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A Clinical Phase II Study of Oral Vinorelbine in HER-2 Negative Metastatic Breast Cancer

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Abstract

Background: Oral vinorelbine, produce an effective and viable treatment option in both the first and second-line settings for patients with metastatic breast cancer (MBC). The present phase II single institution study designed with an aim to analyze the efficacy and safety of oral vinorelbine as first-line therapy for patients with metastatic breast cancer (MBC)

Patients and methods: Twenty-one women aged >18 years with histopathologically confirmed HER-2 negative MBC, were enrolled to receive oral vinorelbine given as a single agent at doses of (60 mg/m^2, day 1 and 8 of a 3-week cycle and thereafter 80 mg/m^2 of days 1 and 8). No prior chemotherapy was allowed for treatment of metastatic disease, patients who received oral vinorelbine as adjuvant or neoadjuvant therapy were excluded.

Results: Objective response was observed in 28.7% of patients (6/21), and tumour control rate was 66.8% (14/21). Only one patient (4.8%) experienced complete response following treatment. The median progression-free survival (PFS) and overall survival (OS) were 6 and 16 months, respectively. The 1-year OS and PFS rates were 64.1% and 16.2%, respectively. Most adverse events were mild to moderate. The most common grade 3/4 hematological toxicities were neutropenia (9.5%), while the most common grade 3/4 non-hematological toxicities were nausea/vomiting (14.3%). No treatment-related mortality was noted in this cohort.

Conclusion: Oral vinorelbine as first-line therapy in patients with MBC appeared to offer an acceptable clinical profile and easy to administer in outpatients. The substitution of oral vinorelbine for intra-venous form is not only feasible, but may be in the patients' best interest.

Keywords: Metastatic breast cancer; Chemotherapy; Oral vinorelbine

Introduction

Despite metastatic breast cancer is incurable, a significant improvement in survival have been reached with the development of systemic and combination chemotherapies [1,2]. The median survival for patients with MBC has improved over time reaching about 18-24 months [3,4]. This improvement in survival, though modest, came at the expense of significant toxicities [5]. Several guidelines exist for the treatment of metastatic/advanced breast cancer and are widely followed. The European society for medical oncology (ESMO) clinical practice guidelines provide many systemic treatment options for MBC patients which include chemotherapy, endocrine therapy, bone-directed agents, and targeted biological agents [6]. The national comprehensive cancer network (NCCN) guidelines panel for breast cancer reported that there is no compelling evidence that combination chemotherapy regimens are more effective than sequential single agents in the treatment of MBC [7]. For most MBC patients, overall survival benefit from the use of single monotherapy are equivalent to combination chemotherapy [6]. Preferred single agent chemotherapy including doxorubicin, paclitaxel, docetaxel, capecitabine, and vinorelbine.

Vinorelbine is a vinca alkaloid that was proved to be active in many tumor types and is currently registered for the treatment of advanced breast cancer (ABC). This agent has a generally favorable safety profile, and may be suitable for special populations unfit for more toxic drugs as the elderly and/or frail patient [8].

Oral formulation of vinorelbine has been introduced in clinical trials since 1994, after increasing interest in the development of oral chemotherapy, driven by patient convenience, preference, and the potential for improved quality of life [9]. A dose-finding study [10] established that 100 mg/m^2 was the maximum tolerated dose (MTD) dose, limiting toxicities being neutropenia, nausea and vomiting, and constipation. The recommended dose was then defined at 80 mg/m^2 per week. The first phase II studies conducted in chemotherapy-naive patients with non-small cell lung cancer (NSCLC) and as first-line chemotherapy in advanced breast cancer (ABC) showed an excessive rate of neutropenia. This led to the adoption of a new schedule in which a lower weekly dose of 60 mg/m^2 was delivered for the first three courses followed by escalating the dose to 80 mg/m^2, with a comparable safety profile to that of intravenous vinorelbine at standard doses [11]. The blood concentrations were equivalent between 80 mg/m^2 oral and 30 mg/m^2 intravenous, and between 60 mg/m^2 oral and 25 mg/m^2 intravenous [12].

