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CLINICAL TRIAL REPORT

Metronomic oral combination chemotherapy with capecitabine and cyclophosphamide: a phase II study in patients with HER2-negative metastatic breast cancer

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Abstract
Purpose Metronomic combination chemotherapy with the oral fluoropyrimidine doxifluridine/5′-deoxy-5-fluorouridine (5 -DFUR) and oral cyclophosphamide (C) showed promising efficacy in a single-arm study. The oral fluoropyrimidine capecitabine was designed to deliver 5-fluorouracil preferentially to tumors, potentially improving efficacy over doxifluridine. We conducted a phase II multicenter study to evaluate an all-oral XC combination in patients with HER2-negative metastatic breast cancer (MBC).
Materials and methods Patients received capecitabine 828 mg/m^2 twice daily with cyclophosphamide 33 mg/m^2 twice daily, days 1–14 every 3 weeks. The primary endpoint was overall response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety.
Results Between May 2007 and April 2009, 51 patients were enrolled and 45 were included in the efficacy analysis. The median follow-up was 18.1 months. ORR was 44.4% and stable disease (≥24 weeks) was achieved in 13.4%, resulting in a 57.8% clinical benefit response rate. Median PFS was 12.3 months (95% confidence interval: 8.9–18.9 months). Median PFS was 10.7 months in triple-negative disease and 13.2 months in estrogen-receptor positive, HER2-negative disease. The 1- and 2-year OS rates were 86 and 71%, respectively. Median OS has not been reached. Grade 3 adverse events comprised leukopenia (26%), neutropenia (16%), and decreased hemoglobin (2%). There was no grade 3 hand-foot syndrome.
Conclusions Oral XC is an effective first- or second-line therapy for MBC, demonstrating high activity in both luminal A and triple-negative disease with few severe side effects. This metronomic oral combination chemotherapy could be beneficial for the treatment of HER2-negative MBC.

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Introduction

Recent advances in chemotherapy for breast cancer have produced remarkable results in the adjuvant setting [1], but less improvement in the metastatic setting [2]. Regimens including anthracyclines and taxanes are widely used, but metastatic breast cancer (MBC) remains an incurable disease, although a small proportion of patients may achieve long-term disease-free survival [3, 4]. Therefore, the main goal of treatment for MBC is to prolong survival and maintain quality of life (QOL). Standard chemotherapy regimens, based on the concept of maximum tolerated dose (MTD), for front line can achieve relatively high response rates, but do not satisfy the needs of patients in terms of survival and QOL because of the short duration of clinical benefit and the detrimental impact of treatment-related toxicity.

In contrast to standard chemotherapy, low-dose metronomic (LDM) chemotherapy describes the prolonged administration of relatively low doses of cytotoxic agents at short, regular intervals without extended breaks. This therapeutic strategy has become widely recognized following the discovery that some cytostatic agents administered using an LDM schedule have significant antiangiogenic activity. Studies have shown that chronic administration of low-dose chemotherapy, including cyclophosphamide, methotrexate, and other agents, produces apoptosis of endothelial cells in the tumor microvasculature, resulting in impairment of repair processes and a reduction in the level of viable circulating endothelial progenitor cells [5]. LDM chemotherapy may provide a strategy to achieve long-term disease control by maintaining tumor dormancy and potentially extending survival, with only mild side effects [6]. The antiangiogenic activity of LDM chemotherapy may also contribute to a decreased susceptibility to drug resistance [7–9]. However, the clinical efficacy of LDM chemotherapy and the optimal regimen has yet to be established.

Capecitabine is a precursor of 5-fluorouracil (5-FU), which is converted to 5′-deoxy-5-fluorouridine (5′-DFUR) in the presence of carboxylesterase and cytidine deaminase mainly in the liver, and then to 5-FU in the presence of thymidine phosphorylase (TP), a strong antiangiogenic factor identical to platelet-derived endothelial cell growth factor [10]. TP, the key enzyme mediating the final activation step, is present at significantly higher concentrations in the tumor than in other tissues, leading to preferential delivery of capecitabine to 5-FU on the tumor site with limited impact on non-tumor tissue. In xenograft models, TP is upregulated by several chemotherapeutic agents, including taxanes, cyclophosphamide, and mitomycin [11, 12]. These findings provide a compelling rationale for combining capecitabine with potentially synergistic anticancer drugs. For example, the combination of capecitabine with either docetaxel or paclitaxel has been evaluated extensively in MBC and demonstrated considerable activity with a modest impact on toxicity [13, 14].

