Cancer Chemother Pharmacol (2012) 69:1467–1475
DOI 10.1007/s00280-012-1856-4

ORIGINAL ARTICLE

Phase I dose-escalation study of vinflunine hard capsules administered twice a day for 2 consecutive days every week in patients with advanced/metastatic solid tumors

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Received: 24 November 2011 / Accepted: 17 February 2012 / Published online: 1 March 2012

Abstract
Background Vinflunine is a new microtubule inhibitor of the vinca-alkaloid family. It is marketed in transitional cell carcinoma of urothelial tract as a 20 min infusion given every 3 weeks in Europe.
Methods In this phase I study, vinflunine was administered to patients with advanced malignancies as hard capsules given twice a day on days 1–2 every week, with 3 weeks cycles. Serial blood samples were collected during the first cycle for pharmacokinetic investigations.
Results Thirty-six patients (pts) were treated at 6 dose levels 150 (3 pts), 190 (3 pts), 230 (8 pts), 300 mg/day (6 pts) and then 250 (3 pts) and 270 mg/day (13 pts). The Maximal Tolerated Dose (MTD) was reached at 300 mg/day where 2 patients out of 6 experienced a dose limiting toxicity (febrile neutropenia with diarrhea). The lower dose level of 270 mg/day was the recommended dose (RD), the toxicity profile being mainly anaemia, neutropenia, fatigue and constipation. The pharmacokinetic analysis demonstrated the adequacy of the flat-fixed dosing regimen, as no correlation between clearance of vinflunine and body surface area was evidenced. Blood concentrations and exposure increased with dose, and a pharmacokinetic accumulation was observed, which is consistent with the terminal half-life of the compounds. The inter-individual exposure variability at the RD was 35%.
Conclusion Repeated weekly administration of oral vinflunine is feasible and exhibits a moderate inter-individual PK variability. The MTD was achieved at 300 mg/day given for 2 consecutive days. According to the protocol rules, the RD was established at 270 mg/day.

Keywords Oral · Vinflunine · Metastatic solid tumors · Phase I

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Introduction

Vinflunine ditartrate is a new microtubule inhibitor belonging to a new generation of *vinca* alkaloids obtained by a semi-synthetic process using super acidic chemistry. The major structural modification from previous generations is the selective introduction of two fluorine atoms at the 20′ position on the catharanthine moiety, which was previously inaccessible by classic chemistry [1, 2]. Vinflunine (VFL) is a specific inhibitor of tubulin that prevents microtubule assembly during mitosis [3] and induces apoptosis. In vitro, low concentrations of vinflunine inhibit both morphogenesis and motility of endothelial cells [4]. In vivo studies in mice using multiple injections have also shown that vinflunine has anti-angiogenic properties, through the inhibition of the endothelial cells migration and their capacity to organize into a network of capillary-like structures [5].

During the early clinical development of the intravenous (i.v). form of vinflunine, three (3) dosing schedules were investigated: once every 3 weeks [6], twice every 3 weeks on Day 1 and Day 8 [7], and a weekly schedule [8]. The

once every 3 weeks schedule has proved its efficacy and is currently registered for use in transitional carcinoma of urothelial cell (TCCU) patients [9]. This dosing schedule is also the most convenient for the patients over the other i.v. schedules, as it requires hospitalization for the i.v infusion only once every 3 weeks.

Conversely, the availability of an oral formulation offers the advantage of an increased convenience for the patient offering a possibility of chronic repeated oral dosing without the need of i.v devices. A neutropenia PK/PD model also showed that vinflunine given orally with a fractionated dosing regimen would be associated with an acceptable tolerability profile [10]. An improved patient convenience and an anti-angiogenic effect driven by low but sustained circulatory concentration were thus expected with oral vinflunine.

In patients, the oral administration of vinflunine as a single agent was preliminary investigated using hard-gelatine capsules (120 mg/m^2) in comparison to i.v. dosing (120 mg/m^2) [11]. This study confirmed the feasibility of the oral dosing, and warranted the evaluation of the Maximal Tolerated Dose (MTD), PK, safety and activity profile of oral vinflunine as a single agent. In the current Phase I study, oral vinflunine was investigated according to a twice daily administration for 2 consecutive days every week in patients with advanced/metastatic solid tumors which failed standard therapy.

