Metronomic Chemotherapy in Veterinary Patients with Cancer

Rethinking the Targets and Strategies of Chemotherapy

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KEYWORDS

• Low-dose chemotherapy • Canine neoplasia • Angiogenesis • Immune modulation • Tumor biomarkers

KEY POINTS

- Metronomic chemotherapy uses old drugs in a new way: at much lower doses and without interruption compared with conventional chemotherapy protocols.
- Rather than targeting the rapidly dividing tumor cell population, metronomic chemotherapy slows or stops tumor growth by inhibiting tumor angiogenesis and evasion from the immune system.
- Most metronomic protocols use oral chemotherapy agents combined with a nonsteroidal antiinflammatory.
- Clinical trials to assess the efficacy of metronomic chemotherapy should include appropriate tumor biomarkers of activity in addition to monitoring changes in tumor volume.

INTRODUCTION

Conventional cytotoxic chemotherapy has been the mainstay of systemic anticancer therapy for more than 50 years. For both human and veterinary patients, most protocols involve administration of single or multiple antiproliferative agents delivered at doses close to the maximum tolerated dose (MTD). Because neoplastic cells are rapidly dividing compared with normal tissues, MTD chemotherapy is intended to kill as much of the neoplastic cell population as possible. A critical aspect of all MTD protocols is inclusion of breaks between drug administrations to allow for

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recovery of drug-sensitive normal tissues, particularly bone marrow progenitors and gastrointestinal epithelial cells. Without these gaps between treatments, unacceptable drug toxicities occur. However, this approach also permits recovery of tumor cells and can lead to tumor regrowth and the development of drug-resistant or metastatic disease. Although conventional chemotherapy has been associated with significant gains in survival for many cancers, it infrequently results in permanent tumor control, particularly in the face of demonstrable metastatic disease.

Research over the past several decades has brought about an exponential increase in understanding of the molecular pathways and mechanisms of cancer metastasis and drug resistance. This work has revealed many reasons for the failure of conventional chemotherapy to limit cancer progression. These reasons include the dynamic heterogeneity and instability of tumor cells, the protective action of the tumor microenvironment, and suppression of antitumor immune responses. However, awareness of these shortcomings is enabling the development of more targeted approaches to cancer therapy including a form of chemotherapy known as metronomic chemotherapy (MC). In contrast with conventional chemotherapy, MC is characterized by the continuous or uninterrupted administration of chemotherapy drugs at doses that are significantly lower than MTD therapy (**Box 1**).[1] As discussed in this article, MC can be thought of as a multitargeted approach and is rapidly emerging as an attractive adjunct or alternative to conventional drug delivery. Although many questions regarding the application of MC to human and veterinary oncology patients await investigation, favorable tumor control and excellent safety profiles support the significant promise of this new anticancer approach.

TARGETS OF MC

Tumor Angiogenesis

Tumor growth is critically dependent on the process of angiogenesis, which occurs through the development of new blood vessels from preexisting, larger vessels. Tumors can also stimulate vasculogenesis, which is defined as new blood vessel formation from bone marrow–derived progenitor cells including circulating endothelial progenitor cells (CEPs).[2–4] Regardless of the pathway, the rapidly dividing tumor cell population requires a blood supply to deliver nutrients and oxygen and to remove waste products; without it, tumor volume is limited to only a few millimeters in size.[5,6]

Box 1
Key differences between conventional chemotherapy and MC

- Conventional chemotherapy uses large doses of drugs that target the rapidly dividing tumor cell population
- Because conventional chemotherapy also kills rapidly dividing cells of the bone marrow and gastrointestinal tract, a break between treatments is necessary to prevent serious toxicity
- MC uses much lower doses of chemotherapy drugs given without any breaks between treatments; the dose is generally too low to kill tumor cells directly
- The targets of MC include the tumor vasculature and certain immune cells that help tumor cells hide from recognition and attack by the immune system
- The success of conventional chemotherapy is based on a significant decrease in tumor volume; treatment responses to MC are often based on achievement of durable stable disease