How to manage intravenous vinflunine in cancer patients with renal impairment: results of a pharmacokinetic and tolerability phase I study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Vinflunine, a novel tubulin-targeted inhibitor, is indicated as a single agent for the treatment of bladder cancers after failure of prior platinum-based therapy.
- In cancer patients, vinflunine is predominantly metabolized by both CYP3A4 and multiple esterases and about one third of a total radiolabelled dose is recovered in urine.

WHAT THIS STUDY ADDS

- The pharmacokinetics and tolerability of vinflunine were evaluated in patients with renal impairment.
- A 12% and 22% dose reduction, respectively, are needed in patients with moderate (creatinine clearance (CL_{cr}) between 40 and 60 ml min⁻¹) and severe renal impairment (CL_{cr} between 20 and <40 ml min⁻¹). A 50% dose reduction is suggested in patients with end stage renal disease undergoing dialysis.

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Keywords

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AIMS

Vinflunine (VFL) ditartrate, a novel tubulin-targeted inhibitor, is registered for the treatment of patients with advanced or metastatic urothelial transitional cell carcinoma. This phase I study assessed the effect of renal impairment on the pharmacokinetics and tolerability of VFL.

METHODS

VFL was infused in patients with advanced/metastatic solid tumours once every 3 weeks with anticipated dose reduction on the first cycle stratified according to the creatinine clearance (CL_{cr}) values. Pharmacokinetic data were collected on the first two cycles in renally impaired patients ($CL_{cr} \leq 60$ ml min⁻¹) and were compared with a control cohort of patients ($CL_{cr} > 60$ ml min⁻¹).

RESULTS

Thirty-three patients (46–86 years) were treated, 13 in group 1 ($40 \text{ ml min}^{-1} \leq CL_{cr} \leq 60 \text{ ml min}^{-1}$) and 20 in group 2 ($20 \text{ ml min}^{-1} \leq CL_{cr} < 40 \text{ ml min}^{-1}$). The renal dysfunction induced a mean decrease in VFL clearance of 12% in group 1 and 28% in group 2, compared with the control group. The anticipated dose reduction given in renally impaired patients (i.e. 280 mg m⁻² and 250 mg m⁻² in groups 1 and 2, respectively) yielded similar drug exposure to control patients. The tolerance profile of VFL in patients with renal dysfunction was similar to that observed in patients with $CL_{cr} > 60$ ml min⁻¹.

CONCLUSION

In conclusion, the recommended doses of intravenous VFL administered once every 3 weeks in cancer patients with renal impairment are 280 mg m⁻² when CL_{cr} is between 40 and 60 ml min⁻¹ and 250 mg m⁻² when CL_{cr} is between 20 and <40 ml min⁻¹.

Introduction

Vinflunine (VFL) ditartrate, is a novel tubulin-targeted inhibitor belonging to the vinca alkaloid family. This bifluorinated semi-synthetic molecule was selected for its particular mechanism of action and its higher level on *in vivo* anti-tumour activity compared with vinblastine or vinorelbine [1–4]. The intravenous (i.v.) formulation of VFL (Javlor®, Pierre Fabre Médicament) received a European marketing authorization as a single agent for the treatment of adult patients with advanced transitional cell carcinoma of the urothelium (TCCU, bladder cancer) after failure of a prior platinum-containing regimen. The recommended regimen is 320 mg m⁻² administered as a 20 min infusion once every 3 weeks. Myelosuppression, particularly neutropenia, is the dose-limiting toxicity for vinflunine and the severity of haematological toxicity is related to drug exposure [5, 6]. The most frequent (incidence >20%) treatment related non-haematological adverse events in patients with advanced TCCU who received vinflunine were gastrointestinal symptoms (e.g. constipation, nausea, vomiting, stomatitis and abdominal pain), asthenia/fatigue, anorexia, alopecia, injection-site reactions and weight loss [7]. In general, all adverse events with vinflunine were non-cumulative and medically manageable. Currently, this drug is undergoing phase III clinical development in advanced breast cancer. The pharmacokinetics (PK) of VFL are linear over the dose range from 30 to 400 mg m⁻² [8]. Following i.v. administration, VFL is eliminated according to a multiexponential decay with a sharp decrease in blood concentrations during the first hour post-infusion then by a slower decrease thereafter, the terminal half-life of VFL being close to 40 h [8]. VFL is characterized by a high total blood clearance (>40 l h⁻¹) and a large volume of distribution (2422 l) suggesting that the drug is extensively distributed into tissues. VFL is moderately bound to plasma proteins (40–78%), with a negligible binding to α_1 -glycoprotein and platelets [9]. As for the other vinca alkaloids, VFL exhibits an important metabolism. It is metabolized by liver cytochromes (mainly CYP3A4 isoenzymes) into several inactive metabolites and by multiple esterases into 4-O-deacetylvinflunine (DVFL), which is the predominant and only active metabolite of vinflunine [10]. In two large studied cohorts of patients with solid tumours (5000 patients each), the prevalence of a glomerular filtration rate (GFR) below 90 ml min⁻¹ was calculated as high as 50% and the incidence of a GFR below 60 ml min⁻¹, corresponding to stage 3 or more kidney disease was 12% [11, 12]. Cancer patients have compromised renal function because of the underlying disease or for other causes such as ageing, high blood pressure, diabetes, infectious and autoimmune disease, or drug-related toxicity. It is now well established that renal dysfunction can affect not only the PK of drugs that are significantly eliminated by renal pathway but also the PK of some drugs that are predomi-

nantly eliminated by a non-renal route. The mechanistic basis for the effect of renal impairment on non-renally eliminated drugs is not well understood, but may be linked to the inhibitory effects of uraemic toxins on drug metabolism enzymes or transporters [13].

