# ROLE OF METRONOMIC CHEMOTHERAPY IN TREATMENT OF METASTATIC BREAST CANCER

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## ABSTRACT

**Background** When breast cancer has spread (metastasized) to other parts of the body, treatments rarely cure the disease, but they can sometimes reduce symptoms and extend a patient's life beyond the general median survival time of 18 to 24 months.Anticancer chemotherapy is thought to be effective by means of direct cytotoxicity on tumor cells. Alternative mechanisms of efficacy have been ascribed to several common anticancer agents postulating an antiangiogenic activity.Metronomic chemotherapy-the chronic administration of chemotherapy at relatively low, minimally toxic doses on a frequent schedule of administration at close regular intervals, with no prolonged drug-free breaks-is a potentially novel approach to the control of advanced cancer disease.It is thought to work primarily through antiangiogenic mechanisms

**Patients and Methods:** We evaluated the clinical efficacy and toxicity of low-dose oral methotrexate(MTX) and cyclophosphamide( CTX) in patients with metastatic breast cancer. MTX was administered 2.5 mg b.d on days 1 and 2 each week and CTX 50 mg/day administered continuously for 2 years. **Results:** CR was observed in 6.7% ,PR in 33.3% with mean time to progression 8 months Grade 2 leucopenia only in 10% of cases, grade 1-2 nausea and vomiting in 20%of cases **conclusion**: Low-dose cyclophosphamide- methotrexate 'metronomic' therapy was assessed to be an effective therapy with minimal toxicity for palliative treatment in metastatic breast caner.

**Key word:** Metronomic – breast cancer- metastatic

## INTRODUCTION

Metastatic breast cancer (MBC) occurs in 20-30% of women with breast cancer and is an incurable disease. Treatment is palliative and directed to prolong survival, decrease symptoms and improve patients' quality of life (1) Despite advances that have been achieved in the treatment of breast cancer, the prognosis for patients with metastatic breast cancer (MBC) remains poor, with a median survival of 2–4 years (2) . No global consensus exists regarding the ideal treatment strategy for MBC, and no guidelines are available. The selection of treatment depends on several factors, including patient and tumor characteristics, aggressiveness of the disease, response to previous therapies, time since last exposure, agents used in the past, and cumulative doses (3).

cytotoxic chemotherapy is indicated for patients with hormone receptor-negative disease or for hormone receptor-positive disease whose disease has became resistant to endocrine therapy and also indicated for patients with symptomatic visceral disease (1,4). A rapidly growing pool of effective treatment options for MBC has increased response rates, progression-free survival(PFS), and/or overall survival (OS)(5). Several chemotherapeutic agents are used, including 5-fluorouracil, taxanes, platinum analogs, vinorelbine, capecitabine and gemcitabine, but a universal standard regimen has not yet been established (6)The taxanes (in particular docetaxel) were considered to be the most effective second-line treatment of MBC in patients failing nthracycline treatment (7). These agents when used at the maximum tolerated doses (MTDs) may be difficult to administer and are often associated with severe side-effects, sometimes requiring hospitalization.So there is a great need for the introduction of new chemotherapeutic era having improved or at least equivalent efficacy but reduced toxicity. Such

approaches could include using less toxic drugs, more convenient routes of administration (e.g. oral) and home-based (outpatient) rather than hospital-based therapies(8).

Certain oral chemotherapy drugs can be used as antiangiogenic agents when administered at low doses at regular, frequent intervals. This type of treatment, called metronomic chemotherapy, offers the advantages of more convenient dosing and less debilitating side effects than conventional infusion chemotherapy (9). Unlike MTD chemotherapy that presumably mainly targets (proliferating) tumor cells, frequent or continuous low-dose chemotherapy appears to inhibit preferentially the endothelial cell activity of the tumors growing vasculature (10). Metronomic chemotherapy has emerged as a useful adjuvant to therapeutic strategies intended to boost the tumor-killing capacity of NK( natural killer)cells and T-cytotoxic cells (11,12). The oral chemotherapy drugs cyclophosphamide and methotrexate are often used together as metronomic therapy for breast cancer. In a clinical study that tested this combination in metastatic breast cancer patients, 21% experienced at least some tumor shrinkage(9). Initial data of metronomic chemotherapy indicates that continuously low-dose cyclophosphamide and methotrexate is minimally toxic and effective in heavily pretreated breast cancer patients(1). The aim of this study was to evaluate oral chemotherapy drugs cyclophosphamide and methotrexate ,together as metronomic therapy,in management of patients with metastatic breast cancer .

