Metronomic Chemotherapy: When Less May Be More
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The use of low dose continuous schedules of chemotherapy (i.e. metronomic chemotherapy), delivered at lower doses by necessity compared to traditional dosing schemes, has become an increasingly popular addition to patient management in veterinary medical oncology. While the concept itself is not new, as low dose, maintenance chemotherapy protocols have been important components of treatment for certain cancers (such as acute lymphoblastic leukemia) for decades, research into the reasons for potential benefit have evolved as more knowledge is acquired in the areas of cancer biology and the tumour microenvironment. There is still much to be learned, however the low cost, ease of administration, and acceptable toxicity profiles, make metronomic chemotherapy protocols both attractive and suitable to veterinary applications. Preliminary clinical trial results have now been reported in both human and veterinary medicine, and further, more powerful studies are ongoing.

Mechanisms
The most logical assumption regarding the mechanism(s) responsible for clinical benefit with metronomic chemotherapy would be the cytotoxic effect of the drugs on the tumour cells themselves. This is, after all, how most of these drugs were discovered and proven to be effective anti-cancer therapeutics. The question becomes whether or not a chemotherapeutic drug that is effective in conventional protocols might also be beneficial at lower dosages, provided the dose chosen enables the drug to reach susceptible tumour cells in a sufficient concentration. Conventionally, the goal has been to raise the dose to the highest level that is tolerated by the patient, the so-called "maximum tolerated dose" (MTD). The evidence to support this has generally been attributed to the work of Skipper, who demonstrated a logarithmic tumour cell kill with increasing chemotherapeutic dose. The rebuttal has generally consisted of an acknowledgement of efficacy in certain "liquid tumours", such as leukemias, but an inapplicability of such experimental results obtained in vitro, to the majority of solid tumours that exist within a complex microenvironment. By eliminating the unavoidable break period that accompanies MTD chemotherapy, tumour cells may be more continuously exposed to drug, which would permit more efficient cell kill as cells continue to cycle—an argument also used in the justification of low dose, continuous radiation therapy schedules.

Tumour angiogenesis
The area of the tumour microenvironment that has perhaps been most studied with respect to the effects of metronomic chemotherapy has been angiogenesis. It was likely the preclinical studies by Browder and Klement that focused attention on this potential mechanism (as well as adoption of the term "metronomic chemotherapy"). Since then, 3 aspects of angiogenesis have been shown to be impacted by continuous chemotherapeutic schedules. The first is a direct cytotoxic effect on the endothelial cells of the blood vessels themselves. Based primarily on cell culture experiments, it has been demonstrated that a variety of chemotherapeutic agents are cytotoxic to endothelial cells at concentrations in the picomolar range, that are well below what was required to produce a similar toxicity to tumour cells or other microenvironmental cells, such as fibroblasts. The second means of decreasing angiogenesis appears to be an indirect effect, brought on by tipping the relative balance of angiogenic growth factors and inhibitors toward the latter, thereby preventing further vessel expansion. The endogenous inhibitor thrombospondin-1 appears to be a critical molecule in this process, and one that is stimulated by metronomic chemotherapy schedules. Finally, the expansion of tumour blood vessels may also require, or at least be influenced by, recruitment of bone marrow-derived endothelial progenitor cells. Continuous scheduling of certain chemotherapy drugs appears to suppress this effect, while MTD schedules appear to promote bone marrow cell recruitment, as part of a vasculogenic rebound effect.

Tumour immunology
An interesting alternative, and perhaps complementary mechanism, involves alterations in immune cells, also present in the tumour microenvironment. These observations focus mainly on a decrease in the number of regulatory T cells, which are normally involved in autoimmune disease prevention as well as tumour-induced tolerance. Low doses of cyclophosphamide are able to decrease CD4\(^+\)CD25\(^+\) regulatory T cells in human cancer patients, and recently these cells have been identified and quantified in canine cancer patients as well. Interestingly, a recent study of immune responses in canine lymphoma and osteosarcoma cases during chemotherapy treatment also revealed a lower impact of chemotherapeutic drugs on T-cell numbers and antibody responses than one would expect based on an assumption that chemotherapy has generally been considered immunosuppressive.
Clinical trials
To date, there have not been any randomized, controlled, phase III clinical trial reports for the use of metronomic chemotherapy, other than perhaps the established maintenance regimens in human oncology, such as with acute lymphoblastic leukemia mentioned above. Conversely, in fact, a veterinary study of the utility of maintenance chemotherapy for canine lymphoma showed no statistical benefit to extension of the UW-Madison protocol beyond 25 weeks. In addition, a study involving the administration of doxorubicin at 10 mg/m² IV weekly, rather than 30 mg/m² IV every 3 weeks showed no response benefit in canine lymphoma, and weekly administration of lower doses of cisplatin (20 mg/m² IV) with the intent to utilize the drug as a radiation sensitizer, resulted in progressive leucopenia beyond 5 consecutive doses.

