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ORIGINAL ARTICLE

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The raltitrexed-vinorelbine combination: a phase I pharmacokinetic and pharmacodynamic trial in advanced breast cancer

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Abstract *Purpose*: Combinations of vinorelbine (VRB) and drugs targeting thymidylate synthase (TS) such as 5-fluorouracil (5-FU) have proven clinical efficacy in the management of advanced breast cancer. Raltitrexed (RTX) is a recent TS inhibitor which shows advantages over 5-FU in terms of a lower incidence of toxicity along with a simpler administration schedule. We conducted a phase I trial of the VRB-RTX combination in 12 patients with advanced breast cancer. *Materials and methods*: Most of the patients were refractory to taxane-anthracycline combination therapy. Their median age was 51 years (range 33–70 years). RTX was given on day 1 and VRB on days 1 and 5 on a 3-week cycle. Three dose levels were initially planned with VRB and RTX increasing from 22.5 to 25 mg/m^2 and from 2.5 to 3 mg/m^2, respectively. *Results*: From a total of 50 cycles (mean 4 cycles per patient, range 1–11), the maximal tolerated dose (MTD) was reached at VRB 25 mg/m^2 and RTX 3 mg/m^2 with grade 3-4 neutropenia as the dose-limiting toxicity (7/16 cycles and 3/5 patients at the MTD). Nine pretreated patients were evaluable for treatment efficacy and three of these showed an objective response (one complete response, two partial responses; mean duration 26 weeks, range 17–38 weeks). Pharmacokinetic follow-up was done for both drugs (RTX by LC-MS-MS and VRB by HPLC-UV detection). There was no interaction between RTX and VRB pharmacokinetics since the VRB AUC was not significantly modified between day 1 and day 5. There was no relationship between RTX AUC and hematological toxicity. In contrast, there was a highly significant relationship between the mean VRB AUC (days 1–5) and the absolute neutrophil count decrease (Emax model, Hill constant = 4.38 ± 2.59, $EC_{50} = 508 \pm 53.2$ μg·h/l, $r = 0.75$, $P = 0.0013$). A similar relationship was noted for the platelet decrease but at the limit of statistical significance. *Conclusions*: The VRB-RTX combination appears to be a valuable treatment option in second-line treatment of advanced breast cancer. It is deliverable on an outpatient basis, shows an acceptable toxicity profile potentially manageable by VRB pharmacokinetic follow-up, and has promising antitumor activity in taxane-anthracycline-refractory patients. The recommended dose for further studies is VRB 22.5 mg/m^2 and RTX 3 mg/m^2.

Keywords Phase I clinical trial · Advanced breast cancer · Raltitrexed · Vinorelbine · Pharmacokinetic-pharmacodynamic study

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Introduction

Despite recent progress in adjuvant treatment of breast cancer, 60% of patients will show locoregional recurrence or metastasis [8]. During the last two decades the chemotherapeutic treatment of advanced breast cancer has mainly been based on the use of anthracyclines, and the recent introduction of taxanes has significantly improved the efficacy of anthracyclines alone [5]. One of the current strategies in advanced breast cancer is to evaluate active second-line treatment after failure of anthracycline-taxane combination treatment.

Vinorelbine has mainly been studied in breast cancer in association with anthracyclines [10]. Vinorelbine has also been evaluated in metastatic breast cancer in combination with other drugs. Interestingly, a phase II study, in which 62 patients received 5-fluorouracil (5-FU) together with vinorelbine revealed a 65% objective response rate with a median survival of 100 weeks [6]. The efficacy of this drug combination has been confirmed by more recent clinical trials [1, 12, 15, 20, 21]. 5-FU-based chemotherapy is not devoid of risk

for more or less severe toxicity due to the presence of dihydropyrimidine dehydrogenase (DPD) deficiency [13], DPD being the key enzyme for 5-FU catabolism [6]. Moreover, women are more prone than men to exhibit DPD deficiency syndrome under 5-FU treatment [14]. Thus, substitutes for 5-FU should be considered for the combination 5-FU plus vinorelbine. Like 5-FU, raltitrexed is a thymidylate synthase (TS) inhibitor which has the advantage over 5-FU that its elimination is not under the control of DPD. Comparisons between raltitrexed and 5-FU have shown less severe toxicity with the former [11]. In addition, by allowing a single monthly administration, raltitrexed alleviates the treatment load for patients and medical staff. Furthermore, raltitrexed has shown promising antitumor activity in advanced breast cancer as a single drug [19]. In total, the combination of raltitrexed and vinorelbine can be considered a valuable alternative to 5-FU plus vinorelbine in the management of advanced breast cancer.

