

Exploratory Results of Capecitabine Metronomic Chemotherapy in Metastatic Breast Cancer Patients after Prior Systemic Therapy for Metastatic Disease– A Single Arm Phase II Study

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Abstract: Purpose: The aim of this study is to investigate efficacy and toxicity of Capecitabine metronomic therapy preceded by prior treatment with at least one drug regimen for metastatic disease. **Methods:** Between June 2013 and February 2015, 38 women with pathologically proven metastatic breast cancer (MBC) with at least one significant lesion, who had received prior chemotherapy for metastatic disease, were enrolled. Patients received oral Capecitabine (Xeloda) metronomic therapy (750 mg/m², twice every day). The primary endpoints of this study were progression-free survival (PFS) rates and safety profile. Secondary end points were tumor response and overall survival (OS). **Results:** Objective response was observed in 23.7% of patients (9/38), and tumor control rate was 84.2% (32/38). Complete response was observed in 2 patients (5.3%) following treatment. The estimated median PFS and OS were 9 and 18 months, respectively. The 1-year OS and PFS rates were 73.6% and 42.1%, respectively. Treatment-related adverse events were manageable with only 2 patients (5.3%) suffered from Grade 3/4 hand-foot syndrome and another 2 patients (5.3%) suffered from Grade 3 diarrhea. No Grade 3/4 hematologic toxicity was recorded. All patients received full doses of Capecitabine and dose reduction was not required in any of our patients throughout the study. **Conclusions:** Capecitabine metronomic therapy in MBC patients after prior chemotherapy in metastatic setting offered a promising clinical benefit and simple way to be administered in outpatients, to the degree that makes it not only feasible, but also may be surpassed by the patients.

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Key words: Metastatic breast cancer, capecitabine metronomic therapy

1. Introduction

Metastatic breast cancer (MBC) represent about 6–10 % of newly diagnosed breast cancer patients. Quite a few of patients with early or localized breast cancer will metastasize during the course of the disease [1]. Despite recent advances in our recognition of the biology of MBC and in the evolution of new types of therapy, the disease is generally considered incurable [2, 3, 4, 5]. The prognosis for these patients remains poor, with a 5-year overall survival of around 20 % [6]. So, the aims of treatment are palliative survival prolongation, control of symptoms, improvement of quality of life, all of which require a balance between treatment efficacy and toxicity [7].

Catania et al [8] in their published research that studied patients with advanced breast cancer, oral chemotherapy was viewed positively by most patients, perceiving it as advantageous (58 %), able to help them feel less ill (77 %) and to reduce the effort in coping with the disease (67 %) [8]. Thus, there has always been an increased interest in developing oral anticancer agents which are adequate to the patient and easy to administer, particularly in the palliative setting as home-based therapy [9, 10].

Many oral anticancer agents have been developed and are now available [11, 12, 13].

Capecitabine mimics continuous infusion of 5-FU [14], and the oral formulation meets with a high degree of acceptance by both patients and physicians [15]. In MBC, as regards the registered monotherapy, the data from retrospective analyses indicate that dose reduction does not weaken efficacy [16], and that lower doses have a more favorable therapeutic index than the standard dosage [17, 18].

Metronomic regimens involve the frequent (daily, or several times a week, or weekly) or continuous administration of chemotherapy agents at low doses, without lengthy drug-free breaks. This approach is proven to enhance the antiangiogenic activity of these drugs [19, 20]. Protracted exposure to low doses of conventional cytotoxic drugs also offers important advantages in reduced toxicity [21]. Its pharmacokinetic characteristics and low toxicity profile make Capecitabine a perfect drug for metronomic administration [22]. In two small randomised trials, continuous use of low-dose Capecitabine (650 or 800 mg/m² b.i.d. with no drug-free breaks) proved to be as effective in MBC patients as intermittent use of higher doses (1000 or 1250 mg/m² b.i.d. days 1–14 every 21 days) [23, 24].

On the basis of this data, we initiated this study to investigate the tolerability, and survival in patients

with MBC who treated with single-agent oral metronomic Capecitabine (750mg/m², twice every day) preceded by prior systemic therapy for metastatic disease.

