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Phase I study of Vinflunine administered as a 10-minute infusion on days 1 and 8 every 3 weeks

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Summary

Vinflunine is a novel vinca alkaloid developed through the selective modification of vinorelbine using super-acidic chemistry. In preclinical testing, vinflunine demonstrated significantly enhanced anti-tumour activity in human tumour xenograft models when compared to its parent compound. A phase I study was conducted to evaluate the safety and toxicity of vinflunine administered as a 10 minute intravenous infusion on days 1 and 8 every three weeks. Sixteen patients with advanced solid tumours were treated. Two of four patients experienced dose limiting toxicities (DLT) at 190 mg/m^2 and this was established as the maximum tolerated dose (MTD). At the MTD, the DLT of vinflunine consisted of constipation and neutropenia. Fatigue was notable but not dose limiting. No objective responses were observed. A dose of 170 mg/m^2 given on a day 1 and 8 schedule every three weeks would be suitable for future studies.

Introduction

The vinca alkaloids are a well established group of cytotoxic agents used in the treatment of a wide variety of malignancies. Originally derived from the Madagascan periwinkle plant, Catharanthus roseus, four vinca alkaloids, vincristine, vinblastine, vindesine and vinorelbine, are in routine clinical use. Vinorelbine (Navelbine®, Laboratoire Pierre-Fabre Médicament, Boulogne-Billancourt, France), a second generation vinca alkaloid, was developed through the semi-synthetic modification of vinblastine and has established activity in malignancies such as breast and non-small cell lung carcinoma [1, 2]. Further modification of vinorelbine through super-acidic chemistry led to the generation of a number of new active derivatives that included vinflunine (Javlor®, Laboratoire Pierre-Fabre Médicament, Boulogne-Billancourt, France) [3]. Vinflunine, (20′, 20′-difluoro-3′, 4′-dihydrovinorelbine) was developed through the insertion of two fluorine atoms at the 20′ position of vinorelbine and reduction of the 3′4′ double bond.

Vinflunine was selected for further evaluation on the basis of preclinical activity. In vitro, vinflunine showed definite cytotoxicity against a selected panel of human tumour cell lines including A549 (lung), DLD-1 (colon), DU 145 (prostate), J82 (bladder), LoVo (colon), MX-1 (breast), OVCAR-3 (ovary), SK-OV-3 (ovary) and T24 (bladder) with IC50 values ranging from 3 × 10–8 to 10–5 M. Animal studies in murine tumour models including the P388 leukaemia and B16 melanoma models, demonstrated vinflunine to have significant and superior anti-tumour activity when compared to vinorelbine or vinblastine [4]. In a panel of eleven subcutaneously implanted human tumour xenografts, vinflunine showed markedly superior anti-tumour activity over vinorelbine with activity in 7 out of 11 versus 3 out of 11 tumours [5].

In common with other vinca alkaloids, vinflunine is a specific inhibitor of tubulin and acts to prevent microtubule assembly during mitosis. Vinflunine effectively interrupts cell cycle progression and will induce cell death via apoptosis although the apoptotic mechanism may depend upon the concentration of vinflunine in the tumour [6–11]. Vinflunine is subject to P-glycoprotein (Pgp) me-

diated drug-resistance although experimental data suggest that it may be only a weak substrate for Pgp [12].

The tubulin affinity profile of vinflunine shows features which suggest that it will have greater effects on mitotic rather than axonal tubulin [13]. This finding has potential clinical relevance and theoretically could be associated with a diminished risk of significant neurotoxicity compared to older vinca alkaloids.

Pre-clinical studies were sufficiently encouraging to warrant phase I studies in patients with refractory solid tumours. The primary objective of this study was to establish the maximum tolerated dose (MTD) of vinflunine administered as a 10-minute intravenous infusion on days 1 and 8 every 3 weeks, a schedule chosen for evaluation on the basis of existing knowledge regarding vinflunine activity, pharmacokinetics, haematological toxicity profile, cell cycle phase specificity and the results of pre-clinical testing showing schedule-dependent efficacy. Secondary objectives were to determine the qualitative and quantitative toxicities of vinflunine, further describe its pharmacokinetic characteristics and assess preliminary evidence of anti-tumour activity.

