# Combination Chemotherapy of Vinorelbine and Cisplatin: A Phase I Pharmacokinetic Study in Patients with Metastatic Solid Tumors

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**Abstract.** *Background: Vinorelbine (VRL)-cisplatin (CDDP) is an active doublet for advanced non-small cell lung cancer. CDDP has a narrow therapeutic index and may produce a cumulative nephrotoxicity over the treatment period. This study was to assess the risks of drug-drug interaction (DDI) over 3 consecutive cycles of VRL-CDDP combined treatments. Patients and Methods: An open-label, nonrandomised, phase I study was carried out. Patients with normal hepatic/renal functions. D1: CDDP 100 mg/m$^2$ - D1, D8: oral VRL 60 mg/m$^2$ q3w. Pharmacokinetics (PK) over the first 3 cycles. PK comparison between cycles and between study vs. literature. Results: Thirteen patients were evaluable for safety and PK. Adverse events were those frequently observed with CDDP or VRL, and consisted of hematological toxicities, nausea, vomiting and constipation. Concerning VRL and CDDP PK, no difference was detected between the 3 administrations nor between the study and reference values. Conclusion: The absence of DDI between CDDP and oral VRL was demonstrated over 3 consecutive cycles of therapy.*

Lung cancer is currently the leading cause of death from malignant disease in both men and women (31% and 26%, respectively (1). Non-small cell histologies represent approximately 70-80% of patients with lung cancer and the majority of these patients has advanced disease (stage III/IV) when diagnosed, with poor prognosis (2). For patients with clinical stages I and II, the 5-year survival rate is about 40% with standard surgical resection, but 70% of patients with advanced stages III and IV disease have poor diagnosis (2, 3).

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Cisplatin-based combination therapy is currently considered the most active treatment for advanced non-small cell lung cancer (NSCLC) (4, 5) and the vinorelbine (VRL)-cisplatin (CDDP) doublet has been demonstrated to be a very effective combination in patients with NSCLC (6-15). CDDP has a low therapeutic index with significant toxicities including severe nausea and vomiting, general malaise, renal toxicity requiring adequate hydration, and ototoxicity (16, 17). This toxicity is cumulative over successive courses and may lead to a certain degree of renal insufficiency.

Since VRL was first developed only as an *i.v.* form, the initial combined treatments were fully *i.v.*. The recent availability of an oral form of VRL offers more flexibility for the VRL regimen that can be either *i.v.* when CDDP is infused followed by oral on the weeks without CDDP infusion, or fully oral. Although many studies on VRL-CDDP combined treatment have been completed and published, no information on potential drug-drug interaction risk is available. This risk could be considered as limited for *i.v.* VRL since the compound was poorly eliminated by the kidney, but might be higher for oral VRL due to its greater bioavailability (18-20). Oral VRL is characterized by a bioavailability close to 40% (18, 21). Its absorption is rapid and absolute bioavailability is not influenced by food although, as expected, the peak of blood concentrations is delayed depending on gastric aperture following food intake (22). Early vomiting does not reduce the absorption, probably because the content of the soft gelatine capsule consists of a small volume of VRL solution that is rapidly available to intestinal mucosa (23, 24).

The distribution volume of VRL is large (about 2,500 l and the drug mostly binds to platelets (78%) in blood, while binding to proteins is low (13.5%) (25). Metabolism involves mostly CYP3A4 except for 4-*O*-deacetyl-vinorelbine (DVRL), the only active metabolite (26) likely to be formed by carboxyl-esterase (27). Bile is the major route of elimination for both VRL and its metabolites (20). Urine is a minor route (≤10%) and mostly concerns the

parent compound (19). Nevertheless, the status of renal function might impact VRL pharmacokinetics since population pharmacokinetic modelling demonstrated the creatinine clearance to be a statistically significant factor influencing the variability, although to a limited extent (24). Therefore, a combined treatment of oral VRL plus CDDP might result in a drug-drug interaction (DDI) due to a cumulative CDDP renal toxicity over successive cycles, likely to alter VRL elimination in urine. This study was aimed at evaluating this risk in a phase I clinical study.

## Patients and Methods

*Study design*. This was an open-label, non-randomized phase I pharmacokinetic study. The primary objective was to check the absence of mutual pharmacokinetic interaction between VRL and CDDP. The secondary objective was to further characterize the tolerability profile of oral VRL when combined with CDDP. To be evaluable for pharmacokinetics, patients had to receive three consecutive cycles of combined treatment, complete schedule of blood sampling and no vomiting within the absorption period following oral VRL administration (*i.e.* 3 hours).