Renal dysfunction may therefore induce important variations of drug exposure, even for some drugs that are predominantly non-renally eliminated, which may result in the alteration of the safety and/or efficacy profile. For vinorelbine, a structurally analogue to vinflunine, a weak correlation was evidenced between drug clearance and creatinine clearance (CL_{cr}) despite the limited role of renal excretion (< 20%) to the total drug elimination [14].

Because the impact of renal impairment is minor, no dose adjustment is recommended for Vinorelbine. For vinflunine, a phase I mass balance study indicates that this drug is predominantly excreted via the biliary route however the renal excretion is not negligible and superior to that observed with vinorelbine: two-thirds of the recovered VFL dose is excreted into the faeces while one-third is excreted into the urine [9]. Consequently, it could be questioned whether a compromised renal function would affect the PK of VFL, possibly resulting in drug overexposure and increased toxicity.

In order to address the above issue, the present study was designed to evaluate the effect of renal dysfunction on the pharmacokinetics and safety of VFL and to propose a dose adjustment if needed.

Methods

This was an open-label dose escalation study of i.v. VFL in patients with renal impairment conducted in five phase I French centres. The study protocol and its amendments were submitted and approved by an Ethics Committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Bourgogne, France) and French Health Authorities. None of the amendments modified the study design. The trial was designed according to the current Declaration of Helsinki [15] and conducted in accordance with Good Clinical Practice. Written informed consent was obtained from each participating patient before study entry.

Patients selection

Patients were eligible for the trial if they were ≥ 18 years and had a histologically proven metastatic solid tumour for which effective and standard therapy was not currently available. Two groups of renally impaired patients were selected based on the values of CL_{cr} as a measure of GFR. The CL_{cr} values were calculated at baseline using the Cockcroft & Gault formula [16] and serum creatinine values were assayed by a unique laboratory. This centralized determination enabled limited experimental variability.

Patients with $CL_{cr} \geq 40$ and ≤ 60 ml min⁻¹ were defined as the moderate renally impaired group (group 1) and patients with a $CL_{cr} \geq 20$ and <40 ml min⁻¹ were defined as the severe renally impaired group (group 2). Both groups of patients were recruited simultaneously. At least 12 patients per group were planned to be included. Other requirements included predicted life expectancy ≥ 3 months; a Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 , no severe or uncontrolled medical conditions, adequate haematologic count, no severe liver impairment according to international standard values and electrocardiogram (ECG) without any clinically significant abnormality. Radiotherapy may have been given provided that 3 weeks had elapsed prior to study entry. Patients must have recovered from adverse events due to agents administered >4 weeks earlier or ≥ 6 weeks for nitrourea or mitomycine C.

Main non-inclusion criteria were concurrent treatment with any other anti-cancer therapy, participation into a clinical study with an investigational drug within 28 days before study entry, history of significant neurological or psychiatric disorders, previous treatment with VFL or another vinca alkaloid; prior extensive radiotherapy, prior known hypersensitivity to the study drug or drugs with similar chemical structures, an uncontrolled medical disorder, pre-existing peripheral neuropathy, uncontrolled hypercalcaemia, pregnancy, lactation or refusal to use effective contraception.

Study drug administration and dose adjustment

The starting dose of VFL was given according to the degree of renal impairment. A patient with $CL_{cr} \geq 40$ and ≤ 60 ml min⁻¹ received 280 mg m⁻² of VFL while a patient with $CL_{cr} \geq 20$ and <40 ml min⁻¹ received 250 mg m⁻². These anticipated dose reductions, respectively 13% and 22% lower than the recommended dose (i.e. 320 mg m⁻²) in patients with normal renal function, were consistent with the magnitude of the recovered dose in urine (i.e. 30%) after radiolabelled drug administration. The drug was administered intravenously diluted in a 100 ml of normal saline over 20 min every 3 weeks, a 3 week period representing 1 cycle.

After the first administration, both pharmacokinetic and safety criteria (see Table 1) were used to adjust the second VFL dose so as to reach blood exposures in the range of those observed at the recommended dose of 320 mg m⁻² in clinical trials to patients with $CL_{cr} > 60$ ml min⁻¹. The pharmacokinetic criterion was calculated from an historical control cohort of 118 patients with $CL_{cr} > 60$ ml min⁻¹, these patients having been included in previous VFL single agent phase I/II studies [8, 17–20]. It was calculated as the dose normalized AUC (AUC divided by dose) corresponding to the upper bound of the 95% parametric confidence interval (CI) from the control population. This upper bound was estimated to be 65 meaning that most of the control patients with $CL_{cr} > 60$ ml min⁻¹ (97.5%) had a lower value.