Patients and methods

Patient selection

Patients, between 18 and 75 years old, were eligible for the study if they had an histologically confirmed solid tumor for which effective standard therapy was not available, or if they had progressive disease after standard therapeutic modalities with a maximum of two lines of prior chemotherapy for locally advanced or metastatic disease (targeted therapy and hormone therapy were not included in chemotherapy lines). The interval between completion of the last chemotherapy or radiotherapy and enrolment in the trial had to be at least 6 weeks for nitrosoureas and mitomycin C based therapy and 3 weeks for all the other treatments. Patients had to have a Karnofsky performance status $\geq$70%, with an estimated life expectancy of at least 3 months. The biological criteria for eligibility were defined by laboratory tests of adequate bone marrow function: haemoglobin >10 g/dl, neutrophils >1.5 $\times$ 10^9/L, platelets >100 $\times$ 10^9/L and adequate liver and kidney functions: total bilirubin $\leq$ Upper Limit of Normal (ULN), aspartate aminotransferase and alanine aminotransferase $\leq$2.5 $\times$ ULN in absence of liver metastases and $\leq$5 $\times$ ULN if liver metastases, alkaline phosphatase $\leq$5 $\times$ ULN (except in patients with documented bone or liver metastases), creatinine < ULN and creatinine clearance $\geq$50 mL/min according to Cockroft and Gault formula. Patients were excluded if they had Central Nervous System (CNS) metastases (unless they have been previously treated for these metastases and were stable by CT scan without cerebral oedema); history of significant neurologic or psychiatric disorders precluding understanding and giving consent; peripheral neuropathy grade >1 (according to the NCI-CTC: National Cancer Institute Common Toxicity Criteria version 3.0); dysphagia grade $\geq$2, malabsorption syndrome, extensive surgery of the stomach or the small bowel, major alterations of gastro intestinal transit such as subocclusive syndrome; or uncontrolled comorbidity such as active serious infection, uncontrolled diabetes or unstable cardiovascular conditions. Some previous treatments were forbidden: high dose chemotherapy with hematopoietic stem cell rescue; extensive radiotherapy up to more than 25% of bone marrow reserve; treatment with vinflunine or a *vinca* alkaloid in the metastatic setting. Participation in another clinical trial within 28 days before study entry and any other concurrent anti-cancer therapy were not permitted.

The study was conducted in three European centers and was approved by the Independent Ethics Committees (IEC) according to the participating countries requirements.

Treatment plan

Oral vinflunine was supplied by Institut de Recherche Pierre Fabre (Boulogne-Billancourt, France) as hard capsules containing 20 or 75 mg of vinflunine base. Vinflunine hard capsules were administered in two equally divided doses given at 12 h interval. Similarly to previous studies with oral vinflunine [11], capsules were given immediately after breakfast and dinner with a glass of water. It was taken on days 1 and 2, on days 8 and 9 and on days 15 and 16 of each cycle. Cycles were repeated every 3 weeks.

Dose limiting toxicities (DLT) were defined as the occurrence during the first cycle of one of the following: (1) haematological toxicity consisting of nadir neutrophils <0.5 $\times$ 10^9/L for $\geq$7 days or grade 3 or 4 neutropenia concomitant with fever $\geq$38.5°C or grade $\geq$3 infection or platelet count <25 $\times$ 10^9/L or <50 $\times$ 10^9/L with bleeding; (2) gastrointestinal toxicity consisting of grade $\geq$3 nausea, vomiting or diarrhea if persistent despite optimal antiemetic or anti-diarrheal treatment or grade 3 intestinal ileus; (3) any other drug-related grade $\geq$3 toxicity and any drug-related adverse event that results in 50% dosing omission during cycle 1 or a delay $\geq$2 weeks in the administration of cycle 2.

Six dose levels (DLs) were tested, ranging from 150 to 300 mg per day (i.e. 75 to 150 mg per administration). Each DL was tested in 3–6 patients. No intra-patient dose

escalation was allowed. If only one out of three patients experienced a DLT, a further three patients were entered at the same level; if no further DLT was experienced, dose escalation was continued.

The Maximal tolerated dose (MTD) was the dose at which 2 out of 3 or 2 out of 6 patients developed a DLT during the first cycle. The Recommended dose (RD) was the dose below the MTD.