*Selection of patients*. Written informed consent was obtained from each patient before entering the study, which was conducted under the approval of the local Ethics Committee.

The main inclusion criteria were: Men and women aged 18-75 years; histologically or cytologically confirmed metastatic solid tumour for which the proposed regimen was the standard treatment in first line; a Karnofsky's Performance Status ≥70%; life expectancy ≥12 weeks; adequate bone marrow, normal hepatic and renal functions; neutrophils $\geq 2.0\times10^9$/l, platelets $\geq 100\times10^9$/l, hemoglobin >10 g/dl; total bilirubin ≤1.5 × upper normal limit (UNL), transaminases <2.5 × UNL; alkaline phosphatases <5 × UNL; serum creatinine ≤UNL (if limit value, creatinine clearance ≥60 ml/min). The main non-inclusion criteria were: pregnancy or lactation or for woman of childbearing potential lack of effective contraception; cardiovascular disease (cardiac failure, myocardial infarction within the previous 3 months, uncontrolled hypertension or arrhythmia); active infection requiring *i.v.* antibiotics within 2 weeks before the beginning of treatment; long-term oxygen therapy; prior surgery within the previous 2 weeks; radiotherapy to major bone marrow areas (≥20% of bone marrow) within 4 weeks prior to study entry; prior chemotherapy with platinum derivative drugs (cisplatin, carboplatin or oxaliplatin); chemotherapy within the previous 4 weeks; concomitant treatment with any other anticancer agent; concomitant treatment with inducers or inhibitors of CYP3A4.

*Treatment*. A cycle was defined as a 3-week period and consisted of oral VRL at 60 mg/m$^2$ on day 1, two hours before CDDP at 100 mg/m$^2$ infused over one hour, and then oral VRL at 60 mg/m$^2$ on day 8 (or day 15 in case of haematological toxicity on day 8). On day 1, hydration and systematic preventive antiemetic treatment prior to oral VRL administration and after CDDP infusion were given with a 5-HT$_3$ antagonist plus a corticosteroid, according to the Institution's rules. Preventative antiemetic treatment with a 5-HT$_3$ antagonist was also recommended on day 8 before oral VRL administration. The duration of treatment was until disease progression unless unacceptable toxicity or patient refusal to continue.

*Pharmacokinetic evaluation*. Pharmacokinetics of VRL and of CDDP (free-platinum) were studied during the first three cycles of treatment. VRL pharmacokinetics were evaluated on days 1 and 8 of the 3 cycles, through Bayesian calculation based on a population pharmacokinetic model and using a limited blood sampling strategy (5 samples) over the first 24 hours following treatment administration (23, 24). Blood samples were immediately frozen at –20˚C and then stored at –80˚C until analysis. VRL was measured in blood by a fully validated LC-MS/MS method (28). Briefly, the technique consisted of deproteinization by methanol, addition of the internal standard vinblastine, separation on a cyano chromatography column and detection through electrospray ionisation. The lower quantification limit was 0.25 ng/ml for both VRL and its metabolite, DVRL. Pharmacokinetic parameters of VRL ($AUC_{inf}$, $C_{max}$, $T_{max}$, $T_{1/2z}$) were obtained through Bayesian analysis with NONMEM and the POST HOC option using the model previously published (23). For DVRL, a model-independent method (Kinetica Software, version 4.1, Thermo Labsystems Inc, USA) was used since no modeling with NONMEM was available and the relatively flat pharmacokinetic profile allowed accurate estimate by trapezoidal rule calculation. To search for any drug interaction between CDDP, VRL and DVRL, pharmacokinetic parameters were compared between cycles and between D1 (combined treatment) and D8 (VRL alone) through a linear mixed-effect model implemented in SAS program, (PROC MIXED) (SAS Institute), allowing fixed effects (cycle and ± CDDP) and covariance effects (patient and interaction patient/cycle) to be assessed. Free platinum pharmacokinetics were evaluated on day 1 of the 3 cycles according to a detailed sampling scheme over 11 h (6 samples). After each sampling, the collected blood was immediately centrifuged. Plasma was then pipetted and free platinum was obtained by ultra-filtration (29). Free platinum was assayed in plasma by an atomic absorption spectrophotometry method (30). The limit of quantification was 5.25 ng/ml. Pharmacokinetic analysis of free platinum consisted of determining $AUC_{inf}$, $Cl_{tot}$, $V_d$ and $T_{½\ z}$, using model-independent analysis on Kinetica Software. To search for any influence of vinorelbine over successive cycles, free platinum pharmacokinetic parameters were compared between the 3 cycles through ANOVA (SAS program).

