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ORIGINAL ARTICLE

A Three-Arm Randomized Phase II Study of Oral Vinorelbine Plus Capecitabine Versus Oral Vinorelbine and Capecitabine in Sequence Versus Docetaxel Plus Capecitabine in Patients with Metastatic Breast Cancer Previously Treated with Anthracyclines

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■ **Abstract:** Owing to the increased number of patients treated with anthracycline-based adjuvant chemotherapy, there is a need for new effective and tolerable nonanthracycline regimens in metastatic breast cancer. Patients with HER2-negative metastatic breast cancer previously treated with anthracyclines in (neo)adjuvant setting were randomized to fully oral 3 weekly cycles of the combination of oral vinorelbine with capecitabine (V + C), to the same drugs alternating every three cycles (V↔C), or to the combination of docetaxel and capecitabine (D + C). V was given at 80 mg/m^2 (after the first cycle at 60 mg/m^2) on days 1 and 8 in the V + C arm and weekly in the V↔C arm, C at 1,000 mg/m^2 bid from days 1 to 14, and D on day 1 at 75 mg/m^2. The primary end point was disease control rate (CR + PR + NC $\geq$ 3 months). A total of 139 patients were randomly assigned to V + C (44 patients), V↔C (47 patients), and D + C (48 patients). After an independent review, the disease control rate in the intent-to-treat population in the V + C, V↔C, and D + C arms [95% CI] was 70.5% [54.8–83.2], 37.0% [23.2–52.5], and 70.8% [55.9–83.1], and the median overall survival 22.2, 19.4, and 24.2 months, respectively. When taken into account the disease control rate, the alternating V↔C regimen seems to be less effective compared with V + C or D + C combinations. Combinations of V + C or D + C showed similar efficacy and a different toxicity profile; V + C induced less neutropenia, infection, hand-foot syndrome, fatigue/asthenia, and alopecia, whereas D + C – less gastrointestinal toxicity. V + C combination constitutes a valuable fully oral alternative option to D + C in patients with metastatic breast cancer previously treated with anthracyclines in (neo)adjuvant setting, while offering the advantages of an all-oral treatment. ■

Key Words: capecitabine, combination, docetaxel, metastatic breast cancer, oral vinorelbine, sequential

The widespread use of anthracyclines in the adjuvant setting and concerns regarding their cumulative cardiotoxicity limit the administration of these compounds in metastatic breast cancer (1,2). During the past decade, other cytotoxic agents, including the taxanes (paclitaxel and docetaxel), vinorelbine, capecitabine, and gemcitabine have been implemented in advanced breast cancer (2–6). The question of whether these drugs should be used in sequence or in various combinations is still a matter of debate.

A combination of docetaxel and capecitabine was the first doublet showing a survival advantage over capecitabine alone, but this was achieved at the

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expense of significant toxicity (5). This combination was the reference arm in this study. The efficacy of capecitabine and oral vinorelbine used as single agents in metastatic breast cancer and the preliminary evidence of their increased activity in combination (6) made them attractive candidates for further clinical testing. Moreover, an all-oral regimen has the advantage of greater patient convenience in the palliative setting of metastatic breast cancer patients (7). Oral vinorelbine in combination or in sequence with capecitabine might constitute a new effective therapeutic option associated with a reduced incidence of grade 3–4 adverse events.

The present randomized phase II study evaluated the disease control rates (CR + PR + NC $\geq$ 3 months) of the combination of oral vinorelbine with capecitabine (V + C), the sequential regimen of oral vinorelbine and capecitabine (V↔C), and the combination of docetaxel and capecitabine (D + C). Because the study protocol allowed inclusion of patients with nonmeasurable disease according to RECIST criteria, disease control rate instead of response rate was chosen as the primary endpoint.

PATIENTS AND METHODS

Patients

Women with histologically or cytologically confirmed advanced adenocarcinoma of the breast were eligible for the study. Patients were required to meet the following inclusion criteria: prior treatment with anthracycline in the neo-adjuvant or adjuvant setting; at least a 12-month disease-free interval (DFI) between the last neo-adjuvant or adjuvant chemotherapy dose; at least one measurable or nonmeasurable lesion according to RECIST criteria (8); HER-2-negative disease (0 or 1+ by immunohistochemistry [IHC] or negative fluorescence in situ hybridization [FISH] or untested); no previous chemotherapy in the metastatic setting; recovery from acute toxicity of any prior treatment; Karnofsky performance status of 70 or greater; absolute neutrophil count $\geq$2,000/μL, hemoglobin level $\geq$ 10 g/dL, platelet count $\geq$100,000/μL; AST and ALT $\leq$ 2.5 $\times$ upper limit of normal (ULN); alkaline phosphatase $\leq$ 5 $\times$ ULN and total bilirubin within normal limits; creatinine clearance $\geq$50 mL/min according to Cockroft–Gault formula. Prior hormonal therapy for breast cancer for adjuvant and/or metastatic disease was allowed, provided that progression was documented at study entry. Prior treatment with taxane in the (neo)adjuvant setting was allowed. Exclusion criteria included prior vinorelbine containing regimen in the (neo)adjuvant setting, prior severe and unexpected reaction to fluoropyrimidine therapy or known sensitivity to 5-fluorouracil, brain metastases and ongoing grade 2 or worse neuropathy.

