Kasr El-Aini J. Clin. Oncol. Nucl. Med.
Vol. 7, No. 1-2, Jan.-April. 2011:17-25

Original article

A Phase II Study of Combination Chemotherapy with Capecitabine and Intravenous Vinorelbine in Patients with Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes: Efficacy and Tolerance

Eman El-Sheikh

Department of Clinical Oncology and Nuclear Medicine Ain-Shams University, Cairo, Egypt

Background: Capecitabine and intravenous (i.v) vinorelbine are both active in metastatic breast cancer with non-overlapping toxicities. This study examined the efficacy and safety of the combination of these agents in patients with pretreated metastatic breast cancer.

Patients and Methods: Patients previously treated for breast cancer, maximum of one prior metastatic regimen, received capecitabine 1000 mg/m2 b.d. for days 1-14 and vinorelbine 25 mg/m2 i.v days 1 and 8 every 21 days. All patients had measurable disease and adequate organ function. The primary endpoints were response, progression free survival (PFS) and overall survival (OS) and the secondary endpoint was toxicity.

Results: This study was designed as a prospective phase II study. Thirty patients were recruited between October 2006 through December 2009 in the department of Clinical Oncology and Nuclear Medicine, Ain-Shams University. All patients pretreated with anthracyclines and taxanes. Median age was 52 years. Patients received a median of 5 cycles. In case of a complete response, patients received two additional cycles of chemotherapy. Patients were treated for a maximum of 6-8 cycles. Patients were withdrawn from the study at any evidence of progressive disease. All patients were evaluated for response and for toxicity. The overall response rate (RR) was 43.3% (13/30), with one (3.3%) complete response and 12 (40%) partial response. Stable disease was observed in 11 patients (36.6%) and 6 patients (20%) experienced disease progression during treatment. Response rates observed by disease site were found in 30.8% of patients with liver metastases, 44.4% of patients with lung metastases, 55.5% of patients with bone lesions and 58.3% of patients with soft tissues metastases. With a follow up period of 6-34 months (median 24 months), the median survival was found to be 11 months (95% CI, 12.13-19.80%), the one and 2 year OS were 36.6% and 23.3% respectively. The median PFS was 10 months (95% CI, 9.22-16.2%). At one and 2 year the PFS were 26.6% and 16.6% respectively. When response was analyzed according to the different prognostic factors, it was found that patients with PS 0/1 showed a significantly better overall RR (p=0.001). The intensity of treatment-related adverse events was mild to moderate (G1-2) in the majority of patients. Only one patient (3.3%) developed G4 toxicity (neutropenia). G3 neutropenia was recorded in 8 patients (26.6%). As regards the non-haematological toxicities, the most frequent adverse events were G1&2 diarrhea (33.3%), hand-foot syndrome (26.6%), peripheral neuropathy (23.3%), fatigue (30%) and constipation (23.3%).

Conclusions: Capecitabine in combination with vinorelbine showed promising efficacy and safety in heavily pretreated patients with MBC. Randomized trials would be of major importance to give further weight to recommending this chemotherapy regimen in patients with disease that is resistant or refractory to anthracycline- and taxane containing regimens or for those patients that for clinical reasons cannot tolerate cardiotoxic drugs.

Key words: Metastatic breast cancer, capecitabine, vinorelbine.

Corresponding author: Eman El-sheikh Email: emanelsheikh.169@gmail.com

Original article

INTRODUCTION

Breast cancer is the most common malignancy in women and the second most common cause of cancer-related death in developed countries. Despite early diagnosis of breast cancer, a large proportion (up to 40%) of breast cancer patients will develop metastatic disease that is incurable with conventional treatment. The average survival time from diagnosis of metastasis for these patients is 18-30 months, although this varies considerably according to the metastatic site[1].

Conventional chemotherapy regimens based on cyclophosphamide, 5-florouracil (5-FU) and methotrexate (CMF) or an anthracycline (FAC,FEC) achieve response rates (RRs) of 40-80% in chemotherapy-naive patients, although further relapse is the rule, usually within months of stopping treatment, moreover the increasing use of chemotherapy, particularly anthracycline-based regimens, in the adjuvant sitting means that new treatment options are required for metastatic disease[2]. Several

agents have been developed including, the taxanes (paclitaxel and docetaxel), capecitabine and vinorelbine and these have become the second-line treatments of choice in many countries[3,4]. Currently there is no standard treatment for metastatic breast cancer (MBC) after failure of anthracyclin- and taxane-containing treatments and consequently, there is a need to find an effective schedule that is non-cross-resistant with these drugs[5].

Capecitabine and vinorelbine are among the drugs of choice for anthracycline- and taxane-resistant breast cancer because they have shown a high level of antitumor activity and are well tolerated in this setting. Capecitabine is an orally administered prodrug that is activated in the liver and at the tumor sites by a series of enzymatic reaction that converts it into its active form, 5-FU. It requires thymidine phosphorylase, an enzyme that is expressed significantly higher in tumors than in healthy tissue. The antimetabolite 5-FU exerts its antitumor effects through several mechanisms, including inhibition of RNA synthesis and function, inhibition of thymidylate synthase activity and incorporation into DNA, leading to DNA strand breaks and subsequent cell death[6].

