur, these patients are usually hospitalized for typically 24-48 hours with supportive care including IV fluids and antibiotics. In my experience most chemotherapy patients can successfully receive that drug again with a dose reduction and prophylactic medications.

**METRONOMIC CHEMOTHERAPY**

In contrast to MTD (high dose) chemotherapy, metronomic chemotherapy is pulse or low-dose chemotherapy. Metronomic chemotherapy is the uninterrupted administration or low doses of cytotoxic drugs at regular, continuous and frequent intervals without breaks. This is typically administered orally daily or every other day. Elimination of breaks between dosages reduces or eliminates the ability of the tumor cells to repair damage or alter their microenvironment.
With MTD chemotherapy, the goal is to target and kill tumor cells directly. The target of metronomic chemotherapy is the tumor-associated vasculature. These are the endothelial cells in that line tumor blood vessel. In contrast to the quiescent endothelial cells throughout the body, tumor endothelial cells are much more proliferative. In metronomic chemotherapy, the result may be that the tumor is stabilized, but this prevents further growth and spread.

The key to metronomic chemotherapy is the reduction or elimination of breaks between dosages – to prevent repair and repopulation of the endothelial cells. This is also different than MTD chemotherapy in which the break between dosages allows for recovery of the normal cell populations, like neutrophils and GI tract cells. Another important distinction of metronomic chemotherapy is that chemotherapy is given at low dosages to allow for the continuous often daily dosages.

Overall, metronomic chemotherapy protocols are well-tolerated with low toxicity profiles. Depending on the drugs used, some protocols are also lower in cost. Common chemotherapy drugs include low dose cyclophosphamide, chlorambucil, and Lomustine. Toceranib (Palladia) is also used in metronomic protocols. Other drugs included in some protocol are NSAIDS and doxycyline. There is still much to be learned including best drugs, dose, schedule, tumor types, and toxicity.

How does metronomic chemotherapy work?

In the cancer patient, tumor angiogenesis occurs locally in the tumor microenvironment where circulating endothelial cells (CECs) are stimulated and due to systemic effects of circulating endothelia progenitor cells (CEPs) that are derived in the bone marrow. Continuous low dosages of many chemotherapy drugs are cytotoxic to both CECs and CEPs. There seems to be little toxic effects on non-endothelia l cells like white blood cells and epithelial cells. Tumor cells are also not effected by metronomic chemotherapy.

Another interesting target is the regulatory T-cell (Treg), a subset of the CD4+ T-lymphocyte population that helps tumor cell survival by contributing the immune suppression. Low dose cyclophosphamide (CYC) has been demonstrated to be selectively toxic to the Treg cells. It is also believed that NSAIDs can also decrease Treg cells with COX inhibition. Many metronomic protocols combine a chemotherapy drug like low dose CYC and a NSAID.

There is concern for the risk of sterile hemorrhagic cystitis (SHC) with cyclophosphamide, and this risk may increase with cumulative CYC administration. Owners should be advised of the risk of SHC and appropriate and regular patient monitoring is highly recommended. Cyclophosphamide should be discontinued.

In some cases when MTD high dose chemo is no longer effective, metronomic chemotherapy may still inhibit tumor growth. This can be considered for some dogs and cats with advanced metastatic disease.

ANTIANGIOGENIC CHEMOTHERAPY WITH RTKI

Most Receptor Tyrosine Kinase Inhibitors (RTKI) target numerous receptors. Toceranib (Palladia) is a RTKI approved for MCT in dogs that targets the mutated c-kit to directly kill tumor cells. In addition, Palladia also inhibits angiogenesis by targeting other receptors like VEGFR and PDGFR. Palladia may be useful in metronomic chemotherapy protocols.

There is evidence that good biologic activity occurs when Palladia dosages are lower than the label dose of 3.25 mg/kg EOD. This was noted in the Phase I study of dogs with a variety of solid tumors where response was noted at 2.5 mg/kg EOD. Additional studies with solid tumors found lower dosages were associated with good clinical activity and reduced side effects. Biologic activity has been observed in anal gland anal sac ACA, thyroid carcinomas, metastatic OSA, nasal carcinoma, and head and neck carcinoma

I typically recommend 3 times per week dosing with a target dose of 2.5 to 2.8 mg/kg (ie MWF) and will use low dose compounded CYC on TuThSat. I typically use a NSAID on non-Palladia days if included.
TOXICITY AND SUPPORTIVE MEDICATIONS

In general, metronomic chemotherapy is well tolerated with minimal toxicity. In my experience, side effects are most likely to occur with Palladia and are usually GI-related. so I typically start Palladia first and make sure the patient is tolerating it before adding additional medications such as low dose CYC. I start omeprazole with Palladia. I avoid metronomic chemotherapy in patients presenting with inappetance and/or vomiting and diarrhea

Gastrointestinal (GI) adverse effects include vomiting, diarrhea, decreased appetite, nausea. I monitor my patients at 2 week intervals for the 1st 4 to 8 weeks. Good patient history and careful monitoring of body weight is critical. All my Palladia patients go home with a “just-in-case” bag including Cerenia, metronidazole and a probiotic, +/- mirtazapine. In some cases experiencing GI issues, I will recommend Cerenia be given 1 hour prior to Palladia, or Palladia dose will be adjusted.

CBC and chemistry panel should be monitored at each visit. Palladia and chlorambucil tend to cause delayed neutropenias and thrombocytopenias after chronic use. I also recommend periodic urinalysis and UPC.

The goal of metronomic chemotherapy is stable disease which requires chronic administration. It is very important our patients are experiencing minimal side effects and a great quality of life on the protocol, so they can stay on the protocol long term.

DOXYCYCLINE

Doxycycline has been documented to have some antiangiogenic effects by inhibiting matrix metalloprotineases, so it is thought that the addition of doxycycline metronomic chemotherapy protocols may enhance the antiangiogenic effects. Further studies are needed to confirm its efficacy and best dosing.

SUMMARY

Conventional chemotherapy is typically ineffective for patients with gross metastatic disease. Metronomic chemotherapy is well tolerated and appealing with the low toxicity and use of oral forms. But metronomic chemotherapy is still in its early use in terms of efficacy and potential for toxicity. Stable disease is typically the goal, so therapy is often chronic and stable disease should be expected to maintain a good QOL for the patient. There is still much to be learned including best drugs, dose, schedule, tumor types, and toxicity.

ADDITIONAL RESOURCES