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ORIGINAL ARTICLE

Vinorelbine/docetaxel combination treatment of metastatic breast cancer: a phase I study

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Abstract
Purpose The aim of this study was to investigate the combination of vinorelbine (VRL) alternating intravenous (i.v.) and oral in combination with docetaxel (DCT) as first-line chemotherapy of patients with metastatic breast cancer.
Patients and methods Tested doses were 60 or 70 mg m^{-2} given on day 1 for DCT, 20 to 25 mg m^{-2} for i.v. VRL on day 1, 60 mg m^{-2} on day 8 or day 15 for oral VRL. Day 1 was administered every 3 weeks. Three to six patients were treated per dose level.
Results The median age of the 30 treated patients was 60 years. Four patients were non evaluable for the maximum tolerated dose (MTD) and were replaced. Reported dose-limiting toxicities were 11 omissions of oral VRL for neutropenia, two cases of febrile neutropenia and two grade 4 neutropenia $\geq$7 days. Dose levels using DCT doses >60 mg m^{-2} and/or i.v. VRL doses >20 mg m^{-2} met the criteria for MTD. Most frequent toxicities were febrile neutropenia in seven patients and neutropenic infection in four patients (one fatal). Therefore, the recommended schedule was established at i.v. VRL 20 mg m^{-2} with DCT 60 mg m^{-2} on day 1 and oral VRL 60 mg m^{-2} given on day 15 every 3 weeks. At this recommended schedule, only one of six patients experienced febrile neutropenia. Among 22 patients evaluable for tumour response, 2 complete and 10 partial responses were reported. Pharmacokinetics of combined VRL and DCT demonstrated the absence of mutual interaction.
Conclusions This phase I study established the recommended doses and schedules of the combination alternating i.v. and oral VRL with DCT, this recommended regimen being further explored in a phase II study.

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

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Introduction

Even with optimal medical management, a high proportion of breast cancer patients diagnosed with an early malignancy eventually develop metastatic disease, which remains incurable. Palliative therapy is

thus the only option left, the objectives of which are the palliation of symptoms and if possible the prolongation of survival and improvement in quality of life.

Anthracycline based regimens still represent the most often prescribed in metastatic breast cancer (MBC), but cumulative doses carry a serious risk of cardiomyopathies and, even in case of tumour response, anthracycline resistance eventually develops in all patients. New cytotoxic agents are being tested to try to provide salvage therapy in MBC patients that have become resistant to anthracyclines.

Among new available agents widely tested in the last decade, taxanes (paclitaxel, docetaxel) and vinorelbine (VRL) were given particular attention both because of high response rates obtained in most studies and lack of cross-resistance with anthracyclines. Specific phase I studies were needed to determine the optimal doses and dosage schedules to be used with limited toxic symptoms.

Four first-line chemotherapy studies with docetaxel (DCT) on a total of 209 patients with MBC who had undergone adjuvant therapy [1–4] gave favourable results in comparison with other agents. Docetaxel was given at doses of 75 mg m^{-2} ($n = 55$) or 100 mg m^{-2} ($n = 154$) and response rates of 40–52 and 56–67% were recorded, respectively.

When used as a single agent, by intravenous (i.v.) route, at doses of 25–30 mg m^{-2}, every 3 weeks, response rates with vinorelbine in advanced breast cancer from 35 to 50% and reversible neutropenia was the major manageable dose-limiting toxicity (DLT) [5–12].

Compared with i.v. vinorelbine, the oral form spares patients psychological trauma of repeated exposure to the cancer ward environment and may thus contribute to improve patient compliance and eventually efficacy of treatment. A switch from an intravenous to an oral form had already been carried out using a powerful crossover study design [13] and had demonstrated bio equivalent blood AUCs between 60–80 mg m^{-2} oral and 25–30 mg m^{-2} i.v. vinorelbine.

In view of the good balance between efficacy and safety both for vinorelbine and docetaxel when used as single agents, it appeared desirable to evaluate the two compounds in combination. Pre-clinical studies had shown that superior activity could be obtained with that combination.

