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ORIGINAL ARTICLE

Evaluation of oral versus intravenous dose of vinorelbine to achieve equivalent blood exposures in patients with solid tumours

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Abstract Patient's preference is for oral chemotherapy when both oral and i.v. are available, provided that efficacy is equivalent. Reliable switch from oral to i.v. is possible if correspondence between respective doses has been established. Vinorelbine oral was developed as a line extension of VRL i.v. on the basis that similar AUCs result in similar activities. From a first crossover study on 24 patients receiving VRL 25 mg/m^2 i.v. and 80 mg/m^2 oral data extrapolation concluded on AUCs bioequivalence between Vinorelbine 30 mg/m^2 i.v. and 80 mg/m^2 oral. A new trial was performed to support this calculation. In a crossover design study on patients (PS 0-1) with advanced solid tumours (44% breast carcinoma), VRL was administered (30 mg/m^2 i.v., 80 mg/m^2 oral) with a standard meal and 5-HT$_3$ antagonists, at 2 weeks interval. Pharmacokinetics was performed over 168 h and VRL was measured by LC-MS/MS. Statistics included bioequivalence tests. Forty-eight patients were evaluable for PK: median age 58 years (25–71), PS0/PS1: 20/28, M/F: 11/37. Mean AUCs were 1,230 ± 290 and 1,216 ± 521 ng/ml for i.v. and oral, respectively. The confidence interval of the AUC ratio (0.83–1.03) was within the required regulatory range (0.8–1.25) and proved the bioequivalence between the two doses. The absolute bioavailability was 37.8 ± 16.0%, and close to the value from the first study (40%). Patient tolerability was globally comparable between both forms with no significant difference on either haematological or non-haematological toxicities (grade 3–4). This new study, conducted on a larger population, confirmed the reliable dose correspondence previously established between vinorelbine 80 mg/m^2 oral and 30 mg/m^2 i.v.

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Introduction

Vinorelbine (5′-noranhydrovinblastine, VRL) is a semi-synthetic anticancer agent of the vinca alkaloid group. VRL cytotoxic effect is mediated through inhibition of the polymerization of tubulin dimmers into microtubules, which results in the disruption of mitotic spindle formation. The efficacy of VRL (Navelbine®, Pierre Fabre Médicament, France) has been demonstrated in non-small cell lung cancer (NSCLC) [5, 6, 10] and advanced breast cancer (ABC) [8, 16, 18]. VRL was initially developed as an intravenous formulation (Navelbine® i.v.) and the recommended therapeutic dose was generally 30 mg/m^2 week as single agent or 25 mg/m^2 week when combined with other chemotherapies. However, few other dosing schedules are

used including day 1 and day 8 every 3 weeks, or day 1 and day 5 every 3 weeks. More recently, an oral form of VRL has been marketed (Navelbine® oral) for the same indications: NSCLC and ABC. Therefore, when combining with other antineoplastic agents and/or radiotherapy, and according to the selected schedule, the available options are either full oral or combined i.v./oral administrations.

Patients' preference for oral chemotherapies (CT) was demonstrated in two surveys [2, 11], and in 89% of patients preferring oral CT the main concern was to be assured of a similar or better efficacy than with i.v. treatment. Therefore, concomitant or alternative use of oral chemotherapies when both oral and i.v. forms of the same drug are available represents a substantial interest provided that adequate oral and i.v. corresponding doses are determined. Navelbine® oral was developed as a line extension of Navelbine® i.v., based on the axioma that a comparable blood exposure achieved from the two forms will result in similar activity. The compound is formulated as a ditartrate salt and therefore presents a large aquous solubility, and is stable in physiological conditions. The absolute bioavailability of oral vinorelbine was evaluated in a phase I study comparing 25 mg/m^2 i.v. to 80 mg/m^2 oral vinorelbine [13]. Higher drug concentrations were observed with the oral dose, and dose-adjusted data indicated that comparable blood concentrations were to be achieved between 30 mg/m^2 i.v. and 80 mg/m^2 oral. Dose-proportional increases of exposures have been demonstrated for both the i.v. form in the 15–45 mg/m^2 range [9] and the oral form in the 60–100 mg/m^2 range [1]. Nevertheless, a new specific study with administration of these two doses was requested by one European Health Agency during the drug approval process. Therefore, the current study was aimed at confirming the exposure equivalence between 80 mg/m^2 oral versus 30 mg/m^2 i.v., by a direct pharmacokinetic comparison within the same patients.