This strategy was performed to enable dose maintenance or dose escalation within the same patient in the case of good tolerance observed during the first cycle, therefore maximizing the probability of administering active doses to patients in cycle 2 while limiting the risk of drug overexposure.

According to the rules depicted in Table 1, in the absence of serious toxicity observed during cycle 1, VFL dose at cycle 2 could be either maintained at 280 or increased to 320 mg m⁻² in patients of group 1 while the dose could be either maintained at 250 mg m⁻² or increased to 320 mg m⁻² in patients in group 2. Once tolerance was judged acceptable for cycle 1, dose maintenance or dose increase depended on the PK criteria. When the $AUC(0,\infty)/Dose$ was below 65 which implied that the individual PK characteristic was within the 95% distribution to that observed in the control population, thus highly suggesting no or clinically irrelevant impact of the renal impairment on VFL clearance, the dose could be escalated to the recommended dose. For groups 1 and 2, the dose increase (respectively 13% and 28%) was judged as reasonable for the individual to benefit from a therapeutic exposure.

When the $AUC(0,\infty)/dose$ was higher than 65, meaning that the individual exposure was within the top 5% distribution to that observed in the control population, the dose was maintained in the second cycle as the tolerance was good during the first cycle.

Table 1
Rules for dose adjustment in cycle 2

$AUC(0,\infty)/dose$ (mg m ⁻²) of VFL in cycle 1	Dose of VFL in cycle 2	
	Group 1 Moderate renal impairment (CL_{cr} from 40 ml min ⁻¹ to 60 ml min ⁻¹) Starting dose: 280 mg m ⁻²	Group 2 Severe renal impairment (CL_{cr} from 20 ml min ⁻¹ to 40 ml min ⁻¹) Starting dose: 250 mg m ⁻²
< 65	320 mg m ⁻² or 250 mg m ⁻² in case of poor tolerance	320 mg m ⁻² or 210 mg m ⁻² in case of poor tolerance
≥ 65	280 mg m ⁻² or 250 mg m ⁻² in case of poor tolerance	250 mg m ⁻² or 210 mg m ⁻² in case of poor tolerance

In the case of grade IV neutropenia ≥ 7 days, febrile neutropenia, constipation grade 3, mucositis grade 2 > 5 days or any grade ≥ 3 toxicity (except untreated nausea or vomiting) observed in cycle 1, the dose of the second cycle was reduced as depicted in Table 1, independently of the blood exposure obtained on the first cycle. No dose re-escalation was allowed after a dose reduction. If a second episode of poor safety was observed or the grade ≥ 3 of toxicity was not resolved to grade ≤ 1 for a maximum of 2 weeks, the patient was withdrawn from the study.

Cohorts of 20 patients were planned in each group of renal impairment. Patients received study treatment until disease progression, evidence of unacceptable toxicity or patient's request to discontinue the therapy.

Treatment evaluation

Safety was assessed by physical examination (including vital signs, weight, ECG, regular reporting of adverse events graded according to the NCI-CTC – version 2.0) and laboratory tests (complete blood cell counts, differential and platelets count, serum chemistry including liver function tests and CL_{cr} , glucose, sodium, potassium, total protein), at baseline, and before each study drug administration in the following cycles. Haematology was performed every 2 days in the case of an absolute neutrophil count $< 1.0 \times 10^9 l^{-1}$ until recovery. Patients who received at least one study treatment administration were considered evaluable for safety analysis unless they were lost to follow-up immediately after the start of treatment.

Efficacy was assessed by using RECIST (version 1.0) [21], the primary efficacy variable being the clinical response. Lesions were categorized into measurable or non-measurable lesions, target or non-target lesions. Tumour assessments were performed at baseline, the end of cycle 2 and then every two cycles.

Clinical statistics

All patients were included in the intent to treat analysis. Safety analysis was done on all treated patients. The analysis was performed for each dose level and for the whole treated population. Categorical variables were summarized with frequency and percentage, and continuous variables were summarized with frequency, median, range and, if relevant, mean and SD.

Pharmacokinetics

Blood sampling for pharmacokinetic assessment was carried out on day 1 of cycle 1 just before the start of administration and then 10 min (mid-infusion), 20 min (end of infusion), 40 min, 1 h, 1.5 h, 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, 96 h and 168 h after the start of infusion. The same sampling scheme was performed after the administration of the second cycle. The PK of VFL were evaluated by measuring its concentrations and those of its only active metabolite DVFL in whole blood using a fully validated LC/MS-MS method with a lower limit of quantification of 0.25 ng ml^{-1} [22].