The primary objective of the present phase I trial was to determine the maximum tolerated dose (MTD) of raltitrexed and vinorelbine when administered in combination. The secondary objective was to examine the pharmacokinetic behavior of each drug in combination and to obtain information about the antitumor efficacy of the combination in pretreated breast cancer patients refractory to anthracyclines and taxanes.

Patients and methods

Patients

Eligibility criteria included documentation of histologically proven advanced metastatic breast cancer following prior chemotherapy. Of 12 patients entered, 11 had one or two metastatic sites. All patients had initially been treated with anthracycline and/or taxane chemotherapy regimens, and seven (58%) were responsive to anthracyclines and three (37%) were responsive to taxanes. In addition, eight patients with estrogen-positive receptors had received prior hormone therapy. The main inclusion criteria were performance status (WHO) ≤ 2, life expectancy greater than 12 weeks and normal hepatic, renal and bone marrow function defined by WBC count $\geq 4\times10^9$/l, absolute neutrophil count $\leq 1.5\times10^9$/l, platelet count $\geq 100\times10^9$/l, hemoglobin ≥ 10 g/dl, serum creatinine not more than 1.5 times the upper limit of normal (ULN), total bilirubin level not more than 1.25 times the ULN, and AST, ALT, and alkaline phosphatase less than 2.5 times the ULN or less than 5 times the ULN if hepatic metastases were present.

Exclusion criteria included chemotherapy or radiotherapy within 4 weeks of study entry prior to chemotherapy with vinorelbine or raltitrexed, previous malignancy, concomitant uncontrolled nonmalignant disease (cardiac, pulmonary, renal or hepatic disease, or active infection), and brain or meningeal involvement of the disease. The protocol was approved by the Local Ethics Committee (CCPPRB) and signed informed consent was obtained from all patients.

Pretreatment evaluation included a complete medical history, physical examination, ECG, chest radiograph, and computed tomography scan of assessable target lesions, although measurability of disease was not a mandatory eligibility requirement. Complete blood cell counts and differential, blood chemistry, and tumor markers (when suitable) were obtained at baseline and before each cycle. Complete blood cell counts were repeated weekly. Patients were evaluated for toxicity weekly while on study, and all toxicities were graded using the National Cancer Institute common toxicity criteria. Dose-limiting toxicities (DLTs) were defined as grade 4 neutropenia lasting more than 7 days, any febrile grade 3 or 4 neutropenia, grade 4 thrombocytopenia, grade 4 vomiting, and grade 3 or 4 other nonhematological toxicity (excluding alopecia). If DLT occurred, the treatment was to be discontinued until recovery to grade 1 or less, and, if clinically indicated, resumed for the subsequent cycle at the dose level immediately below that which resulted in the DLT. Objective responses were recorded according to standard WHO response criteria. An imaging assessment of tumoral target lesions was repeated every two cycles whenever measurable disease was present during the baseline workup.

Treatment plan

Vinorelbine (Navelbine; Pierre Fabre Médicament, France) was diluted in 100 ml saline and administered as a 20-min i.v. infusion on day 1 and on day 5 every 3 weeks. Raltitrexed was diluted in 100 ml 5% dextrose and administered as a single 15-min infusion starting 25 min after the end of the vinorelbine infusion on day 1 and every 3 weeks. The initial dose of both drugs was determined according to the escalation procedure listed in Table 1. No intrapatient dose escalation was allowed.

A minimum of three patients were entered at each dose level, with a minimum of 1 week between the entry of the first patient and the entry of the next two at a given dose level. Before escalating to the next dose level, all three patients should have received at least one treatment cycle and been observed for acute toxicity for a minimum of 2 weeks, with at least one patient receiving two cycles and being observed for acute toxicity for a minimum of 2 weeks. If one of three patients at a given dose level developed a DLT, then at least three more patients were to be entered at the same dose level.

The MTD was defined as the dose that resulted in at least three of six patients developing the same DLT during the first two treatment cycles. The recommended dose was to be the dose immediately below the MTD, provided its feasibility and tolerability in repeated cycles were demonstrated in additional patients. Treatment duration depended on the response to therapy. Patients without objective tumor progression after six cycles could continue treatment until evidence of disease progression, unacceptable toxicity, or patient refusal.