2. Materials and Methods

Patient Eligibility Criteria

Between June 2013 and February 2015, 38 women with pathologically proven metastatic breast cancer (MBC) with at least one significant lesion, in Clinical Oncology Department, Tanta University Hospital were enrolled. Patients were eligible for this study if they had metastases to distant sites and received prior treatment with at least one drug regimen for metastatic disease (neoadjuvant and/or adjuvant chemotherapy or endocrine therapy were not considered in the counting of therapy lines for metastatic disease). Patients were followed up until April 2016.

Patients fulfilled the following criteria:- age between 18-70 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2 , adequate bone marrow reserve (WBC count $\geq 3.5 \times 10^9/L$, ANC count $\geq 1.5 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, and hemoglobin ≥ 10 g/dL), adequate renal function (measured creatinine clearance ≥ 60 mL/min) and adequate liver function (transaminases less than 2 x upper normal limit, and serum bilirubin concentrations below 1.5 mg/dL).

Patients were ineligible for this study if they were pregnant or lactating mothers or had symptoms of the central nervous system, leptomeningeal metastasis, dementia, altered mental status, or any psychiatric condition that would prevent the harmony or rendering of informed consent were excluded from this study. Also, patients with prior exposure to Capecitabine, patients suffering from malabsorption disease, lack of physical integrity of the upper GI tract, or other gastrointestinal disease affecting absorption of oral medications were excluded. In addition, patients with secondary malignancy or concurrent serious, uncontrolled medical illness (e.g. persistent immune-compromised states, uncontrolled infection, and clinically significant cardiac disease) were not eligible. All radiotherapy, chemotherapy, hormonal therapy, and/or targeted therapy had to be discontinued at least 8 weeks before initiation of protocol treatment. Concomitant bisphosphonates were allowed.

Design of the Study

This study is a prospective single-arm phase II single-institution study. The Ethics Committee in Faculty of Medicine, Tanta University, approved the protocol and all patients signed an informed consent before the initiation of any treatment.

Treatment Plan and Dose Medication

Eligible patients received oral Capecitabine (Xeloda) metronomic therapy (750mg/m², twice daily) on an outpatient basis.

Oral Capecitabine (Xeloda) metronomic therapy is discontinued in case of disease progression or high grade toxicities.

To facilitate comparison of results, 28 days of treatment were considered to represent one treatment cycle. Adequate hematological and within normal range organ functions were insured every treatment cycle. Adverse events were monitored throughout the study. Complete resolutions of all toxicities were required except for alopecia and fatigue. If toxicities did not resolve, then a 1- 2 weeks delay was allowed.

Patient assessment

Assessment of clinical benefit

A tumor response assessment was evaluated after every three cycles of treatment. Pre- and on-treatment monitoring consisted of medical history, assessment of body weight and vital signs, performance status, physical and neurological examination, laboratory analyses and radiological imaging. Criteria of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were based on the standard definitions according to RECIST 1.0 criteria [25], with the overall response rate, including complete response and partial response.

Assessment of toxicity

Patients were assessed for adverse events at each site with clinical and laboratory evaluations every 3 weeks and cardiac monitoring, by ECHO, every 3 months. Toxicity grading was based on the terminology criteria for adverse events according to NCI-CTC criteria, version 3.0 [26].

The primary endpoints of this study were progression-free survival (PFS) rates and safety profile. Secondary end points were tumor response and overall survival.

Statistical Analysis:

Overall-survival (OS) rates were calculated from the start of treatment to the time of the last follow-up visit or death. Progression-free survival (PFS) was the length of time during and after the treatment to the date of first evidence of disease progression or death in the absence of disease progression. The Kaplan-Meier method [27] with SPSS [Statistical package] (version 21) is used for estimating survival. The 95% confidence intervals (95% CIs) were calculated with the exact method. All *P* values of ≤ 0.05 were considered significant.

3. Results

Patient characteristics:

Thirty eight patients with pathologically proven MBC were enrolled in this study. The patients'

demographic and clinical characteristics were recorded in table 1.

Table (1): Patients' and tumor characteristics as well as initial treatment modality (N=38).

