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Original article

Metronomic Capecitabine and Vinorelbine as Second Line Therapy in Advanced Breast Cancer

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Background and Aim: Management of metastatic breast cancer (MBC) remains a great challenge for oncologists. The aim of our study was to evaluate the efficacy and toxicity of capecitabine combined with vinorelbine as a second line treatment in MBC.
Materials and Methods: Twenty-three patients with MBC received oral capecitabine (1000 mg/m^2/day) for 14 days plus vinorelbine (oral 60 mg/m^2 days 1, 8 and 15 or intravenous 25 mg/m^2 days 1and 8 according to patients' preference and drug availability).
Results: The median age of patients was 52 years and 61% of them were ER –ve / PR-ve and 91% were HER2 –ve. Eighty-three percent of patients failed treatment with anthracyclines and 48% with taxanes. The majority (83%) received the oral formulation of vinorelbine and the median number of cycles per patient was 3. The overall response rate was 56.5%; however, none of the patients achieved complete remission. The median progression free survival for the whole group of patients was 4.2 month. Grade 3- 4 hematological toxicities were more likely to occur with the oral vinorelbine regimen and there were no treatment-related deaths.
Conclusions: Metronomic capecitabine and vinorelbine combination seems to be tolerable and effective as a second line chemotherapy in MBC. A higher dose of capecitabine in combination with vinorelbine, may improve survival and increase the response rate.

Key words: Metastatic Breast Cancer, Second Line Therapy, Metronomic, Capecitabine, Vinorelbine.
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INTRODUCTION

Breast cancer rates are increasing in developing countries. In Egypt it represents 39% of cancer in females with some variation in the prevalence according to the region where the prevalence was 34%, 27% and 39% in Lower, Middle, and Upper Egypt; respectively[1, 2].

Metastatic breast cancer (MBC) may be either metastatic from the date of diagnosis or develops months or years after a person has completed treatment for early or locally disease. Almost one third of patients diagnosed with early breast cancer may develop metastatic disease[3]. The goals of management of MBC patients include improving their health-related quality of live and increasing progression free survival (PFS) and may be overall survival (OS)[3].

Metronomic chemotherapy is the administration of anti-cancer drugs at low doses without long drug-free period. The frequent administration of certain chemotherapeutic agents at low doses enhances the anti-angiogenic activity of the drugs. The co-administration of another chemotherapeutic agent with tumor formation inhibitory properties is expected to potentiate the effectiveness of metronomic chemotherapy. By using chemotherapeutic agents in a metronomic fashion, toxicity resulting from chemotherapy is minimized while proliferating tumor cells as well as endothelial cells are targeted[4].

Anthracyclines and taxanes are commonly used in the adjuvant setting as well as in the metastatic setting as front-line option. For anthracycline/taxane pre-treated MBC patients, other agents like capecitabine and vinorelbine may be used. An advantage of combining vinorelbine and capecitabine is the synergetic action obtained by this combination. This is because their different mechanisms of action and the lack of overlapping toxicity[5].

In a dose finding study, the administration of metronomic vinorelbine at a dose up to 50 mg thrice/ week was feasible[6]. Another study found the maximum tolerated dose of metronomic vinorelbine to be 60 mg every other day[7].

Combining capecitabine to vinorelbine may result in better outcome when compared to monotherapy in selected populations[8]. As first line for MBC patients, this combination was shown to be feasible and effective[9].

When used in combination with capecitabine, both the intravenous and oral formulations of vinorelbine yielded similar efficacy; however, the oral formulation regimen was better at the level of some quality of life aspects[10].

The aim of the present study was the evaluation of the efficacy and toxicity of metronomic low dose capecitabine combined with vinorelbine as a second line treatment in patients with MBC.

PATIENTS AND METHODS

This study was a prospective; phase II single institution study. The Ethics Committee of the Faculty of Medicine, Assuit University, approved the protocol and all patients signed an informed consent before inclusion.

Patients' selection

Inclusion criteria included: female patient >18 years of age, histopathological confirmation of MBC, at least one bidimensionally measurable metastatic lesion, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, no pregnancy and adequate hematological, renal, and hepatic functions.

Treatment plan

Treatment consisted of capecitabine 1000 mg/m^2/ day for 14 days plus vinorelbine, orally (60 mg/m^2 days 1, 8 and 15) or intravenously (25 mg/m2 days 1 and 8) according to patients' preference and drug availability. The cycle was repeated every 21 days if patient has adequate hematological function. For non-hematological toxicities, the drugs was given at 75% of planned doses or omitted if a toxicity of grade 3 or 4 occurred. In case of a complete response (CR), patients received 2 additional cycles of chemotherapy. Patients with partial response (PR) and stable disease (SD) were treated for a maximum of 12 cycles. Patients were withdrawn from the study at any evidence of progressive disease.

Patients' assessment

Pretreatment assessment included medical history and physical examination, chest X-ray or computed tomography (CT) scan, abdominal ultrasound examination or CT scan and bone scan within 2 weeks before starting treatment.

