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Oral Metronomic Chemo-Hormonal-Therapy of Metastatic Breast Cancer with Cyclophosphamide and Megestrol Acetate

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Summary

Metronomic chemotherapy is an anticancer strategy which uses conventional cytotoxic drugs administered at very low dose in close intervals. We have designed a phase II trial to investigate the safety and antitumor activity of the newest metronomic chemo-hormonal-therapy with daily cyclophosphamide and twice daily megestrol acetate (mCM regimen) in patients with metastatic pretreated breast cancer. Twenty-nine pretreated post-menopausal patients with multiple metastatic sites were enrolled. Four patients had a triple negative status, nineteen a positive hormonal ER

INTRODUCTION

Breast cancer is a major health problem with more than 1,000,000 new cases and 370,000 deaths yearly worldwide, and 25% of patients who relapse in spite of early diagnosis, and appropriate and specific treatment. Today a very large armamentarium of drugs is available for the palliative treatment of patients with relapse and/or metastatic disease. These treatments, which include mon- and multidrug chemotherapy, hormonal manipulation and biological agents, are very active and have the ability to prolong a patient's survival and increase clinical benefit.¹ Their use in selected cases is currently justified in patients with a good performance status who have undergone two or three treatment lines.¹

However, the choice of the specific treatment strategy and

However, the choice of the specific treatment strategy and drugs is mainly based on empirical considerations since very few randomized studies have been completed in this category of patients. It is common opinion that antiharracyclines, cyclophosphamide, taxanes in mono-chemotherapy or hormonal manipulation with megestrole acetate (MA)² represent some of the best treatment options with an average response rate of 20-30% and a time to tumor progression (TTP) and an overall survival (SO) of 3-4 and 7-8 months, respectively³⁻⁵. The main concern for these heavily treated patients regards their performance status, bone marrow reserve and selective drug-induced organ failure which strongly limit their ability to sustain a full-dose treatment regimen. Recently we have evidence that it is possible to administer

Recently we have evidence that it is possible to administer common cytotoxic drugs at a much lower dosage by designing treatment schedules with close and regular administration intervals (daily, weekly, biweekly) until tumor regression⁶. This strategy, designated as metronomic chemotherapy, has been tested in preclinical models and clinical trials, showing minimal toxicity, direct antitumor activity, anti-angiogenic effect, malignant phenotype attenuation (by inducing gene modulation and epigenetic effects) and immunomodulation^{7,8}. Many cytotoxic drugs like cyclophosphamide (CTX)⁹, etoposide, vinorel-

Study design

PATIENTS AND METHODS

bine and taxanes, used on a metronomic schedule, are able to kill endothelial cell precursors, immunosuppressive myeloid precursors and immunoregulatory T cells, thus acquiring a powerful anti-angiogenic and immunomodulating potential¹⁰. Metronomic (weekly or daily) chemotherapy with different drugs has been tested in a number of trials where results demonstrate antitumor activity in breast, prostate, colorectal and non-small cell lung cancer patients¹¹⁻¹³. Based on the results of the previous studies which demonstrated the efficacy of either CTX and MA alone, we have investigated the antitumor activity and toxicity of the newest metronomic chemo-hormonal regimen (mCM) combining oral daily CTX and oral twice-daily MA in heavily pretreated metastatic breast cancer patients.

Key words: Metastatic breast cancer, metronomic chemo-hormonal-therapy, megestrol acetate.

This study was designed as an open label mono-institutional two-step phase II trial to investigate the toxicity and activity of a new schedule of oral chemo-hormonal-therapy combining daily CTX and twice-daily MA in metastatic breast cancer patients. The protocol was approved by our institutional ethical committee. All patients signed an informed consent.

The study was aimed to test the hypothesis that the mCM regimen is active in the treatment of patients with metastatic breast cancer relapsed after at least two treatment lines. For this purpose, at least 25 patients were required in order to maintain alpha and beta errors of 5% and 20%, respectively. By taking into consideration that the average response rate to the pharmacological treatment of this kind of patient is less than 25%, the study could be withdrawn if no objective response was observed in at least two of the first 10 (20%) consecutively enrolled patients. All measures were taken to minimize any pain or discomfort to patients.