Characteristic	No. patients (%)
Age (years)	
Median	50.9 years
Range	29-70
Family history	
+ve	4 (10.5%)
-ve	34 (89.5%)
Initial tumor status	
T2	8 (21.1%)
T3	22 (57.8%)
T4	8 (21.1%)
Menopausal status	
Premenopausal	14 (36.8%)
Postmenopausal	24 (63.2%)
Tumor grade	
G1	4 (10.5%)
G2	8 (21.1%)
G3	26 (68.4%)
Histology	
Invasive duct carcinoma (IDC)	34 (89.5%)
Others	4 (10.5%)
Lymphovascular invasion	
Positive	12 (31.6%)
Negative	26 (68.4%)
Nodal status	
N1	8 (21.1%)
N2	12 (31.5%)
N3	18 (47.4%)
Adjuvant radiation therapy (Rth)	
Yes	30 (78.9)
No	8 (21.1%)
Type of surgery	
Breast conserving surgery (BCS)	4 (10.5%)
Modified radical mastectomy (MRM)	34 (89.5%)
Type of adjuvant chemotherapy	
FAC	8 (21.1%)
FEC	10 (26.3%)
Sequential FEC with taxenes	20 (52.6%)
ECOG	
0	2 (5.3)
1	6 (15.8)
2	30 (78.9)
Metastatic sites	
Liver	12 (31.5%)
Lymph node	26 (68.4%)
Lung	10 (26.3%)
Bone	24 (63.2%)
Type of metastasis	
Single metastasis	24 (63.2%)
Multiple metastases	14 (36.8%)

The median age at diagnosis was 50.9 years (range 29–70 years), with 24 (63.2%) patients were postmenopausal and 14 (36.8%) patients were

premenopausal. The majority of patients had invasive ductal carcinoma (89.5%) and grade III disease (68.4%). T 3 disease constituted 57.8% of all patients at initial presentation prior to any treatment. Most of the patients (94.7%) had ECOG performance status score of ≥ 1 . Thirty four patients (89.5%) underwent mastectomy for their primary tumor, and 4 patients (10.5%) underwent a segmental resection. All patients received combination chemotherapy in the adjuvant and metastatic setting and 30 (78.9%) patients received adjuvant radiation therapy. All patients had metastatic breast cancer (MBC) at the start of the study.

Treatment Administration

All patients received oral capecitabine (Xeloda) metronomic therapy (750 mg/m², twice every day). No dose reduction was recorded and only 2 patients had dose delay for 1 week because of Grade 3 diarrhea (1 patient) and Grade 3/4 hand-foot syndrome (1 patient).

Response to Treatment

In the first 14 patients enrolled in the study, 8 responses were observed that encouraging to proceeding with 38 patients. Overall response rate (complete response and partial response) was 23.7% (9/38), and tumor control rate (overall response and stable disease) was 84.2% (32/38) according to the RECIST criteria (Table 2). Complete response was observed in 2 patients (5.3%). All objective responses were confirmed at least 4 weeks after first observation.

ECOG performance status did not significantly affect response rates ($P = 0.16$). Response rate was significantly higher in patients with non-visceral metastases ($P = 0.03$), patients with solitary metastases ($P = 0.05$), and in patients with tumor grade I/II tumors ($P < 0.0001$). No differences were observed regarding previous radiation therapy ($P = 0.18$).

Table (2): Tumor Response to Treatment (N=38)

Tumor Response	No.	%
Complete response	2	5.3
Partial response	7	18.4
Stable disease	23	60.5
Progressive disease	6	15.8

Toxicity

The main forms of adverse reactions to this regimen observed in the 38 assessable patients are listed in table 2. Most of the hematologic and non-hematological toxicities were mild and controllable. No Grade 3/4 hematologic toxicity was recorded.

Hand-foot syndrome, a common side effect of capecitabine (Xeloda), was the most common treatment-related adverse effect, occurring in 15.8% (6/38) of patients. Four (10.5%) of them were of

Grade 1/2 hand-foot syndrome. While, only 2 cases (5.3%) had Grade 3/4 hand-foot syndrome, which was resolved to grade 0/1 with rest and symptomatic treatment (pyridoxine and topical urea/lactic acid-based cream). Diarrhea was observed in 4 patients (10.6%) with 2 of them (5.3%) had a grade 3 toxicity. Another grade 1/2 non-hematologic toxicities observed were nausea/vomiting in 4 patients (10.5%) and fatigue in 2 patients (5.3%).

