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ORIGINAL ARTICLE

# Phase II study of an all-oral combination of vinorelbine with capecitabine in patients with metastatic breast cancer

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**Abstract**
*Purpose* Combination of intravenous (i.v.) vinorelbine and capecitabine was shown to be feasible and effective in metastatic breast cancer (MBC). In an effort to improve patient convenience and to prolong infusion-free survival, we investigated in first-line treatment a regimen combining oral vinorelbine and capecitabine in a phase II study.
*Patients and methods* Fifty-two patients (median age, 60 years) with MBC received the combination consisting of oral vinorelbine 60 mg/m$^2$ on days 1, 8 and 15 plus capecitabine 1,000 mg/m$^2$ bid given from day 1 to day 14 in an open-label, multicentre phase II study [the recommended doses were established in a phase I study (Nolé et al. in Ann Oncol 17:332–339, 2006)]. Cycles were repeated every 3 weeks.
*Results* Seventy-nine percent of the patients had received prior adjuvant chemotherapy and 81% presented with visceral involvement. The median number of administered cycles per patient was 7 (range 1–18). Twenty-three responses were documented and validated by an independent panel review, yielding response rates of 44.2% (95% CI, 30.5–58.7) in the 52 enrolled patients and 54.8% (95% CI, 38.7–70.2) in the 42 evaluable patients. Median progression-free survival and median overall survival were 8.4 and 25.8 months, respectively. Neutropenia was the main dose-limiting toxicity but complications were uncommon, only one patient having experienced febrile neutropenia. Other frequently reported adverse events included, fatigue, nausea, vomiting, diarrhoea and constipation, stomatitis and hand-foot syndrome, which were rarely severe.
*Conclusions* This regimen combining oral vinorelbine with capecitabine is effective and manageable in the first-line treatment of MBC. Oral vinorelbine on days 1, 8 and 15 with capecitabine from days 1 to 14 every 3 weeks represents a convenient option which offers an all-oral treatment to the patients and prolongs their infusion-free survival.

**Keywords** Metastatic breast cancer · Oral vinorelbine · Capecitabine · Oral chemotherapy

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## Introduction

The development of new combination regimens allowing prolonged survival without impairing the patient's quality of life is a priority in metastatic breast cancer (MBC). The challenge is how to deliver full doses of each agent without causing unacceptable levels of toxicity. Vinorelbine is among the most effective drugs used in the treatment of

MBC and the combination with capecitabine has shown promising results in this setting.

Vinorelbine targets the tubulin–microtubule system inhibiting the tubulin polymerisation [2].

Capecitabine (Xeloda®) is an oral fluoropyrimidine precursor preferentially taken up by tumuor cell and converted to 5-fluorouracil (5-FU) [3].

Intravenous (i.v.) vinorelbine has been intensively investigated in the treatment of MBC and demonstrated a substantial activity [4–10] with an acceptable safety profile which encouraged its combination with other cytotoxics active against MBC.

Oral vinorelbine as a single agent for the first-line treatment of MBC patients was also shown to be an effective and well-tolerated agent [11, 12]. In two phase II studies, consistent response rates of 30% were reported. Median durations of progression-free survival and overall survival fall in the same range: 4.2 and 24 months in one trial and 4.6 and 21 months in the other one. Similar to i.v. vinorelbine, neutropenia was the main dose-limiting toxicity but was rarely complicated; only 4% of patients enrolled in the two phase II studies experienced febrile neutropenia. No severe infection was reported. Even though nausea and vomiting were more frequently reported with oral vinorelbine in contrast to the usually low incidence seen with the i.v. form, they were generally of mild to moderate intensity. In subsequent studies of oral vinorelbine, a primary prophylaxis with oral 5-HT3 antagonist was shown to be effective in nausea and vomiting prophylaxis [13].

