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ORIGINAL ARTICLE

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

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Abstract
Purpose Effective treatment options for patients with metastatic breast cancer (MBC) resistant/refractory to anthracyclines and/or taxanes are limited. Intravenous and oral combination of vinorelbine (VRL) and capecitabine were shown to be feasible and effective in first-line MBC. In order to evaluate the activity of the combination of an all oral regimen in a more advanced setting, we investigated a regimen combining oral VRL and capecitabine in a phase II study as second-line chemotherapy of MBC patients previously treated with anthracyclines and taxanes.
Patients and methods Forty patients (median age 52 years) with MBC received the combination of oral VRL 60 mg/m² on days 1, 8 and 15 plus capecitabine 1,000 mg/m² bid given from day 1 to day 14 in an open-label, international, multicentre, phase II study. Cycles were repeated every 3 weeks. The primary endpoint was response rate (RR) evaluated by an independent panel review. Secondary objectives included safety, duration of response, progression-free survival, overall survival and quality of life.
Results All the patients had received prior chemotherapy with anthracyclines and taxanes, 75% were refractory/resistant to anthracycline and/or taxane, 72.5% presented with visceral involvement and the last prior chemotherapy for 87.5% of the patients was for advanced disease setting. The median number of administered cycles per patient was 4 (range 1–31). Eight responses were documented and validated by an independent panel review, yielding RRs of 20% [95% CI: 9–35.6] in the intent-to-treat (treated) population and 23.5% [95% CI: 10.7–41.2] in the 34 evaluable patients. Median progression-free survival and median overall survival were 3.4 months [95% CI: 2.3–5.5] and 11.3 months [95% CI: 8.1–16.4], respectively. The principal toxicities were anaemia, neutropenia (rarely complicated; only one patient experienced febrile neutropenia), fatigue and gastrointestinal toxicities with very few grade 3–4 non-haematological toxicities.
Conclusions In second-line treatment of MBC patients previously treated with anthracyclines and taxanes, oral VRL plus capecitabine is a safe regimen with an efficacy comparable to the other available combination regimens used in this heavily and resistant/refractory (75% of patients) pre-treated patients' population. Moreover, this

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well-tolerated combination offers the advantages of an all oral regimen.

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

Introduction

Despite the progress in the treatment of breast cancer, the most common malignancy in women, patients with metastatic disease have a poor prognosis, accounting for more than 400,000 deaths annually worldwide [1, 2]. Even though anthracyclines and taxanes are the most active agents in breast cancer, with their increasing use for early breast cancer, treatment failure occurs in substantial number of patients. Moreover, due to resistance to antineoplasic agents either after metastatic or adjuvant treatment, resistance to anthracyclines and taxanes is becoming a limiting factor in breast cancer therapy [3, 4]. Therefore, fewer effective treatment options are available for patients with metastatic disease, and in particular in second-line setting [3, 5].

The development of new efficient combination regimens 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 (VRL) targets the tubulin-microtubule system inhibiting the tubulin polymerisation [6]. Oral VRL as a single agent for the first-line treatment of MBC patients, was shown to be an effective and well-tolerated agent [7, 8]. In these phase II studies, consistent response rates of 30% were reported [7, 8]. Median durations of progression-free survival and median survival fall in the same range: 4.2 and 24 months in one trial and 4.6 and 21 months in the other one [8]**.** 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. Nausea and vomiting were generally of mild to moderate intensity and a primary prophylaxis with oral 5-HT3 antagonist was shown to be effective [9].

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 [10]. Oral VRL (Navelbine® Oral) 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 [11].

Capecitabine (Xeloda®) is an oral fluoropyrimidine precursor preferentially taken up by tumour cells and converted to 5-fluorouracil (5-FU) [12]. Capecitabine has demonstrated activity as a single agent in MBC pre-treated patients with anthracyclines and taxanes, with response rate (RR) ranging from 15 to 36%, time to progression and overall survival of approximately 3 and 12 months, respectively. In this patient population, most treatment-related adverse events were mild to moderate in intensity; the only grade 3/4 occurring in more than 5% of the patients were hand-foot syndrome, diarrhoea, and neutropenia [13, 14].

