

Preliminary Results of Capecitabine Metronomic Chemotherapy Combined with Exemestane in Advanced Breast Cancer – A Single-Arm Phase II Study

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Abstract: Background: Advanced breast cancer is incurable disease and its prognosis is poor. The aim of our trial is the assessment of tolerability and survival outcome of metronomic chemotherapy capecitabine combined with the aromatase inhibitor exemestane in hormone receptor (HR)-positive, HER2- negative advanced breast cancer patients who have a refractory disease following letrozole treatment. **Methods:** Between June 2012 and February 2017, 38 female patients with HR-positive, HER2- negative advanced (locally advanced or metastatic) breast cancer, adequate organ function and performance status (PS) 0-3, who progressed following letrozole treatment received metronomic capecitabine (500mg/m², twice every day) in combination with exemestane (25 mg daily). Treatment was continued until the progression of disease or development of unacceptable toxicity. The primary end point of our study was the assessment of the response rate (RR) and safety while the secondary end point was the assessment of progression free survival (PFS) and overall survival (OS). **Results:** The overall response rate [Complete response, (CR) +Partial response (PR)] was 68.4% (26/38) and the disease control rate [CR+PR+SD (stable disease)] was 78.9 % (30/38 patients). Four patients (10.5%) had stable disease and 8 patients (21.1%) had disease progression. Median PFS and OS were 17 months and 20 months respectively. The 1-year overall survival was 63%. The median duration of treatment was 18 months (range 3-60 months). No toxic death occurred and no grade 3/4 hematological toxicities were documented. Diarrhea and hand-foot syndrome were the commonest grade 3 non-hematological toxicities. **Conclusion:** capecitabine metronomic therapy in combination with exemestane is an effective treatment alternative with manageable toxicity profile which can be used for patients with advanced breast cancer with poor performance status.

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Key words: Metronomic chemotherapy, exemestane, capecitabine, advanced breast cancer.

1. Introduction

The treatment of hormone receptor positive metastatic breast cancer (MBC) who developed disease progression on first line hormonal treatment that included aromatase inhibitors (AI) represents a challenge as those patients ultimately develop resistant disease unresponsive to standard lines of estrogen receptors (ER) blockade [1].

Capecitabine is an oral chemotherapy that mimics continuous infusion of 5-FU with known activity in MBC.[2]It might be preferred because of its tolerability and relatively lower toxicity than other chemotherapeutic agents [3, 4].

Metronomic chemotherapy is defined as the frequent (daily, many times a week, or weekly) or continuous administration of low dose chemotherapeutic agents, without prolonged drug free intervals. This way of administration improve the antiangiogenic activity of chemotherapy[5, 6]. Another important advantage of this approach is the significant reduction in toxicity[7]. The pharmacokinetic characteristics of capecitabine and its

high safety profile make it a suitable drug for metronomic administration [8].

Many studies reported that the overall response rate can be improved by (15.8–21.7%) when metronomic chemotherapy is combined with third-generation aromatase inhibitors.[9, 10]This combination can also decrease the level of both Ki-67 index and VEGF-A significantly in the tumor tissue. Bottini et al reported that the patients who received letrozole plus metronomic chemotherapy achieved higher overall response rate (ORR) than those who received letrozole alone (87.7% vs 71.9% respectively)[10].

Consequently, we initiated our trial to assess the response rate, toxicity and survival in patients with HR-positive, HER2- negative advanced breast cancer, who received metronomic capecitabine in combination with exemestane after progression following treatment with AI letrozole.

2. Materials and methods

Patient Eligibility Criteria

Between June 2012 and February 2017, 38 women with pathologically proven hormone receptor-positive, HER2- negative advanced (locally advanced and/or metastatic) breast cancer, in Clinical Oncology Department, Tanta University Hospital were enrolled. Patients were followed up until November 2018. At the time of analysis, the median follow up duration was 18.1 ± 12.07 months (Range; 3.5-60.6 months).

All patients had refractory disease following letrozole treatment. Patients fulfilled the following criteria:- age between 18-70 years, measurable locally advanced or metastatic disease, postmenopausal or premenopausal women, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 3 , 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, had a history of prior chemotherapy with capecitabine or endocrine treatments with exemestane, or have dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent were excluded from this study. Also, patients suffering from brain metastases or concurrent serious, uncontrolled medical illness (e.g. persistent immune-compromised states, uncontrolled infection, and clinically significant cardiac disease) were not eligible.