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 [14]. Oral vinorelbine belongs to the new generation of oral drugs, and achieves reliable blood exposure. Its bioavailability is about 40% which indicates that 80 mg/m$^2$ orally corresponds to 30 mg/m$^2$ intravenously and 60 mg/m$^2$ orally to 25 mg/m$^2$ intravenously [15].

Capecitabine has demonstrated activity as a single agent in pretreated MBC with response rate (RR) of 25–30% [16, 17].

Preclinical data have suggested that the antitumor activity of the combination of vinorelbine and capecitabine is synergistic, while the combination of vinorelbine with 5-fluorouracil shows only an additive antitumor activity [18].

Several phase I–II studies have investigated this combination of intravenous vinorelbine with capecitabine in heavily pretreated patients with MBC with a RR ranging from 33 to 55% [19–24].

Ghosn et al. [25] investigated the combination as first-line chemotherapy for MBC in a phase II, obtaining a RR of 70% (95% CI: 51–85) among the 30 patients treated with i.v. VRL at 25 mg/m$^2$ and capecitabine 1,650 mg/m$^2$ per day.

Nolè et al. investigated the combination as an all-oral regimen in a phase I dose-finding study where patients with first or second line MBC received oral VRL at 60 or 80 mg/m$^2$ on day 1, day 8 or on a weekly basis with capecitabine at doses ranging from 1,650 to 2,500 mg/m$^2$ per day from day 1 to day 14, every 3 or 4 weeks. Responses were observed in 18 patients (3 CRs and 15 PRs) among the 44 treated ones. The study confirmed the good safety profile of the combination with no pharmacokinetic interaction when both drugs were co-administered [1].

Based on the results of this phase I study, the combination was investigated in the present phase II study as first-line chemotherapy of MBC.

## Patients and methods

### Patient selection

Eligible patients fulfilled all the following criteria: metastatic breast cancer; aged $\geq$18 and $\leq$80 years; Karnofsky performance status $\geq$70%; estimated life expectancy $\geq$12 weeks; adequate bone marrow, hepatic and renal functions [defined as absolute neutrophil count (ANC) $\geq 2.0 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, haemoglobin $\geq$10 g/dl or 6.2 mmol/l, total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), ASAT and ALAT $\leq 2.5 \times$ ULN, calculated creatinine clearance $\geq$50 ml/min]. Patients were required to have at least one bidimensionally measurable target lesion according to WHO criteria, measured within 21 days prior to study entry. Prior therapy was allowed as follows: patients might have had previous hormonal therapy as adjuvant treatment and/or treatment of metastatic disease provided that they had progressive disease at study entry and they had discontinued hormonal therapy before study entry; previous adjuvant chemotherapy which might have contained an anthracycline and/or a taxane was allowed provided that the patient has totally recovered from toxicity of previous chemotherapy. Previous radiation therapy may have been given provided that 4 weeks had elapsed prior to study entry, unless the area involved was <20% of bone marrow volume, in which case the patient could start treatment earlier. However, the measurable target lesions had to be completely outside the radiation field. Prior chemotherapy for MBC was not allowed. Concurrent treatment with any other cancer chemotherapy, participation in any other clinical trial within 30 days prior to study screening, poorly controlled medical disorder (diabetes, hypertension, infection), clinical signs of central nervous system disorder and brain metastases or leptomeningeal infiltration excluded patients from this study.

This study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. Written

approval of Local ethics committees was obtained, and patients signed a written informed consent before enrolment.

### Study drug administration

Oral vinorelbine was administered at a dose of 60 mg/m$^2$ on days 1, 8 and 15 and capecitabine was administered at a dose of 2,000 mg/m$^2$ from day 1 to day 14, every 3 weeks. Complete blood cell counts were performed on days 1, 8 and 15 of each cycle to check that ANC were $\geq 1.5 \times 10^9$/l.