In tumour bearing mice, vinorelbine plus docetaxel combination resulted in a therapeutic synergism and authors indicated that 80–100% of the optimal dose of each agent could be administered without increasing the toxicity to vital normal cells [14]. Fumoleau et al. [15] reported an encouraging response rate of 67% (18 of 27 evaluable patients) in phase I trial which explored i.v. vinorelbine given at 20 or 22.5 mg m^{-2} on days 1 and 5 and docetaxel at doses ranging from 60 to 100 mg m^{-2} on day 1 every 3 weeks. Moreover the pharmacokinetic profiles of both drugs were unaffected and the docetaxel clearance estimate was stable over the dose range explored [16].

Optimal doses and dosing schedules of vinorelbine and docetaxel when combined had first to be determined in a phase I study. Second objectives were to determine DLTs, but also the anti-tumour activity of the combination, and the potential pharmacokinetic interaction between the two compounds. In order to take advantage of the availability of the oral form of vinorelbine, the option was to administer vinorelbine by i.v. infusion when docetaxel had to be given intravenously and orally when docetaxel was not given.

Patients and methods

Ethics

Independent ethics committees according to local requirements prior to the start of the study approved the protocol and its amendments. In addition, this trial was conducted in accordance with the ethical principals set forth in the declaration of Helsinki (Edimburgh, 2000) and good clinical practice. Written informed consent was obtained from each participating patient prior to study entry.

Patient selection

The criteria for enrolment in the trial included histological or cytological proven breast cancer at first diagnosis, evidence of progressive metastatic disease, age between 18 and 70, Karnofsky performance status $\geq$70%, life expectancy $\geq$12 weeks, adequate bone marrow, hepatic and renal functions characterized as follows: neutrophils $\geq 2.0 \times 10^9\ l^{-1}$, platelets $\geq 100 \times 10^9\ l^{-1}$, haemoglobin $\geq$10 g dl^{-1} or 6.2 mmol l^{-1}, total bilirubin $\leq$ ULN (according to each centre), transaminases (ALAT, ASAT) $\leq$2.5 ULN, alkaline phosphatase $\leq 5 \times$ ULN and serum creatinine $\leq 1.5 \times$ ULN.

Complete blood counts (including differential and platelet count) were to be assessed every cycle on days 1, and 8 or 15 within 24 h prior to dosing and at the end of the study (during the first cycle, complete blood counts were requested on days 10 and 12). In case of delay in drug administration, blood counts had to be repeated on the scheduled day for drug administration.

For evaluation of anti-tumour efficacy, the patients had to present with at least one bidimensionally

measurable target lesion, by WHO criteria, measured by appropriate imaging procedures within 21 days prior to study entry.

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

Radiation therapy might have been given provided it did not affect the proposed measurable lesion(s) and was stopped at least 4 weeks prior to study entry.

Non-inclusion 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), active CNS disorder and brain or leptomenigeal metastasis.

Dose levels and escalation scheme

Study drugs were given in 3-week cycles with i.v. administration of docetaxel and vinorelbine on day 1 and oral administration of vinorelbine capsules on day 8 or day 15. The doses of docetaxel were 60 or 70 mg m^{-2}, those of i.v. vinorelbine ranged from 20 to 25 mg m^{-2} and the dose of oral vinorelbine was fixed at 60 mg m^{-2} for all dose levels and for the two schedules (i.v. vinorelbine on day 1 and oral vinorelbine on day 8 or i.v. vinorelbine on day 1 and oral vinorelbine on day 15).

Three patients had to be enrolled per dose level. If one out of the three patients at one dose level experienced a DLT, three more patients had to be treated.

Dose-limiting toxicity, to be determined in the first treatment cycle, were defined as follows:

- Development of grade 4 neutropenia lasting 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 [17],
- Neutropenic infection defined as grade 3 or 4 infection concomitant with grade $\geq$ 3 neutropenia,
- Grade 3 thrombocytopenia,
- Any grade $\geq$ 3 non-haematological toxicity other than alopecia, asthenia, inadequately treated nausea, vomiting or diarrhea,
- Cancellation of oral vinorelbine administration on day 15 of cycle 1 or delay of 1 week or more in the day 1 treatment of cycle 2 due to haematological reason.