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, granted protocol approval and all patients signed an informed consent before the initiation of any treatment.

Treatment Plan and Dose Medication

Eligible patients received prior letrozole treatment. All patients had refractory disease following letrozole endocrine treatments. Prior chemotherapy, endocrine treatments or radiotherapy for advanced disease were allowed. After confirmation of immunohistochemistry status, refractory patients who cannot tolerate conventional chemotherapy or who experienced refractory disease following letrozole treatment received oral capecitabine metronomic therapy ($500\text{mg}/\text{m}^2$, twice every day) in combination with exemestane. (25 mg daily).

Oral capecitabine metronomic therapy in combination with exemestane is discontinued in case of disease progression or major toxicities. Treatment is administered on an outpatient basis.

Adequate hematological and within normal range organ functions were insured every month. Adverse events were monitored throughout the study. A complete resolution of hematologic and non-hematologic toxicity was required except for alopecia and fatigue. If toxicities did not resolve, then a 1- 2 weeks delay of capecitabine were allowed.

Patient Assessment

Assessment of Clinical Benefit, Follow-up and restaging

A tumor response assessment was performed every 2 months of treatment. Pre- and on-treatment monitoring consisted of medical history, physical examination, and bone scan, abdomen and pelvis ultrasound, CT-scan of the chest, abdomen and pelvis, breast ultrasound, MRI and/or mammography. Tumor response was determined according to the Response Evaluation Criteria in Solid Tumors [11], with the overall response rate, including complete response and partial response, while, the disease control rate, including complete response, partial response and stable disease.

Assessment of Toxicity

Patients were evaluated using a directed history and physical examination biweekly during treatment. The occurrence and nature of any adverse events were recorded. Toxicity grading was based on the common terminology criteria for adverse event (NCI-CTC, version 4.0) [12].

Primary and Secondary Endpoints

The primary endpoints of the study were overall response and safety. Secondary end points were the progression-free survival and overall survival. Disease progression was measured from the first dose of oral capecitabine metronomic therapy in combination with exemestane. Disease progression was defined as the appearance of new distant metastatic disease or increase in the size of previously present distant metastatic or local disease as determined by serial axial CT, MRI, breast ultrasound and mammography.

Statistical Analysis:

Thirty eight patients were recruited in the study between June 2012 and February 2017. Patients were followed up until November 2018.

Overall-survival (OS) rates were calculated from the start of oral capecitabine metronomic therapy in combination with exemestane to the time of the last follow-up visit or death using the Kaplan-Meier method [13], with SPSS [Statistical package] (version 21). Progression-free survival was the time elapsed from the date of initiation of oral capecitabine metronomic therapy in combination with exemestane to the date of first evidence of disease progression or death in the absence of disease progression. Overall survival and progression-free survival were compared using the Kaplan–Meier method.

3. Results

Patient characteristics:

Thirty eight patients with pathologically proven hormone receptor-positive, HER2- negative advanced (locally advanced or metastatic) breast cancer were eligible for our study. The baseline characteristics are demonstrated in table 1.

The median age was 50.9 years (range 29–70 years). The majority of patients were postmenopausal 24 (63.2%). Nineteen patients (50.0%) exhibited two or more systemic diseases (diabetes, hypertension, liver insufficiency, renal insufficiency, and myocardial infarction). Invasive ductal carcinoma was the most common pathological subtype (89.5%) and 68.4% of tumors were grade II. 57.8% of patients was initially presented with large tumor size (T3). Twenty two patients (57.9%) had both locally advanced and metastatic breast cancer. More than half of the patients (57.9%) had bone metastasis followed by lung metastasis in 20 patients (52.6%) and 20 (52.6%) patients exhibited at least two metastatic sites. The majority of the patients (94.7%) had good general condition with ECOG performance status score of ≤ 2 . Twenty (52.6%) patients received prior radiation therapy for advanced breast cancer and combination chemotherapy had been received by 12 patients.

Treatment Administration

All patients received oral continuous daily capecitabine (500 mg/m² twice daily) in combination with exemestane (25 mg daily). The last patient stopped capecitabine metronomic therapy at May 2018.

Patients were treated with a median duration of treatment of 18 months (range 3-60 months).