Prophylactic antiemetic regimen with 5-HT$_3$ antagonist was recommended before each administration of oral vinorelbine from the first cycle. For capecitabine, symptomatic treatment had to be initiated once nausea or vomiting had occurred and prophylactic antiemetic treatment should be given for subsequent cycles. On day 1 of the cycles, treatment could be delayed in case of haematological, neurological and hepatic toxicities but the duration of one cycle must not exceed 5 weeks, patients who required a delay by more than 2 weeks were withdrawn from the study.

Administration of oral vinorelbine on day 8 and/or day 15 had to be omitted because of grade $\geq$2 neutropenia or thrombocytopenia but capecitabine was continued. Capecitabine had to be interrupted if treatment-related elevation in bilirubin and/or transaminases occurred. Oral vinorelbine and capecitabine were interrupted when grade 2 diarrhoea occurred until resolution to grade 0–1. If diarrhoea was grade $\geq$3, vinorelbine and capecitabine were to be withheld until resolution to grade 0–1 and subsequent doses of capecitabine were to be reduced by 25% if diarrhoea was grade 3 and by 50% if diarrhoea was grade 4. On occurrence of grade 2 or more severe cardiotoxicity, capecitabine was to be discontinued. In case of grade $\geq$2 neurotoxicity, the cycle had to be delayed until resolution to grade 0–1 and treatment was restarted at the same dose and if grade $\geq$2 peripheral neuropathy or neuroconstipation occurred during a cycle, the day 8 and/or 15 dose of oral vinorelbine was to be skipped. If grade $\geq$2 hand-foot syndrome occurred, capecitabine had to be stopped immediately until resolution to grade 0–1 and was to be reduced at subsequent cycles, by 25% in case of grade 2 and by 50% in case of grade 3 or second occurrence of grade 2.

### Treatment evaluation

Evaluation at study entry included vital signs, physical examination, mammary ultrasound with or without mammography in case of local recurrence, chest X-ray completed by chest CT-scan in case of lung metastases and/or mediastinal involvement, liver ultrasound completed by abdominal CT-scan in case of liver metastases, and bone scintigraphy. Abnormal images were monitored every 2 cycles at the end of the treatment and also at least 28 days after a response had been first observed or at any time in case of progression suspected. Thereafter, patients were followed every 3 months until death. WHO criteria were used to define response. Response rate was the primary efficacy variable. All registered patients were included in the efficacy analysis (intent-to-treat analysis). Patients evaluable for efficacy were defined as those who remained in the study until completion of the first evaluation (after first 2 cycles) as required by protocol and whose baseline lesions were consistently assessed throughout the study period with the same method. An independent radiologist validated all responses except for four patients, one patient progressed at first evaluation and three patients went off after the first cycle of study treatment.

Progression-free survival was calculated from the registration date until the date of progression or death due to any cause. Survival was defined as the time elapsed from registration date until death or last contact.

Toxicity was evaluated by using the National Cancer Institute criteria (version 2.0) except febrile neutropenia, which was assessed according to Pizzo's definition [26]. ECG had to be performed prior to initial administration. Patient who received at least one cycle of study treatment was considered evaluable for safety analysis unless he was lost to follow-up immediately after the start of treatment.

### Statistical analysis

The primary study objective was to assess the response rate. Secondary objectives included safety evaluation, impact on quality of life and determination of the duration of response, progression-free survival and overall survival.

This study was an open-label, multicentre, non-comparative phase II trial. The one-sample multiple testing procedure of Fleming for phase II clinical trials was used. The procedure employed the standard single stage test procedure at the last one of $k$ pre-specified testing, while both allowing for early termination (should extreme results be seen) and essentially preserving the size and power of the single stage procedure. The reference responses rates, acceptable error probabilities, and number of testings selected for this study were as follows: Po = 30%, Pa = 50%, $\alpha = 5\%$, $\beta = 20\%$, $k = 2$. This assumed that 30% was the minimum desirable response rate in evaluable patients for an active combination therapy in this population. Under these conditions, the total sample size was 45 evaluable patients and the first test was performed after 25 evaluable patients.

