Phase I and pharmacokinetic study of the new vinca alkaloid vinflunine administered as a 10-min infusion every 3 weeks in patients with advanced solid tumours

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**Background:** Vinflunine is a novel vinca alkaloid obtained by semi-synthesis using super-acidic chemistry to selectively introduce two fluorine atoms at the 20′ position of vinorelbine. In human tumour xenografts, vinflunine showed definite antitumour activity in seven out of 11 tumours tested compared with three out of 11 for vinorelbine.

**Patients and methods:** In this phase I study, vinflunine was administered to 31 patients with advanced malignancies as a 10-min i.v. infusion every 3 weeks according to an escalating schedule of doses between 30 and 400 mg/m².

**Results:** Pharmacokinetic parameters and toxicities were assessed and, at 400 mg/m², three out of five patients experienced dose-limiting toxicity. At the maximum tolerated dose (MTD), i.e. 400 mg/m², the toxicity profile of vinflunine consisted mainly of mucositis, constipation and neutropenia of short duration. Vinflunine area under the curve increased as a proportion of the administered dose whereas no saturation of elimination was observed.

**Conclusion:** The MTD of vinflunine was achieved at 400 mg/m² every 3 weeks. According to protocol rules, the recommended dose was established at 350 mg/m². A preliminary assessment of first patients included in early phase II trials led to reduction of the recommended dose to 320 mg/m² every 3 weeks for further development of vinflunine. Three partial responses (two in breast carcinoma, one in renal cell carcinoma) suggest that activity is likely to be seen in less heavily pretreated patient populations.

**Key words:** dose-proportionality, pharmacokinetics, phase I study, safety, vinflunine

**Introduction**

Semi-synthetic development of the vinca alkaloids has produced a successful second-generation compound, vinorelbine (Figure 1), which has now been further modified through super-acidic chemistry to generate new and more active derivatives. The process of production involves the insertion of two fluorine atoms at the 20′ position and reduction of the 3′4′ double bond to produce 20′,20′-difluoro-3′,4′-dihydrovinorelbine, known as vinflunine (Javlor®; Laboratoires Pierre Fabre Médicament, Boulogne-Billancourt, France) [1] (Figure 2).

This compound has been selected for clinical development on the basis of preclinical activity in which efficacy was demonstrated against seven out of 11 cutaneously implanted human tumour xenografts in a model where vinorelbine only showed activity in three of the tumours tested [2]. Studies in two murine tumour models, P388 leukaemia and B16 melanoma, also revealed strong activity for vinflunine [3]. The diverse actions of vinflunine on microtubules are likely to produce different effects on mitotic spindle functions, leading to modifications of cell-cycle progression and cell killing [4]. As with other vinca alkaloids, vinflunine is a specific inhibitor of tubulin that prevents microtubule assembly during mitosis [5] and induces apoptosis [6]. Vinflunine exerts effects on microtubule dynamic instability, suppressing the rate and extent of microtubule growing events [7]. The affinity profile of vinflunine shows features which suggest that it will have greater effect on mitotic rather than axonal tubulin [8] and so should significantly reduce the potential neurotoxicity observed with vinca alkaloid agents. Although vinflunine, in common with other vinca alkaloids, participates in P-glycoprotein-mediated drug resistance, recent studies have indicated that vinflunine may only be a weak substrate for P-glycoprotein [9].

Evidence from the preclinical studies was encouraging enough to warrant a phase I study in patients with refractory solid tumours; the primary objective of the study was to establish the maximum tolerated dose (MTD) of vinflunine administered as a 10-min i.v. infusion every 3 weeks. Secondary objectives were to determine the qualitative and quantitative toxicities of vinflunine,
describe the pharmacokinetic characteristics and assess preliminary evidence of antitumour activity.