Once the MTD was defined, the RD was refined by investigating an intermediate dose level between the MTD and the dose below MTD with 15% increment. At the RD, a total of at least 12 patients had to be enrolled to confirm its tolerability. NCI-CTC AE (version 3.0) was used for grading adverse events, clinical and laboratory results.

Strong inhibitors of the cytochrome P450 isoform 3A4 were prohibited during study treatment. Erythropoietin was prohibited too, during the first cycle unless it was initiated at least 4 weeks before study treatment. Granulocyte Colony Stimulating Factor (G-CSF) was not to be used during the first cycle on a prophylactic intent.

Treatment procedure

Patients who responded or had stable disease after 6 cycles could continue treatment at the discretion of the investigator and underwent the same monitoring as during the first 6 cycles. No dose reduction of vinflunine dose was required for patients whose calculated creatinine clearance decreased to $<$50 ml/min during treatment period. If creatinine clearance was $\leq$20 ml/min, the study drug had to be stopped. Neutrophils count had to be $\geq 1.5 \times 10^9$/L (grade 1) and platelet count $\geq 75.0 \times 10^9$/L (grade 1) before each new cycle. In case of febrile neutropenia or grade $\geq$3 neutropenia concomitant with grade 3–4 infection, treatment might be stopped until next cycle and for the next cycles, the dose was adjusted at the next lower dose level. Primary prophylaxis using 5-HT3 antagonists was recommended but if grade 2 nausea and/or vomiting occurred during a cycle while the patient had received a prophylactic treatment with 5-HT3 antagonists before each drug intake, the cycle was discontinued and the next cycle was given at the next lower dose level.

If grade 3 diarrhea, constipation or stomatitis or grade 2 sensory neuropathy occurred, the study drug was held until resolution or grade 1 diarrhea, symptomatic treatment was initiated and the study drug was continued at the next lower dose level. In any case, a grade $\geq$3 toxicity which did not resolve within 2 weeks led to permanent treatment discontinuation.

Pretreatment follow-up examinations

At entry to the study, patients were evaluated with medical history, complete physical examination (including weight, vital signs, performance status score), 12-lead ECG, complete blood cell count (CBC), serum chemistry, chest X-ray, radiographic methods to define the extent of the disease. Throughout the treatment period, patients were monitored with physical examination, symptoms description on days 1, 2, 8, 9, 15, 16 of cycle 1 and before the administration of the next cycles. A 12-lead surface ECG was performed at screening and just before drug administration on day 2 of the first cycle and then before each cycle. In addition, collection of ECG at day 2 was performed 3, 9 and 24 h after vinflunine administration. Blinded ECG tracing of day 2 were analysed in order to detect any effect of the drug on QT/QTc interval, using on-screen calipers and a computer-based measurement. CBC had to be performed twice a week during the first cycle, then once a week. Serum biochemistry including AST, ALT, alkaline phosphatase, total bilirubin, urea, creatinine had to be done biweekly for the first cycle and then weekly for subsequent cycles. Complete assessment of all lesions by imaging procedures had to be performed every two cycles and every 4 weeks by tumour markers. Tumour response was assessed by using RECIST [12].

Methods (PK)

Blood sampling for the pharmacokinetic assessment was to be carried out on days 1, 2, and 3 of cycle 1 ($n = 13$ samples). Pre-dose samples were also collected at the end of each week of the first cycle (i.e. on Days 8 and 15 of cycle 1), and on Day 1 of cycle 2.

Blood concentrations of vinflunine and 4-O-deacetyl vinflunine (DVFL) were quantified using a fully validated LC–MS/MS method with a lower limit of quantification of 0.25 ng/mL for both compounds [13]. Pharmacokinetic parameters after the first administration were derived using non-compartmental methods.

The accumulation ratio was evaluated between each of the 4 consecutive administrations during the first week. It was calculated for VFL and DVFL as the ratio of C_{12h} after each of the doses # 2, 3 and 4 related to C_{12h} after dose # 1. Similarly, the accumulation ratio between successive weeks was calculated as the ratio of C_{trough} concentrations, i.e. residual concentrations measured in Pre-dose samples collected as described above.

Results

Patients

Thirty-six patients were enrolled in the study between 2 February 2007 and 29 October 2009. Their demographic

data are shown in Table 1. The majority of patients (29 of 36, 80.6%) have been previously treated by chemotherapy.