This study was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice, and all patients provided written informed consent.

Study Design and Treatment

This was a randomized, active control, parallel-group, open-label, multicenter study. Patients were randomly assigned (1:1:1) to either fully oral 3 weekly cycles of V + C (oral vinorelbine on days 1, 8 at a dose of 80 mg/m^2 after the first cycle at 60 mg/m^2, capecitabine at 1,000 mg/m^2 bid from day 1 to 14), or V↔C (oral vinorelbine on days 1, 8, 15 alternating with capecitabine every three cycles at the same doses as in the V + C arm), or 3 weekly cycles of D + C (docetaxel on day 1 at a dose of 75 mg/m^2, capecitabine at 1,000 mg/m^2 bid from days 1 to 14). Patients were randomly stratified according to prior cytotoxic chemotherapy in (neo)adjuvant setting (fluoropyrimidine, taxane therapy or other), age (<60 or $\geq$ 60 years), and center. No additional anticancer or hormonal treatment was allowed during the study. Patients were allowed to receive hematopoietic cytokines after the first cycle of treatment. Transfusions, antiinfective treatments, and antiemetics were administered according to recognized treatment guidelines and institutional practices. Prophylactic antiemetic regimen with oral $5HT_3$ antagonists was recommended before each administration of oral vinorelbine from the first cycle in the V + C and V↔C arms. In the D + C arm, patients received dexamethasone (8 mg orally twice-a-day) for 3 days beginning the day before each treatment cycle.

Treatment had to be administered until the documented disease progression, unacceptable toxicity, or patient's refusal. In the case of documented progression occurring before the first disease evaluation (3 weeks after start of treatment), the treatment was discontinued and the response to treatment was recorded as early progression. If one drug of the combination arm was discontinued because of toxicity before disease progression, the patient was considered

"off treatment". The other drug could be further given at the recommended dose in monotherapy, at the discretion of the investigator.

Study End Points

The primary end point was the disease control rate, defined as the sum of the complete and partial response and stabilization for at least 3 months. Response was evaluated according to RECIST criteria (8). Secondary objectives included the safety profile, the response rate (sum of the complete and partial response), the duration of response, the duration of disease control, the duration of stable disease, the progression-free survival (time from randomization until the date of progression or date of death), time-to-treatment failure (interval between randomization and progression, relapse, death, withdrawal due to adverse event, patient's refusal, lost to follow-up or start of new anticancer therapy without progression), and overall survival.

Assessment

In all three arms, disease assessments were performed every two cycles until progressive disease. For patients who discontinued study medication prior to progression, disease assessments were requested every 6 weeks until the documentation of disease progression. Safety variables included adverse event (AE) reports, changes in clinical laboratory findings, and tests for cardiac function (multiple uptake gated acquisition/echocardiogram, ECG) performed at the local institution. Toxicity was graded according to the NCI CTC version 2.0, and coded according to MedDRA dictionary, except for febrile neutropenia, which was defined according to Pizzo's definition (9).

Dose Modification

Treatment was to be modified in the case of hematological and/or nonhematological toxicity. Before day 1 of each cycle, patients had to have an adequate absolute neutrophil count or platelet count. All nonhematological toxicities (except for alopecia) had to have subsided to grade 1 or less. Patients were discontinued if 2 weeks or more was required for recovery. Patients who required a dose reduction on day 1 continued on the same dose.

Capecitabine therapy was interrupted at the first or second occurrence of a grade 2 or 3 toxicity and was restarted at 100%, 75%, or 50% dose (depending on the grade and frequency of the toxicity) when the toxicity decreased to grade 1. In the case of grade 4 toxicity, treatment was discontinued or interrupted until toxicity resolved or decreased to grade 1, and treatment restarted at 50% dose.

Day 8 and/or day 15 of oral vinorelbine was omitted in the case of neutrophils $<1.5 \times 10^9$/L or platelets $<75.0 \times 10^9$/L. Grade ≥ 3 neutropenia lasting more than 7 days or grade 4 neutropenia in the previous cycle led to no dose escalation of oral vinorelbine at cycle 2 or to decrease to 60 mg/m^2.

The administration of docetaxel was delayed in the case of neutrophils $<1.5 \times 10^9$/L or platelets $<75.0 \times 10^9$/L. Patients with grade 4 neutropenia for more than 1 week or with febrile neutropenia were allowed to receive prophylactic hematopoietic growth factors in subsequent cycles. If neutropenia occurred despite this treatment, the docetaxel dose had to be reduced to 55 mg/m^2. For grade 2 peripheral neuropathy, docetaxel was reduced to 55 mg/m^2 and discontinued for grade 3. Treatment had to be delayed in the case of bilirubin greater than the upper limit of normal (ULN) and/or alkaline phosphatase $>5 \times$ ULN and/or transaminases $>5 \times$ ULN. Patients were discontinued for grade 3 or 4 fluid retention or grade 3 anaphylaxis.

