Low Dose Docetaxel Combined With Low Dose Capecitabine in Treatment of Metastatic Breast Cancer Previously Treated With Anthracycline

Rabab Mahmoud and Omnia Abd-elfattah

Clinical Oncology Department, Faculty of Medicine, Tanta University, Egypt
Rabab_ms@yahoo.com

Abstract: Metastatic breast cancer (MBC) is the leading cause of death from cancer among women worldwide, accounting for more than 400,000 death per year. Given the generally unfavorable prognosis of MBC and the modest improvements in survival with active treatment, quality of life (QOL) and palliation of symptoms are important treatment goals. For this reason, preferred Successful therapeutic regimens in MBC must balance efficacy and tolerability. This phase II study investigated whether low dose docetaxel in combination with low dose capecitabine could improve the therapeutic index of this regimen .**Patients and Methods:** Patients with anthracycline-pretreated metastatic breast cancer were eligible. Treatment consisted of docetaxel 30 mg/m^2 on days 1 and 8 in combination with capecitabine 825 mg/m^2 twice daily on days 1-14 of a 3-week cycle. Forty two women were enrolled. Median age was 47 years (range, 28-66 years). 35 patients had a performance status of 0-1. Twenty eight patients had triple-negative disease, 13 patients had ER and/PR positive disease Sites of metastasis were as follows: visceral metastasis (n = 14); non visceral (n=8) and both (n = 20). No patients had only bone disease. Eighteen patients had presented with metastasis at initial presentation. **Results:** Of 42 patients who received study treatment two had a complete response, 19 had a partial response, 6 had stable disease and 15 had progressive disease. Overall response rate was 50%. The overall clinical benefit rate was 64, 2%. With a median follow-up of 13 months, median overall and progressive disease survival was 19.3and 10 months respectively. Toxicity was acceptable: 8 patients (19 %) had grade 3/4 adverse events. **Conclusion:** Split low dose docetaxel with low dose capecitabine is an effective combination in the treatment of patients with MBC with manageable toxicity profile, making it an attractive regimen for further larger studies.

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1. Introduction

Metastatic breast cancer is the leading cause of death from cancer among women worldwide, accounting for more than 400,000 deaths per year. Over the past several decades, moderate improvements in survival have been observed for women with MBC.[1]

A population based study from the Surveillance, Epidemiology, and End Results registry of women with newly diagnosed stage IV breast cancer demonstrated that both overall survival OS and breast cancer–specific survival increased between 1988 and 2003. Median breast cancer – specific survival was 23 months (1988-1993, 20 months; 1994-1998, 21 months; 1999-2003, 25 months)**.** Given the generally unfavorable prognosis of MBC and the modest improvements in survival with active treatment, quality of life (QOL) and palliation of symptoms are important treatment goals. For this reason, preferred. Successful therapeutic regimens in metastatic breast cancer (MBC) must balance efficacy and tolerability . [2,3]

Capecitabine and docetaxel are highly active as single agents, with distinct mechanisms of action and little overlap of key toxicities[4, 5]. In addition, taxanes further upregulate thymidine phosphorylase in tumor tissue and are synergistic with capecitabine in breast cancer xenograft models. Therefore combination of capecitabine and docetaxel would offer high antitumor activity. Antitumor activity of the combination is schedule dependent, the most potent schedule was a combination of oral capecitabine for 14 days with docetaxel on days 1, 8, or 15. Maximum tolerated doses seen in phase I studies are weekly docetaxel at 30-36 mg/m^2 with capecitabine 625-825 mg/m^2 twice daily for 14 days[6].

Phase III clinical trial has proven that capecitabine increases response rates (RRs) and median survival compared with docetaxel as a single agent. This improvement in clinical outcomes is partly offset by a parallel increase in the incidence of adverse events with the combination. However, a retrospective analysis of this trial has shown that patients who had dose reductions do not seem to have worse outcomes than those who continued treatment at full doses [7, 8]

The aim of this study is to assess tolerability and efficacy of split low dose docetaxel in

combination with low-dose capecitabine in treatment of MBC previously treated with anthracycline

2. Patients and Method

This prospective phase II study included 42 patients diagnosed with metastatic breast cancer previously treated with anthracycline. Patients treated and followed up at Clinical Oncology Department Tanta University during the period from October 2009 to June 2012.written informed consent was obtained from all patients .

