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ORIGINAL ARTICLE

# Phase II study of vinorelbine (alternating intravenous and oral) in combination with docetaxel as first-line chemotherapy in metastatic breast cancer

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**Abstract**
*Purpose* Combination of intravenous (i.v.) vinorelbine and docetaxel was shown to be feasible and effective in metastatic breast cancer (MBC). In an effort to improve patient convenience, we investigated in first-line treatment a regimen alternating i.v. and oral vinorelbine in combination with docetaxel.
*Patients and methods* Forty-nine patients (median age, 53 years) with MBC received a maximum of 6 cycles consisting of i.v. vinorelbine 20 mg/m² plus docetaxel 60 mg/m² given on day 1, and oral vinorelbine 60 mg/m² on day 15 every 3 weeks in an open-label, multicentre phase II study (recommended dose established in phase I study [1]).
*Results* Sixty-three percent of the patient had received prior adjuvant chemotherapy and 78% presented visceral involvement. Twenty-four responses were documented and validated by an independent panel review, yielding response rates of 49% (95% CI: 34–64) in the 49 enrolled patients and 55.8% (95% CI: 40–71) in the 43 evaluable patients. Median duration of response was 9.4 months. Median progression-free survival and median overall survival were 5.5 and 33.2 months, respectively. Neutropenia was the main dose-limiting toxicity but complications were uncommon, four patients having experienced febrile neutropenia and one having developed neutropenic infection. Other frequently reported adverse events included alopecia, fatigue, stomatitis, constipation, diarrhoea and nausea, which were rarely severe.
*Conclusions* This regimen alternating oral and i.v. vinorelbine in combination with docetaxel is effective and manageable. Vinorelbine i.v. per oral day 1 per day 15-docetaxel day 1 every 3 weeks represents a convenient option to combine docetaxel and vinorelbine for the palliative treatment of MBC.

**Keywords** Metastatic breast cancer · Oral vinorelbine · Docetaxel · 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. Docetaxel and vinorelbine are among the most effective drugs used in the treatment of MBC and their combination has shown promising results in this setting.

Vinorelbine and taxanes both target the tubulin–microtubule system either inhibiting the tubulin polymerisation in the case of vinorelbine or inhibiting microtubule depolymerisation in the case of taxoids [2]. In tumour bearing mice, combination of vinorelbine plus docetaxel resulted in a

therapeutic synergism and authors indicated that 80–100% of the optimal dose of each agent could be administered without increasing the toxicity to vital normal cells [3].

Intravenous (i.v.) vinorelbine has been intensively investigated in the treatment of MBC. Response rates of 35–50% have consistently been demonstrated for first-line single agent vinorelbine [4–10]. Acceptable safety profile of i.v. vinorelbine encourages its combination with other cytotoxics active against MBC.

Oral vinorelbine as a single agent for the first-line treatment of MBC patients was 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 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/m² orally corresponds to 30 mg/m² intravenously and 60 mg/m² orally to 25 mg/m² intravenously [15].

For combination regimens, which contain a cytotoxic that is not orally available, a regimen using i.v. vinorelbine on the day the other cytotoxic is infused and oral vinorelbine for the rest of the cycle was investigated in an effort to improve patient convenience. Therefore, the present study was designed to evaluate vinorelbine, alternating i.v. on day 1 and oral on day 15, in combination with docetaxel infused on day 1 every 3 weeks given as first-line treatment of MBC patients. The doses of each study drug and their schedule of administration were established in a phase I study conducted in 30 patients with MBC [1]. Neutropenia was the dose-limiting toxicity, which precluded the administration of oral vinorelbine on day 8. The recommended schedule was thus established at i.v. vinorelbine 20 mg/m² with docetaxel 60 mg/m² on day 1 and oral vinorelbine 60 mg/m² on day 15 every 3 weeks and was used in the present study.

## Patients and methods

### Patient selection

Eligible patients fulfilled all the following criteria: metastatic breast cancer; aged $\geq 18$ and $\leq 70$ 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 $\leq$ upper limit of normal (ULN), ASAT and ALAT $\leq 2.5 \times$ ULN, alkaline phosphatase $\leq 5 \times$ ULN, serum creatinine $\leq 1.5 \times$ ULN). Patients were required to have at least one bidimensionally measurable target lesion (documented by CT-scan or MRI according to WHO criteria), measured within 21 days of inclusion in the study. Prior therapy was permitted as follows: a minimum of 2 weeks had to have elapsed between surgery and inclusion in the study; 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 neo-adjuvant and/or adjuvant chemotherapy which might have contained an anthracycline was allowed provided that an interval of at least 12 months had elapsed between the end of adjuvant chemotherapy and disease progression. Previous radiation therapy may have been given provided that 4 weeks had elapsed prior to study entry. However, the measurable target lesions had to be completely outside the radiation field. Prior adjuvant chemotherapy with vinca derivatives or taxanes and 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