Therefore, we designed this trial to evaluate the preliminary results of oral vinorelbine, given as a single agent at doses of (60 mg/m^2, day 1 and 8 of a 3-week cycle and thereafter 80 mg/m^2 of days 1 and 8) in patients with MBC. The objectives of the current trial were evaluation of the response rate, toxicity, and survival of patients who were treated with this dose and schedule of oral vinorelbine.

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Materials and Methods

Patient eligibility criteria

Between June 2012 and February 2014, 21 women with pathologically proven metastatic breast cancer (MBC) with at least 1 measurable lesion, in Clinical Oncology Department, Tanta University Hospital were enrolled. Patients were eligible for this study if they had metastases to distant sites and with histopathologically confirmed HER-2 negativity either by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) test.

Patients were required to have no prior treatment for metastatic disease (neoadjuvant and/or adjuvant chemotherapy with anthracyclines and/or taxanes or endocrine therapy was allowed, and not considered in the counting of therapy lines for metastatic disease). Prior adjuvant or neoadjuvant chemotherapy and/or radiotherapy 3 months prior to study entry were allowed. Concomitant bisphosphonates, were allowed. Patients were followed up until June 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 ≥3.5 × 10^9/L, ANC count ≥1.5 × 10^9/L, platelets ≥100 × 10^9/L, and hemoglobin ≥10 g/dL), adequate renal and liver function (transaminases less than 2x 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, symptoms of central nervous system or leptomeningeal metastasis, or have dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent. Also, patients with prior exposure to vinorelbine, patients suffering from malabsorpation 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 other than skin cancer or concurrent serious, comorbid condition (e.g. immune-compromised states, uncontrolled infection, and clinically significant cardiac troubles) were excluded.

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 a written informed consent before starting treatment.

Treatment plan and dose medication

Eligible patients received oral vinorelbine (60 mg/m^2, day 1 and 8 of a 3-week cycle and thereafter 80 mg/m^2 of days 1 and 8). Oral vinorelbine is discontinued if there was a clinical evidence of disease progression, intolerability, or major toxicities. Chemotherapy is administered on an outpatient basis. Adverse events were recorded throughout the study. A complete resolution of hematologic and non-hematologic toxicity except for alopecia and fatigue was required before proceeding to the next cycle. If toxicities did not resolve, then a 1-2 weeks' delay were allowed. Dose reduction was allowed according to clinical judgment. Hormonal therapy was not allowed during chemotherapy. Metastasectomy was allowed in patients with a clinically relevant tumour response. Patients with treatment delay of more than 3 weeks were withdrawn from the study.

Patient assessment

Assessment of clinical benefit: Assessment of tumour response was planned after every three cycles from the beginning of treatment. Pre- and on-treatment monitoring consisted of medical history, assessment of performance status, physical and neurological examination, and laboratory analyses. Radiological assessment included, CT chest, abdomen and pelvis, bone scan, MRI and CT scan of the brain if indicated. Criteria of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were based on the standard definitions according to RECIST (response evaluation criteria in solid tumors) 1.0 criteria [13], with the overall response rate, including complete and partial response.

Assessment of toxicity: Patients were assessed for adverse events at each visit with clinical and laboratory evaluations every 3 weeks and by ECHO for cardiac monitoring, every 12 weeks. Toxicity grading was based on the common terminology criteria for adverse events (NCI-CTC, version 3.0) [14].

Primary and secondary endpoints

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

Statistical analysis

Overall-survival (OS) rates were calculated from the date of start of treatment to the date of death or the last follow-up visit using the Kaplan-Meier method [15] with SPSS (Statistical package-version 21.0). Progression-free survival (PFS) was the time elapsed from the date of initiation of treatment to the date of first documentation of disease progression or the date of death in the absence of disease progression. Kaplan Meier method [15] is used for estimating survival. The 95% confidence intervals (95% CIs) were calculated with the exact method. All *P* values were two-tailed; a *P* value of 0.05 was considered significant.

Results

Patient characteristics

Twenty-one HER-2 negative MBC patients were enrolled in this study. The baseline demographic and clinical characteristics of all enrolled patients were listed in Table 1.