The primary end point of this study was to demonstrate efficacy of low-dose capecitabine and split low does docetaxel in terms of progression-free survival (PFS), which was defined as the time from study to documented disease progression or death. Os was defined as the time from diagnosis to death or last follow up. Overall response rate [complete response (CR) plus partial response (PR)] and overall clinical benefit rate [CR ,PR plus stable disease (SD) divided by the total number of treated patients]. Secondary end point were to evaluate safety according to National Cancer Institute—Common Terminology Criteria for Adverse Events [9]

Patients

Eligible patients were females, aged ≥ 18 years, had histologically or cytologically confirmed metastatic breast cancer, previously treated with anthracycline. Measurable disease was required. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2. Adequate organ function as evidenced by the following parameters was also required: hemoglobin ≥ 10 mg/dL, absolute neutrophil count ≥ 1500/μL, platelet count ≥ 100,000/μL, normal serum creatinine, bilirubin < 2 × the upper limit of normal (ULN) institutional values, transaminases ≤ 3 × (ULN) institutional values in patients with known liver metastasis. Patients were ineligible if they had previously received docetaxel as therapy in the adjuvant or metastatic settings or if they had received ≥ 3 chemotherapy regimens for metastatic disease. Other criteria for exclusion were as follows: a history of severe allergic reactions attributed to compounds of similar chemical or biologic composition to docetaxel and capecitabine, or comorbid illnesses that would make participation in the study dangerous to the patient; and grade ≥ 2 peripheral neuropathy from any cause

Study design

Treatment regimen consisted of docetaxel 30 mg/m2 intravenously on days 1and 8 in combination with capecitabine 825 mg/m^2 orally twice daily on days 1-14 of a 21-day cycle. Doses of both docetaxel and capecitabine were reduced by 25% for most adverse events for patients who had grade ≥ 3 toxicity when they recovered from it. The dose for capecitabine alone was reduced if the severe adverse event (SAE) was palmarplantar erythrodysesthesia (PPE). Patients were taken off study if they had progressive disease (PD) or SAEs, SAEs, defined as grade 3/4 toxicity that did not improve within 3week to grade ≤ 2 or if treatment was held for > 3 weeks. Patients who exhibited a response or stable disease after 6 weeks of therapy continued to receive treatment until disease progression or the development of unacceptable toxicity.

Treatment Assessment

A complete medical history and physical examination, tumor measurement, and evaluation of PS were performed before initiations of therapy, Baseline imaging studies were done no longer than 2 weeks before enrollment. Medical history and physical examination were repeated at least once every 3 weeks during treatment. Complete blood count (CBC) and chemistry panel were performed on days 1 of therapy, CBC was performed at day 8. All patients who received study therapy were assessed for toxicity and response.

Patients were evaluable for response if they received 2 cycles of treatment and had a repeat imaging study for disease assessment. Imaging studies were repeated every 2 cycles and Response Evaluation Criteria in Solid Tumors (RECIST) were used for response assessment [10] , Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [9].

Statistical Method

Survival was calculated by using the Kaplan-Meier method. Statistical testing of significance between survival rates was performed using the log rank method. All calculations were performed with SPSS 18.0 for Windows (SPSS Inc, Chicago, Ill, USA).

3. Results

Patient and tumor characteristics at baseline

Forty two women were enrolled. Median age was 47years (range, 28-65 years). 35 patients had a performance status of 0-1 and 7 patients had performance 2.The majority of patients had ductal breast cancer (88%) .Nodal positive disease was 42, 8% and T3 T4 were 66, 6%. 28 patients had triple-negative disease, 13(30,9) patients had ER and/PR positive disease. Sites of metastasis were as follows: visceral only (n = 14patients); non visceral (n = 8patients) and both (n = 20 patients). No patients had bone-only disease.28, 5%presented with solitary lesion. Eighteen patients had presented with metastasis at initial presentation. Baseline characteristic are summarized in table 1

Table (1) Patient and tumor characteristics at baseline

	N	%
Age		
<40.	14	33.33
40-60.	20	47.62
>60.	8	19.05
Median	47y	
Range	28-65y	
ECOG PS		
0	4	9.52
1	31	73.81
2	7	16.67
Subtypes		
Ductal	37	88
Lobular	4	9.6
Inflammatory	1	2.4
Nodal status		
N0	10	23.81
N+	18	42.86
Unknown	14	33.33
Tumor size		
T1-2	14	33.33
T3-4	28	66.67
Time for development of metastasis		
After adjuvant therapy	24	57.14
At initial presentation	18	42.86
Hormone receptor status		
Positive for ER,PR or both	13	30.95
Negative ER and PR	29	69.05
Her-2 neu		
Positive	6	14.29
Negative	36	85.71
Triple negative	28	66.67
No. of metastatic sites		
1	12	28.57
>1	30	71.43
Metastatic site		
Visceral	14	33.33
Non visceral	8	19.05
Both	20	47.62