Determination of the MTD

The 36 patients were enrolled at 6 different dose levels: three each at 150 and 190 mg/day, 8 at 230 mg/day, 3 at 250 mg/day, 13 at 270 mg/day and 6 at 300 mg/day. Because of the occurrence of DLTs (grade 4 febrile neutropenia and grade 3 diarrhea) in the first patient enrolled at 300 mg/day, 6 patients were included in this dose level. Criteria for the MTD were met at this level since a second patient at this level developed DLTs (grade 4 febrile neutropenia and grade 3 diarrhea) and died in a context of refractory acute respiratory insufficiency.

Consequently, lower dose levels were explored. Five (5) additional patients up to a total of 8 received 230 mg/day because two were not evaluable for the determination of the MTD since they did not complete the first cycle because of early disease progression. One of the 6 evaluable patients experienced DLTs (grade 3 nausea and vomiting). So, as per study protocol, two intermediate dose levels (250 and 270 mg/day) were investigated in order to refine the recommended dose. At dose level 250 mg/day, 3 patients were treated and none experienced DLT. At dose level 270 mg/day, the first 3 treated patients did not experience DLT, 10 additional patients were treated and only 2 patients experienced DLTs (grade 3 febrile neutropenia and grade 4 neutropenia lasting more than 7 days). This dose level (270 mg/day) was defined as the recommended dose (Table 2).

Table 1 Demographic data

Demographic data	Included patients ($n = 36$)
Sex	
Male	24
Female	12
Karnofsky performance status	
70	6
80	14
90	11
100	5
Age (years)	
Median (Range)	60 (24.3–73.6)
Primary cancer	
Non-small-cell lung cancer	5
Melanoma	4
Digestive cancer	
Esophagus	2
Anus	1
Hepatocarcinoma	1
Cholangiocarcinoma	1
Gynaecological cancer	
Cervix	2
Endometrium	1
Mesothelioma	2
Gastro intestinal stromal tumor	1
Thyroïd	2
Breast	3
Bladder	2
Small-cell lung cancer	1
Prostate	2
Penile cancer	1
Chondrosarcoma	1
Head and neck	3
Carcinoma of unknown origin	1
Prior chemotherapy regimen for advanced disease median (range)	1 (0–4)
Prior radiotherapy	25

Drug delivery

A total of 172 cycles were delivered with a median of 4 by patient (range 1–22) (Table 3).

Dose delay related to study drug toxicities was observed in 11 patients and 19 cycles. For 9 patients and 17 cycles, cycle delay was due to haematological toxicity (neutropenia, febrile neutropenia and anaemia) and for 2 patients and 2 cycles, cycle delay was due to non-haematological toxicity (grade 4 stomatitis and grade 2 ALT increase). Dose reductions was reported only at levels 270 and 300 mg/day. Dose reduction was reported in 3 patients and 3 cycles for drug-related haematological toxicity (2 febrile neutropenia and 1 grade 4 neutropenia) and in 2 patients and 2 cycles for drug-related non-haematological toxicity (grade 4 stomatitis and grade 2 ALT increase). Dose cancellation was observed in 7 patients and 17 cycles for haematological toxicity and in 4 patients and 5 cycles for non-haematological toxicity.

Toxicity

All 36 patients were assessable for toxicity. As shown in Table 3, the main toxicity was haematological toxicity. Anaemia was observed in 35 (97.2%) patients. Severity was mostly grade 1 or 2. Grade 3–4 anaemia was seen at the two highest dose levels (except one grade 3 at 230 mg/day): 1 grade 4 (16.7%) at MTD and 1 grade 3 and 2 grade 4 (15.4%) at RD. Of note, 25 (69.4%) patients had already anaemia at baseline, of whom 23 had grade 1, 1 a grade 2 and 1 a grade 3. Neutropenia was observed in 26 (72.2%) patients. Grade 3 neutropenia was recorded in 5 patients (13.9%) out of the 36 treated patients while grade 4

Table 2 DLTs during the first cycle per dose level

Dose level mg/day	Evaluable patients/ treated patients	Patients with at least one DLT	DLT
150	3/3	0	
190	3/3	0	
230	6/8	1	Gr 3 nausea and gr 3 vomiting
250	3/3	0	
270	13/13	2	Gr 3 febrile neutropenia
			Gr 4 neutropenia >7 days
300	6/6	2	Gr 4 febrile neutropenia and gr 3 diarrhea
			Gr 4 febrile neutropenia and gr 3 diarrhea