*Safety evaluation*. The safety profile was studied by physical examination and vital signs, performance status, complete blood cell counts, serum biochemistry, clinical safety, adverse events by using the NCI common toxicity criteria (version 2.0.).

## Results

A total of 13 patients were included in the study and received VRL + CDDP. Thirteen patients were eligible for safety and 11 for pharmacokinetics [one patient received only one cycle due to worsening of his general status, not drug related, and one patient received antifungal medications [(CYP3A4 inhibitors) at cycles 2 and 3]. The 13 patients, 7 males and 6 females, had a median age of 52 years (range 44-69 years) 1, 4 and 8 with a Karnofsky score of 100, 90 and 80%, respectively. Seventy-nine percent of patients (9/13) had a metastatic disease at study entry, 46% (6/13) had prior radiotherapy and 31% (4/13) had prior chemotherapy. The primary tumour site was the lung in 4

Table I. *Number of patients with NCI / CTC adverse events related to study drugs.*

| Adverse events by NCI / CTC | Number of evaluable patients | Overall incidence n | Grade 3 n | Grade 4 n |
|---|---|---|---|---|
| Haematological | | | | |
| Neutropenia | 13 | 8 | 3 | 2 |
| Leucopenia | 13 | 8 | 3 | 1 |
| Anaemia | 13 | 13 | 4 | 0 |
| Thrombocytopenia | 13 | 7 | 1 | 0 |
| Nonhaematological | | | | |
| Cardiovascular | | | | |
| Sinus tachycardia | 13 | 1 | 1 | 0 |
| Other | 13 | 1 | 0 | 0 |
| Dermatological | | | | |
| Alopecia | 13 | 2 | 0 | 0 |
| Other | 13 | 1 | 0 | 0 |
| Flu-like symptoms | | | | |
| Chills | 13 | 1 | 0 | 0 |
| Fatigue | 13 | 10 | 1 | 0 |
| Fever without neutropenia | 13 | 3 | 0 | 0 |
| Gastrointestinal | | | | |
| Anorexia | 13 | 3 | 0 | 0 |
| Constipation | 13 | 8 | 0 | 1 |
| Diarrhoea | 13 | 6 | 0 | 0 |
| Nausea | 13 | 12 | 2 | 0 |
| Proctitis | 13 | 1 | 0 | 0 |
| Vomiting | 13 | 11 | 2 | 0 |
| Hearing | | | | |
| Inner ear | 13 | 2 | 0 | 1 |

patients, uterus in 3 patients and various origins in the others. With the exception of an antifungal treatment necessary for one patient, deviations from the study protocol were limited and minor and without significant impact on the study.

*Safety results*. The most frequent adverse events related to study drugs (Table I) were as follows. Concerning haematological toxicity, anaemia was the main toxicity (all patients), while 4 patients experienced at least one grade 3 toxicity. Of note, 53.8% of patients (7/13) had anaemia at study entry. One patient required blood transfusion during study treatment. Neutropenia was observed in 61.5% of patients (8/13) (grade 3-4 in 38.5% of patients (3/13)). The median day of nadir for grade 3-4 neutropenia was observed at day 21 of the cycle, range 13-22 days. Only one patient experienced a complicated neutropenia, febrile neutropenia defined as a grade 4 neutropenia concomitant with grade ≥2 fever. No case of neutropenic infection was reported. Thrombocytopenia occurred in 53.8% of patients (7/13) (one patient had a grade 3 thrombocytopenia). Concerning non-haematological toxicity, as expected with CDDP, the frequency of nausea and vomiting in patients was 92.3% (12/13) and 84.6% (11/13), respectively, grade 3 being observed in 2 patients for each adverse event. Constipation occurred in 61.5% of patients (8/13) (grade 4, ileocolitis, in one patient). Other events with an incidence ≥15% included: fatigue (76.9%, 10/13), abdominal pain (30.8%, 4/13), headache, neurosensory disorder, fever without neutropenia, anorexia, hypomagnesemia (23.1%, 3/13, each), alopecia, inner-ear disorders and weight loss (15.4%, 2/13, each). There were no clinically relevant modifications of liver function. In 61.5% of patients (8/13), there was a moderate increase of plasma creatinine, without grade 3 or 4 toxicity. There was no death during the study period, from the first administration up to 30 days after the last administration. Two patients out of 13 experienced serious drug-related adverse events consisting of febrile neutropenia at cycle 3 for one patient (he recovered 6 days later with antibiotics), and in worsening of tinnitus and grade 4 hearing loss 15 days after the last administration in cycle 3 for the other patient. The relative dose intensity (RDI) was 99.5% for CDDP, 99.3% and 94.6% for VRL at D1 and D8, respectively. The slight decrease of VRL RDI value at D8 vs. D1 was due to the cancellation of one VRL administration in the patient who withdrew from the study at cycle 1, before D8.

