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Evaluation of the Effect of Combination Chemotherapy with Five-day Infusion of Fluorouracil plus Vinorelbine in Pretreated Metastatic Breast Cancer Patients

Mai Ezz El Din[1]*, Rasha Salah[2], Tarek Kamel[1], Ahmed Nagy[1]
[1]Department of Clinical Oncology, Faculty of Medicine, Ain Shams University, Egypt
[2]Department of Clinical Oncology, El Salam Oncology Centre, Cairo, Egypt
***Corresponding author:** Mai Ezz El Din, **Mobile:** (+20) 01223176730,
E-Mail: mai.ezzeldin@med.asu.edu.eg; maiooyaz@yahoo.com

ABSTRACT

Background: Continuous infusion (CI) of 5-fluorouracil (5FU) and vinorelbine, individually and in combination, has been proven in several studies to be active and well tolerated for advanced pretreated breast cancer.

Objective: This study sought to evaluate the clinical activity and side effects of their combination in pretreated metastatic breast cancer patients.

Patients and Methods: This retrospective study collected and analysed the medical records of fifty-four patients who attended El-Salam Oncology Center and Ain Shams University Hospitals, Department of Clinical Oncology during the period from July 2013 to June 2018. Combination chemotherapy received was 5FU 600 mg/m^2/d for 5 consecutive days as a CI and vinorelbine 25 mg/m^2 on days 1 and 5 as a short intravenous (IV) infusion every 3 weeks.

Results: Eleven (20.4%) complete responses, 20 (37%) partial responses and 14 (25.9%) stable disease were documented, accounting for a clinical benefit rate of 83.3%. The median progression free survival was 6.8 months. The median overall survival (mOS) was 25.8 months. Treatment was well tolerated, with grade 3 anemia, febrile neutropenia and stomatitis in 9.3%, 5.6% and 1.9% respectively as the main adverse reactions.

Conclusions: This drug combination is active in metastatic previously treated breast cancer patients with an acceptable toxicity profile and continues to be present in the treatment armamentarium in this setting.

Keywords: Chemotherapy, Fluorouracil (Infusion), Metastatic Breast Cancer, Vinorelbine.

INTRODUCTION

Breast cancer has surpassed lung cancer as the most commonly diagnosed cancer worldwide, accounting for over two million cases each year including low- and middle-income countries [(1)]. Despite the gains in early detection, up to 30% of women with early-stage, non-metastatic breast cancer at diagnosis will develop distant metastatic disease. Although metastatic breast cancer is unlikely to be cured, meaningful improvements in survival have been seen, which can be explained by the introduction of newer systemic therapies [(2-4)].

For selected patients, the use of a combination regimen rather than a single agent is preferred because combination therapy results in a higher response rate, which may justify the risks of treatment [(5)]. Apart from new agents, another treatment strategy is represented by different ways of administering known drugs with a possible enhancement of their therapeutic activity.

Vinorelbine is active as a single agent (Objective response rate (ORR) 25- 45%) even in heavily pretreated patients [(6-8)], some authors also reported a possible lack of cross-resistance with anthracyclines [(9-10)].The effectiveness of CI 5FU in adenocarcinoma is well established [(11)], where low dose CI 5FU has been shown to offer useful palliation for advanced breast cancer, with an ORR ranging from 16% to 53% [(12)]. In addition to its moderate hematologic toxicity, which allows for combinations with other myelosuppressive agents, this route of administration is usually associated with an acceptable toxicity profile mainly consisting of mucositis and hand-foot syndrome [(13)].

In fact, compared with conventional route, increasing the duration of exposure to fluorouracil can potentially enhance tumor cell kill, and low drug levels are generally detected in bone marrow, a finding consistent with the absence of myelodepression reported after protracted infusion of this compound [(14-15)].

One randomised phase III study [(16)] demonstrated that docetaxel showed comparable efficacy to 5-fluorouracil+vinorelbine in anthracycline-pretreated metastatic breast cancer patients with docetaxel.