Pharmacokinetics

A pharmacokinetic study was planned to determine the extent of any pharmacokinetic interaction between the drugs and to analyze the pharmacokinetic-pharmacodynamic relationships. Biological samples (10 ml from venepuncture into EDTA tubes, immediately centrifuged at $+4$°C and plasma stored at –20°C) for drug measurements were obtained in cycle 1 and cycle 4 as follows: day 1 at time 0, at 20 min (end of vinorelbine infusion) and 45 min, at 1 h (end of raltitrexed infusion), 3 h and 24 h, and on day 5 at time 0, at 20 min (end of vinorelbine infusion), and at 1 h, 3 h and 24 h. Plasma concentrations of vinorelbine were measured by high-pressure liquid chromatography according to an internal Pierre Fabre Médicament procedure with a lower limit of quantification of 10 ng/ml and an accuracy of 5% (interday CV). Plasma concentrations of raltitrexed were determined by LC-MS-MS by

Table 1 Dose-escalation procedure

Planned levels to be explored	Vinorelbine (mg/m^2)	Raltitrexed (mg/m^2)
I	22,5	2,5
II	22,5	3
III	25	3
IV	27,5	3
V	30	3

CEDRA corporation (Austin, Tx.) with a lower limit of quantification of 0.5 ng/ml and accuracy < 7.0% (interday CV). Values of drug area under the curve (vinorelbine AUC_{t0-24h}, raltitrexed AUC_{t0-24h}, concentration×time) were computed using the trapezoidal rule.

Statistics

Paired comparisons were performed with the Wilcoxon paired test and group comparisons were based on the Mann-Whitney test. The pharmacodynamics of hematological toxicity were evaluated by the sigmoidal Emax model with Hill correction using Micropharm software (Paris, France). All statistical determinations were performed using SPSS software (Paris, France).

Results

Study patients

A total of 50 cycles (12 patients) were delivered from dose level I to III. Each patient received an average of 4 cycles (1–11). The study was stopped at the planned dose level III at which the MTD was reached. The mean age of the patients was 51 years (33–70 years). All study patients were assessable for toxicity and efficacy. A summary of the patient characteristics is given in Table 2. Most patients (63%) had a performance status 1 or better.

Table 2 Patient characteristics ($n = 12$)

		%
Age (years)		
Median	51	
Range	33–70	
WHO performance status		
0	4	33
1	6	50
2	2	17
Initial node involvement		
–	4	34
+	8	66
Estradiol receptor-positive	7	58
Progesterone receptor-positive	6	50
Metastatic sites		
Bone	5	41
Lung	4	33
Liver	7	58
Soft tissues	4	33
Number of metastatic sites		
1–2	11	92
> 2	1	8
Chemotherapy during metastatic phase		
1	12	100
2	8	67

Safety

Hematological toxicity was predominant with 7 of 12 patients (58%) exhibiting grade 3-4 neutropenia including febrile neutropenia (3 of 12, 25%). There were no treatment-related deaths. Table 3 gives the percentage of grade 3-4 neutropenia by patient and cycle. Hematological toxicity had a median time of onset of day 12 and a median duration of 5 days. No patient was given granulocyte colony-stimulating factor (G-CSF) on a prophylactic basis and two patients received G-CSF with a curative intent. In addition to neutropenia, two patients at dose level III developed grade 4 anemia which necessitated red blood cell transfusion. Two patients at dose level III showed grade 3 thrombocytopenia without needing platelet transfusion. Nonhematological toxicities are shown in Table 4; asthenia and transaminase elevations were the most frequent toxic events after hematological toxicity.

Establishment of the MTD

At dose level I, four patients were included because one patient left the study at this dose level. No DLT was observed at dose levels I and II. At dose level III (vinorelbine 25 mg/m^2, raltitrexed 3 mg/m^2), three patients exhibited DLT. The study was stopped at this stage with this dose level being considered as the MTD. One patient had grade 3 constipation associated with grade 4 febrile neutropenia. The two other patients had grade 4 febrile neutropenia. The recommended dose for future phase II studies is considered to be dose level II (vinorelbine 22.5 mg/m^2, raltitrexed 3 mg/m^2).