Intravenous vinorelbine 20 mg/m² and docetaxel 60 mg/m² were administered on day 1 and oral vinorelbine was administered at a dose of 60 mg/m² on day 15, every 3 weeks. Complete blood cell counts were performed on days 1 and 15 of each cycle to check that ANC was $\geq 1.5 \times 10^9$/l. Each patient received a maximum of 6 cycles unless disease progression or unacceptable toxicity.

Corticosteroid premedication was mandatory prior, during and after the day of the administration of docetaxel in order to prevent hypersensitivity reactions and to reduce or delay the occurrence of skin toxicity and fluid retention. Prophylactic anti-emetic regimen with 5-$HT_3$ antagonist was recommended before each administration of oral vinorelbine from the first cycle. Treatment could be delayed in case of haematological, neurological and hepatic toxicities occurred, but the duration of one cycle was not to exceed 5 weeks.

Administration of oral vinorelbine on day 15 had to be omitted because of grade $\geq 2$ neutropenia, elevation of bilirubin and/or transaminases, grade $\geq 2$ neurotoxicity. The dose of docetaxel was reduced in case of grade 3 stomatitis, elevation of bilirubin and/or transaminases.

### Treatment evaluation

Evaluation at study entry included vital signs, physical examination, chest X-ray completed by chest CT-scan if lung metastases, liver ultrasound completed by abdominal CT-scan if liver metastases, and bone scintigraphy. Abnormal images were monitored every 2 cycles and at the end of the treatment. 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. An independent radiologist validated all responses.

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 [16]. Cardiac monitoring during the study treatment and at the end of the treatment included ECG before each cycle, if clinically indicated. 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. A minimum of 20 evaluable patients and a maximum of 40 evaluable patients depending on the response rate observed in the first 20 subjects were required. 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 = 50%, Pa = 70%, $\alpha = 5\%$, $\beta = 20\%$, $k = 2$. This assumed that 50% 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 40 evaluable patients and the first test was performed after 20 evaluable patients. Among the first 20 evaluable patients, 13 patients achieved a confirmed partial response; therefore, the recruitment was pursued until enrolment of at least 40 evaluable patients.

## Results

### Patient's characteristics

Patient's characteristics are shown in Table 1. Forty-nine patients were enrolled between June 2002 and July 2004. Median age was 53 years; Karnosfsky performance status was $\geq 90\%$ in 61% of patients; 16 patients (33%) had a disease free interval $< 2$ years; 31 patients (63%) received prior chemotherapy in the neo-adjuvant/adjuvant setting of whom 17 received anthracyclines (35%) with or without CMF; 17 patients (35%) and 22 (45%) had 2 organs involved or more than 2, respectively. Thirty-eight patients (78%) had visceral involvement.

### Treatment delivery

A total of 261 cycles were given among the 49 patients treated. The median number of cycles for the whole population was 6 with a range between 1 and 6 cycles. Thirty-five patients (71% of the whole population) received 6 cycles. Disease progression and excessive toxicity were responsible for the study discontinuation of eight patients (16%) and one patient (2%), respectively. Other reasons included non-toxic death for two patients (4%), toxic death, intercurrent event and patient's refusal for one patient each.

The median relative dose intensities of intravenous vinorelbine and docetaxel were 99 and 99.6%, respectively. The median relative dose intensity of oral vinorelbine was 76%.

**Table 1** Patient and tumour characteristics

| Total number of patients (%) | Number of patients | (%) |
|---|---|---|
| | 49 | (100) |
| Age (years) | | |
| Median | 53.8 | |
| Range | 32.5–70.7 | |
| Disease-free interval (years) | | |
| Median | 2.7 | |
| ≥2 | 32 | (65.3) |
| <2 | 16 | (32.7) |
| Menopausal status | | |
| Pre | 24 | (49.0) |
| Post | 25 | (51.0) |
| Oestrogen receptors | | |
| Positive | 21 | (42.9) |
| Negative | 12 | (24.5) |
| Unknown | 16 | (32.7) |
| Prior therapy | | |
| Radiotherapy | 19 | (38.8) |
| Chemotherapy | 31 | (63.3) |
| Anthracycline | 17 | (34.7) |
| CMF | 17 | (34.7) |
| Hormonotherapy | 29 | (59.2) |
| Karnofsky performance status (%) | | |
| 90–100 | 30 | (61.2) |
| 80 | 14 | (28.6) |
| 70 | 5 | (10.2) |
| Visceral involvement | 38 | (77.6) |
| Number of organs involved | | |
| 1 | 10 | (20.4) |
| 2 | 17 | (34.7) |
| ≥3 | 22 | (44.9) |