Based on previously reported preclinical and clinical results [15, 16], we evaluated a metronomic oral combination chemotherapy regimen of doxifluridine and cyclophosphamide. The regimen demonstrated encouraging efficacy, which we considered may be further improved by replacing doxifluridine with capecitabine [17]. Capecitabine combined with oral cyclophosphamide was shown to be feasible and tolerable in a pilot phase I study [18]. We therefore conducted a single-arm phase II study of the capecitabine/cyclophosphamide (XC) regimen as treatment for HER2-negative MBC.

Patients and methods

Patients

Patients eligible for inclusion in the study were aged >20 years at time of enrollment and had histologically or cytologically confirmed advanced or recurrent breast cancer that was measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) and determined to be HER2-negative by immunohistochemistry (IHC 0 or 1+) or fluorescence in situ hybridization (FISH negative). Patients with unknown HER2 status were eligible. All patients were required to have a life expectancy of at least 6 months, an Eastern cooperative oncology group performance status (ECOG PS) of 0–2 (except for patients with pain of PS 3 caused by bone metastasis), sufficient organ function to allow safety evaluation, and to be capable of receiving oral therapy. Eligible patients had received no more than 1 prior chemotherapy regimen, no previous treatment with the combination with doxifluridine and cyclophosphamide or capecitabine-containing therapy, and were required to have no carry-over effects from previous treatments. Prior radiotherapy to the target measurable lesion was not permitted. The study was approved by the ethics committees at participating institutions, and all patients provided written informed consent.

Study design

Capecitabine (828 mg/m^2 twice daily) and cyclophosphamide (33 mg/m^2 twice daily) were both administered orally, days 1–14, followed by a 7-day drug-free interval (days 15–21). Treatment was continued for at least 6 cycles or disease progression. Delay in treatment cycle due to

toxicity was allowed if the interval was ≤14 days, otherwise the patient was required to discontinue study treatment.

During the study, drug dosage was adjusted in patients experiencing treatment-related adverse events of grade 2 or higher intensity, graded according to Common Terminology Criteria for Adverse Events (CTCAE) v 3.0 [19]. At the first occurrence of a grade 2 event, treatment was interrupted until resolution to grade 1 or 0 and resumed at the original dose. Recurrences of grade 2 events were managed by treatment interruption followed by a 25% dose reduction. If grade 3 or 4 toxicity occurred, treatment was interrupted and continued with a 25 or 50% dose reduction, respectively. If the same grade 2 toxicity occurred for a third time, treatment was interrupted until the adverse event resolved to grade 0–1 and then continued at 50% of the original dose. At the third occurrence of a given toxicity (grade 3 severity), treatment was discontinued and the patient withdrawn from the study.

Study endpoints

The primary endpoint was overall response rate (ORR), and secondary endpoints were progression-free survival (PFS), overall survival (OS), clinical benefit response (CBR) defined as complete response (CR) plus partial response (PR) plus long-term (≥24 weeks) stable disease (LSD), and safety.

Assessment of response rate and adverse events

Tumor response was assessed according to RECIST version 1.0 [20]. Evaluation of response was performed after every 2 cycles during the treatment. Adverse events were graded according to CTCAE v 3.0 [19].

Statistical analysis

Assuming an ORR of 50% and a threshold ORR of 30%, based on the literature [13, 14, 21], a sample size of 43 patients was required to give 80% power with $\alpha = 0.05$. Therefore, the target sample size was 50 patients over a 1-year period, allowing for dropouts and inclusion of non-evaluable patients.

Analyses of efficacy and safety were performed in the per-protocol set (PPS) population. The PPS population comprised subjects fulfilling the study inclusion criteria. PFS was estimated by the Kaplan–Meier method.

Results

Between May 2007 and April 2009, 51 patients were enrolled. The median duration of follow-up was 18.1 months. The baseline characteristics of patients are shown in Table 1. The median age of patients was 61 years (range, 32–82) and the majority (38 of 51) of patients had PS 0. Efficacy was evaluated in 45 patients excluding ineligible patients including 1 patient with HER2-positive breast cancer and 5 patients with no target region. Safety was evaluated in 51 patients.

