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ORIGINAL ARTICLE

Oral vinorelbine/paclitaxel combination treatment of metastatic breast cancer: a phase I study

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Abstract
Purpose Intravenous (i.v.) vinorelbine (VRL) generally given on days 1 and 8 of an every three-week cycle in combination with paclitaxel (PTX) is an effective option for the treatment of metastatic breast cancer (MBC). In an effort to improve both patient and chemotherapy unit convenience, oral VRL was used at equivalent doses of i.v. VRL.
Patients and methods The maximal tolerated dose (MTD) was determined during the first cycle of oral VRL given on days 1 and 8 or 15 and PTX infused over 3 h on day 1 every 3 weeks, maximum of 6 cycles. The dose of oral VRL was escalated from 60 to 80 mg/m^2 in 10 mg/m^2 increments. Paclitaxel was administered at 110 and then 135 mg/m^2. The combination regimen was given as first-line chemotherapy of MBC. Three to six patients per cohort were treated.
Results Twenty-two patients were treated in the first four cohorts (oral VRL/PTX): 60/110, 70/110, 80/110 and 80/135. In cohort 4, seven patients were treated, one patient being non-evaluable for MTD, three of them presented a dose-limiting toxicity (DLT) consisting of febrile neutropenia and neutropenic infection. Therefore 80/135 was the MTD. Because 36% of oral VRL administrations on day 8 were delayed to day 15 at 80/110, two additional cohorts were tested: in cohort 5, oral VRL 60 mg/m^2 on days 1 and 15 and PTX 135 mg/m^2 on day 1 and in cohort 6, oral VRL 80 mg/m^2 on days 1 and 15 and PTX 110 mg/m^2 on day 1, every 3 weeks. In cohort 5, six out of eight patients had DLTs: omission of oral VRL on day 15 for five patients, grade 4 neutropenia >7 days for another one. Therefore the recommended dose (RD) for further clinical testing was oral VRL 80 mg/m^2 on days 1 and 15 and PTX 110 mg/m^2 on day 1 of an every 3-week cycle. Two of the three evaluable patients treated at the RD had a partial response. The pharmacokinetics of VRL and PTX is being analysed and will be further presented in a separate publication.
Conclusions This phase I study has determined the doses of oral VRL and PTX to be used in combination for the benefit of the patient and of the chemotherapy unit in term of nurse's workload. The recommended regimen of oral VRL 80 mg/m^2 on days 1 and 15 and PTX 110 mg/m^2 on day 1 given every 3 weeks will be further tested in phase II.

Keywords Metastatic breast cancer · Oral vinorelbine · Paclitaxel · Phase I · Recommended dose

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Introduction

Anthracycline based regimens still represents the first-line palliative chemotherapy but the increasing use of it in the adjuvant setting led to develop non-anthracycline combination regimens to provide salvage therapy in metastatic breast cancers that have become resistant to anthracyclines or to avoid the cumulative risk of cardiomyopathy.

Taxoids and vinca-alkaloids have a solid rationale to be combined because both types poison the mitotic spindle. Paclitaxel (PTX) and vinorelbine (VRL) have both a documented anti-tumour activity as single agent. They have no cross-resistance with anthracyclines. In combination, these new agents can generate significant toxic symptoms. Specific phase I studies were thus needed to determine the optimal dose and dosage schedule to be used in metastatic breast cancer (MBC) patients.

The development of an oral form opened new vistas for the practical management of VRL therapy. Indeed the oral form spares the patients the drawback of i.v. infusions and the psychological trauma of repeated exposure to the cancer ward environment. It may thus contribute to improve patient convenience. Even when administered in the hospital chemotherapy unit, oral forms are of easier management and save nursing time. The bio-availability of oral VRL is about 40% which indicated that the dose equivalence is between 30 mg/m^2 i.v. and 80 mg/m^2 oral, and between 25 mg/m^2 i.v. and 60 mg/m^2 oral treatments [1–3]. Furthermore, inter-patient variability in drug exposure has proved to be in the same order (38%) with the oral form as with i.v. infusion.