For VFL, the calculated pharmacokinetic parameters were the peak concentration (C_{max}), the area under the blood concentration vs. time curve extrapolated from zero to infinity ($AUC(0,\infty)$), the total blood clearance (CL_{tot}), the terminal volume of distribution ($V_{d,z}$) and the terminal blood half-life ($t_{1/2,z}$). For DVFL, the peak concentration (C_{max}), the area under the blood concentration vs. time curve from zero to the last quantifiable concentration ($AUC(0,t_{last})$) and the metabolic ratio calculated as the ratio of DVFL $AUC(0,t_{last})$: VFL $AUC(0,t_{last})$ were also calculated. All PK parameters were derived from a model-independent approach using Kinetica (v. 4.4) software (Thermo Electron Corp., USA). The PK parameters of VFL and DVFL from each renally impaired group (test groups) were compared with those obtained from historical control groups representing patients with normal renal function ($CL_{cr} > 60 \text{ ml min}^{-1}$). For VFL, the control group included a total of 118 patients from both single agent phase I and phase II clinical trials and for DVFL, the control group included a total of 44 patients from exclusively single agent phase I clinical trials. The potential impact of renal impairment was evaluated by calculating the 90% CI for the test (each group separately) : control ratio of geometric means of total blood clearance for VFL and of the metabolic ratio for DVFL. As defined in the regulatory guidelines [23], a lack of impact was concluded if the calculated 90% CI was included within the acceptance range of 0.80–1.25. A regression model (i.e. linear model) based on data of all groups (tests and control) was performed to characterize adequately the relationship between drug clearance and renal function. All statistics were done using the SAS software (version 8.2. Cary, USA).

Results

Patients' characteristics

Patients' characteristics are shown in Table 2. Thirty-three patients were treated between August 2005 and April 2010 in five centres, 13 in group 1 (moderate renal impairment) and 20 in group 2. (severe renal impairment).

The median CL_{cr} value was 45.3 ml min^{-1} (40.8–51.1) in group 1 and 33.8 ml min^{-1} (20.7–39.9) in group 2.

The patients had a large variety of tumour types. The most frequent histology was adenocarcinoma (51.5%). All treated patients presented with metastatic disease.

For the control group, 118 patients coming from prior phase I/II studies were selected based on a $GFR > 60 \text{ ml min}^{-1}$. The mean value of GFR was 90.0 ml min^{-1} and ranged between 60.7 to 162 ml min^{-1} . Most of the control group patients were male (76%) and their mean age was 56 years (range: 25–78).

Treatment delivery

A total of 100 cycles were delivered among the 33 treated patients. The median number of cycles was 2 with a range

Table 2

Patients, baseline demographics and disease characteristics

Demographic data	Group 1 (n = 13)	Patients n = 33 Group 2 (n = 20)	Overall
Gender: n (%)			
Male	10 (76.9)	9 (45)	19 (57.6)
Female	3 (23.1)	11 (55)	14 (42.4)
ECOG performance status: n (%)			
0	4 (30.8)	3 (15)	7 (21.2)
1	7 (53.8)	14 (70)	21 (63.6)
2	2 (15.4)	3 (15)	5 (15.2)
Age (years)			
Median	68.1	70.3	70
Range	45.5–76.1	52.6–85.7	45.5–85.7
Body weight (kg)			
Males			
Median	71.5	68	70
Range	55–94	54–82	54–94
Females			
Median	46	55	54
Range	43–55	42–66	42–66
Body surface area (m ²)			
Males			
Median	1.8	1.8	1.8
Range	1.6–2.3	1.6–2.0	1.6–2.3
Females			
Median	1.4	1.6	1.5
Range	1.4–1.6	1.5–1.7	1.4–1.7
Creatinine clearance (ml min ⁻¹)			
Median	45.3	33.8	38.4
Range	40.8–51.1	20.7–39.9	20.7–51.1
Primary site: n (%)			
Colorectal	1 (7.7)	4 (20)	5 (15)
Bladder	2 (15.4)	2 (10)	4 (12)
NSCLC	2 (15.4)	2 (10)	4 (12)
Ovarian	1 (7.7)	2 (10)	3 (9)
Pancreas	1 (7.7)	2 (10)	3 (9)
Breast	–	3 (15)	3 (9)
Prostate	1 (7.7)	1 (5)	2 (6)
Kidney/urinary	1 (7.7)	1 (5)	2 (6)
Others	4 (30.8)	3 (15)	7 (21)
Numbers of organs involved: n (%)			
0 organ	–	2 (10)	2 (6.1)
1 organ	2 (15.4)	5 (25)	7 (21.2)
2 organs	6 (46.1)	7 (35)	13 (39.4)
≥ 3 organs	5 (38.5)	6 (30)	11 (33.3)

Others: primary site included oesophageal cancer (1), endometrium cancer (1), hepatocarcinoma (1), small cell lung cancer (1), soft tissue sarcoma (1), Vater's ampulla (1), unknown primary (1).

of 1 to 12 cycles. Twelve patients (36.4%) received at least 3 cycles. The median relative dose intensity of i.v. VFL was 95.6% (80.3–105.7) in group 1 and 94.5% (74.3–109.9) in group 2. As per protocol, a total of 16 patients (48.4%) had a VFL dose increase (seven patients in group 1 and nine patients in group 2) between cycle 1 and cycle 2.

In the first group (n = 13) after the first administration of 280 mg m⁻² of VFL, two patients were withdrawn after cycle 1 due to disease progression. In the same group, four patients had dose reduction for the second cycle due to grade 3 dehydration and asthenia (two patients), grade 3

constipation (one patient) and grade 4 neutropenia and grade 3 fatigue (one patient). Two additional dose reductions to 280 mg m⁻² for patients who received 320 mg m⁻² on cycle 2 were applied in this group for cycle 3 due to grade 3 constipation.