Treatment schedule and clinical assessments

All the patients enrolled received treatment until disease progression with oral CTX (50 mg/daily from day 1 to 21/q28) and fractionated MA (80 mg twice a day from day 1-28).

Before treatment, a complete history was made of all patients, who also underwent a physical examination, complete blood count, serum chemistry tests, and complete disease staging by means of chest X-rays, brain, chest and abdominal computed tomography (CT), and liver and pelvic ultrasound scan. The staging examinations were repeated every 2 months, whereas full blood counts, biochemistry profile, liver function tests, electrocardiography (ECG), and a urine analysis were performed every 3 weeks.

Toxicity and response criteria

This was an intention-to-treat study and for this reason all of the eligible patients were evaluable for response, toxicity, time-to-progression (TTP) and overall survival (OS). All of the patients received treatment until disease progression or unacceptable toxicity. OS was measured from the date of diagnosis to the date of death or the date of the last follow-up examination. TTP was evaluated from the enrolment to the demonstration of disease progression or the date of the last follow-up examination. Response was assessed according to RECIST criteria, toxicity was reported according to CTCAE v 3.0.

RESULTS

Demography

Twenty-nine post-menopausal patients (mean age 72.3 years with a 45-86 range) with advanced breast cancer were enrolled in the study. Eighteen patients were older than 70. Twenty-six had received previous breast surgery, while all of them presented an ECOG performance status ≤ 3 and had received a previous line of chemotherapy and/or hormonal manipulation (7, one line; 7, two lines; 11, three or more lines) for advanced disease. When enrolled in the study, the 7 patients who had received just one previous chemotherapy line for advanced disease, had also received adjuvant chemotherapy and hormonal therapy and presented a poor performance status that prevented the use of more aggressive treatments. Twenty-three patients had ductal carcinoma, 4 lobular carcinoma, and 2 undifferentiated carcinoma. The most common histological grades were 2 and 3. The ER/PgR status was considered positive in 19 cases, while ERB-B2 was over-expressed only in 3 cases. In the study there were 4 patients with a triple negative status.

Twenty patients showed metastatic sites in the bone, 10 in the liver, 10 in the lung, 8 in the lymph nodes, and 7 in other sites (soft tissues, peritoneum, pleura etc.) (Table 1).

Toxicity

The treatment was very well tolerated and no grade 4 adverse events or treatment-related deaths were observed during the study. Hematological toxicity was the most common event. Grade 2 diarrhea and transient transaminase rise was observed in 5 patients.

Activity

The regimen was very active with an objective response (OR) of 31.0% (including 2 complete and 6 partial responses), disease stabilization (SD) of 10.3% and an overall disease control rate (which includes partial and complete responses and stable disease) of 41.3%. We observed a mean TTP of 7.4 months (CI 95%, 3.8-10.88, range 1-48 months) and a mean OS of 13.4 months (CI 95%, 7.24-17.18, range 1-53 months) (Table 2). Objective responses were also observed in 5 patients with ER-status.

TABLE 1 - Demography.

N. of Patients		29 females
Median Age		72.3 (range 45-86)
Histology	Ductal carcinoma	23
	Lobular carcinoma	4
	Undifferentiated	2
Grading	G1	1
	G2	16
	G3	7
Stage	IV	29
Metastatic Site	Bone	20
	Liver	10
	Nodes	8
	Lung	10
	Other	7
Surgery	Yes	26
	No	3
Hormonal Status	Positive	19
	Negative	10
Erb-B2	Positive	3
	Negative	16
Ki67	<10	13
	>10	16
Adjuvant Therapy	Hormonal therapy	5
	Chemo/hormonal therapy	12
	Chemotherapy	12
Previous Line	1 previous line	7
	2 previous lines	7
	3/+ previous lines	11

DISCUSSION

This is the first study which investigates an oral metronomic chemo-hormonal therapy regimen (mCM) with daily CTX and twice-daily fractionated MA, designed to combine the specific cytotoxic and biological activities of the two drugs which include: direct tumor cell killing and inhibition of tumor cell proliferation by either drugs, inflammatory cytokine inhibition by MA and anti-angiogenetic and immunomodulating activity of both drugs, mainly derived from the "metronomic" administration modality (low dose, tight intervals, prolonged treatments). In our study the mCM regimen was well tolerated, active and with a very low cost in metastatic breast cancer patients who had been largely pretreated with either chemotherapy and/or hormonal manipulation, some of whom were elderly or presented a very poor performance status.