Patients and methods

Patient selection

Patients were eligible for the study if they had solid tumours for which effective standard therapy was not available or if they had developed progressive disease after standard treatment. No patient had received more than 2 prior chemotherapeutic regimens for advanced or metastatic disease. All patients had completed prior anticancer therapy at least 4 weeks prior to enrolment in the trial. Patients were aged between 18 and 75 years old, with World Health Organization (WHO) Performance Status (PS) score of 0 to 2 and an estimated life expectancy of at least 12 weeks. All patients had adequate haematological, hepatic and renal function as indicated by the following laboratory tests: Haematology; total white blood cell count (WBC) $\geq 4.0 \times 10^9$/L, absolute neutrophil count $\geq 2.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, haemoglobin ≥ 9 g/dL; Biochemistry; AST and ALT ≤ 2.6 times the upper limit of normal (UNL), serum bilirubin $\leq$ UNL and serum creatinine $\leq$UNL. All patients had at least one measurable or evaluable lesion outside a previous radiation field. Measurable lesions were identified as those with at least one diameter of 20 mm on computed tomography (CT) scan. Patients were excluded if they had clinical evidence of brain or leptomeningeal metastasis, symptomatic peripheral neuropathy of grade 2 or greater (NCIC-CTC scale: version 2) [14], uncontrolled hypercalcaemia or unstable cardiovascular conditions (heart failure, uncontrolled angina, uncontrolled hypertension and/or myocardial infarction within previous 6 months). Concurrent treatment with other experimental drugs or participation in other clinical trials within the 30-day period prior to study entry was not permitted. The study was approved by the Ethics Committees of the three participating centres. All patients gave written informed consent prior to study entry.

Treatment plan

Vinflunine was supplied by Institut de Recherche Pierre Fabre, Boulogne-Billancourt, France at a concentration of 30 mg/mL in sterile water for injection. For administration, the appropriate dose of vinflunine was diluted in 50 ml normal saline and infused over 10 minutes via an intravenous line.

Starting dose and dose escalation procedure

In contrast to conventional phase I studies, where starting doses equivalent to 1/10th of the maximum tolerated dose seen in animal studies are commonly employed, a higher starting dose of 210 mg/m^2 vinflunine on days 1 and 8 of a 21 day cycle was selected. The dose was based on available data regarding the pharmacokinetics and metabolism of the parent vinca alkaloid vinorelbine and pharmacokinetic data available from an additional, ongoing, phase I study of vinflunine administered as a 10 minute infusion once every 21 days (21 sc)[15]. Information available from the vinflunine 21 sc study at that time confirmed linear pharmacokinetics for vinflunine at all doses studied (30–250 mg/m^2 dose levels); subsequent information confirmed dose linearity for vinflunine 21 sc at doses up to 400 mg/m^2. At the time of trial initiation, the MTD for the vinflunine 21 sc had not been reached at a dose level of 250 mg/m^2 and a further dose escalation to 320 mg/m^2 was planned giving an anticipated MTD of 21 sc vinflunine of at least 320 mg/m^2. By comparison, the MTD for vinorelbine given on a 21 day schedule (21 sc) was known to be 45 mg/m^2, and the recommended dose of vinorelbine given on a day 1 and 8 schedule, 30 mg/m^2. An MTD dose ratio between vinorelbine and vinflunine was postulated as 7:1 (320:45), predicting a starting dose of 210 mg/m^2 (7×30 mg) that was likely to be close to the MTD of vinflunine given by day 1 and 8 schedule. This novel approach was taken to facilitate rapid but safe dosing of vinflunine to the MTD, thereby avoiding unnecessary exposure of patients to low dose levels of vinflunine with a low likelihood of clinical benefit.