Dose omissions of capecitabine or oral vinorelbine were not replaced or restored. If one drug had to be discontinued in one arm because of a specific toxicity, the patient was off treatment.

Statistical Analyses

The required number of patients was determined according to the one-sample multiple testing procedure described by Fleming (10) with the following hypotheses for the three study arms: maximal inefficacy disease control rate = 50%, minimal efficacy disease control rate = 75%, alpha = 5% and beta = 10%, and two stages. Under these conditions, the required sample size was 40 evaluable patients in each treatment arm. Assuming that about 10% of patients would be nonevaluable, 45 patients were to be enrolled in each arm (a total of 135 patients had to be included).

All randomized and treated patients were included in the intent-to-treat population and analyzed in the arm they were assigned by randomization. To be

considered evaluable, the patients had to be eligible, evaluable for tumor response, and treated in the arm assigned by randomization. Patients evaluable for tumor response were defined as patients who remained on study until the first evaluation (two cycles) and who were evaluated; the patients who progressed before the first evaluation were considered as "early progression" and the patients who died from malignant disease before the first evaluation were considered "early death". All baseline lesions had to be assessed at least once (after the second cycle), with the same method of measurement as at baseline. Radiologists blind of the study treatment reviewed all imaging studies and relevant clinical data (e.g., photographs of skin) to assess tumor response of patients in complete response, partial response, and stable disease. The independent reviewer assessment results were the basis for the analyses of disease control rate and response rate. The progression-free survival and time-to-treatment failure analyses were reported according to the investigator's evaluation of the progression.

Continuous data were summarized using median, minimum, and maximum values. Categorical data were presented in the contingency tables with frequencies and percentages. Confidence intervals were calculated at the 95% level. Time-dependent parameters were analyzed using the Kaplan–Meier method and 95% confidence interval for the median was reported.

Safety analyses were performed on the population of patients having received at least one dose of study treatment. Worst NCI CTC grade for hematological and nonhematological adverse events was presented.

All statistical analyses were carried out with 8.2 version of SAS® for Windows® (SAS Inc, Cary, NC, USA).

RESULTS

Patients and Treatment

A total of 139 patients were recruited from 3 June 2005 to 14 April 2008 in 28 study sites and nine countries; 44 patients were allocated to V + C arm, 47 to V↔C arm, and 48 to D + C arm (zFig. 1). The cutoff date for the present analysis was 31 May 2009; survival information was recently updated with a new cutoff date on 22 May 2010. One patient in the V↔C arm was never treated because of the worsening of her liver enzymes just after inclusion. Seventeen patients were not evaluable for response, of whom three (one in each arm) were not eligible; one patient had a HER-2-positive status discovered after the randomization, one had no distant metastasis according to independent review, and one had 5 months of disease-free interval. Two patients were still on treatment at the cutoff date. Baseline demographics were generally well balanced across the three study arms (Table 1). The mean patient age was 54.2 years (range, 27.4–75.0 years) with 84.1% of patients aged between 35 and 64 years, 26.8% of patients were aged 60 years or above. The majority of the patients (71.1%) had a good performance status i.e., Karnofsky index of 90–100%. All patients were HER-2 negative or unselected for HER-2 status, except for one patient whose HER-2-positive status was determined after randomization. As per protocol, all patients had received anthracyclines in the (neo)adjuvant setting, except for one patient who received anthracenedione. Associated cytotoxics were taxanes in 18.1% and 5-FU in 73.9% of patients. Median disease-free interval was 2.8 years for the whole population and was similar between the three arms. The proportion of patients with at least three organs involved in the V + C V"C and D + C arms was 54.5%, 41.3%, and 45.8%, respectively, and with the visceral involvement 91.3%, 65.9%, and 64.6%, respectively.

Drug Exposure

The median number of cycles administered was highest in the V + C arm: eight cycles (range, 1–38 cycles) versus six cycles in D + C arm (range, 1–23 cycles) and four cycles in V↔C arm (range, 1–25 cycles). A total of 63% of patients assigned to the V↔C arm could receive the sequential treatment i.e., three cycles of oral vinorelbine followed by three cycles of capecitabine. The median relative dose intensity for both drugs was highest in the V↔C arm. The median relative dose intensity of capecitabine in the D + C, V + C, and V↔C arms was 77%, 88%, and 99%, respectively.