The maximum tolerated doses (MTD) were the doses at which $\geq$50% of patients developed a DLT during the first cycle. The recommended dose was the dose level below the MTD.

Drug administration

On day 1 of each cycle, i.v. vinorelbine was first to be injected during a 6–10 min infusion. The injection of docetaxel started immediately thereafter and lasted one hour. On day 8 or day 15, depending on the dosing schedule, oral vinorelbine was delivered in the form of softgel capsules to be swallowed, with some food to reduce risks of vomiting, under the visual control of nursing personnel to assure compliance.

Each patient was expected to receive a maximum of six cycles, unless documented disease progression, unacceptable toxicity or patient refusal. Because no survival benefit has been demonstrated when comparing long versus short duration of chemotherapy [18, 19], the study protocol set a maximum of 6 cycles. 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.

Patients had to receive full supportive care as required by their clinical condition. Anti-emetic prophylaxis with oral 5-HT3 antagonists was specifically recommended before each oral vinorelbine intake. No prophylaxis with colony-stimulating factor (CSF) was allowed during the first treatment cycle but according to institutions rules secondary prophylaxis with CSF could be given 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 lesions.

Pharmacokinetics of both vinorelbine and docetaxel were assessed during the first cycle. Because CYP3A4 is largely involved in the metabolism of both drugs, substrate competition might occur resulting in a drug-drug interaction that is likely to increase blood concentrations of either one or both drugs. Due to the study design, vinorelbine pharmacokinetic was assessed at day 1 (vinorelbine + docetaxel combined) and day 15 (vinorelbine alone) while docetaxel pharmacokinetic was assessed only at day 1 (when combined). Pharmacokinetic data

were obtained on a total of 19 patients (no data available at the first dose level explored: vinorelbine 25 mg m^{-2} i.v. day 1 and 60 mg m^{-2} oral day 8 and docetaxel 60 mg m^{-2} i.v. day 1).

For vinorelbine, 5 and 4 blood samples were collected on day 1 and day 15, respectively. Pre-dose, end of infusion, 1, 6, 24 h after start of infusion for the i.v. dosing and pre-dose, 1.5, 3, 24 h after intake for the oral dosing. Vinorelbine blood concentrations were measured by LC-MS/MS method.

For docetaxel, 5 blood samples were drawn on day 1: pre-dose, end of infusion and 2, 6, 24 h after start of infusion. Plasma docetaxel concentrations were measured by HPLC method with UV detection.

Docetaxel

According to the limited sampling strategy used for docetaxel, Cl_{tot} was calculated by a Bayesian approach through a population pharmacokinetic model for docetaxel [20] using NONMEM program. Cl_{tot} of docetaxel was compared to data of literature.

Vinorelbine

At first, the Bayesian pharmacokinetic parameters of vinorelbine obtained using the population pharmacokinetic model previously described [21, 22]. Pharmacokinetic parameters of vinorelbine combined with docetaxel on day 1 were compared between docetaxel dose levels by one-way analysis of variance. The analysis was conducted on Cl_{tot} and $T_{½z}$.

The potential effect of docetaxel co-administration on the pharmacokinetics of vinorelbine was evaluated by comparison between exposure to vinorelbine (AUC_{inf}) when associated to docetaxel on day 1, and exposure to oral vinorelbine when administered alone on day 15.

The latter was considered as the reference for this evaluation. For this comparison, individual AUC_{inf} after i.v. dosing on day 1 were normalized to 25 mg m^{-2}, which was demonstrated to provide equivalent exposure to oral vinorelbine administered at 60 mg m^{-2} [13]. The statistical analysis consisted in a paired *t*-test comparison on log-transformed data.

Results

Patient characteristics

Thirty patients, recruited by four centres in Poland and France, were enrolled in this study between November 2000 and May 2003. They ranged in age from 34 to 70 years (median 60 years). The Karnofsky performance status was 100% for 15 patients, 90% for 3 of them, 80% for 11 of them and 70% for a single patient.

For most patients (70%), more than 2 years had elapsed between original diagnosis and relapse. Fourteen of them (46.7%) had received adjuvant chemotherapy, consisting of anthracyclines for 11 of them. Prior treatments also included hormonotherapy (63.3% of the patients) and radiation therapy (43.3%). The most frequent sites of metastases were lymph nodes (56.7%), bone and lung (33.3% each) and liver (30%). Visceral involvement was documented in 73% of patients.