## Results

### Patients characteristics

Patients characteristics are shown in Table 1. Fifty-two patients were enrolled between February 2004 and January 2006. Median age was 60 years; Karnofsky performance status was ≥90% in 85% of patients; 43 patients (83%) had a disease-free interval ≥2 years; 41 patients (79%) received prior chemotherapy in the neo-adjuvant/adjuvant setting mainly CMF with or without anthracyclines and only three patients received adjuvant taxanes. Forty-two patients (81%) had visceral involvement and most of the patients had at least two organs involved.

**Table 1** Patient and tumour characteristics

| | Number of patients (%) | (%) |
|---|---|---|
| Total number of patients (%) | 52 | (100) |
| Age (years) | | |
| Median | 60 | |
| Range | 29–77 | |
| Disease-free interval (years) | | |
| Median (range) | 3.5 (0–22.7) | |
| ≥2 | 43 | (82.7) |
| <2 | 9 | (17.3) |
| Menopausal status | | |
| Pre | 26 | (50.0) |
| Post | 26 | (50.0) |
| Oestrogen receptors | | |
| Positive | 41 | (78.8) |
| Negative | 8 | (15.4) |
| Unknown | 3 | (5.8) |
| Prior therapy | | |
| Surgery | 51 | (98.1) |
| Radiotherapy | 22 | (42.3) |
| Neo/adjuvant chemotherapy | 41 | (78.8) |
| CMF | 16 | (38.1) |
| Anthracycline | 12 | (28.5) |
| CMF and anthracyclines | 11 | (26.2) |
| Anthracyclines + taxanes | 3 | (5.8) |
| Hormonotherapy | 45 | (86.5) |
| Karnofsky performance status (%) | | |
| 100 | 42 | (80.8) |
| 90 | 2 | (3.8) |
| 80 | 6 | (11.5) |
| 70 | 2 | (3.8) |
| Visceral involvement | 42 | (80.8) |
| Number of organs involved | | |
| 1 | 9 | (17.3) |
| 2 | 22 | (42.3) |
| ≥3 | 21 | (40.4) |

### Treatment delivery

A total of 396 cycles were given among the 52 patients treated. The median number of cycles for the whole population was seven with a range between 1 and 18 cycles. Thirty-two patients (61.5% of the whole population) received at least 6 cycles. Disease progression and drug-related adverse events were responsible for the study discontinuation of 21 patients (40%) and 10 patients (19%), respectively. Adverse events which required drug discontinuation included neutropenia, sensory neuropathy, asthenia/fatigue, stomatitis, thrombocytopenia, gastralgia and abdominal cramps.

The median relative dose intensities of oral vinorelbine and capecitabine were 71 and 83%, respectively. Cycles were delayed for more than 3 days in 32 patients out of the 52 enrolled (61.5%) and in 74 cycles (21.5%). The main reason for cycle delay was haematological toxicity for 41 cycles (55.4%) and patient's convenience (13.5%). Seventeen patients (32.7%) had capecitabine dose reduction ≥25%. The reasons were grade ≥3 neutropenia (eight patients), elevation of AST/ALT or bilirubin (three patients), gastro-intestinal toxicity (four patients) and patient's mistake (one patient).

### Efficacy

Among the 52 enrolled patients, 42 were evaluable for efficacy according to independent panel review. The reasons for non-evaluability were, premature discontinuation for four patients after one cycle (because of related adverse events for three patients and death due to cerebral haemorrhage for one patient), noneligibility for four patients (no distant metastasis for one patient, absence of measurable lesion for three patients), and missing baseline imaging for two patients.

A total of 23 responses (2 complete and 21 partial) were reported, yielding a response rate of 44% (95% CI, 30–59) in the intent-to-treat analysis and 54.8% (95% CI, 39–70) in the 42 evaluable population (Table 2). The median age of responders was the same as the median age of the study population, i.e. 60 years. All had visceral involvement, except one with lymph node and bone involvement. Eighteen of them (78%) had received prior neo and/or adjuvant chemotherapy.