Patients and methods

Study design

This trial was an open, phase I, multicentre, randomized, crossover pharmacokinetic study. Fourteen clinical centers in four European countries were involved. The study was authorized by the National Health authorities according to legal requirements, and the protocol was approved by the local Ethics Committees before the inclusion of patients. The study was performed in accordance with the principles stated in the Declaration of Helsinki and in accordance with the European Good Clinical Practice guidelines. Patients were randomized to receive first either 80 mg/m^2 oral or 30 mg/m^2 i.v. VRL, followed by the opposite form after a 2-week washout period. For both administrations, patients were overnight fasted, were allowed to have a meal 2 h after dosing, and were administered oral 5HT3 antagonists 2 h before VRL administrations. For intravenous administration, VRL supplied as 10 mg/ml vials (Navelbine® i.v.) was infused through an electric pump driver over a 10 min period, whereas for oral administration VRL supplied as 20 and 30 mg capsules (Navelbine® oral) had to be rapidly swallowed under nurse control with a glass of water without chewing or sucking the capsules. For BSA > 2 m^2, the total administered dose was limited to 60 mg for i.v. and 160 mg for oral administrations, as stated in the drug approval. A total of 48 evaluable patients were planned for pharmacokinetics (PK), i.e. complete blood sampling for the full sequence (oral–i.v. or i.v.–oral) and no vomiting during the first 3 h after oral dosing. The sample size was determined according to Diletti et al. [7] to attain a power of 80% in the case of multiplicative model, $\propto$ = 5%, range (0.80–1.25) and a coefficient of variation of residual error at 22% determined from Marty et al. study [13].

Patients selection

To be eligible for the study, the following criteria had to be fulfilled: male or female patients aged 18–70 years, any kind of cytologically or historically confirmed malignant solid tumour or lymphoma, two lines maximum prior chemotherapies and stopped 4 weeks before, PS0-1, normal blood cell count and normal renal and liver functions. The main non-inclusion criteria were pregnant or lactating women, symptomatic involvement of the brain, long term oxygen therapy, active infection, clinically relevant cardiovascular disease, any alteration of gastro-intestinal tract likely to impact on drug absorption/elimination, concomitant treatment with known inducers/inhibitors of CYP3A4.

Pharmacokinetics

Pharmacokinetics was assessed during the first and the second administrations of VRL. Blood samples (3 ml) were collected as follows, according to the administered form. For i.v. VRL: pre-dose, 10 min, 20 min, 40 min, 1, 1.5, 3, 6, 9, 24, 48, 96 and 168 h. For oral VRL: pre-dose, 15 min, 30 min, 45 min, 1, 1.5, 3, 6, 9, 24, 48, 96 and 168 h. 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 [17] routinely used for VRL PK studies. Briefly, the technique consisted in a deproteinisation by methanol, addition of vinblastine as internal standard, separation on a cyano-chromatographic column and detection through electrospray ionization. The lower limit of quantification (LLOQ) was 0.25 mg/ml. The

inter- and intra-assay variabilities expressed as coefficient of variation were both lower than 6%.

Pharmacokinetic parameters were calculated through a model-independent method using Kinetica (v. 4.1) software under Windows NT4 for oral VRL while a model-dependent population PK approach was used for i.v. VRL [14]. Use of a model approach for i.v. was necessary since two blood samplings were missing in the distribution phase before the protocol was amended. Blood samples of few patients ($n = 13$) were analysed to control the study experimental conditions. Results evidenced that the sampling scheme was inadequate to describe the i.v. profile (insufficient sampling in the pharmacokinetic distribution phase) and that two additional blood samplings during the first hour were necessary.

Additional blood samplings

Three samplings were initially collected over the first hour: pre-dose, 10 min and 1 h. Since vinorelbine was infused over 10 min, two additional samplings were necessary between the end of infusion and 1 h. The absence of samplings at 20 and 40 min produced large bias on the blood exposure after i.v. administration.