In the second group (n = 20), after the first administration of 250 mg m⁻² of VFL, three patients were withdrawn after cycle 1 due to either safety reasons, patient decision or protocol deviation. In the same group, five patients had a dose reduction for the second cycle due to grade 3 constipation, grade 3 asthenia, grade 3 neutropenic infection,

Table 3A

Evolution of vinflunine dose schedule during the study in patients in group 1

Evolution of vinflunine dose schedule during study Group 1 starting dose at cycle 1 = 280 mg m ⁻²	n	%
Decrease to 210 mg m ⁻² at cycle 2 – up to cycle 3	1	7.7
Decrease to 250 mg m ⁻² at cycle 2 – up to cycle 2	2	15.4
Decrease to 250 mg m ⁻² at cycle 2 – up to cycle 4	1	7.7
Increase to 320 mg m ⁻² at cycle 2 – up to cycle 2	3	23.1
Increase to 320 mg m ⁻² at cycle 2 – up to cycle 3	1	7.7
Increase to 320 mg m ⁻² at cycle 2 – up to cycle 6	1	7.7
Increase to 320 mg m ⁻² at cycle 2, decrease to 280 mg m ⁻² at cycle 3 – up to cycle 4	1	7.7
Increase to 320 mg m ⁻² at cycle 2, decrease to 280 mg m ⁻² at cycle 3 – up to cycle 7	1	7.7
Not treated after cycle 1	2	15.4
Number of patients	13	100.0

Table 3B

Evolution of vinflunine dose schedule during the study in patients in group 2

Evolution of vinflunine dose schedule during study Group 2 starting dose at cycle 1 = 250 mg m ⁻²	n	%
Decrease to 210 mg m ⁻² at cycle 2 – up to cycle 2	4	20.0
Decrease to 210 mg m ⁻² at cycle 2 – up to cycle 4	1	5.0
Increase to 280 mg m ⁻² at cycle 2 – up to cycle 3	1	5.0
Increase to 320 mg m ⁻² at cycle 2 – up to cycle 12	1	5.0
Increase to 320 mg m ⁻² at cycle 2 – up to cycle 2	5	25.0
Increase to 320 mg m ⁻² at cycle 2, decrease to 250 mg/m ⁻² at cycle 3 – up to cycle 11	1	5.0
Increase to 320 mg m ⁻² at cycle 2, decrease to 280 mg/m ⁻² at cycle 3 – up to cycle 3	1	5.0
No change up to cycle 2	2	10.0
No change up to cycle 3	1	5.0
Not treated after cycle 1	3	15.0
Number of patients	20	100.0

grade 4 neutropenia and grade 3 arthralgia (one patient each). One additional dose reduction to 280 mg m⁻² was applied for cycle 3 in one patient for whom VFL was administered at 320 mg m⁻² at cycle 2 due to grade 2 jaw pain. In three patients, no dose modification was applied.

Tables 3A and B display an overview of doses changes per group.

Safety

All patients in each group were evaluable for safety at cycle 1. At cycle 2, 10 and 16 patients were evaluable in group 1 and 2, respectively. No toxic death occurred during the study and no unexpected adverse events were recorded.

The worst grade of haematological toxicities by patient (33 patients, 100 cycles) are depicted in Table 4. Grade 3

febrile neutropenia was reported in two patients from group 1 after cycle 1 (280 mg m⁻²) and 3 (210 mg m⁻²), respectively. Throughout the study, treatment related non-haematological adverse events were as follows. Asthenia was the most frequent adverse event (AE) whatever the group, concerning nine out of 13 patients in group 1, and 14 out of 20 patients in group 2. Gastrointestinal disorders were also frequent. The main gastrointestinal adverse event was constipation reported in eight and 14 patients in groups 1 and 2, respectively. Although no grade 4 constipation was recorded during the study, eight patients (three patients in group 1 and five patients in group 2) experienced eight episodes of grade 3 constipation. Anorexia was frequently reported in 61% of the group 1 patients (one grade 3 and two grade 4) and in 40% of the group 2 patients (one grade 4). Nausea and vomiting were also reported (group 1: eight patients, no grade 3/4; group 2: seven patients, no grade 3/4). Eight patients had stomatitis but none had a grade 3 or 4. Six patients experienced diarrhoea without any grade 3 or 4. One patient in group 2 experienced one episode of grade 4 dysphagia. The major pain observed during the study was abdominal pain: 31% in group 1 and 60% in group 2 experienced this AE with one grade 3 in each group and one grade 4 in group 2). Myalgia was reported in 23% of patients in group 1 (one grade 3) and in 30% of patients in group 2. Arthralgia was only reported in 15% of patients in the group 1 and 5% of the patients in the group 2 with one grade 3). Cardiovascular AEs were infrequent, one patient presented with one episode of grade 1 tachycardia and one patient one episode of grade 4 myocardial infarction. Grade 3 dehydration was observed in two patients out of 13 in group 1 and in one patient in group 2.

Efficacy

Efficacy was assessed by using RECIST (version 1.0). Five patients were unevaluable for response, one in the moderate renal impairment group and four in the severe group. No partial response was observed. A total of 11 disease stabilizations (at least 2 cycles of treatment) was achieved (33.3%). The median duration of stabilization and the median progression-free survival were 5.3 months (95% CI 2.6, 6.6) and 1.7 months (95% CI 1.4, 3.1), respectively. With a median follow up of 39 months, the median overall survival was 6.1 months (95% CI 3.7, 9.4).