Efficacy

The efficacy results were presented in the intent-to-treat population. An independent radiologist reviewed the images of 114 patients to confirm the responses (CR, PR) or stabilization, whereas the date of progression was based on investigator's assessment. Following the review, the disease control rate (CR + PR + NC $\geq$ 3 months) in V + C, V↔C, and D + C arms

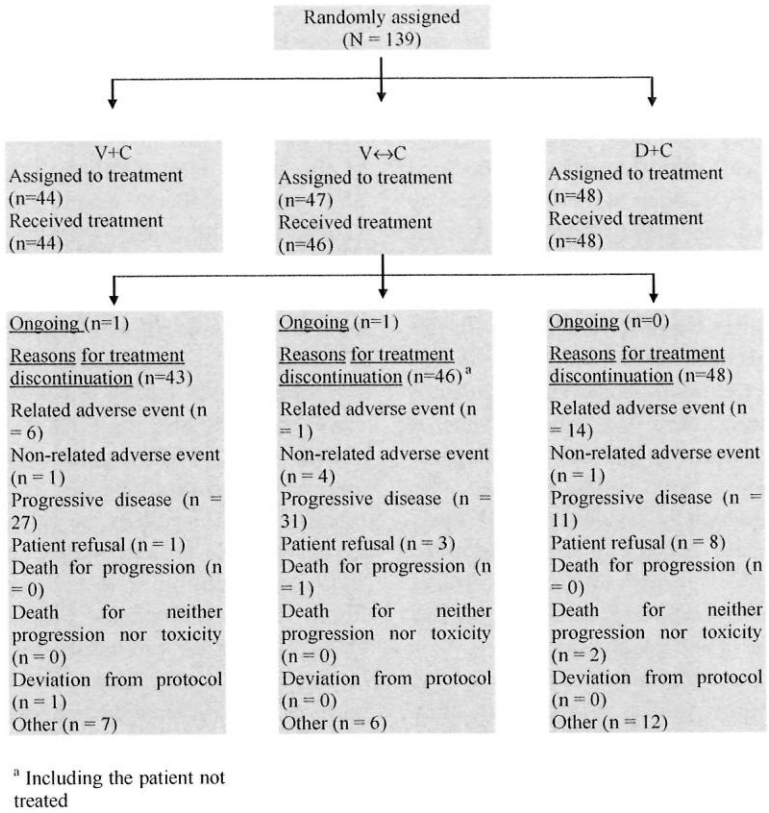

Figure 1. Consort flow diagram.

[95% CI] was 70.5% [54.8–83.2], 37.0% [23.2–52.5], and 70.8% [55.9–83.1], respectively (Table 2). The response rate in the V + C, V↔C, and D + C arms [95% CI] was 31.8% [18.6–47.6], 8.7% [2.4–20.8], and 35.4% [22.2–50.5], respectively. Characteristics of responding patients and patients with NC $\geq$ 3 months were not different across the three arms. The median duration of disease control in the V + C, V↔C, and D + C arms [95% CI] was 7.6 months [5.8–9.5], 9.2 months [6.9–14.4], and 9.0 months [7.8–15.4], respectively, and the median duration of stable disease 5.8 months [5.3–8.9], 6.9 months [4.1–10.1], and 7.2 months [5.5–9.0], respectively. The median duration of progression-free survival in the V + C, V↔C, and D + C arms [95% CI] was 7.2 months [5.3–8.9], 3.4 months [2.6–5.6], and 8.9 months [7.2–12.0], respectively (Fig. 2). The median time-to-treatment failure for V + C, V↔C, and D + C arms [95% CI] was 5.6 months [4.2–6.5], 3.0 months [1.8–4.4], and 4.3 months [4.0–5.0], respectively. The final analysis of overall survival was performed after 90 deaths had occurred (i.e., 64.7% of randomly assigned patients). The median overall survival in the V + C, V↔C, and D + C arms [95% CI] was 22.2 [18.8; 29.9], 19.4 [12.5; 35.4], and 24.2 [14.2; 38.5] months, respectively (Fig. 3).

Safety

The main hematological toxicity was leukopenia in the V + C arm, neutropenia in the V"C, and leukopenia/neutropenia in the D + C arm (Table 3). The incidence of grade 3/4 neutropenia was higher in the D + C arm (83.3%) compared with V + C and V↔C arms (47.7% and 39.1%, respectively) by patient, and 40.6% versus 18.0% and 11.5% by cycle. Febrile neutropenia was reported in one patient (2.3%) in the V + C arm and in three (6.3%) in the D + C arm. In the V↔C arm, febrile neutropenia was not observed, and there was a single episode of neutropenic infection (infection concomitant with grade 3–4 neutropenia). This toxicity was seen in 12.5% of patients in the D + C arm and in none in the V + C arm. Two of these seven episodes of neutropenic infection were