A dose escalation of 30% from entry dose level was proposed in the absence of significant toxicity. It was planned to treat at least 3 evaluable patients at each dose levels proceeding with dose escalation according

to the following rules: If no patient experienced toxicity, treatment would be escalated to the next dose level; if 1 patient out of 3 experienced dose limiting toxicity (DLT), an additional 3 patients were to be treated at the same dose level and escalation only undertaken if no more than 2/6 experienced DLT; if 3 out of 6 patients experienced DLT, the MTD was considered to have been reached and a further 3 patients were to be treated at the preceding lower dose level. DLT was defined by any of the following events occurring during the first treatment cycle: Haematological toxicity consisting of nadir absolute neutrophil count $< 0.5 \times 10^9$/L (Grade IV) for at least 7 days or $< 0.1 \times 10^9$/L for at least 3 days; febrile neutropenia defined as absolute neutrophil count $< 0.5 \times 10^9$/L and fever (three measured temperatures $>38^\circ$C in 24 hours or $1 > 38.5^\circ$C); thrombocytopenia $< 25 \times 10^9$/L (Grade IV) or thrombocytopenia with bleeding or requiring platelet transfusion, any grade III/IV major organ toxicity except alopecia or un-premedicated nausea/vomiting.

Treatment procedure

Vinflunine treatment was administered on days 1 and 8 every 21 days up to a maximum of 6 cycles or more at the discretion of the clinician. The following rules were followed for treatment delay of the next cycle: Haematological toxicity on day 1 consisting of absolute neutrophil count $<1.5 \times 10^9$/L and/or platelets $<100 \times 10^9$/L; grade 3/4 non-haematological toxicity (except nausea/vomiting despite adequate anti-emetic therapy) which did not recover to $\leq$grade 1; worsening of WHO Performance Status >2. If the above changes had not resolved by 2 weeks after the scheduled date of the next treatment, therapy was discontinued. Haematological toxicity at day 8 consisting of absolute neutrophil count $<1.0 \times 10^9$/L or platelets $< 100 \times 10^9$/L resulted in omission of the dose.

Pre-treatment and follow-up examinations

At entry to the study, patients were evaluated with a complete medical history and physical examination that included measurement of vital signs (temperature, pulse rate, blood pressure), electrocardiogram (ECG), full blood count (FBC), serum electrolytes, hepatic and renal function and chest X-ray. Computed tomography (CT) or magnetic resonance imaging (MRI) was required to define the extent of tumour involvement. During the treatment period, patients were monitored with FBC and biochemical tests twice weekly for the first 2 cycles and on day 1 of each planned cycle thereafter. ECGs were performed prior to each infusion. Toxicity assessments using the NCIC-CTC scale were made at baseline to record residual toxicity from previous therapy and prior to each cycle. Tumour response was assessed according to WHO modified criteria [16]. Complete response (CR) was defined as the total disappearance of all known tumour, partial response (PR) as a decrease of at least 50% in the sum of the products of the longest diameters of measurable lesions without an increase ($<25\%$) of any known lesions or development of new lesions. Both CR and PR required confirmation of response by repeat assessment 4 weeks apart.

Pharmacokinetics

Serial blood samples were collected from a peripheral venous cannula in the contralateral arm following the first two cycles of vinflunine. On cycle one, heparinised blood samples were collected over a 96-hour period according to a detailed sampling scheme (14 samples per patient at Baseline, 5, 10, 30, 60, 90 minutes then 2, 4, 8, 12, 24, 48, 72 and 96 hours). An additional sample was collected at 168 hours (immediately prior to administration of the day 8 dose). Following the second (day 8 of cycle 1), third (day 1 of cycle 2) and fourth (day 8 of cycle 2) administration of vinflunine, blood samples were collected according to a limited blood sampling strategy designed to maximise the data obtained from the number of patients treated. All samples were frozen to -20°C immediately and transferred to -80°C storage within 24 hours. The 3 centres in the study took samples at different time points to allow a full profile to be constructed, thus Centre 1 sampled at Baseline, 15, 30 minutes, 8 and 48 hours; Centre 2 at Baseline, 15 minutes, 1, 24 and 72 hours and Centre 3 at Baseline, 15, 90 minutes, 6 and 36 hours. Samples were analysed according to reference guidelines [17–19]. Vinflunine blood concentrations were quantified by a fully validated, high performance liquid chromatography (HPLC) method with UV detection. The HPLC method also allowed characterisation of several other HPLC peaks attributed to circulating metabolites. Biological samples were extracted with diethylether. The lower limit of quantification was 2 ng/ml and linearity assessed up to 200 ng/ml. Interbatch reproducibility estimated from quality control samples assayed within each analytical series was higher than 92%. Biological samples were found to be stable over 2 years at -80°C. The pharmacokinetic analysis was carried out by a conventional model-independent approach using Kinetica® (Innaphase) and Excel® (Microsoft) software. Area under the curve extrapolated to infinite (AUC_{inf}), terminal half-life ($T_{1/2\ z}$), terminal volume of distribution (V_d) and total body clearance (Cl_{tot}) were calculated. Based on the pharmacokinetic data of the first administration, a repeated doses simulation analysis was performed using an arithmetic supposition principle.