The median progression-free survival (Fig. 1) was 8.4 months (95% CI, 4.8–9.9) in the intent-to-treat population. After a median follow-up of 30.3 months, 29 patients were dead, 23 patients alive. The median overall survival (Fig. 2) was 25.8 months (95% CI, 21.6–33.6) in the intent-to-treat population.

**Table 2** WHO overall response rate (after panel review)

| Overall response | Intent-to-treat population ($N = 52$) | | Evaluable population ($N = 42$) | |
|---|---|---|---|---|
| | Number | % | Number | % |
| Complete response (CR) | 2 | 3.8 | 2 | 4.8 |
| Partial response (PR) | 21 | 40.4 | 21 | 50.0 |
| Response rate (CR + PR) | 23 | 44.2 | 23 | 54.8 |
| No change | 15 | 28.8 | 15 | 35.7 |
| Disease control (CR + PR + NC) | 38 | 73.1 | 38 | 90.5 |
| Progressive disease (PD) | 4 | 7.7 | 4 | 9.5 |
| Non-evaluable | 10 | 19.2 | – | – |

## Safety

Toxicity profile is presented in Table 3. As expected, neutropenia was the most common side-effect. Grades 3 and 4 neutropenia was seen in 11 (21.2%) and 13 (25.0%) patients, respectively. Febrile neutropenia defined as three elevations of oral temperature >38°C during a 24-h period or a single elevation to >38.5°C concomitant with grade 4 neutropenia requiring i.v. antibiotics or hospitalisation, was observed in a single patient (1.9%) during cycle 3 and resolved under antibiotic therapy. Neutropenic infection defined as grade $\geq$3 infection concomitant with grade $\geq$3 neutropenia was not observed.

The most frequent non-haematological toxicitiy was gastrointestinal. However, the incidence of grade 3 was low and there was only one episode of grade 4. Grade 3 vomiting was reported in 4 patients (7.7%) and constipation, diarrhoea and nausea in 1 patient (1.9%) each. Grade 3 stomatitis was reported in 3 patients (5.8%). Grade 4 was observed only with abdominal pain in 1 patient (1.9%). As expected with a capecitabine-containing regimen, hand-foot syndrome was observed but grade 3 was reported in only 1 patient (1.9%). Regarding vascular toxicity, 5 patients developed a grade 3 thrombosis and recovered under anticoagulant. Neuro-sensory disorders were of low incidence and grade 3 was reported in only 2 patients (3.8%) leading to treatment discontinuation.

Four patients experienced a total of four serious drug-related adverse events. These serious adverse events were of non-haematological origin, i.e. grade 3 mucositis, grade 2 paresthesia, grade 3 deep vein thrombosis and grade 3 vomiting. For one patient (mucositis), it led to permanent discontinuation of study treatment; of note a moderate deficit in dihydropyrimidine dehydrogenase activity was found. For another patient who experienced vomiting the dose of both study drugs was reduced by 25%; two other patients could continue study treatment.

## Discussion

Regimens combining anthracyclines and taxanes are becoming standard adjuvant treatment for early breast cancer; therefore, a need for new options in the treatment of MBC is warranted. Vinorelbine is a highly active drug in the treatment of MBC, both as single agent or in combination regimens. Vinorelbine is well tolerated, with a low incidence of severe toxicities. Because of its favourable