Consequently, additional sampling between 10 min and 1 h (T_0 + 20 min and T_0 + 40 min) was required to obtain accurate and reliable values of blood exposures for the i.v. route.

Pharmacokinetic data analysis

A bias on AUC estimates occurred when using trapezoidal calculations on insufficient sampling schemes while it was circumvented when using a population PK modelling.

Therefore a population PK model was set up using all the patients (with or without full sampling) and individual PK parameters were calculated by Bayesian approach using POSTHOC option in NONMEM. Descriptive statistics were performed using PROC SUMMARY procedure of SAS software (v. 8.2.).

In order to assess whether comparable VRL AUCs were achieved between the 30 mg/m^2 i.v. and 80 mg/m^2 oral dosings, statistical analysis of equivalence of exposure were performed on AUC_{inf}: Differences between 80 mg/m^2 oral (test compound) and 30 mg/m^2 i.v. (reference compound) vinorelbine on log-transformed AUC_{inf} were investigated using an analysis of variance (cross-over analysis with patient (sequence) and route × sequence testing) by PROC GLM procedure of SAS software.

The confidence interval at 90% ($CI_{90\%}$) of the ratio [test (oral)/reference (i.v.)] was calculated and compared with the interval (0.8–1.25), as recommended by international guidelines.

If $CI_{90\%}$ was included in this interval, the two routes of administration could be stated as bioequivalent AUCs [4].

Pharmacokinetic/pharmacodynamic analysis

Relationships between VRL blood exposure and haematological toxicities on white blood cells (WBC) and neutrophils were studied.

The variation of blood cell counts at nadir after the administration of vinorelbine was calculated by:

$$\%\ \text{nadir} = 100 \times \frac{\text{Count at nadir} - \text{Count at baseline}}{\text{Count at baseline}}$$

Linear correlations between VRL AUC_{inf} and % nadir WBC or neutrophils were searched for using Excel worksheets (version 2000), taking account the administration number and the route of administration.

Safety assessment

Tumour evaluation, electrocardiogram, and complete medical history with special focus on previous treatments for the disease were performed before treatment. Then, physical examination, haematology, serum biochemistry and reporting of all adverse events graded according to NCI Common Toxicity Criteria (version 2.0) were collected after each administration.

Results

Fifty-five patients were included in the study to obtain the 48 patients evaluable for pharmacokinetics. Among the seven patients non-evaluable for PK, one was included but not treated, two received only one administration, and four did not comply with the protocol. In the evaluable group, 23 patients received the sequence oral/i.v. while 25 patients received the opposite sequence. A brief description of patients' characteristics is presented in Table 1.

The median age of the whole population was 57.9 years and more than half of them had a performance status equal to one. Breast was the most frequent primary tumour site (44%) followed by lung (14%). Other solid tumours included head and neck (6%), melanoma (6%), kidney (8%), cervix uteri and ovary (13%). The majority of patients in each arm had at least two organs involved and lung was the most frequent organ (about 57%).

The tolerability of the two administrations, 80 mg/m^2 oral and 30 mg/m^2 i.v. vinorelbine, was acceptable with a very small incidence of grade 3–4 toxicities that were comparable for both routes of administration (Table 2). No sequence effect was detected, allowing to merge data collected during periods 1 and 2 for a same route of administration

Table 1 Patient characteristics

	Oral followed by i.v. *N* (%)	i.v. followed by oral *N* (%)	Total *N* (%)
Evaluable for pharmacokinetics	23	25	48
Median age (range)	58.6 (40.5–71.3)	57.2 (25.3–70.9)	57.9 (25.3–71.3)
WHO PS = 0/1	10 (44)/13 (57)	10 (40)/15 (60)	20 (42)/28 (58)
Gender: female	19 (83)	18 (72)	37 (77)
Primary tumour site			
Breast	10 (44)	11 (44)	21 (44)
Lung	3 (13)	4 (16)	7 (14)
Others	10 (43)	10 (40)	20 (42)
Metastatic disease	20 (87)	24 (96)	44 (92)
Liver involvement	7 (30)	7 (28)	14 (29)