Table 3 Total number of cycles administered per vinflunine (VFL) dose level

VFL dose level (mg/day)	Number of patients	Number of cycles		
		Total	Median	Range
150	3	7	2	1–4
190	3	14	2	2–10
230	8	21	2	1–6
250	3	13	4	2–7
270	13	88	5	2–22
300	6	29	2	1–17

occurred at the two highest dose levels, 8 patients (61.5%) at 270 mg/day (RD) and 2 patients (33.3%) at 300 mg/day (MTD). Among them, febrile neutropenia was reported in 2 (33.3%) out of the 6 patients treated at the MTD, in 3 (23.1%) out of the 13 patients treated at the RD and neutropenic infection in 1 patient (7.7%) at the RD. Five (5) patients received G-CSF and 9 patients had red blood cells transfusion. There was no grade 3 or 4 thrombocytopenia. The most frequent non-haematological toxicities were general disorders: asthenia in 21 (58.3%) patients and gastrointestinal disorders: nausea in 20 (55.6%) patients, constipation in 16 (44.4%) patients, vomiting in 15 (41.7%) patients, diarrhea in 11 (30.6%) patients, abdominal pain in 8 (22.2%) patients and stomatitis in 5 (13.9%) patients. Severity was moderate as grade 3 and 4 were unfrequent. At RD, only one grade 4 non-haematological toxicitiy was reported, grade 4 stomatitis.

Grade 3 events at RD were reported in 4 patients, one patient had grade 3 nausea and vomiting and 3 patients had grade 3 asthenia. Incidence of neurotoxicity was low and severity was grade 1 or 2 with 4 (11.1%) paraesthesia, 3 at 270 and 1 at 230 mg/day, 1 peripheral motor neuropathy at 150 mg/day and 1 peripheral sensory neuropathy at 270 mg/day.

Grade 3–4 biological modifications observed including transaminases increase, alkaline phosphatase increase, hyperbilirubinemia, hyponatremia, hypokalaemia and hypocalcemia were mostly related to the disease, except for 2 patients at RD (1 grade 3 ALT increase and 1 grade 3 alkaline phosphatase increase). Among the 36 patients, 35 were evaluable for ECG analysis of QT/QTc interval. No time-related change was observed for heart rate, PR and QTcF intervals (Table 4).

Efficacy

Thirty-four patients out of the 36 treated patients were assessable for response, with one patient achieving a partial response. Twenty-three patients (67.6% of evaluable patients) had a stable disease and ten patients (29.4% of evaluable patients) had disease progression. The patient who achieved a partial response was a 73.6 years old man treated for a metastatic bladder carcinoma. He received 4 cycles of vinflunine 270 mg/day.

Pharmacokinetics

Blood VFL concentrations increased with the dose level, and C_{max} was observed at about 2–3 h after oral administration of vinflunine hard capsules. The inter-individual coefficient of variation (CV) of blood AUC_{0-12h} (Dose # 1) at the RD (270 mg/day) was calculated at 35%. The mean VFL accumulation ratio slightly increased between doses of the first week from 1.6 (Dose # 2) to 2.2 (Dose # 4) (Fig. 1). Mean calculated accumulation ratio remained constant, at about 1.13 and 1.05, when comparing respectively week 2 and week 3 to week 1. No correlation was observed between AUC_{0-12h}/Dose and the BSA of the patients (Fig. 2).

Blood DVFL concentrations also increased with the dose level. No PK parameter was calculated due to the short dosing interval (12 h) compared to the half-life of DVFL. The mean DVFL accumulation ratio between doses of the first week increased from 1.97 (Dose #2) to 3.7 (Dose # 4), and it was about 1.4 between successive weeks of treatment (week 2 = 1.36, week 3 = 1.48) (Fig. 1).