So, in this retrospective study we evaluated the effect of the combination of 5-days CI of fluorouracil plus IV vinorelbine in pretreated metastatic breast cancer patients.

PATIENTS AND METHODS

This retrospective study collected and analysed the medical records of fifty-four patients who attended El-Salam Oncology Center and Ain Shams University Hospitals, Department of Clinical Oncology during the period from July 2013 to June 2018.

For patients entered in this study, the diagnosis of breast carcinoma had been histologically confirmed. Eligibility criteria included metastatic disease, previous chemotherapy administration in the metastatic setting and Eastern Cooperative Oncology Group (ECOG) score less than 3 with normal hematological, hepatic and renal functions.

Treatment plan:

Fluorouracil was administered at the dose of 600 mg/m^2 CI for five days and vinorelbine 25 mg/m^2 IV bolus, was delivered on day 1 and 5. Cycles were planned every three weeks.

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Treatment evaluation:

A chart review of the medical history, physical examination and full laboratory investigations prior to treatment with recorded scans and evaluations of response to therapy were collected. Toxicity was evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [(17)].

Antitumour activity was assessed every 2-3 cycles on all target lesions. Tumour responses and time-related parameters were assessed using response evaluation criteria in solid tumors (RECIST) 1.1 [(18)]. The clinical benefit rate (CBR) was defined as the percentage of patients with complete response (CR) or partial response (PR) or stationary disease (SD). Progression free survival (PFS) was calculated as the time interval from receiving the chemotherapy protocol till disease progression or death due to any cause and overall survival (OS), which is the time interval from chemotherapy to the patient's death, was also calculated.

Ethical consent:

An approval of the study was obtained from Ain Shams University Academic and Ethical Committee. Every patient signed an informed written consent for participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical methods:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for the Social Sciences) version 21 for Windows® (IBM SPSS Inc, Chicago, IL, USA). The primary endpoint of the study was clinical benefit rate (CBR) with PFS, OS and toxicity set as secondary end points. Frequencies and percentages had been used to summarize categorical data. For continuous data, median or mean and interquartile range or standard deviation had been used to describe centrality and dispersion respectively according to normality of the data. OS and PFS had been evaluated with the Kaplan–Meier method and groups had been compared with the log-rank test. Cox regression had been used to calculate unadjusted and adjusted hazard ratios, 95% confidence intervals and associated p values. Two-sided p value <0.05 was considered as a cut-off value for statistical significance.

RESULTS

Patient characteristics

From July 2013 to June 2018, the medical records of 54 patients were analysed. The median age was 46.5 years with 61.1% of patients being premenopausal and 11 cases were de novo metastatic. The majority of patients (64.8%) had visceral metastases. A total of 274 cycles were administered with a median of 6 cycles ranging from 2 to 9 with half of the study cohort having received 6 doses. All of them had received at least one line of chemotherapy in the metastatic setting. Table 1 outlines the main characteristics of the patients.

Table (1): Patient's characteristics

			Frequency	Percent
Age	<46.5		27	50
	>46.5		27	50
ECOG Performance status	0		14	25.9
	1		30	55.6
	2		10	18.5
Comorbidity	Yes	D.M	9	7	16.7	12.96
		HTN		6		11.11
	No		45	83.3
Family history	Positive		4	7.4
	Negative		50	92.6
Menopausal status	Premenopausal		33	61.1
	Postmenopausal		21	38.9
Molecular subtype	Luminal A		25	46.3
	Luminal B		11	20.4
	HER-2 Over-expression		1	1.9
	TNBC		17	31.5
Site of metastasis	Liver		23	42.6
	Lung		23	42.6
	Bone		13	24.1
	Lymph nodes		9	16.7
	Local recurrence		18	33.3
	Contralateral		4	7.4
	Adrenal gland		1	1.9
Number of line in metastatic setting	2		30	55.6
	3		11	20.4
	4		8	14.8
	5		2	3.7
	6		3	5.6