*Vinorelbine pharmacokinetics*. The mean concentration profile of VRL in blood is presented in Figure 1 (model-independent plot). The limited sampling schedule used for blood collection did not enable the accurate definition of the

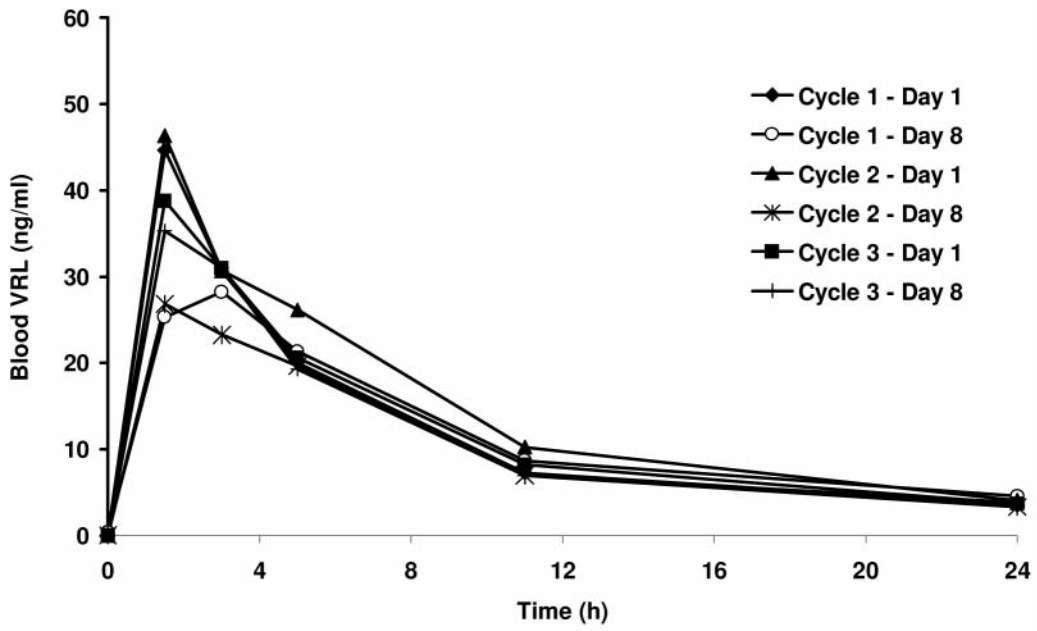


Figure 1. *Mean VRL blood concentration vs. time profiles on cycles 1, 2 and 3 (n=11).*

typical pharmacokinetic profile consisting of a 3 exponential decay with a terminal half-life close to 40 hours (23). Nevertheless, the peak of VRL concentrations in the blood occurred within the first 3 hours in most patients and the concentration at the last sampling time (24 h) was above the limit of quantification of the assay (0.25 ng/ml) in all patients, enabling a complete concentration dataset for further pharmacokinetic modelling.

Mean blood profiles were similar amongst the 3 cycles, and between D1 (VRL + CDDP) and D8 (VRL alone) of each cycle. The apparent decrease of the peak on D8 at cycles 1 and 2 was likely due to the limited sampling schedule, which did not enable the peak between the two consecutive scheduled samplings (1.5 and 3 h) to be caught. This is supported by the Bayesian estimates of $C_{max}$ and $T_{max}$ (Table II), which were used for the statistical analysis. The mean $C_{max}$ and $AUC_{inf}$ values, as well as their range of variability (standard deviations), were very similar between days and between cycles (Table II). The statistical analysis on VRL exposures confirmed the absence of difference between the 3 cycles, and the absence of any influence of CDDP on VRL pharmacokinetics.

