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CLINICAL TRIAL

A phase I clinical and pharmacological study evaluating vinflunine in combination with doxorubicin as first line treatment in metastatic breast cancer

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Abstract Vinfunine (VFL) is a novel bifluorinated tubulin-targeted agent of the vinca alkaloids class active in advanced stage breast cancer. We conducted a phase I study combining VFL with doxorubicin (DXR) to define the recommended dose (RD), safety, pharmacokinetic (PK) interaction and efficacy. Two schedules (day 1 every 3 weeks; days 1 and 8 every 3 weeks) were investigated as first line chemotherapy in metastatic breast cancer patients. Thirty-two patients received a total of 162 cycles of the VFL–DXR combination (median 6). The RDs were VFL 250 mg/m^2/DXR 40 mg/m^2 every 3 weeks for schedule 1 and VFL 120 mg/m^2/DXR 25 mg/m^2 days 1 and 8 every 3 weeks for schedule 2. The main dose-limiting toxicity was neutropenia. The most frequent non-hematological adverse events were nausea, fatigue, constipation, vomiting, anorexia, stomatitis and dyspnea. Objective response rate was reached in 47.1% of the patients. No PK interaction was observed. VFL–DXR combination is feasible with manageable toxicity. The antitumor activity was promising and supports further evaluation.

Keywords Breast cancer · Advanced stage · Vinflunine · Doxorubicin · Phase I · Pharmacokinetics

Introduction

Breast cancer (BC) is the most frequent malignancy in women. Systemic adjuvant therapies have improved the cure rate of the disease [1]. Nevertheless less than 10% of the patients present with concomitant metastasis and more than 20% with initially localized disease eventually develop distant metastasis [2].

Although these patients cannot be cured, multiple therapeutic options allow the disease to be controlled for a long time. Chemotherapy currently remains one of the cornerstones of systemic therapy [3]. During these last decades the availability of a larger number of new drugs has led to continued improvement in progression free survival (PFS), overall survival (OS) and quality of life of metastatic patients [4]. However median survival of the advanced stage breast cancer (ABC) patients remains around 2–3 years. The development of other non cross-resistant and well tolerated substances is, therefore, one of the priorities in oncology research.

Vinflunine (VFL, Javlor®, Pierre Fabre Medicament) is a new microtubule inhibitor belonging to the family of the vinca alkaloids [5]. It blocks cells at the G2/M cell cycle phase and induces apoptosis. The introduction of two fluorine atoms into the catharantine moiety has conferred on this molecule a different and broader spectrum of activity compared to the previous vinca alkaloids, vinorelbine, or vinblastine. VFL inhibits tubulin assembly, but

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as a consequence of its new design it binds relatively weakly to this structure, therefore the risk of neurotoxicity is less than with other spindle poisons. Single agent VFL has been shown to be clinically active in BC [6, 7], non small cell lung cancer [8, 9] and transitional cell carcinoma of the bladder [10]. As second and third line chemotherapy after taxanes and anthracyclines an objective response rate (ORR) of 13–30% and a stable disease rate of 30–35% were observed in ABC [11].

Currently no chemotherapeutic regimen is widely accepted as a standard in the treatment of ABC patients. Sequential use of single agent chemotherapies may be sufficient to treat asymptomatic patients. However combination treatments result in a higher ORR and a longer time to disease progression [3, 12]. Multiagents treatments are more adequate in the case of severe symptoms, rapid progression or high tumor burden [13, 14]. Doxorubicin (DXR) is one of the drugs most active against BC and the reference drug in the anthracycline family. Furthermore tumors relapsing >12 months after anthracycline-based adjuvant treatment may still be sensitive, allowing the reintroduction of these drugs. The mechanism of action of DXR, as a topoisomerase II inhibitor and DNA intercalator, is different to that of VFL supporting the hypothesis of synergic antitumor activity. Due to the higher efficacy of the association VFL–DXR without increased toxicity in animal models [15], we conducted a phase I study of this combination. We report the results of two different schedules, weekly (day 1 and day 8 every 3 weeks) and 3-weekly, of VFL combined with DXR as first line chemotherapy for ABC.

Patients and methods

Design

This was an open label, non-randomized, multicenter, phase I study. A traditional 3 + 3 dose-escalation design was used [16]. The primary objective of the study was to establish the recommended dose (RD) of the VFL–DXR combination. The secondary objectives were toxicity assessment and safety, pharmacokinetic (PK) drug-drug interaction and antitumor activity.