Toxicity

The main treatment related toxicity is showed in table 2. Most of the adverse events were mild and manageable. No Grade 3/4 hematologic toxicity was documented.

The most frequent treatment-related adverse event was Hand-foot syndrome, occurring in 47.3% (18/38) of patients. Grade 1/2 hand-foot syndrome was shown in fourteen patients (36.8%) and grade 3 in only 4 cases (10.5%) which rapidly improved after drug discontinuation and symptomatic treatment. Diarrhea was reported in 4 cases (10.5%) and grade 3 was recorded in two (5.3%) of them. The other reported grade 1/2 non-hematologic adverse events were nausea/vomiting observed 4 patients (10.5%) and fatigue in 2 patients (5.3%).

All patients received the prescribed dose of capecitabine and aromazine. No dose reduction was recorded. The treatment was delayed for one week in six patients due to grade 3 hand-foot syndrome (4 patients) and Grade 3 diarrhea (2 patients). Only 2 patients with grade 3 diarrhoea required hospital admission and improved quickly with anti-diarrhoeal measurement.

Treatment response

The overall response rate (CR+PR) was 68.4% (26/38) and the disease control rate (CR+PR+SD) was 78.9 % (30 patients). Four patients (10.5%) had stable disease and 8 patients (21.1%) had disease progression (Table3).

Table (1): Patients' and tumor characteristics.

Characteristic	No. patients (%)
Age (years)	
Median	50.9 years
Range	(29-70)
SD	± 9.7
Family history	
+ve	4(10.5%)
-ve	34 (89.5%)
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	26 (68.4%)
G3	8 (21.1%)
Histology	
Invasive duct carcinoma (IDC)	34(89.5%)
Others	4 (10.5%)

Lymphovascular invasion	
Positive	26 (68.4%)
Negative	12 (31.6%)
Nodal status	
N1	18 (47.4%)
N2	12 (31.5%)
N3	8 (21.1%)
Presence of Two or more systemic diseases	
	19 (50%)
Prior radiation therapy (Rth)	
Yes	20 (52.6%)
No	18 (47.4%)
First-line endocrine therapy failure	
	22 (57.9%)
Multi-line chemotherapy failure	
	12 (31.5%)
Type of Tumor	
Locally advanced	10 (26.3%)
Locally advanced and metastatic	22 (57.9%)
Metastatic	6 (15.8)
Metastatic sites	
Liver	8 (21.1%)
Bone	22 (57.9%)
Lung	20 (52.6%)
Number of sites involved	
1	18 (47.4%)
2	12 (31.5%)
≥3	8 (21.1%)
ECOG	
1	6 (15.8)
2	30 (78.9)
3	2 (5.3)

Table (2): Hematologic and non-hematologic toxicity.

Toxicity	Grade 1/2 No. (%)	Grade 3/4 No. (%)
Non-hematologic Toxicity		
Hand-foot syndrome	14 (36.8%)	4 (10.5%)
Diarrhea	2 (5.3%)	2 (5.3%)
Nausea/vomiting	4 (10.5%)	0.0
fatigue	2 (5.3%)	0.0
Hematologic Toxicity		
Anemia	12 (31.5)	0.0
Leucopenia	14 (36.8)	0.0
thrombocytopenia	12(31.5)	0.0

Table (3). Treatment response

Evaluable patients	No.	(%)
Complete response (CR)	2	5.3
Partial response (PR)	24	63.2
Stable disease (SD)	4	10.5
Progressive disease (PD)	8	21.1

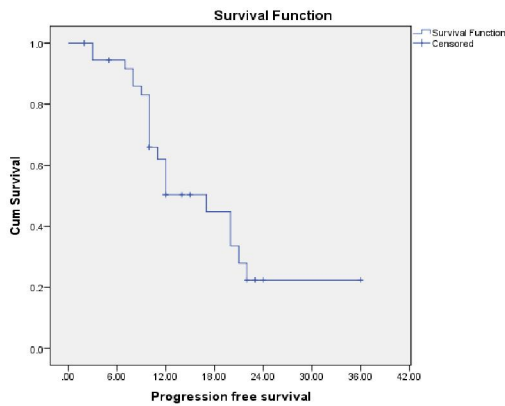
Survival

The median follow-up time was 18.1±12.07months (Range; 3.5-60.6 months).

The median progression free survival (PFS) was 17 ± 3.375 months (95% CI 10.38–23.61) (Fig.1).