In view of the anti-tumour activity and generally good tolerance of VRL and PTX when used as single agents, it appeared desirable to evaluate the two compounds in combination. The combination of i.v. VRL and PTX is one of the active combinations used in the treatment of advanced breast cancer. In the first line metastatic setting, an interesting efficacy with a response rate of 60–67% [4, 5] was reported.

This phase I study was primarily designed to determine the doses of the two compounds and the dosing schedule to be recommended for subsequent phase II studies and to determine the dose-limiting toxicities of oral VRL and PTX when combined. Evaluation of the pharmacokinetic interaction between the two compounds and of the anti-tumour activity of the combination was secondary objectives of the trial.

Results of the pharmacokinetic evaluation will be presented separately.

Patients and methods

Patient selection

The criteria for enrolment in the trial included histologically or cytologically proven breast cancer at first diagnosis, evidence of progressive metastatic disease, age between 18 and 75, karnofsky performance status $\geq$70, life expectancy $\geq$12 weeks, adequate bone marrow, hepatic and renal functions characterized as follows: neutrophils $\geq 2.0 \times 10^9$ per l, platelets $\geq 100 \times 10^9$ per l, haemoglobin $\geq$10 g/dl or 6.2 mmol/l, total bilirubin $\leq 1.25 \times$ ULN, transaminases (ALAT, ASAT) $\leq$1.5 ULN, and serum creatinine $\leq 1.5 \times$ ULN.

For evaluation of anti-tumor efficacy, the patients had to present with at least one bidimensionally measurable target lesion, by World Health Organization criteria, measured by appropriate imaging procedures within 21 days prior to entry into the study.

Regarding previous cancer therapy, surgery had to have taken place 2 weeks or more prior to entry into the study, while hormonal therapy could be continued until study entry but had been discontinued then.

If the patient had received any adjuvant or neo-adjuvant chemotherapy, 12 months or more should have elapsed since the end of that therapy. To be eligible, patients must have not received palliative chemotherapy for metastatic breast cancer. Radiation therapy was allowed been given provided it did not affect the proposed measurable lesion(s) and was stopped at least 4 weeks prior to study entry.

Exclusion criteria included prior adjuvant chemotherapy with vinca derivatives or taxanes, concurrent treatment with any other cancer chemotherapy, participation in any other clinical trial within 30 days prior to study screening, poorly controlled medical disorder (diabetes, hypertension, infection), clinical signs of CNS disorder and brain or leptomeningeal metastasis.

Dose levels and escalation scheme

Study drugs were given in 3-week cycles with oral VRL given on day 1 and 8 or 15 and i.v. administration of PTX on day 1. The doses of PTX were 110 and 135 and the doses of oral VRL 60, 70 and 80 mg/m^2. Three to six patients were to be enrolled per dose level. If one out of the three patients at one dose level experienced a dose-limiting toxicity (DLT) three more patients had to be entered at the same dose level.

The DLT, to be determined in the first treatment cycle, was defined in the protocol as follows:

- Development of grade 4 neutropenia lasting for 7 days or more,
- Febrile neutropenia (single elevation in oral temperature to 38.5°C or three elevations to >38°C during a 24 h period concomitant with grade 4 neutropenia, according to Pizzo's definition [6],
- Neutropenic infection defined as grade 3 or 4 infection concomitant with grade ≥3 neutropenia,
- grade 3 thrombocytopenia,
- Any grade ≥3 non-haematological toxicity other than asthenia, inadequately treated nausea, vomiting or diarrhoea,
- Delays in oral VRL administration beyond day 15 of cycle 1 or delay of 1 week or more in the day 1 administration of cycle 2.

The maximum tolerated dose (MTD) was the dose level at which ≥50% of patients developed a DLT during the first cycle. The recommended dose (RD) was the dose level below the MTD.

Drug administration

Pierre Fabre Médicament (France), represented by Institut de Recherche Pierre Fabre supplied oral VRL (NVB® oral) to the investigational centre as softgel capsules of two different strengths 20 and 30 mg and PTX (Taxol®) as single dose vials (100 mg/16.7 ml). The softgel capsules of VRL had to be rapidly swallowed, without chewing or sucking them, in the presence of a physician or a nurse of the department.

