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A sequence-dependent combination of docetaxel and vinorelbine: pharmacokinetic interactions

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Abstract

We studied possible pharmacokinetic interactions between docetaxel (DTX) and vinorelbine (VNR) in patients affected by different types of cancer. Patients with metastatic breast cancer or recurrent head and neck cancer received the following schedules: Protocol A: 11 patients were i.v. infused for 1 h with DTX (80 mg/m^2) at once, followed by VNR (25 mg/m^2) as slow i.v. bolus; Protocol B: VNR (25 mg/m^2) as a slow 10 min i.v. bolus was administered to 12 patients, immediately followed by 1 h i.v. infusion of DTX (80 mg/m^2). In both schedules, VNR and DTX plasma concentrations versus time were analysed by HPLC obtaining the corresponding non-compartmental pharmacokinetic parameters. VNR appeared pharmacokinetically affected by the sequential administration of DTX, since with protocol B, C_{max} and AUC were significantly higher and clearance lower than in protocol A. Moreover, a significant increase in the VNR plasma level was observed in correspondence with the peak plasma level of DTX. By contrast, C_{max}, AUC and clearance of DTX did not vary in the two protocols. Also the number of neutrophils at nadir on day 8 of treatment varied significantly in the two schedules. In conclusion we observed altered pharmacokinetic parameters between protocol A (DTX/VNR) and protocol B (VNR/DTX). In particular, patients following protocol B seemed to be exposed to higher VNR plasma concentration and to higher haematological toxicity.

Keywords: Pharmacokinetics; Docetaxel; Vinorelbine; Breast cancer; Head and Neck cancer; Haematological toxicity

1. Introduction

Vinorelbine (VNR) is a semisynthetic derivative of vinblastine that differs structurally from the natural *Vinca* alkaloids at the catharanthine ring, where a hydroxyl group has been removed from 5′ [1,2]. Docetaxel (DTX) is a semisynthetic taxoid developed from a non-cytotoxic precursor extracted from the needles of the European yew tree, *Taxus baccata* [3]. In comparison with paclitaxel, DTX presents linearity within the range of pharmacological doses, a lower incidence of side-effects and greater independence from the administration schedule [4–6].

Both drugs arrest the metaphase in dividing cells, but by different mechanisms. DTX promotes tubulin assembly into microtubules, stabilizes microtubules and inhibits depolymerisation to free tubulin [3,7]. Conversely, VNR induces a disruption of microtubules by their reversible binding to tubulin, resulting in mitotic spindle dissolution [8].

A strong rationale exists to support the association between DTX and VNR. Extensive preclinical evidence has shown that DTX and VNR act synergistically and could effectively be combined [9,10]. The synergism between DTX and VNR is schedule-dependent: the greatest activity against non-small-cell lung cancer (NSCLC) was achieved when the two drugs were administered simultaneously [11,12]. In an in vitro study [13], on undifferentiated cells, the sequential combina-

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tion VNR/DTX was more efficient than DTX/VNR. For low doses of compounds, synergism occurred, then additivity and finally antagonism when one of the compounds was at the concentration inducing mitotic block. The two drugs present no cross-resistance [14].

The two drugs have non-overlapping side-effect profiles; the toxicity resulting from the association of DTX and VNR was neutropenia, febrile neutropenia and mucositis [15] with peripheral neurotoxicity less severe than expected, given the neurotoxicity of each drug as a single agent [16]. Numerous phase II studies have confirmed that the toxicity of the combination is strongly dependent on the administration schedule [17]. The lowest toxicity was found when the two drugs were administrated simultaneously on day 1 every 2 or 3 weeks [18–21] with a DTX dose 60–75 mg/m^2 and VNR 24–30 mg/m^2. When VNR and DTX were administrated on different days (mainly on days 1 and 2), a high incidence of complicated neutropenia was observed [22]. Three patients also developed colitis with 60 mg/m^2 DTX on day 1 and VNR 20 mg/m^2 on days 1 and 5 [23].

Only two pharmacokinetics studies of DTX/VNR association have been reported in the form of abstracts. In both schedules in which VNR 20–22.5 mg/m^2 was followed immediately by DTX 60–100 mg/m^2 the pharmacokinetic profiles of both drugs were unaffected and the DTX clearance estimate was stable over the dose range of VNR investigated [24–26].

These findings justify further evaluation of DTX/VNR combination using alternating schedules in order to obtain an optimal intensification of the regimen and a lower incidence of side-effects. In the present study we compared the possible variations of the pharmacokinetic parameters by administering DTX (80 mg/m^2) and VNR (25 mg/m^2) following two different schedules: DTX immediately followed by VNR on day 1 every 3 weeks (schedule A); and VNR immediately followed by DTX on day 1 every 3 weeks (schedule B).