There has been reasonable speculation as to whether or not certain chemotherapy drugs will be more or less useful for a metronomic scheduling approach, and indeed, most single-agent and doublet metronomic chemotherapy clinical trials published have utilized cyclophosphamide (or trophosphamide). The study by Colleoni et al, was one of the first to utilize cyclophosphamide in this way. This trial in metastatic breast cancer patients treated with metronomic cyclophosphamide and methotrexate resulted in an overall benefit rate of 31.7%, with a median response duration of 6.8 months. Since that time, numerous other trials have been conducted for treatment of tumours such as prostate and non-small cell lung carcinoma, among others. Interestingly, there have also been beneficial results obtained with tumours of particular veterinary relevance, such as non-Hodgkin's lymphoma, melanoma, and sarcomas, including human angiosarcoma.

Veterinary trials published to date include an investigation of metronomic cyclophosphamide and etoposide with piroxicam for the treatment of stage II hemangiosarcoma. This trial evaluated 9 dogs and compared the results to a historical control population of 24 dogs treated with doxorubicin. The median disease free interval and median survival were comparable (178/178 days vs. 133/126 days) between the 2 populations, and little toxicity was observed with the metronomic protocol. Another study, utilizing metronomic cyclophosphamide and piroxicam for incompletely resected canine soft tissue sarcomas showed a significant improvement in disease-free interval in the 30 dogs that underwent this adjuvant treatment, when compared to 55 historical control dogs treated with surgery alone.

Future directions
Clinical trial evaluation of low dose, continuous chemotherapy regimens continues in both human and veterinary oncology. As more trial results are reported, we will gain an increased understanding of those diseases, drug combinations, and schedules that will be most relevant for this type of treatment strategy. Possible new applications of continuous dosing schedules may be found in the combination with standard drug dosing, or long term use with newer targeted oncology drugs, that are also meant to be given on a continuous basis at the optimal biologic dose.

Conventional versus metronomic chemotherapy

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<thead>
<tr>
<th></th>
<th>Conventional chemotherapy</th>
<th>Metronomic low dose chemotherapy</th>
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<tbody>
<tr>
<td><strong>Goal</strong></td>
<td>Short term eradication or control of cancer (i.e. Complete [CR] or Partial response [PR])</td>
<td>Long term control of Cancer (i.e. stable disease)</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>Maximum tolerated dose (MTD) (e.g. cyclophosphamide 250-300 m/m²)</td>
<td>Optimal Biologic Dose (OBD) (e.g. cyclophosphamide 15-25 mg/m²)</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td>Expected (High toxicity profile)</td>
<td>Not expected (low toxicity) well suited for combination therapy</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>Episodic (e.g. weekly); prolonged breaks</td>
<td>Continuous (e.g. daily) or frequent; no prolonged breaks</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Dividing Cancer cells</td>
<td>(&quot;activated&quot;) Dividing Endothelial cells (stromal, inflammatory, immune cells?)</td>
</tr>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Cancer cell damage ± killing</td>
<td>Antiangiogenesis</td>
</tr>
<tr>
<td><strong>Acquired resistance to Chemotherapy</strong></td>
<td>Likely (high probability) main cause of treatment failure</td>
<td>Less likely (genetically stable endothelial cells targeted)</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Established clinical criteria endpoints (PR, CR, SD, PD)</td>
<td>Feasibility of long-term administration</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Toxicity, resistance</td>
<td>Monitoring Response, Uncertain dosing &amp; scheduling</td>
</tr>
<tr>
<td><strong>Strategy to increase efficacy</strong></td>
<td>Dose-dense schedules; combination with molecularly targeted drugs</td>
<td>Combination with angiogenesis inhibitors ± other molecularly targeted drugs</td>
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### Small-molecule Tyrosine Kinase Inhibitors (TKIs) in veterinary medicine

<table>
<thead>
<tr>
<th>TKI</th>
<th>Targets</th>
<th>Tumour types</th>
<th>Species</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Palladia® (Toceranib)</strong></td>
<td>Kit (CD117) VEGFR PDGFR Flt-3</td>
<td>MCT sarcoma carcinoma melanoma myeloma</td>
<td>Dogs</td>
<td>3.25 mg/kg q 48 h (or 2.5 - 2.7 mg/kg Monday, Wednesday, Friday)</td>
</tr>
<tr>
<td><strong>Kinavet® Masivet® (Masitinib)</strong></td>
<td>Kit (CD117) PDGFR Lyn FGFR3 FAK</td>
<td>MCT</td>
<td>Dogs</td>
<td>12.5 mg/kg q 24 h</td>
</tr>
<tr>
<td><strong>Gleevec® (Imatinib)</strong></td>
<td>Kit (CD117) Abl PDGFR</td>
<td>MCT sarcoma</td>
<td>Dogs/Cats</td>
<td>5 - 10 mg/kg q 24 h</td>
</tr>
</tbody>
</table>

- VEGFR vascular endothelial growth factor receptor,
- PDGFR platelet-derived growth factor receptor
- FAK focal adhesion kinase
- MCT mast cell tumour

### References
- Woods JP, ACVIM Forum 2009
- Woods JP et al. VCS 2011
- Marchetti V, et al. Invest New Drugs 2011