The median age at disease diagnosis was 43.9 years (range 31-70 years), with most (61.9%) patients were in the postmenopausal state. Most patients had invasive ductal carcinoma (90.5%) and grade III disease (66.7%). T3 disease constituted 57.1% of all patients at initial presentation prior to any treatment. Most of the patients (76.2%) had ECOG performance status score of ≥1. Nineteen patients (90.5%) underwent mastectomy for their primary tumor, and 2 patients (9.5%) underwent a segmental resection. All patients received combination chemotherapy either as a neoadjuvant and/or adjuvant therapy and 16 (76.2%) patients received adjuvant radiation therapy following surgery and combination chemotherapy. All patients had HER-2 negative metastatic breast cancer (MBC) at our study entry. Most of the patients (76.2% {16/21}) had multiple metastases, with liver, bone, and lung being the most frequent sites of metastases (Table 1).

Treatment administration

All patients received initially oral vinorelbine (60 mg/m^2, day 1 and 8 of a 3-week cycle and thereafter 80 mg/m^2 of days 1 and 8). A total of 128 chemotherapy cycles were given. The median number of cycles of oral vinorelbine was 6 cycles (range 3-19 cycles). Dose reduction was

Characteristic	No. patients (%)
Age (years)	
Median	43.9 years
Range	31-70
Family history	
+ve	2 (9.5%)
-ve	19 (90.5%)
Initial tumor status	
T2	5 (23.8%)
T3	12 (57.1%)
T4	4 (19.1%)
Menopausal status	
Premenopausal	8 (38.1)
Postmenopausal	13 (61.9)
Tumor grade	
G1	2 (9.5%)
G2	5 (23.8%)
G3	14 (66.7)
Histology	
Invasive duct carcinoma (IDC)	19 (90.5%)
Others	2 (9.5%)
Lymphovascular invasion	
Positive	7 (33.3%)
Negative	14 (66.7)
Nodal status at presentation	
N1	5 (23.8%)
N2	7 (33.3%)
N3	9 (42.9%)
Adjuvant radiation therapy (Rth)	
Yes	16 (76.2%)
No	5 (23.8%)
Type of surgery	
Breast conserving surgery (BCS)	2 (9.5%)
Modified radical mastectomy (MRM)	19 (90.5%)
Type of neoadjuvant and/or adjuvant chemotherapy	
FAC	5 (23.8)
FEC	6 (28.6%)
Sequential FEC with taxenes	10(47.6%)
ECOG	
0	5 (23.8%)
1	14 (66.7%)
2	2 (9.5%)
Metastatic sites	
Liver	14 (66.7%)
Lymph node	6 (28.6%)
Lung	7 (33.3%)
Bone	13 (61.9)
Type of metastasis	
Single metastasis	5 (23.8%)
Multiple metastases	16 (76.2)

Table 1: Patients' and tumour characteristics as well as initial treatment modality of the 21 MBC patients managed by oral vinorelbine.

recorded in 7 patients (33.3%). Oral vinorelbine was interrupted for up to 2 weeks in case of greater than Grade 3 adverse reactions.

Response to treatment

In the first 10 patients enrolled in the study, 5 responses were observed, allowing the total accrual of 21 patients. Overall response rate (complete response and partial response) was 28.7% (6/21), and tumor control rate (overall response and stable disease) was 66.8% (14/21) according to the RECIST criteria [13], (Table 2). Complete response was observed in 1 patient (4.8%). 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 histopathological grade I/II tumors (P=0.02). No differences were observed regarding previous radiation therapy (P=0.18).

Survival

All our patients were followed up regularly, with no one having lost follow up in this study. The median follow up duration was 16 months (95% CI; 12.01-19.99 months).

Median progression free survival (PFS) was 6 months (95% CI 2.02-9.98) (Figure 1). The 1-year PFS rate was 16.2% (Figure 1).

Median overall survival (OS) was 16 months, with its 95% CI 12.01-19.99) (Figure 2). The 1-year OS rate was 64.1% (Figure 2).

Toxicity

To determine hematologic and non-hematologic toxicities (Table 3), patients were evaluated for adverse events and toxicity using the common terminology criteria for adverse event (NCI-CTC, version 3.0) [14]. To date, most of hematologic and non-hematological toxicities to this regimen observed in the 21 assessable patients were mild and manageable. Most common grade 3-4 hematological toxicities were neutropenia in 2 patients (9.5%), with 1 patient (4.8%) suffered from febrile neutropenia, and 1 patient (4.8%) developed grade 3-4 thrombocytopenia.

