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Metronomic therapy and breast cancer: A systematic review

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ABSTRACT

Metronomic therapy (MT) refers to repetitive, low doses of chemotherapy drugs.

MT exerts an effect not only on tumour cells, but also on their microenvironment. In particular, the low-dose schedule compromises the repairing process of endothelial cells, leading to an anti-angiogenic effect.

In addition to the anti-angiogenic effect, MT could have an immunological action through the restoration of the anticancer effect of the immune system and induction of tumour dormancy. Consequently the association of targeted therapy with anti-angiogenic properties or specific immunologic drugs could enhance the efficacy of MT. During the past 15 years, several studies have been published evaluating the metronomic strategy in breast cancer. We conducted a systematic review of the results of phase I, II and III studies testing MT in breast cancer patients. The analyses included the efficacy and toxicity data of MT, and the future development of this strategy in breast cancer are also discussed.

The systematic review presented here suggests that MT is a treatment option for breast cancer patients, has a low toxicity profile, efficacy in most patients and has potentially significant cost-effective advantages for public health.

Introduction

Metastatic breast cancer (MBC) is generally an incurable disease. The median survival rate of the patient with metastasis is within the range of 3 years [1]. However, some patients with metastatic involvement live several years after diagnosis [2]. In such a scenario, one would wish to consider a therapeutic strategy with a low toxicity profile, good tumor control and economically viable for the healthcare system. Moreover, a therapeutic program of metastatic disease must be driven by multiple considerations, including not only the heterogeneity of breast cancer subtypes but also the heterogeneity of breast cancer patients, taking into account patient age, preferences, frailty, co-morbidities and possible contraindications to more intensive regimens.

Although there is as yet no universally accepted definition, the metronomic schedule refers to repetitive, low doses of chemotherapy drugs administered at close regular intervals with no extended interruption. The term "metronomic" was used for the first time by Hanahan et al. commenting on two papers on the use of continuous, low dose chemotherapy in cancer treatment [3–5].

Metronomic therapy (MT) has an effect not only on tumor cells, but also on their microenvironment. In particular, the low-dose schedule compromises the repairing process of endothelial cells, leading to an anti-angiogenic effect [4]. In addition to the anti-angiogenic effect, MT could exert an immunological action through the restoration of the anticancer effect of the immune system and induction of tumor dormancy [6]. Over the years, different drugs have been tested with a metronomic schedule in different types of tumors [7–8]. Moreover, a hybrid approach including higher-doses of chemotherapy with planned treatment breaks combined with metronomic drugs has also been evaluated.

We conducted a systematic review of the results of phase I, II and III studies testing MT in breast cancer patients. The Medline database was searched for fully published articles using the key words 'metronomic' and 'chemotherapy' and 'cancer' or 'breast'. The search was restricted to the English language. Exclusion criteria included the following: pediatric trials, studies applying MT in all tumor sites, not only the breast, editorials, case reports and review articles. For studies with multiple presentations and/or publications, only the latest versions were included in the analysis.

Metronomic therapy in breast cancer patients

The first study on MT in metastatic breast cancer was published in 2002 [9].

From 2002 the number of published papers has increased, especially in the most recent years, as reported in Fig. 1. Patients

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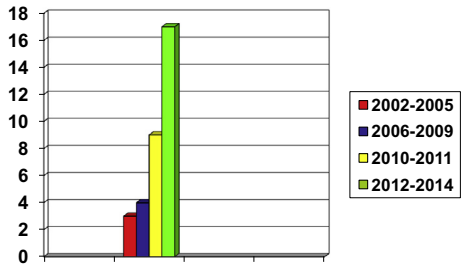

Fig. 1. Number of published papers over the years.

included in early trials who were candidates for MT were frail or heavily pretreated while the most recent trials also included patients at the first or second line of therapy.

The results from a national survey conducted in Italy indicated a significant interest in MT, with 72% of responders having been administered a regimen of MT at least once [10]. This interest is confirmed by the higher number of publications on MT reporting Italian studies, as shown in Fig. 2.

The largest number of published studies are phase II trials with a relatively low of number of patients as reported in Table 1.

In the development of the MT strategy, several drugs were tested, in particular those with an oral formulation. Nevertheless, the identification of the optimal dosage has yet to be established [11].

The classical metronomic drug, widely clinically tested, is cyclophosphamide.

Initial studies reported the efficacy data of single or combined metronomic chemotherapy drugs.

Subsequent studies evaluated how to enhance the metronomic activity by an association with hormonal therapy, biological drugs or other agents.

Single or combined metronomic chemotherapy in breast cancer patients

The first trial on MT for MBC patients was conducted by Colleoni et al.