The study was conducted in accordance with the Declaration of Helsinki and in compliance with good clinical and laboratory practice. Written informed consent was obtained from each patient prior to entry into the study.

Patient selection

Inclusion criteria included women aged between 18 and 75 years, with metastatic BC, ECOG performance status of 0–2, no prior chemotherapy for ABC, more than 6 months since the end of neo/adjuvant chemotherapy if applicable, previous cumulative dose of DXR, epirubicin or anthracenedione not exceeding 250, 450 and 72 mg/m^2, respectively and at least one measurable lesion according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 [17]. Adequate biological parameters were required: absolute neutrophil count (ANC) $\geq 2.0 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, hemoglobin $\geq$10 g/dl, total bilirubin $\leq 1.5 \times$ upper limit of normal value (ULN), transaminases $\leq 2.5 \times$ ULN ($\leq 5 \times$ ULN in the presence of liver metastasis), creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq$50 ml/min. Exclusion criteria were: brain or leptomeningeal metastasis; peripheral neuropathy grade $\geq$2 according to the NCI Common Toxicity Criteria version 2.0 (NCI-CTC v. 2.0); occlusive or subocclusive intestinal disease; recent myocardial infarction (<6 months) or serious underlying cardiovascular diseases; left ventricular ejection fraction (LVEF) <50% or any significant electrocardiogram abnormality; uncontrolled hypercalcaemia; prior high-dose chemotherapy with stem cell rescue; radiation therapy in the 4 weeks prior to the start of treatment; pregnant or breast-feeding women.

Treatment regimen

VFL was given intravenously as a 20 min infusion followed by DXR as a 30 min infusion. Antiemetics were administered according to local standards and prophylactic use of laxatives was recommended. Two schedules of administration were studied (Table 1). In schedule 1 both drugs were administered on day 1 of each 3 week cycle. In schedule 2, they were infused on days 1 and 8 of each 3 week cycle. The dose levels are described in the Table 1. Upfront prophylactic use of hematopoietic growth factors (G-CSF) was not allowed during the first cycle.

Each patient received at least 2 cycles of treatment unless there was documented disease progression, unacceptable toxicity, prohibitive intercurrent illness, investigator's decision, patient's refusal or when the total cumulative dose of DXR reached 550 mg/m^2. After 4 cycles of treatment continuation was allowed according to the investigator's discretion.

Table 1 Schedules with each dose level

		Vinflunine (mg/m^2)	Doxorubicin (mg/m^2)
Schedule 1[a]	Level 1	250	50
	Level-1	250	40
Schedule 2[b]	Level 1	150	25
	Level-1	120	25

[a] Day 1 every 3 weeks

[b] Day 1 and 8 every 3 weeks

Table 2 Patients' characteristics

	Schedule 1 $n = 15$	Schedule 2 $n = 17$
Median age (range)	56.0 years (44.2–74.6)	59.9 years (48.8–73.9)
Performance status (%)		
0–1	93.3	88.2
2	6.7	11.8
Histological type (%)		
Ductal	60	70.6
Lobular	26.7	17.6
Others	13.3	11.8
Tumor initial grade (%)		
1	6.7	11.8
2–3	80.0	64.7
Unknown	13.3	23.6
Median disease free interval (%)		
$\geq$ 2 years	46.7	70.6
$<$ 2 years	53.3	29.4
Number of organs involved (%)		
1	26.7	17.6
$\geq$ 2	73.3	82.4
Visceral involvement (%)	80.0	82.4
Prior surgery (%)	80.0	88.2
Prior radiotherapy (%)	53.3	88.2
Prior endocrine therapy (%)	40.0	76.5
Prior chemotherapy (%)	26.7	23.5
Anthracyclines	20.0	23.5

Treatment modifications: on day 1, treatment was delayed for 1 week if ANC $<1.5 \times 10^9$/l or platelets $<100 \times 10^9$/l; in schedule 2 only, on day 8, one dose level reduction was required if ANC 0.5–1.0 $\times 10^9$/l or platelets 50–100 $\times 10^9$/l. The treatment was delayed if ANC or platelets were less than 0.5 and 50 $\times 10^9$/l, respectively. In the event of febrile neutropenia (FN), grade 4 thrombocytopenia or grade 4 neutropenia for $\geq$7 days, doses were reduced to the next lower level. A maximum of two dose reductions was allowed. In case of organ toxicity >grade 2, treatment on day 1 was delayed by 1 week and treatment on day 8 (schedule 2 only) was cancelled. The doses of the next cycle were decreased by 1 level in case of grade 2 mucositis and constipation for more than 5 days or any grade $\geq$3 toxicity. In case of >2 week delay because of any toxicity, the patient was withdrawn from the study.

