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Mini-review

Metronomic chemotherapy for advanced breast cancer patients

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ABSTRACT

Metronomic chemotherapy refers to the minimum biologically effective dose of a chemotherapy agent given as a continuous dosing regimen with no prolonged drug-free breaks that leads to antitumor activity. This schedule seems to have not only a direct cytotoxicity on cancer cells but also an effect on the tumor microenvironment by inhibiting tumor angiogenesis and modulating immune response.

Metronomic chemotherapy was widely investigated in patients with breast cancer. The results of these studies showed that this strategy is not only effective but has a low toxicity profile too, proposing as a promising strategy for breast cancer patients. In this review we summarize the results of Phase II and III studies evaluating metronomic therapy in metastatic breast cancer.

Introduction

Metastatic breast cancer (MBC) is an incurable disease and patients are expected to have a life-span/expectancy ranging between 6 months and 2 years according to the different expression of hormone receptors and Human Epidermal Growth Factor Receptor 2 (HER2) [1].

Different strategies can be efficaciously used to reach disease control, such as chemotherapy, endocrine therapy and more recently therapy with target agents.

Nevertheless, despite the unequivocal improvement in overall survival (OS) observed in the last decades, mainly related to the contributions of various therapies rather than to a single drug or regimen, metastatic disease remains the primary cause of death in the majority of patients with breast cancer.

So far, in the last years the focus of clinicians and researchers has moved to the aim of prolonging disease control, which ultimately translates into an improvement in overall survival [2].

In this context, metronomic chemotherapy could represent one of the most promising strategies to reach this goal, considering that the main peculiarity of this treatment is the use of doses well below the Maximum Tolerated Dose (MTD), without significant bone marrow toxicity and for this reason the ideal therapy to be administered for a long period of time.

The present article presents an overview of the literature data available as of today relatively to metronomic chemotherapy used as single agent or in combination with other chemotherapy drugs, endocrine treatments or target agents, in order to offer an updated scenario to clinicians and allow them to better identify potential patients for this kind of treatment.

Metronomic chemotherapy: a long way to define the right dose

The emergence of molecular targeted agents in oncology has not only revolutionized the care of cancer patients, but also changed the daily practice of medical oncologists. Molecular targeted agents indeed often differ from traditional cytotoxic agents due to their administration schedules and routes, their toxicity profiles and their antitumor activity [3]. For some aspects, the development of metronomic chemotherapy is quite similar to the one of targeted agents: rather than a direct antitumor effect, metronomic chemotherapy mainly exerts indirect effects on tumor cells but also on their microenvironment by inhibiting tumor angiogenesis, stimulating anticancer immune response and acting on stromal tissue [4] and could therefore be considered a multi-target therapy itself. In contrast to conventional, pulsatile, maximum tolerated dose (MTD)

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chemotherapy, the main primary target of metronomic chemotherapy is the tumor's neovasculature [5]. This is the main reason why the selection of the right dose cannot be done in the classical way, but requires the identification of a biomarker. Despite promising preliminary results presented in different clinical studies using mostly oral metronomic chemotherapy-based regimens [6–8], few data were available for a long time regarding the right dose of the different drugs to be used in the metronomic administration. So far, the undeniable advantages of metronomic chemotherapy observed in clinical trials, such as the low toxicity, the high efficacy and the possibility to enhance some mechanisms of specific target agents, have been compromised by the empiricism associated with the determination of the optimal biologic dose (OBD). In a milestone paper, Shaked et al. [9], using 4 distinct metronomic chemotherapy regimens in 4 different preclinical tumor models, have defined OBD as the dose able to cause maximum reduction in the tumor volume with no or minimal toxicity. The authors further assessed that OBD were 20 mg/kg for cyclophosphamide (CTX) daily, 0.33 mg/kg for vinblastine, 9 mg/kg for vinorelbine (VNR) and 1 mg/kg for cisplatin. They further established that each OBD was strikingly correlated with the maximum reduction in viable peripheral blood circulating vascular endothelial growth factor receptor 2-positive (VEGFR-2^+) endothelial precursors. Thanks to the results of this study and the possibility to convert the drug dosage from one animal species to another by using the body surface area normalization method [10], it is now possible to design metronomic chemotherapy trials, being sure to use the right dose based on the specific biological effect.

The most favorite compounds for metronomic administration are those administered orally, due to the potential long-term use of this treatment.

In this context, the most studied drugs for metronomic chemotherapy in advanced breast cancer are CTX, methotrexate (MTX), capecitabine (CAPE) and oral VNR.

Different metronomic drug concentrations and schedules might affect different prevalent mechanisms of antitumor action, which suggest that therapy protocols could be selected on the basis of different prevalent effects.

