METRONOMIC CHEMOTHERAPY

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Shasta Lynch looks at the promising results being achieved in cancer cases where cytotoxic drugs are being administered without a break

Summary

Metronomic chemotherapy is the administration of frequent low doses of cytotoxic drugs without a break period. This method of chemotherapy administration has been successful for a variety of human tumours. The mechanism of action is believed to be a combination of anti-angiogenic activity and modulation of the immune system. Metronomic chemotherapy has the advantages of low toxicity, ease of administration and improved quality of life. Limited veterinary-specific information has been published and treatment to date has been largely empirically based on human studies and anecdotal evidence. However, the results of initial canine studies are promising and, as more canine and feline specific dosing and scheduling data becomes available, the applications of this treatment method are expected to increase.

Key words

metronomic, chemotherapy, oncology, anti-angiogenic

IN the past few decades, the field of veterinary oncology has advanced dramatically. The treatment of a variety of tumours with chemotherapy has improved the quality of life and survival times of many dogs and cats with cancer.

Traditionally, chemotherapy has been administered utilising the maximum tolerated dose of a
cytotoxic drug, followed by a break period to allow normal cells, such as intestinal epithelium and bone marrow precursor cells, to recover. This is based on the long-held premise that delivering the maximum dose of chemotherapy that can be safely administered results in optimal tumour cell kill and, therefore, potentially longer survival\textsuperscript{1}.

This traditional method of administering chemotherapy has shown a survival benefit for many tumour types, but a cure is achieved only rarely and tumours frequently develop resistance to cytotoxic drugs\textsuperscript{2}. In recent years the focus has largely shifted to developing new methods of treating cancer, such as metronomic chemotherapy, to use in combination with existing therapies.

**What is metronomic chemotherapy?**

Metronomic chemotherapy developed in human oncology over the past decade. It involves the uninterrupted, chronic administration of low doses of chemotherapeutic drugs at regular, frequent intervals with no prolonged drug-free breaks.

In human clinical oncology, metronomic chemotherapy has led to stable disease or tumour response in a number of patients that were refractory to traditional chemotherapy\textsuperscript{3}.

In veterinary oncology, metronomic chemotherapy is in the early stages of evaluation, but it is expected to also gain favour as more defined dosing and efficacy data becomes available.

The concept of metronomic chemotherapy first developed in 2000 when a reduction in tumour burden was reported in mice treated with low, frequent doses of chemotherapy\textsuperscript{4,5,6}.

Chemotherapy administered in this way was also shown to be effective where previous drug resistance had developed\textsuperscript{4}. Current evidence indicates metronomic chemotherapy is effective by both anti-angiogenic activity and modulation of the immune system.

**Anti-angiogenesis**

Angiogenesis is the in-growth of blood vessels from previously existing vascular structures and is essential for tumour growth and development. In contrast to the direct cytotoxic effects of traditional chemotherapy, metronomic chemotherapy targets the tumour-associated vasculature and exerts its effects largely through inhibition of angiogenesis\textsuperscript{7,8}. It has been proposed that targeting vascular cells that support a tumour rather than actual tumour cells may lead to reduced drug resistance due to the relative genetic stability of endothelial cells\textsuperscript{9}.

Current evidence indicates the anti-angiogenic function of metronomic chemotherapy is a result of specific action on endothelial cells and endothelial progenitor cells (from the bone marrow) and increased production of endogenous angiogenic inhibitors such as thrombospondin-1\textsuperscript{7,10,11,12}. 
Immunomodulation

More recent evidence has suggested an additional role of metronomic chemotherapy in improving the immune response to cancers in part by targeting regulatory T cells (Tregs)\(^\text{13}\). Tregs are a subset of CD4+ T lymphocytes that can inhibit the anti-tumour immune response thereby aiding tumour growth\(^\text{13}\). Treg numbers have been shown to be elevated in the blood of canine patients with a variety of types of cancer\(^\text{14}\). A recent study showed dogs receiving metronomic cyclophosphamide to have significantly reduced Treg numbers in the peripheral blood following treatment\(^\text{13}\). In addition, increased numbers of Th17 cells and decreased Treg numbers were seen in mice treated with metronomic cyclophosphamide\(^\text{15}\). Th17 cells are thought to ameliorate tumourinduced immunosuppression primarily through pro-inflammatory effects\(^\text{15}\). The effect of metronomic chemotherapy on the immune system is in the early stages of investigation, but current evidence supports a role in stimulating the anti-tumour immune response.