Preclinical data have suggested that the antitumour activity of the combination of VRL and capecitabine is synergistic, while the combination of VRL with 5-FU shows only an additive antitumor activity [15]. Several phase I–II studies have investigated this combination of intravenous VRL with capecitabine in heavily pretreated patients with MBC with a RR ranging from 33 to 55% [16–21].

Ghosn et al. [22] 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 25 mg/m^2 and capecitabine 1,650 mg/m^2/day).

Nolè et al. [23] 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 days 1 and 8 or on a weekly basis with capecitabine at doses ranging from 1,650 to 2,500 mg/m^2/day) from day 1 to day 14, every 3 or 4 weeks. Responses were observed in 18 patients [3 complete response (CR) and 15 partial response (PR)] 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.

At the recommended regimen of oral VRL 60 mg/m^2 on days 1, 8 and 15 with capecitabine 2,000 mg/m^2/day) from day 1 to day 14, every 3 weeks in 2 phase II studies, this all oral combination was confirmed to be an effective and well-tolerated treatment, as first-line [24] and first- or second-line [25] chemotherapy of MBC, improving treatment acceptability, home based-therapy quality of life and increasing infusion-free survival: in first-line, 23 responses (2 complete and 21 partial) among the 52 treated patients were reported, yielding a RR of 44.2% [95% CI: 30–59] in the intent-to-treat analysis and 54.8% [95% CI: 39–70] in the evaluable population [24]. Among 115 treated patients, who had received prior anthracycline-based chemotherapy, an objective response was achieved in 65 patients (56.5%) in the intent-to treat population: CR was achieved in 22 patients (19.1%); PR in 43 patients (37.4%); stable disease in 36 patients (31.3%). The PFS was 10.5 months and the median survival was 17.5 months [25].

In order to evaluate the activity of this combination in more advanced MBC patients, the present phase II study

was set up in the second-line treatment of patients who have failed anthracyclines and taxanes.

Patients and methods

Patient selection

Inclusion criteria

Eligible patients fulfilled all the following criteria: female patients with MBC; aged ≥18 and ≤75 years; Karnofsky performance status ≥70%; adequate haematological, 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 ≥10 g/dl, total bilirubin ≤1.5 × upper limit of normal (ULN), ASAT, and ALAT ≤2.5 × ULN, calculated creatinine clearance ≥50 mL/min], at least one bidimensionally measurable target lesion. Patients were required to have been previously treated with anthracyclines and taxanes. They were then classified according to their anthracyclines and taxanes response as follows: Refractory, when progression occurred during adjuvant chemotherapy or when progression was the best response during palliative treatment; resistant, when progression occurred in responding or initially stable disease either within 3 months of completing chemotherapy for MBC or within 6 months of completing adjuvant chemotherapy; failure, when stable disease while on palliative chemotherapy for a minimum of four cycles; or response to chemotherapy followed by progression more than 3 months of completing palliative chemotherapy, or relapse more than 6 months after adjuvant chemotherapy. Prior hormonal therapy was allowed in adjuvant treatment and/or in metastatic setting provided that they had progressive disease at study entry and had discontinued hormonal therapy before study entry. Previous radiation therapy may have been given provided that 4 weeks had elapsed prior to study entry. Of note, patients' hormonal receptor status was collected but HER 2 status was not requested at the time this phase II study started in 2004, with the combination given as second-line chemotherapy setting.

Exclusion criteria

Patients had to be excluded from this study, if they presented concurrent treatment with any other anti-cancer therapy; poor prognosis disease such T4d disease; brain or leptomeningeal metastases; previous treatment with vinca-alkaloid; prior history of high-dose chemotherapy followed by bone marrow or peripheral stem cell support; prior severe and unexpected reaction to fluoropyrimidine therapy or known hypersensitivity to 5-FU; uncontrolled medical disorder; pre-existing peripheral neuropathy ≥2 using NCI criteria and symptomatic lung lymphangitis; malabsorption syndrome or disease significantly affecting gastro-intestinal function or major resection of the stomach, proximal small bowel or grade ≥2 dysphagia.