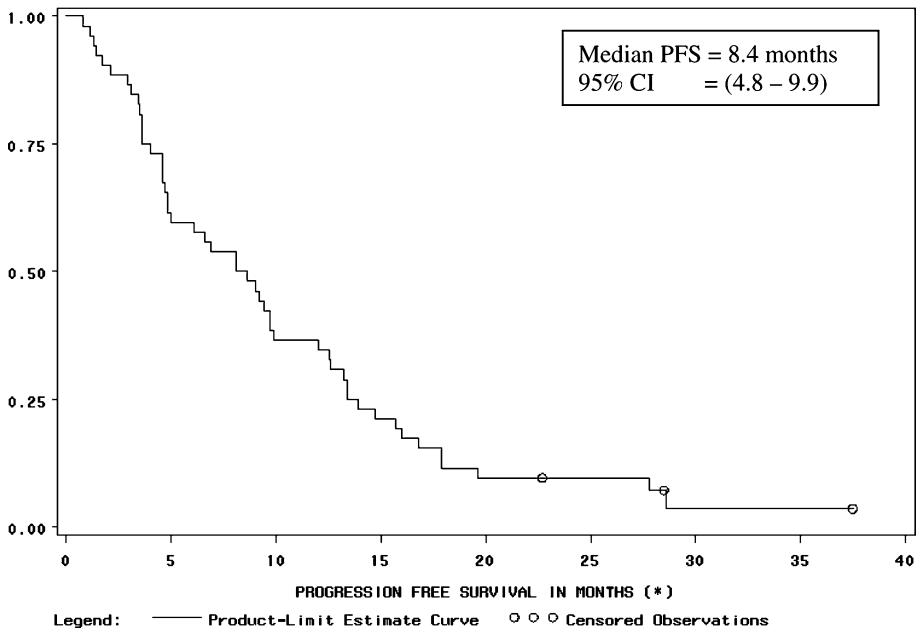


**Fig. 1** Progression-free survival in the ITT population

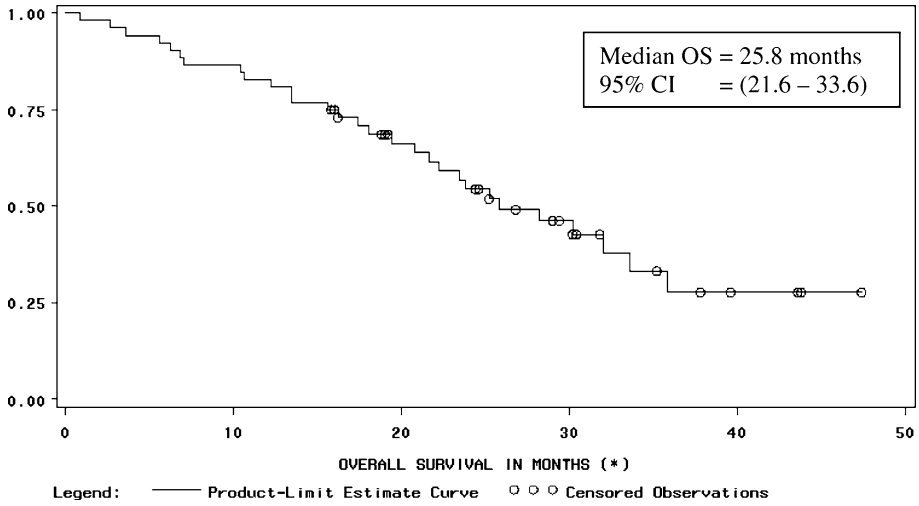


**Fig. 2** Overall survival in the ITT population

safety profile and activity, vinorelbine is a valuable option for the treatment of MBC patients and is considered as an effective treatment in this palliative setting by the European Society of Medical oncology (ESMO) in the updated clinical recommendations.

Capecitabine is an oral fluoropyrimidine that mimics 5FU, with significant activity in breast cancer. As a single agent, capecitabine has demonstrated consistent activity in first-line setting as well as after anthracycline/taxane failure [16, 27].

Oral chemotherapy offers significant advantages over i.v. administration because of its greater convenience for the patient and, its ease of administration avoiding hospitalisation. In the palliative treatment of MBC, oral vinorelbine used as a single agent was shown to be an effective and well-tolerated treatment [11, 12]. To improve patient convenience and global efficiency of chemotherapy, oral vinorelbine has been increasingly used in combination regimens, and has been shown to be as efficient as i.v. vinorelbine.