Six dose levels and dosing schedules were tested. No patient was moved from one dose level to another. Four patients were not evaluable for MTD determination and were replaced. The reasons were: one patient was underdosed, while three others received G-CSF during first cycle.

Eighteen patients (60%) received the 6 cycles of combination therapy scheduled in the protocol. One patient was discontinued for intercurrent event (hip surgery) and eight for progressive disease. Another patient died after having received 2 cycles: she developed a septic shock secondary to neutropenic infection and died the following day despite antibiotic and cardiotonic treatment. The last two patients were withdrawn from study due to excessive toxicity after having received 5 cycles: one patient experienced a grade 2 increase of bilirubin and the other had grade 3 neuromotor toxicity.

Dose levels and dose intensity

The exposure to vinorelbine and docetaxel—and the degree of toxicity—varied from one dose level to the other, as expected (Table 1). Table 2 summarizes DLT per dose level. The median relative dose intensities of intravenous vinorelbine and docetaxel were above 90% without obvious difference between dose levels. However a secondary prophylaxis with growth factors was permitted and might explain high dose intensities observed at all dose levels. The median relative dose intensity of oral vinorelbine ranged from 32.8 to 93.5%. This wide range could be explained by frequent dosing cancellation on day 8 and/or day 15 administrations secondary to neutropenia in most instances.

At initial dose levels 1 and 2 (i.v.: 25 mg m^{-2} at day 1 and oral 60 mg m^{-2} at day 8) docetaxel raised from 60 to 70 mg m^{-2}, these two dose levels generated severe neutropenia meeting the criteria of DLTs during the first 3-week cycle. Other combinations were thus tested

Table 1 Drug exposure and overall safety results

Dose level		1	1bis	2	**3**	4	5
Dose i.v. VRL/oral VRL/DCT		25/60/60	25/60/60	25/60/70	**20/60/60**	22.5/60/60	20/60/70
Schedule		day 1–day 8	day 1–day 15	day 1–day 8	**day 1–day 15**	day 1–day 15	day 1–day 15
Number of patients		3	3	8	**6**	3	7
Number of cycles		16	14	36	**30**	14	34
Median relative dose intensity (%)							
i.v. vinorelbine		92	99.3	98.4	**99**	99.7	97.8
Oral vinorelbine		78.2	32.8	66.4	**79.1**	85.4	93.5
Docetaxel		91	92.9	97.1	**99.5**	100.1	99.6
Incidence							
Grade ¾ neutropenia	By patients	3	3	8	**5**	3	7
	By cycle	13 (81.3%)	10 (71.4%)	32 (88.9%)	**15 (50.0%)**	6 (42.8%)	10 (29.4%)
Febrile neutropenia	By patients	–	2	3	**1**	1	–
	By cycle	–	2 (14.3%)	7 (19.4%)	**1 (3.3%)**	1 (7.1%)	–
Neutropenic infection	By patients	1	1	1	**–**	1	–
	By cycle	1 (6.3%)	1 (7.1%)	1 (2.8%)	**–**	1 (7.1%)	–
Grade ¾ stomatitis	By patients	–	–	1	**1**	1	–
	By cycle	–	–	1 (2.8%)	**1 (3.3%)**	1 (7.1%)	–
Grade ¾ vomiting	By patients	–	–	1	**1**	1	–
	By cycle	–	–	1 (2.8%)	**1 (3.3%)**	1 (7.1%)	–
Grade ¾ peripheral neuropathy	By patients	–	–	–	**–**	–	1
	By cycle	–	–	–	**–**	–	1 (2.9%)