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 VRL was administered at a dose of 60 mg/m² on days 1, 8 and 15 and capecitabine at a dose of 2,000 mg/m² 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 VRL from the first cycle. For capecitabine, symptomatic treatment was to be initiated once nausea or vomiting had occurred, and prophylactic antiemetic treatment should be given for subsequent cycles. In case of haematological, neurological and hepatic toxicities, treatment could be delayed up to 2 weeks, then the duration of one cycle could not exceed 5 weeks. Patients who required a delay by more than 2 weeks were withdrawn from the study.

Administration of oral VRL on day 8 and/or day 15 was to be omitted if grade ≥2 neutropenia or thrombocytopenia occurred but capecitabine was continued. Capecitabine was to be interrupted if treatment-related elevation in bilirubin and/or transaminases occurred. Oral VRL and capecitabine were interrupted when grade 2 diarrhoea occurred until resolution to grade 0–1. If diarrhoea was grade ≥3, VRL 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 cardiotoxicity, capecitabine was to be discontinued. In case of grade ≥2 neurotoxicity, the cycle was to be delayed until resolution to grade 0–1 and treatment was restarted at the same dose. If grade ≥2 neurological toxicity occurred during a cycle, the study treatment was to be discontinued. If grade ≥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, ECG, blood tests, mammary ultrasound with

or without mammography, chest X-ray, abdominal ultrasound, and bone scintigraphy. If an abnormality was detected (i.e. metastases on chest X-ray or on liver ultrasound), then CT scan (or other appropriate imaging technique) would be done. The same methods of tumor assessment performed at baseline should be used every two 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. Adapted SWOG criteria were used to define response [26]. An independent radiologist validated all patients with CR, PR and stable disease. 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 [27]. Patient who received at least one cycle of study treatment was considered evaluable for safety analysis unless she was lost to follow-up immediately after the start of treatment.

Statistical analysis

This study was an open-label, international, multicentre, phase II trial. Response rate was the primary efficacy variable. 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 = 20%, Pa = 40%, $\alpha = 5\%$, $\beta = 15\%$, $k = 2$. Under these conditions, the total sample size was 40 evaluable patients.

All treated patients were included in the efficacy analysis (intent-to-treat analysis). Response rate was also presented on the evaluable population. Patients evaluable for efficacy were defined as those eligible patients who remained in the study until completion of the first evaluation, after first two cycles (except early progression or early death for progression) and whose baseline lesions were consistently assessed throughout the study period with the same method.

Secondary objectives included safety evaluation, determination of the duration of response, progression-free survival and overall survival. Time dependent parameters were estimated by Kaplan Meier method.

Results

Patients' characteristics

Patients' characteristics are shown in Table 1. Forty-two patients were enrolled between October 2004 and December 2006, and forty patients were treated. Median age was 52 years; Karnofsky performance status was ≥90% in 80% of patients; 38 patients (95%) had a disease-free interval <2 years. Twenty-nine patients (72.5%) had visceral involvement and 38 patients (95%) had at least two organs involved. All patients had prior chemotherapy with anthracycline and taxane, as requested by protocol. For 87.5% of the patients, the last prior chemotherapy was for advanced disease setting. Patients were classified according to their previous anthracyclines and taxanes response: overall, 30 patients (75%) were refractory/resistant to anthracycline and/or taxane: 3 patients (7.5%) were refractory and 12 patients (30%) were resistant to both anthracyclines and taxanes, 5 patients (12.5%) were refractory and 10 patients (25%) were resistant to taxanes. Considering the definitions detailed in section "Patients and methods", there were 8 (20%) refractory patients, 22 (55%) resistant patients and 10 (25%) patients who failed, as shown in Table 1.

Treatment delivery

A total of 254 cycles were given among the 40 treated patients. The median number of cycles for the whole population was four with a range between 1 and 31 cycles. Nineteen patients (47.5% of the treated population) received at least six cycles. Disease progression and drug-related adverse events were responsible for the study discontinuation of 29 patients (69%) and 6 patients (11.9%), respectively, in the 42 enrolled patients. Adverse events which required drug discontinuation included grade 3–4 peripheral neuropathy, 3rd appearance of grade ≥2 hand-foot syndrome and fatigue.