Only 2 patients required hospitalization, because of grade 3 diarrhea. All patients received full doses of Capecitabine and dose reduction was not required in any of our patients. However, only 2 patients had dose delay for 1 week because of Grade 3 diarrhea (1 patient) and Grade 3/4 hand-foot syndrome (1 patient).

Table (3): Hematologic and non-hematologic toxicity of Capecitabine metronomic therapy (N=38).

Toxicity	Grade 1/2 No. (%)	Grade 3/4 No. (%)
Non-hematologic Toxicity		
Hand-foot syndrome	4 (10.5%)	2 (5.3%)
Diarrhea	2 (5.3%)	2 (5.3%)
Nausea/vomiting	4 (10.5%)	0.0
fatigue	2 (5.3%)	0.0
Hematologic Toxicity		
Anemia	12 (31.6)	0.0

Survival

All patients were followed up regularly as mentioned previously in patients and methods, with no one had lost follow-up in this study. The median follow-up period was 18 months.

Median progression free survival (PFS) was 9 months, with its 95% CI; 6.99 - 11.01 months (Fig.1). The 1-year and 2 years PFS rates were 42.1% and 25.8%, respectively (Fig.1).

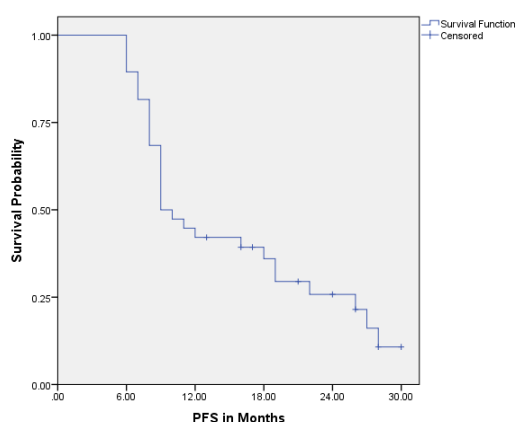


Figure 1: Kaplan–Meier curve of progression-free survival for patients with MBC.

Median overall survival (OS) was 18 months, with its 95% CI; 13.29- 22.71 months (Fig.2). The 1-year and 2 years OS rates were 73.6% and 40.7%, respectively (Fig.2).

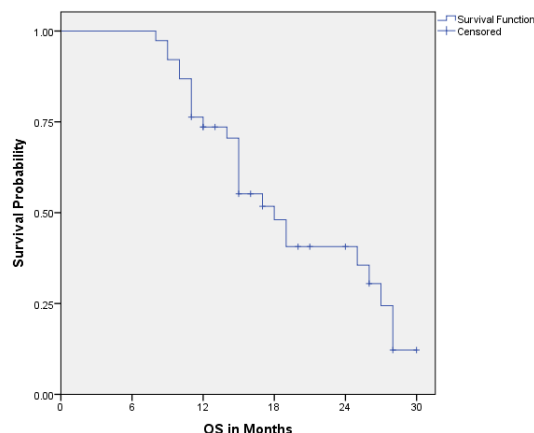


Figure 2: Kaplan–Meier curve of overall survival for patients with MBC.

4. Discussion

Female breast cancer is the most common malignancy worldwide that comprises about 23 % of all cases of cancer in women [28]. Metastatic breast cancer represents 6–10 % of newly diagnosed breast cancer patients. A substantial number of patients with early breast cancer will metastasize during the course of their disease [1]. Metastatic breast cancer is generally considered not curable by currently available therapy and there is no preferred standard form of chemotherapy [4, 5]. The prognosis for these patients remains poor, with an estimated 5-year overall survival of around 20 % [6]. The goals of therapy in the metastatic setting include symptomatic palliation, delay of disease progression, and prolonging overall survival time [1].

Other strategies have been adopted to improve the clinical outcome of patients with MBC. Antiangiogenic therapy has been studied in several clinical trials as first-line [29, 30, 31] and second-line [32] treatment of metastatic breast cancer. Epidermal growth factor receptor (EGFR)-targeted agents also studied in MBC assumed the high-level EGFR of expression in some of these cancers [33]. EGFR inhibitors have demonstrated low efficacy as single agents in MBC, but in combination may improve the efficacy of other agents, such as taxanes or platinum. However, these agents have a limited role and could not be used widely for MBC patients in our country because of limited resources.