Pharmacokinetics

For the first cycle, 13 and 16 patients provided full and interpretable PK results in the moderate (280 mg m⁻²) and severe (250 mg m⁻²) renally impaired group, respectively. For the second cycle, interpretable PK results were available in 10 patients for each group. The main PK parameters calculated for the first cycle stratified by group are reported in Table 5.

For VFL, C_{max} and AUC(0,∞) showed similar mean and range values between moderate and severe renally

Table 4
Haematological toxicities (worst grade on study by patient)

Haematological parameter	Group 1 Moderate renal impairment			Group 2 Severe renal impairment		
	Grade ≥ 1 <i>n</i> (%)	<i>n</i> = 13 Grade 3 <i>n</i> (%)	Grade 4 <i>n</i> (%)	Grade ≥ 1 <i>n</i> (%)	<i>n</i> = 20 Grade 3 <i>n</i> (%)	Grade 4 <i>n</i> (%)
Anaemia	12 (100)	4 (30.8)	–	20 (100)	2 (10)	–
Leucopenia	10 (76.9)	2 (15.4)	3 (23.1)	18 (90)	10 (50)	3 (15)
Neutropenia	12 (92.3)	6 (46.2)	3 (23.1)	17 (85)	5 (25)	10 (50)
Thrombocytopenia	9 (69.2)	2 (15.4)	–	13 (65)	–	–

impaired groups whereas both the total blood clearance and the terminal volume of distribution decreased with the severity of renal impairment. As a consequence of a similar decrease for both PK parameters (CL_{tot} and $V_{d,z}$), the mean terminal half-life was comparable between the two groups.

For DVFL, values of C_{max} , $AUC(0,t_{last})$ and metabolic ratio were in the same range for moderate and severe renally impaired groups. Although based on a small number of patients per group and dose, the same trends were observed for VFL and DVFL PK parameters for cycle 2 (data not shown).

Owing to the limited number of patients with evaluable PK data at cycle 2 ($n < 12$), statistical analyses were performed for the PK parameters of cycle 1 only.

For VFL, a 12% and 28% decrease in VFL clearance mean values was estimated respectively for the moderate and the severe renally impaired group as compared with the control patients with $CL_{cr} > 60 \text{ ml min}^{-1}$ (Table 6).

When each renally impaired group was compared with the control group, CIs were calculated outside the acceptance range of 0.80–1.25 illustrating a non-equivalent clearance between each test group and the control group. The decrease in total blood clearance according to the severity of renal dysfunction was further confirmed by investigating the relationship between the VFL blood clearance obtained in cycle 1 and 2 and the CL_{cr} normalized to a body surface area of 1.73 m^2 (Figure 1). No significant correlation was observed in patients with a CL_{cr} higher than $60 \text{ ml min}^{-1} 1.73 \text{ m}^2$ whereas a highly significant correlation ($r = 0.40$, $P < 0.01$, Pearson's test) was demonstrated in patients with a CL_{cr} lower than $60 \text{ ml min}^{-1} 1.73 \text{ m}^2$. In renally impaired patients, the regression equation was $VFL \text{ CL}_{tot} (\text{l h}^{-1} \text{ m}^{-2}) = 0.217 \times CL_{cr} (\text{ml min}^{-1} 1.73 \text{ m}^2) + 10.1$. Of note, it can be observed on Figure 1 that the clearance data distribution between cycle 1 and cycle 2 were similar. Individual values of VFL $AUC(0,\infty)$ obtained in cycle 1 are depicted in Figure 2. While the total blood clearance of VFL was demonstrated to be significantly lower in each renally impaired group compared with the control group, the observed drug exposure showed comparable distribution between groups, with mean $\pm$ SD values of $14\,212 \pm 3483$, $14\,422 \pm$

4358 and $15\,521 \pm 3723 \text{ ng ml}^{-1} \text{ h}$ for the control, moderate and severe renally impaired groups, respectively.

For DVFL, a 19% and 2% increase in the metabolic ratio were estimated respectively for the moderate and the severe renally impaired groups as compared with the control group (Table 6). A lack of equivalence was observed between moderate and control groups whereas equivalence was shown between severe and control groups. This discrepancy could be explained by two patients from the moderate renally impaired group presenting higher metabolic ratios than the normal range values.

The mean DVFL exposure ($AUC(0,t_{last})$) was slightly higher in each renally impaired group compared with the control group (Table 5). The difference was borderline statistically significant ($P < 0.045$, t -test) between the moderate and control groups and there was no statistically significant difference between the severe and control groups ($P < 0.20$, t -test). Should an impact of renal impairment on DVFL elimination occur, the DVFL exposure in the severe group would have been significantly higher than that observed in the control and moderate groups. In addition, the individual values of DVFL exposure illustrated comparable distributions among groups (Figure 2). It was therefore considered that DVFL exposure in the renal dysfunction groups was essentially similar to that observed in the control group.