Evidence for metronomic chemotherapy in veterinary oncology

- Metronomic chemotherapy protocols in veterinary oncology generally incorporate cyclophosphamide, chlorambucil or lomustine, often in combination with an NSAID, which also possess anti-angiogenic and immunomodulatory effects\(^\text{16}, \text{17}, \text{18}\).

Limited published studies are available evaluating these protocols in dogs and none in cats. Metronomic chemotherapy has been evaluated in dogs with incompletely resected soft tissue sarcomas, splenic hemangiosarcoma, transitional cell carcinoma of the urinary bladder and a variety of other late stage tumours (Table\(^1\)\(^\text{18}, \text{19}, \text{20}, \text{21}\). These studies offer a good starting point, but are limited by low patient numbers, non-uniformity of selected patients, lack of appropriate control groups and, often, retrospective nature. Overall, however, a number of positive responses are reported.

- Metronomic cyclophosphamide and piroxicam has been shown to delay recurrence of incompletely resected soft tissue sarcomas and may be indicated where revision surgery or adjunctive radiotherapy is not possible\(^\text{18}\).

Metronomic chemotherapy has also been used in the adjuvant setting in dogs with stage II (no metastasis) splenic haemangiosarcoma, post-splenectomy. No significant difference in survival was found between these dogs and historical controls treated with doxorubicin chemotherapy. However, the number of dogs included in this study was particularly low (n=9) making it difficult to draw conclusions\(^\text{21}\). Preliminary data evaluating metronomic chlorambucil (+/-NSAID) in dogs with transitional cell carcinoma of the urinary bladder showed a 70 per cent response rate (stable disease or partial response)\(^\text{19}\). In another preliminary study, metronomic chlorambucil also showed a 58 per cent response (stable disease or partial response) in dogs with a variety of late stage tumours that had failed before with conventional therapies\(^\text{20}\).
Cyclophosphamide and chlorambucil are well tolerated in metronomic protocols with low toxicity reported\textsuperscript{18,20}. Cyclophosphamide-induced sterile haemorrhagic cystitis is the most concerning adverse effect and has been reported in approximately 10 per cent to 22 per cent of treated dogs depending on the dose administered (note that the 22 per cent reported here was in a study of nine dogs receiving higher doses of cyclophosphamide than generally prescribed)\textsuperscript{18,21}. The search for drugs with high efficacy and an improved safety profile is ongoing. One study evaluated metronomic lomustine for tolerability in dogs with a variety of primary and metastatic tumours (some heavily pre-treated) and showed a low to moderate toxicity profile\textsuperscript{22}. Although the aim of this study was to evaluate toxicity, response to lomustine was also assessed where possible and 36 per cent of dogs achieved stable disease or partial remission (although some dogs received additional adjunctive therapy)\textsuperscript{22}.

Metronomic satraplatin has also been evaluated for tolerability in dogs with a variety of tumour types. Of the 24 dogs assessed for response, 17 had a response or stable disease and overall the drug was well tolerated\textsuperscript{23}. Determining safety and efficacy for further drugs increases the options for metronomic treatment in the individual patient.

When evaluating these results it is important to note that the majority of studies have included patients with late stage disease (in the palliative setting).

This is common when evaluating a new treatment method, to allow for monitoring of measurable disease. It does, however, risk bias by positively selecting patients with a worse prognosis. It is likely the results of metronomic chemotherapy would be better in patients treated earlier in the disease course and future studies are expected to evaluate this further.