Concerning elimination half-life, a significant influence of both factors, cycle and CDDP, was detected. The calculated values were 6% higher at D8 than at D1, and increased slightly (6%) from cycle 1 to cycle 3. However, the span of the modifications was limited (35.3 h to 39.3 h) and was considered not clinically relevant. Concerning the main metabolite in blood, DVRL, its concentrations were very low (<2 ng/ml) and peaked between 5 and 11 h, indicating the slow metabolic production already described (18, 19, 20, 31). For each cycle, DVRL concentrations at pre-dose were non-detectable at D1, whereas values close to 0.5 ng/ml at D8 indicated a slight accumulation (Figure 2). However, the impact of this accumulation was very limited since no statistical difference in AUCs was detected between D1 and D8, or between the 3 cycles (Table III).

*Free platinum pharmacokinetics*. The free platinum concentrations in plasma peaked at the end of the infusion (1 h) and then decreased according to a mono-exponential decay (Figure 3). The pharmacokinetic parameters (AUC, volume of distribution, clearance and elimination half-life) were not statistically different amongst the 3 cycles, which illustrated reproducible pharmacokinetics (Table IV).

## Discussion

Concerning the safety aspect of the study, these results are in line with those well-described for VRL-CDDP combined chemotherapy and particularly when the dose of CDDP is ≥100 $mg/m^2$, which induces more pronounced neutropenia, anaemia, nausea and vomiting (32). From the pharmacokinetics standpoint, a previous study conducted with intravenous vinorelbine (33) seeking drug-drug interaction during VRL-CDDP combined treatment found the absence of any pharmacokinetic interaction on VRL parameters. The study was carried out with a parallel group design and compared

Table II. *Mean (standard deviation) blood pharmacokinetic parameters of vinorelbine at D1 and D8 administration.*

| Pharmacokinetic parameters (n=11) | Bayesian $AUC_{inf}$ (h ng/ml) | | Bayesian $C_{max}$, (ng/ml) | | Bayesian $T_{max}$, (h) | | Bayesian $T_{1/2z}$ (h) | |
|---|---|---|---|---|---|---|---|---|
| | Day 1 | Day 8 | Day 1 | Day 8 | Day 1 | Day 8 | Day 1 | Day 8 |
| Cycle 1 | 489 | 568 | 55.3 | 54.9 | 0.719 | 0.875 | 35.3 | 37.5 |
| | (153) | (345) | (22.4) | (22.6) | (0.389) | (0.922) | (5.13) | (5.40) |
| Cycle 2 | 573 | 485 | 58.2 | 50.9 | 0.693 | 0.673 | 36.4 | 38.8 |
| | (339) | (186) | (18.3) | (25.7) | (0.315) | (0.314) | (4.51) | (6.04) |
| Cycle 3 | 510 | 501 | 53.1 | 51.6 | 0.755 | 0.665 | 37.1 | 39.3 |
| | (227) | (210) | (19.2) | (24.5) | (0.530) | (0.271) | (5.04) | (5.61) |
| PROC MIXED analysis | | | | | | | | |
| Cycle effect[1] | NS | | NS | | NS | | $p<0.005$ | |
| CDDP effect[2] | NS | | NS | | NS | | $p<0.001$ | |

[1]Cycle 1 *vs*. cycle 2 *vs*. cycle 3; [2]day 1 (with CDDP) *vs*. day 8 (without CDDP); $AUC_{inf}$: area under the curve from 0 to infinity; $C_{max}$: peak concentration; $T_{max}$: time to peak concentration; $T_{1/2z}$: terminal half-life.

Table III. *Mean (standard deviation) blood $AUC_{0\text{-}24h}$ of 4-O-deacetyl vinorelbine at D1 and D8 administration.*

| Pharmacokinetic parameters (n=11) | $AUC_{0\text{-}24h}$ (h ng/ml) | | PROC MIXED analysis | |
|---|---|---|---|---|
| | Day 1 | Day 8 | Cycle effect | CDDP effect |
| Cycle 1 | 29.9 | 34.7 | | |
| | (17.4) | (27.5) | | |
| Cycle 2 | 39.1 | 38.5 | NS | NS |
| | (28.5) | (30.6) | | |
| Cycle 3 | 30.8 | 36.5 | | |
| | (15.4) | (23.7) | | |

$AUC_{0\text{-}24h}$: Area under the curve calculated from 0 to 24 h.