Table 1 Demographic characteristics of 16 patients.

Characteristics	Number of patients
Sex	
Male	7
Female	9
WHO P.S	
0	1
1	13
2	2
Age (Years)	
Mean	51
Median Range	39–70
Malignancy	
Renal cell carcinoma	1
Colorectal cancer	4
Mesothelioma	3
Melanoma	2
Tongue carcinoma	1
Sarcoma	2
Gynaecological cancer	2
NSCLC	1
Prior therapy	
Surgery	12
Radiation therapy	10
Chemotherapy	13
Immunotherapy	2
Hormone therapy	1

Results

Patients

Seventeen patients were enrolled onto the study and were assigned to three dose levels. One patient was subsequently excluded because of renal insufficiency and did not receive vinflunine, confining the study population to sixteen patients. Demographic data are shown in Table 1 and are typical for a phase I trial of a cytotoxic agent. The majority of patients (13/16) had been previously treated by chemotherapy. The three patients not treated with prior chemotherapy all had a diagnosis of malignant mesothelioma.

Drug delivery

Vinflunine was administered at an initial dose of 210 mg/m^2 on days 1 and 8. Anti-emetics were not administered routinely but were given with subsequent treatments if patients suffered with significant nausea. One of the first three patients experienced DLT (grade 4 constipation) which may have been complicated by concurrent opiate administration. The cohort was therefore extended to six patients and two of the next three patients experienced DLT. Toxicity comprised grade 3 myalgia and grade 3 constipation (without exposure to significant concurrent medication such as opiates) during the cycle 1 observation period. This prompted an unplanned dose de-escalation of 10% and the second cohort of patients was treated at 190 mg/m^2 on days 1 and 8. Four patients were treated at this dose-level; an additional patient being enrolled in-lieu of a patient who received only day 1 of cycle 1 because of early disease progression. Two of four patients who received treatment at this level experienced DLT (both patients with febrile neutropenia, one patient also with grade 3 constipation and abdominal pain). A further 10% dose de-escalation was therefore implemented with 6 further patients being treated at 170 mg/m^2 on days 1 and 8. Two patients experienced DLT at this dose level (both with grade 3 fatigue, one with grade 3 constipation and febrile neutropenia; one with two brief episodes of chest pain (grade 3) at the site of the tumour with pain temporally related to drug administration). 190 mg/m^2 was therefore determined to be the MTD and 170 mg/m^2 was identified as a possible dose for further studies of vinflunine given on days 1 and 8 of a 21 day cycle.

A total of 34 cycles (60 administrations) were delivered with a median of 2 cycles per patient (range 1–4). The overall dose intensity was affected by delays or omissions at each dose level. 82% of the planned dose was delivered at 210 mg/m^2, 70% at 190 mg/m^2 and 90% at 170 mg/m^2. The day 8 dose of vinflunine was omitted eight times in 7/16 patients (on four occasions because of toxicity, three occasions because of progressive disease and once because of an unrelated episode of septicaemia). Omission of the day 8 dose was seen at all dose levels occurring in four out of sixteen (25%) cycles at 210 mg/m^2, two out of eight (25%) at 190 mg/m^2 and two out of ten (20%) at 170 mg/m^2. Overall, significant delays (four or more days) in starting subsequent treatment cycles were deemed necessary in twelve out of eighteen cycles, mostly at the higher dose levels. For ten cycles this was to allow recovery from treatment related toxicity; for two cycles because of unrelated clinical events.