TNBC: Triple negative breast cancer

Primary endpoint: CBR:

The vast majority of patients achieved a Partial Response (PR) 37% (20/54), with 20.4% (11/54) achieving Complete Response (CR), 25.9% (14/54) achieved Stationary Disease (SD) and 16.7% (9/54) progressed on vinorelbine/5FU (PD). Thus a CBR of 83.3 % (45/54) was achieved and the objective response rate (ORR) was 57.4%.

Secondary end points:

A median PFS of 6.8 months (Figure 1) and mOS of 25.8 months (Figure 2) were demonstrated. By the end of the study 24 (44.4%) cases remained alive. Main toxicities (grade 3) were anemia, febrile neutropenia, peripheral neuropathy and mucositis (Table 2).

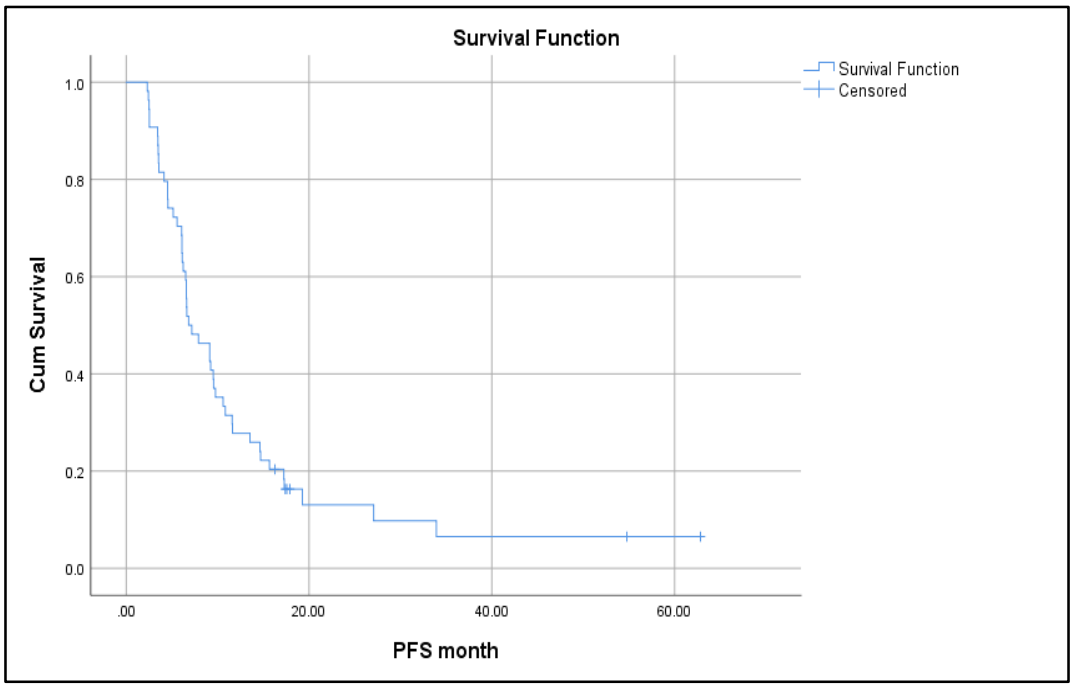

Figure (1): Kaplan–Meier for progression free survival

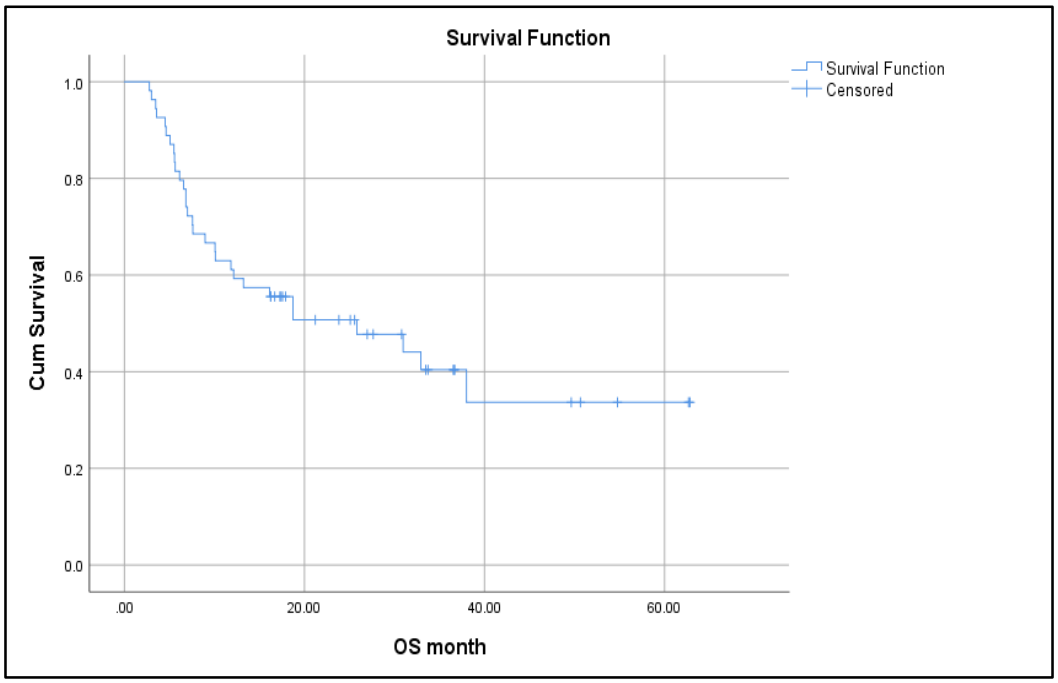

Figure (2): Kaplan–Meier for overall survival

Table (2): Adverse events with grade and timing of occurrence relative to cycle number

Adverse events	Grade Cycle	Frequency	Percent (%)
Peripheral Neuropathy	1-2 $2^{nd}/3^{rd}$	3	5.6
Anemia	2-3 $2^{nd}/3^{rd}/4^{th}$	5	9.3
Febrile Neutropenia	3 $4^{th}/5^{th}$	3	5.6
Mucositis	3 3^{rd}	1	1.9

Univariate and multivariate analysis:

The objective of these analyses was to determine significant prognostic factors for CBR, PFS and OS (Tables 3, 4 and 5). First, a univariate analysis was performed on 5 factors of which two displayed statistical