The authors analyzed, in 63 pretreated MBC patients, a combination of metronomic chemotherapy with low-dose oral cyclophosphamide, 50 mg daily, and methotrexate, 2.5 mg twice daily, 2 days per week. This regimen was active and well tolerated, yielding an objective response rate (ORR) of about 20% and a clinical benefit (CB) (objective response and stable disease for at least 24 weeks) of 31.7%, in the absence of serious toxicity [9].

A few years later, the same authors reported results and long-term follow-up for patients with MBC who obtained prolonged CB (for 12 months or more) with metronomic cyclophosphamide and methotrexate (CM). Of one-hundred and fifty-three patients, 15.7% achieved prolonged CB with a time to progression (TTP) of 21 months [12].

Clinical activity and the absence of severe grades of toxicity of metronomic cyclophosphamide combined or not combined with methotrexate were also confirmed by the study of Miscoria et al.

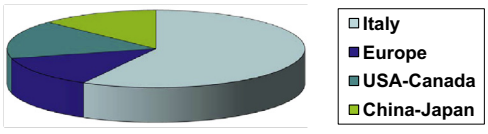

Fig. 2. Number of published papers according to country/region.

and by a retrospective analysis conducted on 61 MBC patients [13–14].

Continuous infusion of 5-fluorouracil (5-FU) has been developed in an attempt to improve efficacy and has been shown to exert antiangiogenic activity in preclinical models. The combination of low dose oral 5-FU with eniluracil is a simpler and convenient alternative to continuous infusion of 5-FU. In the study of Smith et al., 33 untreated MBC patients received oral 5-FU 1.0 mg/m2 with eniluracil 10 mg/m2, both administered twice daily for the first 28 days of each 35-day cycle, continuing until disease progression or unmanageable toxicity. Sixteen partial responses were seen in 29 assessable patients. Seven patients had stable disease for at least 3 months with symptom improvement. Toxicity was mild [15].

Moreover, the oral daily administration of capecitabine mimics the activity of a continuous intravenous infusion of fluorouracil and the pharmacokinetics and toxicity profile render capecitabine particularly suitable for metronomic administration.

In two small randomized trials, continuous use of low dose capecitabine (650 or 800 mg/m2 b.i.d. with no drug-free breaks) proved to be just as effective in MBC patients as did the intermittent use of higher doses (1000 or 1250 mg/m2 b.i.d. days 1–14 every 21 days) [16–17].

Taguchi et al. used a low dose schedule of capecitabine (852 mg/m2 twice daily on days 1–21 of a 28-day cycle) as first-line therapy for 33 MBC patients. The authors reported a median progression-free survival (PFS) of 6.9 months with an overall survival (OS) of 24.8 months, and grade 3 toxicities which included hand and foot syndrome (15%) and neutropenia (6%) [18].

The metronomic schedule of capecitabine was also evaluated in heavily pretreated patients with MBC. Sixty patients received oral capecitabine in a single daily dose of 1500 mg. The CB was 62% and the OS was 17 months. Grade 3–4 adverse events were uncommon [19].

Other studies evaluated the efficacy and safety of an all-oral doublet combination of MT including cyclophosphamide and capecitabine. In the study of Wang et al., 68 anthracycline- and taxane-pretreated MBC patients received 21-day cycles of oral cyclophosphamide (65 mg/m2 daily) and oral capecitabine (1000 mg/m2 twice daily on days 1–14 followed by a 7-day rest period). The median time to progression was 5.2 months and the OS was 16.9 months. The ORR and CB were 30.3% and 53.0% respectively. Treatment was well tolerated, and grade 3 hand–foot syndrome was reported by the 4.4% of patients [20].

The same combination of MT with different dosages was evaluated in the study of Yoshimoto et al. Fifty-one patients received capecitabine 828 mg/m2 twice daily with cyclophosphamide 33 mg/m2 twice daily, days 1–14 every 3 weeks. ORR was 44.4% and the CB was 57.8%. Hematologic toxicity included grade 3 leucopenia (26%) and neutropenia (16%). No grade 3 hand-foot syndrome was reported [21].

Given the availability of an oral formulation and due to its pharmacokinetic profile, vinorelbine can be used with a metronomic schedule.

In the Phase I trial conducted by Briasoulis et al. in advanced cancer, the vinorelbine dose of 50 mg given three times a week was identified as the optimal dose for a metronomic schedule, yielding sustainable antitumor activity without overt toxicity [22].

In 34 elderly patients not pretreated for MBC, vinorelbine was administered at 70 mg/m2, fractionated on days 1, 3, and 5, for 3 weeks on and 1 week off, every 4 weeks. The ORR was 38%. Median PFS and median OS were 7.7 and 15.9 months respectively. The treatment was well tolerated [23].

According to the synergistic activity of the vinorelbine and capecitabine combination, Saridaki et al. conducted a phase I study to identify the metronomic dosage of this doublet, using eight