Clinically, capecitabine activity mimics continuous infusion of 5-FU. In contrast to intravenously administered 5-FU and some other oral fluoropyrimidines (e.g, UFT and oral 5-FU eniluracil), capecitabine generates 5-FU predominantly within tumor tissue through the exploitation of high intratumoral concentrations of the enzyme thymidine phosphorylase. The preferential generation of 5 FU at the tumor site reduces systemic exposure to 5-FU, thereby potentially reducing the risk of significant toxicity, also patients can receive capecitabine at home, thus fulfilling important requirements of palliative therapy for refractory metastatic tumors[6]. In phase I/II studies, capecitabine gave RRs of 20 - 30% in patients with paclitaxel- refractory MBC, along with minimal bone marrow suppression[7,8].

Vinorelbine, a semisynthetic vinca alkaloid, inhibits microtubule assembly and thus its activity is cell cycle specific, this compound blocks formation of the mitotic spindle apparatus at metaphase and prevents cell division. It has a higher therapeutic index and less neurotoxicity than other vinca alkaloids related to the lower degree of damage of axonal microtubules. Clinical resistance to taxanes often results from the decreased stability of tubulin complexes in tumor cells. Vinorelbine also acts on tubulin but via another cellular mechanism to destabilize microtubules, with the result that a patient resistant to taxanes is not necessarily resistant to vinorelbine[9]. The assessment of vinorelbine in the management of breast carcinoma has been extensive and was initiated after promising results were obtained in phase II trials in which the RRs ranged from 40%-60% in previously untreated patients[10,11] and of about 30% when used as a second or third-line therapy[12,13].

The impressive effectiveness observed with vinorelbine as a single agent and its favorable toxicity profile led to its testing in combination with other cytotoxic drugs in MBC setting. Vinorelbine combined with 5-FU administered either as a bolus or in continuous infusion is able to achieve impressive results, with RRs of 50%-64% in first-line treatment and a long duration of response(up to 1 year) and overall survival (up to 23 months). This level of activity is observed even in anthracycline pretreated patients as well as in patients with visceral involvement[14,15].

Due to their different mechanisms of anti-tumor activity, their differing toxicity profile and synergistic effect of both drugs, the combination of capecitabine and vinorelbine would be a reasonable choice for chemotherapy of MBC. The preliminary data of this combination from phase I/II studies in second-line therapy have shown impressive RRs of 40-55%[16,17,18]. Based on these encouraging studies we carried out this study to assess the efficacy and tolerability of capecitabine and vinorelbine combination and its implication on survival in MBC patients previously treated with both anthracycline and taxane containing regimens.

PATIENTS AND METHODS

Eligible patients fulfilled all the following criteria: female patients with MBC, aged >18 and < 70 years, an Eastern Cooperative Oncology Group performance status (PS) < 2[19], a life expectancy > 3 months, with at least one bidimensionally measurable lesion and adequate bone marrow, hepatic, renal and cardiac functions (defined as absolute neutrophil count >2000 /mL, platelets >100,000/ mL and hemoglobin level of > 10g/dl, total bilirubin < 1.5 x upper limit of normal (ULN), serum transaminase < 2.5 x ULN, serum creatinine < 1.5 x ULN or a creatinine clearance of > 60 mL / min). Patients were required to have been previously treated with anthracyclines and taxanes in the adjuvant setting or as first-line chemotherapy for metastatic disease.

Patients were excluded if they had received >2 previous regimens of chemotherapy for metastatic disease or showed previous hypersensitivity to 5-FU, or received chemotherapy, hormonal treatment, radiotherapy less than 4 weeks before study entry. Also patients who were pregnant or lactating, those with only brain or isolated bone metastases, had grade >2 peripheral neuropathy, or with history of other serious illness (e.g., congestive heart failure, angina pectoris, uncontrolled hypertension

or diabetes, neurologic or psychiatric disorders, disease significantly affecting gastro-intestinal function) were excluded.

Pretreatment Evaluation:

Pretreatment evaluation included: history taking, clinical examination, laboratory tests (complete blood counts, liver and kidney function tests), electrocardiogram, echocardiography, chest x- ray, thoracic and/or abdomino-pelvic CT scan and bone scan (as clinically indicated).

Treatment Plan:

Treatment consisted of capecitabine given in a dose of 1000 mg/m² twice daily (12+2 hours apart), days 1-14. It was supplied as film-coated tablets at 500mg administered orally within 30 minutes after a meal (ideally after breakfast and dinner), with approximately 200 ml of water. Vinorelbine was given in a dose of 25mg/m² diluted with 75-125 ml of normal saline or dextrose 5% and administered on days 1 and 8 by a 20 minute slow intravenous (IV) push followed by vigorous hydration with 250 ml of normal saline in one hour. Treatment cycle was repeated every 3 weeks.