Tumor Response	No.	%
Complete response	1	4.8
Partial response	5	23.9
Stable disease	8	38.1
Progressive disease	7	33.2

Table 2: Tumour response to treatment.

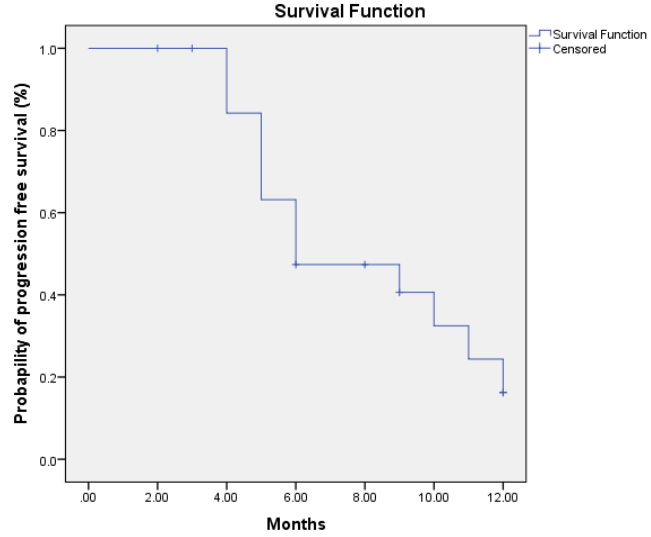

Figure 1: Kaplan-Meier curve of progression-free survival (PFS). Median PFS was 6 months.

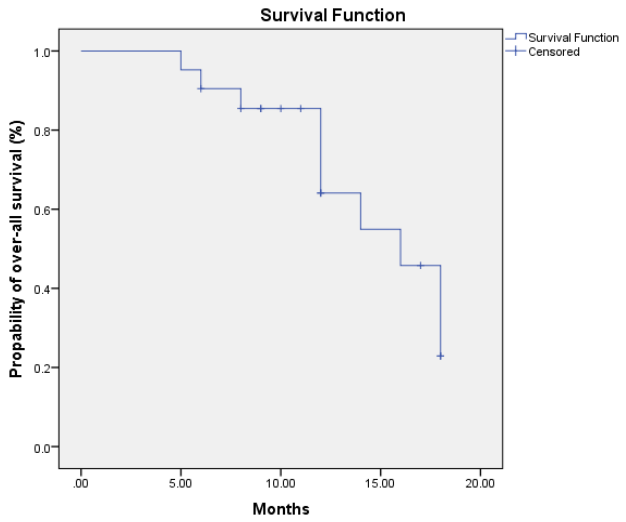

Figure 2: Kaplan-Meier curve of overall survival. Median overall survival time was 16 months.

	All Grades No. (%)	Grade 3/4 No. (%)
Non-hematologic Toxicity		
Nausea/vomiting	7 (33.3)	3 (14.3)
Anorexia	2 (9.5)	0
Numbness	2 (9.5)	0
Diarrhea	1 (4.8)	0
fatigue	1 (4.8)	0
Hematologic Toxicity		
Neutropenia	3 (14.3)	2 (9.5)
Anemia	7 (33.3)	0
Thrombocytopenia	2 (9.5)	1 (4.8)
Febrile neutropenia	2 (9.5)	1 (4.8)

Table 3: Hematologic and non-hematologic toxicity of oral vinorelbine therapy used in the management of the 21 patients with MBC.

Nausea/vomiting, a frequent side effect of oral vinorelbine, was the most common non-hematologic treatment-related adverse event, occurring in 33.3% (7/21) of patients. Four (19.04%) of them were of grade 1/2 nausea/vomiting. While, the remaining 3 cases (14.3%) had grade 3/4 nausea/vomiting, which were rapidly resolved to grade 0/1 with treatment delay and symptomatic treatment. Other grade 1/2 non-hematologic toxicities observed were diarrhoea which was experienced by 1 patient (4.8%), numbness in 2 patients (9.5%) and fatigue in 1 patient (4.8%).