The median-relative dose intensities of oral VRL and capecitabine were 88% [47–112] and 90% [47–108], respectively. During the study, 183 cycles (85.5%) were not delayed. Cycle delay of more than 3 days occurred in 21 (52.5%) patients for only 31 cycles (14.5%): the main reasons for these 31-cycle delays were haematological toxicity for 11 cycles (35.5%), patient's convenience for 10 cycles (32.3%) and non-haematology toxicities for 7 cycles (22.6%). According to protocol, VRL dose reduction was not allowed and no protocol deviation occurred with this issue. A total of 58 VRL administrations (Days 8 and 15) among the 254 planned (22.8%) were cancelled (representing 6.7% for Day 8 and 16.1% for Day 15 VRL administration). Thirty-three (57%) of these 58 administrations cancellations were due to haematological toxicity, i.e.

Table 1 Patient tumour and characteristics

	Number of patients (%)
Total number of patients (%)	40 (100)
Age (years)	
Median	52.1
Range	31.4–78.8
Disease-free interval (years)	
Median [range]	0.2 [0–7.0]
≥2	2 (5)
<2	38 (95)
Menopausal status	
Pre	22 (55)
Post	18 (45)
Estrogen receptors	
Positive	24 (60)
Negative	15 (37.5)
Unknown	1 (2.5)
Progesterone receptors	
Positive	14 (35)
Negative	19 (47.5)
Unknown	7 (17.5)
Prior therapy	
Surgery	37 (92.5)
Radiotherapy	33 (82.5)
Chemotherapy	40 (100)
(Setting[a])	
Neo-adjuvant	4 (10)
Adjuvant	1 (2.5)
Advanced disease	35 (87.5)
Hormonotherapy	28 (70)
Other therapy	5 (12.5)
Karnofsky performance status (%)	
100	20 (50)
90	12 (30)
80	7 (17.5)
70	1 (2.5)
Visceral involvement	29 (72.5)
Number of organs involved	
1	2 (5)
2	16 (40)
≥3	22 (55)
Classification	
Anthracycline	
Refractory	0 (0)
Resistant	0 (0)
Taxane	
Refractory	5 (12.5)
Resistant	10 (25)
Both (Anthracycline & Taxane)	
Refractory	3 (7.5)
Resistant	12 (30)
Failure	10 (25)

[a] Intent of last prior chemotherapy

neutropenia. According to protocol procedures, 15 patients (37.5%) had at least one dose reduction of capecitabine ≥25% and 11 patients (27.5%) had at least one capecitabine administration cancellation. The reasons for capecitabine cancellation were grade ≥3 neutropenia (three patients), gastro-intestinal toxicity (three patients), grade 3 sensory neuropathy, hand-foot syndrome, non-study drug-related adverse event, investigator's mistake, administrative reason and patient's convenience (one patient, each).

Efficacy

Among the 42 registered patients, 40 were treated and 34 were evaluable for efficacy according to independent panel review. A total of eight patients were not evaluable for response: two patients were not treated (one patient due to creatinine clearance outside of eligibility criteria and the other patient, by investigator's decision); three patients received only one cycle of treatment (two patients due to not related adverse event and one for related peripheral sensory neuropathy) and three patients were not eligible due to the absence of bi-dimensionally measurable lesion).

The RR validated by an independent panel was 20% [95% CI: 9–35.6] in the intent-to-treat population and 23.5% [95% CI: 10.7–41.2] in the evaluable patients with a disease control of 62.5% [95% CI: 45.8–77.2] and 73.5% [95% CI: 55.6–87.2], respectively (Table 2). The median age of responders was 49.5 years with a range from 37 to 75 years. All had visceral involvement, except one with skin involvement and all were treated for advanced disease.

Patients classified failure to anthracycline-taxane treatment, have a RR of 40%, with a disease control of 60%. However, two responses were seen in the eight patients refractory to anthracycline and/or taxane and two responses were seen in the 22 patients resistant to anthracycline and/or taxane (Table 2).

The median progression-free survival (Fig. 1) was 3.4 months [95% CI: 2.2–5.5] in the intent-to-treat population. The median overall survival (Fig. 2) was 11.3 months [95% CI: 8.1–16.4] in the intent-to-treat population. The median duration of response for the 11 responding patients was 6.7 months [95% CI: 5.6–12.4] according to investigator in the intent-to-treat population.