Toxicities and dose Modification:

Drug dosage was adjusted at any time during the study on the basis of grade 2 or greater related adverse events as defined by the National Cancer Institute (NCI) Toxicity Criteria[20]. At the first occurrence of grade 2 toxicity, treatment was interrupted and then resumed at the original dose after resolution to grade 1 or 0. Subsequent occurrences of the same grade 2 toxicity were managed by treatment interruption followed by 25% dose reduction. If Grade 3 or 4 toxicity occurred, treatment was interrupted and the dose was reduced by 25% or 50%, respectively. At the third appearance of a given grade 2 toxicity or the second appearance of a given grade 3 toxicity, treatment was interrupted until the toxicity resolved to grade 1 or 0 and treatment then continued at 50% of the original dose. At the third occurrence of a given grade 3 toxicity or the second appearance of a given grade 4 toxicity, treatment was discontinued and the patient was withdrawn from the study.

Study Assessment:

Patients were assessed prior to each chemotherapy cycle by clinical examination, complete blood count and blood chemistries. Appropriate radiological investigations were done every 2 cycles and at the time of withdrawal from the study at disease progression or unacceptable toxicity observation. Bone scans were repeated at 6 months interval.

Response to Therapy:

Tumor response was assessed according to WHO criteria[21]. Complete response (CR) was defined as the disappearance of all the clinical evidence of active tumor clinically, radiologically and /or histopathologically for a minimum four weeks. Partial response (PR) was defined as > 50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions, without the appearance of any new lesions for at least four weeks. Progressive disease (PD) was defined as the unequivocal appearance of any new lesion or an increase of > 25% in the sum of the perpendicular diameter of any measurable lesion. Patients with disease that did not meet the criteria for either a PR or PD were classified as stable disease (SD).

Assessment of response was made every two cycles. Patients were considered evaluable for response if they had measurable disease and completed at least two cycles of chemotherapy. In case of a CR, patients received two additional cycles of chemotherapy. Patients with PR and SD were treated for a maximum of 6-8 cycles. Patients were withdrawn from the study at any evidence of progressive disease. Tumor responses had to be confirmed 4-6 weeks after their initial observation.

Study End Points:

The primary endpoints were estimation of RRs at the end of treatment, progression free survival (PFS) and overall survival (OS) and the secondary endpoint was treatment related toxicity. The PFS was determined from the date of entry to the study to the date of disease progression. The OS was estimated from the first treatment day till last follow -up or death.

Statistical analysis:

PASW statistical software package (V. 18.0, IBM Corp., USA, 2010) was used for data analysis. Date were expressed as Mean ± SD and median and confidence intervals at 95P for quantitative measures and both number and percentage for categorized dat. Chi-square test was done to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data. The probability of error at 0.05 was considered significant, while at 0.01 and 0.001 are highly significant. Also Kaplan-Meier[22] analysis including the estimation of the survival rate at each point in time and the log-rank test for comparison between 2 different rates were done.

RESULTS

This study was designed as a prospective phase II study. A total of 30 patients were recruited between October 2006 through December 2009 in Clinical Oncology and Nuclear Medicine department, Ain-Shams University. Table (1) summarizes the characteristics of the study patients. The median age was 52 years (range

30-70), the most common recorded PS was 2 (53.3%). Twenty two patients (73.3%) had visceral metastases, 12 of them (40%) also had soft tissue metastases, while 9 patients (30%) had both visceral and bone metastases. A total of 160 cycles were administered (median 5 cycles per patient, range 3-12).

All patients were pretreated with anthracycline and taxane containing regimens, to which the disease was primarily refractory, or patients relapsed after initial response. All patients were evaluated for response and for toxicity.

Response to treatment:

All patients entered the study had bidimensionally measurable disease and were considered evaluable for treatment response. The overall RR was 43.3% (13/30), with one (3.3%) CR and 12 (40%) PR. Stable disease was observed in 11 patients (36.6%) and 6 patients (20%) experienced disease progression during treatment Table (2). Response rates observed by disease site were; 30.8% (4/13) of patients with liver metastases, 58.3% (7/12) of patients with soft tissues metastases and 44.4% (4/9) of patients with lung metastases. Patients with bone lesions showed RR of 55.5% (5/9) as recalcification of osteolytic disease, although in these patients zoledronic acid was given concurrently to chemotherapy. Regarding previous response to anthracycline-taxane first-line chemotherapy, of 20 patients responsive to first-line, 50% of patients (10/20) responded to capecitabine/vinorelbine regimen as compared to 30% of patients (3/10) refractory to anthracycline-taxane therapy.

When response was analyzed according to the different prognostic factors, patients with PS 0/1 had a better RR of 71.4% (10/14) than patients with PS 2, 18.7% (3/16), a difference that was found to be statistically highly significant (P=0.001). Patients >50 years of age, post- menopausal and patients with < 2 metastatic sites showed a better overall RR although they did not reach a statistical significance.