Oral VRL was given on days 1 and 8 or 15 and PTX infused over 3 h on day 1 every 3 weeks. Prophylactic medication regimen was mandatory prior to administration of PTX in order to prevent hypersensitivity reactions. This regimen consisted of a corticosteroid, diphenhydramine or its equivalent, and an H_2 antagonist.

Each patient was expected to receive a maximum of six cycles, unless documented disease progression, unacceptable toxicity or patient refusal called for discontinuation of the treatment. Dose adjustments and treatment delays were allowed in case of severe haematological or non-haematological toxicities. If the time interval between two day 1 administrations were to exceed 5 weeks, the patient was considered as off study, unless some clinical benefit was evident. Similarly, if treatment with one study drug had to be stopped because of toxicity, the patient was withdrawn from the study.

The patients were to receive full supportive care (analgesics, antibiotics, transfusion of blood products, stool softeners, etc), as required by their clinical condition. Anti-emetic prophylaxis with oral 5-HT3 antagonists was recommended before each oral VRL intake. No prophylaxis with colony-stimulating factor (CSF) was allowed during the first treatment cycle but CSF could be administered in later cycles in case of febrile neutropenia or neutropenic infection. Palliative radiation therapy was allowed when needed to alleviate spinal cord compression or offset the risk of imminent fracture provided it concerned less than 10% of the bone marrow reserve and spared the evaluable or measurable lesion.

Clinical staging was performed for all patients and included complete history and physical examination with tumour measurement. Complete blood cell counts were performed within a 2-week period prior to study entry on days 1 and 8 or 15 at the first cycle, then before each administration of oral VRL for the subsequent cycles. Biochemical profile was performed prior to treatment and then before each treatment cycle. An electrocardiogram was also required before starting treatment. To be evaluable for safety analysis, patient had to receive at least one administration of study drugs. Adverse events were graded according to NCI common toxicity version 2.0, except febrile neutropenia for which Pizzo's definition was used [6].

Evaluation at study entry included physical examination, chest-ray completed by chest CT scan if lung metastases, liver ultrasound completed by abdominal CT scan if liver metastases and bone scintigraphy.

Thereafter patients were followed every 3 months until death. World Health Organization [7] criteria with the modifications suggested by the European Organization for Research and Treatment of Cancer [8] were used to define response. Response rate was the primary efficacy variable. All registered patients were included in the efficacy analysis (intent-to-treat analysis). Patients evaluable for efficacy were defined as those who remained in the study until completion of the first evaluation (after first two cycles) as required by protocol and whose baseline lesions were all assessed with the same method of measurement throughout the study period. An independent radiologist validated all responses.

Results

Patient characteristics

Thirty-four patients, recruited by four centers in Poland, France and Germany, were enrolled and 33 were treated in this study between December 2000 and July 2002. All of them had signed an informed consent

form before their registration and the initiation of study specific procedures. They ranged in age from 38 to 67 years (median 48 years). The karnofsky performance status was 100 for 24 patients (72.7%), 90 for 5 of them and 80 for 4 of them.

For half of the patients (48.5%), more than 2 years had elapsed between original diagnosis and relapse. The majority of patients (84.8%) had been treated by loco-regional surgery and 22 of them (66.7%) had received adjuvant chemotherapy, which contained anthracycline for 16 of them. Prior treatments also included hormone therapy (in 42.4% of the patients) and radiation therapy (in 69.7%). The most frequent sites of metastases were liver (57.6%), bone (54.5%), lymph nodes (45.5%) and lung (33.3%).

Dose levels MTD and recommended dose

Six dose levels and dosing schedules were tested. No patient was moved from one dose level to another. Thirty-three patients were treated in total and 32 were evaluable for the MTD determination. One patient was not evaluable for MTD determination because of under dosage of oral VRL at dose level IV and was replaced.

