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Short Communication

Mild to moderate liver dysfunction does not require dose reduction of oral or intravenous vinorelbine: Results of a pharmacokinetic study

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ABSTRACT

We studied the pharmacokinetic profile of weekly oral and intravenous vinorelbine in cancer patients with various degrees of hepatic function, and assessed an intra-patient comparison of the pharmacokinetics of i.v. versus oral vinorelbine. In this open-label study, patients were randomised to receive an initial dose of vinorelbine at day 1 by either i.v. or the oral route followed by a second dose on day 8 via the alternative route.

A total of 16 patients were included, 12 patients received the planned two administrations. Toxicities were similar for all cohorts and were mainly of haematological and gastrointestinal origin. Pharmacokinetic analysis of both routes did not reveal any differences between cohort I and II.

Based on these findings in patients with mild to moderate liver dysfunction no dose modifications of vinorelbine have to be taken into consideration.

1. Introduction

Vinorelbine, 5′-nor-anhydrovinblastine, is a hemi-synthetic vinca-alkaloid with a mechanism of action, i.e. disruption of microtubules by the reversible binding to tubulin resulting in mitotic spindle dissolution and metaphase arrest in dividing cells, similar to that of other vinca-alkaloids. Recently an oral formulation of vinorelbine was developed that appeared to be safe, albeit with a relatively sharp therapeutic threshold between 60 and 80 mg/m^2.[1–7] Pharmacokinetics (PK) of vinorelbine are linear. Vinorelbine undergoes substantial hepatic metabolism in humans and 34–85% of vinorelbine can be discovered in faeces suggesting excretion in bile. As a consequence, liver impairment could be a possible confounding factor in vinorelbine pharmacokinetics. Yet, for i.v. vinorelbine only severe liver impairment was suggested to affect clearance.[8] We studied the pharmacokinetic profile of weekly oral and intravenous vinorelbine in cancer patients with various degrees of hepatic function, based on bilirubin and AST/ALT levels and assessed an intra-patient comparison of the pharmacokinetics of i.v. versus oral vinorelbine.

2. Patients and methods

2.1. Eligibility criteria

Patients with a cytologically or histologically confirmed diagnosis of a solid tumour refractory to standard therapy or for

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whom no standard therapy options existed or for whom vinorelbine was considered a standard therapeutic option were eligible. Additional criteria included age between 18 and 75 years; Karnofsky performance status $\geqslant$70%; a life expectancy $\geqslant$4 weeks; $\geqslant$3 weeks between the last chemotherapy, radiotherapy and/or hormonal therapy and start of VRL therapy; resolution of the toxic effects of prior therapies; an adequate bone marrow (haemoglobin $\geqslant$10 g/dl, absolute neutrophil count $\geqslant 2.0 \times 10^9$/L, platelet count $\geqslant 100 \times 10^9$/L) and renal function (serum creatinine $\leqslant 1.5 \times$ ULN or creatinine clearance >60 mL/min). Specific exclusion criteria included malabsorption syndrome; major resection of the stomach or proximal small bowel and/or concomitant medication known to inhibit or induce enzymatic activity in the liver e.g. CYP 3A4, amongst others. This study was approved by the local ethics committees and all patients gave written informed consent prior to study entry.

2.2. Study design

This was an open-label, pharmacokinetic study in which patients were randomised to receive an initial dose of vinorelbine (VRL) at day 1, by either i.v. or the oral route. The second dose on day 8 was administered by the alternative administration route. Starting doses depended on the cohort the patient was assigned to according to liver function (Table 1). Based on the oral bioavailability of vinorelbine of 36–43%, oral doses were determined equivalent to i.v. dose of 25 mg/m^2, 20 mg/m^2 and 15 mg/m^2 resulting in oral doses of 60 mg/m^2, 50 mg/m^2 and 40 mg/m^2, respectively.

Six evaluable patients were required in each cohort. Inclusion of patients in cohort III could only start after inclusion of patients in cohort I and II was completed.

Treatment modifications were based on complete blood counts obtained within 24 h prior to dosing.

