Five Years of Clinical Experience with Metronomic Chemotherapy: Achievements and Perspectives

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Over the last few years the positive results of several phase III trials involving bevacizumab, sunitinib and sorafenib have definitively established antiangiogenic therapy as a novel clinical modality for the treatment of cancer [1, 2]. However, in retrospect, the study of tumor angiogenesis from a therapeutic perspective also revealed that some new molecularly targeted agents which were not developed as antiangiogenic drugs, as well as many conventional cytotoxic drugs, can exert ‘accidental’ antiangiogenic effects [3, 4]. In this regard, two preclinical studies published in 2000 suggested that the frequent or continuous administration of conventional cytotoxic drugs in comparatively low doses over extended periods with no prolonged breaks not only seems to optimize the antiangiogenic properties of chemotherapeutic drugs, but also has the added benefit of significantly reduced toxicity, compared to maximum tolerated chemotherapy administration [5–7]. This form of antiangiogenic [5] or – as now more commonly called – ‘metronomic’ [8] chemotherapy is being intensively studied clinically. In addition to antiangiogenic effects, other mechanisms of action mediated by metronomic chemotherapy might apply, such as the depletion of regulatory T cells [7, 9].

Since the publication of the results of a trial of metronomic cyclophosphamide and methotrexate for the treatment of advanced breast cancer by Colleoni et al. 5 years ago [10], numerous studies evaluating variations of this approach in breast [11, 12], prostate [13, 14] and ovarian cancer [15] among other tumor types [7, 16] have been reported. All these studies confirm the excellent safety profile of metronomic chemotherapy regimens, which in many instances involves the administration of oral cyclophosphamide. With few exceptions [17], the results have been considered worthy of further clinical evaluation. The published metronomic protocols are commonly complemented with agents having antiangiogenic properties such as cyclooxygenase-2 (COX-2) inhibitors, glitazones, thalidomide and bevacizumab. The most striking results so far

have been achieved when metronomic chemotherapy was combined with bevacizumab [15, 18, 19].

The phase II study by Steinbild et al. [20] in this issue of ONKOLOGIE describes the combination of continuous capecitabine (500 mg bid) and celecoxib (400 mg bid) in 37 patients with progressive locally advanced or metastatic cancer following at least one line of conventional cytotoxic therapy. Colorectal (12 patients) and renal cell (10 patients) cancer were the most common tumor types included. This study appears to corroborate findings of other metronomic trials but also provides some new aspects. The results show (i) a lack of consequential side-effects with only very few grade 3 (anemia, transaminitis, fatigue) and no grade 4 toxicities, (ii) a reasonable benefit with a stable disease rate of 30% after 3 cycles (12 weeks) of treatment, and (iii) a limited benefit of this type of therapy in patients with rapidly progressive disease at study entry. Interestingly, 5 of the 11 patients that received more than 3 cycles of metronomic capecitabine therapy had been exposed to 5-fluorouracil (5-FU) in the past. This would appear to be consistent with the hypothesis that resistance to maximum tolerated doses of a certain type of cytotoxic drug (i.e., 5-FU and its precursor capecitabine) does not necessarily preclude its later (beneficial) use, if administered in a metronomic dose and schedule [5].

Although capecitabine has been used clinically in metronomic-like regimens [21], the study by Steinbild et al. establishes the potential use of this drug in the metronomic chemotherapy context. Furthermore, the authors are the first to show clinical DCE-MRI data of patients undergoing metronomic therapy. Despite extensive variation between individual patients with respect to K^{trans} profiles, some patients with stable disease showed a reduction of > 40% of this blood flow and vessel permeability parameter, which is indicative of significant antiangiogenic activity. Conversely, the K^{trans} changes in patients with progressive disease were only minor. Interestingly,

the mean K^{trans} changes after 1 and 3 months of metronomic therapy in patients with stable disease suggest more pronounced antiangiogenic activity after 3 months. This could be an explanation for the often delayed effects of metronomic regimens which could preclude the use of such therapy as the only treatment modality in the context of rapidly progressive disease. Although reduced K^{trans} readings were also obtained in patients with progressive disease at 3 months of therapy, these changes were only minor and seemingly not sufficient to control tumor growth. Alternatively, tumor growth despite demonstration of antiangiogenic activity could be explained by the phenomenon of reduced vascular dependence, i.e., a tumor cell phenotype characterized by increased resistance to conditions created/exacerbated by chronic antiangiogenic therapy such as severe hypoxia, acidosis and lack of nutrients [22].

The results of Steinbild et al. also highlight another potentially important finding for the clinical application of metronomic chemotherapy – the use of oral fluoropyrimidines, such as capecitabine, UFT or S1. Indeed, one preclinical study showed that a ‘doublet’ oral combination of metronomic UFT and metronomic cyclophosphamide had striking therapeutic effects in a new model of advanced visceral human metastatic breast cancer in immunodeficient mice [23]. Given the use of cyclophosphamide in most published metronomic chemotherapy trial reports, as discussed above, the doublet combination of cyclophosphamide with UFT, S1, or capecitabine, especially when combined with an antiangiogenic drug such as bevacizumab, may be particularly promising, and convenient, for metronomic chemotherapy treatment of certain types of cancer [19], including in the adjuvant setting [24].

The study by Steinbild et al. was not designed to answer some of the questions that will be important for the further development of metronomic capecitabine regimens in particular, and the field of metronomic therapy in general. First, although the DCE-MRI data indicates antiangiogenic effects of capecitabine at the dose of 500 mg bid, this might not be the optimal antiangiogenic dose. Interestingly, Rocca et al. describe clinical activity and excellent tolerance of a regimen of

daily capecitabine 500 mg tid (plus cyclophosphamide (50 mg/day) and bi-weekly bevacizumab) for the treatment of metastatic breast cancer [19]. With respect to dosing, the analysis of circulating endothelial (progenitor) cells or intra-patient dose-escalation up to the ‘individualized maximum repeatable dose’ have been proposed, but further refinement is clearly needed [25, 26]. Second, while COX-2 inhibitors have been previously studied in combination with metronomic chemotherapy [16, 27, 28] the benefit of such a combination remains to be demonstrated in a randomized trial. In fact, not all agents with antiangiogenic activity can be expected to synergize with metronomic regimens, as has been shown for thalidomide and minocycline [11, 28]. The choice of combination partners might also be guided by the safety profile of such agents, the risk of pharmacokinetic/dynamic interference, the ease of administration, and costs. Third, similar to other anti-cancer therapies, criteria are needed to define which patients are most likely to benefit from metronomic therapies. This might not only include aspects related to the individual patient, but also the clinical context (e.g., adjuvant versus palliative disease setting; bulky disease versus residual disease following induction therapy; integration with other treatment modalities, etc.) and the choice of cytotoxic drug. Finally, better tools are needed to monitor the antiangiogenic effects of metronomic regimens.

The first 5 years of clinical experience with metronomic regimens, including the study by Steinbild et al., have provided us with a body of information to begin tackling these challenges. Hopefully in the near future phase III data will better define the role of this antiangiogenic treatment approach compared to drugs such as bevacizumab, sunitinib and sorafenib, and how it may be best integrated with the latter biologic agents or with other types of biologic agents such as letrozole [12], trastuzumab [29], and tumor vaccines/immunotherapy [9].

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