Fourteen patients (66.7%) received full doses of oral vinorelbine throughout the study. A dose reduction was performed in 7 patients (33.3%). The dose reductions were decided all because of grade 3-4 thrombocytopenia, neutropenia, febrile neutropenia and nausea/vomiting. Oral vinorelbine was interrupted for up to 2 weeks in case of greater than grade 3 adverse reactions. Six patients received no more than 3 cycles due to rapid disease progression (n=5) or treatment-related uncontrolled major toxicity (n=1), which was in the form of grade 4 neutropenia associated with febrile neutropenia.

A total of 5 patients (23.9%) required hospitalization, as follows: grade 3-4 neutropenia in 1 patients, neutropenic fever in 1, bleeding in 1, and grade 3/4 nausea/vomiting in 2. There was no treatment-related death.

Discussion

The treatment of MBC has become increasingly complex and medical oncologists now are faced with multiple chemotherapeutic regimens from which they should choice the appropriate regimen [16]. The use of combination therapy versus single chemotherapeutic agents remains a big challenge facing oncologists and it still needs to be resolved. The guidelines recommend that the choice of therapy should be based on tumour biology, clinical characteristics, quality of life, safety, and ease of administration [17]. In this point of view, an active and tolerated oral chemotherapy drug can be beneficial for patients especially that patients prefer it whenever it is available.

Vinorelbine is a cytotoxic drug which was introduced for the treatment of breast cancer in the 1990s, it was of proven efficacy as a first line treatment of MBC [18]. Therefore, it seems appropriate to assess the efficacy and tolerability of oral vinorelbine in the treatment MBC. We designed this phase II study to assess the efficacy and toxicity of single agent oral vinorelbine as a first-line treatment in MBC.

Single agent oral vinorelbine compare favourably with the other studies of intravenous form [19,20]. Previous trials reported activity of Oral vinorelbine as monotherapy or in combination for patients with MBC.

All our patients in the current study had received adjuvant and/or neoadjuvant anthracyclines with or without taxanes before taking vinorelbine. In previous phase III trials conducted by the Spanish breast cancer research group (GEICAM), patients received gemcitabine plus vinorelbine had better progression-free survival compared with those received vinorelbine alone [21]. OS was similar for the two groups; 15.9 months for the vinorelbine plus gemcitabine group and 16.4 months for the vinorelbine group (p=0.8046). Although toxicity was manageable, more haematological side effects were recorded in patients in the combined group [21]. Moreover, similar results were reported in phase II study comparing vinorelbine with capecitabine in patients pre-treated with anthracyclines and taxanes. Median PFS was 2.8 and 2.6 months, and median OS was 9.3 and 11.0 months, in the capecitabine and vinorelbine arms, respectively [22].

In addition, previous studies reported activity of single agent oral vinorelbine in patients with metastatic breast cancer. One of these studies enrolled 64 patients, 12 with locally advanced and 52 with MBC [23]. Most patients had lung or liver metastases and multiple organ involvement. In 58 evaluable patients, the overall response rate was 31% (4 patients had a complete response, 14 had a partial response). Median PFS and OS was 17.4 weeks and 24 months respectively. Main Grade 3-4 toxicities were neutropenia (39%), febrile neutropenia (4.7%), nausea (3%), vomiting (5%), diarrhoea (5%), and stomatitis (3%) [23]. Another trial, evaluating oral vinorelbine in forty-five patients reported an overall response rate of 29.5% with manageable low incidence of Grade 3-4 adverse events [24].

The aim of our study was to assess the efficacy and toxicity of single agent oral vinorelbine in HER-2 negative MBC. In the current study, the administration of single agent oral vinorelbine is effective in MBC. Oral vinorelbine was associated with a 28.7% overall response rate, and 38.1% disease stabilization. Response rate was independent of baseline ECOG performance status, and previous radiation therapy. However, patients with non-visceral metastases, solitary metastases, or grade I/II tumors, had higher response rates than others, even though the number of patients in this study was low. The median PFS and overall survival were 6 months (95% CI 2.02-9.98) and 16 months (95% CI 12.01-19.99), respectively, and the overall survival rate was 64.1% at 1 year. These results were comparable with that reported by Mansour

et al. [25], who demonstrated that the objective response rate was 35%, disease stabilization was achieved in 39% of the patients, median progression-free survival and overall survival were 5.2 months (95% CI 2.8-7.5) and 16 months (95% CI 11.3-20.7), respectively, [25]. In addition, our results of oral vinorelbine were comparable with that reported by Freyer et al. [23], Blancas et al. [24] and Amadori et al. [26] phase II studies.

