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Mini-review

Metronomic chemotherapy and nanocarrier platforms

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ABSTRACT

The therapeutic concept of administering chemotherapeutic agents continuously at lower doses, relative to the maximum tolerated dose (MTD) without drug-free breaks over extended periods —known as "metronomic chemotherapy"— is a promising approach for anti-angiogenic cancer therapy. In comparison with MTD chemotherapy regimens, metronomic chemotherapy has demonstrated reduced toxicity. However, as a monotherapy, metronomic chemotherapy has failed to provide convincing results in clinical trials. Therapeutic approaches including combining the anti-angiogenic "metronomic" therapy with conventional radio-/chemo-therapy and/or targeted delivery of chemotherapeutic agents to tumor tissues via their encapsulation with nanocarrier-based platforms have proven to potentiate the overall therapeutic outcomes. In this review, therefore, we focused on the mutual contribution made by nanoscale drug delivery platforms to the therapeutic efficacy of metronomic-based chemotherapy. In addition, the influence that the dosing schedule has on the overall therapeutic efficacy of metronomic chemotherapy is discussed.

Introduction

Angiogenesis, or the formation of new blood vessels, is known to be vital for cancer growth and dissemination, which makes it an attractive therapeutic target for cancer therapy [1–3]. The targeting of genetically stable and easily accessible tumor vascular endothelial cells (ECs), rather than the tumor cells themselves, by chemotherapeutic agents is assumed to reduce the likelihood of developing drug resistance and overcomes the physiological barriers that might hinder the effective delivery of drugs to tumors [4,5]. Metronomic chemotherapy, which was originally designed to inhibit tumor angiogenesis when using conventional chemotherapeutic agents, is currently regarded as a promising strategy for anti-angiogenic cancer therapy in both preclinical studies and clinical trials [6,7]. Metronomic chemotherapy is characterized by the frequent administration of comparatively lower doses of cytotoxic agents at close regular intervals without prolonged drug-free breaks compared with conventional maximum tolerated dose (MTD) chemotherapy.

The major pharmacological basis of metronomic chemotherapy is that, by comparison with normal or other types of tumor cells, tumor vascular endothelial cells (ECs) are highly sensitive to low doses of chemotherapeutic agents when exposed in a frequent or continuous manner. In addition, metronomic chemotherapy can suppress systemic angiogenesis that is mediated by circulating bone marrow-derived pro-angiogenic cells, such as circulating endothelial progenitors (CEPs), and it induces the secretion of endogenous angiogenesis inhibitors such as thrombospondin 1 (TSP-1) that suppresses tumor neovascularization [6,7]. Furthermore, the administration regimen of metronomic chemotherapy efficiently shortens the time between dosing cycles, and, thus, it prevents the recovery of the damaged tumor vasculature [6].

Nevertheless, contrary to common opinion, a growing body of evidence has shown that the anti-angiogenic potential of metronomic chemotherapy could enhance the intratumor distribution and delivery of drugs and/or macromolecules, which includes drug-delivery carriers. This notion is associated with a reduction in the tumor micro-vessel density that is accompanied by morphological and functional maturity, resulting in what is known as "intratumor vascular normalization." Such "vascular normalization" is thought to trigger better perfusion and improved drug delivery and efficacy [8–10]. Accordingly, in addition to direct anti-angiogenic activity, metronomic chemotherapy might also augment the therapeutic efficacy of co-administered drugs and/or macromolecules including drug-delivery carriers.

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Mechanism(s) of action for metronomic chemotherapy

Tumor progression is a complex process that involves the interaction of cancer cells with non-malignant surrounding microenvironments [11,12]. Accordingly, efficient cancer treatment might require a fight against multiple possible targets such as cancer cells, cancer stem cells, tumor vasculature, extracellular matrix, and/or immune cells infiltrating the tumor. In fact, metronomic scheduling of chemotherapeutic agents, namely "metronomic chemotherapy," is currently considered a multi-targeted treatment. In this section, we focus briefly on the possible anticancer mechanisms that could be attributed to metronomic scheduling (Fig. 1).

Anti-angiogenic activity

A mounting body of evidence has declared that the anticancer activity of metronomic chemotherapy is mediated predominantly by inhibiting tumor angiogenesis. Browder et al. [13] have emphasized that chemotherapeutic agents can cause apoptosis of tumor-associated vessels in ectopically growing mouse tumors. Such anti-angiogenic potential is more prominent with protracted exposure to low doses of chemotherapeutic agents from frequent administrations during "metronomic administration" compared with conventional administration at MTD. In addition, recent studies have revealed that the anti-angiogenic potential of metronomic chemotherapy can also be mediated via a suppression of the mobilization of CEPs [14,15] and the inductive production of an anti-angiogenic glycoprotein referred to as TSP-1, which is an endogenous inhibitor of angiogenesis, in order to reduce tumor neo-vascularization [6,16,17]. Nonetheless, it is worth noting that other mechanisms might contribute to the antitumor response of several cytotoxic drugs when administered on a metronomic schedule.