Our findings are in line with the results of clinical trials in

TABLE 2 - Clinical responses.

Total Evaluable Number	PR	CR	SD	RR (PR + CR)	DC (PR + SD + CR)	PD
29	7	2	3	9	12	11
100%	24.13%	6.89%	10.34%	31.03%	41.37%	37.93%

CR = complete response; PR = partial response; SD = stable disease; DC = disease control; PD = progressive disease; RR = response rate.
 Mean time to tumor progression: 7.4 months (CI 95%, 3.8-10.8, range 1-48 months)
 Mean overall survival: 13.4 months (CI 95%, 7.24-17.18, range 1-53 months)

pretreated patients with metastatic breast cancer, which suggest that this subset of patients may benefit from treatment with hormonal manipulation and/or mono-poly-chemotherapy.¹⁴ Several regimens including antihypertensive-based combinations, docetaxel plus vinorelbine, or mitomycin C and fluorouracil have shown antitumor activity of 20-25% response rate with a median TTP and OS of 4-5 and 10-11 months, respectively. These treatments were however, associated with significant toxicity including grade 3/4 neutropenia in more than 30% of the patients, neutropenic fever in 10-15% and grade 3/4 mucositis in 10-15%.¹⁵⁻¹⁸ The results of the majority of these studies suggest that a good performance status and the responsiveness to a first/second chemotherapy line are two important parameters in predicting a good treatment response to subsequent treatment lines.

In our study, neither ER/PgR status nor the number of previous treatment lines were correlated with response rate, however, many more patients would be necessary to evaluate the predictive and prognostic value of these parameters.

Our mCM regimen is based on the combination of two known antitumor agents active in the treatment of advanced breast cancer. MA in particular, was the first progestational agent to be active in the hormonal therapy of advanced breast cancer and many other malignancies due to its progestational potency, excellent safety profile and powerful anti-cachectic activity. As single-agent therapy in ER/PgR positive metastatic breast cancer patients, the average overall response rate to MA used at higher doses (320-480 mg) was equivalent to that reported for tamoxifen which had a better safety profile.¹⁹ MA however, exerts a unique anti-anorexia and anti-cachexia effect which can lead to significant weight gain and clinical benefit also in hormone receptor ER/PgR-negative patients. This feature of MA seems to be related to its ability to down-regulate the production of inflammatory cytokines (like IL-1, IL-6, IL-5) and pro-angiogenic molecules (VEGF, PDGF, FGF etc) associated with the cancer phenotype and which in the long run may be responsible for the occurrence of malignant cachexia.^{20,21} Several studies have clearly shown that MA may be taken into consideration for the treatment of advanced breast cancer patients and that its administration is safe even if it is associated with weight gain, edema (swelling, usually in the feet or hands), breakthrough menstural bleeding or spotting (10-30% of cases). These side effects usually occur when higher blood levels of ME are achieved. In our study, its dosage was fractionated and the drug was administered twice a day at very low dosage (80 mg). In this way, we were able to provide a continuous hormonal effect on the neoplastic cells, associated with a continuous state of inflammatory cytokine inhibition, also avoiding dangerous serum peaks and side effects.

CTX is an alkylating agent frequently recommended and active in breast cancer treatment. It is stable and well absorbed when given orally. This drug has been largely investigated in metronomic and dose-dense modalities showing significant antitumor activity *in vitro* and *in vivo*. CTX is a pro-drug that needs to be activated in the liver and partially in the cancer cells

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by a chemical reaction mediated by p450 cytochrome 22. CTX has shown direct antitumor activity, immunobiological modulation and anti-angiogenic effect. Considering that MA may actively interfere with each one of these points a synergistic interaction may be hypothesized.

In conclusion, the results of this study suggest that the mCM metronomic regimen of chemo-hormonal therapy with CTX and MA is well tolerated and active in largely pretreated metastatic breast cancer patients and deserves to be investigated in larger studies. Additionally, considering the very low cost of the treatment, the mCM regimen deserves to be investigated as maintenance therapy after first-line induction chemotherapy.

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