Table 4 Drug-related adverse events and worst grade per patient, according to vinflunine dose

Grades	150 mg/d *n* = 3			190 mg/d *n* = 3			230 mg/d *n* = 8			250 mg/d *n* = 3			270 mg/d *n* = 13			300 mg/d *n* = 6		
	All *N*	3 *N*	4 *N*	All *N*	3 *N*	4 *N*	All *N*	3 *N*	4 *N*	All *N*	3 *N*	4 *N*	All *N*	3 *N*	4 *N*	All *N*	3 *N*	4 *N*
Haematologic toxicity																		
Anaemia	3	0	0	2	0	0	8	1	0	3	0	0	13	1	2	6	0	1
Neutropenia	2	1	0	2	0	0	3	0	0	3	0	0	11	3	8	5	1	2
Febrile neutropenia	0	0	0	0	0	0	0	0	0	0	0	0	3	3	0	2	0	2
Neutropenic infection	0	0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	0	0
Non-haematologic toxicity																		
Asthenia	0	0	0	2	0	0	3	0	0	2	1	0	10	3	0	4	0	0
Nausea	2	1	0	1	0	0	5	1	0	1	0	0	7	1	0	4	0	0
Constipation	0	0	0	3	0	0	3	0	0	2	0	0	6	0	0	2	0	0
Vomiting	2	0	0	0	0	0	2	1	0	2	0	0	6	1	0	3	0	0
Dry mouth	0	0	0	1	0	0	3	0	0	1	0	0	8	0	0	1	0	0
Diarrhea	0	0	0	1	0	0	0	0	0	1	0	0	6	0	0	3	2	0
Abdominal pain	0	0	0	0	0	0	3	0	0	0	0	0	3	0	0	2	0	0
Anorexia	1	0	0	0	0	0	1	0	0	2	0	0	4	0	0	1	0	0
Stomatitis	0	0	0	0	0	0	0	0	0	1	0	0	4	0	1	0	0	0
Alopecia	0	0	0	1	0	0	0	0	0	1	0	0	4	0	0	0	0	0
Paresthesia	0	0	0	0	0	0	1	0	0	0	0	0	3	0	0	0	0	0
Peripheral motor neuropathy	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Peripheral sensory neuropathy	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0

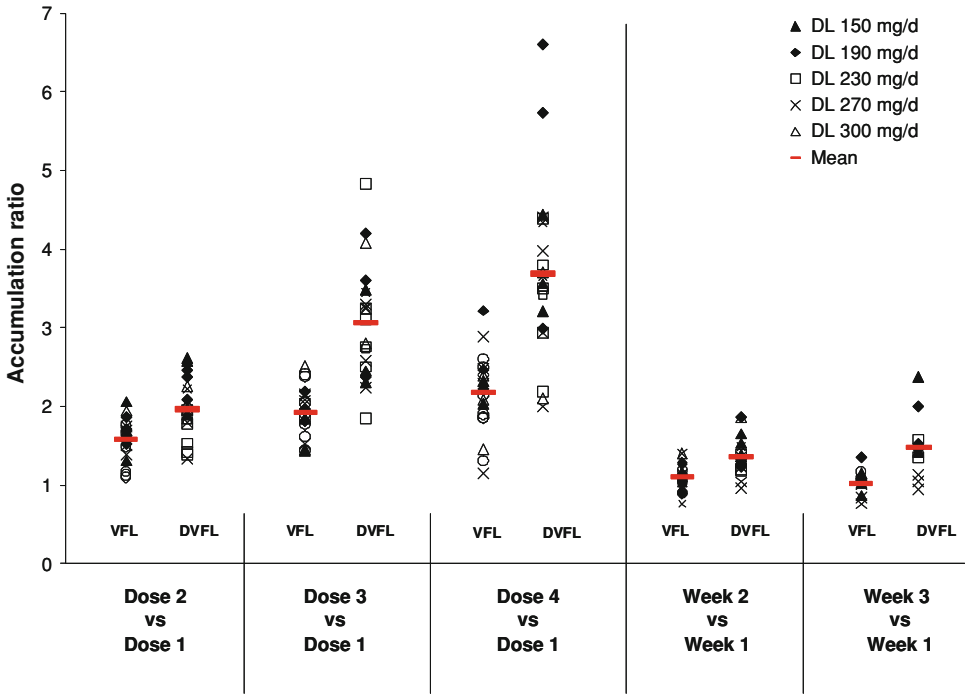

Fig. 1 Individual and mean accumulation ratios of Vinflunine and 4-O-deacetylvinflunine