significance with CBR; triple negative breast cancer (TNBC) vs. other molecular subtypes and vinorelbine/5FU received as second line. Then multivariate analysis was performed for the 5 prognostic factors regarding PFS and OS but no statistical significance was detected (Table 6).

Table (3): Correlations between CBR and patients characteristics

			Clinical Benefit Rate*		Total	Pearson Chi-Square		Fisher's Exact Test
			0	1		Value	Exact Sig. (2-sided)	Exact Sig. (2-sided)
Age	<46.5	Count	5	22	27	0.133	-	1.00 {Exact Sig. (1 sided): 0.500 }
		%	18.5%	81.5%	100.0%			
	>46.5	Count	4	23	27			
		%	14.8%	85.2%	100.0%			
Menstrual status	Post	Count	3	18	21	0.140	-	1.000
		%	14.3%	85.7%	100.0%			
	Pre	Count	6	27	33			
		%	18.2%	81.8%	100.0%			
Molecular Subtype	Luminal A	Count	6	19	25	5.459	0.141	-
		%	24.0%	76.0%	100.0%			
	Luminal B	Count	3	8	11			
		%	27.3%	72.7%	100.0%			
	HER-2 overexpression	Count	0	1	1			
		%	0.0%	100.0%	100.0%			
	TNBC	Count	0	17	17			
		%	0.0%	100.0%	100.0%			
TND vs. other molecular subtypes	Other	Count	9	28	37	4.962	-	**0.044**
		%	24.3%	75.7%	100.0%			
	TND	Count	0	17	17			
		%	0.0%	100.0%	100.0%			
Visceral metastasis	no	Count	2	17	19	0.796	-	0.468
		%	10.5%	89.5%	100.0%			
	yes	Count	7	28	35			
		%	20.0%	80.0%	100.0%			
Vinorelbine/5FU line number	>2nd	Count	8	16	24	8.640	-	**0.007**
		%	33.3%	66.7%	100.0%			
	2nd	Count	1	29	30			
		%	3.3%	96.7%	100.0%			