Patients and methods

Patient selection

Patients were candidates for the study if they had solid tumours for which effective standard therapy was not available or if they had progressive disease after standard therapeutic modalities and had received no more than two prior regimens for advanced or metastatic disease. The interval between completion of the last chemotherapy and/or immunotherapy and/or radiotherapy and enrolment in the trial had to be at least 4 weeks. Recruited patients were between 18 and 75 years old, with World Health Organization (WHO) performance status (PS) score of 0–2 and an estimated life expectancy of at least 12 weeks. The biological criteria for eligibility were defined by laboratory tests of adequate haematological function: white blood cell (WBC) count ≥4.0 × 10^9/l, neutrophils ≥2.0 × 10^9/l, platelets ≥100 × 10^9/l, haemoglobin ≥9 g/dl. Biochemistry: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.6 × the upper normal limits (UNL), serum bilirubin ≤UNL and serum creatinine ≤UNL. At least one measurable or evaluable lesion outside of a previous radiation field was required. Measurable lesions were identified as those with a diameter ≥20 mm on computed tomography (CT) scan. Patients were excluded if they had clinical evidence of brain or leptomeningeal metastasis, symptomatic peripheral neuropathy grade ≥2 [according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale], uncontrolled hypercalcaemia or unstable cardiovascular conditions (heart failure, uncontrolled angina, uncontrolled hypertension, myocardial infarction within 6 months). Concurrent treatment with other experimental drugs or participation in another clinical trial within the 30-day period prior to study entry were not permitted. The study was approved by the Ethics Committee of the Hôpital St Louis, Paris, France and was conducted in three centres; all patients gave written informed consent before entry into the study.

Treatment plan

Vinflunine was supplied by Institut de Recherche Pierre Fabre (Boulogne-Billancourt, France) at a concentration of 30 mg/ml solution in water for injection in sterile neutral glass vials of 3 ml. For administration, the appropriate dose of vinflunine was diluted in normal saline 50 ml and infused over 10 min via a central venous line.

The starting dose of 30 mg/m^2 was based on preclinical toxicity models representing one-sixth of the LD_{50} for mice and one-sixth of the MTD for dogs and monkeys. It was planned to enroll a single patient at 30 and 60 mg/m^2 in order to minimise the number of patients treated at non-therapeutic levels, then treat a maximum of three evaluable patients at subsequent doses. At each level a dose adaptation calculated on the basis of the haematological toxicity was used to determine progress to the next level or escalation within the level being evaluated. Leucopenia and neutropenia are frequently the major dose-limiting toxicities (DLTs) for vinca alkaloids, and particularly for vinorelbine. During phase I trials with i.v. vinorelbine, a dose-proportional increase of blood exposure (area under the curve, AUC) was demonstrated in the range 20–40 mg/m^2 [10] as well as a significant pharmacokinetic/pharmacodynamic (PK/PD) relationship between blood cell count (per cent decrease at nadir) and AUC [11]. These results suggested that doses inducing a 50% decrease in WBCs were well tolerated and that DLTs were generally observed when the decrease was close to 80%. Pharmacokinetic modelling of preclinical data through a scaling-up approach, combined with a wide experience on the vinorelbine PK/PD relationship, allowed us to predict that the MTD should be reached at a dose level >300 mg/m^2. Therefore, an accelerated dose escalation was designed for the initial levels, followed by a more conventional Fibonacci’s scheme for further levels when WBC count decreased by ≥50%. Therefore, if the required number of evaluable patients did not experience haematological toxicity (WBC count ≥50% of baseline value, neutrophil nadir ≥1.5 × 10^9/l), the next dose level was twice the previous level; if haematological toxicity was seen by these criteria, the dose had to be increased by one-third, then one-quarter for three steps (Figure 3). Dose escalations using these rules were to be continued until at least one out of three patients experienced during cycle 1 DLT defined as: (i) haematological toxicity consisting of nadir neutrophils <0.5 × 10^9/l for at least 7 days or <0.1 × 10^9/l for at least 3 days, thrombocytopenia <25 × 10^9/l or thrombocytopenia with bleeding or requiring platelet transfusion; (ii) febrile neutropenia defined as absolute neutrophil count <0.5 × 10^9/l and fever (three measured temperatures >38°C in 24 h or one >38.5°C); and/or (iii) any grade 3/4 major organ toxicity except alopecia or unpremedicated nausea/vomiting. If only one out of three patients experienced a DLT, a further three patients were entered at the same dose level; if, however, no further DLT was experienced by the additional patients dose escalation was continued. Conversely, if two out of the first three patients or three out of the six patients experienced DLT an additional three patients were treated on the preceding lower dose. The MTD was defined as the dose at which either two out of three or three out of six patients experienced DLT after the first administration of vinflunine.

Treatment procedure

Treatment was planned to be administered every 21 days up to a maximum of six doses or more, at the discretion of the clinician with the following rules for delay of the next dose: haematological toxicity consisting of neutrophils <1.5 × 10^9/l and/or platelets 100 × 10^9/l; non-haematological toxicity (except nausea/vomiting despite adequate antiemetic therapy) at grade 3/4 which did not recover to grade 1; worsening of WHO PS >2.
If the above changes had not resolved by 2 weeks after the scheduled date of the next treatment, therapy was stopped. On an individual patient basis, dose reduction (dose level $n$ to dose level $n - 1$) was applied in case of occurrence during the previous cycle of neutropenia <0.5 $\times 10^9/l$, lasting at least 7 days, or <0.1 $\times 10^9/l$, lasting at least 3 days, and/or major organ toxicity or grade $\geq 3$ (except for nausea and vomiting despite adequate premedication).