Table 1. Patient Characteristics

Characteristics	V + C (n = 44) No. (%)	V↔C (n = 46) No. (%)	D + C (n = 48) No. (%)	Total (n = 138) No. (%)
Age (years)				
Median (range)	55.0 (31.7–73.1)	56.7 (37.0–72.4)	52.2 (27.4–75.0)	54.2 (27.4–75.0)
<60 years	33 (75.0)	33 (71.7)	35 (72.9)	101 (73.2)
≥ 60 years	11 (25.0)	13 (28.3)	13 (27.1)	37 (26.8)
Karnofsky performance status				
90–100%	30 (68.2)	33 (71.7)	35 (72.9)	98 (71.1)
70–80%	14 (31.8)	13 (28.2)	13 (27.1)	40 (29.0)
Prior chemotherapy intent				
Neo-adjuvant	6 (13.7)	5 (10.9)	3 (6.3)	14 (10.1)
Adjuvant	30 (68.2)	35 (76.1)	35 (72.9)	100 (72.4)
Both	8 (18.2)	6 (13.0)	10 (20.8)	24 (17.4)
Anthracycline-based regimen*	44 (100)	46 (100)	47 (97.9)	137 (99.3)
Without taxanes	36 (81.8)	38 (82.6)	38 (79.2)	112 (81.2)
With taxanes	8 (18.2)	8 (17.4)	9 (18.8)	25 (18.1)
None (other regimens)	–	–	1 (2.1)	1 (0.7)
Prior hormonotherapy	32 (72.7)	29 (63.0)	35 (72.9)	96 (69.6)
Disease-free interval (years)				
Median (range)	2.9 (0.9–12.6)	2.6 (0.8–19.8)	2.8 (0.1–11.4)	2.8 (0.1–19.8)
<1 year	2 (4.5)	1 (2.2)	1 (2.1)	4 (2.9)
≥ 1 year	42 (95.5)	45 (97.8)	47 (97.9)	134 (97.1)
HER-2 status				
Negative	33 (75.0)	36 (78.3)	38 (79.2)	107 (77.5)
Positive†	1 (2.3)	–	–	1 (0.7)
Unknown	10 (22.7)	10 (21.7)	10 (20.8)	30 (21.7)
Estrogen receptors				
Positive	29 (65.9)	27 (58.7)	28 (58.3)	84 (60.9)
Negative	12 (27.3)	17 (37.0)	16 (33.3)	45 (32.6)
Unknown	3 (6.8)	2 (4.3)	4 (8.3)	9 (6.5)
Progesterone receptors				
Positive	23 (52.3)	23 (50.0)	21 (43.8)	67 (48.6)
Negative	18 (40.9)	21 (45.7)	21 (43.8)	60 (43.5)
Unknown	3 (6.8)	2 (4.3)	6 (12.5)	11 (8.0)
Number of organs involved				
1	10 (22.7)	9 (19.6)	11 (22.9)	30 (21.7)
2	10 (22.7)	18 (39.1)	15 (31.3)	43 (31.2)
≥ 3	24 (54.5)	19 (41.3)	22 (45.8)	65 (47.1)
Visceral involvement‡	29 (65.9)	42 (91.3)	31 (64.6)	102 (73.9)
Measurable disease	40 (90.9)	46 (100)	42 (87.5)	128 (92.8)

*One patient received anthracenedione.
†Documented after patient's randomization.
‡Visceral involvement includes at least one of the following: liver and/or lung.

notified as serious adverse events. Antibiotics were prescribed in 36.4% of patients in the V + C arm, 15.2% in the V↔C arm, and 52.1% in the D + C arm. Hematological toxicity was the most frequent reason of treatment delays, dose cancellations, and dose reductions. This toxicity accounted for 75.7% of cycle delays in the V + C arm, 58.3% in the V↔C arm, and 10.5% in the D + C arm; for 67.6% of oral vinorelbine dose cancellations in the V + C arm and 75.0% in the V↔C arm; for 70.0% of oral vinorelbine dose reductions in the V + C arm and 100% in the V↔C arm; and for 66.7% of docetaxel dose reductions in the D + C arm. Gastrointestinal toxicities were the most frequent nonhematological toxicities observed in all arms, with some differences regarding the type and the incidence. Nausea and diarrhea occurred in ≥ 45% patients in each arm with the highest incidence per patient in the V + C arm (nausea/diarrhea: 65.9%/56.8% versus 50.0%/45.7% in the V↔C arm versus 52.1%/45.8% in the D + C arm). Vomiting was also more frequent in the V + C arm (45.5%) than in the V↔C (30.4%) and D + C arms (18.8%). Stomatitis incidence was ≥ 30% in all arms, with the highest incidence in the D + C arm (56.3% versus 31.8% in the V + C arm and 34.8% in the V↔C arm). For each of these toxicities, no grade 4 was observed.