Discussion

The results of a recent study showed that the prevalence of renal insufficiency in cancer patents may be as high as 60% [11, 12]. Despite this relatively high frequency, the information concerning dosage adjustment in renally impaired patients is infrequently available. Phases II/III clinical trials supporting drug development are performed in patients with normal organ function and poor information exists on the pharmacokinetics and/or pharmacodynamics of drugs in patients with organ dysfunction, and especially in renally impaired cancer patients. This practice poses a significant challenge to the treating physicians on how to select appropriate dosing. In a conservative

Table 5

Group and initial dose level	C _{max} (ng ml ⁻¹)	AUC(0, ∞) (ng ml ⁻¹ h)	Vinflunine CL _{tot} (l h ⁻¹)	V _{d,z} (l)	t _{1/2,z} (h)	C _{max} (ng ml ⁻¹)	AUC(0, t _{last}) (ng ml ⁻¹ h)	4-O-deacetyl vinflunine AUC(0, t _{last}) (ng ml ⁻¹ h)	Metabolic ratio
Moderate renal impairment (n = 13) 280 mg m ⁻²	6552 (2469–11616)	14422 (8697–22169)	35.9 (24.4–50.8)	1790 (1286–2560)	35.8 (28.5–45.4)	51.3 (26.1–103)	5551 (2097–9729)	5551 (2097–9729)	0.386 (0.231–0.677)
Severe renal impairment (n = 16) 250 mg m ⁻²	6757 (4293–8877)	15521 (10612–22827)	28.1 (19.4–37.2)	1476 (823–2400)	37.3 (28.9–44.7)	49.9 (18.5–90.1)	5211 (1895–10073)	5211 (1895–10073)	0.331 (0.177–0.523)
Control (n = 118) 320 mg m ⁻²	n.c.*	14212 (7648–27070)	42.9 (19.5–74.0)	2355 (739–4379)	38.5 (15.0–68)	45.6 (21.6–130)	4251 (1935–8731)	4251 (1935–8731)	0.321 (0.160–0.576)

* $n_{c, C_{max}}$ for the control group was not calculated since the duration of infusion was shorter (10 min) than in the renal impairment groups (20 min). $AUC(0, \infty)$, area under the curve of the blood concentration–time data; Cl_{CR} , vinflunine blood absolute clearance; $C_{max, obs}$ observed maximal blood concentration; $t_{1/2, term}$ terminal half-life estimated from the log-linear concentration–time data of the terminal phase; $V_{d, z}$ volume of distribution of the terminal phase.

approach, oncologists withhold systemic chemotherapy for patients with severe renal dysfunction. This situation does not benefit patients with organ dysfunction who may have no available therapy. In order to address this issue, specific phase I trials are encouraged by regulatory agencies who recommend study designs evaluating the PK of drugs over a full range of renal function, from normal GFR ($> 80 \text{ ml min}^{-1}$) to severely impaired GFR ($< 30 \text{ ml min}^{-1}$) [24]. It is well acknowledged that such a full range design is difficult to conduct in cancer patients and that the recruitment could be long. In the present case, an original study design was carried out in renally impaired patients with the use of all pertinent PK data collected during the drug development prior to initiating the current study. Indeed, the clinical programme for VFL authorized the inclusion of patients with a CL_{cr} value higher or equal to 50 ml min^{-1} . As a consequence, PK data were available in the range of $\text{CL}_{\text{cr}} > 80 \text{ ml min}^{-1}$ corresponding to normal renal function as well as in the range of $\text{CL}_{\text{cr}} \geq 50$ to $\leq 80 \text{ ml min}^{-1}$ corresponding to mild impaired renal function. These background data demonstrated no PK difference between patients with $\text{GFR} > 80 \text{ ml min}^{-1}$ and patients with GFR ranging from 60 to 80 ml min^{-1} . This prior information enabled us to define patients with a $\text{GFR} > 60 \text{ ml min}^{-1}$ as a control group, to use this historical data and to investigate two groups with impaired renal function with the same length interval: $40\text{--}60 \text{ ml min}^{-1}$ and 20 to $<40 \text{ ml min}^{-1}$. This study design was successful to discriminate reliably a decreased clearance value of 12% in the first group and a more substantial decrease of 28% in the second group when compared with the control group. Based on a 90% CI approach, both reduced values were evidenced as non-equivalent compared with the control group, therefore justifying clinically the dose adjustments.

Although no reliable information was available in patients with moderate to severe renal dysfunction at the time of designing the current study protocol, the starting dose were reduced from 320 mg m⁻² to 280 mg m⁻² and 250 mg m⁻² in patients in groups 1 and 2, respectively. These dose reductions are in close agreement with the magnitude of decrease in drug clearance. In both groups of renal dysfunction, VFL and DVFL exposure in the first cycle was found to be comparable with that expected in a population treated at the recommended dose of 320 mg m⁻² and having a GFR > 60 ml min⁻¹ (Figure 2). The homogeneous distribution of blood exposure to VFL and to its active metabolite across the different groups confirmed the validity of dose reduction in renally impaired patients.