Pretreatment and follow-up examinations

At entry to the study, patients were evaluated with a complete medical history and physical examination including measurement of vital signs (temperature, pulse rate and blood pressure), electrocardiogram (ECG), complete blood count (CBC), serum electrolytes, hepatic and renal function, chest X-ray and CT or magnetic resonance imaging (MRI) scans to define the extent of tumour involvement. During the treatment period patients were monitored with CBC and biochemical tests twice weekly for the first two cycles then subsequently on day 1 of each planned cycle. ECGs were scheduled at 30 min, 3 and 6 h after the end of the vinflunine infusion on cycle 1 and before each subsequent infusion. Toxicity assessments using the NCI-CTC scale [8] were made at baseline to record residual toxicity from previous therapy and before each cycle. Tumour response was assessed according to the WHO criteria [12, 13].

Pharmacokinetics

Blood and urine samples were collected following vinflunine administration on the first cycle of treatment. During the first cycle, blood samples were collected over a 96-h period. Elimination in urine was followed over a 48-h period. This shorter period of collection was considered as a compromise between getting enough scientific data and assuring complete and accurate urine collection without inconveniencing patients over a protracted period. Vinflunine blood and urinary concentrations were quantified by a fully validated high-performance liquid chromatography method. Vinflunine was extracted from the biological fluid by diethyl ether in alkaline conditions followed by a back-extraction in acidic conditions. Vinflunine was separated from other compounds on a reverse phase column and quantified by ultraviolet detection. The limits of quantification were 2 ng/ml and 20 ng/ml in blood and urine, respectively. Precision and accuracy of the method were $>93\%$ and $98\%$, respectively.

The pharmacokinetic analysis was carried out by a conventional model-independent approach. The main pharmacokinetic parameters [area under the curve extrapolated to infinity ($AUC_{\infty}$), terminal half-life ($T_{1/2}$), terminal volume of distribution ($V_d$) and total body clearance ($Cl_{tot}$)] were calculated.

Results

Patients

Thirty-one patients were entered onto the study between 1 December 1998 and 23 March 2000 and were assigned to nine dose levels. Their demographic data are shown in Table 1 and are typical for a population in a phase I trial of a cytotoxic agent, with the majority of patients (29 of 31) having been previously treated by chemotherapy.

Drug delivery

Patients were enrolled at nine different dose levels: one each at 30 and 60 mg/m², respectively, then three each at 120, 160, 200 and 250 mg/m²; at 320 mg/m², six patients were enrolled. At the 400 mg/m² level, of the five patients included, three experienced DLT. This was therefore designated the MTD. Since the 320 mg/m² dose level was considered to be safe, a further six patients were treated at an intermediate dose level, 350 mg/m².

A total of 96 cycles were delivered with a median of two per patient (range 1–8); six patients received six cycles of therapy (Table 2). All patients were evaluable for toxicity, and 25 were evaluable for response with the following exclusions: four patients received only one dose of vinflunine (one patient because of PS deterioration, one patient died of septic shock and two patients withdrew as a result of toxicity); one patient died due to disease progression after the second dose of vinflunine and one patient was still on treatment at the study cut-off date but too early for tumour response assessment.
Toxicity