Assessment of efficacy

Chemotherapy cycles were ranged from 5-20 with median of 13 cycles. Of 42 patients 2 had CR, 19 patients had PR, 6 Patients had SD and 15patients had PD. Over all response rate (ORR) and over all clinical benefit rate were (50% and 64, 2%) respectively these results are shown in table (2). With median follow up13 months PFS and OS were (10 month and 19, 3months) respectively as shown in figures 1and 2 .Factor affecting PFS in a univariate analysis were: hormonal status; triple-ve and no of metastatic site. When multivariate analysis was performed, hormonal status and No of metastasis were only independent determinants of survival as shown in Figs 3and 4.

Table (2) Assessment of response

Responses	N	%
CR	2	4,76
PR	19	45,24
SD	6	14,29
PD	15	35,7
ORR	21	50
Overall clinical benefit rate	27	64,2

Adverse events

The most common grade 1-2 adverse events were gastrointestinal disorder including nausea, vomiting, diarrhea and stomatitis (60%).Eight patients (19,3%) had grade 3-4 toxicity ,febrile neutopenia in 3 patients, anemia in one patient, thrompocytopenia also in one patient while PPE in 2 patients and peripheral neuropathy in only one patients, ¾ toxicity.

docetaxel and capecitabine were reduced by 25% for six patients (five patients with hematological toxicity and one with peripheral neuropathy) who had grade ≥ 3 toxicity when they recovered from it while the dose for capecitabine alone was reduced for the two patients who suffered from PPE after recovery**.** No patient withdrawal due to grade ¾ toxicity. Table(4) shows grade 3/4 adverse events.

4. Discussion

In the present study split low-dose docetaxel in combination with low-dose capecitabine treatment of metastatic breast cancer pre treated with anthracycline demonstrated RRs of 50% and overall clinical benefit rates was 64, 2%. With a median follow-up of 13 months, median PFS and OS were (10 months and 19.3months) respectively these efficacy results are similar to those obtained in other studies in which higher doses of capecitabine and 3-weekly docetaxel were used. (Table5).

In a phase III randomized trial of 511 patients with MBC, capecitabine 1250 mg/m2 twice daily on days 1-14 in combination with docetaxel 75 mg/m2 on day 1 of a 3-week cycle showed improved outcomes that were statistically significant compared with docetaxel as a single agent (100 mg/m2 every 3 weeks) with increase toxicity and dose reductions. A retrospective analysis of this phase III trial assessed the tolerability and efficacy in patients who underwent dose reductions (docetaxel 55 mg/m2 on day 1 and capecitabine 950 mg/m2 twice daily on days1-14) .Grade 3/4 adverse events was almost

halved with no differences in median time to disease progression (6.2 months vs. 6.8 months) and median OS (14.6 months vs. 15 months).[8]

Mrozek et al. (2006) have assessed weekly docetaxel in combination low dose capecitabine in the treatment of patient with MBC, 39 patients received docetaxel 30 mg/m2 on days 1, 8, and 15 with capecitabine at a dose of 800 mg/m2 twice daily for 21 days of a 28-day cycle. The ORR was 44% and the median TTP was 5.5 months Grade 3 toxicities were asthenia (18%), diarrhea (18%), nausea/vomiting (13%), stomatitis (13%), neutropenia (13%), and PPE (10%). Two patients had a grade 4 adverse event: 1 had febrile neutropenia and another had pulmonary embolism.[12]

Mackey et al. (2004), 20 patients received docetaxel 30 mg/m2 weekly and capecitabine at a dose of 900 mg/m2 twice daily for 14 days the median TTF was 10 weeks and the median OS was 82 weeks. Toxicity led to treatment discontinuation in 10 of 20 patients with increase incidence of grade3 -4 toxicities. In both trials, the planned doses of docetaxel and capecitabine were higher than in ours study, which explains the greater incidence of adverse events and treatment discontinuation. [13]