*: 0: not achieved clinical benefit rate. 1: achieved clinical benefit rate.

Table (4): Correlations between patients' characteristics and PFS

		Median PFS			Log Rank (Mantel-Cox)	
		Estimate	95% Confidence Interval			
			Lower Bound	Upper Bound	Chi-Square	P value
Age	<46.5	6.567	5.945	7.189	0.001	0.969
	>46.5	9.233	6.463	12.004		
Menstrual status	Post	9.133	5.545	12.722	0.106	0.745
	Pre	6.600	5.850	7.350		
TND vs. other molecular subtypes	Other	6.633	5.839	7.428	0.056	0.813
	TNBC	9.533	5.276	13.791		
Visceral metastasis	no	7.900	3.682	12.118	0.002	0.961
	yes	6.833	3.903	9.763		
Vinorelbine/5FU line number	>2nd	6.633	4.473	8.794	0.005	0.945
	2nd	7.167	3.722	10.611		

Table (5): Correlations between patients' characteristics and OS

		Median OS			Log Rank (Mantel-Cox)	
		Estimate	95% Confidence Interval		Chi-Square	Sig.
			Lower Bound	Upper Bound		
Age	<46.5	25.833	8.129	43.538	0.009	0.925
	>46.5	18.733	0.000	38.534		
Menstrual status	Post	13.233	0.000	31.134	0.196	0.658
	Pre	25.833	10.953	40.713		
TND vs. other molecular subtypes	Other	18.733	0.000	38.383	0.061	0.805
	TNBC	30.967	5.863	56.071		
Visceral metastasis	no	38.000	21.243	54.757	2.954	0.086
	yes	11.833	0.312	23.355		
Vinorelbine/5FU line number	>2nd	25.833	8.435	43.232	0.086	0.769
	2nd	18.733	0.000	45.302		

Table (6): Multivariate analysis for PFS and OS

	PFS				OS			
Variable	**HR**	**95.0% CI for HR**		**P value**	**HR**	**95.0% CI for HR**		**P value**
		Lower	**Upper**			**Lower**	**Upper**	
Age	1.195	0.479	2.980	0.703	1.019	0.356	2.917	0.973
Menstrual status	1.261	0.494	3.214	0.628	1.100	0.384	3.149	0.859
Molecular group	1.037	0.552	1.950	0.910	1.055	0.471	2.363	0.897
Visceral metastasis	1.046	0.566	1.936	0.885	0.506	0.222	1.152	0.105
No. in line group	0.987	0.532	1.830	0.967	1.066	0.488	2.332	0.872

DISCUSSION

Metastatic breast cancer treatment remains challenging as it necessitates picking a life prolonging treatment with tolerable toxicity that doesn't compromise quality of life [19-21]. Although OS has long been established as the most relevant endpoint for treatment efficacy, PFS is increasingly being utilised as well[22]. Furthermore, comparisons of objective response rates are often used to determine relative treatment efficacy, however high response rates are not always translated into clinically meaningful increases in survival [23-24]. In addition, symptom relief without measurable disease response and achievement of stable disease as compared with disease progression is clinically relevant [25].