After starting treatment, assessment was done every 2 cycles, at the end of treatment and every 2 months thereafter till evidence of disease progression with the appropriate tests for all patients, clinically and radiological.

The therapeutic efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 every two cycles. The efficacy was evaluated as complete remission (CR), partial responses (PR), stable disease (SD), and progressive disease (PD). The overall response rate (ORR) = (CR+ PR)/case number ×100. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) was applied in this study.

The primary end point of this study was to assess the efficacy of this regimen: Overall response rate (ORR) and progression free survival (PFS), while the secondary end point was to assess the safety and toxicity profile of this combination.

Statistical analysis

PFS was defined as the time elapsed between combined treatment initiation and tumor progression or death during the combination therapy or maintenance therapy. Kaplan-Meier survival analysis was performed. Statistical analysis was performed using SPSS version 17.0.

RESULTS

From January 2010 to December 2013, 23 female patients with MBC were enrolled in this study at Assiut University Hospital. Their characteristics are shown in Table 1.

The median age was 52 years (range: 37 – 75), they were ER−/PR− in 61% of patients and HER2− ve in 91% of patients .Number of metastatic site was ≥2 in 61% of patients. Liver was the commonest site of metastasis in 56.5% of patients, followed by bone in 47.7% and lung in 43.5%. Eighty-three percent of patients had experienced treatment failure with previous anthracyclines and 48% of patients had experienced treatment failure with taxanes.

Nineteen patients received oral formulation of vinorelbine while only four patients received the intravenous formulation. A total of 98 cycles were administered and the median number of cycles per patient was three (Range1 to 9).

The overall response rate was 56.5% all are partial response (Table 2).

The median PFS was 4.2 month (Figure 1).

The treatment-related toxicities are illustrated in Table 3

Differently from the intravenous formulation, oral vinorelbine was associated with more frequent grade 3 -4 hematological toxicities (anemia in 13% of patients with oral vinorelbine versus 4% of patients with intravenous vinorelbine and neutropenia in 9 % of patients with oral vinorelbine versus 0% of patient with intravenous vinorelbine. Nausea, vomiting and diarrhea were mainly grade 1- 2 toxicities (nausea and vomiting in 30% of patients with oral vinorelbine versus 9% of patients with intravenous vinorelbine, diarrhea in 22% of patients with oral vinorelbine versus 4% of patients with intravenous vinorelbine. Abdominal pain occurred in 17% of patients with oral vinorelbine. Hand-foot syndrome encountered in 9% of patients all are grade 2 and no treatment-associated death was noted.

Table 1: Patients' characteristics.

Characteristic	No.	%
Age (years)		
Median (range)	52 (37-75)	
ECOG performance status		
0-1	17	74
2	6	26
Hisological subtype		
Ductal carcinoma	18	78.3
Lobular carcinoma	5	21.7
Hormone receptor status		
ER+ve / PR-ve	3	13
ER-ve / PR-ve	14	61
ER+ve / PR+ve	6	26
HER2 status		
HER2 -ve	21	91
HER2 +ve	2	9
Site of distant metastases		
Liver	13	56.5
Bone	11	47.7
Lung	10	43.5
Brain	3	13
Number of metastatic sites		
1	9	39
≥ 2	14	61
Prior therapy for metastatic disease		
Chemotherapy		
Anthracyclines	19	83
Taxanes	11	48
Hormonal	9	39

Table 2: Response to treatment with capecitabine-vinorelbine combination

Response	No.	%
Partial response	13	56.5
Stable disease	8	34.8
Progressive disease	2	8.7

Table 3: Toxicities related to treatment with capecitabine-vinorelbine combination

Toxicity	Grade, n (%)				
	1	2	3	4	Total
Hematological					
Anemia	0	0	3 (13)	1 (4)	4 (17)
Neutropenia	0	0	1 (4)	1 (4)	2 (9)
Non-hematological					
Nausea-vomiting	2 (9)	7 (30)	0	0	9 (39)
Diarrhea	4 (17)	2 (9)	0	0	6 (26)
Abdominal pain	1 (4)	3 (13)	0	0	4 (17)
Hand –Foot syndrome	0	2 (9)	0	0	2 (9)
Stomatitis	1 (4)	1 (4)	0	0	2 (9)

Table 4: Studies evaluating capecitabine-vinorelbine combination as 1st or 2nd line treatment in metastatic breast cancer

Author	No. of patients	Capecitabine (days 1 to 14)	Vinorelbine (days 1 & 8)	Overall response rate	Median TTP (months)
		Dose (mg/m2)			
1st Line					
Elghazaly et al [11]	45	2000	25	64%	9
Hess et al [12]	70	1000, 1300	20	43%, 57%	4.3, 7.0
2nd Line					
Xu B et al [14]	77	1900	25	47%	6
Davis et al [17]	22	2000	25	33%	5.8
Ahn et al [18]	44	2500	25	50%	5.3
The present study	23	1000	25	56.5%	4.2