Table 2 Dose-limiting toxicities during the first cycle

Dose level	1	1bis	2	**3**	4	5	All
Dose i.v. VRL/oral VRL/DCT	25/60/60	25/60/60	25/60/70	**20/60/60**	22.5/60/60	20/60/70	
Schedule	day 1–day 8	day 1–day 15	day 1–day 8	**day 1–day 15**	day 1–day 15	day 1–day 15	
Number of treated patients	3	3	8	**6**	3	7	30
Number of patients evaluable for MTD	2[a]	3	6	**6**	3	6	26
Number of patients with at least one DLT	1	2	5	**2**	2	3	15
Detail of DLTs[b]							
G4 neutropenia ≥ 7 days	1	1	–	**–**	–	2	4
Febrile neutropenia	–	1	2	**–**	1	–	4
Day 8–day 15 cancellation for haematotoxicity	1	2	3	**2**	2	1	11
MTD	NE	Yes	Yes	**No**	Yes	Yes	

[a] One patient could not be replaced

[b] The same patient could present with several DLT

with a day 1–day 15 schedule (dose level 1bis) plus an increase of either vinorelbine (dose level 4) or docetaxel (dose level 5), ending up to failure due to overly high toxicity.

Dose level 3 was a good compromise between good relative dose intensity and toxicity. Consequently, it was eventually designated as the recommended dose.

Safety

Table 1 summarizes also the overall safety results. The main toxicity was neutropenia, which was complicated (febrile neutropenia or neutropenic infection) in three patients at level 2, two patients at level 1bis and one patient at levels 1, 3 and 4. Note that three patients experienced several episodes of complicated neutropenia. At the recommended dose, one patient reported febrile neutropenia and the incidence by cycle of grade 3 or 4 neutropenia was 50%. Secondary prophylaxis with growth factors were given to 13 patients (43%), 8 of them being treated at level 1bis or 2.

In the overall population non-haematological drug-related toxicities were rarely severe and remained easily manageable. Main types were gastrointestinal symptoms, fatigue and neuro-sensory disorders. No grade 3 or 4 hepatic and renal toxicities were observed. In terms of cumulative toxicities, nail changes were reported in a single patient treated at dose level 5 which used docetaxel at 70 mg m^{-2}. Grade 1 or 2 constipation was seen in five patients: one patient each at dose levels 1 and 1bis and three patients at dose level 3. Grade 3 or 4 stomatitis was observed only at levels 2, 3 and 4. Neither fluid retention, nor canalicular stenosis were seen in the present study.

Anti-tumour activity

Twenty-two patients were evaluable for the anti-tumour activity. Two patients had locally advanced disease without distant metastases and were consequently non evaluable. In six patients, lesions to be measured bidimensionally were only measured by physical examination, not on images obtained by CT-scan or MRI and were also considered as non evaluable.

Table 3 gives the responses by dose level. Among 22 evaluable patients with MBC, 2 complete and 10 partial responses were obtained, including two partial responses at the recommended dose level (dose level 3).

The median age of responders was 58 years and ranged from 35 to 71 years. Five of them had received prior adjuvant chemotherapy and 8 prior adjuvant hormonotherapy. Nine patients had a disease free interval more than 2 years. Of note, eight of the responders had visceral involvement and most of them (nine patients) had at least two organs involved.

"No change" responses were also obtained in six patients. The four remaining patients were progressive. No obvious dose–response relationship was observed but the number evaluable patients were to small to conclude.

Pharmacokinetics

The last 19 patients enrolled in the study were evaluated for pharmacokinetics. Seven of them had the day 15 dosing cancelled because of haematotoxicity. Consequently, the number of patients evaluable for pharmacokinetics was 19 on day 1 and 12 on day 15.

The potential effect of docetaxel co-administration on the pharmacokinetics of vinorelbine was evaluated by comparison of the exposure (AUC_{inf}) between day 1, when associated to docetaxel, and day 15, when oral vinorelbine was administered alone. The latter was considered as the reference and the 12 patients treated on both day 1 and day 15 were evaluated. For this comparison, the individual AUC_{inf} after i.v. dosing on day 1 was normalized to the dose of 25 mg m^{-2}, which was demonstrated to provide equivalent exposure to oral vinorelbine mono-therapy at 60 mg m^{-2} [13]. It was demonstrated that the exposure to vinorelbine after day 1 dosing (1,314 ± 310 ng ml^{-1} h, when combined with docetaxel) was not statistically different to exposure obtained at day 15 (1,116 ± 434 ng ml^{-1} h for vinorelbine administered alone) [$P = 0.11$, NS].