Table 1 Patient characteristics ($n = 51$)

Median age, years (range)	61 (32–82)
PS (ECOG): 0/1/2/unknown	38/9/3/1
Tumor histological types[a]: scirrhous/solid-tubular/papillotubular carcinoma/other	21/12/14/4
HER2 status[b]: positive/negative/unknown	1/42/8
ER status: positive/negative/unknown	32/18/1
PgR status: positive/negative/unknown	29/21/1
Triple negative (ER-, PgR-, and HER2-negative)	10
Surgical operation for primary breast cancer: yes/no	44/7
Post-operative radiation therapy: yes/no	25/26
Prior adjuvant treatment[c]	
Anthracyclines	23
Taxanes	17
Anthracyclines and taxanes	17
Hormone therapy	31
Others (CMF, 5′DFUR, UFT, 5-FU)	13
Number of prior chemotherapy regimens for MBC: 0/1	41/10
Prior MBC treatment	
Anthracyclines[d]	6
Taxanes	3
Hormone therapy	17
Others (doxifluridine)	2

PS, performance status; *ECOG*, Eastern co-operative oncology group; *HER2* human epidermal growth factor receptor type 2; *ER*, estrogen receptor; *PgR*, progesterone receptor; *CMF*, cyclophosphamide, methotrexate, 5-flourouracil; *5′-DFUR*, doxifluridine; *UFT,* tegafur uracil; *5-FU*, 5-flourouracil; *MBC*, metastatic breast cancer

[a] According to the pathological classification of the Japanese breast cancer societyl

[b] One HER2-positive patient was excluded from our analysis

[c] Some patients received more than 1 chemotherapy regimen

[d] One patient received epirubicin and paclitaxel

Efficacy

Among the 45 patients evaluable for efficacy, 4 achieved a CR and 16 achieved a PR, giving an ORR of 44.4%. SD and PD were reported 11 and 7 patients, respectively. LSD was reported in an additional 6 patients, and therefore, the CBR (CR + PR + LSD) was 57.8% (Table 2). A subanalysis of clinical response according to hormone-receptor status showed that the CR and PR rates among patients

Table 2 Response to the treatment ($n = 45$)[a]

	CR	PR	ORR (%)	CBR (%)
All patients	4	16	44.4	57.8
Hormone receptor ($n = 44$)[b]				
ER-positive ($n = 28$)	2	11	46.4	64.3
ER-negative ($n = 17$)	2	5	41.2	47.1
PgR-positive ($n = 26$)	3	8	42.3	53.8
PgR-negative ($n = 19$)	1	8	47.4	63.2
Triple negative (ER-, PgR-, and HER2-negative) ($n = 9$)	0	4	44.4	55.6
Prior anthracyclines; Adjuvant+MBC ($n = 23$)	3	6	39.1	52.2
Prior taxanes; Adjuvant + MBC ($n = 13$)	2	4	46.2	53.8
Major metastatic organ[c]				
Organ (liver and lung) ($n = 33$)	3	12	45.5	57.6
Bone ($n = 7$)	0	5	71.4	85.7
Soft tissue only (lymph node and skin) ($n = 10$)	1	7	40.0	50.0
Hand-foot syndrome				
Yes ($n = 24$)	2	9	45.8	62.5
No ($n = 21$)	2	6	38.1	47.6

CR, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease; *NE*, not evaluable; *ORR*, overall response; *CBR*, clinical benefit rate (CR+PR+LSD); *LSD*, long-term (≥24 weeks) stable disease; *ER*, estrogen receptor; *PgR*, progesterone receptor; *HER2*, human epidermal growth factor receptor type 2; *MBC*, metastatic breast cancer

[a] Evaluable patient excluding no target region

[b] One patient, unknown

[c] Patients may have metastases at more than 1 major organ site

with estrogen receptor (ER)-positive disease were 2 of 28 and 11 of 28, respectively, producing an ORR of 46.4%, while a further 5 patients achieved LSD, resulting in a CBR of 64.3%. In comparison, 4 of 9 patients with triple-negative disease achieved a PR (ORR 44.4%) and 1 patient achieved LSD resulting in a CBR of 55.6%.

