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Cyclophosphamide-based metronomic chemotherapy: After 10 years of experience, where do we stand and where are we going?

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Abstract

Metronomic (low-dose, long-term and frequently administered) chemotherapy has attracted renewed interest for the past few years, in particular because of possible positive association with molecular targeted agents. Cyclophosphamide is the most widely-explored agent in such an approach. The main possible mechanisms of actions identified in preclinical models, whatever the histology of tumor, are the stimulation of the immune system and anti-angiogenic action. Retrospective studies and numerous phase II clinical trials have been published in diverse clinical settings, mainly in patients with highly pretreated advanced tumors. The tolerance seems to be acceptable; some objective

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responses have been reported. Nevertheless, the regimens were very heterogeneous, and most of these studies are not randomized. This makes it difficult to objectively evaluate the additional value of the metronomic administration of cyclophosphamide. Further clinical trials integrating translational research are necessary to better evaluate the clinical benefit of this promising approach.

Keywords: Cyclophosphamide; Metronomic chemotherapy; Anti-angiogenic drug; Immuno-stimulant drug; Micro-environment

1. Introduction

Metronomic chemotherapy refers to the frequent, even daily, administration of cytotoxic drugs at doses significantly less than the maximum tolerated dose, with no prolonged drug-free breaks [1]. This treatment is regarded as an anti-angiogenic one. This approach has attracted renewed interest for the past few years, in particular because of possible synergistic association with molecular targeted agents.

Cyclophosphamide (CTX) is a nitrogen mustard alkylating agent, from the oxazophorines group. It is the cornerstone of many combination regimens for the treatment of lymphomas, multiple myeloma, mycosis fungoides, neuroblastoma, small cell lung carcinoma or ovary or breast adenocarcinoma. In the conventional regimen, CTX is usually intravenously administered at the dose 600–750 mg/m^2/3 weeks (for example, 600 mg/m^2 in the "AC" combination or 750 mg/m^2 in the CHOP protocol). Its main toxicities are hematoxicities and urinary toxicity.

Besides the conventional method of administration, oral CTX-based metronomic chemotherapy (CTX) is the most widely studied metronomic regimen as a single-agent treatment or in combination. Considering the great number of recent publications, we aimed to synthesize the preclinical and clinical data investigating oral CTX-based metronomic chemotherapy alone or in combination. These data are classified in the following categories here: *in vitro* studies, studies in mice bearing transplanted tumor cells, treatment of dogs with spontaneous sarcomas by low-dose CTX and clinical trials in humans.

2. *In vitro* studies

In vitro explorations are limited by the fact that CTX is a pro-drug requiring a metabolization into several active derivates, such as 4-hydroxy-CTX [2–4]. The exposure to the 4-hydroxy-CTX of various cellular lines suggests that this drug acts in a different way according to cell types. The proliferation of endothelial cells is sensitive to the lowest doses of 4-hydroxy-CTX; whereas established fibroblast lines and cancer cells are sensitive to the highest doses [2]. Moreover, low concentrations of 4-hydroxy-CTX induce apoptosis of macro- and micro-vascular endothelial cells [2] and up-regulate thrombospondin-1 (TSP-1), an endogenous inhibitor of angiogenesis, in the same cells [4]. Furthermore, acrolein, another derivate of CTX, which is responsible for the vesical toxicity of CTX, seems to have some anti-tumor effect as the results of cytoskeleton alteration, enhancement of anti-angiogenic factors expression (such as TSP-1) or induction of pro-apoptotic signal (NF-κ_B) [3].

Table 1
Non-exhaustive list of mice bearing transplanted tumor cells used to explored low-dose cyclophosphamide metronomic regimens.

Tumors cells	References
Multiple myeloma (5T2MM cells)	[6]
Lymphoma (L-TACB or J774 cells)	[7–12]
Brain tumor ((9L and BT4An cells)	[13,14]
Sarcoma	[8]
Cutaneous or uveal melanoma (B16F10)	[15–17]
Colorectal carcinoma (HT-29, Dks-8)	[17–21,29]
Pancreas carcinoma	[17]
Hepatocarcinoma	[22]
Lung carcinoma (TC-1 cells)	[23]
Prostate carcinoma (PC-3 and AT-1 cells)	[24–27]
Breast carcinoma (MDA-MB-231 and EMT-6 cells)	[18,21,25,28]

3. Mice bearing transplanted tumor cells

3.1. Evidence of activity

Many models have been studied in the two last decades. The dose used in the metronomic schedule is far from the maximum tolerated dose (MTD). In mice, the MTD is about 105 mg/kg on days 1, 3 and 5 every 14 days [5] or 150 mg/kg for 5 consecutive days every 21 days [6]. The metronomic schedule is based on daily protracted administration (usually through drinking water) of 10 mg/kg [6] to 25 mg/kg [5] without a break. This daily dose administered in this metronomic schedule represents about 2–6% of the MTD in mice [5,6].

At this range of dose CTX provides some signs of activity in a vast variety of mice bearing transplanted cells (Table 1 [7–29]). For example, CTX given at the dose of 10 mg/kg three times a week blocks the metastatic growth in 100% of implanted lymphomas and 83% of implanted sarcomas [8]. In all cases, the survival of mice treated with low-dose CTX is improved and the tumor burden significantly decreases. This suggests that the anti-tumoral effect is not driven by the histological type of tumor.

Furthermore, several experimental preclinical studies show that the cancer cells are minimally affected by low-dose CTX [30,31]. For example, Browder et al. have shown that giving low-dose CTX every 6 days to mice bearing transplanted tumors markedly inhibited growth; even in Lewis Lung carcinoma cell lines selected *in vivo* for resistance to conventional CTX. The low-dose CTX was more effective