Survival analysis:

With a follow up period of 6 -34 months (median 24 months), the median survival was found to be 11 months (95% CI, 12.13-19.80%), the one and 2 year OS were 36.6% (11/30) and 23.3% (7/30), respectively Figure (1). The median PFS was 10 months (95% CI, 9.22-16.2%). At one and 2 year the PFS were 26.6% (8/30) and 16.6% (5/30), respectively (Figure2).

Treatment related toxicity:

The intensity of treatment-related adverse events was mild to moderate (G 1-2) in the majority of patients. There were no treatment related deaths reported. Only one patient (3.3%) developed G4 toxicity (neutropenia). G3 neutropenia was recorded in 26.6% (8 patients), 3 patients were hospitalized for neutropenic fever and treated with antibiotics. G-CSF was given for all patients experiencing G3 neutropenia.

As regards the non-haematological toxicities, the most frequent adverse events were grade 1&2 diarrhea (33.3%), hand-foot syndrome (26.6%), peripheral neuropathy (23.3%), fatigue (30%) and constipation (23.3%).

Reduction of the dose by 25% was done for 10 (33.3%) patients experiencing various G3 toxicities, while reduction of the dose by 50% was done in one patient (3.3%) experiencing G4 neutropenia. Chemotherapy had to be delayed in 54/160 (34.4%) cycles, primarily due to hematologic toxicity in 40 cycles, but it was delayed for personal reasons in 12 cycles and for hand-foot syndrome in two cycles.

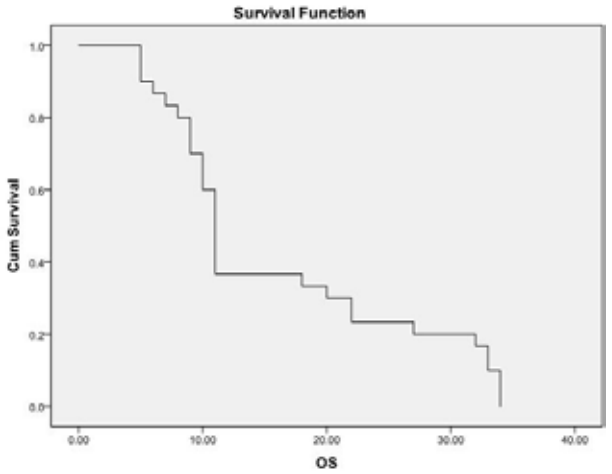

Figure 1: Kaplan- Meier Estimate of Overall Survival.

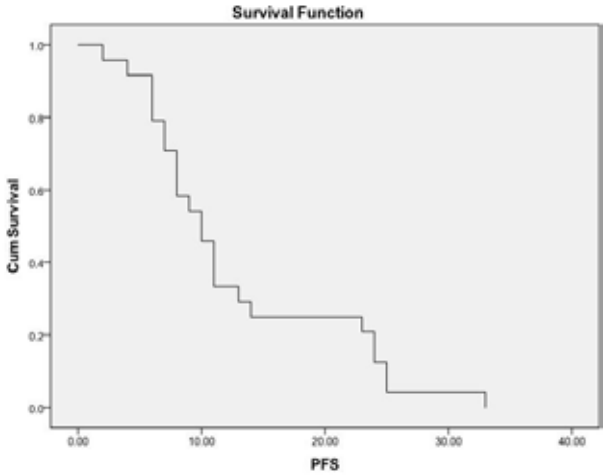

Figure 2: Kaplan- Meier Estimate of Prgression Free Survival.

Table 1: Patient Characteristics (n = 30).

Charactaristic	Number	%
Median age, years (range)	**52 (30-70)**	
PS (ECOG)		
0/1	14	46.6
2	16	53.3
Disease free interval ≥ 2	3	10
< 2	27	90
Pre-menopausal	14	46.6
Post-menopausal	16	53.3
Infilterating ductal	26	86.6
Lobular	3	10
Medullary	1	3.3
Tumor Grade II	12	40
III	18	60
Estrogen receptors		
positive	20	66.6
negative	10	33.3
Progesterone receptors		
positive	11	36.6
negative	14	46.6
HER-2 +++ or FISH positive	11	36.6
negative	13	43.3
unknown	6	20
Prior therapy - Chemotherapy		
anthracycline	adjuvant/palliative(23/7)	(76.6 / 23.3)
taxane	adjuvant/palliative(3/30) adjuvant/	(100)
- Radiotherapy	palliative(21/18)	(70/ 60)
- Hormonal	adjuvant/palliative(20/5)	(66.6)
No. of metastatic involved sites		
≤ 2	13	43.3
> 2	17	56.6
Sites of metastases Visceral	27	90
Soft tissue	12	40
Bone	9	30

Table 2: Response Rate (n=30).

Response	No.	%
Complete response	1	3.3
Partial response	12	40
Stable disease	11	36.6
Progressive disease	6	20
Overall response rate	13/30	43.3

Table 3: treatment-related toxicity (n= 30).