Assessments

Baseline examinations included: medical history, physical examination, ECOG performance status, electrocardiogram (EKG), LVEF assessment, complete blood cell count, biochemistry measurements, and tumor assessment by bone scan, CT scan and/or MRI. Medical history, clinical examination, blood tests and EKG were repeated on day 1 of each cycle. LVEF and tumor assessment were repeated every 2 cycles. Complete blood cell count was measured at least on days 1, 3, 8 and 15 and every 2 days when ANC was $<0.5 \times 10^9$/l. After completion of the study, the patients were followed lifelong every 3 months.

Safety was assessed according to the NCI-CTC v. 2.0. Dose limiting toxicity (DLT) was defined as any of the following adverse events occurring during the first cycle: non-hematological toxicity grade $\geq$3 (except alopecia and inadequately premedicated nausea/vomiting); neutropenia $<0.5 \times 10^9$/l for $\geq$7 days or $<0.1 \times 10^9$/l for $\geq$3 days; platelets $<25 \times 10^9$/l or thrombocytopenia with bleeding or requiring platelets transfusion; FN. The recommended dose (RD) was defined as the dose level immediately below the maximum tolerated dose (MTD) resulting from a DLT with at least 6 patients treated at the RD.

Efficacy was determined by the response rate according to the RECIST v. 1.0 [17] in all patients having received at least 2 cycles of treatment.

Pharmacokinetics (PK)

Eleven blood samples were collected from pre-dose to 168 h after VFL administration on day 1 for schedule 1 and on day 8 for schedule 2. Drug concentrations were

measured in centralized bioanalytical laboratories: VFL and its active metabolite 4-O-deacetylvinflunine (DVFL) were assayed in whole blood. DXR and its active metabolite doxorubicinol were assayed in plasma. The PK analysis involved a graphical approach based on drug concentration results, and the calculation of PK parameters using a population PK model for VFL [18], and using a noncompartmental method for DXR and doxorubicinol.

Potential impact of DXR on the PK of VFL was assessed by comparing Bayesian values of total blood clearance (Cl_{tot}) with those of a reference dataset made up of 3 Phase I dose escalating studies with VFL monotherapy. Conversely, a potential impact of VFL on the PK of DXR and doxorubicinol were assessed by comparing their PK parameters to published data on DXR administered as a single agent.

Results

Recommended dose, tolerability and safety (Table 3)

Schedule 1

Fifteen patients (Table 2) received a total of 73 cycles with a median of 6 and a range of 1–8 cycles. The median relative dose intensities of VFL and DXR were 99.2% [92.6–100.8] and 98.8% [76.7–103.7], respectively.

At dose level 1, two of the 6 evaluable patients experienced a DLT (2 patients were not evaluable for MTD because of inadequate blood monitoring): one neutropenia $<0.1 \times 10^9$/l for $\geq$3 days and one episode of neutropenic infection. This level was identified as the MTD. At dose level-1 seven patients were included and no DLT was observed, therefore the RD was established as VFL 250 mg/m^2 and DXR 40 mg/m^2 on day 1 every 3 weeks.

The most frequently reported hematological toxicity was neutropenia. Grade 3 occurred in 1 patient (6.7%) and grade 4 in 11 patients (73.3%) and 43.8% of cycles At MTD the 8 patients treated (100.0%) developed grade 4 neutropenia. Among them, 2 episodes of FN were reported in 2 patients (25.0%) and 2 episodes of neutropenic infection in 2 patients (25.0%). At RD 4 out of 7 patients (57.2%) developed severe neutropenia, one grade 3 and three grade 4. Two cases of grade 3 anemia were observed at MTD and none at RD. Three patients experienced grade 3 thrombocytopenia at the MTD and none at the RD.

The main non-hematological adverse events related to study treatment were gastrointestinal disorders: nausea in 12 patients (80.0%), constipation and vomiting in 6 patients each (40.0%), stomatitis and abdominal pain in 3 patients each (20.0%); general disorder: fatigue in 11 patients (73.3%); skin disorder: alopecia in 10 patients (66.7%); and nutritional disorder: anorexia in 5 patients (33.3%). Study drug related cardiac toxicities included asymptomatic decrease in LVEF (grade 1 and 2) experienced by four patients (26.7%), 3 at MTD and 1 at RD and a grade 1 diastolic dysfunction in one patient at MTD. One case of cardiomyopathy was observed 2 months after the end of the study treatment and improved after corrective treatment. No treatment related death occurred. In general overall toxicity was manageable, especially at the RD, where hematological toxicity was moderate and reversible. At RD, no grade 3/4 non-hematological toxicity was observed except in 1 patient who suffered grade 3 fatigue. In total, two out of the 15 patients in schedule 1 discontinued the treatment because of a study drug-related adverse event after 2 and 4 cycles, respectively, both patients were at MTD.