Cycles were delayed for more than 3 days in 8 patients out of the 49 enrolled (16%) and for only 13 cycles (6%). The main reason for cycle delay was drug-related adverse events (neutropenia or hepatic enzyme elevation), for 6 cycles out of 13 (46%) and patient's convenience (31%). Day 15 oral vinorelbine administration was omitted in 29 patients (59%) and 33% of the cycles mainly because of neutropenia. Six patients experienced docetaxel dose reduction, corresponding to 6 cycles. The reasons were febrile neutropenia (one patient), grade 4 neutropenia (two patients), grade 3 mucositis (one patient), grade 2 elevation of ALT (one patient) and investigator decision (one patient).

## Efficacy

Among the 49 enrolled patients, 43 were evaluable for efficacy. The reasons for non-evaluability were premature discontinuation for one patient after one cycle because of drug-unrelated adverse event and five patients were not eligible (no distant metastasis for two patients, no bidimensionally measurable lesion in two patients and previous chemotherapy for metastatic disease and one bidimensionally measured lesion by physical examination only for one patient).

A total of 24 responses (1 complete and 23 partial) were reported, yielding a response rate of 49% (95% CI: 34–64) in the intent-to-treat analysis and 56% (95% CI = 40–71) in the 43 evaluable population. (Table 2). Out of the five not eligible patients, two were assessed as partial responder, two had stable disease and one progressed after two cycles. The median age of responders was the same as the median age of the study population, i.e. 53 years. Sixteen of them (67%) had received prior adjuvant chemotherapy and 15 prior adjuvant hormonotherapy.

Seventeen patients had a disease free interval of 2 years or longer. Of note, 19 responders had visceral involvement including 15 patients with liver metastases and most of them had at least 2 organs involved.

The median duration of response was 9.4 months. The median progression-free survival (Fig. 1) was 5.5 months (95% CI: 4–7) in the intent-to-treat population. At the cut-off date of September 2007, 31 patients were dead, 18 patients were alive and 1 patient was lost to follow-up. The median overall survival (Fig. 2) was 33.2 months (95% CI: 21–53) in the intent-to-treat population. Of note, the majority of patients (73.5%) received second-line chemotherapy.

## Safety

Toxicity profile is presented in Table 3. As expected, neutropenia was the main dose-limiting toxicity. Grade 3 and 4 neutropenia was seen in 6 (12%) and 25 (51%) patients, respectively. Febrile neutropenia defined as grade 4 neutropenia concomitant with fever > 38°C was observed in

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

| Overall response | Intent-to-treat population $N = 49$ | | Evaluable population $N = 43$ | |
|---|---|---|---|---|
| | Number | % | Number | % |
| Complete response (CR) | 1 | 2.0 | 1 | 2.3 |
| Partial response (PR) | 23 | 46.9 | 23 | 53.5 |
| Response rate (CR + PR) | 24 | 49.0 | 24 | 55.8 |
| No change | 16 | 32.7 | 14 | 32.6 |
| Disease control (CR + PR + NC) | 40 | 81.6 | 38 | 88.4 |
| Progressive disease (PD) | 6 | 12.2 | 5 | 11.6 |
| Non evaluable | 3 | 6.1 | – | – |