Additionally, it is necessary to adjust clinical expectations when assessing results of metronomic and other anti-angiogenic therapy. Like many therapies targeting the tumour-associated vasculature, results with metronomic chemotherapy are expected to be slow to develop. In some cases, objective responses (complete or partial responses) might not occur, yet stable disease (lack of tumour progression) could be achieved for some time.

Viewing stable disease as a successful endpoint is valid if it allows for good quality of life and extended survival. In this way patients with cancer can be viewed similarly to patients with other chronic illness – where the treatment is aimed at prolonging good quality of life rather than expecting a cure.

What does this mean for the general practitioner?

There are several practical benefits to metronomic chemotherapy in veterinary patients.

For the patient, minimal toxicity and improved ease of administration should equate with improved quality of life. For owners, fewer trips to the vet and reduced cost provide a clear benefit. For the
general practitioner metronomic chemotherapy is likely to increase the option for greater involvement in ongoing treatment, although initial referral to a veterinary oncologist is recommended, particularly while metronomic treatment protocols are still being developed and new data is emerging.

In addition, it is important for all possible treatment options to be explored for an individual patient at the outset of treatment.

Situations traditionally associated with a poor prognosis (for example, cases with metastatic disease) may be candidates for metronomic chemotherapy. In these cases, treatment is aimed at managing clinical signs and improving survival time and quality of life.

For the general practitioner this means, where appropriate, offering options for minimally invasive treatment, such as metronomic chemotherapy for patients that previously may not have had any treatment options. The low toxicity profile, lower cost, increased client convenience and improved quality of life that may be achieved with metronomic chemotherapy make it a good candidate for use in palliative therapy.

Metronomic chemotherapy may also be indicated early in the disease course for particular tumour types or where other more invasive options are not elected due to patient or client factors (such as cost, compliance, patient temperament). Establishing which tumours are responsive, and ideal dosing and scheduling is largely the aim of the current clinical investigations.

Practically, metronomic chemotherapy is likely to require cytotoxic drugs to be reformulated to allow for lower dose rates. This can be safely done by a compounding pharmacy and should not be attempted in practice.

It is important to remember that cytotoxic drugs cannot be split or crushed for health and safety reasons (Figure 1). Although the risk of patient toxicity is generally low, cumulative dosing can cause delayed toxicity and ongoing monitoring of haematology, biochemistry and urine analysis is recommended at regular intervals, with frequency specific to the drugs involved (generally four to 12-weekly depending on the protocol).

**Future directions**

A significant challenge in designing metronomic chemotherapy protocols is determining dosing schedules. Where traditional chemotherapy protocols are dosed largely based on the toxicity profile of the drugs concerned, metronomic chemotherapy dosing cannot be guided by toxicity.

One recent report evaluated Treg numbers and tumour microvessel density as biomarkers in dogs treated with various doses of cyclophosphamide to suggest optimal dosing regimes. As this, and similar technology, becomes more available, future studies are also likely to incorporate biomarkers.
to assess the efficacy of drugs and improve the accuracy of dosing and protocol design.

Combining metronomic chemotherapy with existing multimodality cancer therapy (surgery, radiation therapy and molecular targeted therapies) should offer the best chance of improving quality of life and survival in veterinary patients with cancer.

Certain treatment strategies are likely to be more useful at different stages of tumour progression and further research is needed to better understand how and when to combine these different treatment modalities to achieve optimal effect.

In addition, it is likely the benefits of metronomic dosing are maximised at the lowest tumour burden and further evaluation of the use of metronomic therapy early in the minimal disease setting is warranted.

Metronomic chemotherapy is an area of active research and its application is likely to expand as more data emerges. General practitioners are encouraged to contact their veterinary oncologist to discuss whether metronomic or other therapy may improve the quality and length of life of their veterinary patients with cancer.

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