Toxicity	G 1& 2		G 3& 4	
	No	(%)	No	(%)
Neutropenia	12	(40)	9	(30)
Anemia	2	(6.6)	-	-
Thrombocytopenia	5	(16.6)	-	-
Diarrhia	10	(33.3)	2	(6.6)
Hand-foot syndrome	8	(26.6)	1	(3.3)
Periphral neuropathy	7	(23.3)	-	-
Fatigue	9	(30)	-	-
Constipation	7	(23.3)	-	-
Stomatitis	6	(20)	1	(3.3)
Nausea/vomiting	3	(10)	-	-
Alopecia	5	(16.6)	-	-

Table 4: Efficacy and safety of the combination of vinorelbine (i.v) and capecitabine in phase II studies

Author Year	Patient no.	Line of treatment	Vinorelbine (mg/m²)	Capecitabine (mg/m²)	Response rate %	G3/4 Toxicity %	TTP months	OS months
Ahn (25) 2004	44	II/III	25 d1+8	2500 d1-14	50	neutropenia 68.2	5.3	17
Welt (26) 2005	33	II	25-30 d1+8	2000 d1-14	55	neutropenia 39	8	19.2
Goshn (27) 2006	30	I	25 d1+8	1650 d 1-14	70	neutropenia 6.6	10	30.4
Davis (28) 2007	22	II	25 d1+8	2000 d1-14	33	neutropenia 50	5.8	13.5
Estevez (29) 2008	31	II	25 d1+8	2000 d1-14	49	neutropenia 48 Vomiting 16	7.6	27.2
Fan (30) 2010	72	II	25 d1+8	2000 d1-14	45.8	neutropenia 41.7	7.7	26.1
Lorusso (31) 2010	38	II	25 d1+8	2000 d1-14	37	neutropenia 9.4	6.8	11.3

DISCUSSION

Advanced breast cancer is still a therapeutic challenge for the medical oncologist. In fact, increased exposure to chemotherapy with the most active drugs, namely anthracyclines and taxanes, in the adjuvant setting or in the first- line treatment of metastatic disease, makes treatment of relapsed or progressing patients more problematic. Patients in whom previous chemotherapy schedules have failed demonstrate lower RRs and a shorter duration of response and survival with subsequent therapies compared with patients not previously exposed to chemotherapy[23].

Combination chemotherapy regimens are generally thought to be more effective than single-agent chemotherapy in advanced breast cancer. The high remission rates observed with vinorelbine as a single agent as well as its low toxicity profile, makes it a very attractive proposition for combination with other active compounds. Since capecitabine mimics continuous infusion of 5-fluorouracil without the inconvenience and complications associated with this method of administration, this makes it a good candidate to combine with vinorelbine[24]. So the combination of vinorelbine and capecitabine tested in the current study was selected in an attempt to obtain a regimen with considerable efficacy and a favorable outline of subjective toxicity.

In the current study the combination of capecitabine and i.v vinorelbine showed an overall RR of 43.3% (13/30), with one patient (3.3%) had CR, 12 patients (40%) had PR, 11 patients (36.6%) had SD and 6 patients (20%) had PD. The responses achieved were to some extent short lasting with a median PFS of 10 months (9.22-16.2%) and median OS of 11 months (12.13-19.80%).

In other phase II trials in which the combination of capecitabine and vinorelbine was administered to patients with breast cancer pretreated with anthracyclines and taxanes Table (4)[25-31], the RRs obtained ranged between 33% and 70%. In these studies, the median time to progression (TTP) ranged from 4.5 months to 10 months and the median OS was within 10 months and 30.4 months. These values are consistent with the current study results and further confirm the benefit of using this combination of drugs. Data variability among different studies is mostly likely a result of the differences in the number and type of drugs previously administered. For example, in one of these studies in which higher efficacy rates were observed, with an ORR of 70%, a median TTP of 10 months and a median OS of 30.4 months, the treatment was first-line therapy in all cases and only 67% of the patients had previously received adjuvant anthracyclines and taxanes[27]. In the present study, all patients had to have been previously treated with taxanes and anthracyclines.

Welt et al.[26] completed a phase I/II study of capecitabine and vinorelbine in 33 patients with pretreated MBC and defined the maximum tolerated dose at the same doses used in this study. The objective RR was 59 with a median TTP of 8 months (95% CI 4.3-11.7) and OS of 19.2 months (95% CI 11.3-27.1). The patient group in the study of Welt et al. was similar to the current study group and the results, although numerically slightly superior, are consistent, allowing for the small numbers and wide confidence intervals in both studies.

In a recent phase II study done by Fan et al.[30] on 72 patients with MBC pretreated with taxanes and anthracyclines treated by the same regimen of

combination chemotherapy used in the current study, a higher results were achieved. The response rate was 53.8% in patients that were resistant to anthracyclines and taxanes with a median survival of 26.1 months (95% CI 19.6-32.6%).

Similar results have also been reported in phase II and III trials in which vinorelbine was administered with continuous infusion of 5-FU to patients with advanced breast cancer pretreated with anthracyclines and/or taxanes[32,33]. In these studies, ORRs ranged from 38% to 63%, TTP was between 5.1 months and 15 months and OS ranged from 12.3 months to 22 months. Again, the variability between results obtained would most probably be influenced by differences in the number and type of treatments previously administered to these patients.