There are several studies which explore the role of Capecitabine in MBC [7, 34, 11, 12, 35, 36, 37]. Capecitabine is an oral Fluoropyrimidine carbamate

that acts as a 5-fluorouracil (5-FU) prodrug and mimics continuous infusion of 5-FU [14]. Patients often prefer the convenience of an oral treatment versus intravenous chemotherapy [38, 15].

In the past few years, several studies have emphasized the role of metronomic chemotherapy to be used in MBC [34, 12, 35, 36]. Some metronomic regimens can have surprisingly potent antitumor effects in preclinical models compared with respective maximum tolerated dose (MTD) regimens, despite being less toxic [39].

Because of the high variability of the metronomic Capecitabine treatment dose ranging from a tenth to a third of the maximum tolerated dose [40]. We designed this phase II trial to investigate the efficacy and tolerability of Capecitabine (Xeloda) metronomic therapy at a dose of 750mg/m², twice every day in MBC previously, received systemic intravenous chemotherapy in the metastatic setting. The primary endpoints of this study were PFS and safety profile. Secondary end points were OS and response to treatment.

We sought to document the use of metronomic Capecitabine and its efficacy and tolerance in MBC patients treated at Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital, as to our knowledge, this is the first prospective study to assess metronomic capecitabine in patients with MBC in our institution. Despite low rates of adverse events and use of dose modifications, Capecitabine was found to be clinically effective in both MBC and non-metastatic patients. Regimen toxicity did not reduce overall response and survival [7, 34, 11, 12, 35, 36, 37].

In our study, responses were observed in 23.7% (9/38) of patients which were similar to the results of Fedele et al trial [7] on metronomic Capecitabine, in patients with MBC published in 2012, (RR was 24%).

In our study, the disease control rate (CR+PR+SD) of 84.2% (32/38) was comparable to the results of the Fedele et al trial [7] (disease control rate of 86%).

The estimated median OS in our study was 18 months, similar to the 17 months reported in Fedele et al [7] study.

The median progression-free survival in our study was 9 months, higher than that published in 2012, by Fedele et al [7], (median progression-free survival was 7 months).

Our study confirms the overall acceptable tolerability of metronomic Capecitabine. The metronomic Capecitabine treatment did not appreciably increase the incidence of hematologic and non-hematologic toxicity compared with previous reports administering metronomic Capecitabine to MBC patients [7, 36].

To date, most of the adverse reactions to this regimen observed in our 38 assessable patients were mild and manageable. Grade 3–4 hematologic toxicity was not recorded. Hand-foot syndrome, a frequent side effect of Capecitabine (Xeloda), was the most common adverse event, occurring in 15.8% (6/38) of patients. Four (10.5%) of them were of Grade 1/2 hand-foot syndrome. While, only 2 cases (5.3%) had grade 3/4 hand-foot syndrome, which was rapidly resolved to grade 0/1 with complete rest and symptomatic treatment. Diarrhea was experienced by 4 patients (10.6%) with 2 of them (5.3%) suffered from grade 3 toxicity. Another grade 1/2 non-hematologic toxicities observed were nausea/vomiting in 4 patients (10.5%) and fatigue in 2 patients (5.3%).

Only 2 patients required hospitalization, because of grade 3 diarrhea. All patients received full doses of Capecitabine throughout the study and dose reduction was not required in any of our patients. However, only 2 patients had dose delay for 1 week because of Grade 3 diarrhea (1 patient) and Grade 3/4 hand-foot syndrome (1 patient).