The 1-year and 3-year PFS rate were 62% and 22% respectively (Fig.1).

The median overall survival (OS) was 20± 3.705 months (Fig.2). The 1-year and 2-year OS rate was 63% and 44% respectively (Fig.2).

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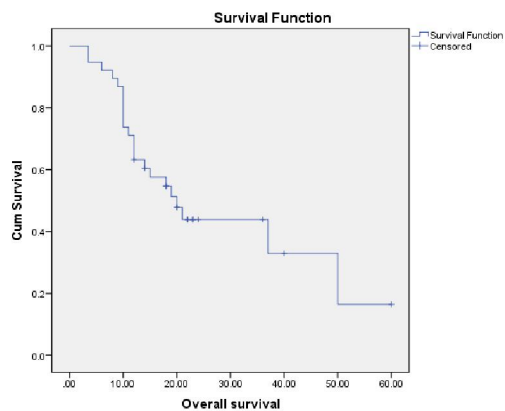
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Fig. 2. Kaplan–Meier curves for overall survival time.

4. Discussion

Endocrine treatment is the preferred treatment to start with in patients with hormone responsive MBC with indolent disease with confirmed improvement in survival [14]. Many trials reported that systemic chemotherapy increase the treatment efficacy in advanced breast cancer [15-17], and the improvement in chemotherapeutic drugs may be more beneficial especially in those patients with high proliferation rates and defective DNA repair.

Other approaches have been assumed to increase the treatment efficacy in patients with advanced breast cancer. One strategy which was explored in many studies is the combination of capecitabine and AI in ER - positive cell lines with expected enhancement in antitumor efficacy [14, 18].

Capecitabine is an oral 5-fluorouracil (5-FU) prodrug which is similar to continuous infusion of 5-FU [2]. Oral chemotherapy is more convenient and is

preferred by the patients than intravenous drugs[19, 20].

Many recent trials have confirmed the role of metronomic chemotherapy in advanced breast cancer [1, 14, 18]. In spite of less toxicity, some metronomic protocols can have unexpectedly strong antitumor effects in preclinical models compared with respected maximum tolerated dose (MTD) protocols [21].

The metronomic dose of capecitabine is highly variable in different regimens and ranges from 1/10 to 1/3 of the MTD.[1, 18, 22-27] So, we planned this study to explore the efficacy and tolerability of twice daily capecitabine at a dose of 500mg/m² as a metronomic chemotherapy, in combination with exemestane (25 mg daily) for patients who progressed after treatment with letrozole.

We think that this is the first prospective trial to study this issue in our country. The results confirm the safety of metronomic capecitabine in combination with exemestane. In our study, most of the treatment related side effects were mild and manageable. The incidence of hematologic and non- hematologic toxicity didn't significantly increase in comparison to previous studies with similar design[14, 18].

The safety of metronomic capecitabine in combination with AIs has been investigated in two previous phase II studies[14, 18]. Shankar et al [14] investigated the response and toxicity of metronomic capecitabine (650mg/m² twice daily) in combination with Letrozole or Anastrozole once daily in 31 metastatic breast cancer patients. The treatment protocol was safe. Leucopenia (Grade 3) was reported in 1 patient. Hand-foot syndrome, the most commonly reported non-hematologic side effect, was mild to moderate (Grade 1 and 2 in 32.2% of patients), and simply treated with standard medications. Similarly, hand-foot syndrome was the most frequently reported non-hematologic treatment-related toxicity in our study occurring in 36.8% (14/38) of patients, with only 4 cases (10.5%) had Grade 3 hand-foot syndrome compared to 14.3% grade 3 or 4 hand-foot syndrome reported by Shankar et al [14]. This could be explained by the higher doses [capecitabine (650mg/m² twice daily)] used in Shankar et al [14] trial than that used in our study [capecitabine (500mg/m² twice daily)]. Shankar et al.[14]reported marked increase in the frequency of vomiting (35.4%) compared to our study (10.5%). While no grade 3 or 4 nausea/vomiting was documented in our trial, Shankar et al reported 9.5% grade 3 or 4 nausea/vomiting [14]. This may be due to effect of higher doses of capecitabine in their trial. Overall, the incidence of diarrhea was lower (10.5%) in our trial compared to that reported by Shankar et al (32.4%) [14]. Again, this may be explained by higher doses of capecitabine used in Shankar et al [14]study. No Grade 3/4 fatigue

was reported in our trial compared to 6.4% in Shankar et al [14] study which is mostly due to lower doses of capecitabine used in our study.