2.3. Study drug administration

Oral and i.v. vinorelbine were supplied by Pierre Fabre Medicament. Intravenous VRL was administered at doses of 17, 21 or 25 mg/m^2 and oral VRL was administered at doses of 40, 50 or 60 mg/m^2 depending on the cohort. For patients with a BSA >2.0 m^2, a BSA of 2.0m^2 was used for dose calculation for safety reasons, in the absence of appropriate data. The reconstituted VRL for i.v. infusion was mixed in 50 mL of normal saline 0.9% and then infused during 6–10 min using the side injection port of a peripheral line running 500 mL of normal saline 0.9%. The oral VRL capsules were taken with food. The study drug was given once by i.v. and once by oral route on a weekly basis for 2 weeks unless disease progression and/or unacceptable toxicity. After the end of the pharmacokinetic study, treatment could be continued with i.v. vinorelbine at the discretion of the investigator. Before treatment concomitant medication was checked for known interference with enzyme activity in the liver.

2.4. Pharmacokinetic sampling and data analysis

For pharmacokinetic analysis, two blood samples of 2.5 mL each were collected using an indwelling i.v. canula in the opposite arm to the infusion before dosing and 10 and 30 min, and 1, 1.5, 3, 6, 9, 24, 48, 96 and 168 h after start of VRL infusion or before dosing and 15, 30 and 45 min, and 1, 1.5, 3, 6, 9, 24, 48, 96 and 168 h after intake of oral VRL. The samples were collected in heparinised, siliconised treated glass tubes and were immediately frozen at −20 °C after collection.

Pharmacokinetic analysis included the observed peak blood concentration (C_{max}), the time to reach C_{max} (T_{max}), the area under the concentration versus time curve (AUC_{last}), the area under the concentration versus time curve extrapolated to infinity (AUC_{inf}), the terminal blood half-life ($T_{1/2}$), the apparent total clearance Cl_{tot}/F, the apparent volume of distribution at steady-state (Vd_{ss}/F) and the absolute bioavailability (F). Considering the low number of patients in this study, the statistical analysis was only exploratory. Comparison of body exposure between i.v. and oral routes was performed by analysis of variance. AUC_{inf} and AUC_{last} were compared between the i.v. and oral administration, and between the sub-groups of liver impairment. Additionally, bioavailability (F) was compared between sub-groups of liver impairment.

3. Results

Amongst the 16 patients treated in the study, 12 patients received the two administrations as planned per protocol. A total of 35 cycles were given. No differences in toxicities were observed between the different cohorts and between the oral and i.v. formulation.

3.1. Pharmacokinetics

Following i.v. vinorelbine administration blood concentrations decreased sharply over the first hours, and then slower distribution and elimination phases took place. There was no obvious difference between cohorts I and II. Higher concentrations were observed in the single patient available in cohort III.

Table 1 – Cohorts according to liver impairment.

Bilirubin	Transaminases (ALT and/or AST)	Cohort	Dose level		Number of evaluable patients
			i.v. VRL (mg/m^2)	Oral VRL (mg/m^2)	
<1.5 × ULN	1.5–2.5 × ULN	I	25	60	6
1.5–3 × ULN	Any	II	20	50	6
>3–10 × ULN	Any	III	15	40	0

Table 2 – Pharmacokinetic parameters of vinorelbine (mean, SD).

Cohort	Route and dose (mg/m^2)	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} [(ng/mL) h]	AUC_{inf} [(ng/mL) h]	Cl_{tot} (L/h)	Vd_z (L)	$T_{½\ z}$ (h)	F (%)
I	IV – 25 (n = 8)	–	1231.1 (693.0)	1076 (325)	1135 (335)	43.2 (14.6)	2705 (1390)	44.6 (14.2)	–
	Oral – 60 (n = 7)[a]	2.08 (1.22)	129.3 (72.1)	646 (460)	705 (460)	–	–	54.1 (12.9)	24.7 (9.9)
II[(1)]	IV – 21 (n = 5)[ab]	–	944.4 (497.5)	1029 (404)	1085 (404)	40.3 (14.4)	2854 (1082)	51.2 (11.8)	–
	Oral – 50 (n = 6)[b]	1.39 (0.90)	105.3 (63.5)	676 (384)	865 (416)[c]	–	–	40.9 (11.1)[c]	31.6 (14.8)[ac]
III	IV – 17 (n = 1)[a]	–	1603.9	2245	2641	11.7	373	22.7	–