Furthermore, when comparing vinorelbine total clearance and terminal half-life between two groups of patients receiving vinorelbine with docetaxel at either 60 or 70 mg m^{-2}, no difference was observed (Table 4): Cl_{tot} (mean ± SD) were 37.5 ± 11.1 and 35.5 ± 9.18 l h^{-1} in the 60 mg m^{-2} ($n = 12$ patients) and 70 mg m^{-2} ($n = 7$ patients) groups, respectively (NS). $T_{½z}$ (mean ± SD) was 34.9 ± 3.39 and 35.1 ± 4.18 h in the 60 mg m^{-2} ($n = 12$ patients) and 70 mg m^{-2} ($n = 7$ patients) groups, respectively (NS).

Pharmacokinetic parameters of vinorelbine were furthermore compared with reference data for i.v. and oral vinorelbine administered alone. The reference values were derived from the reference database on vinorelbine [21]. The analysis evidenced that vinorelbine pharmacokinetics in the study were similar to those of the reference (Tables 5, 6), except for CI/F of day 15 oral vinorelbine which was slightly lower in the study group ($P = 0.048$).

However this difference is unlikely to be related to co-administration of docetaxel since docetaxel had already been eliminated at day 15, and no modification of i.v. vinorelbine clearance was observed after docetaxel administration.

The Bayesian Cl_{tot} obtained for docetaxel were 38.4 ± 12.6 and 31.8 ± 10.9 l h^{-1} m^{-2} for the 60 mg m^{-2} ($n = 12$ patients) and 70 mg m^{-2} ($n = 7$ patients) groups, respectively (Table 7). Thus, pharmacokinetics of docetaxel was not altered when combined with vinorelbine in the present study.

Table 3 Overall response according to the investigator in the evaluable population, per dose level

Dose level	1	1bis	2	**3**	4	5	All
Number of patients	2	2	7	**3**	2	6	22
Complete response	–	–	1	**–**	–	1	2
Partial response	1	–	3	**2**	1	3	10
No change	1	2	1	**1**	–	1	6
Progression	–	–	2	**–**	1	1	4

Table 4 Analysis of variance—comparison of vinorelbine pharmacokinetic parameters (mean ± SD) between docetaxel doses levels

Bayesian pharmacokinetic parameters	Docetaxel dose level (mg/m²)		ANOVA (dose level factor)
	60 ($n = 12$)	70 ($n = 7$)	
Cl_{tot} (l h^{-1})	37.5 ± 11.1	35.5 ± 9.18	$P = 0.70$, NS
$T_{½z}$ (h)	34.9 ± 3.39	35.1 ± 4.18	$P = 0.89$, NS

NS Not significant

Table 5 Statistical analysis of vinorelbine pharmacokinetic parameters (mean ± SD)—comparison to reference data for intravenous dosing

Bayesian pharmacokinetic parameters	Test PM0259CA101B0 – day 1 (n = 19)	Reference (n = 49)	t-test
Cl_{tot} (l h^{-1} m^{-2})	21.9 ± 5.37	23.8 ± 4.67	P = 0.16, NS
$T_{½z}$ (h)	34.9 ± 3.59	33.3 ± 3.32	P = 0.07, NS

NS Not significant

Table 6 Statistical analysis of vinorelbine pharmacokinetic parameters (mean ± SD)—comparison to reference data for oral dosing

Bayesian pharmacokinetic parameters	Test PM0259CA101B0 – day 15 (n = 12)	Reference (n = 121)	t-test
Cl/F (l h^{-1} m^{-2})	65.3 ± 34.1	84.8 ± 38.0	P = 0.048
$T_{½z}$ (h)	32.6 ± 2.88	34.3 ± 3.49	P = 0.1, NS

NS Not significant

Table 7 Mean (SD) pharmacokinetic parameters of docetaxel

	Number of patients	Cl_{tot} (l h^{-1})	Cl_{tot} (l h^{-1} m^{-2})	$T_{½z}$ (h)
Docetaxel (60 mg m^{-2})	12	61.7 (20.0)	38.4 (12.6)	10.4 (3.7)
Docetaxel (70 mg m^{-2})	7	54.8 (17.4)	31.8 (10.9)	12.9 (4.0)
All	19	59.1 (19.4)	36.0 (12.4)	11.4 (4.1)