2. Material and methods

2.1. Patients and treatment plan

Patients with histologically confirmed metastatic breast cancer or recurrent head and neck cancer were eligible for the study. Other eligibility criteria included expected survival >3 months, age <65 years, an Estern Cooperative Oncology Group (ECOG) performance status score ≤ 2, lesions that could be measured or otherwise evaluated, adequate haematological function (leukocyte count $>3500/\mu l$, platelet count $>100\,000/\mu l$, and haemoglobin >9.00 g/dl) and hepatic function (total serum bilirubin <2 mg/dl, and glutamic oxalacetic transaminase and glutamic pyruvic transaminase less than twice the upper limit of the normal range). Patients with breast cancer received anthracycline-based therapy for metastatic disease and/or adjuvant therapy. Patients with head and neck cancer had received considerable previous treatment: previous therapy included surgery, radiotherapy, and chemotherapy with concomitant radiotherapy. Exclusion criteria were prior exposure to VNR or a taxane.

VNR (25 mg/m^2) was administered as a slow (10 min) i.v. bolus on day 1. DTX (80 mg/m^2) was administered as a 1 h i.v. infusion on day 1. The treatment was repeated every 3 weeks. Oral steroid medication (8 mg dexamethasone) was given together with cytotoxic drug and continued on days 1 and 2.

2.2. Pharmacokinetic study design

The study comprised 23 patients who received VNR and DTX. 11 patients (schedule A) received DTX immediately followed by VNR, and 12 patients (schedule B) received VNR immediately followed by DTX infusion.

In schedule A, blood samples for analysis were obtained at the following times: prior to the start of DTX infusion, at mid-infusion, 5 min before the end of DTX infusion, immediately before VNR administration, at the end of VNR infusion, 30 min and 1 h 20 min after the end of VNR infusion, and 24 h after the start of DTX infusion. In schedule B, blood samples were obtained at the following times: prior to the start of VNR administration, at the end of VNR infusion, at DTX mid-infusion, 5 min before the end of DTX infusion, 10, 30, 50, and 1h 20 min after the end of DTX infusion, and 24 h after the beginning of VNR infusion.

VNR plasma levels at 24 h were below the limits of detection (<15–20 ng/ml).

Blood samples were collected in tubes containing potassium edetic acid from a large vein in the arm not receiving the drug infusion. Plasma was separated by centrifugation at $1000 \times g$ for 15 min at 4 °C and stored in polypropylene vials at -20 °C until analysis.

The Ethical Committee of the 'S. Giovanni Antica Sede' Hospital, Turin, Italy approved the trial and its pharmacokinetic amendments. All patients gave their witnessed informed consent, as required by Italian law.

2.3. Materials

VNR (Navelbine®) was from Pierre Fabre Labs. (Paris, France) as 1-ml vials containing 10 mg of drug in water for injection. DTX (Taxotere®) was from Rhône Poulenc Rorer (Antony, France) as a concentrated sterile solution that contained 40 mg/ml in a 2 ml vial in polysorbate 80 (Tween 80). The appropriate amount of the drug to be administered to the patient

was diluted in 5% dextrose solution so that the maximum DTX concentration was 1 mg/ml. DTX pure powder was supplied by Rhône Poulenc Rorer (Antony, France) in a vial containing 100 mg of drug. Acetonitrile and methanol were from Carlo Erba (Milan, Italy). Phosphoric acid and KH_2PO_4 were purchased from Bracco Merck (Milan, Italy). Laboratory grade distilled water was purified with removal of residuals ions and organic impurities with a Milli-Q water purification system (Millipore S.A., Molsheim, France) and filtered through a 0.25-μm membrane filter. Solid-phase extractions were performed with Sep-Pak C_{18} 3 cc (200 mg) and tC2 1 cc (100 mg) cartridges (Waters Chromatography, Milford, MA, USA). Plasma extracts were filtered through Millex SLCR (25 mm, 0.5 μm) filters (Millipore). The HPLC system consisted of a Shimadzu LC-10ADvp pump and a Shimadzu SPD-10Avp UV spectrometer. The analytical column was a stainless-steel tube Symmetry C_{18} (250 × 4.6 mm i.d.), with a Symmetry C_{18} precolumn (Waters).