PFS curves for the overall population and according to hormone-receptor status are shown in Fig. 1. The median PFS for the overall population was 12.3 months (95% confidence interval [CI]: 8.9–18.9 months). The median PFS in 34 patients with ER- and/or progesterone receptor (PgR)-positive disease was 13.2 months (95% CI: 8.9–23.7 months), while in 10 patients with ER- and PgR-negative and HER2-negative (triple-negative) disease, it was 10.7 months (95% CI: 3.9–20.0 months). A subanalysis of efficacy according to use of prior chemotherapy in the adjuvant or metastatic disease settings showed that median PFS was 9.3 months (95% CI: 5.1–18.9 months) in 24 patients previously treated with anthracycline-containing therapy and 13.9 months (95% CI: 8.5–23.7 months) in 22 anthracycline-naïve patients (figure not shown). Median OS has not been reached (Fig. 2). The 1- and 2-year cumulative OS rate were 86% (95% CI: 76–96%) and 71% (95% CI: 54–88%), respectively.

Safety

Safety was evaluated in 51 patients (Table 3). The most commonly reported adverse events of grade 3 or higher intensity were leukopenia in 13 patients (25%), neutropenia in 8 (16%), decreased hemoglobin in 1 (2%), and alkaline phosphatase elevation in 1 (2%). Hand-foot syndrome (HFS) of any grade was reported in 27 patients (53%); however, the severity was only grade 1 or 2 in all cases. No patient experienced grade 3 HFS. Grade 1 alopecia was reported in 1 patient (2%). No patient was withdrawn from the study because of adverse events.

Discussion

Although standard chemotherapy may eradicate breast cancer micrometastases and improve the cure rate of patients with breast cancer in the adjuvant setting, such an approach is inevitably unsuccessful for overt metastatic cancers even when dose-intensive regimens are administered, as evidenced by the failure of high-dose chemotherapy strategies in clinical trials [22]. The limitations of standard chemotherapy may be related to the mechanism of action of anticancer agents and the dynamics of tumor growth. The cytotoxicity of the majority of anticancer drugs is attributable to direct DNA damage and disruption of DNA replication, especially in proliferating cells. However, based on the assumption that proliferating cells comprise only a minor proportion of the tumor and the proliferation period is very short [23], it is unlikely that bulky metastatic tumors could be eradicated by standard chemotherapy regimens administered using short-period, intermittent schedules. Furthermore, it is not practical to administer standard chemotherapy successfully for prolonged periods because of severe cumulative toxicities, which requires relatively long treatment-free recovery