Discussion

The majority of patients received combination chemotherapy regimen as first-line chemotherapy of MBC. The standard practice has been to combine agents with different mechanisms of action with the expectation that short-term and cumulative DLT will be different and that no cross-resistance will develop. In view of the encouraging clinical results with taxanes and vinorelbine when used in mono-therapy, 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 and taxanes are known to inhibit tubulin polymerization and microtubule depolymerization, respectively. Pre-clinical studies had indeed demonstrated a definite synergy between docetaxel and vinorelbine [14].

This study is the first attempt to define recommended dose of an alternating regimen of intravenous and oral vinorelbine combined with docetaxel in the palliative treatment of MBC. Moreover two schedules of oral vinorelbine administration were explored in order to select the most tolerable dosing. Earlier phase I studies with the same objective but using a fully intravenous regimen has been reported: Fumoleau et al. [15] have run a study which led them to recommend doses of 75–85 mg m^{-2} for docetaxel on day 1 and 20 mg m^{-2} for intravenous vinorelbine on day 1 and day 5. At this dose level, six patients were treated and 66.7% of them experienced grade 4 neutropenia and febrile neutropenia was reported in 9% of cycles.

Marti et al. [23] in Spain started a study in MBC patients previously treated with anthracyclines with a combination of docetaxel 75 mg m^{-2} and intravenous vinorelbine 30 mg m^{-2}, both on day 1 of 3-week cycles. Eight of their first 13 patients developed neutropenic fever, which led them to reduce the doses for subsequent patients to 60 mg m^{-2} for docetaxel and to 24 mg m^{-2} for intravenous vinorelbine.

When intravenous vinorelbine was given on day 1 and day 5 in combination with docetaxel on day 1 it was administered before the occurrence of neutrophils nadir generally observed around day 7 [24]. Therefore, actual and planned dose intensities were very close but at the expense of marked myelosuppression. Intravenous vinorelbine given on day 1 and day 8 with docetaxel on day 1 was also associated with a high degree of myelosuppression.

By using this regimen, Pectasides's et al. [25] reported seven patients (17.9%) who experienced episodes of febrile neutropenia that required hospitalisation, one patient with grade 4 neutropenia and sepsis leading to death despite the use of G-CSF and broad-spectrum antibiotics.

Figures for MTD and recommended dose coming out of the present study largely match those obtained in earlier studies if one keeps in mind the differences in

dosing schedules (no second dose of vinorelbine in Marti's study [23], a second dose on day 5 in Fumoleau's [15] before neutrophils nadir).

This study supports that recommended doses of intravenous vinorelbine 20 mg m^{-2} and docetaxel 60 mg m^{-2} on day 1 combined to oral vinorelbine 60 mg m^{-2} on day 15 offer a definite advantage for the practical management of this combination therapy. Furthermore and from a pharmacokinetic standpoint, results of this study demonstrated the absence of mutual interaction when vinorelbine and docetaxel are co-administered.

Data from this study were consistent with those of literature. Rosing et al. [26] described mean total clearance of 34.8 ± 9.3 l h^{-1} m^{-2}, ranging from 19.2 to 53.8 l h^{-1} m^{-2} and mean $T_{½z}$ of 10.8 ± 14.1 h, ranging from 2.1 to 69.3 h. Van den Neste et al. [27] in a study combining 5-fluorouracil that concluded to the absence of interaction reported variable clearance with mean value of 36.4 ± 4.0 l h^{-1} m^{-2} when dosing at 60 mg m^{-2}. Thus, results of the current study are in accordance with the results of Campone et al. [28] concluding that the pharmacokinetics of vinorelbine and docetaxel were not modified when the two drugs were combined.

In this study, like in previous clinical studies in MBC the docetaxel/vinorelbine combination, irrespective of doses and schedules tested, gave encouraging results in terms of tumour control [24, 25, 29–33]. In all cases, neutropenia appears as the main DLT and limited dose escalation of the two drugs. Reported results determined the recommended dose and schedule which will be further explored in phase II.

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