Schedule 2

Seventeen patients received a total of 89 cycles with a median of 6 and a range of 1–8 cycles. Median relative dose intensities of VFL and DXR were 75.0% [38.3–115.7] and 77.3% [36.7–92.5], respectively.

At dose level 1, 2 out of 4 evaluable patients experienced at least one DLT (5 patients were not evaluable for MTD determination, because of missing information on blood cell count tests) : neutrophils $<0.5 \times 10^9$/l for $\geq$7 days, neutropenic infection, grade 3 constipation and arm deep venous thrombosis. This level was defined as the MTD. At dose level-1, eight patients were included and one DLT (ANC <0.5 g/l for $\geq$7 days) was observed out of the 6 evaluable patients, therefore the RD was established as VFL 120 mg/m^2 and DXR 25 mg/m^2 on day 1 and day 8 every 3 weeks.

The major hematological toxicity was neutropenia. Grade 3 occurred in 2 patients (11.8%) and grade 4 in 12 patients (70.6%) and 41.6% of cycles. At MTD, 8 out of the 9 patients treated (88.9%) developed grade 4 neutropenia. Among them, one episode of FN was reported in one patient (12.5%) and 4 episodes of neutropenic infection in 4 patients (50.0%) all at MTD. At RD, 7 out of the 8 patients (87.5%) developed neutropenia, one grade 3 (12.5%) and four grade 4 (50.0%). One grade 3 anemia was observed at MTD and none at RD. Two cases of grade 3 thrombocytopenia occurred, 1 at MTD and 1 at RD.

The main non-hematological adverse events related to study treatments were gastrointestinal disorders: constipation and nausea in 13 patients each (76.5%), vomiting in 11 patients (64.7%), stomatitis in 7 patients (41.2%), diarrhea and abdominal pain in 4 patients each (23.5%); general disorder: fatigue in 14 patients (82.4%); nutritional disorder: anorexia in 6 patients (35.3%). Two grade 3 fatigue, one grade 3 constipation, one grade 3 vomiting and three grade 3 vein thrombosis were reported and occurred at MTD,

Table 3 Hematological and non-hematological grade 3 and 4 toxicities

	Schedule 1				Schedule 2			
	Level 1 *n* (%)		Level-1 *n* (%)		Level 1 *n* (%)		Level-1 *n* (%)	
	G3	G4	G3	G4	G3	G4	G3	G4
Hematological								
Anemia	2 (25.0)				1 (11.1)			
Febrile neutropenia	2 (25.0)					1 (11.1)		
Neutropenia		8 (100.0)	1 (14.3)	3 (42.9)	1 (11.1)	8 (88.9)	1 (12.5)	4 (50.0)
Thrombocytopenia	3 (37.5)				1 (11.1)		1 (12.5)	
Non-hematological								
Vomiting					1 (11.1)			
Constipation					1 (11.1)			
Stomatitis		1 (12.5)						
Colitis	1 (12.5)							
Fatigue	2 (25.0)		1 (14.3)		2 (22.2)			
Anorexia		1 (12.5)						
Neuropathic pain	1 (12.5)							
Arthralgia	1 (12.5)							
Deep vein thrombosis					3 (33.3)			

while no non-hematological grade 3/4 toxicity was observed at RD. Study drug related cardiac toxicities included grade 1 palpitations in 2 patients (one at MTD and one at RD) and a grade 1 tachycardia in one patient at MTD. Asymptomatic LVEF decrease was observed in 1 patient at RD, not related to the study drugs according to the investigator. One death occurred within 30 days after last study drug administration but according to the investigator was not related to the study treatment. In total, overall toxicity was manageable and the hematological toxicity was reversible. In total, for schedule 2, one patient out of 17, treated at MTD, discontinued the treatment because of a study drug-related adverse event after 4 cycles (fatigue grade 3).