Hand-foot syndrome related to capecitabine administration was most frequent in the D + C arm (54.2%) versus 43.2% in the V + C arm and 21.7%

Table 2. Summary of Clinical Outcomes in the Intent-To-Treat Population by Treatment Arm

Outcome	V + C (n = 44) No. (%)	V↔C (n = 46) No. (%)	D + C (n = 48) No.(%)
Response*			
Complete response (CR)	–	–	1 (2.1)
Partial response (PR)	14 (31.8)	4 (8.7)	16 (33.3)
Response rate (CR + PR) [95% CI]	14 (31.8) [18.6–47.6]	4 (8.7) [2.4–20.8]	17 (35.4) [22.2–50.5]
NC ≥ 3 months	17 (38.6)	13 (28.3)	17 (35.4)
Disease control rate (CR + PR + NC ≥ 3 months) [95% CI]	31 (70.5) [54.8–83.2]	17 (37.0) [23.2–52.5]	34 (70.8) [55.9–83.1]
Not evaluable	2 (4.5)	4 (8.7)	6 (12.5)
Other outcomes† (months)			
Median time to first response [95% CI]	1.6 [1.4–2.8]	1.4 [0.9–4.5]	1.5 [1.4–2.1]
Median duration of response [95% CI]	6.3 [4.4–9.8]	7.9 [4.1–9.9]	13.6 [5.3–14.3]
Median duration of disease control [95% CI]	7.6 [5.8–9.5]	9.2 [6.9–14.4]	9.0 [7.8–15.4]
Median progression-free survival [95% CI]	7.2 [5.3–8.9]	3.4 [2.6–5.6]	8.9 [7.2–12.0]
Median time to treatment failure [95% CI]	5.6 [4.2–6.5]	3.0 [1.8–4.4]	4.3 [4.0–5.0]
Overall survival [95% CI]	22.2 [18.8–29.9]	19.4 [12.5–35.4]	24.2 [14.2–38.5]

*According to panel review.
†According to the investigator's evaluation.

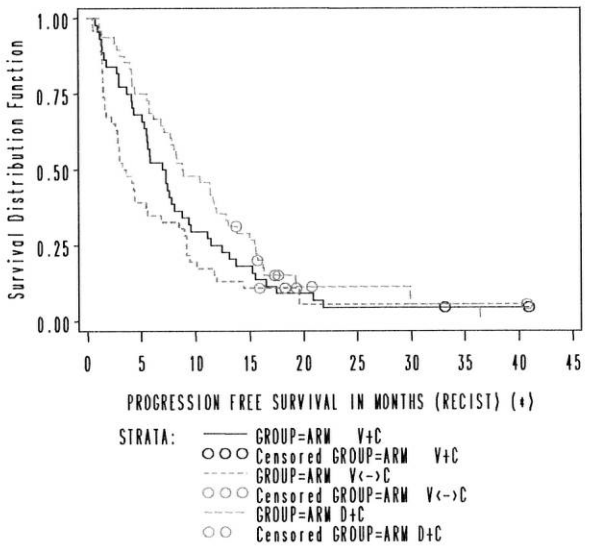

Figure 2. Progression-free survival in the intent-to-treat population (investigator's evaluation).

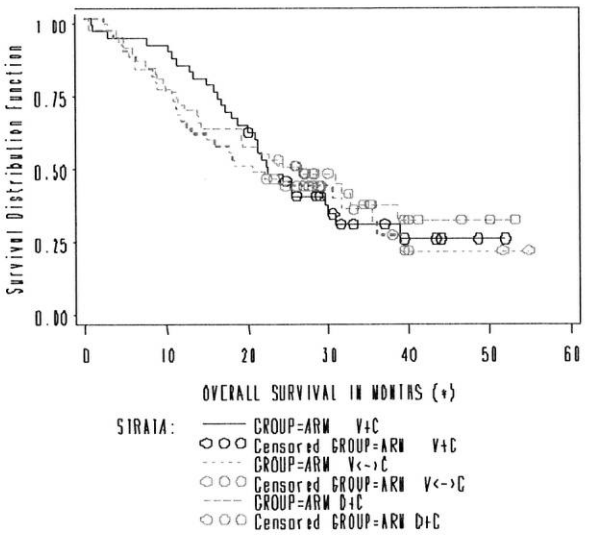

Figure 3. Overall survival.

in the V↔C arm. No grade 4 hand-foot syndrome was observed. Fatigue/asthenia was slightly less frequent in the V↔C arm (30.4%/4.3%) versus V + C (40.9%/11.4%) and D + C (50.0%/12.5%) arms, with no grade 4 occurrence. Alopecia was most frequent in the D + C arm (54.2%) versus V + C (18.2%) and V↔C arms (13.0%).

In all arms, the drug related nonhematological adverse events were the most frequent reason of capecitabine dose cancellations and dose reductions (77.2% of dose cancellations in the V + C arm, 58.6% in the V↔C arm, and 19.5% in the D + C arm; 54.6% of dose reductions in the V + C arm, 100% in the V↔C arm, and 37.0% in the D + C arm). Drug-related serious adverse events occurred in one patient in the V↔C arm (2.2%), five patients (11.4%) in the V + C arm, and four patients (8.3%) in the D + C arm.