Most of the hematologic and non-hematological toxicities during the metronomic Capecitabine treatment were better than that of other previous reports [36, 7]. Two phase II trials had studied the toxicity profile of metronomic Capecitabine in MBC patients. El-Arab et al [36] had studied the clinical efficacy and tolerability of low dose, Capecitabine (500 mg twice daily) combined with oral cyclophosphamide (at a dose of 50 mg once daily) in 60 patients with MBC. The overall regimen was well tolerated. Myelosuppression, a well-documented side effect of therapy in particular leucopenia (Grades 1/2) was observed in (17%) patients. Hand-foot syndrome, the most frequently reported non-hematologic adverse reactions, were also mild to moderate (Grades 1 and 2 in 36.7% of cases), and could be readily controlled with rest and the administration of standard medications. Also in our study hand-foot syndrome, was the most common treatment-related adverse event, occurring in 15.8% (6/38) of patients, with only 2 cases (5.3%) of Grade 3/4. While in El-Arab et al [36] study no grade 3 or 4 toxicity was recorded. The use of lower doses of metronomic Capecitabine in El-Arab et al [36] study to that we used in our study could explain the absence of grade 3 or 4 toxicities in their study. Vomiting in El-Arab et al [36] study was much higher (28.3%) in comparison to that (10.5%) in our study; this may be due to the effect of oral Cyclophosphamide in their study. Diarrhea in our study was lower (10.5%) in comparison to that (20%) in the study by El-Arab et al [36]. However, in our study 2 patients (5.3%) suffered from grade 3 diarrhea, while in El-Arab et al [36] study no grade 3 or 4 toxicity was recorded. Again this could be explained

by the use of lower doses of metronomic Capecitabine in El-Arab et al [36] study to that we used in our study. In El-Arab et al [36] study grade 3 serum transaminases elevation was reported in 8% of patients [36]. In our study, no hepatic toxicity occurred. This difference could be explained by the addition of oral Cyclophosphamide to Xeloda in El-Arab et al [36] study.

In another report published by Fedele et al [7] evaluating efficacy and safety of low-dose metronomic Capecitabine in heavily pretreated patients with metastatic breast cancer, 60 patients received continuous metronomic Capecitabine monotherapy (1500 mg/ day). Hematologic toxicity was infrequent and mild. Hand-foot syndrome (10%) and diarrhea (7%) were the most common adverse events, vomiting occurred in (2%). There were only three cases of grade 3 toxicity, all involving hand-foot syndrome [7]. These results were comparable to our results with no hepatic toxicity was recorded.

Conclusion

In conclusion, the current results suggest continuous metronomic Capecitabine is an effective and safe chemotherapy regimen for patients with MBC. The preliminary results of our study demonstrated that, continuous metronomic Capecitabine treatment, for patients with MBC has gained increased acceptance due to the improving tolerability, response rates, time to progression, and overall survival with acceptable toxicity profile, in addition, the metronomic Capecitabine is easy to administer in outpatients. Considering the efficacy and lower toxicity, continuous metronomic Capecitabine could be a viable option in heavily pretreated patients with MBC in terms of the impact on improving the level of treatment-related quality of life. The regimen was so well tolerated that its widespread use at this point in time is recommended by several authorities in the field.

Further prospective investigation of metronomic Capecitabine to optimize doses and scheduling is necessary. In addition, the combination with targeted agent in future clinical trials may be considered to increase the response with acceptable toxicities. Evaluation of molecular markers may further help to stratify patients to a risk-adapted approach and may help us to refine further the answers to the two most valuable questions: Who to treat? And, what to treat with?

Compliance with Ethical Standards

Conflict of Interest

The author Mohamed F. Sheta declared that he has no conflict of interest. The author Rasha Abd El-

Ghany Khedr declared that she has no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