The patient distribution is described in Table 1. At the initial dose levels tested (levels I, II and III) PTX was given at the same dose of 110 mg/m^2 while VRL was escalated from 60 to 80 mg/m^2 by increments of 10 mg/m^2. Those three dose levels generated no DLT, which led the investigators to increase the dose of PTX to 135 mg/m^2 at which three out of six patients reported DLT during the first 3-week cycle.

Dose-limiting toxicities reported during the first cycle are depicted in Table 2. Of note, none of the patients but one treated at dose levels III and V received the planned dose of oral VRL at C1D8. Instead, they received oral VRL on C1D15 whenever it was possible, which corresponded in terms of dose and schedule to the dose level IIIbis and Vbis, respectively. Therefore DLT, baseline characteristics and safety data were pooled for dose levels III and IIIbis and for dose levels V and Vbis, respectively.

Out of six evaluable patients for MTD at dose level I, two presented with a DLT: (neutropenic infection and febrile neutropenia).

One patient out of three treated at dose level II presented DLT: oral VRL could not be given on day 15.

Among the nine evaluable patients at dose level III + IIIbis, four patients could not be administered oral VRL on day 8 and 15 because of neutropenia.

At dose level IV, among the six evaluable patients, one patient could not receive day 15 oral VRL dosing because of non-complicated neutropenia, two patients presented neutropenic infection and one presented febrile neutropenia.

Finally, at dose level V + Vbis, among the eight evaluable patients, one patient presented a grade 4 neutropenia lasting 7 days, and five patients could not be given oral VRL on day 15 because of non-complicated neutropenia.

As a result, dose levels IV and V + Vbis represented maximal tolerated dose.

The RD was established at the dose level IIIbis that combined oral VRL given at 80 mg/m^2 on day 1 and day 15 and PTX 110 mg/m^2 on day 1 every 3 weeks.

Table 1 Patient distribution

Dose level	I	II	III	IV	V	IIIbis	Vbis	All
Oral VRL/PTX doses	60/110	70/110	80/110	80/135	60/135	80/110	60/135	
Schedule	D1–D8	D1–D8	D1–D8	D1–D8	D1–D8	D1–D15	D1–D15	
Number of treated patients	6	3	6	7	6	3	2	33

Table 2 Dose-limiting toxicities during the first cycle

Dose level	I	II	III + IIIbis	IV	V + Vbis	All
Dose oral VRL/PTX	60/110	70/110	80/110	80/135	60/135	
Number of treated patients	6	3	9	7	8	33
Number of patients evaluable for MTD	6	3	9	6	8	32
Number of patients with at least one DLT	2	1	4	4	6	17
Detail of DLTs						
G4 neutropenia ≥ 7 days	–	–	–	–	1	1
Febrile neutropenia	1	–	–	1	–	2
Neutropenic infection	1	–	–	2	–	3
D15 cancelled for haematotoxicity	–	1	4	1	5	11
MTD	No	No	No	Yes	Yes	

Safety

Tables 3 and 4 show the frequency of the main adverse events. Dose-limiting toxicity was neutropenia that was complicated in two patients at level I, one patient at level II, three patients at level III + IIIbis and four patients at level V + Vbis. At the RD (level III + IIIbis) three out of nine patients reported febrile neutropenia and no neutropenic infection occurred. The incidence by cycle of grade 3–4 neutropenia was 63.8%.

Non-haematological drug-related toxicities were rarely severe and remained easily manageable. They consisted in alopecia (overall incidence 88%) nausea (72.7%) and fatigue (69.7%), stomatitis (36.4%), diarrhoea (24.2%), vomiting (45.5%), myalgia (39.4%) neuropathy neurosensory (33.3%). Only for fatigue and stomatitis, grade 3 events were reported.

There was no grade 4 non-haematological related toxicity. No toxic death was reported. Grade 3 toxicities included stomatitis and anxiety in one patient each at dose level I, myalgia for one patient in level III + IIIbis, fatigue at level IV for one patient and fatigue and diarrhoea in one patient each at level V + Vbis.