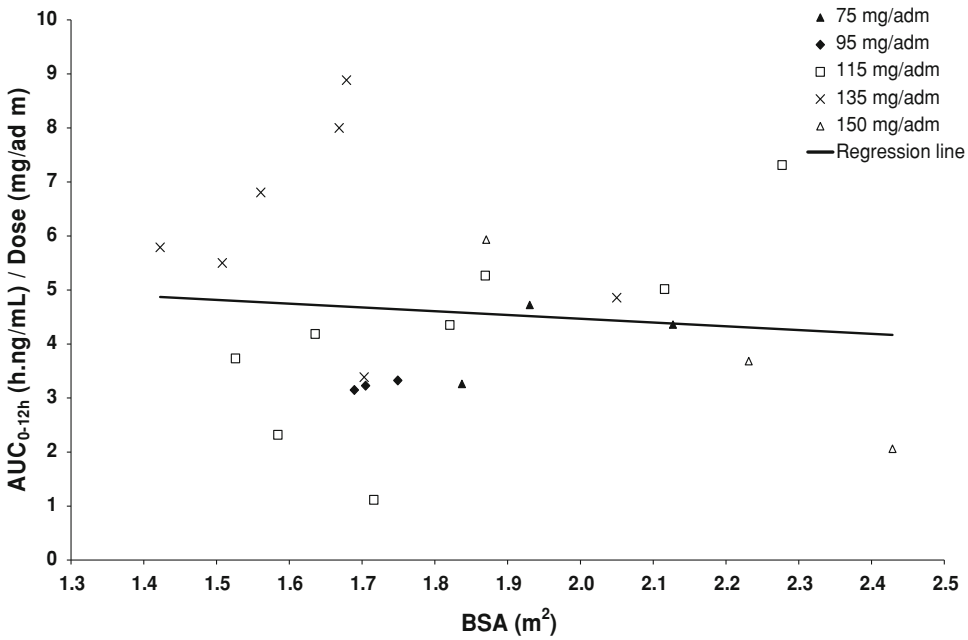

Fig. 2 Graphical representation of individual Vinflunine AUC_{0-12h}/Dose as a function of individual body surface areas

Discussion

The present study details the results of a phase I dose-finding study of vinflunine hard capsules administered in patients with advanced/metastatic solid tumours. The primary objective of this trial was to establish the MTD for oral vinflunine given twice daily for 2 consecutive days every week. MTD was achieved at 300 mg/day. At 150, 190 and 230 mg/day there was no DLT but at 300 mg/day, 2 patients out of 6 experienced a DLT (febrile neutropenia and diarrhea), one patient died in a context of refractory acute respiratory insufficiency. Thus, lower dose levels were explored (250 and 270 mg/day). The dose level of 250 mg/day was tested in 3 patients who did not experience DLT. At 270 mg/day, 2 out of 13 patients experienced a DLT (febrile neutropenia and neutropenia grade 4 lasting more than 7 days). According to the protocol rules, the recommended dose was established at 270 mg/day.

The recommended dose for i.v. vinflunine weekly schedule was previously established at 120 mg/m^2/week in a phase I study [8], and helped in optimizing the selection of the starting dose for the oral route, according to the following rationale: the i.v. weekly dose was virtually split into 4 consecutive i.v. administrations of 30 mg/m^2, each given every 12 h. The absolute oral bioavailability of vinflunine capsules was evaluated at about 58% [11]. Therefore, each single 30 mg/m^2 i.v. dose would correspond to about 50 mg/m^2 given orally, i.e. 90 mg for a reference body surface area of 1.8 m^2. In this study, the initial dose selected was 75 mg/administration (150 mg/day), which correspond to about 80% of the recommended dose extrapolated from the i.v. weekly schedule. This strategy allowed to rapidly reach the recommended dose level (135 mg/administration) at about 180% of the initial dose.

During previous i.v. studies using the once every 3 weeks dosing schedule, no accumulation was observed for either VFL or DVFL [9]. In the current study with a fractionated oral regimen, the accumulation was predictable: the slight accumulation observed for VFL over the 4 consecutive administrations of the first week (inter-dosing interval of 12 h) and the absence of accumulation between successive weeks (inter-dosing interval of 132 h) are consistent with the known terminal half-life of VFL (about 40 h) [9]. The higher accumulation ratios calculated for DVFL are also consistent with the longer terminal half-life reported for DVFL (about 4–6 days) [9].