Several phase I/II studies of i.v. vinorelbine associated with capecitabine were conducted mainly in heavily pretreated patients in which different schedules of this regimen were tested. Response rates varied from 33 to 55%, and tolerance profile was satisfactory [19–24].

Based on the encouraging activity reported with i.v. vinorelbine plus capecitabine and the advantages of an all-oral combination, the present study was set up in order to investigate oral vinorelbine plus capecitabine. The majority of patients (80.2%) had visceral involvement with 82.7% having at least 2 organs involved. Among the 52 patients treated, 2 patients (3.8%) achieved a complete response and 21 patients (40.4%) achieved a partial response yielding a response rate of 44.2% (95% CI, 30.5–58.7) in the intent-to-treat population and 54.8% (95% CI, 38.7–70.2) in the evaluable population. Median progression-free survival and median survival were 8.4 (95% CI, 4.8–9.9) and 25.8 months (95% CI, 21.6–33.6).

The most frequently related adverse events were haematological events related to vinorelbine myelotoxicity, mainly neutropenia as expected. Grade 3 neutropenia was reported in 11 patients (21.2%) and grade 4 in 13 patients (25.0%). However, neutropenia was short-lasting with a median duration of 7 days and rarely complicated as only one episode of febrile neutropenia was reported, without any episode of neutropenic infection.

The most common non-haematological related adverse events were gastro-intestinal events including, nausea, diarrhoea, vomiting, stomatitis, abdominal pain, and fatigue and hand-foot syndrome. These common side effects related to vinorelbine and/or capecitabine were rarely severe. Grade 4 was observed only in one patient with abdominal pain. The most severe intensity was grade 3 occurring in less than 4% of cycles for gastro-intestinal side effects and in less than 2% of cycles for fatigue. Grade 3 hand-foot syndrome occurred in only 1 patient in 1 cycle.

The selected doses for vinorelbine and capecitabine in this phase II trial were established on the basis of the findings of a phase I study which investigated three schedules: oral vinorelbine given on day 1, 8, and weekly regimens (day 1, 8 and 15) with a 14-day course of capecitabine, every 3 weeks and a day 1 and 8 regimen of oral vinorelbine with a 14-day course of capecitabine every 4 weeks [1]. Oral vinorelbine was given at a fixed dose of 60 or 80 mg/m$^2$ and capecitabine doses ranged from 1,650 to 2,500 mg/m$^2$. Neutropenia was the main dose-limiting toxicity, with a nadir occurring after day 15 and lasting no more than 7 days. The weekly schedule displayed the highest dose intensities for both drugs compared to days 1 and 8 schedules and clinical responses were observed with this weekly schedule. Therefore, the recommended schedule