Safety

Toxicity profile is presented in Table 3. As expected, neutropenia was the most common side-effect (anaemia was reported in 82.5% of the patients but 27.5% of the patients had anaemia at baseline). Eight patients (20%) experienced grade 3 neutropenia and eight patients (20%) experienced grade 4 neutropenia. Febrile neutropenia defined as three elevations of oral temperature >38°C during a 24-h period

Table 2 Adapted SWOG overall response rate (after panel review)

Overall response	Refractory		Resistant		Failure	ITT population	Evaluable population
	Taxane	Both	Taxane	Both			
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Complete response (CR)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Partial response (PR)	1 (20)	1 (33.3)	1 (10)	1 (8.3)	4 (40)	8 (20)	8 (23.5)
Response rate (CR + PR)	**1 (20)**	**1 (33.3)**	**1 (10)**	**1 (8.3)**	**4 (40)**	**8 (20)**	**8 (23.5)**
No change	3 (60)	2 (66.7)	5 (50)	5 (41.7)	2 (20)	17 (42.5)	17 (50)
Disease control (CR + PR + NC)	**4 (80)**	**3 (33.3)**	**6 (60)**	**6 (50)**	**6 (60)**	**25 (62.5)**	**25 (73.5)**
Progressive disease	1 (20)	0 (0)	3 (30)	4 (33.3)	1 (10)	9 (22.5)	9 (26.5)
Non evaluable	0 (0)	0 (0)	1 (10)	2 (16.7)	3 (30)	6 (15)	–
Total	5 (100)	3 (100)	10 (100)	12 (100)	10 (100)	40 (100)	34 (100)

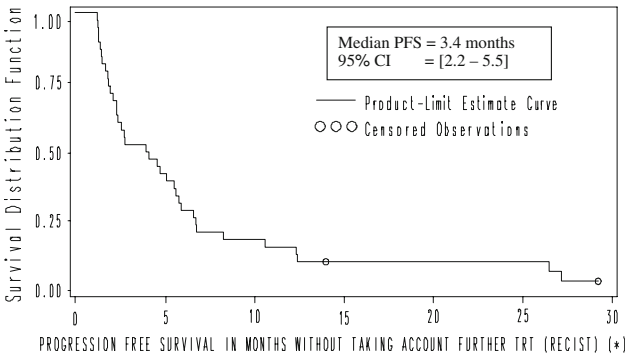

Fig. 1 Progression-free survival in the ITT population

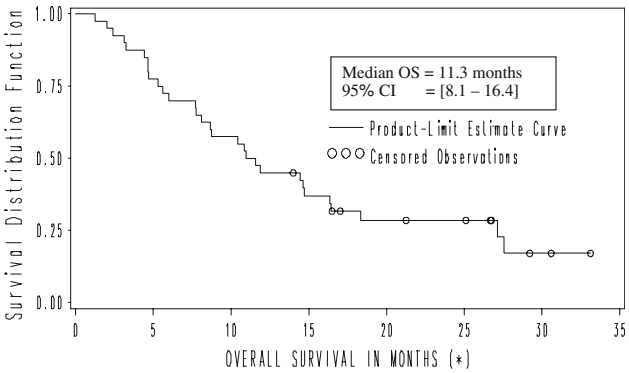

Fig. 2 Overall survival in the ITT population

or a single elevation to >38°C concomitant with grade 4 neutropenia requiring i.v. antibiotics or hospitalisation [27], was observed in a single patient (2.5%) during cycle 1 and resolved under antibiotic therapy. Neutropenic infection defined as grade ≥3 infection concomitant with grade ≥3 neutropenia was not observed.

The most frequent non-haematological toxicities were gastrointestinal disorders (including nausea, diarrhoea, vomiting, stomatitis and abdominal pain) and fatigue. However, the incidence of grade 3 was low and there was only two episodes of grade 4. Grade 3 diarrhoea was reported in four patients (10%) and, grade 3 abdominal pain and stomatitis in one patient (2.5%) each. Grade 3 fatigue was reported in two patients (5%). Grade 4 was observed only with fatigue and hypokalaemia in one patient (2.5%) each. As expected with a capecitabine-containing regimen, palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome) was observed in 15 patients (37.5%) but only one grade 3 was reported in one patient (2.5%). Regarding the other grade 3 toxicities, they occurred with lower respiratory tract infection, ALAT increase and peripheral sensory neuropathy in one patient (2.5%) each.