Table 2 Overall incidence of adverse events

	Oral VRL		i.v. VRL	
	All *n* (%)	Grade 3–4 *n* (%)	All *n* (%)	Grade 3–4 *n* (%)
Haematological toxicity				
Leucopenia	16 (37.2)	2 (4.7)	20 (43.5)	1 (2.2)
Neutropenia	12 (27.9)	3 (7.0)	21 (45.7)	3 (6.5)
Anaemia	24 (55.8)	0	25 (54.3)	0
Thrombocytopenia	3 (7.0)	0	5 (10.9)	1 (2.2)
Non-haematologicaltoxicity				
Nausea	19 (39.6)	0	10 (20.8)	0
Vomiting	16 (33.3)	0	11 (22.9)	0
Diarrhoea	13 (27.1)	0	7 (14.6)	1 (2.1)
Constipation	6 (12.5)	0	11 (22.9)	0
Fatigue	12 (25.0)	1 (2.1)	14 (29.2)	1 (2.1)
Anorexia	4 (8.3)	0	4 (8.3)	
Neuro-sensory	3 (6.3)	0	2 (4.2)	0

Pharmacokinetics

Mean PK profiles are plotted on Fig. 1. They illustrate very close concentrations achieved following the oral and i.v. respective doses. A very sharp decrease of VRL blood concentrations occurred during the first minutes following the end of intravenous infusion. In the meanwhile, blood concentrations increased rapidly during the absorption process following oral administration. As a result, a similar range of blood concentration was achieved for both routes 1 h after VRL administration (Fig. 2).

As a consequence, very similar blood AUCs (mean ± SD) were obtained: 1,230 ± 290 and 1,216 ± 521 ng/ml^{-1} h for 30 mg/m^2 i.v. and 80 mg/m^2 oral VRL, respectively. The resulting absolute bioavailability of oral VRL calculated on AUC_{inf} was 37.8 ± 16.0%.

In order to evaluate whether the oral and i.v. AUCs were bioequivalent, an analysis of variance and a test of bioequivalence were carried out in a similar way to what was done in the first bioavailability study [13]. Sequence or period effects were not significant, nor was the route of administration. A patient effect, commonly detected in bioequivalence studies with crossover design, was observed, and reflected the inter-patient variability. The 90% confidence interval ($CI_{90\%}$) of the AUCs ratio was (0.826–1.025) and was within the required regulatory interval (0.80–1.25), allowing to conclude that the AUCs following oral and i.v. dosing were bioequivalent (Table 3).

Pharmacokinetics/pharmacodynamics

Although very limited severe toxicities were reported a decrease in blood formulae was observed, as expected, haematological toxicity being the major dose-limiting toxicity of VRL treatment. The PK/PD analysis was focused on the first dosing period because blood formulae during the second period is highly influenced by the first dosing. A significant relationship was observed between the percentage of blood cell count decrease at nadir *vs.* baseline and blood AUCs (Fig. 3).

The mean decrease values of cell count were –40.6 and –37.2% for WBC, –50.4 and –47.9% for PNN, for i.v. and oral dosing, respectively. As expected, the relationship was very comparable between the two routes of administration, supporting the axiom that a defined effect is produced by a defined AUC whatever the route of administration.

Discussion

The availability of two routes of administration and therefore of two pharmaceutical forms of a cytotoxic drug may represent a real advantage for the patient and the oncologist. Because oral VRL was developed as a line extension of i.v. VRL, a reliable dose correspondence must

