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Metronomic chemotherapy from rationale to clinical studies: A dream or reality?

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Abstract

Metronomic chemotherapy (MC) refers to the close administration of a chemotherapeutic drug for a long time with no extended drug-free breaks. It was developed to overcome drug resistance, partly by shifting the therapeutic target from tumor cells to the tumor vasculature, with less toxicity. Because of this peculiar way of administration, MC can be viewed as a form of long-term 'maintenance' treatment, and can be integrated with standard and conventional chemotherapy in a "chemo-switching" strategy. Additional mechanisms are involved in its antitumor activity, such as activation of immunity, induction of tumor dormancy, chemotherapy-driven dependency of cancer cells, and the '4D effect'. In this paper we report the most important studies that have analyzed these processes. In fact, a number of preclinical and clinical studies in solid tumors as well as in multiple myeloma, have been reported regarding several chemotherapy drugs which have been proposed with a metronomic schedule: vinorelbine, cyclophosphamide, capecitabine, methotrexate, bevacizumab, etoposide, gemcitabine, sorafenib, everolimus and temozolomide. The results of these studies have been sometimes conflicting, highlighting the need to develop reliable tools for patient selection and stratification. However, a more precise evaluation of MC strategies with the ongoing randomized phase II/III clinical is fundamental, because of the strict correlation of this approach with translational research and target therapy. Moreover, because of the low toxicity of MC, these studies will also help to better evaluate the clinical benefit of this treatment, with a special focus on elderly and low performance status patients.

Keywords: Angiogenesis; Bevacizumab; Chemo-switching; Cyclophosphamide; Immunity; Maintenance; Metronomic chemotherapy; Toxicity

1. General: Definition of metronomic chemotherapy and antiangiogenic power

Chemotherapy represents the mainstay of cancer medicine for both locally and advanced neoplasms, the maximum tolerated dose being the regular model for the past 50 years [1]. However, clinicians must fight against collateral and side effects linked to high-dose and cyclic schedules, which limit dosing and hamper anti-tumor efficacy. What is more, despite impressive tumor regression or even remission, regrowth and recurrence are common events in metastatic and high-risk tumors [2]. Accordingly, dosing and scheduling of chemotherapy to redirect it toward antiangiogenic efficacy is entailed by low-dose metronomic chemotherapy [2,3].

"Metronomic chemotherapy" was first coined by Hanahan, and refers to the close, regular administration of a chemotherapeutic drug for a long time with no extended drug-free breaks [4]. It was originally developed to overcome drug resistance by shifting the therapeutic target from tumor cells to the tumor vasculature [5,6]. The rationale stems from the low-rate of endothelial cell division compared to tumor cells: by using the standard chemotherapy cycles this causes only weak endothelial cell damage [2,7]. Endothelial cells therefore became able to repair themselves and recover during the rest period. Since endothelial cells support tumor growth, their regrowth produces tumor resistance. This concept led to the hypothesis that more compressed or accelerated schedules of drug administration using much smaller individual doses would be more effective and less toxic [8,9].

Several preliminary experiments showed that metronomic continuous administration of chemotherapy drugs in cultures induced endothelial cell death in conjunction with tumor cell death [10]. Metronomic chemotherapy also induces the antiangiogenic glycoprotein *Thrombospondin-1* (TSP1), which is endowed with further anti-tumor effects [11–13]. In fact, it also inhibits proliferation and/or induces apoptosis of activated endothelial cells, it inhibits endothelial cell migration, and decreases levels and viability of bone marrow-derived endothelial progenitor cells [14–17].

Since these mechanisms are typical of other antiangiogenic drugs which determine only mild antitumor effects when used alone, it is plausible that other mechanisms underlie the higher antitumor effect of metronomic chemotherapy. The initial intuition of Folkman, father of angiogenic theory [18], was developed by Browder and Kerbel, who first highlighted the anti-angiogenic metronomic schedule of cyclophosphamide which was more effective than the conventional schedule in overcoming drug resistance in cultured breast cancer cells [2,19].

In addition, cancer in the elderly or in patients with several co-morbidities and suboptimal performance status must be managed carefully. These patients may be the ideal candidate for a first-line or second-line oral metronomic therapy due to the low toxicity profile of this approach [20].

Possible different activities of metronomic chemotherapy are resumed in Fig. 1.

2. Dose-dense chemotherapy and new concepts: "Maintenance" and "chemo-switching"

Metronomic use of anti-cancer drugs can be considered a type of "dose-dense" chemotherapy, although differing from *classical* dose-dense administration. First, it is neither "dose-intense" since it doesn't deliver more total drug per unit time, nor is it a cyclic maximum tolerated dose regimen with three week break periods between cycles [1]. Hence, the metronomic regimens are less toxic, and have reduced bone marrow toxicity and gastrointestinal disorders, including vomiting, nausea, and mucositis. This good toxicity profile is evident also in heavily pre-treated cancer patients [21,22]. In fact, the schedule, usually, does not