References

1. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. *Oncologist* 2005; 10 (3): 20–29. doi:10.1634/theoncologist.10-90003-20.
2. Smith I. Goals of treatment for patients with metastatic breast cancer. *Semin Oncol* 2006; 33(1 Suppl. 2): S2–5.
3. Gralow JR. Optimising the treatment of metastatic breast cancer. *Breast Cancer Res Treat* 2005; 89(Suppl. 1): S9–15.
4. Esteva FJ, Valero V, Pusztai L, Boehnke-Michaud L, Buzdar AU, Hortobagyi GN. Chemotherapy of metastatic breast cancer: what to expect in 2001 and beyond. *Oncologist* 2001; 6(2):133–146.
5. Jones SE. Metastatic breast cancer: the treatment challenge. *Clin Breast Cancer* 2008; 8(3):224–233. doi:10.3816/CBC.2008.n.025.
6. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. *Oncologist* 2007; 12(1):20–37. doi:10.1634/theoncologist.12-1-20.
7. Fedele P, Marino A, Orlando L, Schiavone P, Nacci A, Sponziello F, et al. Efficacy and safety of low-dose metronomic chemotherapy with capecitabine in heavily pretreated patients. *EUROPEAN JOURNAL OF CANCER* 2012; 48: 24–29.
8. Catania C, Didier F, Leon ME, Sbanotto A, Mariani L, Nole F, Leida E, Rocca A, De Pas T, Goldhirsch A. Perception that oral anticancer treatments are less efficacious: development of a questionnaire to assess the possible prejudices of patients with cancer. *Breast Cancer Res Treat* 2005; 92(3):265–272. doi: 10.1007/s10549-005-3376-y.
9. Findlay M, von Minckwitz G, Wardley A. Effective oral chemotherapy for breast cancer: pillars of strength. *Ann Oncol* 2008; 19(2):212–222. doi:10.1093/annonc/mdm285.

10. Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol* 1997; 15(1):110–115.
11. Babacan T, Efe O, Hasirci AS, Demirci F, Buyukhatipoglu H, Balakan O, Sarici F, Kertmen N, Esin E, Akin S, Ates O, Aksoy S, Sever AR, Altundag K. Efficacy of capecitabine monotherapy as the first-line treatment of metastatic HER2-negative breast cancer. *Tumori*. 2015; 101(4): 418-23.
12. Munzone E & Colleoni M. Clinical overview of metronomic chemotherapy in breast cancer. *Nature Reviews Clinical Oncology* 2015; 12: 631–644.
13. Kuppens IE, Breedveld P, Beijnen JH, Schellens JH. Modulation of oral drug bioavailability: from preclinical mechanism to therapeutic application. *Cancer Invest* 2005; 23(5):443–464.
14. Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, et al. Xeloda Colorectal Cancer Study Group. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol* 2001; 19 (21): 4097–106.
15. Finek J, Holubec L, Svoboda T, Sefrhansova L, Pavlikova I, Votavova M, et al. A phase II trial of oral vinorelbine and capecitabine in anthracycline pretreated patients with metastatic breast cancer. *Anticancer Res* 2009; 29 (2): 667–70.
16. O'Shaughnessy J, Blum J. A retrospective evaluation of the impact of dose reduction in patients treated with Xeloda (capecitabine). *Proc Am Soc Clin Oncol* 2000; 19 [abstr 400].
17. Yap YS, Kendall A, Walsh G, Banerji U, Johnston SRD, Smith IE, et al. Clinical efficacy of capecitabine as first-line chemotherapy in metastatic breast cancer – how low can you go? *Breast* 2007; 16 (4): 420–4.
18. Sezgin C, Kurt E, Evrensel T, Ozdemir N, Manavoglu O, Goker E. Efficacy of lower dose capecitabine in patients with metastatic breast cancer and factors influencing therapeutic response and outcome. *South Med J* 2007; 100 (1): 27–32.
19. Munzone E, Di Pietro A, Goldhirsch A, Minchella I, Verri E, Cossu Rocca M, et al. Metronomic administration of pegylated liposomal doxorubicin in extensively pre-treated metastatic breast cancer patients: a mono-institutional case-series report. *Breast* 2009; 19 (1): 33–7.
20. Mehta RS. Dose-dense and/or metronomic schedules of specific chemotherapies consolidate the chemosensitivity of triple-negative breast cancer: a step toward reversing triplenegative paradox. *J Clin Oncol* 2008; 26 (19):3286–8.
21. Emmenegger U, Kerbel RS. Five years of clinical experience with metronomic chemotherapy: achievements and perspectives. *Onkologie* 2007; 30 (12):606–8.
22. Zielinski C, Gralow J, Martin M. Optimizing the dose of capecitabine in metastatic breast cancer: confused, clarified or confirmed? *Ann Oncol* 2010; doi:10.1093/annonc/mdq069.
23. Stockler M, Sourjina T, Grimison P, Gebiski V, Byrne M, Harvey V, et al. A randomized trial of capecitabine (C) given intermittently (IC) rather than continuously (CC) compared to classical CMF as first line chemotherapy for advanced breast cancer. *ASCO Annual Meeting Proceedings Part I. J Clin Oncol* 2007; 25 (18S): 1031.
24. Martin M, Calvo L, Martinez N, Ramos M, Muñoz M, Zamora P, et al. Randomized, phase II trial comparing continuous versus intermittent capecitabine monotherapy for metastatic breast cancer (MBC). *ASCO Annual Meeting Proceedings Part I. J Clin Oncol* 2009; 27(15S): 1086.
25. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92 (3): 205-16. doi: 10.1093/jnci/92.3.205.
26. National Cancer Institute, US. NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0) [online]. available at: http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v3.pdf (accessed April 7, 2014).
27. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53: 457-81. DOI:10.1080/01621459.1958.10501452.
28. Mansour M, Mourad C. Phase II study of single agent oral vinorelbine as first-line treatment in patients with HER-2 negative metastatic breast cancer. *Cancer Chemother Pharmacol* 2013; 72:429–435.
29. Miles DW, Chan A, Dirix LY, Cortés J, Pivrot X, Tomczak P, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol* 2010; 28 (20): 3239–47.