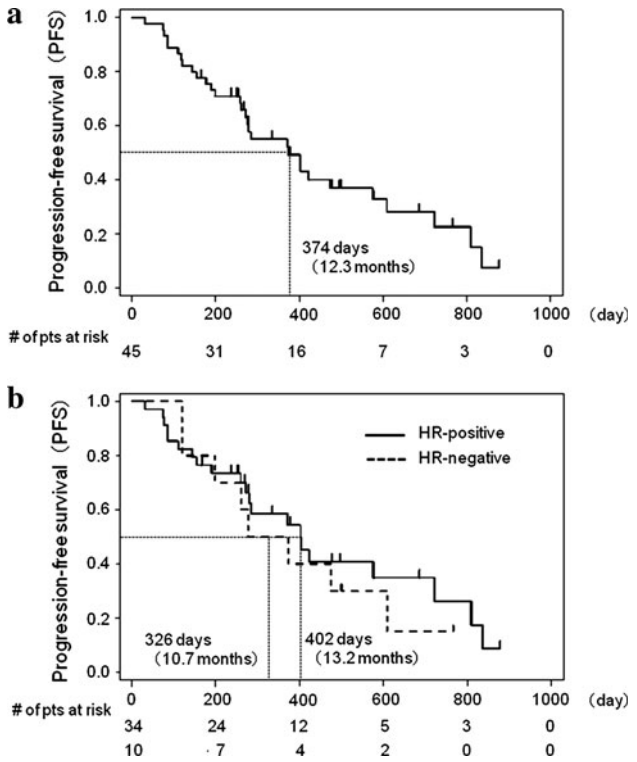

Fig. 1 Progression-free survival (PFS). **a** PFS for 45 patients treated with oral capecitabine/cyclophosphamide therapy and evaluable for efficacy. Median PFS was 12.3 months (95% CI; 8.6–18.9 months). **b** PFS analyzed according to hormone-receptor (HR) status. HR-positive ($n = 34$) was defined as estrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive. Median PFS for patients with HR-positive disease was 13.2 months (95% CI; 8.9–23.7 months; *solid line*). HR-negative ($n = 9$) was defined as triple-negative breast cancer (ER-, PgR-, and HER2-negative) and its median PFS was 10.7 months (95% CI; 3.9–20.0 months; *dotted line*)

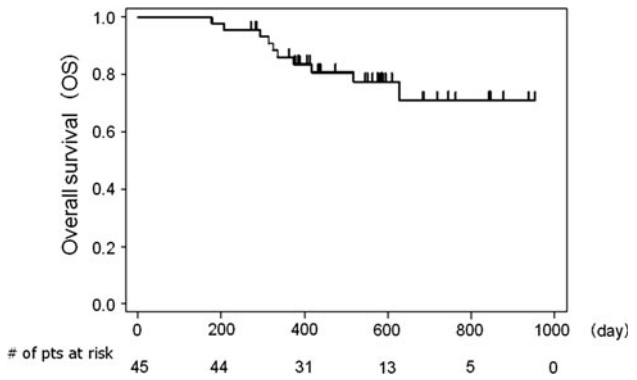

Fig. 2 Overall survival (OS). Median OS was not reached. The 1- and 2-year cumulative OS rate was 86% (95% CI: 76–96%) and 71% (95% CI: 54–88%), respectively

periods that allow regrowth of the tumor [6]. The potential limitations of standard chemotherapy are particularly relevant in the treatment of patients with slowly growing

Table 3 Toxicity ($n = 51$)

	All grades (%)	≥Grade 3 (%)
Hematological toxicity		
Leukopenia	36 (70.6)	13 (25.5)
Neutropenia	20 (39.2)	8 (15.7)
Decreased hemoglobin	37 (72.5)	1 (2.0)
Thrombocytopenia	7 (13.7)	0 (0)
Non-hematological toxicity		
Nausea	10 (19.6)	0 (0)
Vomiting	3 (5.9)	0 (0)
Diarrhea	3 (5.9)	0 (0)
Stomatitis	6 (11.8)	0 (0)
Dysgeusia	2 (3.9)	0 (0)
Anorexia	12 (23.5)	0 (0)
Fatigue	10 (19.6)	0 (0)
Hyperpigmentation	16 (31.4)	0 (0)
Dizziness	5 (9.8)	0 (0)
Palpitations	3 (5.9)	0 (0)
HFS	27 (52.9)	0 (0)
Alopecia	1 (2.0)	0 (0)
Liver dysfunction		
AST	20 (39.2)	0 (0)
ALT	13 (25.5)	0 (0)

All enrolled patients were included in the safety analysis

HFS, hand-foot syndrome; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase

breast cancers, such as the ER-positive, HER2-negative (luminal A) subtype. In this clinical scenario, conventional standard chemotherapy regimens may be less effective in slowly growing than in more rapidly growing breast cancer subtypes. It is apparent, therefore, that standard chemotherapy has inherent limitations for the treatment of MBC. Alternatively, it has been suggested that continuous, chronic administration of anticancer drugs (metronomic chemotherapy) may be required for the additional effective treatment of bulky metastatic breast tumors. If this hypothesis is correct, then the introduction of metronomic chemotherapy provides a new paradigm to overcome the shortcomings of conventional standard chemotherapy for patients with MBC.

Metronomic chemotherapy is based on more frequent administration of low-dose cytotoxic agents compared with conventional standard chemotherapy and is designed to prevent tumor angiogenesis. The potential of metronomic chemotherapy was first demonstrated in animal models a decade ago [8], and the efficacy of this approach has been confirmed in the clinic [6, 7]. Although variable outcomes have been achieved with metronomic chemotherapy, clinical studies have shown that this new treatment strategy represents an interesting alternative for the management of

patients with MBC [16]. Accumulating evidence suggests that the efficacy of metronomic chemotherapy is not only attributable to its antiangiogenic activity. Potential new mechanisms of action also include restoration of the anticancer immune response and the induction of "tumor dormancy," which may contribute to prolongation of survival [24].