All 31 patients were evaluable for toxicity, which is summarized in Table 3. Leucopenia and neutropenia were the main haematological toxicities with evaluations after cycle 1, and although grade 3 toxicity (neutropenia) was first recorded in one out of three patients treated at 120 mg/m², a consistent pattern of suppression was not then seen until the 250 mg/m² dose level and above. Neutropenia at grade 3 was recorded in one out of three patients at 250 mg/m², at grade 4 in two out of six patients at 320 mg/m², and at grade 4 in three out of five patients at 400 mg/m², with the nadir falling between days 11 and 16 (but not constituting DLT); grade 3 was recorded in one out of six patients and grade 4 in one out of six patients at the final tested level of 350 mg/m². Significant thrombocytopenia and anaemia were infrequent (grade 3 thrombocytopenia after cycle 1 in one patient treated at 320 mg/m² and grade 3 anaemia in one patient treated at 320 mg/m²). Grades 3 and 4 non-haematological toxicities were infrequently recorded during the first cycle at dose levels up to 250 mg/m² (one episode each of grade 3 anorexia, nausea and fatigue), but above this level grade 3/4 toxicities were recorded consisting of febrile neutropenia (one grade 3 at 350 mg/m²), infection (one grade 3 at 320 mg/m²), vomiting (one grade 3 at 320 mg/m²), stomatitis (one grade 3 and one grade 4 at 320 mg/m²), oesophagitis (one grade 3 at 320 mg/m²), cardiac function (one grade 3 at 400 mg/m²), hypertension (one grade 3 at 350 mg/m²), tachycardia (one grade 3 at 320 mg/m²), venous irritation (one grade 3 at 350 mg/m², resulting from tumour compression unrelated to study drug), dyspnoea (two grade 3 at 350 mg/m², one grade 4 at 400 mg/m²), constipation (two grade 3 at 320 mg/m² and one grade 3 at 400 mg/m²), abdominal pain (one grade 3 at 320 mg/m², one grade 4 at 400 mg/m²) and fatigue (one grade 3 at 320 mg/m², two grade 3 at 350 mg/m²). The grade 3 cardiac toxicity occurred 90 min after the end of the vinflunine infusion. Echocardiography revealed a left ventricular akinesia without cardiac enzyme modifications. Coronary angiography was subsequently normal and the patient recovered to anterior clinical status after an adapted medical treatment with a normalisation of the left ventricular shortening fraction on echocardiography. No grade 3/4 toxicity was recorded related to diarrhoea, neurosensory and neuromotor parameters, arthralgia, myalgia, local toxicity or fever.

The contribution of these events to the definition of DLT in the three highest dose levels was as follows: two out of six patients treated at 320 mg/m² experienced DLT (one with grade 3 stomatitis, the other with grade 4 stomatitis plus grade 3 constipation and grade 3 oesophagitis); three out of five patients treated at 400 mg/m² experienced DLT (one with grade 4 abdominal pain, one with grade 3 constipation and one with grade 3 heart failure); two out of six patients treated at 350 mg/m² experienced DLT (one with fatal febrile neutropenia/septic shock, the other with grade 3 dyspnoea and grade 3 hypertension). Three of these patients, who continued vinflunine after cycle 1 and the occurrence of DLTs, were subsequently treated with lower doses: 250 mg/m² instead of 320 mg/m² in one patient, and 320 and 350 mg/m² instead of 400 mg/m² in two cases.

No patient experienced DLT by haematological criteria alone (as defined by neutropenia <0.5 × 10⁹/l for 7 days or <0.1 × 10⁹/l for ≥3 days).

Pharmacokinetics

Mean blood pharmacokinetic profiles are illustrated in Figure 4 for the 30–400 mg/m² dose range explored. Blood concentrations increased up to the end of vinflunine infusion and then a tri-exponential decay was observed with a sharp decrease during the
first phase. Concentrations are easily quantified at the last sampling time (96 h) for the highest dose levels. Volume of distribution is large (1517 ± 503 l), indicating an important degree of tissue distribution. Total clearance is substantial (41.4 ± 12.9 l/h). The resulting mean half-life value was assessed at 25.5 ± 3.9 h based on a 96-h sampling period. A dose-proportional increase of blood exposure concentration was demonstrated on both AUC and Cmax. The interindividual variability is moderate, ranging from 10% to 40%.

Urinary excretion of vinflunine was relatively low, with only 11.2 ± 3.8% of the drug excreted during the first 48 h. The renal clearance of vinflunine averaged 5.3 ± 2.7 l/h (88.3 ± 45.0 ml/min), which is close to the glomerular flow rate (~120 ml/min). The value of vinflunine renal clearance was not modified by the dose level. Pharmacokinetic/pharmacodynamic relationships were observed for haematological toxicities (leucopenia and neutropenia). The nadir neutrophil count was significantly related to the vinflunine AUC (Figure 5), whereas no relationship was found with Cmax. The non-haematological toxicities at the highest blood exposures was suggested, but insufficient data were collected to explore the PK/PD relationship with any confidence. These toxicities were observed in relatively few patients during cycle 1 on which the pharmacokinetic profiles were assessed.