Treatment efficacy

Although clinical response was not the primary end point, efficacy was noted in nine patients evaluable for response. One patient at dose level II (a patient resistant to anthracyclines and taxanes) had hepatic metastases

Table 3 Grade 3-4 hematological toxicity per patient and cycle

	Dose levels of combined vinorelbine/raltitrexed (mg/m^2)					
	I (22.5/2.5)		II (22.5/3)		III (25/3)	
	Patients	Cycles	Patients	Cycles	Patients	Cycles
Total no.	4	22	3	12	5	16
Neutropenia	3 (75%)	4 (18%)	1 (33%)	2 (16%)	3 (60%)	7 (44%)
Febrile neutropenia	0	0	0	0	3 (60%)	3 (44%)

Table 4 Non-hematological toxicity

Dose level	No. of patients	Type of toxicity with grade					
		Constipation Grade 3	Nausea and vomiting Grade 3	Peripheral neuropathy Grade 1	Diarrhea Grade 3	Transaminase elevations Grade 1-2	Transaminase elevations Grade 3-4
I	4	0	0	1	0	2	0
II	3	0	0	0	0	3	0
III	5	1	1	0	1	3	2
Total	12	1	1	1	1	8	2

and showed a complete response to treatment after the third cycle. Two other patients showed a partial response in node and cutaneous metastases at dose levels I and II, respectively. The mean duration of response was 26 weeks (17–38 weeks).

Pharmacokinetic data

Vinorelbine

There was no significant difference between day-1 AUC and day-5 AUC (mean ± SD 786 ± 311 and 1067 ± 545 μg·h/l, respectively; $P = 0.239$, $n = 12$). This suggests that the presence of raltitrexed on day 1 had no significant impact on the pharmacokinetic behavior of vinorelbine, since the latter was given alone on day 5. Thus, the mean of the AUCs on day 1 and day 5 was taken when considering treatment cycles. There was a significant difference between the AUC resulting from dose level I and II (vinorelbine at 22.5 mg/m^2 in both, 24 cycles, mean ± SD 776 ± 363 μg·h/l) and that observed at dose level III (vinorelbine at 25 mg/m^2, 10 cycles, 1092 ± 459 μg·h/l, $P = 0.034$). There was a significant increase in AUC between cycle 1 and cycle 4 (695 ± 274 and 1005 ± 329 μg·h/l, respectively, $P = 0.028$, $n = 6$). An association was observed between the limiting toxicity and drug exposure. Indeed, Fig. 1 shows the highly significant link between the percentage decrease in absolute neutrophil count (ANC) and the value of vinorelbine AUC (Emax model, $P = 0.0013$). A similar relationship close to statistical significance was also noted between the percentage decrease in platelets and vinorelbine AUC (Emax model, $P = 0.059$, not shown).

Raltitrexed

There was no significant difference in raltitrexed AUC values between dose level II (raltitrexed 3 mg/m^2, vinorelbine 22.5 mg/m^2) and dose level III (raltitrexed 3 mg/m^2, vinorelbine 25 mg/m^2): the AUC values were 1610 ± 791 and 1158 ± 765 μg·h/l, respectively ($P = 0.34$). Thus, raltitrexed AUC values for dose levels II and III were grouped together and compared with those observed at dose level I (raltitrexed 2.5 mg/m^2, vinorelbine 22.5 mg/m^2). In this case, there was no statistically significant difference (1384 ± 760 and 1244 ± 468 μg·h/l, respectively). There was no evidence of a relationship between raltitrexed AUC and pharmacodynamic observations.

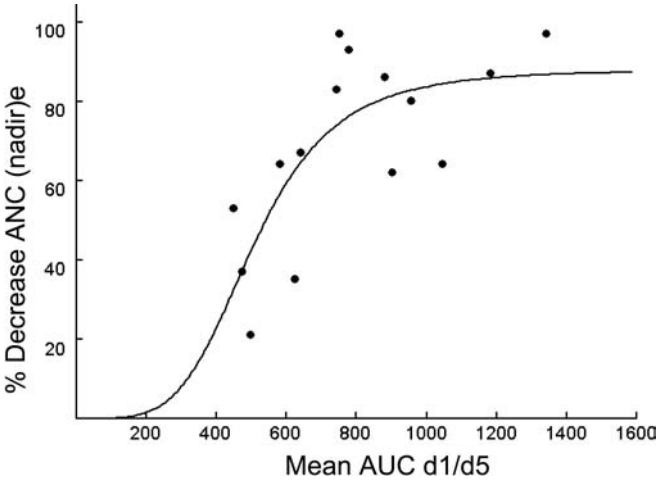

Fig. 1 Relationship between mean vinorelbine cycle AUC (day 1 to day 5, μg·h/l) and cycle-related percent decrease in ANC (nadir; 15 cycles evaluated). Emax model with Hill correction: Emax = 88.03 ± 12%, EC_{50} = 508.6 ± 53.2 μg·h/l, H = 4.38 ± 2.59; $P = 0.0013$, $r = 0.748$ half-maximal activation concentration