Toxicity

All sixteen patients and thirty four cycles of treatment were evaluable for toxicity which is summarised in Table 2.

Haematological toxicity

Leucopenia and neutropenia were the main haematological toxicities. Grade 3 or 4 myelosuppression was seen

Table 2 Adverse events according to vinflunine dose: worst grade (excluding grade 0) at cycle 1.

	Dose level								
	210 mg/m^2 N = 6			190 mg/m^2 N = 4			170 mg/m^2 N = 6		
Adverse Events	All grades	G3	G4	All grades	G3	G4	All grades	G3	G4
Leucopenia	6	3	1	4	2	2	4	1	2
Neutropenia	6	2	2	4	0	4	4	0	2
Febrile Neutropenia	0	0	–	2	2	–	1	1	–
Gastro-Intestinal									
Anorexia	0	0	0	4	0	0	2	0	0
Nausea	4	0	–	3	0	–	4	1	–
Vomiting	2	1	0	2	0	0	2	0	0
Stomatitis	5	0	0	2	0	0	0	0	0
Abdominal pain	4	0	0	2	1	0	2	0	0
Constipation	4	1	1	2	1	0	2	1	0
Cardiovascular									
Hypotension	0	0	0	2	1	1	0	0	0
Flu-like symptoms									
Fatigue	5	0	0	3	0	0	6	2	0
Myalgia	3	1	0	1	0	0	0	0	0
Skin									
Local toxicity	3	0	0	0	0	0	0	0	0
Alopecia	2	0	0	2	0	0	1	0	0
Chest pain	0	0	0	0	0	0	1	1	0

at all dose levels with the first cycle of treatment; (grade 3/4 neutropenia in 4/6 patients at 210 mg/m^2, 4/4 patients at 190 mg/m^2 and 2/6 patients at 170 mg/m^2) with nadir values being observed on day 14 at the 170 mg/m^2 dose level. Three patients experienced grade III anaemia for a total of 4 cycles and a single patient, withdrawn because of early progression after day 1, cycle 1, experienced one episode of grade III thrombocytopenia.

Non-haematological toxicities

Grade III/IV non-haematological toxicities were seen at all dose levels. Constipation was the main non-haematological toxicity; (grade three in five cycles and grade four in one cycle). Constipation when present generally lasted about one week and although occasionally severe, usually responded to standard therapeutic interventions. Three episodes of hypotension were documented although two were associated with concurrent infections; no ECG changes were observed. Fourteen out of sixteen patients experienced significant fatigue which was felt to be drug related in six patients; (three treated at 210 mg/m^2, two at 190 mg/m^2 and one at 170 mg/m^2). Grade three fatigue was experienced by two out of six patients at the 170 mg/m^2 dose level. Fatigue generally appeared at day three to five following administration of vinflunine and lasted five to seven days.

Dose limiting toxicity (DLT)

Seven patients experienced DLT. Constipation was dose limiting in four patients and febrile neutropenia was dose limiting in three patients; no patient experienced DLT by haematological criteria alone.

Pharmacokinetics

15/16 patients were evaluable for pharmacokinetic analysis; the remaining patient treated at 190 mg/m^2 who was withdrawn after dose 1 of cycle 1 because of early progression had samples that could not be processed because of a tube labelling protocol violation. Among these fifteen patients, six were treated at 210 mg/m^2, three at 190 mg/m^2 and six at 170 mg/m^2.

Vinflunine was moderately protein bound (78 $\pm$ 2.9%). Mean blood concentrations of vinflunine increased rapidly during the infusion reaching a mean maximum blood concentration of 8.4 $\pm$ 3.4 μg/ml at the 170 mg/m^2 dose-level (Figure 1). After the end of the infusion,

