PRECLINICAL AND CLINICAL STUDIES OF LOW DOSE METRONOMIC (ANTIANGIOGENIC) CHEMOTHERAPY FOR TREATMENT OF ADVANCED METASTATIC DISEASE

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The importance of dosing, and especially scheduling, on the efficacy and toxicity of antiangiogenic therapies, is especially illustrated by low dose metronomic chemotherapy. Metronomic chemotherapy refers to the close, regular administration of a chemotherapeutic drug, over prolonged periods, with no extended drug-free break periods (1). As such it is a form of “dose dense” chemotherapy but differs from most forms of the latter in several ways (2). First, it is not necessarily “dose intense” where the objective is to deliver more total drug per unit time, compared to pulsatile maximum tolerated dose (MTD) regimens with three week break periods between successive cycles of drug administration. Second, as such, metronomic regimens are less toxic and do not usually require growth factor support, or other supportive care measures (3,4). Metronomic chemotherapy can thus be viewed as a form of long term ‘maintenance’ chemotherapy that can be used on its own (1,2), or combined with long-term biologic targeted therapies, especially antiangiogenic drugs such as anti-VEGFR-2 antibodies (5) or small molecule multi-targeted VEGFR-2 antagonist receptor tyrosine kinase inhibitors (6). It can also be integrated with standard MTD type chemotherapy where brief courses of such therapy is followed by long term maintenance metronomic chemotherapy combined with concurrent targeted therapies (5,6), called “chemo-switching” (6). Among the advantages of metronomic chemotherapy include reduced acute toxicities such as high grade myelosuppression, vomiting, nausea, mucositis, etc. (3,4), good activity against drug resistant tumors (1), reduced costs when using off patent chemotherapeutic drugs, and increased convenience when using oral drugs which can be taken at
These potential advantages could be useful for long term adjuvant therapy of early stage cancers, e.g. long term daily oral administration of a drug such as UFT (a 5-FU prodrug) for 2 years with no breaks (7).

There is, however, at least one significant disadvantage: the empiricism associated with determining the optimal ‘low’ dose, i.e., optimal biologic or therapeutic dose (OBD). Because the predominant mechanism for metronomic chemotherapy is thought to be antiangiogenesis (1,2,5), as a result of targeting both dividing endothelial cells in a tumor’s growing vasculature (1) and bone marrow derived circulating VEGFR-2+ cells, including endothelial progenitor cells (CEPs) (8), we decided to investigate whether the latter cells and/or circulating endothelial cells (CECs) could be used as a surrogate marker in mice for determining the OBD of both targeted antiangiogenic drugs (9) or various metronomic chemotherapy regimens (10). The results showed CEPs can indeed be used successfully for such a purpose (9,10). Thus, we can reduce the level of empiricism, at least in mice, when testing metronomic chemotherapy regimens. To this end, we have been determining the anti-tumor effects of single versus two chemotherapeutic drug combinations, dosed and administered in a metronomic fashion, i.e., daily (by oral delivery) in a model of advanced high volume (end stage) visceral metastatic disease where therapy is initiated in terminal stages of disease (11). One drug used was cyclophosphamide administered at 20 mg/kg/day – the OBD determined by effects on CEPs, administered through the drinking water (12). The other drug is UFT administered by gavage for 140 days non stop with or without cyclophosphamide. Remarkable long-term survival effects were observed with the combination treatment (11).

We are also experimenting with modified metronomic chemotherapy protocols such as ‘slow plus fast’ metronomic chemotherapy where cyclophosphamide is given orally on an extended daily schedule punctuated by bolus dose injections of the same drug every 3 to 6 weeks at 1/3 the MTD – a protocol which is also associated with only modest toxicity and significantly improved efficacy.

Metronomic chemotherapy regimens have moved into phase II clinical trial testing both in the adjuvant and metastatic settings, combined with a targeted
antiangiogenic drug such as bevacizumab (Avastin®). Some interim results look extremely promising (13,14).

Finally, our functional studies on “CEPs” have resulted in some recent findings which definitely implicate a role of these cells in tumor angiogenesis and the mode of action of vascular disrupting agents (VDAs) such as combretastatin, or Oxi-4503 as well as antiangiogenic drugs (15). VDAs can actually cause a rapid and transient increase in viable CEP levels which appear to contribute to the regrowth from the viable tumor rim that remains after treatment with such drugs. Consequently, combination treatment with a drug that prevents the CEP spike, e.g. anti-VEGFR-2 antibodies, can maximize the vascular targeting effects of CA4P or Oxi-4503 and virtually obliterate the viable tumor rim, even after only a single injection of both types of drug spaced 24 hours apart. These results provide an indication of the functional importance of ‘CEPs’, and/or other bone marrow-derived pro-angiogenic VEGFR-2⁺ circulating cells, and how they can be exploited therapeutically. They also suggest that even if very low levels of such cells are detectable in unperturbed tumors they may nevertheless have considerable importance in situations where they are ‘called upon’ to transiently induce/facilitate angiogenesis.

In summary, our preclinical results show the following:

1. Chemotherapy can inhibit tumor angiogenesis by targeting either tumor associated endothelial cells and/or bone marrow derived circulating proangiogenic cells, including CEPs.

2. Combination therapy with a targeted antiangiogenic drug, such as anti-VEGF(R2) antibodies, can amplify these effects.

3. Antiangiogenic efficacy of chemotherapy can be optimized by low-dose metronomic regimens and combination with a targeted antiangiogenic and/or another chemotherapy drug.

4. The OBD for metronomic chemotherapy may be possible to determine by using “CEPs” as a surrogate marker for angiogenesis.
5. The treatment strategy can have significant efficacy on advanced end stage metastatic disease.

Ongoing, planned or recently completed phase II clinical trials of metronomic chemotherapy combined with an agent such as bevacizumab should indicate whether or not this treatment strategy has promise in the treatment of metastatic and/or early stage human cancer.

Reference List