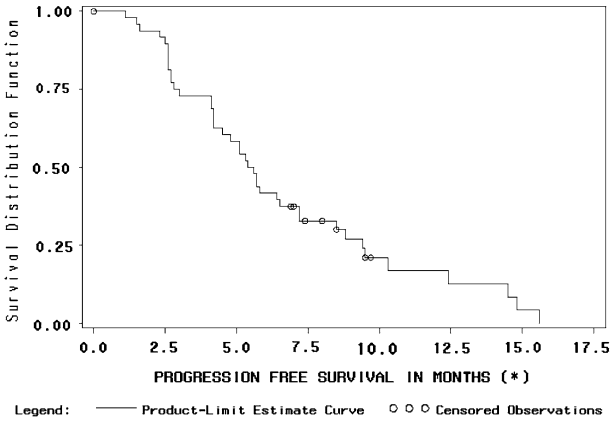


**Fig. 1** Progression-free survival time of the ITT population

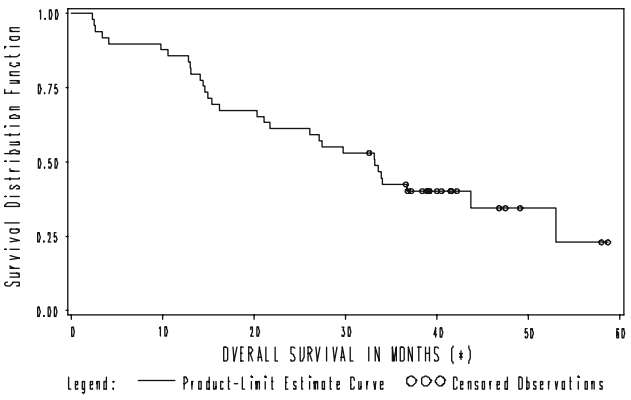


**Fig. 2** Overall survival in the ITT population

4 patients (8%) and 4 cycles (2%) and neutropenic infection defined as grade $\geq 3$ infection concomitant with grade $\geq 3$ neutropenia was seen in 1 patient (2%) due to abscess of teeth. In all instances, these complications resolved under antibiotic therapy.

Gastrointestinal toxicities were the most frequent non-haematological toxicities: nausea and vomiting were observed in 14 and 12% of patients, respectively, corresponding to 3 and 4% of cycles. Of note, 48 out of 49 patients received a prophylactic anti-emetic treatment as per protocol. Constipation and diarrhoea were experienced by 14% of patients each (corresponding to 3% of cycles each). Stomatitis was reported for 16% of patients, corresponding to 6% of cycles. Grade 3 stomatitis and vomiting were reported in 4% of patients each and constipation, diarrhoea and nausea in 2% of patients each. As expected with a docetaxel-containing regimen, alopecia was common and was reported for 61% of patients. Fatigue was frequent (22% of patients) but rarely severe (2% of patients). Regarding cardiac toxicity, no severe cardiac symptoms was reported. Neuro-sensory disorders were never reported.

Eight patients experienced a total of ten serious drug-related adverse events. Seven out of these ten related serious adverse events were of haematological origin, i.e. neutropenic complication in four instances and neutropenia in three instances. One patient died from hypovolemic shock due to dehydration at cycle 4, as a result of grade 3 diarrhoea and vomiting lasting 5 days without symptomatic 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. Docetaxel and vinorelbine are highly active drugs in the treatment of MBC, both as single agents or in combination regimens. Vinorelbine is well tolerated, with a low incidence of severe toxicities. Because of its favourable safety profile and activity, vinorelbine is a valuable option for the treatment of MBC patients in the palliative setting.

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. In combination regimens, which include another i.v. cytotoxic, the utility and feasibility of alternating oral and i.v. vinorelbine were reported by Addeo et al. [25]. Vinorelbine plus pegylated doxorubicin was administered intravenously on day 1 and oral vinorelbine on day 15 every 4 weeks in 34 elderly women in the MBC. The regimen achieved a 50% response rate and was well tolerated.

The combination of i.v. vinorelbine with docetaxel has been assessed as first-line therapy in patients with MBC [17–22]. Response rates ranging from 40 to 64% have been reported in phase II trials using different doses and schedules. In a phase I study, testing a 3-week schedule with i.v. vinorelbine on days 1 and 5 and docetaxel on day 1, Campone et al. [23] reported a response rate of 71% in the thirty-four MBC women treated with the combination as first-line chemotherapy. The highest activity was observed at the dose level of docetaxel 85 mg/m² and vinorelbine 20 mg/m², with one complete response and seven partial responses in ten evaluable patients. Moreover, it has been shown that the pharmacokinetic profiles of docetaxel and vinorelbine were not modified when both drugs were combined and the estimated docetaxel clearance remained stable over the dose range of vinorelbine 20–22.5 mg/m² followed by docetaxel 60–100 mg/m² [23].