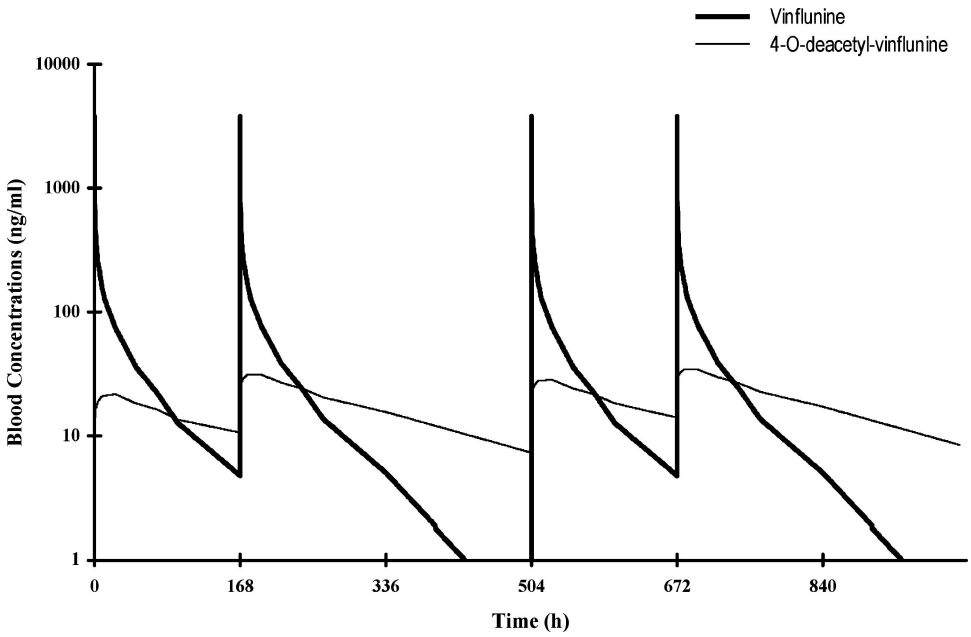

Figure 1. Vinflunine and 4-0-deacetyl-vinflunine blood concentrations, day 1 and day 8 every three weeks dosing regimen at 170 mg/m.[2]

blood concentrations of vinflunine decreased sharply up to 1 hour post-dosing then more slowly thereafter. At 168 hours post-dosing (the pre-dose sample on day 8), the mean blood concentration of vinflunine was 4.84 ± 3.84 ng/mL at the 170 mg/m^2 dose level. Vinflunine concentrations measured after the second and subsequent administrations were similar. In keeping with repeat dose simulation analyses, there was no accumulation of vinflunine between successive cycles of treatment. Mean pharmacokinetic parameters of vinflunine were calculated in all patients. A high total body clearance was observed with an overall mean value of 39.1 ± 10.0 L/h (0.6 ± 0.15 L/h/kg). The volume of distribution was large at 2223 ± 602 L (31.4 ± 7.1 L/kg). The elimination phase of vinflunine was accurately evaluated using the final time-point of 168 hrs after day 1 administration. The average terminal half life ($T_{1/2z}$) of vinflunine was estimated at 40.3 ± 9.6 hrs. Given the narrow dose range studied in this clinical trial, pharmacokinetic dose-proportionality was assessed by comparison with historical data. The