The results from the present study showed that metronomic chemotherapy comprising an all-oral combination of capecitabine and cyclophosphamide achieved an acceptably high response rate of 44.4%, CBR of 57.8%, and sufficiently long PFS of 12.3 months for patients with HER2-negative MBC. The median OS was not reached at the time of reporting, and the 1-year cumulative OS rate was as high as 86%.

These results are comparable in terms of the magnitude of clinical benefit to those achieved with other standard chemotherapeutic regimens, although the characteristics of patients included in studies were different. In phase III clinical trials in MBC, single-agent treatment with docetaxel or paclitaxel produced ORRs in the range 14–43% and time to progression of 3.5-7.0 months [25]. In comparison, the results of our study, ORR 44.4% and PFS 12.3 months, appear to be relatively favorable.

The side effects of XC chemotherapy were mild, and the administration schedule was feasible. There were no nonhematological side effects occurring at an intensity of grade 3 or higher. HFS was reported in 53% of patients, but all cases were categorized as grade 1 or 2. Long-term treatment was tolerable, and the major reason for discontinuation was tumor progression.

It is thought that synergistic activity between capecitabine and cyclophosphamide, probably associated with TP activation by cyclophosphamide, contributes at least in part to these results. The promising efficacy seen in the present study may also be attributable to the lower risk of toxicity and immunosuppression associated with both capecitabine and cyclophosphamide than standard polychemotherapy regimens [26]. In addition, combining these two agents is rational based on their non-overlapping dose-limiting toxicities (HFS and liver toxicity with capecitabine and hematological toxicity with cyclophosphamide) and complementary mechanisms of anticancer action, with capecitabine having activity against cyclophosphamide-resistant cancer cells [15] and cyclophosphamide-inhibiting tumor neovascularization.

These results suggest that metronomic chemotherapy with XC offers many advantages over standard parenterally administered chemotherapy. The convenience of oral administration increases treatment options for many patients with MBC while the lack of severe side effects helps patients to maintain their QOL. An additional advantage is that oral XC should reduce the costs associated with the treatment of MBC because it does not require hospital admission, rescue treatments such as granulocyte-colony stimulating factor, or other supportive care for gastrointestinal symptoms. In addition, mild and gradual decreases in bone marrow function permit extended intervals between hematologic monitoring.

It has been suggested that chemotherapy is less effective for patients with ER-positive, HER2-negative tumors than for ER-negative tumors [27–30]. It is notable that in our study, the oral combination of capecitabine and cyclophosphamide produced similar response rates in ER-positive and ER-negative MBC, although this observation is based on a retrospective subgroup analysis. The ORR, CBR, and median PFS reported in our study were 46.4 versus 41.2%, 64.3 versus 47.1%, and 13.2 versus 10.7 months for patients with ER-positive and ER-negative MBC, respectively. In a previous report, oral combination chemotherapy with doxifluridine and cyclophosphamide achieved superior results in patients with ER-positive than ER-negative MBC [16]. Additionally, the results of that study showed a trend toward superior ORR in patients with a longer disease-free interval than in those with a shorter disease-free interval for MBC. They showed that the response rates according to disease-free intervals of $\leq$2 years, 2–5 years, and >5 years were 50, 64, and 68%, respectively (the differences were not significant) [16]. On the basis that ER-positivity and a longer disease-free interval characterize less aggressive, slowly proliferating breast cancers, which may be less responsive to chemotherapy than ER-negative tumors and/or those with a shorter disease-free interval [31], it is hypothesized that metronomic chemotherapy as used in the present study may be better suited than conventional regimens for patients with slowly growing tumors or luminal A breast cancer.

In conclusion, the oral combination of capecitabine and cyclophosphamide was shown to be a very feasible and convenient regimen with mild side effects and substantial efficacy in patients with HER2-negative MBC regardless of ER status. The XC regimen may fulfill several requirements for the ideal metronomic treatment. This metronomic chemotherapy regimen may offer an additional new option for patients with MBC, especially for those with ER-positive, HER2-negative (luminal A) breast cancer. Additional research to confirm these promising results is warranted.

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