Anti-tumor activity

Twenty-seven patients were evaluable for the anti-tumor activity. Two patients did not present with bidimensionnally lesion at study entry, while in two patients, measurable lesions were only evaluated by physical examination.

As illustrated in Table 5, at the various dose levels tested, 12 partial responses (PR) by WHO criteria, were obtained in the 27 evaluable patients (RR 44.4%), including four partial responses at the RD level (III + IIIbis).

Discussion

The majority of patients received combination chemotherapy regimen as first line chemotherapy of metastatic breast cancer. The standard practice has been to combine agents with different mechanisms of action with the expectation that short-term and cumulative dose-limiting toxicities will not be additive and that no cross-resistance will develop. In view of the encouraging clinical results obtained, independently, with the taxanes and with VRL when used in monotherapy,

Table 3 Worst drug-related haematological toxicity (NCI/CTC) by cycle

Dose levels	I	II	III + IIIbis	IV	V + Vbis
Dose oral VRL/PTX	60/110	70/110	80/110	80/135	60/135
Nb of evaluable cycles	23	14	47	34	39
Grade 3 neutropenia (%)	4 (17.4)	4 (28.6)	7 (14.9)	10 (29.4)	4 (10.3)
Grade 4 neutropenia (%)	6 (26.1)	4 (28.6)	23 (48.9)	13 (38.2)	17 (43.6)
Febrile neutropenia (%)	1 (4.3)	–	5 (10.6)	2 (5.9)	–
Neutropenic infection (%)	1 (4.3)	2 (14.3)	–	2 (5.9)	–

Table 4 Main worst drug related non-haematological toxicity (NCI/CTC) by cycle

Dose levels	I		II		III + IIIbis		IV		V + Vbis	
Nb of evaluable cycles	23		14		47		34		39	
Grade	Overall N (%)	3 N (%)	Overall N (%)	3 N (%)	Overall N (%)	3 N (%)	Overall N (%)	3 N (%)	Overall N (%)	3 N (%)
Gastrointestinal										
Nausea	5 (21.7)	–	3 (21.4)	–	14 (29.8)	–	18 (52.9)	–	9 (23.1)	–
Vomiting	4 (17.4)	–	3 (21.4)	–	6 (12.8)	–	9 (26.5)	–	2 (5.1)	–
Diarrhoea	–	–	1 (7.1)	–	2 (4.3)	–	6 (17.6)	–	2 (5.1)	1 (2.6)
Anorexia	1 (4.3)	–	–	–	–	–	4 (11.8)	–	1 (2.6)	–
Stomatitis	3 (13.0)	1 (4.3)	2 (14.3)	–	5 (10.6)	–	4 (11.8)	–	3 (7.7)	–
Constipation	–	–	1 (7.1)	–	1 (2.1)	–	2 (5.9)	–	3 (7.7)	–
Neurological										
Neurosensory	2 (8.7)	–	2 (14.3)	–	9 (19.1)	–	11 (32.4)	–	4 (10.2)	–
Constitutional										
Fatigue	5 (21.7)	–	5 (35.7)	–	9 (19.1)	–	14 (41.2)	1 (2.9)	17 (43.6)	1 (2.6)
Weight loss	1 (4.3)	–	–	–	–	–	–	–	1 (2.6)	–
Allergy										
Hypersensitivity	–	–	–	–	2 (4.3)	–	–	–	–	–

Table 5 Best overall response-evaluable population

Dose level	I	II	III + IIIbis	IV	V + Vbis
Dose oral VRL/PTX	60/110	70/110	80/110	80/135	60/135
Number of treated patients	6	3	9	7	8
Number of evaluable patients	4	2	8	6	7
PR	2	–	4	3	3
NC	–	–	3	1	3
PD	2	2	1	2	1

attempts have been made to combine the two drugs. The fact that both share the same target, the tubulin–microtubule system, was not a major objection since vinca alkaloids are known to inhibit tubulin polymerization whereas the taxanes inhibit microtubule depolymerization in vitro experiments indicated a synergistic effect of these two drugs when administered concurrently [9].