The study results were better than those reported for other chemotherapy combinations: oxaliplatin plus vinorelbine,with RR of 27% and median PFS of 3.4 months[34] and gemcitabine plus cisplatin, RR of 9% and median PFS of 4 months[35]. Vinorelbine plus cisplatin combination was also explored with RR of 43% when used as second- or third-line treatment in patients with MBC, after failure of anthracycline- and/or paclitaxel-containing regimens[36].

The response attained in the current study was similar to the results of O,Shaughnessy et al. who used capecitabine/ docetaxel therapy in anthracycline- pretreated patients with MBC and They reported objective tumor RR of 42%. However, more grade 3 adverse events occurred in 71% of patients, including neutropenia, hand-foot syndrome and stomatitis. Approximately two thirds of patients (65%) required dose reduction for adverse events[37].

In terms of safety, in the current study treatment was well tolerated, the majority of reported adverse events were mild to moderate in intensity (G1-2). Only one patient (3.3%) developed G 4 neutropenia. Grade 3 adverse events were recorded in 12 patients (40%); as 8 patients (26.6%), 2 patients (6.6%) and one patient (3.3%) had grade 3 neutropenia, diarrhea, stomatitis and hand-foot syndrome, respectively. Granulocyte-colony stimulating factor was given to the 9 patients who developed G 3/4 neutropenia. Dose reduction by 25% was done for the 12 patients who developed G 3 toxicities and for the patients who developed G 4 neutropenia, the dose were reduced by 50%. There were no treatment related deaths. However, these side effects are generally manageable and consistent with the known toxicities of individual agents.

In other phase II trials[25-31], the treatment was also safe and well tolerated. The most common severe hematologic toxicity was G3/4 neutropenia, probably a result of vinorelbine administration (6.6%-68.2%). Severe non-hematologic toxicities were minimal and manageable. Adverse events were controlled by treatment interruption and dose reduction and rarely resulted in life-threatening consequences. However, Ahn et al.[25] examined the same combination of capecitabine and vinorelbine in 44 pretreated patients, using a slightly higher dose of capecitabine (1250 mg/m2 b.d.) and the same dose of vinorelbine. At the higher doses of capecitabine used in their study, there was a considerable increase in the incidence of G3 HFS compared with the current study patients (27.2% vs 3.3%) and a more frequent need for capecitabine dose reduction.

It is possible that treatment with capecitabine plus vinorelbine has a better safety profile compared with other chemotherapy combinations. In some phase II and III trials in which a continuous infusion of 5-FU was administered with vinorelbine in patients with advanced breast cancer, the incidence of neutropenia was between 67% and 90%. Also, severe stomatitis ranged between 32% and 40% of patients, being the most frequent non-hematologic toxicity[38,15]. In a phase II study involving oxaliplatin/ vinorelbine combination, 79% of the patients developing grade 3–4 neutropenia and severe constipations requiring hospitalization were observed[34].

The interest of oral drugs in the management of cancer patients in the palliative setting is growing, in parallel to the preference of the patients for oral chemotherapy provided that the efficacy and toxicity of these agents are comparable to that of their i.v counterparts[39]. There are other clear advantages of oral intake compared with intravenous therapy. For example, oral administration allows outpatient treatment avoiding inconvenience and problems associated with I.V. infusions and potentially reduces the cost of parenteral treatment. In addition, this treatment is also well tolerated in elderly patients[40].

A phase I study of all oral vinorelbine and capecitabine has established a recommended dose of vinorelbine 60 mg/m2 per week and capecitabine 2000 mg/m2 days 1–14 every 3 weeks[41] and a phase II study of the oral combination in pretreated MBC has shown a response rate of 39%. Although it has not been directly compared with other active combination regimens, such as docetaxel and capecitabine or paclitaxel and gemcitabine, it provides a reasonable alternative or second/third line option with an acceptable therapeutic index[42].

CONCLUSION

Capecitabine in combination with vinorelbine showed promising efficacy and safety in heavily pretreated patients with MBC. Randomized trials would be of major

Importance to give further weight to recommending this chemotherapy regimen in

Patients with disease that is resistant or refractory to anthracycline- and taxane containing regimens or for those patients that for clinical reasons cannot tolerate cardiotoxic drugs. Given the frequent and increasing use of both anthracyclines and taxanes in the adjuvant setting, this combination is an ideal candidate as first-line chemotherapy for metastatic disease. It is likely that oral vinorelbine will become readily available in the near future, providing a more convenient, fully oral combination regimen for patients with pretreated MBC.