In this study, vinflunine hard capsules were given according to a flat-fixed dosing to all patients, with no adaptation to body surface area (BSA). This was based on preliminary PK data with the oral route, for which poor correlation was observed between total blood clearance of vinflunine and BSA [11]. The PK results obtained from the current study seem to confirm the adequacy of this dosing strategy, as no correlation was observed between $AUC_{0-12\ h}$/Dose and the BSA of patients included, although covering a wide range of BSA from 1.4 to 2.4 m^2. The feasibility of this flat-fixed dosing was confirmed by the inter individual variability of blood exposure ($AUC_{0-12\ h}$) which was maintained at low levels (CV of about 35% at the RD). This is comparable to the inter-individual variability estimated at 10–40% with intravenous VFL dosed according to the body surface area [14]. Orally administrated agents have often a larger PK variability than intravenous agents which may lead to a high range of possible exposures

between patients. For anticancer agents especially, for which neither over exposure nor subtherapeutic exposure should be encountered, high variability may restrict the use of the oral route. Thus, the moderate inter-individual variability observed in this study is a favorable finding to enable using the oral route for vinflunine. This variability seems comparable to that previously reported at 37% [15] and 43% [16] for vinorelbine, another vinca alkaloid derivative currently available for use by the oral route.

Since 2009, vinflunine has been approved by EMEA for the treatment of advanced or metastatic transitional cell carcinoma of urothelial tract (TCCU) after a first line of treatment with platinum based chemotherapy. IV vinflunine is given as a 20 min intravenous infusion at 320 mg/m^2 every 3 weeks. The phase III study [17] comparing vinflunine plus best supportive care to best supportive care alone in 370 patients with TCCU in progression after platinum based chemotherapy, showed an overall survival of 6.9 versus 4.3 months in favor of vinflunine. In this phase I study, there is one partial response in a patient with bladder metastatic cancer and for 23 patients disease was stabilized.

Our results from this phase I study with vinflunine hard capsules administered twice a day for 2 consecutive days every week showed that oral vinflunine toxicity profile observed is similar to what is reported with intravenous vinflunine, based on published data of two phase III studies comparing 320 mg/m^2 of i.v vinflunine administered every 3 weeks as second-line therapy to a control arm in patients with advanced transitional cell carcinoma of the urothelial tract (TCCU) [17] and in patients with non-small-cell lung cancer (NSCLC) [18].

Safety profile of both studies showed that myelotoxicity is the most frequent toxicity reported in the vinflunine arm (253 patients in TCCU study and 274 patients in NSCLC study) with predominantly anaemia in 93.1% of patients in TCCU study and in 82.1% of patients in NSCLC study and neutropenia in 50.0% of patients in TCCU study and 49.3% of patients in NSCLC study. Febrile neutropenia was reported in 6.0% of patients in TCCU study and in 3.3% of patients in NSCLC study and neutropenic infection in 3.3% of patients in NSCLC study. Similarly, myelotoxicity was the main toxicity of the oral form. However the frequency of febrile neutropenia seems greater with the oral form and was the main dose-limiting toxicity.

The main non-haematological toxicities reported were also fatigue/asthenia in 50 and 36.6% of patients, and gastrointestinal disorders with constipation in 47.6 and 39.2% of patients, nausea in 39.1 and 26.7% of patients, vomiting in 29.0 and 23.8% of patients, stomatitis in 28.6 and 19.4% of patients and abdominal pain in 15.7 and 20.1% of patients in TCCU and NSCLC studies respectively. Although incidence of constipation is similar between iv and oral formulation, it is to be noticed that no grade 3/4 were observed with oral formulation, while 16 and 7% of patients had grade 3/4 constipation in TCCU and NSCLCC studies. Diarrhea was reported in only 6.2% of patients in NSCLC study. Higher incidence of diarrhea observed in our phase I study may be explained by the oral route of administration. Neurotoxicity was also minimal with neuropathy sensory in 11.1 and 10.7% patients in TCCU and NSCLC studies respectively.

In conclusion, the results of this phase I study warrants further investigations in phase II trials as a single agent or in combination with other active drugs like capecitabine in breast cancer or erlotinib in non-small-cell lung cancer in order to have a combination of an all oral treatment.

Conflict of interest None.

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