**Table 3** Drug related toxicity by patient (incidence ≥5%) and by cycle (NCI/CTC grading)

| Adverse events by NCI/CTC | By patient | | | By cycle | | |
|---|---|---|---|---|---|---|
| | Overall incidence (*N*) (%) | Grade 3 (*N*) (%) | Grade 4 (*N*) (%) | Overall incidence (*N*) (%) | Grade 3 (*N*) (%) | Grade 4 (*N*) (%) |
| Haematological | | | | | | |
| Leucopenia | 40 (76.9) | 10 (19.2) | 6 (11.5) | 211 (53.3) | 33 (8.3) | 7 (1.8) |
| Neutropenia | 40 (76.9) | 11 (21.2) | 13 (25.0) | 200 (50.5) | 29 (7.3) | 27 (6.8) |
| Febrile neutropenia[a] | 1 (1.9.) | – | 1 (1.9) | 1 (0.2) | – | 1 (0.2) |
| Anaemia | 45 (86.5) | 1 (1.9) | – | 225 (56.8) | 1 (0.3) | – |
| Thrombocytopenia | 15 (28.8) | 1 (1.9) | – | 54 (13.6) | 4 (1.0) | – |
| Dermatologic | | | | | | |
| Alopecia | 11 (21.2) | – | – | 91 (23.0) | – | – |
| Nail changes | 5 (9.6) | – | – | 16 (4.0) | – | – |
| Hand-foot syndrome | 19 (36.5) | 1 (1.9) | – | 91 (23.0) | 1 (0.3) | – |
| Infection without neutropenia | 14 (26.9) | – | – | 21 (5.3) | – | |
| Vascular | | | | | | |
| Thrombosis | 5 (9.6) | 5 (9.6) | – | 18 (4.5) | 18 (4.5) | – |
| Flu-like symptoms | | | | | | |
| Fatigue | 37 (71.2) | 4 (7.7) | – | 117 (29.5) | 4 (1.0) | – |
| Fever without neutropenia | 11 (21.2) | – | – | 17 (4.3) | – | – |
| Gastrointestinal | | | | | | |
| Constipation | 17 (32.7) | 1 (1.9) | – | 45 (11.4) | 1 (0.3) | – |
| Diarrhoea | 35 (67.3) | 1 (1.9) | – | 85 (21.5) | 1 (0.3) | – |
| Nausea | 39 (75.0) | 1 (1.9) | NA | 116 (29.3) | 1 (0.3) | NA |
| Stomatitis | 21 (40.4) | 3 (5.8) | – | 43 (10.9) | 3 (0.8) | – |
| Vomiting | 24 (46.2) | 4 (7.7) | – | 55 (13.9) | 4 (1.0) | – |
| Anorexia | 6 (11.5) | 1 (1.9) | – | 14 (3.5) | 2 (0.5) | – |
| Dyspepsia | 8 (15.4) | – | – | 20 (5.1) | – | – |
| Gastritis | 3 (5.8) | – | – | 4 (1.0) | – | – |
| Taste | 7 (13.5) | – | – | 13 (3.3) | – | – |
| Other | 6 (11.5) | – | – | 7 (1.8) | – | – |
| Neurology | | | | | | |
| Neuropathy-motor | 3 (5.8) | – | – | 6 (1.5) | – | – |
| Neuropathy-sensory | 10 (19.2) | 2 (3.8) | – | 25 (6.3) | 2 (0.5) | – |
| Pain | | | | | | |
| Abdominal pain | 18 (34.6) | 4 (7.7) | 1 (1.9) | 37 (9.3) | 4 (1.0) | 1 (0.3) |
| Bone pain | 3 (5.8) | – | – | 9 (2.3) | – | – |
| Head ache | 6 (11.5) | – | – | 11 (2.8) | – | – |
| Myalgia | 6 (11.5) | – | – | 9 (2.3) | – | – |
| Weight | | | | | | |
| Weight gain | 8 (15.4) | – | – | 47 (11.9) | – | – |
| Weight loss | 5 (9.6) | 1 (1.9) | – | 25 (6.3) | 5 (1.3) | – |
| Ocular | | | | | | |
| Conjunctivitis | 3 (5.8) | – | – | 5 (1.3) | – | – |
| Tearing | 3 (5.8) | – | – | 7 (1.8) | – | – |

396 cycles were evaluable for toxicity

[a] Pizzo's definition

was established at 60 mg/m$^2$ of oral vinorelbine on day 1, 8 and 15 combined with capecitabine at 2,000 mg/m$^2$ days 1–14 every 3 weeks.

The adverse events associated with this dosing schedule were predictable and manageable and overlapping toxicities between both drugs were minor. Safety data reported in

the present phase II study are consistent with the previously reported clinical experience of the phase I study.

In conclusion, the results of the current study confirm that the combination of oral vinorelbine and capecitabine is an effective treatment in the first-line treatment of metastatic breast cancer and is well tolerated. As the administration of both drugs is oral and well tolerated it may improve the acceptability of the treatment by the patient and the patient's quality of life allowing a home-based therapy and increasing the infusion-free survival.

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