**Table 3** Toxicity by patient (incidence ≥ 5%) and by cycle NCI/CTC

| Adverse events by NCI/CTC | By patient | | | By cycle | | |
|---|---|---|---|---|---|---|
| | Overall incidence | Grade 3 | Grade 4 | Overall incidence | Grade 3 | Grade 4 |
| | *N* (%) | *N* (%) | *N* (%) | *N* (%) | *N* (%) | *N* (%) |
| Haematological | | | | | | |
| Leucopenia | 39 (79.6) | 11 (22.4) | 7 (14.3) | 138 (53.5) | 27 (10.5) | 8 (3.1) |
| Neutropenia | 40 (81.6) | 6 (12.2) | 25 (51.0) | 141 (54.7) | 32 (12.4) | 57 (22.1) |
| Febrile neutropenia[a] | 4 (8.2) | – | – | 4 (1.5) | – | – |
| Anaemia | 43 (87.8) | – | 1 (2.0) | 192 (74.4) | – | 1 (0.4) |
| Thrombocytopenia | 7 (14.3) | – | – | 13 (5.0) | – | – |
| Dermatologic | | | | | | |
| Alopecia | 30 (61.2) | – | – | 139 (53.3) | – | – |
| Nail changes | 3 (6.1) | – | – | 12 (4.6) | – | – |
| Flu-like symptoms | | | | | | |
| Fatigue | 11 (22.4) | 1 (2.0) | – | 28 (10.7) | 2 (0.8) | – |
| Fever without neutropenia | 6 (12.2) | – | – | 8 (3.1) | – | – |
| Gastrointestinal | | | | | | |
| Constipation | 7 (14.3) | 1 (2.0) | – | 9 (3.4) | 1 (0.4) | – |
| Diarrhoea | 7 (14.3) | 1 (2.0) | – | 8 (3.1) | 1 (0.4) | – |
| Nausea | 7 (14.3) | 1 (2.0) | – | 8 (3.1) | 1 (0.4) | – |
| Stomatitis | 8 (16.3) | 2 (4.1) | – | 16 (6.1) | 2 (0.8) | – |
| Vomiting | 6 (12.2) | 2 (4.1) | – | 10 (3.8) | 2 (0.8) | – |
| Sexual function | | | | | | |
| Irregular menses | 3 (6.1) | 2 (4.1) | – | 11 (4.2) | 7 (2.7) | – |

258 cycles were evaluable for haematological toxicity, 261 cycles were evaluable for non-haematological toxicity

[a] Pizzo's definition

The present study included a majority of patients (77.6%) with rapidly growing visceral metastases for which polychemotherapy was indicated. Among the 49 patients treated, one patient achieved a complete response and 23 patients achieved a partial response yielding a response rate of 49% (95% CI: 34–64) in the intent-to-treat population and 55.8% (95% CI: 40–71) in the evaluable population. These results are consistent with the published data on vinorelbine given only by i.v. route [17–22].

Docetaxel and vinorelbine are both myelosuppressive agents; however, haematological toxicity of both drugs is short-lasting and allows their administration in a more frequent schedule than once every 3 weeks. No standard doses or schedules for this combination were established. The majority of the studies in MBC have used various doses for vinorelbine and docetaxel as well as different schedules. Vinorelbine was given either on days 1 and 5, or days 1 and 8 or on a weekly schedule in combination with docetaxel on day 1 every 3 weeks. The selected doses for vinorelbine and docetaxel in this phase II trial were established on the basis of the findings of the phase I part of the study which investigated two schedules: i.v. vinorelbine and docetaxel on day 1 and oral vinorelbine given either on day 8 or on day 15, every 3 weeks [1, 24]. The doses of i.v. vinorelbine ranged from 20 to 25 mg/m². Oral vinorelbine was given at a fixed dose of 60 mg/m² and docetaxel doses ranged from 60 to 70 mg/m². Neutropenia was the dose-limiting toxicity, which led to the cancellation of day 8 administration of oral vinorelbine. Indeed, neutrophils nadir is generally observed around day 7 [26] which made the day 1-day 8 regimen of i.v./oral vinorelbine unfeasible. Therefore, the recommended schedule was established at 20 mg/m² of i.v. vinorelbine combined with 60 mg/m² of docetaxel on day 1 and oral vinorelbine at 60 mg/m² on day 15 every 3 weeks.

As previously reported, with the all i.v. combination regimens of vinorelbine and docetaxel, the main grade 3–4 toxicity encountered in this phase II study was neutropenia observed in 63% of patients and related events such as febrile neutropenia (8% of patients) and neutropenic infection (2% of patients).

The most frequent gastrointestinal side effects included nausea (14% of patients and 3% of cycles), vomiting (12% of patients and 4% of cycles), diarrhoea and constipation, which were observed in 14% of patients each, and 3% of cycles each. Stomatitis was reported for 16% of patients,

and 6% of cycles. Interestingly, grade 3 events were rare and reported in less than 1% of cycles.

## Conclusions

In conclusion, this study showed that the combination of docetaxel with alternating intravenous/oral vinorelbine given every 3 weeks, is active and well tolerated in the first-line treatment of MBC. Such treatment is convenient and acceptable to patients, who can take oral vinorelbine in an out-patient basis avoiding hospitalisation on day 15 of each cycle.

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