Three patients were hospitalised for related adverse events, corresponding to 27.3% of hospitalizations reported in the study. Three serious adverse events were of non-haematological origin, i.e. grade 3 diarrhoea, grade 4 hypokalaemia, grade 3 lower respiratory tract infection and one was grade 3 febrile neutropenia. For one patient (febrile neutropenia), during the hospitalisation, a grade 4 dihydropyrimidine dehydrogenase deficit was diagnosed; and after febrile neutropenia resolution within 9 days, study treatment was permanently discontinued. For another patient who experienced diarrhoea and hypokalaemia, study treatment was continued but the dose of capecitabine was reduced by 75%. The other patient (lower respiratory tract infection) was already withdrawn of the study for progressive disease.

Quality of life

Quality of life was analysed according to EORTC study group recommendations by using QLQ-C30 and QLQ-BR23 questionnaires: among the 40 treated patients, only 29 (72.5%) filled in a questionnaire at baseline, 25 (62.5%) were evaluable at the first evaluation (6 weeks after start of treatment) and 11 (27.5%) were evaluable at the third evaluation (18 weeks after start of treatment). Questionnaire

Table 3 Drug-related toxicity by patient and by cycle (MedDRA SOC, PT & NCI/CTC grading) (Overall incidence > 5% or ≤5% with Grade 3–4 toxicity)

Adverse events by MedDRA SOC, PT and Worst grade 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	31 (77.5)	10 (25.0)	1(2.5)	121 (47.6)	18 (7.1)	1 (0.4)
Neutropenia	29 (72.5)	8 (20.0)	8 (20.0)	109 (42.9)	20 (7.9)	9 (3.5)
Febrile neutropenia[a]	1 (2.5)	1 (2.5)	–	1 (0.4)	1 (0.4)	–
Anaemia	33 (82.5)	1 (2.5)	–	153 (60.2)	1 (0.4)	–
Thrombocytopenia	9 (22.5)	1 (2.5)	–	21 (8.3)	1 (0.4)	–
Non-haematological						
Gastrointestinal disorders						
Abdominal pain	10 (25.0)	1 (2.5)	–	18 (7.1)	1 (0.4)	–
Constipation	5 (12.5)	–	–	8 (3.2)	–	–
Diarrhoea	18 (45.0)	4 (10.0)	–	35 (13.8)	4 (1.6)	–
Nausea	21 (52.5)	–	–	42 (16.6)	–	–
Stomatitis	10 (25.0)	1 (2.5)	–	16 (6.3)	1 (0.4)	–
Vomiting	15 (37.5)	–	–	19 (7.5)	–	–
General disorders and administration site conditions						
Fatigue	21 (52.5)	2(5.0)	1 (2.5)	64 (25.3)	2(0.8)	1(0.4)
Investigations						
ALAT increased[a]	22 (55.0)	1 (2.5)	–	–	–	–
ASAT increased[a]	20 (50.0)	–	–	–	–	–
Weight decreased	4 (10.0)	–	–	17 (6.7)	–	–
Hypokalaemia	1 (2.5)	–	1 (2.5)	1 (0.4)	–	1 (0.4)
Nervous system disorders						
Headache	4 (10.0)	–	–	8 (3.2)	–	–
Paraesthesia	3 (7.5)	–	–	24 (9.5)	–	–
Peripheral sensory neuropathy	8 (20.0)	1 (2.5)	–	24 (9.5)	1 (0.4)	–
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysaesthesia syndrome	15 (37.5)	1 (2.5)	–	54 (21.3)	1 (0.4)	–

[a] ALT/AST increased not tabulated by cycle

was evaluable, if one was filled at baseline and at least another one after beginning of study treatment, with at least 2/3 of the questions answered.

Patients' global health status improved in comparison to baseline. The functional and symptoms score remained stable during treatment period. Patients felt less worried about their health in the future and they tended to have a better physical and emotional functioning.