## PATIENTS AND METHODS

Thirty cases of breast cancer patients who were previously treated in Clinical Oncology Department Zagazig University Hospitals ; had histologically confirmed to be metastatic breast carcinoma (MBC) that had progressed, after a first line chemotherapy for metastatic disease or no clinical benefit after three consecutive endocrine regimens ;those patients had been included in our study after written concent where all patients were subjected to complete clinical examination ,laboratory investigation including complete blood picture ,liver and kidney function tests ,tumor marker CA15-3 ,and radiological investigation including pelviabdominal & chest CT and bone scan . Oral cyclophosphamide was administered at a dose of 50 mg/day, every day and methotrexate was administered on days 1 and 2, orally (2-2.5 mg/day) every week ;this regimen of treatment was given to the patients with no breaks for up to 2 years. Follow up of the cases during two years was every two weeks for laboratory tests, subjective response and clinical evaluation; and every three months as regard radiological examination. All cases was evaluated as regard survival and response (complete response ,partial response ,stable disease ,and progressive disease)

## RESULTS

From July 2007 to December 2008 , thirty female patients with metastatic breast cancer was included in this study where they received continuous low doses of cyclophosphamide and methotrexate. Age ranged between 30 and 70 years (mean 55) table 1 shows patients criteria .

Among the 30 evaluable patients, there were 2 (6.7%) has got complete remissions (CR), 10(33.3%) has got partial remissions (PR) and the disease was stable> 6 months in 9 (30%) while the disease has progressed < 6months in 9(30%) of cases . CR was observed in cases with single metastatic site after 10 months of treatment and remission continuous for another 14 month with no progression. Even in cases who has got progressive disease it occurs slowly (3-14 months) mean time to progression was 8 month . As regard treatment toxicities only grade 2 leucopenia was observed in 3(10%) of cases . Grade 1,2 nausea & vomiting was observed in 6(20%)cases and was managed medically ,low grade fatigue was the main complain of 80% of cases. 4 cases died ,1-3 months after disease progression .

**Table(1) :** Patients characterstics

| | No. | % | range | mean |
|---|---|---|---|---|
| Age (years) | | | 30-70 | 55 |
| Tumor marker (CA15-3) | | | | |
| Hormone receptor | | | | |
| Positive | 22 | 73.3 | | |
| Negative | 8 | 26.7 | | |
| Metastatic site | | | | |
| Bone | 17 | 56.7 | | |
| Liver | 14 | 46.7 | | |
| Lung | 15 | 50 | | |
| Performance status (ECOG) | | | | |
| II | 12 | 40 | | |
| III | 15 | 50 | | |
| IV | 3 | 10 | | |
| Number of metastatic site | | | | |
| 1 site | 10 | 33.3 | | |
| >1site | 20 | 66.7 | | |
| Regimen for metastatic disease | | | | |
| 1Cth regimen | 18 | 60 | | |
| > 1 Cth regimen | 6 | 20 | | |
| 3 failed endocrine regimen | 6 | 20 | | |

**Table (2) :** Response rate

| Response | No. | % | range | mean |
|---|---|---|---|---|
| Complete response | 2 | 6.7 | | |
| Partial response | 10 | 33.3 | | |
| Stable disease | 9 | 30 | | |
| Progressive disease | 9 | 30 | | |
| Time to progression | | | 3-14 month | 8 |

