Antiangiogenic Metronomic Chemotherapy

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Metronomic chemotherapy (MC) refers to the close, rhythmic administration of low doses of cytotoxic drugs, with minimal or no drug-free breaks, over prolonged periods. It represents a novel therapeutic anticancer treatment strategy via a mechanism that differs from the conventional maximum tolerable dose (MTD) chemotherapy, based on antiangiogenic activity. Tumor related angiogenesis is a multi-step process initiated by a cascade of proangiogenic factors secreted by both tumor and host cells [1–3]. Inhibition of the proangiogenic mechanisms has become a major challenge for the development of anti-cancer treatment modalities.

Antiangiogenic therapy primarily targets tumor associated proliferating endothelial cells, which are necessary for tumor growth, progression and metastasis. By blocking the supply of essential nutrients and the removal of metabolites, antiangiogenic therapies delay both primary tumor and metastasis growth. There are several theoretical advantages and opportunities for MC: activity against both the parenchymal and stromal components, proapoptotic activity, reduction of the likelihood of emergence of acquired resistance, feasibility of long-term administration and acceptable systemic side effects. However, there are also potential problems and challenges in terms of appropriate experimental study design and clinical testing [4, 5].

A major clinical advantage of MC is that it minimizes the toxic effects, allowing feasible combinations with selective inhibitors of angiogenesis. In fact, preclinical studies suggest that the combination of selective antiangiogenic agents (i.e. anti-vascular endothelial growth factor drugs) with MC induces synergistic anti-tumor activity in vivo [6]. However, there may exist a minimum concentration of drug below which no tumor inhibition takes place. Thus, the definition of the range of true metronomic doses for clinical trials is a crucial but still undefined challenge. In experimental studies, MC was tested by reducing the MTD of each single agent by at least 33%.

Most of the phase I–II clinical studies performed up to now used ‘metronomic-like’ schedules of cytostatic agents, often administered using weekly schedules of vinca alkaloids, taxanes, anthracyclines or alkylating agents resulting, however, in high dose-density treatments. A rational identification of a true metronomic schedule of a cytotoxic drug needs the design of ad hoc phase I studies, capable to define the range of doses with proven antiangiogenic activity (by determination of thrombospondin-1, circulating endothelial cell kinetics, proangiogenic biomarkers, etc.) and then to select the minimally useful dosage for further clinical trials [7–10].

As an example, Correale et al. [11] designed a pilot phase II study to investigate the toxicity and activity of the novel metronomic regimen of weekly cisplatin (CDDP) and oral etoposide (VP16) in high-risk patients with NSCLC. 31 patients received weekly CDDP 30 mg/m² on days 1, 8, 14 and 28 and oral daily VP16 50 mg/m² during 21 of the 28 days of the cycle. Most frequent adverse events were grade III leukopenia and anemia; 3 patients died of pulmonary embolism. Objective response rate was 45.2%, disease control was 58.1%, mean time to progression and survival were 9 and 13 months, respectively. Pharmacokinetic analysis showed that this regimen allowed a greater median monthly area under the curve of the drugs than conventional schedules.

Regarding the study design of MC, no published clinical study is currently available in which MC is prospectively compared with conventional schedules, or showing reproducible in vitro or in vivo methods of monitoring the antiangiogenic activity. In this issue of ONKOLOGIE, Görn et al. [12] report the results of a phase II study investigating the combination of docetaxel and trofosfamide given in a metronomic schedule as second-line treatment in patients with metastatic NSCLC. 21 patients previously treated with standard chemotherapy regimens (71.4% with platinum-based and 28.6% with platinum-free combinations) were enrolled. The patients received docetaxel

at the dose of 25 mg/m² on days 1, 8, and 15, every 28 days (75 mg/m² at cycle) in combination with trofosfamide 50 mg daily. The Authors reported 1 complete response and 3 partial remissions, 9 patients had stable disease; 8 experienced progression of disease. The clinical benefit was of 61.9%. The median survival was 6.9 months; the 1-year survival rate was 28.6% and the median progression-free survival time was of 2.9 months. No dose reduction for both the drugs was necessary; no grade IV toxicity and no treatment-induced death occurred. The most common hematological toxicity was grade III neutropenia observed in 4 patients.

The clinical results reported should be considered promising, even if obtained in a small cohort of patients, but the authors failed to demonstrate any documented antiangiogenic activity

because no pharmacodynamic analysis was performed. Indeed, the authors evaluated an original chemotherapy regimen only testing a 'metronomic-like' schedule not compared with the same drugs given at standard dosages, thus precluding the possibility to show any superiority of one schedule over another.

Finally, taking into account that, in general, the most evident effect of selective antiangiogenic agents (i.e. bevacizumab) is the significant prolonging of the duration of response obtainable by chemotherapy alone, with the aim to minimize the possible side effects of cytotoxic agents given in association with them for long periods of time, MC should be considered both as novel up-front or maintenance treatment in patients with biologically poorly aggressive advanced cancer diseases.

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