Table IV. *Mean (standard deviation) plasma pharmacokinetic parameters of free platinum after D1 administration (n=11).*

| | $AUC_{inf}$ h ng/ml | $T_{1/2z}$ h | $Cl_{tot}$ l/h | $V_z$ l | $V_{ss}$ l |
|---|---|---|---|---|---|
| Cycle 1 | 3169 | 0.865 | 37.6 | 47.8 | 56.3 |
| | (282) | (0.198) | (6.06) | (17.9) | (7.06) |
| Cycle 2 | 3585 | 0.777 | 33.4 | 37.6 | 49.4 |
| | (543) | (0.150) | (6.15) | (10.9) | (11.1) |
| Cycle 3 | 3565 | 0.756 | 34.0 | 37.1 | 55.3 |
| | (715) | (0.0580) | (7.12) | (8.69) | (9.01) |
| ANOVA | NS | NS | NS | NS | NS |

$T_{1/2z}$: Terminal half-life; $Cl_{tot}$: total clearance; $V_z$: apparent volume of distribution; $V_{ss}$: volume of distribution at steady-steate.

patients receiving *i.v.* VRL alone 30 mg/m$^2$ (n=5) with patients receiving the same VRL dose plus CDDP 80 mg/m$^2$ *i.v.* (n=4). Phase I DDI studies are generally carried out by comparing one administration of two-combined drugs with one administration of a single drug. The interest of the current study is the search for DDI over 3 consecutive cycles. This design enables assessment of whether a late cisplatin renal toxicity over repeated cycles would alter the VRL pharmacokinetics, and thus its safety. The opposite risk in VRL altering CDDP pharmacokinetics, although more unlikely, was also examined. Concerning VRL pharmacokinetics, the dose-adjusted blood AUCs (≈700 h ng/ml) observed in this study were lower than those already published (18, 21) and using a full sampling scheme and a 80 mg/m$^2$ oral VRL dose ($AUC_{inf}$≈1,300 h ng/ml). No obvious reason was found to explain this discrepancy, except that a model-independent calculation was performed in the published results whereas a Bayesian calculation through the combined oral and *i.v.* population model was used in the current study (23). However, since a common methodology was used to compare the 3 cycle values in the current study, the close AUC values observed between cycles indicated the absence of impact of CDDP administration on both VRL and DVRL pharmacokinetics. The reproducible and statistically significant decrease (6%) of elimination half-life at D1 (combined therapy) when compared with D8 (VRL alone) was very unlikely to have any clinical consequence. Of note, the patient who was removed from the analysis due to protocol deviation received antifungal treatments (metronidazole and fluconazole) at cycle 2 and cycle 3. Because the information was obtained at the end of the study, blood samples had already been collected and therefore analysed. Interestingly, an increase of VRL AUCs was