## DISCUSSION

While less than 10% of newly diagnosed breast cancer patients present with locally advanced or metastatic disease(13) ;nearly 30% to 50% of patients diagnosed at earlier stages will subsequently develop metastatic disease, despite the use of adjuvant endocrine and chemotherapy regimens(14). For a long time, most advanced breast cancer chemotherapy

included drugs from the anthracycline family, such as doxorubicin and epirubicin Then during the 1990s, members of a family of drugs called the taxanes – which include docetaxel and paclitaxel– were shown to be effective in the first-line (initial) treatment of advanced breast cancer as well as in the treatment of women who had developed resistance to the anthracyclines(15). Once first-line treatment of MBC has failed, management becomes even more challenging. The likelihood of response
subsequently decreases by approximately one-half with each prior regimen the patient has received as either adjuvant or MBC treatment. Response rates may be as high as 60%–80% with first-line treatment in patients who have not received adjuvant therapy and are 30% and 15%, respectively, in patients who have received two or three prior regimens(16).Breast cancer is considered incurable following metastasis, and therapeutic goals are palliative in nature. Moreover, earlier and more aggressive use of cytotoxic regimens has increased the incidence of treatment-resistant metastatic disease(17)
When the tumors were known to be resistant to the chemotherapeutic drugs . The solution to this problem was that the chemotherapy was used to slow or prevent angiogenesis. The endothelial cells engaged in angiogenesis are extremely sensitive to killing by the chemotherapeutic drugs, much more so than most cancer cells. Thus, when low-dose chemotherapy is administered on a daily schedule (known as "metronomic" because it is regular and even like the beat of a metronome) the continual death of endothelial cells attempting to form new blood vessels can substantially disrupt the angiogenic process, slowing it down (18) Although metronomic long-term low-dose chemotherapy (with no prolonged drug-free break periods) has been uncommon in adult oncology practice (19) ,but many attempts; such as Colleoni et al(20) who performed a non-randomized phase II clinical trial for the treatment of metastatic breast cancer patients, and reported an impressive efficacy using this generally well tolerated protocol. Cyclophosphamide was administered at a dose of 50 mg/day, every day, with no breaks for up to 2 years and methotrexate was administered on days 1 and 2, orally (2-2.5mg/day) every week. Encouragingly, the overall clinical benefit (CR,PR andSD) was 31.7% . This was achieved in the absence of any serious adverse events in 64 patients.
On the same way many clinical trials were perfopmed using, metronomic chemotherapy alone(21-23) or in combination with letrozole (24) trastuzumab(25) or bevacizumab (26,27);concluded that those regimens were effective ,with minimal toxic effects for either primary systemic or palliative treatment of advanced, metastatic and/or resistant breast cancer patients. Average response rates complete response (CR) plus partial response (PR),and overall clinical benefit (CR + PR + stable disease [SD] >6 months) of metronomic chemotherapy reported in these studies were 39% (range 12–88%) and 57% (range 24–93%), respectively. Following metronomic chemotherapy with cyclophosphamide and metho trexate in combination with trastuzumab, a clinical benefit of 46% was reported for all patients, and 27% in the subgroup of patients that were already resistant to trastuzumab(25),there was coincidence between the results of this small, non- randomized clinical trial and a pre-clinical study of metronomic cyclophosphamide in combination with trastuzumab(28); these results suggest that this combination could possibly prevent breast cancer relapse by delaying and/or overcoming acquired resistance to trastuzumab.
Two recent trials(1) with newer cytotoxic agents showed controversial results; whereas one study concluded that the policy of prolonging treatment in chemotherapy-sensitive patients, after aggressive modern combination chemotherapy cannot be recommended for women with MBC, the other study showed

that maintenance therapy with pegylated liposomal doxorubicin significantly prolonged time to progression in MBC patients after first-line chemotherapy without significant clinical toxicity. Results of our study is in accordance with the above mentioned studies response rate (CR+PR)was 40% when we add stable disease >6 months the clinical benefit was 70%. Treatment toxicities was tolerable and of mild degree and could be managed medically . In conclusion maintenance chemotherapy is a reasonable strategy that prolongs time to progression in patients with MBC. However, this benefit should be considered together with toxicities of treatment and the patient's preference(1).Pre-clinical and clinical evidence supports metronomic chemotherapy as an efficient tool to fight certain types of cancer. However, the development of metronomic chemo therapy faces *terra incognita*. it seems very unlikely that a single metronomic regimen will have universal efficacy and the optimal combination regimens of metronomic chemotherapy remain to be determined for any given tumor type. Future preclinical and clinical studies will need to define the best agents to use according to tumor type, the number of agents to be incorporated, the doses of each agent to be used alone or in combi nation, and the timing of drug administration(29).

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