Table (3) Univariate analysis of factors influencing PFS

		Median	SE	Log Rank	*P*-value
Age	**<40.**	13	2.77	1.41	0.4934
	40-60.	13	1.71		
	>60	11.5	0.46		
Subtypes	**Ductal**	11	0.36	1.7	0.842
	Lobular	12.42	0.56		
	Inflammatory	10	1.31		
Nodal status	**N0**	10.56	0.94	0.54	0.7617
	N+	10	1.73		
	Unknown	11.21	0.91		
Tumor size	**T1-2**	10	1.19	0.14	0.7102
	T3-4	12	1.84		
Hormonal status	**Positive**	13.18	0.53	9.2	0.0024
	Negative	10	0.56		
Her-2neu	**Positive**	13	0.91	2.33	0.1266
	Negative	10	0.54		
Tripple-ve	**Triple negative**	10	0.55	7.07	0.0078
	Not triple negative	12.81	0.61		
No of metastasis	**1**	13	0.75	5.86	0.0155
	>1	9	0.85		

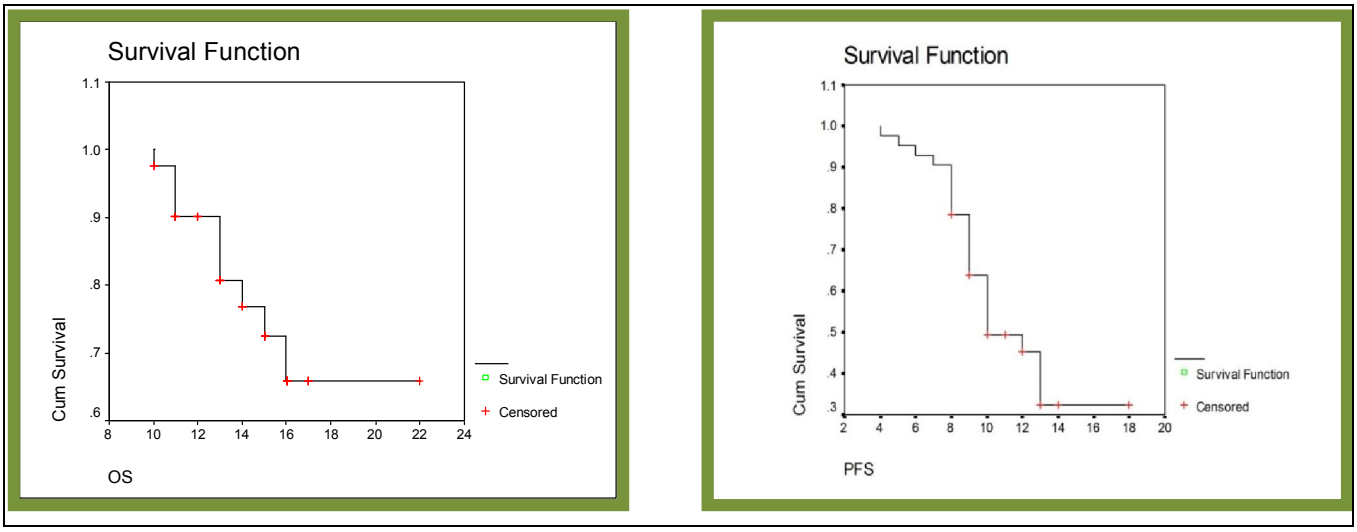

Fig (1) Overall survival of all patients **median OS 19.3 months**

Fig (2) Progression free survival of all patients **median PFS 10 months**

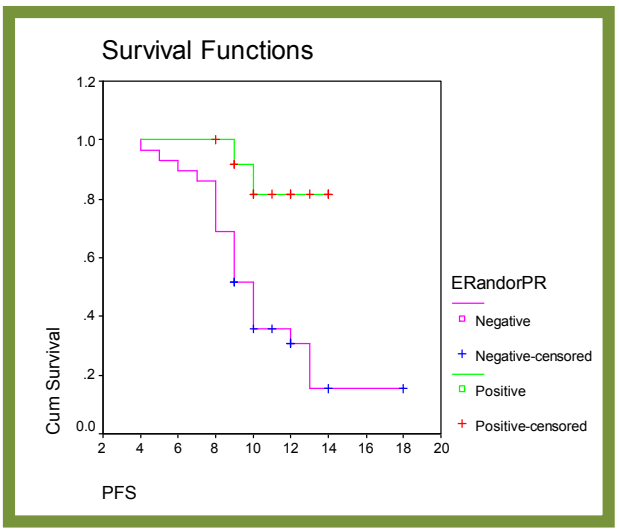

Fig (3) PFS according to hormonal status

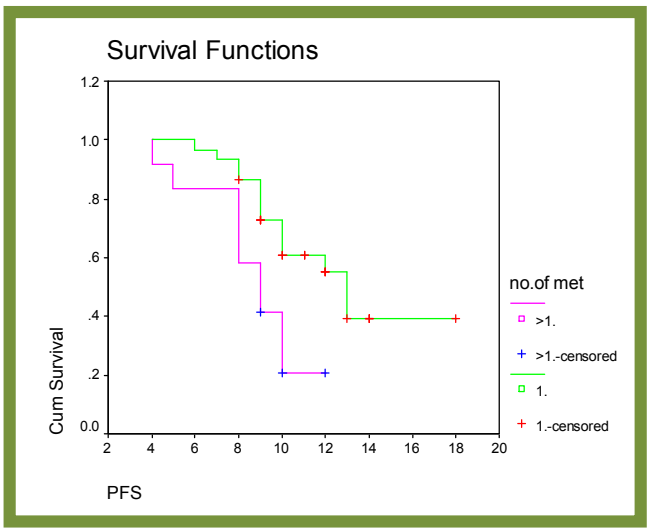

Fig (4) PFS according to No of metastasis

Table (4) Grade ¾ adverse events

Adverse events	N	%
Heamatological toxicities	5	11.90
Neutropenic fever	3	7,1
Anemia	1	2,4
Thrompocytopenia	1	2,4
Non Heamatological toxicities	3	7.4
PPE	2	4.76
Diarrhea	0	0.00
nausea/vomiting	0	0.00
Nail change	0	0.00
Peripheral neuropathy	1	2.38
Mucositis	0	0.00
Alopecia	0	0.00
Treatment related death	0	0.00

Table (5) Studies utilizing docetaxel in combination with capecitabine in treatment of MBC

Study	phase	N	Docetaxel	Capecitabine	Os	TTP	CR+PR	Overall clinical benefit
O'Shaughnessy et al [7]	III	255 256	75 mg/m2 day 1 100 mg/m2 day 1	1250 mg/m2 twice daily on days 1-14	14.5 11.5	6.1 4.2	42% 30%	80% 74%