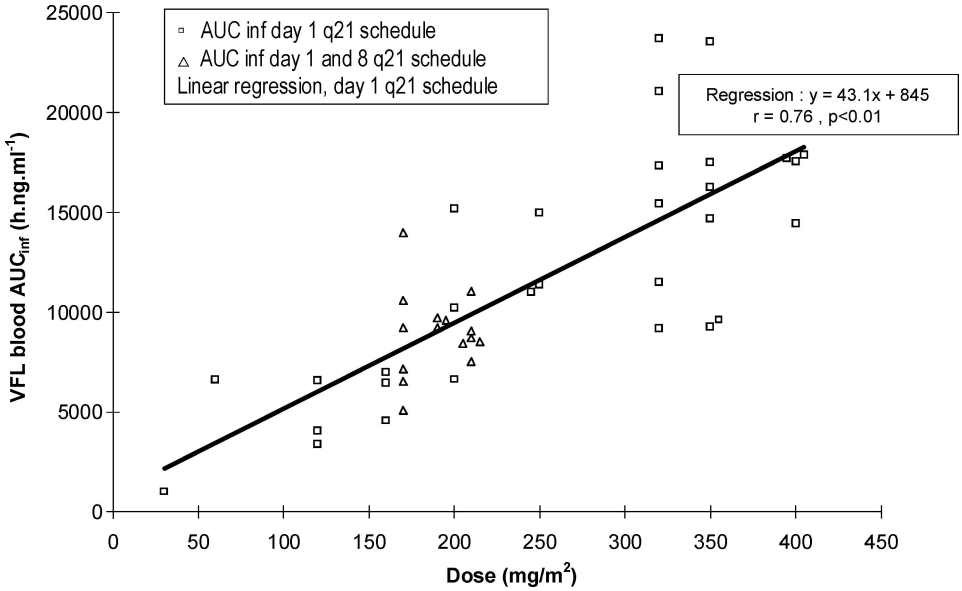

Figure 2. Relationship between the AUC and dose administered in two different schedules of vinflunine.

drug exposure data from the current study were plotted against data observed in a larger dose range study (from 30 to 400 mg/m^2) where vinflunine was administered once every three weeks in 32 patients [15]. Figure 2 demonstrates the area under the curve (AUC) from this study to be homogeneously distributed around the regression line calculated from the previous study, a result in agreement with linear vinflunine pharmacokinetics related to dose. 4-0-deacetyl vinflunine, the main active metabolite of vinflunine, could be detected during the two cycles where pharmacokinetic sampling was undertaken, even when present at low concentrations compared to vinflunine (Figure 1). The terminal half-life of 4-0-deacetyl vinflunine was estimated to be about four to six days. For 4-0-deacetyl vinflunine, minor increases in blood concentrations were observed after day one and day 8 dosing but there was no accumulation of 4-0-deacetyl vinflunine between cycles. Steady state was reached during the second cycle of treatment.

Pharmacokinetic-pharmacodynamic relationship

The effect of vinflunine on leucocytes and neutrophils is characterised by a well defined period of reversible myelosuppression with a nadir at about day 14. Correlation of these effects with total drug exposure (AUC_{in}) after the first two administrations was evaluated in the 14 patients who received vinflunine on days 1 and 8 without a delay. Results of the regression analysis show a significant relationship between AUC_{inf} and leucopenia / neutropenia (Figure 3).

Efficacy

Fourteen patients were assessable for response; no objective responses were seen. Stable disease was observed in six patients, progressive disease was observed in eight patients.

Discussion

This phase I study of vinflunine, a novel third-generation vinca alkaloid, represents one of the initial trials evaluating vinflunine and the first study to evaluate treatment given by 10-minute intravenous infusion on days 1 and 8 of a 21 day schedule. In-vitro and animal studies had demonstrated vinflunine to have superior preclinical activity when compared to its parent drug vinorelbine, supporting its evaluation in phase I clinical studies. The schedule chosen for this study was pragmatic, identical to the schedule in routine use for vinorelbine and based on animal data suggesting repeat dosing to be superior to single dosing, as is logical for a cell cycle-specific agent. The pharmacokinetic studies performed indicate that this schedule is feasible, with measurable drug levels at day 8 but without significant accumulation of parent drug or metabolites between cycles. However, the need to omit the day 8 dose in a significant number of cycles may indicate a need for further dose de-escalation in more heavily pre-treated subjects.

In this phase I study, the DLTs of vinflunine were febrile neutropenia and constipation, findings in keeping with the now published phase I trial of single dose vinflunine administered on day 1 of a 21 day schedule [15]. The MTD