Antitumor activity assessment

Tumor best response in the ITT population is reported in the Table 4. In schedule 1, 7 patients reached an objective response (46.7%) according to the investigator's assessment. In the evaluable population 6 objective responses were reported (46.2%). The best overall response was partial response. In schedule 2, 8 patients presented an objective response (47.1%). In the evaluable population 8 objective responses were reported (53.3%).

Pharmacokinetics

Schedule 1

Fifteen patients were evaluable for DXR and doxorubicinol, and 14 patients for VFL and DVFL PK. For VFL, a difference in mean Cl_{tot} values was suggested between the 2 dose levels of DXR (40 and 50 mg/m^2). This difference was not confirmed as all the individual values were fully overlapped by the Phase I monotherapy dataset values (Fig. 1). For DVFL, no modifications of blood concentrations were observed when compared to the dose-adjusted reference values.

PK parameters of DXR and doxorubicinol were not modified by VFL, as their values were consistent with the published data on DXR administered as a single agent [19]. For doxorubicinol the mean terminal half-life was also in line with published data [20].

Schedule 2

For VFL and DXR, a total of 15 out of 17 patients enrolled were evaluable for PK assessment. For VFL, a slight difference in mean Cl_{tot} values was suggested between the 2 dose levels of VFL (120 and 150 mg/m^2). Similarly as for schedule 1, the graphical analysis showed a full overlap between all the individual VFL clearance values compared to the reference dataset (Fig. 2). No modification was detected for DVFL and DXR/doxorubicinol, similarly as described above for schedule 1.

Discussion

The objective of this phase I study was to establish the recommended dose of VFL administered in combination with DXR. No dose escalation could be performed as the

Table 4 Treatment efficacy (best response) in ITT population

	Schedule 1 $n = 15$		Schedule 2 $n = 17$	
	Level 1 $n = 8$ (%)	Level-1 $n = 7$ (%)	Level 1 $n = 9$ (%)	Level-1 $n = 8$ (%)
Partial response	4 (50.0)	3 (42.9)	5 (55.6)	3 (37.5)
Stable disease	1 (12.5)	3 (42.9)	3 (33.3)	3 (37.5)
Progressive disease	2 (25.0)	1 (14.3)	1 (11.1)	1 (12.5)
Not evaluable	1 (12.5)	0	0	1 (12.5)

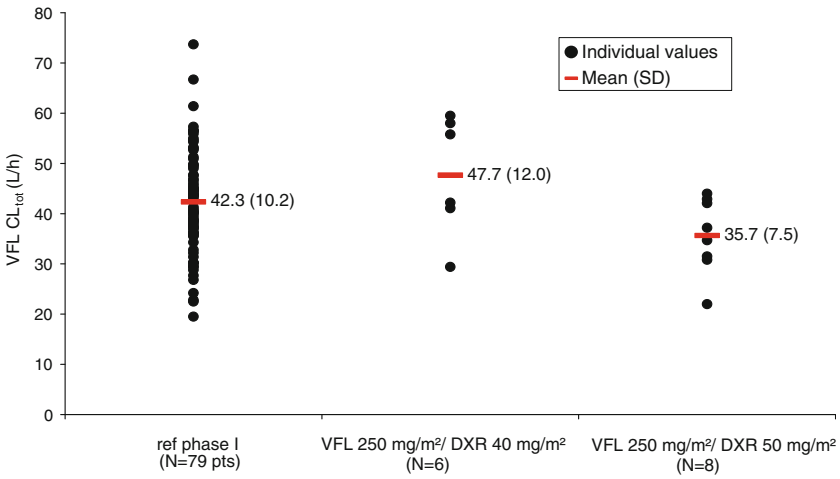

Fig. 1 Individual Cl_{tot} of vinflunine compared between dose levels and with reference dataset—Schedule 1