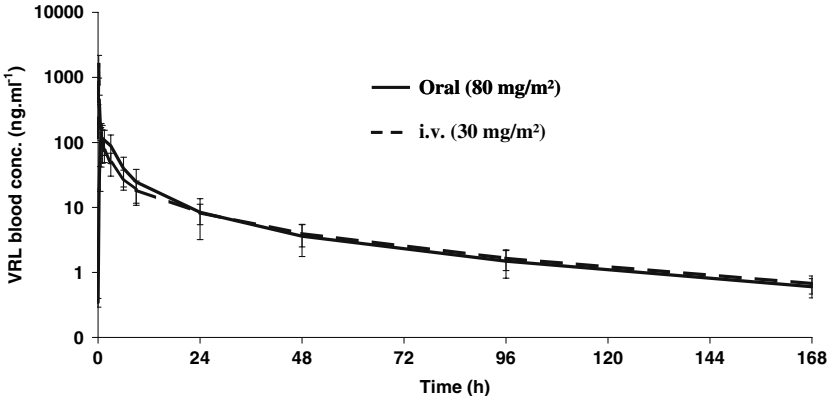

Fig. 1 Mean VRL blood concentration profiles (n = 48). Scale 0–168 h

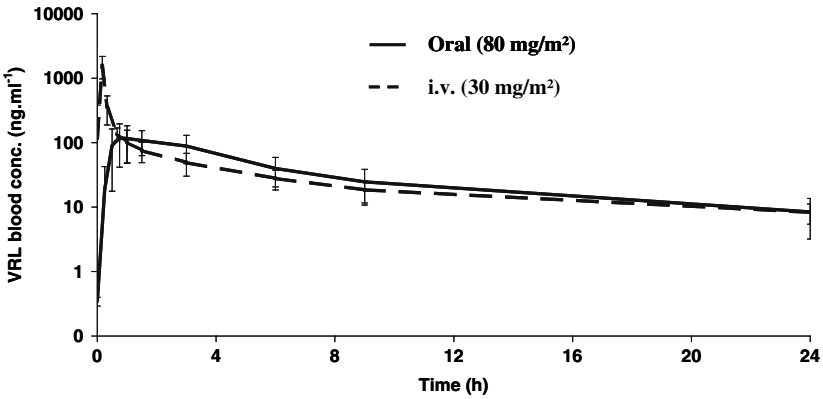

Fig. 2 Mean VRL blood concentration profiles (n = 48). Scale 0–24 h

be established between oral and i.v. dosing in order to fully benefit from the acquired knowledge from the i.v. form.

When administering i.v. or oral VRL, the PK profiles may differ, obviously on C_{max} and possibly on AUCs. Both parameters may have an influence on drug activity (efficacy/toxicity), and therefore must be investigated in order to detect whether they are relevant for oral and i.v. dosing comparison. Since leucopenia and neutropenia represent the major dose-limiting toxicities of VRL treatment, the relevance of C_{max} and AUC was assessed on their PK/PD relationship with haematological toxicity. Data from 113 patients from phase I/II studies illustrated a significant relationship of leucopenia and neutropenia with either C_{max} or AUCs (Figs. 4, 5). However, when considering the PD effect, a defined neutropenia or leucopenia could be produced by C_{max} ranging 0–400 and 600–2,000 ng/ml for oral and i.v. VRL, respectively, illustrating the non-relevance of this parameter. The relationship

Table 3 Comparison (mean ± SD) PK parameters

Parameters	Marty et al. study [13] (n = 24)		Current study (n = 48)		Lush et al. study [12] (n = 19)	
	Oral route (80 mg/m^2)	i.v. route (25 mg/m^2)	Oral route (80 mg/m^2)	i.v. route (30 mg/m^2)	Oral route (70 mg/m^2)	i.v. route (30 mg/m^2)
T_{max} (h)	1.4 ± 1	0.3 ± 0.1[a]	1.6 ± 1.15	0.20 ± 0.13[a]	1.0 ± 0.6	0.3 ± 0.1
C_{max} (ng/ml)	133 ± 42	762 ± 185[a]	143 ± 68	1505 ± 747[a]	138 ± 66	1,877 ± 882
AUC_{last} (h ng/ml)	1,148 ± 436	883 ± 346	1,165 ± 518	–	940 ± 527	1,212 ± 366
AUC_{inf} (h ng/ml)	1,299 ± 487	1,042 ± 392	1,216 ± 521	1,230 ± 290	1,062 ± 583	1,397 ± 380
$T_{1/2z}$ (h)	29.4 ± 7.9	37.9 ± 10.2	50.5 ± 11.0	48.4 ± 7.9	51.1 ± 12.1	49.1 ± 10.0
Cl_{tot}/F (l/h kg)	1.88 ± 0.76	0.72 ± 0.25	2.14 ± 1.54	0.67 ± 0.19	–	46.7 ± 10.9[b]
V_{ss}/F (l/kg)	49.9 ± 28.6	21.2 ± 9.2	63.2 ± 34.1	21.7 ± 8.1	–	–
F (%) on AUC_{inf}	40.0 ± 10.0	–	37.8 ± 14.0	–	33.0 ± 18.0	–

