

## Metronomics (Antiangiogenic Therapy)

Cancers in dogs depend on angiogenesis (the creation of new blood vessels) to survive and proliferate. Tumors create new blood vessels that supply them with oxygen and nutrients, allowing them to grow in size and spread throughout the body. Antiangiogenic therapy cuts off these new blood vessels, effectively starving tumors and preventing their growth. Cancers may be controlled with effective doses of antiangiogenic drugs. Angiogenesis inhibitors are designed to attack tumors by depriving cancer cells of their blood. Some antiangiogenic drugs may also be combined in order to hit multiple targets and improve their effectiveness.

Antiangiogenic therapy offers a number of advantages over traditional therapies for cancer:

- Tumor cells often mutate and become resistant to chemotherapy. Because antiangiogenic drugs only target normal endothelial cells, these cells are less likely to develop acquired drug resistance.
- All tumors rely upon host vessels. Antiangiogenic agents are therefore effective against a broad range of cancers.
- Conventional chemotherapy and radiotherapy indiscriminately attacks all dividing cells in the body, leading to side effects such as diarrhea, mouth ulcers, hair loss, and weakened immunity. Antiangiogenic drugs selectively target dividing blood vessels and cause fewer side effects.
- Antiangiogenic drugs are relatively nontoxic and work at levels well below the maximum tolerated dose, so may be given in lower doses over longer periods of time.
- Antiangiogenic treatment may take weeks or even months to exhibit its full beneficial effect, but this allows for continuous, chronic control of disease.
- Antiangiogenic drugs may also serve as a powerful supplement to traditional chemotherapy or radiation therapy.

There are multiple mechanisms, which are currently undergoing research. The ones that we chose to utilize include:

- x An alkalating agent
- x A Non Steroidal Anti Inflammatory (NSAID)
- x Doxycycline
- x Fish Oil

**Alkalating agent:** These all have antiangiogenic properties at continuous low doses.

- x Alkeran
- x Leukeran
- x Cyclophosphamide

*Metronomics (Antiangiogenic Therapy), continued*

**Non Steroidal Anti Inflammatory (Rimadyl, Metacam, etc.):**

Many NSAIDS have cyclooxygenase inhibitory action, particularly COX-2. Many tumors have been shown to over express COX-2 and this is thought to contribute to tumor progression.

- x Rimadyl
- x Metacam
- x Piroxicam, etc.
- x Sometimes prednisone is substituted for an NSAID (ex: mast cell tumors)

**Doxycycline:**

Doxycycline has been shown to inhibit metalloproteinases, a family of enzymes that are involved in tumor invasion.

- x Dosage: 5 mg/kg daily
- x Side effects may include nausea, inappetence which may be relieved by administration with a meal.

**Fish Oil:**

Fish oil has the ability to inhibit tumor growth; DHA shrinks tumors by promoting cell differentiation. The recommended dosage is EPA: DHA, 4:3