2.4. Analytical procedures

2.4.1. Vinorelbine analysis and plasma extraction

The concentration of VNR in plasma was measured by a modification of a known procedure [27]. To 1-ml plasma samples, 1 ml 66 mM PBS (pH 7) and 5 ml diethylether were added. After vortex-mixing, light-protected rest and centrifugation at 3000 r.p.m for 10 min, the samples were placed in freezer at −20 °C until the water phase froze. The organic phase was then transferred into new HDPP screw-cap tubes and dried under a nitrogen stream at 25 °C. The residue was dissolved in 800 μl of the HPLC mobile phase, vortex-mixed and filtered through Millex SLCR filters; 200 μl were injected into the HPLC system. We tested various materials for compatibility with VNR and we found that both HDPP and glass tubes did not interfere with VNR analyses.

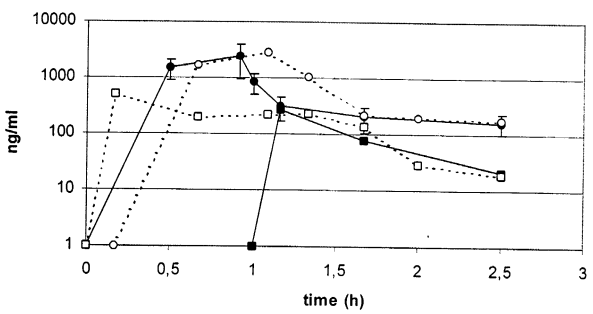

Fig. 1. Mean plasmatic levels of DTX and VNR in two administration schedules. Solid circles and squares describe the concentration versus time curves of DTX and VNR, respectively, in schedule A. Outline circles and squares describe the concentration versus time curves of DTX and VNR, respectively, in schedule B. Cp of DTX at 24 h (not reported in figure) was identical to that already found in a previous paper [28].

VNR was determined using a UV detector at a fixed wavelength of 289 nm. The mobile phase was filtered through a 0.5 μm filter (Millipore) and consisted of a mixture CH_3CN:PBS 25 mm pH ≅ 6.4 (50:50 v/v) containing 0.1 g/l sodium dodecylsulphate. The flow rate was 1 ml/min and, in these chromatographic conditions, the retention time for VNR was about 12 min. The calculated recovery was 90% at all concentrations. The limit of detection was 19 ng/ml. The inter-assay coefficient of variation ranged from 2 to 10%. Blank plasma from each patient and each cycle was also analysed and never interfered with detection. The calibration graph was determined by unweighted least-squares linear regression of peak height versus concentration.

2.4.2. Docetaxel analysis and plasma extraction

DTX was assayed in plasma using the above-described HPLC system with a solid-phase extraction following a procedure described elsewhere [28].

2.4.3. Pharmacokinetic calculations

The following non-compartmental pharmacokinetic parameters were calculated: C_{max} (peak plasma concentration), AUC (area under concentration curve) were calculated with the trapezoidal rule from 0 to the last measure (24 h); Cl (clearance), was estimated by the equation Cl = dose/AUC.

To calculate mean residence time (MRT), we used a non-compartmental modelling approach with the KINETICA 2000™ software (Innaphase, France).

C/t plasma curves were obtained by plotting at each point the mean values of docetaxel or vinorelbine obtained from 23 patients.

3. Results and discussion

The pharmacokinetics of DTX and VNR was investigated in 23 patients. Fig. 1 shows the mean plasmatic level of DTX and VNR in the two administration schedules. DTX plasma levels were similar to those previously reported [28] in both schedules A and B. VNR [29] showed a rapid plasma clearance: the initial peak level of 275–500 ng/ml decays rapidly to about 20 ng/ml after 2.5 h. VNR Cp values below this value are undetectable by HPLC.

Table 1 shows the main pharmacokinetic parameters obtained from non-compartmental analysis of the two drugs in schedules A and B. AUC, C_{max} and clearance of DTX were very little affected whether DTX infusion was before or after VNR administration (Table 1). Only MRT was effected. Instead, AUC, C_{max}, MRT and clearance of VNR were much affected by the administration sequence. The mean values of AUC, MRT and C_{max} of VNR were significantly lower for

Table 1
Non-compartmental pharmacokinetic parameters of DTX and VNR

Pharmacokinetic parameter	DTX schedule A 11 Patients Mean value ± SD	DTX schedule B 12 Patients Mean value ± SD	P *	VNR Schedule A 11 patients Mean value ± SD	VNR Schedule B 12 patients Mean value ± SD	P *
C_{max} (ng/ml)	2406 ± 1457	2822 ± 1301	n.s.	275.7 ± 125.1	499.5 ± 279.5	0.05
AUC (h·ng/ml)	2253 ± 1535	2139 ± 721	n.s.	123.5 ± 67.79	278.1 ± 88.27	<0.001
MRT (h)	0.89 ± 0.35	0.46 ± 0.14	<0.001	0.38 ± 0.08	0.81 ± 0.52	0.04
Cl (l/h)	71.89 ± 33.82	64.84 ± 37.55	n.s.	231.07 ± 94.83	112.12 ± 44.06	0.002