C_{max}; the observed peak blood concentration. T_{max}; the time to reach C_{max}. AUC_{last}; the area under the concentration time curve. AUC_{inf}; the area under the concentration time curve extrapolated to infinity. Cl_{tot}; total clearance. Vd; the volume of distribution. $T_{1/2}$; the terminal blood half-life. F; absolute bioavailability.

[a] One VRL administration missing in the OR/IV or IV/OR sequence.

[b] One patient not included (received 17 mg/m^2 VRL and presented unreliable oral profile).

[c] Two patients with extrapolated AUC >15% and less than three values for terminal slope calculation.

Following oral vinorelbine administration blood concentrations peaked rapidly in both cohorts I and II at 1.5–2 h, and no difference was observed in the elimination phase between the two cohorts. The single patient of cohort III withdrew from the study after the i.v. administration and therefore no data for the oral period were available. Pharmacokinetic parameters were very similar between cohorts I and II: 43.2 ± 14.6 versus 40.3 ± 14.4 L/h for total clearance and 2705 ± 1390 versus 2854 ± 1082 L for apparent volume of distribution (see Table 2). The single patient from cohort III presented very low values for both total clearance and volume of distribution, resulting in a short elimination half-life (22.7 h).

The absolute bioavailability of the oral form was 24.7 ± 9.9% and 31.6 ± 14.8% in cohorts I and II, respectively.

4. Discussion

We studied the pharmacokinetic and safety profile of weekly oral and intravenous vinorelbine in cancer patients with various degrees of hepatic function, based on bilirubin and AST/ALT levels, and assessed an intra-patient comparison of the pharmacokinetics of i.v. versus oral vinorelbine. Our main objective was to determine whether the PK of oral or i.v. vinorelbine was modified in patients presenting with liver dysfunctions.

Surprisingly, while liver dysfunction (LD) was expected to impact the metabolism by reducing the first-pass effect, and as a consequence to increase the absolute bioavailability of oral vinorelbine, an apparent decrease of bioavailability was observed in the mild (cohort I) and moderate (cohort II) LD groups. The first-pass effect seems unlikely to be the origin of the decrease in bioavailability since the opposite effect is generally expected in liver dysfunction and since, no effect was observed with the i.v. administration. This was further supported by the very low levels of DVRL (4-O-deacetyl-vinorelbine) observed in this study as compared to those described by Marty.[2] The slightly higher absolute bioavailability observed in the moderate (31.6%) group as compared to that observed in the mild (24.7%) group was probably the consequence of lower number of values (n = 3) in the moderate group since, when including the two patients with over-extrapolation of AUC (>15%), mean absolute bioavailability was 26.3%. The inclusion of only one patient in cohort III makes it rather impossible to draw any conclusions on required dose modification in the case of severe liver dysfunctions.

Pharmacokinetic parameters after the i.v. administration of VRL in mild to moderate liver dysfunction were very similar to those obtained in patients with normal liver function.[1,9,10] Neither drug clearance nor steady-state volume of distribution was modified in patients with liver dysfunction. As a consequence, the pharmacokinetic modification observed in the oral administration of vinorelbine was specific to that route.

These results contrast with those from other vinca-alkaloids. With vincristine and vinblastine, altered pharmacokinetics and increased exposures were observed following i.v. administrations in patients presenting with liver dysfunction.[3] Conversely, in the current study, the blood exposures following both oral and i.v. vinorelbine administrations were independent of the bilirubin levels, the criteria used to classify liver dysfunction.

Based on these findings in patients with mild to moderate liver dysfunction no dose modifications of vinorelbine have to be taken into consideration.

Conflict of interest statement

None declared.

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