Modulation of antitumor immunity

Despite the fact that high doses of chemotherapeutic agents sometimes trigger host inflammatory immune responses that can ablate immune surveillance [18], such detrimental effects on a host's immune system can be reversed by changing the dosing and timing of the chemotherapy. Several pre-clinical and clinical studies have emphasized that lower doses and more frequent administration of chemotherapeutic agents, consistent with the metronomic basis of therapy, can restore antitumor immunity and suppress pro-tumor immune responses. This happens predominantly via the selective depletion of immunosuppressive regulatory T cells (T_{regs}), which is a $Foxp3^{+}CD25^{+}CD4^{+}$ subpopulation of T cells that inhibits antigen-specific immune responses via both cytokine-dependent and cell contact-dependent processes [18–22]. In addition, metronomic chemotherapy could induce apoptotic tumor cells to release tumor-specific antigens that could be taken up by antigen-presenting cells, where they would then be processed and presented to antigen-specific $CD8^{+}$ T cells [23–25]. Furthermore, the signals released by killed tumor cells could induce the maturation of dendritic cells (DCs) and enhance their phagocytic ability [26–30]. An extensive review of the immunoregulatory effects of metronomic chemotherapy has recently been published [31].

Induction of tumor dormancy

Experimental and clinical evidence supports the existence and the crucial role of tumor dormancy both in repression of cancer progression and in cancer relapse [32,33]. Tumor dormancy occurs as a result of cell-cycle arrest or a dynamic equilibrium between cell proliferation and apoptosis [32–34]. Three different mechanisms are reported to participate in the induction of tumor dormancy: suppression of angiogenesis, induction of apoptosis in cancer cells, and tumor immune surveillance [20,35]. Thus, it is easy to postulate

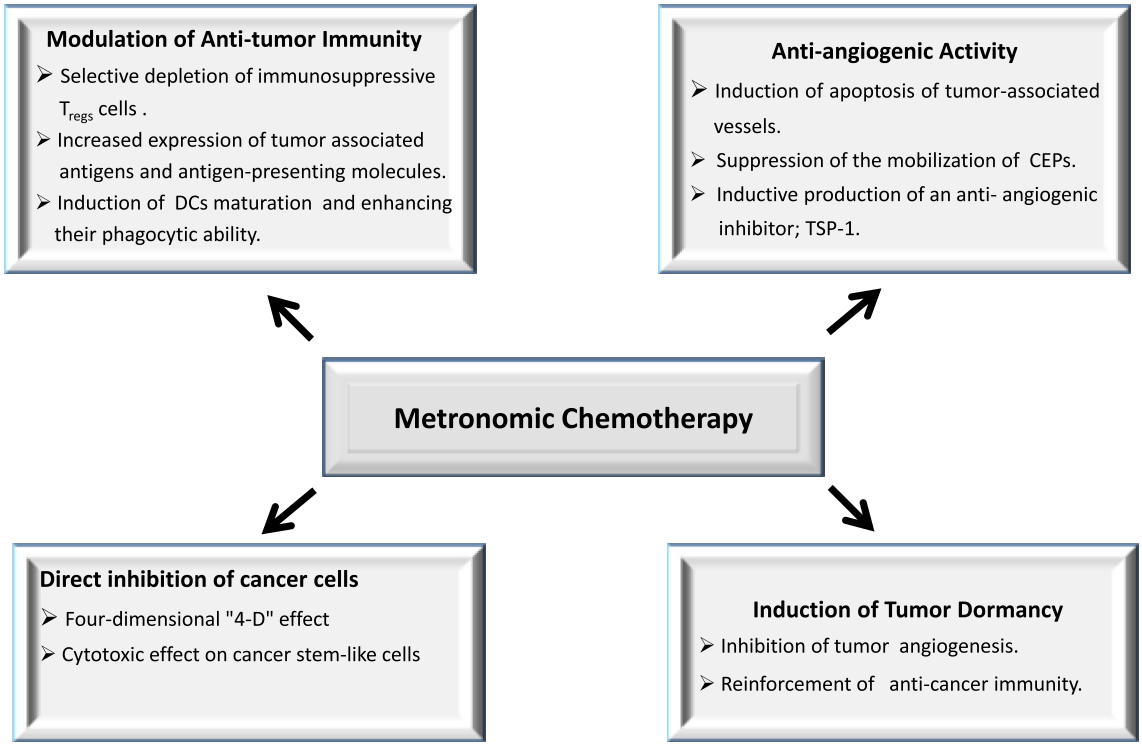

Fig. 1. Illustrating diagram for the possible mechanism(s) of action of metronomic chemotherapy.