Overall, the safety profile of the V↔C arm was better than that of the two combination arms, with less complicated neutropenia, hand-foot syndrome, fatigue/asthenia, alopecia, and serious adverse events. The V + C regimen induced less neutropenia, infection, hand-foot syndrome, fatigue/asthenia and alopecia

Table 3. Related Adverse Events during Treatment – Worst Grade by Patient

Adverse events	V + C (n = 44)			V↔C (n = 46)			D + C (n = 48)		
	Overall No. (%)	G3 No. (%)	G4 No. (%)	Overall No. (%)	G3 No. (%)	G4 No. (%)	Overall No. (%)	G3 No. (%)	G4 No. (%)
Hematological									
Anemia	33 (75.0)	–	–	33 (71.7)	2 (4.3)	–	41 (85.4)	–	1 (2.1)
Leukopenia	34 (77.3)	9 (20.5)	4 (9.1)	35 (76.1)	10 (21.7)	1 (2.2)	45 (93.8)	29 (60.4)	4 (8.3)
Neutropenia	31 (70.5)	10 (22.7)	11 (25.0)	36 (78.3)	8 (17.4)	10 (21.7)	45 (93.8)	8 (16.7)	32 (66.7)
Febrile neutropenia	1 (2.3)	1 (2.3)	–	–	–	–	3 (6.3)	3 (6.3)	–
Neutropenic infection	–	–	–	1 (2.2)	1 (2.2)	–	6 (12.5)	6 (12.5)	–
Thrombocytopenia	18 (40.9)	–	–	14 (30.4)	–	–	19 (39.6)	–	–
Non-hematological*									
Lacrimation increased	–	–	–	–	–	–	5 (10.4)	–	–
Abdominal pain	12 (27.3)	2 (4.5)	–	9 (19.6)	1 (2.2)	–	4 (8.3)	1 (2.1)	–
Constipation	4 (9.1)	–	–	8 (17.4)	–	–	5 (10.4)	1 (2.1)	–
Diarrhea	25 (56.8)	4 (9.1)	–	21 (45.7)	1 (2.2)	–	22 (45.8)	2 (4.2)	–
Dyspepsia	8 (18.2)	–	–	4 (8.7)	–	–	4 (8.3)	–	–
Nausea	29 (65.9)	1 (2.3)	–	23 (50.0)	1 (2.2)	–	25 (52.1)	–	–
Stomatitis	14 (31.8)	2 (4.5)	–	16 (34.8)	–	–	27 (56.3)	1 (2.1)	–
Vomiting	20 (45.5)	2 (4.5)	–	14 (30.4)	2 (4.3)	–	9 (18.8)	1 (2.1)	–
Asthenia	5 (11.4)	–	–	2 (4.3)	1 (2.2)	–	6 (12.5)	2 (4.2)	–
Fatigue	18 (40.9)	2 (4.5)	–	14 (30.4)	2 (4.3)	–	24 (50.0)	4 (8.3)	–
Edema peripheral	2 (4.5)	–	–	–	–	–	6 (12.5)	–	–
Pyrexia	3 (6.8)	–	–	2 (4.3)	–	–	5 (10.4)	–	–
Weight decreased	7 (15.9)	–	–	7 (15.2)	–	–	7 (14.6)	–	–
Anorexia	10 (22.7)	–	–	7 (15.2)	–	–	12 (25.0)	–	–
Arthralgia	1 (2.3)	–	–	3 (6.5)	–	–	6 (12.5)	–	–
Myalgia	8 (18.2)	1 (2.3)	–	6 (13.0)	–	–	10 (20.8)	1 (2.1)	–
Dizziness	2 (4.5)	–	–	2 (4.3)	1 (2.2)	–	5 (10.4)	–	–
Dysgeusia	2 (4.5)	–	–	2 (4.3)	–	–	6 (12.5)	–	–
Headache	1 (2.3)	–	–	5 (10.9)	–	–	1 (2.1)	–	–
Paresthesia	6 (13.6)	–	–	5 (10.9)	–	–	6 (12.5)	1 (2.1)	–
Peripheral sensory neuropathy	5 (11.4)	–	–	1 (2.2)	–	–	6 (12.5)	2 (4.2)	–
Alopecia	8 (18.2)	–	–	6 (13.0)	–	–	26 (54.2)	–	–
Nail disorder	2 (4.5)	–	–	2 (4.3)	–	–	18 (37.5)	–	–
Hand-foot syndrome†	19 (43.2)	2 (4.5)	–	10 (21.7)	1 (2.2)	–	26 (54.2)	9 (18.8)	–
Rash	2 (4.5)	–	–	1 (2.2)	–	–	11 (22.9)	–	–

*Reported by ≥ 10% of patients.
†NCI/CTC term.

than the D + C regimen. The V + C regimen was associated with more nausea, vomiting, and diarrhea but less stomatitis.

DISCUSSION

Although this three-arm randomized phase II study did not allow for formal comparison between treatment arms, the efficacy of the two combination arms (V + C and D + C arms) was similar in terms of disease control and response rate, The sequential arm seems to be less effective than the two combinations arms for these two parameters. However, this trial was not powered to demonstrate major differences in progression-free survival or overall survival. Moreover, owing to small numbers of patients per arm, the results may be due to chance imbalances.