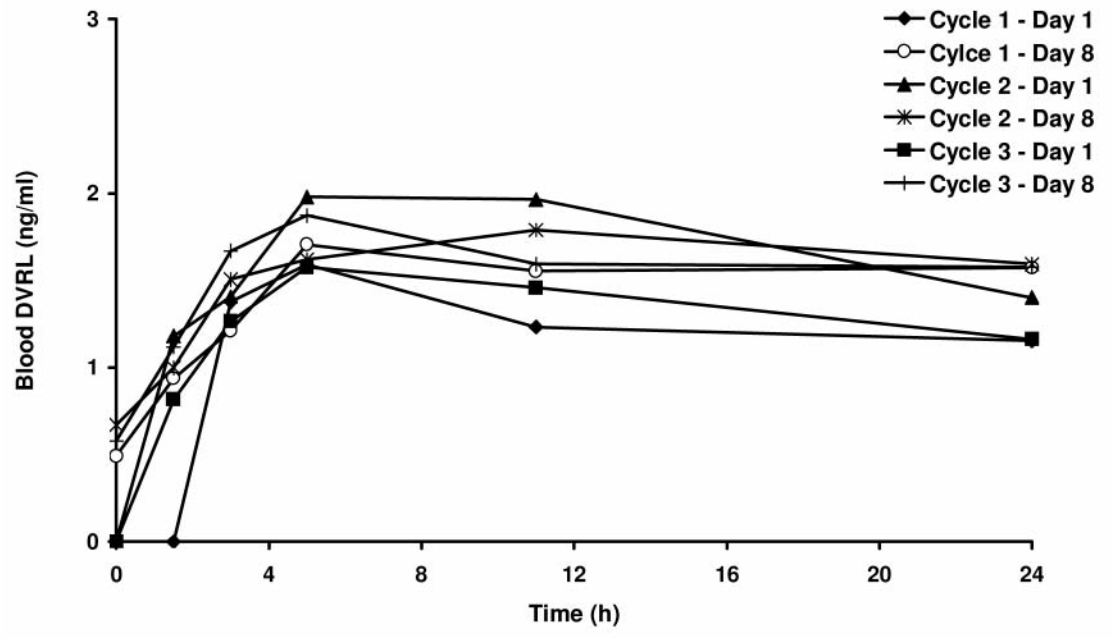


Figure 2. *Mean blood profiles of deacetyl-vinorelbine at D1 and D8 during the first three cycles (n=11).*

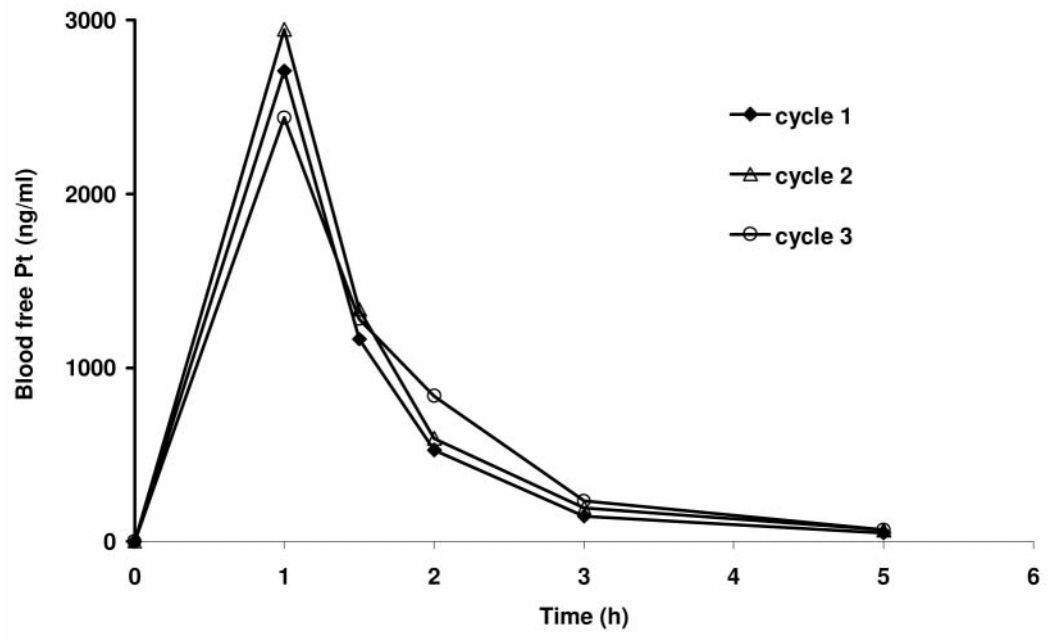


Figure 3. *Mean blood profiles of free platinum at D1 of cycle 1, 2 and 3 (n=11).*

observed at cycle 3 as compared to cycles 1 and 2 (140 and 200%, respectively), suggesting an impact on VRL metabolism through CYP3A4 inhibition. This increase in exposure was probably associated with pharmacodynamic effects since this patient presented febrile neutropenia on day 11 of the 3rd cycle, with recovery 6 days later with *i.v.* antibiotics. Concerning free platinum pharmacokinetics, a nonsignificant difference was detected on AUCs between the 3 cycles, and the inter-individual variability, generally wide in the literature, was moderate in the current study (CV=9 to 20%, cycles 1 to 3).

Data were consistent with literature published on similar dosing conditions (70 to 100 mg/m$^2$ infused over 1 to 2 h) (34 - 38). The total clearance of free platinum was 35.0±6.5 l/h in this study and ranged in the literature from 18.2±1.32 l/h (37) to 42.4±14.1 l/h (34).

## Conclusion

The results of this study demonstrated that neither VRL nor cisplatin interact with each other's pharmacokinetics when co-administered for at least 3 consecutive cycles in a combined chemotherapy.

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