In addition to the anticipated dose reductions for the first cycle, both pharmacokinetic and safety criteria were introduced for further dose modifications in the second cycle (Table 1), therefore limiting the risk of underexposure and maximizing the probability of administering active doses. On average, dose modifications (increase or decrease) following cycle 1 did not result in a significant

Table 6
Bioequivalence analysis of vinflunine blood clearance and of 4-O-deacetyl vinflunine metabolic ratio

Group and initial dose level	Vinflunine		4-O-deacetyl vinflunine	
	Geometric mean ± CV of clearance (l h ⁻¹ m ⁻²)	Ratio and 90% CI Test : reference	Geometric mean ± CV of metabolic ratio	Ratio and 90% CI Test : reference
Test: Moderate renal impairment (n = 13) 280 mg m ⁻²	20.3 ± 31%	0.88 (0.78, 0.98)*	0.369 ± 31%	1.19 (1.02, 1.38)*
Test: Severe renal impairment (n = 16) 250 mg m ⁻²	16.4 ± 24%	0.72 (0.65, 0.79)**	0.315 ± 34%	1.02 (0.88, 1.17)
Control (n = 118) ^o 320 mg m ⁻²	23.1 ± 24%	-	0.310 ± 37%	-

*/**Not bioequivalent. ^o Sample size for control of 4-O-deacetyl vinflunine metabolic ratio is 44.

Figure 1
Relationship between individual vinflunine blood clearance and creatinine clearance. Open circles: data from control patients; Filled squares: data at cycle 1 from renally impaired patients; Open triangles: data at cycle 2 from renally impaired patients. A regression line was separately calculated between patients with renal impaired function (creatinine clearance ≤ 60 ml min⁻¹ 1.73 m⁻², y = 0.217x + 10.1) vs. control patients (creatinine clearance > 60 ml min⁻¹ 1.73 m⁻², y = 0.0361x + 20.5). The correlation coefficient was statistically significant (r² = 0.16, P < 0.01) for patients with impaired renal function whereas it was not statistically significant (r² = 0.015, NS) for control patients

change in the initial dosing (i.e. 280 and 250 mg m⁻² in groups 1 and 2, respectively) as illustrated by the median dose intensities (96% and 95% in groups 1 and 2, respectively).

Intravenous VFL administered to patients with renal impairment once every 3 weeks was found to be safe and well tolerated. Dose limiting toxicity (grade 3 febrile neutropenia) was experienced by two patients at 280 mg m⁻² and 210 mg m⁻² in group 1. Among all the 33 patients, the most common non-haematological related adverse events were gastrointestinal events (66.6%) and asthenia (69.6%). These common side effects related to VFL were rarely severe. Safety data reported in the present phase I study were not unexpected and were consistent

with the previously reported clinical experience with VFL in patients with GFR > 60 ml min⁻¹ [25–27].

One limitation of the present study was that no PK and safety data were obtained in patients with end-stage renal disease (ESRD) on dialysis. These types of patients may present with a GFR far below 20 ml min⁻¹ and are rarely included in clinical trials. Extrapolating the regression equation of VFL CL_{tot} vs. CL_{cr} in renally impaired patients [VFL CL_{tot} (l h⁻¹ m⁻²) = 0.217 × CL_{cr} (ml min⁻¹ 1.73 m⁻²) + 10.1] to the lower edge of CL_{cr} values may bring some pieces of information. Assuming that the linear regression still holds true for the lowest values of CL_{cr}, a roughly 40–57% decreased VFL CL_{tot} is predicted when CL_{cr} ranges from below 20 ml min⁻¹ to strictly no functional renal

Figure 2

Individual vinflunine (A) and 4-O-deacetyl vinflunine (B) AUC between control and renally impaired groups. Red lines represents the mean values for each group

function ($CL_{cr} = 0 \text{ ml min}^{-1}$) as compared with a normal renal function ($CL_{cr} \geq 80 \text{ ml min}^{-1}$). It can be therefore postulated that a 50% dose reduction in ESRD patients may be necessary to obtain equivalent drug exposure to that expected for patients with normal renal function. Another issue in ESRD is that the drug may be removed by dialysis and this must be taken into account for appropriate handling between chemotherapy timing and dialysis sessions. Concerning VFL, it can be hypothesized that its PK characteristics do not favour the removal of the drug by dialysis. A high volume of distribution, a long terminal half-life and the predominantly non-renal clearance exhibited by VFL likely limit the ability of the drug to be removed from the body by intermittent dialysis sessions. However, owing the absence of any data on the dialysis clearance of VFL, the administration of the drug could be done after dialysis sessions or on non-dilaysis days.

This study established that VFL should be administered once every 3 weeks to cancer patients with renal impairment at 280 mg m^{-2} when CL_{cr} is included between 40 and 60 ml min^{-1} and at 250 mg m^{-2} when CL_{cr} is higher than 20 ml min^{-1} and strictly lower than 40 ml min^{-1} . Moreover, even if the response rate was not a primary end point of the study it is noteworthy that in this heavily pretreated cancer patient population, 11 patients (33%) achieved disease stabilization for at least 6 weeks.

These recommended doses in renally impaired patients enabled blood exposure to VFL and to its active metabolite to be similar to that achieved in patients with $GFR > 60 \text{ ml min}^{-1}$ treated at 320 mg m^{-2} . Safety data at

these doses in renally impaired patients demonstrated no unexpected toxicities and comparable tolerability profiles with patients with normal renal function.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

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