Baslija et al [11]	III	50 50	75 mg/m2 on day 1 100mg/m2d1	1250 mg/m2 twice daily on days 1-14 Same as above but in sequence not combination	22 19	9.3 7.7	68% 40%	Not available Not available
Mackey et al [13]	II	20	30 mg/m2 weekly	900 mg/m2 twice daily on days 1-14	20.5	6.5	18%	71%
Mrozek et al [12]	II	39	30 mg/m2 on days 1, 8, 15	800 mg/m2 twice daily on days 1-21	Not available	5.5	44%	Not available
Silva et al [14]	II	39	25 mg/on days 1, 8	750 mg/m2 twice daily on days 1-14	Not reached	Not Available	50%	69%
In our study	II	42	30 mg/on days 1, 8	800 mg/m2 twice daily on days 1-14	19.3	10	50%	64.3

Silva et al. (2008), assess the efficacy, a of split low-dose docetaxel in combination with low-dose capecitabine in the treatment of patients with metastatic, HER2/neu–negative breast cancer where 39 patients treated with docetaxel 25 mg/m2 intravenously on days 1 and 8 in combination with capecitabine 750 mg/m2 orally twice daily on days 1-14 of a 21-day cycle. Overall response rate was 50% in evaluable patients. The overall clinical benefit rate was 69%. With a median follow-up of 25 months, median time to treatment failure was 4.25 months and median overall survival has not yet been reached. Toxicity was moderate: 15 patients (41%) had grade 3/4 adverse events.[14]

5. Conclusion

Our results suggest that split; low-dose docetaxel and low-dose capecitabine is effective combination in the treatment of patients with MBC pretreated with anthracycline with mild grade3/4toxicity, making it an attractive regimen for further larger studies with longer follow up.

Corresponding Author
Rabab Mahmoud Abo sbaa .MD.
Clinical Oncology Department .Faculty Of Medicine. Tanta University, Ahmed Maher St El-Mahlla El Kubra Gharbia ,Egypt
E.mail: Rabab_ms@yahoo.com

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