In another study, Li et al [18] investigated the efficacy and toxicity of metronomic capecitabine in advanced breast cancer patients who received multiple lines of chemotherapy. 44 patients received capecitabine 500 mg 3 times per day, without interruption, combined with AIs. No significant Hematological adverse events were reported. The most common documented toxicity was Hand- foot syndrome (43.2%) and GI disorders (18.1%). The documented grade III toxicity was only Hand- foot syndrome and it was reported in only 9.1% of patients.[18]. These results are comparable to our results.

A phase III ongoing study is planned to compare the clinical benefit after treatment with AI combined with metronomic capecitabine versus AI alone in patients with HR-positive, Her2-negative, advanced breast cancer who didn't receive previous chemotherapy or hormonal therapy[28]. This study differs from our trial which is a prospective single arm study. Furthermore, in our study unlike this phase III ongoing study, patients who received prior systemic treatment were not excluded and all our patients received prior therapy before extended capecitabine in combination with aromatase inhibitor treatment.

The dose of capecitabine differs between this phase III ongoing trial [28] and our study. In this phase III ongoing trial, the patients are planned to receive a metronomic capecitabine dose of 625mg/m², orally twice daily (continuously), while in our study the patients received capecitabine 500mg/m² only. We chose lower doses as they are expected to be less toxic, less costly especially in our country with limited resources. Unfortunately, there is no reported data about the adverse events in this phase III study till now. It is estimated to be completed at May 2021 [28].

There are only few studies which addressed the issue of combined metronomic chemotherapy and hormonal treatment[1, 10, 14, 18]. In our study, the response rate was 68.4% (26/38) which is similar to that reported in the study of Li et al (RR was 70.5%) published at October 2018 with a much similar design to our study [18].

In another study, a higher overall response rate (87.7%) was achieved through the combination of letrozole and metronomic cyclophosphamide (50 mg/daily, 6 months) in ER-positive breast cancer patients (T2-4 N0-1). This higher therapeutic efficacy may be due to exclusion of metastatic patients in this study.[10] In our study, 73.7% of patients are metastatic.

Metronomic chemotherapy alone was studied by investigators at Fudan University Shanghai Cancer

Center (FUSCC) who treated advanced breast cancer patients with 500 mg capecitabine three times daily; after first- or second-line hormonal therapy failure and reported response rates of 60% [18]. The response rates in our study was higher (68.4%), thus confirming the better efficacy of combined metronomic chemotherapy and AIs than metronomic chemotherapy alone.

In our study, the disease control rate (CR+PR+SD) was 78.9 % (30 patients) which was consistent with that stated by Li et al [18] who reported disease control rate of 77.3%.

However, our results were better than the results of similar metronomic chemotherapy studies with clinical benefit rates of 31–42% [24, 29]. This difference may be due to the hormonal receptor - positive status of the patients enrolled in our study.

Metastatic breast cancer accounts for a disproportionate number of BC deaths [17]. Most clinical trials indicate a negative effect of MBC on patient survival [30, 31]. Despite the improvements in management, MBC is still an incurable disease and new treatment modalities are needed to extend survival, and delay progression. Importantly, the prognosis of MBC is dependent on tumor grade, age, nodal status, tumor size, hormone receptors, Her2neu status, and treatment [15].

At the time of the final analysis of our study, the 2-year overall survival rate was 44%, which is comparable to that reported by Shankar et al (45%) [14]. The median progression-free survival in our study was 17 months, similar to the 18 months reported by Shankar et al [14], and better than that recently reported by Li et al (16.2 months). [18]

Conclusion

To our knowledge, this is the first study of metronomic capecitabine in combination with exemestane in the treatment of advanced breast cancer in our country. The preliminary results of this trial demonstrated that this combination is a promising effective regimen with acceptable toxicity profile. Thus, we propose that capecitabine metronomic therapy in combination with exemestane treatment is an alternative modality with tolerable toxicities for patients with advanced breast cancer. Nevertheless, the challenge remains to improve clinical outcomes further. To confirm this, a multicenter, meta-analysis and randomized studies with a large number of patients are needed in the near future.

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