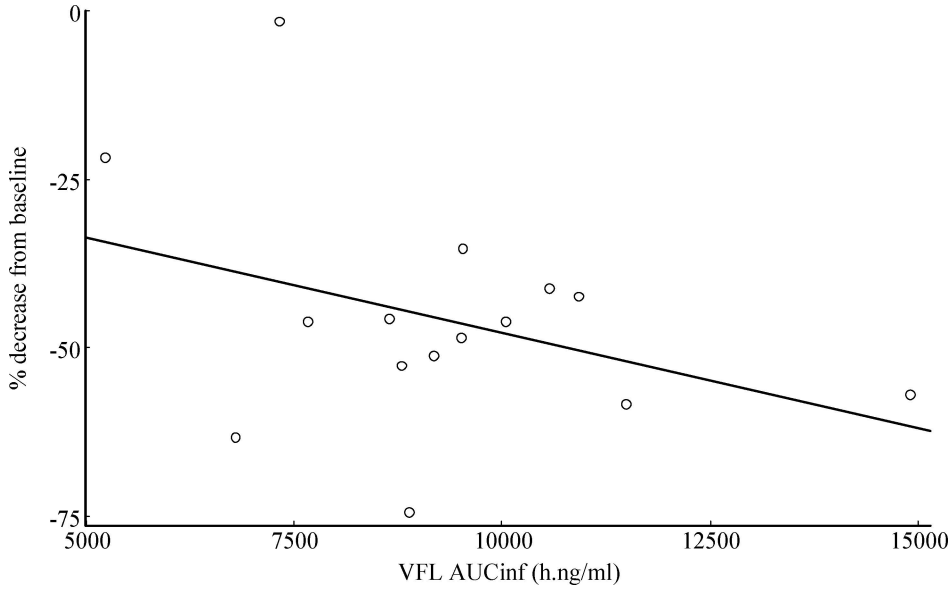

Figure 3. PK/PD relationship between neutrophil count decrease (percent from baseline) and blood body exposure (AUC_{inf}) on the first administration.

of vinflunine, given on days one and eight of a 21 day schedule was established as 190 mg/m^2, with 170 mg/m^2 established as a possible dose for future studies of vinflunine given by this schedule. Grade 3/4 neutropenia occurred in twenty cycles (58%) and was observed at all doses. The duration of neutrophil suppression was relatively brief and did not exceed five days, even at the highest dose level. Pharmacokinetic/pharmacodynamic relationships demonstrate a high correlation between body exposure to vinflunine and maximum neutrophil count decrease from baseline. Constipation was occasionally severe and was dose limiting in four patients; in common with other vinca alkaloids constipation was presumed to be related to autonomic neuropathy.

The superior anti-tumour efficacy of vinflunine over its parent compound vinorelbine in preclinical experimental models led to its evaluation in this phase I clinical trial. In preclinical in-vitro and in-vivo models, vinflunine showed activity in tumour cell lines resistant to other vinca alkaloids. Disappointingly, no tumour responses were seen using vinflunine in a day one and eight schedule in this study population, in contrast to the three partial responses seen out of twenty five assessable patients treated in the published trial administering vinflunine on day 1 of a 21 day schedule [15]. Two of these responses were seen in patients with breast cancer, a tumour type not represented in this study.

In contrast to classical phase I trials where starting doses are based on toxicological data gathered from animal models, pharmacokinetic information gathered from the day Sc21 vinflunine study and knowledge regarding the pharmacokinetics and metabolism of the parent alkaloid vinorelbine, led to the estimation of a higher than normal starting dose for the day 1 and 8 schedule study. This novel approach was aimed at minimising the number of patients needed to determine the MTD, avoiding the need to treat patients at low dose levels with little likelihood of clinical activity. In practice, clinical experience with vinflunine revealed the chosen first dose level to be above the MTD, necessitating two dose de-escalations in order to establish a true MTD and a viable dose. With hindsight, a more conservative initial dose level (e.g., 75% of predicted MTD) would have been preferable.

Results of this study indicate vinflunine to be an agent with febrile neutropenia and constipation as its major dose-limiting toxicities. Fatigue was notable but non dose limiting. With appropriate supportive management such toxicities are manageable; myelosuppression is a common DLT for cytotoxic agents, constipation is less common but appropriate pre- and post-chemotherapy laxative therapy may effectively minimise or prevent this toxicity.

In summary, vinflunine can be administered on a day 1 and 8 schedule every 21 days. The MTD for this schedule was established at 190 mg/m^2 and the dose for future studies using this schedule identified as 170 mg/m^2. The toxicity profile is predictable and manageable with appropriate supportive care, particularly prophylaxis against constipation. These findings, in parallel with the clinical activity seen with the day 1, 21 day schedule, make vinflunine suitable for wider evaluation in phase II trials in a less heavily pre-treated population.

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