Discussion

Regimens combining anthracyclines and taxanes are becoming more standard adjuvant treatment for early breast cancer. Therefore, a need for new options in the treatment of MBC is warranted, especially for patients previously treated with anthracyclines and/or taxanes and who become refractory or resistant to anthracyclines and/or taxanes.

Based on the encouraging activity reported with oral VRL plus capecitabine in first-line setting [24], and first- or second-line setting in patients previously treated with anthracycline [25] and the advantages of an all oral combination, the present study was set up in order to investigate oral VRL plus capecitabine in MBC patients previously treated with anthracyclines and taxanes. Furthermore, the Cochrane breast cancer group has found an advantage in women with MBC for combination regimens compared to single agents but associated with more toxicity [28, 29].

The majority of patients (72.5%) had visceral involvement with 95% having at least two organs involved.

Furthermore, 75% of the patients were refractory/resistant to anthracycline and/or taxane and for 87.5% of them, the last prior chemotherapy was given in the advanced disease setting. Among the 40 patients treated, 8 patients achieved a PR yielding a RR of 20% [95% CI: 9–35.6] in the intent-to-treat population and 23.5% [95% CI: 10.7–41.2] in the evaluable population. Median progression-free survival was 3.4 months [95% CI: 2.3–5.5] and, at the cut-off date, the median overall survival was 11.3 months [95% CI: 8.1–16.4] in the intent-to-treat population. The median duration of response was 6.7 months [95% CI: 5.6–12.4].

Comparable results were observed with objective RR (30 and 35%), median PFS (3.8 and 5.8 months) and median duration of response (6.9 and 6.4 months) in phase II and III studies with combination of ixabepilone plus capecitabine in anthracycline-pretreated/resistant and taxane-resistant MBC and in MBC patients progressing after anthracycline and taxane treatment, respectively [30, 31]. Dean-Colomb et al. [32] provided an overview of established agents and emerging ones, used either as single agent or combination ones in the treatment of anthracycline and/or taxane refractory/resistant MBC: regarding the combinations of two agents (mainly i.v. ones), overall RR ranges from 9 to 58% and median PFS ranges from 3.4 to 5.3 months, reflecting the heterogeneity of the study populations. The study results are in the range of those reported for other chemotherapy combinations: oxaliplatin plus VRL, with RR of 27% and median PFS of 3.4 months [33] and gemcitabine plus cisplatin, RR of 9% and median PFS of 4 months [34]. 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 [35].

In the current study, the most frequent related adverse events were haematological events with grade 3 and 4 neutropenia, reported in eight patients (20%), each. However, neutropenia was 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, fatigue, hand-foot syndrome and peripheral sensory neuropathy. These common side effects related to VRL and/or capecitabine were rarely severe. Grade 4 was observed with hypokalaemia and fatigue, only in one patient for each. The most severe intensity was generally grade 3 occurring in less than 2% of cycles for gastro-intestinal side effects and for fatigue. Grade 3 hand-foot syndrome occurred in only one patient in one cycle.

In a recent phase II study involving oxaliplatin/VRL combination, 79% of the patients developing grade 3–4 neutropenia and severe constipations requiring hospitalisation were observed [33]. The more frequent toxicities reported in another recent phase III study, comparing the combination of ixabepilone plus capecitabine versus capecitabine, were grade 3–4 sensory neuropathy (21 vs. 0%), fatigue (9 vs. 3%) and neutropenia (68 vs. 11%) but with a rate of death as result of toxicity [3 vs. 1%, with patients with liver dysfunction (≥grade 2 liver function tests) at greater risk] [31].

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 in two phase I and II studies. Of note, studies recently published (or under press) tested a Day 1 to Day 8 regimen of oral VRL given every 3 weeks [16, 25, 36]. Efficacy and safety results could not be compared because of the different patient populations enrolled.

In conclusion, the results of the current study confirm that, in second-line treatment, the combination of oral VRL and capecitabine is a safe regimen with an efficacy comparable to the other available combination regimens used in this heavily and resistant/refractory anthracycline and/or taxane (75% of patients) pre-treated MBC patient population. Moreover, this well-tolerated combination offers the advantages of an all oral regimen.

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