30. Robert NJ, Dieras V, Glaspy J, Brufsky AM, Bondarenko I, Lipatov ON, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J Clin Oncol* 2011; 29 (10): 1252–60.
31. Montagna E, Cancellò G, Bagnardi V, Pastrello D, Dellapasqua S, Perri G, Viale G, Veronesi P, Luini A, Intra M, Calleri A, Rampinelli C, Goldhirsch A, Bertolini F, Colleoni M. Metronomic chemotherapy combined with bevacizumab and erlotinib in patients with metastatic HER2-negative breast cancer: clinical and biological activity. *Clin Breast Cancer*. 2012; 12(3):207-14.
32. Brufsky A, Valero V, Tiangco B, Dakhil SR, Brize A, Bousfoul N, et al. Impact of bevacizumab (BEV) on efficacy of second-line chemotherapy (CT) for triple-negative breast cancer (TNBC): analysis of RIBBON-2. *J Clin Oncol* 2011; 29 (15s): Abstr 1010.
33. Baselga J, Stemmer S, Pego A, Chan A, Goeminne J-C, Graas M-P, et al. Cetuximab + cisplatin in estrogen receptor-negative, progesterone receptor-negative, HER2-negative (triple-negative) metastatic breast cancer: results of the randomized phase II BALI-1 trial. *Cancer Res* 2010; 70 (24): S2: Abstr PD01-01. doi: 10.1158/0008-5472.SABCS10-PD01-01.
34. Ambros T, Zeichner SB, Zaravinos J, Montero AJ, Ahn E, Aruna M, Kronish L, Mahtani RL, Vogel CL. A retrospective study evaluating a fixed low dose capecitabine monotherapy in women with HER-2 negative metastatic breast cancer. *Breast Cancer Res Treat*. 2014; 146(1):7-14.
35. Wang Z, Lu J, Leaw S, Hong X, Wang J, Shao Z, Hu X. An all-oral combination of metronomic cyclophosphamide plus capecitabine in patients with anthracycline- and taxane-pretreated metastatic breast cancer: a phase II study. *Cancer Chemother. Pharmacol*. 2012; 69, 515–522.
36. El-Arab LR, Swellam M, El Mahdy MM. Metronomic chemotherapy in metastatic breast cancer: impact on VEGF. *J Egypt Natl Canc Inst*. 2012; 24(1): 15-22.
37. Gelmona K, Chanb A, Harbeckc N. The Role of Capecitabine in First-Line Treatment for Patients with Metastatic Breast Cancer. *The Oncologist* 2006;11 (1): 42–51.
38. Joensuu H, Gligorov J. Adjuvant treatments for triple negative breast cancers. *Ann Oncol* 2012; 23 (6): 40-5. doi:10.1093/annonc/mds194.
39. Shaked Y, Emmenegger U, Man S, Cervi D, Bertolini F, Ben-David Y, et al. Optimal biologic dose of metronomic chemotherapy regimens is associated with maximum antiangiogenic activity. *Blood* 2005; 106 (9): 3058-61.
40. Gasparini G. Metronomic scheduling: the future of chemotherapy? *Lancet Oncol* 2:733-40, 2001.

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