Nausea/vomiting, a frequent side effect of oral vinorelbine, was the most common non-hematologic treatment-related adverse event, occurring in 33.3% (7/21) of patients, 3 (14.3%) of them were of Grade 3/4 nausea/vomiting. The commonest grade 3-4 hematologic toxicity was neutropenia, reported in 9.5% of patients. We had one case of febrile neutropenia and we had no cases Grade 3-4 anaemia. The frequency of the toxicity profile of this regimen was somewhat comparable with that previously reported in other study using the same dose of oral vinorelbine, (9.7% of patients developed Grade 3-4 neutropenia, 6.4% developed Grade 3 thrombocytopenia, and 16.1% of patients developed Grade 3 nausea-vomiting) [25]. Our rates of Grade 3-4 neutropenia (9.5%) were much lower than that observed by Freyer et al. (39%) [23] and Amadori et al. (28.6%) [26].

The results of an international, retrospective observational study of patients with metastatic breast cancer treated with oral vinorelbine based-chemotherapy were published by Garcia-Palomo et al. [27]. They analyzed 216 patients with breast cancer, 116 of whom were started on single oral vinorelbine at 13 centers in 7 countries from 2006 to 2008. Data from these retrospective observations from every-day practice were comparable with the data observed by individual trials described before in terms of efficacy and tolerability. The principle grade 3-4 toxicities observed with single agent vinorelbine were: neutropenia 6%, anaemia 3%, thrombocytopenia 3%, febrile neutropenia/neutropenic infection 2%, nausea 9%, vomiting 4%, diarrhoea 3%, fatigue 3%, neuropathy 2%, renal failure 1%, and alopecia 2% [27]. The haematological toxicities with vinorelbine were comparable to capecitabine single agent. However, capecitabine is associated with high rate of grade 3-4 non-haematological toxicities as hand-foot syndrome that reaches 18% [28,29], diarrhoea in 12%, and gastrointestinal disorders in 36% [29]. Looking at the toxicities experienced by patients in this study, the results match the previous clinical experience of oral vinorelbine in metastatic breast cancer, reporting a favourable safety profile of the drug with a low incidence of myelosuppression and without alopecia. The main haematological adverse event was neutropenia and non-haematological adverse events were gastro-intestinal (mostly nausea/vomiting). No alopecia was noted proving the differential advantage of oral vinorelbine as alopecia is an important factor of concern for women with breast cancer affecting quality of life. Although some patients experienced neutropenia; however, only one of them developed febrile neutropenia which indicates the good tolerability of the drug compared to other treatments used in this setting.

The patients' characteristics in our study reflect a relatively aggressive disease. We had a young cohort with a median age of 43.9 years (range 31-70 years). Most of our patients (76.2%) had multiple sites of metastasis at enrolment, and the majority (>70%) had visceral involvement. **our results were comparable with that reported** in Mansour et al. [25] **study, they** had a young cohort with a median age of 42 years, 55% of patients had multiple sites of metastasis at enrolment, and most of them (87.1%) had visceral involvement. The finding of aggressive disease in young patients was **comparable with** previous results from Saudi Arabia; it is well documented that the median age of patients with breast cancer including MBC is 10-15 years less than in industrial Western countries [30-32]. In this group with unfavourable breast cancer profile, our results with single agent oral vinorelbine are encouraging.

In conclusion, the current results suggest that single agent oral vinorelbine is an active reasonable treatment choice with accepted results in metastatic breast cancer patients previously treated with anthracyclines and/or taxanes containing regimes. Because the tolerability, response rates, time to progression, and overall survival of the single agent oral vinorelbine was not inferior to previous studies of intravenous form, in addition the oral vinorelbine is easy to administer in outpatients. This constitutes a marked advantage over regimens of intravenous form in terms of the impact on improving the level of treatment-related quality of life.

Further prospective investigations of this agent 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 lower toxicities. The incorporation 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?

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