REFERENCES

1. Perez EA. Current management of metastatic breast cancer. Semin.Oncol. 1999 Aug;26(4 Suppl 12):1-10.
2. Leonard RC. Oral fluoropyrimidines among the new drugs for patients with metastatic breast cancer. Br.J.Cancer 2001 Jun 1;84(11):1437-42.
3. Jassem J, Pienkowski T, Pluzanska A, Jelic S, Gorbunova V, Mrsic Krmpotic Z, et al. Doxorubicin and paclitaxel versus fluorouracil, doxorubicin and cyclophosphamide as first-line therapy for women with metastatic breast cancer: Final results of a randomized phase III multicenter trial. J.Clin.Oncol. 2001 Mar 15;19(6):1707-15.
4. Nabholtz JM, Reese DM, Lindsay MA, Riva A. Docetaxel in the treatment of breast cancer: An update on recent studies. Semin.Oncol. 2002 Jun;29(3 Suppl 12):28-34.
5. Gralow JR. Optimizing the treatment of metastatic breast cancer. Breast Cancer Res.Treat. 2005;89 Suppl 1:S9-S15.
6. Lamont EB, Schilsky RL. The oral fluoropyrimidines in cancer chemotherapy. Clin.Cancer Res. 1999 Sep;5(9):2289-96.
7. Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, Vogel C, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J.Clin. Oncol. 1999 Feb;17(2):485-93.
8. Blum JL, Dieras V, Lo Russo PM, Horton J, Rutman O, Buzdar A, et al. Multicenter, Phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. Cancer 2001 Oct 1;92(7):1759-68.
9. Budman DR. Vinorelbine (Navelbine): A third-generation vinca alkaloid. Cancer Invest. 1997;15(5):475-90.
10. Romero A, Rabinovich MG, Vallejo CT, Perez JE, Rodriguez R, Cuevas MA, et al. Vinorelbine as first-line chemotherapy for metastatic breast carcinoma. J.Clin. Oncol. 1994 Feb;12(2):336-41.
11. Johnson SA, Harper P, Hortobagyi GN, Pouillart P. Vinorelbine: An overview. Cancer Treat.Rev. 1996 Mar;22(2):127-42.
12. Weber BL, Vogel C, Jones S, Harvey H, Hutchins L, Bigley J, et al. Intravenous vinorelbine as first-line and second-line therapy in advanced breast cancer. J.Clin. Oncol. 1995 Nov;13(11):2722-30.
13. Fumoleau P, Blum JL, Reichardt P. Weekly vinorelbine is an effective palliative regimen after failure with anthracyclines and taxanes in metastatic breast carcinoma. Cancer 2003 Sep 15;98(6):1325-6; author reply 1326-7.
14. Hochster HS, Vogel CL, Burman SL, White R. Activity and safety of vinorelbine combined with doxorubicin or fluorouracil as first-line therapy in advanced breast cancer: A stratified phase II study. Oncologist 2001;6(3):269-77.
15. Bonneterre J, Roche H, Monnier A, Guastalla JP, Namer M, Fargeot P, et al. Docetaxel vs 5-fluorouracil plus vinorelbine in metastatic breast cancer after anthracycline therapy failure. Br.J.Cancer 2002 Nov 18;87(11):1210-5.
16. Lorusso V, Crucitta E, Silvestris N, Guida M, Misino A, Latorre A, et al. A phase I study of capecitabine in combination with vinorelbine in advanced breast cancer. Clin.Breast Cancer. 2003 Jun;4(2):138-41.
17. Chan A, Verrill M. Capecitabine and vinorelbine in metastatic breast cancer. Eur.J.Cancer 2009;45(13):2253-65.
18. Orphanos G, Alexopoulos A, Ioannidis G, Kandylis C, Ardavanis A, Stavrakakis J, et al. High efficacy and low toxicity of the combination of vinorelbine and capecitabine as second line treatment in metastatic breast cancer previously treated with taxanes and/or anthracyclines. Proc.Am.Soc.Clin.Oncol. 2006;24(18S):10719.
19. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am.J.Clin.Oncol. 1982 Dec;5(6):649-55.
20. Baquiran BC. National Cancer Institute toxicity scale. Cancer chemotherapy handbook. 2nd ed.: Lippincott; 2001. p. 414-93.
21. Beretta G. Cancer treatment medical guide. 10th ed. Milano: Farmitalia Carlo Erba-Erbamont; 1991.
22. Kaplan EL, Meier P. Nonparanietric estimation from incomplete observations. J.Am.Stat.Assoc. 1958;53:457-81.
23. Esteva FJ, Valero V, Pusztai L, Boehnke Michaud L, Buzdar AU, Hortobagyi GN. Chemotherapy of metastatic breast cancer: What to expect in 2001 and beyond. Oncologist 2001;6(2):133-46.
24. Nole F, de Braud F, Aapro M, Minchella I, De Pas M, Zampino MG, et al. Phase I-II study of vinorelbine in combination with 5-fluorouracil and folinic acid as first-line chemotherapy in metastatic breast cancer: A regimen with a low subjective toxic burden. Ann.Oncol. 1997 Sep;8(9):865-70.
25. Ahn JH, Kim SB, Kim TW, Ahn SH, Kim SM, Park JM, et al. Capecitabine and vinorelbine in patients with metastatic breast cancer previously treated with anthracycline and taxane. J.Korean Med.Sci. 2004;19(4):547-53.
26. Welt A, von Minckwitz G, Oberhoff C, Borquez D, Schleucher R, Loibl S, et al. Phase I/II study of