The D + C regimen was reported to be active but associated with significant toxicity in anthracycline pretreated metastatic breast cancer patients (5). In the phase III study comparing capecitabine plus docetaxel versus capecitabine, the patient characteristics were slightly different compared with this study. Namely, 35% of patients received study therapy as first line treatment for metastatic disease and the remaining two thirds received study therapy as second or third-line treatment; 64% had at least three organs involved (4). Response rate with the D + C regimen was after panel review (intent-to-treat analysis) at the same range: 32% in the phase III study versus 35.4% in our study. The median relative dose intensity of capecitabine was 77% in both studies. It is of note that the intended dose of capecitabine was 1,000 mg/m² twice daily in D + C arm of this study, whereas the initial dose of capecitabine used in the phase III study was 1,250 mg/m² twice daily. However, the majority of patients enrolled in the D + C arm of the phase III study had dose reduction of capecitabine to 2,000 mg/m²/day from the cycle 2.

The interest in the oral drugs in the management of cancer patients in palliative setting is growing, in parallel to the preferences of the patients, provided the efficacy and toxicity of these agents are comparable with their intravenous counterparts (7). In addition to the advantages of an all-oral regimen, vinorelbine and capecitabine have nonoverlapping toxicities. The response rate of V + C arm appears slightly lower than that in previously published two phases II nonrandomized trials (44.2% and 46.3%)(11,12). The disease control rate in all three studies cannot be directly compared due to various criteria employed: the Nolé's study (11) did not take into account the duration of stable disease and in the Tubiana-Mathieu's study (12) the duration of stable disease was restricted to at least 6 months. The safety profile of the V + C combination was similar in these three studies; neutropenia was infrequently associated with infections; nausea, vomiting, diarrhea, stomatitis, and hand-foot syndrome were rarely severe. Notably, the safety profile of the two combination arms of this study was different. The V + C regimen induced slightly more nausea, vomiting, and diarrhea but less neutropenia, infection, hand-foot syndrome, fatigue/asthenia, and alopecia than the D + C regimen.

There are various approaches to shifting to another chemotherapy regimen in advanced breast cancer (13). Some studies started treatment with a second agent following a predefined number of cycles of initial noncross-resistant monotherapy, but the majority requested symptomatic and/or radiographic progression as the trigger for switching therapy. In this study, the sequential V↔C arm was defined with a planned multicourse sequence of oral vinorelbine followed by capecitabine without interruption between treatment regimens, to deliver high dose of two noncross-resistant drugs. The objective was to identify whether this sequence was effective and associated with a reduced incidence of grade 3–4 events. In this study, the safety profile of the V↔C arm was slightly better than that of the two combination arms, especially when taking into account the overall incidence of hand-foot syndrome, fatigue/asthenia and alopecia. Lower disease control rate in the sequential arm could be due to higher prevalence of patients with visceral disease in this arm (91% in comparison to 65.9% in V + C and 64.6% in D + C arm).

To date, nine randomized studies have directly compared multidrug versus sequential monotherapy, in metastatic breast cancer, but only one was large and adequately powered (14). In this study, 739 patients were assigned to either sequential single-agent therapy with doxorubicin or paclitaxel or to the combination of both drugs as front-line chemotherapy. Higher response rate and longer time-to-treatment failure were seen in the combination arm, but this was achieved at the expense of increased toxicity and did not result in survival benefit. Eight other small phase II or phase III studies comparing sequential versus combination approaches showed different results. Two (15,16) showed a better response rate in the combination arm, whereas others showed similar efficacy of both approaches (17–22). Safety profile was better in the sequential arm in three of these eight trials (17–19), whereas two trials showed similar toxicity (15,20) and in three hematological toxicity was higher in the sequential arm (16,21,22). However, the interpretation of these studies is difficult owing to the differences in their design and conduct. It appears that overall combination therapy is associated with an improved response rate and time-to-progression compared with sequential therapy, at the expense of greater toxicity (13).

Our study indicates that the alternating V↔C regimen seems to be less effective in terms of disease control and response rate compared with V + C and D + C combinations, whereas combinations of V + C or D + C seem to have similar efficacy and different toxicity profile. Due to the small number of patients in each arm, the results of progression-free survival and survival should therefore be interpreted with caution and may be due to chance imbalances. V + C combination induced less neutropenia, infection, hand-foot syndrome, fatigue/asthenia, and alopecia than D + C, whereas gastrointestinal side effects were lower with the D + C regimen. In conclusion, V + C combination can be considered a valuable alternative to D + C in patients with metastatic breast cancer who have failed anthracyclines, while offering the advantages of an all-oral treatment.

CONFLICT OF INTEREST STATEMENT

M. Campone, N. Dobrovolskaya, S. Tjulandin, S.-C. Chen, S.-J. Fourie, F. Mefti, M. Konstantinova, and J. Jassem declare no conflict of interest; F. Lefresne and N. Meheust are Pierre Fabre's employees.

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