However, the lack of well-established pharmacokinetic profiles represents now the most serious clinical limitation when adopting metronomic chemotherapy regimens. Key aspects for future development of these regimens include for example the optimal steady-state Concentration (C_{SS}), at which both the antiangiogenic and the immunologically mediated mechanisms prevail with a minimal level of low-grade adverse drug reactions [11].

Metronomic chemotherapy for advanced breast cancer: overview of the last ten years of publication

A great number of Phase II studies have been published starting from mid-2000s, showing an increasing interest of clinicians on this topic [12]. Among the 80 publications selected for the systematic literature analysis by Lien and colleagues, 21 trials covered the topic of breast cancer involving 1135 patients. The authors identified 107 treatment regimens with at least one metronomic drug, being CTX, CAPE, etoposide and VNR the most frequently used. The mean Response Rate (RR) of the pooled treatment regimens was 26%, with a mean Disease Control Rate (DCR) of 56.3%. Median duration of response was 4.6 months on average. This systematic literature review, even if not focused on breast cancer patients, confirmed that severe side-effects are rare, being observed in less than 5% of patients and the treatment-associated fatalities are very rare (0.4%) too, despite the fact that most study patients had an advanced disease, refractory to often multiple prior conventional systemic therapies. Regarding efficacy, the authors did not observe any statistical association between DCR and Relative Dose Intensity ($p = 0.68$), Dosing Density ($p = 0.73$), regimen type ($p = 0.73$), cancer type ($p = 0.88$) or metronomic drug(s) used ($p = 0.37$).

What stands out for its absence in the recent literature is the complete lack of randomized Phase III trials, which are now strongly recommended before adopting metronomic strategy in the daily practice.

Metronomic chemotherapy and endocrine treatment: what evidence?

One of the first and more interesting trials, which studied the combination of a metronomic chemotherapy regimen in combination with an endocrine drug was the randomized Phase II study done by Bottini et al., in 2006 [13]: the trial aimed to investigate the activity of letrozole, in combination or not with oral metronomic CTX, as primary systemic treatment in a group of 114 elderly breast cancer patients. Patients received letrozole (2.5 mg daily for 6 months) or a combination of letrozole plus oral CTX (50 mg/daily for 6 months). Overall response rates (ORRs) were 71.9% (95% CI, 60.0–83.8) and 87.7% (95% CI, 78.6–96.2), respectively. The authors concluded that both letrozole and letrozole plus CTX treatments appeared active as primary therapy in elderly breast cancer patients. Considering the potential antiangiogenic effect of metronomic schedule of CTX, they warranted a further testing in a randomized Phase III trial, at the moment never conducted.

In a Phase II trial, Licchetta et al. [14] evaluated the safety and the antitumor activity of the metronomic chemo-hormonal therapy with CTX (50 mg/daily day 1–21 q28) and megestrol acetate (80 mg twice a day) in patients with metastatic pretreated breast cancer. ORR was 31.0%, DCR 41.3%, median time to progression (TTP) 7.4 months (CI 95%, 3.8–10.88, range 1–48 months) and median OS 13.4 months (CI 95%, 7.24–17.18, range 1–53 months). The regimen was active and well tolerated.

More recently, Schwartzberg et al. investigated the efficacy and toxicity of the combination of fulvestrant and low dose metronomic CAPE depending on the patient's weight (1500 mg/daily if the weight was less than 80 kg or 2000 mg/daily if it was more than 80 kg) in 41 hormone receptors positive (HR +ve), metastatic breast cancer patients [15]. They received fulvestrant loading dose 500 mg on day 1, 250 mg on days 15 and 29 followed by 250 mg every 28 days along with continuous oral CAPE. Median PFS was 14.9 months (95% confidence interval [CI], 7.26 – upper limit [UL] not estimated) and median TTP was 26.9 months (95% CI, 7.26 – UL not estimated). Median OS was 28.65 months (95% CI, 23.95 – UL not estimated). Treatment was well tolerated with <10% Grade 3 palmar-plantar erythrodysesthesia. Overall, the most frequent adverse events were palmar-plantar erythrodysesthesia, fatigue, and nausea. The combination of fulvestrant with metronomic CAPE demonstrated substantial activity in HR +ve MBC and was well tolerated.

Data regarding the combination of endocrine therapy and metronomic strategies are summarized in Table 1.

Are there sufficient data at the moment to suggest the use of endocrine therapy in combination with metronomic chemotherapy in the clinical practice?

It is our opinion that this strategy could not be adopted as routine clinical practice in the daily treatment of metastatic breast cancer patients, due to the following considerations: 1) there is no evidence that the addition of chemotherapy to endocrine therapy, when patients are still considered endocrine-sensitive, could induce a substantial benefit in terms of clinical activity; 2) as long as HR +ve breast cancers are endocrine sensitive, patients should be treated with endocrine treatment alone, or at least in combination with targeted agents, as stated in various consensus conferences [16].