[a] End of the infusion

[b] l/h

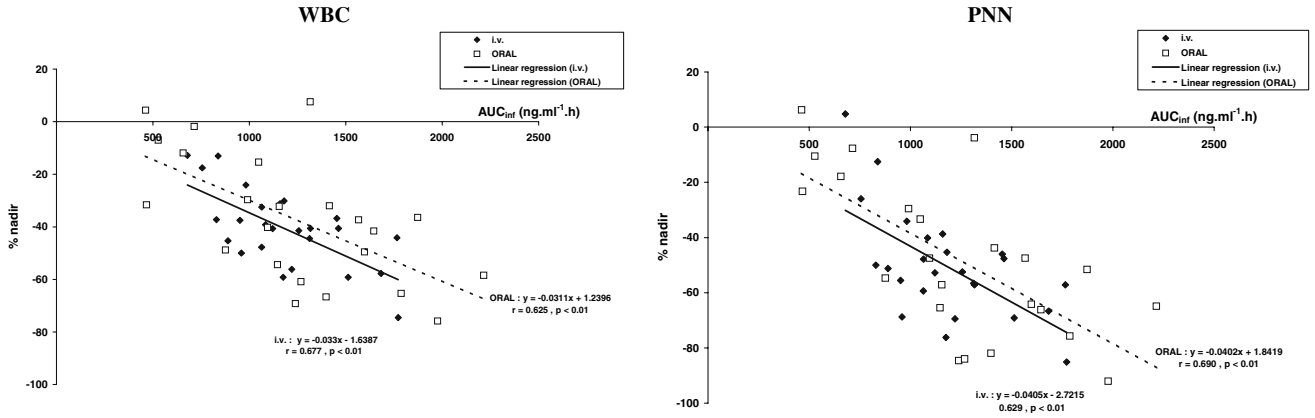

Fig. 3 Pharmacokinetic/pharmacodynamic relationships between % nadir and vinorelbine AUC_{inf} after the first administration

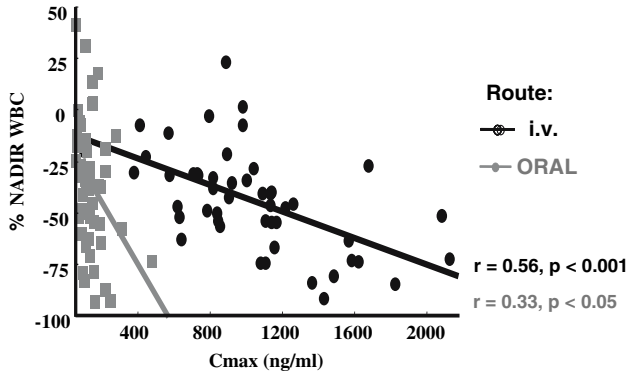

Fig. 4 VRL PK/PD relationship: C_{max} with leucopenia

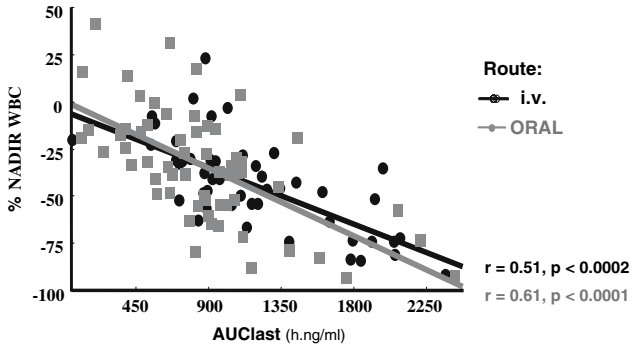

Fig. 5 VRL PK/PD relationship: AUC with leucopenia

between C_{max} and PD was due to the very strong relationship between C_{max} and AUC. These two parameters are not independent and C_{max} reflects the strong relationship between PD and AUC. As a consequence, AUC alone was the selected criteria to determine reliable dose correspondence between oral and i.v. VRL.