* P was the two-tailed probability level associated with the t-value in the Student's t-test for comparison between schedule A and B (n.s., statistically non-significant difference; $P<0.001$, highly significant difference).

schedule A (123.5 h·ng/ml, 0.38 h and 275.7 ng/ml, respectively) than for schedule B (278.1 h·ng/ml, 0.81 h and 499.5 ng/ml, respectively). The mean values of clearance of VNR were significantly higher for schedule A (231.07 l/h) than for schedule B (112.12 l/h).

VNR plasma levels (Fig. 1) and pharmacokinetic data (Table 1) showed evidence of drug interaction: they suggested that DTX infusion was associated with a rebound in VNR disposition only in patients treated with schedule B.

A possible correlation between haematological toxicity and administration protocol was also found: in protocol A, the number of neutrophils/μl at the nadir of day 8 of treatment as mean value for 12 patients was significantly higher ($P<0.001$) (315/μl ± SD = 178/μl) than those found in protocol B (12 patients) (83/μl ± SD = 40/μl). Moreover, we found a strong correlation ($P=0.037$) between the AUC of VNR and the count of neutrophils at the nadir (Fig. 2).

It is noteworthy that patients exposed to a higher plasma level of VNR (protocol B) showed a significant decrease of leukocyte count, which in turn was positively correlated to the corresponding AUC. Lastly, the plasma level of VNR showed strong interpatient variability, which may be related to its high hepatic extraction and the CytP450-dependent metabolic transformation.

DTX and VNR have shown synergistic activity in preclinical studies as well as favourable results in a phase I/II study when they were combined [9–12]. Neutropenia and neurotoxicity, which were the most prominent toxicities in most VNR/taxane combination studies, appear strongly dependent on the administration schedule [15,17,21]. No pharmacokinetic studies have been undertaken to investigate a possible relationship between adverse effects, scheduling and plasma level of the two drugs to date.

In this study, VNR appeared pharmacokinetically affected by sequential administration with DTX. Indeed, the main non-compartmental parameters, such as C_{max} and AUC, were significantly higher and clearance was lower when DTX immediately followed VNR administration (protocol B). This correlated with a significant increase of VNR plasma level corresponding to the DTX plasma peak level (C_{max}).

There are two possible ways in which the two drugs may interfere: through metabolism or the MDR (multi drug resistance) effect. Both drugs are transformed by cytochrome P450 mixed-function oxidase system (CYP3A subfamily) and the biotransformation has wide interindividual variability, which may partially explain the variability of their pharmacokinetic parameters [25,29–31]. P-glycoprotein (Gp-170), the surface plasma membrane glycoprotein overexpressed in drug-resistant tumour cells, which actively extrudes intracellular drugs [32] was found to be a receptor for both drugs albeit at different levels [33,34]. As the two drugs are excreted by a saturable mechanism, such as bile excretion, which is mediated by P-glycoprotein, it is possible that interference during the late elimination phase may increase the plasma level of one of them.

In conclusion, by studying the pharmacokinetic parameters obtained after sequential administration of DTX and VNR in cancer patients, we found some significant alteration (in particular for VNR). It is possible that, in analogy to our previous study on DTX/epirubicin interactions [28], polysorbate 80, present in the DTX formulation, may interfere with P-glycoprotein [35], producing a higher VNR cell level and thus a corresponding increase in plasma level.

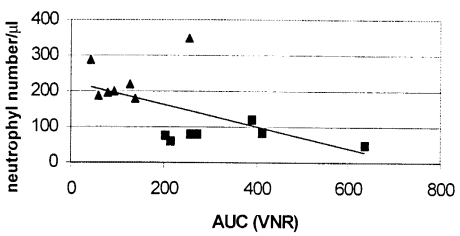

Fig. 2. Relationship between neutrophils (number/μl) and VNR AUC calculated by least-squares regression analysis. Triangles and squares describe data, respectively, in schedule A and B. The significance level of the correlation was obtained by Pearson's parameter. The critical limit of refusal of the null-hypothesis for $r=0$ was set at $\alpha=0.05$. $y=-0.31x+226.15$; $r=-0.56$; $P=0.037$

Much more work will be necessary to reach clear conclusions. At the moment it may be suggested that protocol A (DTX/VNR) may be safer for patients than protocol B (VNR/DTX) since they are exposed to lower VNR plasma level, as well as to fewer pharmacokinetic interactions and lower haematological toxicity.

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