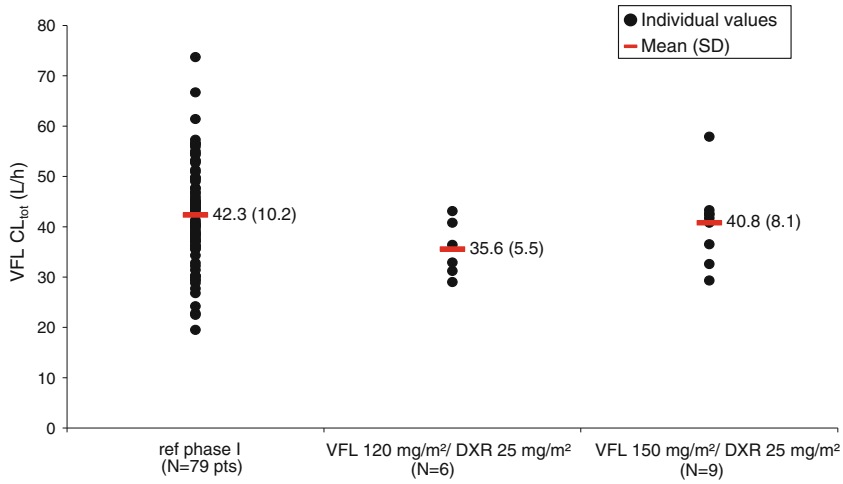

Fig. 2 Individual Cltot of vinflunine compared between dose levels and with the ref. dataset—Schedule 2

starting dose level 1 was established as the MTD. The dose limiting toxicity was neutropenia in these patients who were not receiving G-CSF as primary prophylaxis. Dividing the doses of both study drugs into two doses administered on days 1 and 8 of every 3-week cycle (schedule 2) did not improve the hematological toxicity.

The incidence of neutropenia was similar in both schedules, but a higher rate of complications was reported for schedule 2 (cycle delay, dose reduction, growth factor administration and neutropenic infection). The final recommended schedule was therefore defined as VFL 250 mg/m^2 and DXR 40 mg/m^2 on day 1 every 3 weeks.

Combination chemotherapy regimens improve antitumor response to the treatment compared to monotherapies, but increase adverse events, especially neutropenia [12]. Indeed, the association of docetaxel 75 mg/m^2 and DXR 50 mg/m^2 resulted in 97% of grade 3/4 neutropenia and 33% of FN [21]. Other well known combinations such as gemcitabine–docetaxel, capecitabine–docetaxel [22] or ixabepilone–capecitabine [23] showed, respectively 84, 79 and 68% grade 3 and 4 neutropenia.

The most frequent non-hematological adverse events were fatigue, constipation, nausea, vomiting, stomatitis and loss of appetite. At the RD, they were all mild or moderate

(grade 1 or 2), except for one patient who presented a grade 3 fatigue. No treatment discontinuation was related to the study treatment at the RD. Constipation is an issue when patients are treated with VFL [11], but the prophylactic use of laxatives efficiently prevents this inconvenience in most patients. Concerning peripheral neuropathy, which is known to be related to the spindle poisons, no grade 3 or 4 adverse event was reported. The systematic follow up of cardiac function showed a good safety profile of the combination in this population of patients where about 20% were pretreated with anthracyclines.

As common metabolic and elimination pathways were identified for both drugs [24, 25] a PK drug–drug interaction might have been suspected. In this combination study, no PK interaction was evidenced, as clearance values and/or circulating concentrations of VFL, DXR and their active metabolites were consistent with reference data of each drug administered as monotherapy. Thus the tolerance profile of the combination should only be analyzed from a pharmacodynamic point of view rather than from a PK interaction between both substances.

About 80% of the patients had visceral metastasis and $\geq$2 organs were involved in 73–82% (Table 2). The ORR were 46.7% in schedule 1 and 47.1% in schedule 2. Thus despite the unfeasibility of dose escalation, the antitumor activity of the combination of VFL–DXR was promising compared to those of the other usual combinations. The phase III study comparing gemcitabine plus docetaxel to capecitabine plus docetaxel showed ORR of 43 and 29% in the first-line population [22]. Ixabepilone associated with capecitabine achieved an ORR of 42% [23]. The interim results of liposomal DXR associated with docetaxel showed an ORR of 35% [26]. Finally paclitaxel with bevacizumab reached an ORR of 36.9% in the E2100 trial [27]. Thus even if the direct comparison of the ORR between these different studies is arguable because of differences in population selection, the antitumor activity of VFL with DXR appears interesting. Other studies assessing VFL alone or in association with gemcitabine, capecitabine and trastuzumab are ongoing in ABC.

In conclusion, the combination of VFL and DXR administered day 1 every 3 weeks is feasible and demonstrates an encouraging anti-tumor activity with manageable adverse events. With the smaller size of the primary tumors thanks to screening mammography and the efforts to avoid chemotherapy in patients with early stage endocrine sensitive tumors [28, 29], adjuvant chemotherapy will probably be used less frequently in the future. On the other hand non anthracycline chemotherapy regimens are increasingly used in the adjuvant setting [30–32]. Therefore the administration of an anthracycline combination is a valuable and interesting option in the metastatic setting. Further studies are needed to confirm the benefit of the new combination of VFL and DXR.

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