Hence, in this study we evaluated the effect of vinorelbine/5FU regimen in pretreated metastatic breast cancer as regards CBR primarily. The current study found the CBR at 83.3%, ORR of 57.4% along with an mPFS of 6.8 months and mOS of 25.8 months. Treatment was well tolerated, with minimal grade 3 anemia, febrile neutropenia and stomatitis.

The high therapeutic activity of the combination of fluorouracil 5-days continuous infusion with vinorelbine in metastatic patients had been already reported by other phase II studies [26–29]. **Zambetti and colleagues** examined this regimen in pretreated metastatic breast cancer women first on 24 patients[26] and then 56 patients [27] reporting response rates of 66% and 48% respectively with mild toxicity. **Dieras *et al.*** [28] administered it in the first line setting and 41 of the 62 cases displayed an objective response, median time to progression was 8.4 months and mOS was 23 months. Toxicities were reported but a concern for neutropenia in 90% of cases was worrisome but in most patients this did not require hospitalization and median dose intensity was 86%.

In anthracycline-pretreated metastatic breast cancer 176 patients participated in a randomized phase III study [16] that concluded that docetaxel showed comparable efficacy to 5FU/vinorelbine reported response rate, time to progression (TTP) and OS were 38.8%, 5.1 months and 15 months respectively which were lower than this current study's with 57.4% ORR., 6.8 months PFS and 25.8 months OS. The main toxicity reported for our study was hematological with grade 3 anaemia of 9.3% and febrile neutropenia at 5.6%, again this is less than **Bonneterre *et al.*** [16] who found a 67% neutropenia, 10% thrombocytopenia but a similar anaemia rate (8%).

Intriguingly, an initial CBR statistical advantage was observed for the use of this protocol in TNBC and in the second line setting, unfortunately this was not reflected on survival outcomes. The small sample size may partly explain this and the natural phenomenon of a diminishing PFS and OS with subsequent therapies.

This regimen was further pursued in an oral formulation. Anthracycline/taxane resistant metastatic breast cancer patients achieved an ORR of 37–54% with mTTP of 6.3–7.7 months with capecitabine/vinorelbine however this was associated with a higher incidence of grade 3 leucopenia[30,31].

The oral formulations; capecitabine and vinorelbine (VNR) have proven efficacy as their IV counterparts in the European Organisation for Research and Treatment of Cancer (EORTC) prospective Phase II trial 10001[32], a systematic review of 27 trials[33] and even a recent Italian description of its use in first line triple-negative or hormone-resistant advanced breast carcinoma chemotherapy naïve patients[34]. However, despite the availability and the convenience of an all oral formulation the current study is a portrayal of the real word setting, even with the advent of oral formulations and novel therapies such as cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, poly (ADP-ribose) polymerase inhibitors, phosphatidylinositol 3-kinase (PI3K) α-specific inhibitor and immunotherapy, finances remain prohibitive to their widespread use and adoption throughout many parts of the world.

Being retrospective is one of the limitations of this study in that insufficient data capture such as possible underreporting of toxicity may have occurred. Also information on further lines of treatment was not collected, and this could have impacted the overall survival.

Positively this work presents the efficacy of a relatively cheap and widely available regimen displaying good outcomes in an aggressive cohort of patients (mostly premenopausal, high visceral metastases, triple negative and some heavily pretreated). It sets a reminder that practicality dictates real world practise.

CONCLUSIONS

In the end, despite the recent advances in the field, vinorelbine/5FU doublet is an active regimen in pretreated metastatic breast cancer patients with good tolerance. It remains an attractive option especially in the limited resource setting.

Conflict of interest: The authors declare no conflict of interest.

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Author contribution: TK and RS were responsible for the conception and design of this study. RS performed the study selection and data extraction. ME and RS collected statistical output and were major contributors in writing the manuscript. All authors contributed to the article and approved the submitted version.

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