Discussion

Anthracyclines and taxanes are currently among the most efficient anticancer drugs in first-line chemotherapy for breast cancer patients [2]. The combination of vinorelbine and 5-FU is among the reference protocols for second-line chemotherapy [1]. As a palliative treatment, prolonged infusion of 5-FU improves the efficacy of this drug combination [1, 12, 15, 20, 21], but leads to an enhancement of side effects. The objective of the present clinical trial was to maintain the association of two drugs with distinct mechanisms of action while replacing 5-FU by raltitrexed, both drugs having TS as a common target. The potential advantage of raltitrexed over 5-FU is the simplification of treatment with a single monthly administration which impacts positively on the patients' quality of life without a detrimental effect on antitumor efficacy. On the other hand, it is important to underline that vinorelbine and raltitrexed are eliminated by different pathways with the biliary route for the former [10] and renal clearance for the latter [11].

This study was based on analysis of a relatively high number of cycles ($n = 50$) which compensated for the relatively low number of patients ($n = 12$). The MTD was found to be dose level III (vinorelbine 25 mg/m^2, raltitrexed 3 mg/m^2) with the DLT hematological in origin. At the recommended MTD, grade 3-4 neutropenia occurred in 2 of 12 cycles (17%). This hematological toxicity was attributable to vinorelbine and also predominates in the combinations between vinorelbine and 5-FU [7]. The feasibility of this combination regimen is highlighted by the fact that, despite the relatively low number of patients, many had long treatment durations (up to 11 cycles) with several cycles delivered per patient (four cycles on average). Although clinical response was not the primary end point, activity was noted in nine evaluable patients. This potential activity was observed in advanced breast cancer patients refractory to taxanes and anthracyclines. These observations indicate that further clinical investigations are warranted.

Part of the present study was devoted to pharmacological investigations on both drugs. The AUC values of raltitrexed given in association with vinorelbine compare well with previously published data [4]: mean AUC values found in the previous study for a dose of 3.0 mg/m^2 were around 1100 μg·h/l, which is in the range found in the present study. This may suggest an absence of a marked impact of vinorelbine on the pharmacokinetic behavior of raltitrexed. This consideration is in line with the fact that the drugs are cleared by different routes. However, it must be stressed that a definitive conclusion regarding the presence or not of a pharmacokinetic interaction between these drugs should be based on a specifically designed study. This was not within the scope of the present study. On the other hand, there was no evidence of any impact of raltitrexed on the pharmacokinetics of vinorelbine since there was no significant difference in the AUC values of vinorelbine between day 1 and day 5.

It was noted that repeated treatment modified the pharmacokinetic profile of vinorelbine from cycle 1 to cycle 4 as indicated by a significant increase in AUC from 695 ± 274 to 1005 ± 329 μg·h/l). To our knowledge, this apparent loss in the clearance value of vinorelbine throughout the treatment course has not been previously reported. A previous study by Robieux et al. [16] has shown a close relationship between the results of the monoethyl glycine xylidide test (a quantitative liver function test based on lidocaine metabolite formation) and the clearance of vinorelbine. Thus, a possible explanation for the decrease in vinorelbine clearance through the treatment course could be an alteration in hepatic function (grade 3-4) encountered with raltitrexed administration which has been reported in 15% of patients treated for colorectal or breast cancer [3, 17] and/or with liver metastases due to progressive disease.

Previous studies are not in agreement regarding a link between vinorelbine exposure and pharmacodynamic effects. Thus, a lack of a pharmacokinetic-pharmacodynamic relationship has been reported by Sorio et al. [18]. In contrast, Gauvin et al. [9] have recently demonstrated a significant correlation between vinorelbine AUC and the decrease in ANC. The results of the present study concur well with these latter findings since a significant relationship according to the Emax model was established between drug exposure and the percentage decrease in ANC (Fig. 1). Such a relationship opens the possibility of identifying risk thresholds for the AUC of vinorelbine and of promoting improvements in the current protocol, for example by examining drug exposure on day 1 and adjusting doses on the following days of the cycle.

In conclusion, the combination of vinorelbine and raltitrexed appears to be a promising second-line treatment option for advanced breast cancer. It is deliverable on an outpatient basis, shows an acceptable toxicity profile potentially manageable by vinorelbine pharmacokinetic follow-up, and has a potentially interesting antitumor activity in taxane-anthracycline-refractory patients. The recommended dose for further studies is vinorelbine 22.5 mg/m^2 and raltitrexed 3 mg/m^2.

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