capecitabine and vinorelbine in pretreated patients with metastatic breast cancer. Ann.Oncol. 2005 Jan;16(1):64-9.
27. Ghosn M, Kattan J, Farhat F, Younes F, Gasmi J. Phase II trial of capecitabine and vinorelbine as first-line chemotherapy for metastatic breast cancer patients. Anticancer Res. 2006 May-Jun;26(3B):2451-6.
28. Davis AJ, Brew S, Gebski VJ, Lewis CR, Moylan E, Parnis FX, et al. Multicenter phase II study of combination chemotherapy with capecitabine and intravenous vinorelbine in patients with pretreated metastatic breast cancer. Asia-Pac.J.Clin.Oncol. 2007;3(1):37-43.
29. Estévez LG, Batista N, Sánchez Rovira P, Velasco A, Provencio M, León A, et al. A phase II study of capecitabine and vinorelbine in patients with metastatic breast cancer pretreated with anthracyclines and taxanes. Clin.Breast Cancer 2008;8(2):149-54.
30. Fan Y, Xu B, Yuan P, Wang J, Ma F, Li Q, et al. Prospective study of vinorelbine and capecitabine combination therapy in chinese patients with metastatic breast cancer pretreated with anthracyclines and taxanes. Chemotherapy 2010;56(4):340-7.
31. Lorusso V, Cinieri S, Giampaglia M, Ciccarese M, Tinelli A, Chiuri V, et al. Intravenous versus oral vinorelbine plus capecitabine as second-line treatment in advanced breast cancer patients. A retrospective comparison of two consecutive phase II studies. Breast 2010;19(3):214-8.
32. Berruti A, Sperone P, Bottini A, Gorzegno G, Lorusso V, Brunelli A, et al. Phase II study of vinorelbine with protracted fluorouracil infusion as a second- or third-line approach for advanced breast cancer patients previously treated with anthracyclines. J.Clin.Oncol. 2000 Oct 1;18(19):3370-7.
33. Zambelli A, Robustelli della Cuna FS, Ponchio L, Ucci G, Da Prada GA, Robustelli della Cuna G. Four-day infusion of fluorouracil plus vinorelbine as salvage treatment of heavily pretreated metastatic breast cancer. Breast Cancer Res.Treat. 2000 Jun;61(3):241-7.
34. Petit T, Benider A, Yovine A, Bougnoux P, Spaeth D, Maindrault Goebel F, et al. Phase II study of an oxaliplatin/vinorelbine combination in patients with anthracycline- and taxane-pre-treated metastatic breast cancer. Anticancer Drugs 2006 Mar;17(3):337-43.
35. Sánchez Escribano Morcuende R, Alés Martínez JE, Aramburo González PM. Low dose Gemcitabine plus cisplatin in a weekly-based regimen as salvage therapy for relapsed breast cancer after taxane-anthracycline-containing regimens. Clin.Transl.Oncol. 2007;9(7):459-64.
36. Ray Coquard I, Biron P, Bachelot T, Guastalla JP, Catimel G, Merrouche Y, et al. Vinorelbine and cisplatin (CIVIC regimen) for the treatment of metastatic breast carcinoma after failure of anthracycline- and/or paclitaxel-containing regimens. Cancer 1998 Jan 1;82(1):134-40.
37. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results. J.Clin.Oncol. 2002 Jun 15;20(12):2812-23.
38. Froudarakis ME, Catimel G, Guastalla JP, Rebattu P, Clavel M. Phase II trial of navelbine and fluorouracil as second-line chemotherapy in metastatic breast carcinoma. Oncology 1998 Jan-Feb;55(1):87-8.
39. Jones A, O'Brien M, Sommer H, Nowara E, Welt A, Pienkowski T, et al. Phase II study of oral vinorelbine in combination with capecitabine as second line chemotherapy in metastatic breast cancer patients previously treated with anthracyclines and taxanes. Cancer Chemother.Pharmacol. 2010;65(4):755-63.
40. Hess D, Thürlimann B, Pagani O, Aebi S, Rauch D, Ballabeni P, et al. Capecitabine and vinorelbine in elderly patients (≥65 years) with metastatic breast cancer: A phase I trial (SAKK 25/99). Ann.Oncol. 2004;15(12):1760-5.
41. Nole F, Catania C, Sanna G, Imadalou K, Munzone E, Adamoli L, et al. Dose-finding and pharmacokinetic study of an all-oral combination regimen of oral vinorelbine and capecitabine for patients with metastatic breast cancer. Ann.Oncol. 2006 Feb;17(2):322-9.
42. Lorusso V, Spada M, Giampaglia M, Misino A, Calabrese R, Latorre A, et al. Oral vinorelbine plus capecitabine (oral vincap) combination in patients with advanced breast cancer (ABC). A phase II study of the GOIM (Gruppo Oncologico dell'Italia Meridionale). Ann.Oncol. 2006;17(Suppl. 7):vii15-7.