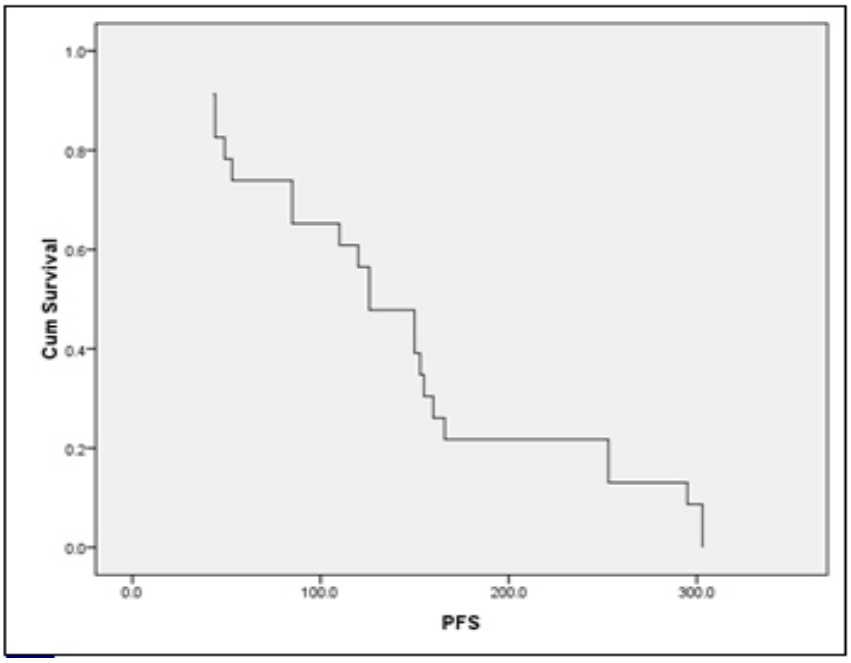

Figure 1: Kaplan Meier curves showing progression free survival (in days) of 23 patients treated with capecitabine plus vinorelbine

DISCUSSION

The management of MBC is a challenge which is made more difficult by the availability of many new active agents and the increasing number of therapeutic plans15, 16. In the MBC treatment setting, chemotherapeutic agents can be used as monotherapy or combination. Vinorelbine is among the drugs that have been found to be effective in MBC when administered as monotherapy13. The capecitabine-vinorelbine combination was demonstrated to be active in metastatic MBC patients as a second line with a good response rate. An important advantage of combinations like capecitabine-vinorelbine is the feasibility of administering them for relatively long periods as long as the disease is controlled, which is not possible with anthracycline or taxane combinations due to toxicities.

The outcome of a number of trials in which capecitabine-vinorelbine combination was used in MBC patients as a first or second line with comparison to the results of the present study are shown in Table 4.

In our study the response rate was 57% which is higher than that reported in some other trials, in which capecitabine-vinorelbine combination was used in pretreated MBC patients, and ranged from 33% to 50%[14, 17, 18].

On the other hand, the PFS in the present study (4.2 months) was lower than that reported in other studies. In studies that assessed the efficacy of capecitabine-vinorelbine combination as a second line in MBC, the time to progression ranged from 5.3 to 6 months[14, 17, 18].

The lower survival in our study may be because we used a relatively lower dose of capecitabine (1000 mg/m^2). In the other studies with higher survival rates, the dose of capecitabine was higher than ours and ranged from 1900 mg/m^2 to 2500 mg/m^2. [14, 17, 18] Another factors that may have contributed to the lower survival in our study is the lower median number of treatment cycle and the small sample size.

As a first line treatment for MBC patients, capecitabine-vinorelbine combination showed more or less comparable response rate and PFS among studies. However, the data suggest that capecitabine-vinorelbine combination with a higher dose capecitabine (1300-1700 mg/m2) has a higher response rate and longer PFS11, 12.

Results of other studies showed that there is a substantial equivalence between the intravenous and oral formulations of vinorelbine, even if the latter is characterized by a higher rate of hematological toxicity,[19-21] which agrees with our results. In addition, oral vinorelbine in our study was associated with more frequent nausea, vomiting and diarrhea justifying antiemetics administration. Although the toxicity may be higher, the use of oral formulations of vinorelbine may be more convenient with reduced hospitalization and is considered an attractive option in the elderly.

Overall, treatment-related toxicities were acceptable and manageable. Treatment toxicity was controlled by treatment interruption and dose reduction and no treatment-associated death was noted. Grade 3-4 toxicities were hematological in the present study (anemia in 17%, neutropenia in 9 % of patients) and these occurred mainly 10-13 days after chemotherapy administration and resolved after management using granulocyte colony-stimulating factor. Non-hematologic toxicities were grade 1-2 gastro-intestinal toxicities and grade 2 hand-foot syndrome and they were treated with symptomatic treatment and the patients could continue to receive the following treatment cycles.

In conclusion, capecitabine-vinorelbine combination seems to be tolerable and effective as a second line chemotherapy in MBC. A higher dose of capcitabine in capecitabine-vinorelbine combination may improve PFS with acceptable treatment toxicity and higher response rate.

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