As with all such combinations, optimal dosing schedules and dose levels had to be determined before phase II and phase III clinical studies could be started. This study is the first attempt to define recommended doses of oral VRL combined with PTX in the palliative treatment of metastatic breast cancer. Earlier phase I studies with the same objective had been reported but using a fully i.v. regimen.

Tortoriello et al. [10] have run a study on 34 MBC patients treated once every 21 days with a fixed dose of 30 mg/m^2 i.v. VRL, and PTX started at 90 mg/m^2 subsequently escalated up to 240 mg/m^2. Their recommended doses for the phase II were VRL 30 mg/m^2 and PTX 210 mg/m^2, however, it is worth noting that neurotoxicity was the DLT and haematological toxicity led them to systematically add G-CSF from dose level 150 mg/m^2, which means that without G-CSF support the RD of PTX could not exceed 120 mg/m^2. In our study neurotoxicity was not significant, however, this may be due to the fact that the dose of PTX was less than that used in other studies of this combination.

Ibrahim et al. [11] entered 38 patients on a similar study of i.v. VRL and PTX administered simultaneously over 3 h and repeated every 21 days for MBC to determine the MTD and whether the addition of G-CSF would allow administration of higher doses of the combination. Twenty-five patients (group 1) were treated with VRL ranging from 25 to 36 mg/m^2 and with PTX ranging from 150 to 175 mg/m^2 without prophylactic G-CSF. Thirteen patients (group 2) were treated with VRL ranging from 25 to 46 mg/m^2 with PTX at 150 mg/m^2 with G-CSF support. Their RD for this combination without G-CSF was 25 mg/m^2 of VRL and 150 mg/m^2 of PTX. The figures for the recommended doses coming out of these studies largely match those obtained in our study if one keeps in mind the difference in dosing of VRL and in schedule (no day 8 or day 15 dose of VRL).

Phase II studies of the PTX/VRL combination in metastatic breast cancer, using various doses and dose schedules, appears highly active in terms of tumor response as shown in Table 6.

Vici et al. [12], Martin et al. [4] and Polyzos et al. [13], administered one dose of VRL every 3 weeks, while Cocconi et al. [14] and Spano et al. [15] gave VRL on day 1 and at the end of 96 h PTX infusion, or on day 15, respectively.

In all cases leukopenia and particularly neutropenia appear as the main dose-limiting toxicities, with occasional complications such as neutropenic fever and neutropenic infection. The incidence and severity of neurotoxicity was manageable for the PTX/i.v. VRL combination in clinical practice.

Results of the present study are consistent with the prior clinical experience with the fully i.v. regimen. Neutropenia was the main DLT and led to postpone

Table 6 Intravenous vinorelbine/paclitaxel q3 phase II

Reference	Line	VRL Every 3 weeks	PTX	G-CSF	Included/evaluable pts	RR	95% CI	Median OS (months)
Vici et al. [12]	1	25 mg/m^2 d1	150 mg/m^2 d1	Systematically for 10 pts	43/41	49%	(34–64)	22
Martin et al. [4]	1, 2, 3	30 mg/m^2 d1	135 d1	Not available	56	46%	(33–60)	–
Polyzos et al. [13]	2	30 mg/m^2 d1	175 mg/m^2 d1	Systematically	34	32%	(16.3–47.7)	8
Cocconi et al. [14]	≥2	15 mg/m^2 d1, d5	90 mg/m^2 d1–d5	Not available	27	52%	(42–62)	11.7
Spano et al. [15]	2	20 mg/m^2 d1, d15	175 mg/m^2 d1	65.5%	26	48%	(35–61)	11.8

the administration of oral VRL from day 8 to day 15. The response rate of 44% falls in the expected range.

The oral formulation of VRL offers a definite plus for the practical management of this combination therapy for the patient, by avoiding venous administration on day 15 reducing time spent in hospital, and for the unit of care, decreases preparation and administration time.

Reported results determined the RD and schedule which will be further explored in terms of efficacy and safety: oral VRL 80 mg/m^2 D1-D15 and PTX 110 mg/m^2 D1 every 3 weeks in phase II study.

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