In this perspective, a crossover study design is the most powerful when there is no carry-over effect of one period onto the following one. Due to the use in the current study of a LC–MS/MS method ten times more sensitive than the HPLC one used in previous studies, the two administrations were separated by 2 weeks instead of one in a weekly schedule to prevent residual blood concentrations before the second VRL administration [1, 3, 9, 13].

The absolute bioavailability of oral vinorelbine soft capsules has been evaluated in two previous studies. In the first study conducted with a similar design on 24 evaluable patients, Marty et al. [13] compared 25 mg/m^2 i.v. to 80 mg/m^2 oral. They demonstrated that VRL blood concentrations were higher following the oral dosing than following the i.v. and therefore that the respective dosing did not produce bioequivalent exposures. Based on the linearity of the VRL PK, they adjusted the oral and i.v. concentration datasets to simulate 30 mg/m^2 i.v. dosing, and concluded on bioequivalent AUCs between 80 mg/m^2 oral and 30 mg/m^2 i.v. VRL.

The second bioavailability study published by Lush et al. [12] was conducted with a similar design on 19 evaluable patients, and compared 30 mg/m^2 i.v. with 70 mg/m^2 oral VRL. The authors concluded that the mean absolute bioavailability of oral VRL was 33% and as a consequence that 30 mg/m^2 i.v. and 90 mg/m^2 oral should generate comparable AUCs.

These first two studies have been accurately compared in order to investigate the origin of the apparent differences in the dose equivalence [15]. It was demonstrated that the discrepancies were due mostly to a difference on AUCs during the i.v. infusion period whereas AUCs following oral administrations were very close between both studies.

The dose-adjusted indirect comparison completed in the first study [13] was not accepted by one European Health Agency and this was the reason for the current study. Results collected on 48 evaluable patients confirmed the

previous conclusions from Marty et al. [13], and reproducible data were collected (see Table 3). Concerning oral administrations, time to peak was about 1 h-and-a-half in the two studies, and C_{max} were comparable. The elimination half-life is longer in the current study (50 vs. 29 h) and is the direct consequence of longer sampling time (7 vs. 3 days). However, this late part of the PK profile has a very little contribution in the blood AUC. Total AUCs (0–∞) calculated on either 29 or 50 h half-life values were similar, as were AUCs 0–72 h or AUCs 0–168 h. Concerning i.v. administration, the current data confirmed those calculated by dose-adjustment [15] in Marty's study [13]. Concerning the inter-patient variability on oral AUCs, the coefficient of variation (CV % = 100 × SD/mean) in the current study (43%) is close to that calculated in Marty's study (37%) but lower than that calculated in Lush's study (55%). For the i.v. route, CV is 27% in the current study vs. 38% in Marty's and 27% in Lush's whereas it was 37% in Khayat's study [9] exploring the PK linearity of i.v. vinorelbine on 18 patients. It is worthy to note that the two studies provided very similar data and conclusions although they differed in some methodological aspects. In the first study, the comparison between 25 mg/m^2 i.v. and 80 mg/m^2 oral was considered inadequate by one Agency since dose-adjusted data based on linearity assumption were used. The current study compared directly the adequate doses. Blood samples were collected over 72 h (1–2 half-lives) in the first study versus 168 h (4 half-lives) in the current study. LC–MS/MS was used in the present study instead of HPLC (less sensitive) and, lastly, twice more patients were enrolled in the current study.

In conclusion, the current study conducted on 48 evaluable patients confirmed the reliability of bioequivalent AUCs achieved with 80 mg/m^2 oral VRL versus 30 mg/m^2 i.v. VRL. This has resulted in similar haematological toxicity, the major DLT of treatment, used as a surrogate marker of activity. The i.v./oral dose correspondence will enable oncologists to benefit from their previous experience on i.v. dosing when switching to equivalent oral VRL dosing.

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