### Efficacy

Twenty-five out of the 31 patients were assessable for response, with three patients achieving a partial response. Two women with breast carcinoma previously treated with one adjuvant and two lines of chemotherapy for metastatic disease showed evidence of objective response (one in liver metastases and the other in lymph nodes). One patient had previously received adjuvant chemotherapy with a combination of 5-fluorouracil (5-FU), cyclophosphamide and epirubicin plus docetaxel, followed by capectabine for metastatic disease. Partial response was confirmed after the study cut-off date. Progression was observed after the ninth cycle. The second patient had previously received adjuvant chemotherapy with a combination of 5-FU, cyclophosphamide and epirubicin, and second lines of chemotherapy, including docetaxel, 5-FU and vinorelbine for metastatic disease. At study withdrawal and after six cycles of vinflunine, the partial response was confirmed. A chemonaive patient with metastatic renal carcinoma showed an objective response in lung metastases. Partial response on evaluable lung metastases was seen after two cycles.

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<th>350 mg/m² (n = 6)</th>
<th>400 mg/m² (n = 5)</th>
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and progression was identified after the fifth cycle. The breast cancer patients were treated at 400 and 350 mg/m² and the renal carcinoma patient received vinflunine 350 mg/m². Four patients had stable disease and 18 patients had disease progression after two cycles.

Discussion

This study is the first clinical trial conducted in humans with vinflunine, a new third-generation vinca alkaloid. The intracellular mode of action of vinflunine is similar to that of its parent compound vinorelbine, but there is clear evidence of superior antitumour activity in experimental models which has justified evaluation of its therapeutic activity.

In this phase I study, the schedule of vinflunine evaluated consisted of 10-min i.v. infusions every 3 weeks. The experimental findings suggest that the DLT of this mode of administration are febrile neutropenia, constipation and mucosal toxicity. The PK/PD relationship demonstrated a high correlation between body exposure to vinflunine and maximum neutrophil count decrease from baseline. Given that AUC increases with the administered dose, occurrence of severe neutropenia was more

Figure 4. Mean blood pharmacokinetic profile observed after increasing intravenous doses of vinflunine.

Figure 5. Pharmacokinetic/pharmacodynamic relationship between neutrophil count decrease (per cent from baseline) at nadir and blood body exposure (AUC).
frequent at doses ranging from 320 to 400 mg/m², corresponding to the highest body exposures. Grade 4 neutropenia occurred in 11 cycles (11%) and was observed at doses from 320 to 400 mg/m². However, the duration of neutrophil suppression was relatively brief, not exceeding 5 days, even at the highest dose level. Neutropenia was only responsible for treatment delay (of at least 4 days beyond the date the next dose was due) in three patients, and resulted in dose reduction in one patient. One infection complicating a period of neutropenia after a dose of 350 mg/m² resulted in death due to septic shock. This was the only drug-related death to occur in the study. Stomatitis or oesophagitis were recorded as the DLT in two patients treated at 320 mg/m² and abdominal pain or constipation, presumed to be related to autonomic neuropathy, was recorded as the DLT in three patients (one treated at 320 mg/m² and two treated at 400 mg/m²).

In one patient, grade 3 cardiac failure was diagnosed within 90 min of completing the infusion of vinflunine at 400 mg/m²; this patient (locally advanced non-small-cell lung cancer previously irradiated on the mediastinum) was withdrawn from the study and recovered without clinical consequences. The method in preclinical data of cardiac toxicity events did not lead to a requirement for intensive clinical cardiac patient monitoring. All the ECGs recorded during the study were reviewed centrally, and no abnormality was seen, except for this particular patient.

A second patient developed grade 3 dyspnoea with moderate hypertension 5 days after the first injection of vinflunine 350 mg/m² and recovered; a further injection of vinflunine was administered without any side-effect. The role of vinflunine in these manifestations is unclear but it does not appear to result in cumulative or irreversible toxicity.

None of the patients treated at the lower dose levels of vinflunine in this study experienced DLT of any sort (30–250 mg/m²); at the higher dose levels two out of six patients treated at 320 mg/m² (one stomatitis, one stomatitis/oesophagitis and constipation) and three out of five patients treated at 400 mg/m² (one abdominal pain, one stomatitis, one heart failure) experienced DLT. The final dose level explored was lower than the MTD of 400 mg/m², but higher than the previously tested dose of 320 mg/m². Two out of six patients treated at 350 mg/m² experienced DLT (one dyspnoea/hypertension and one fatal neutropenic fever/septic shock). According to protocol rules and definitions the recommended dose was established at 350 mg/m².

Nevertheless, data from early phase II trials have shown that due to toxicity the vinflunine single-agent suitable dose is 320 mg/m² once every 3 weeks.

In this phase I study, which was conducted in patients with refractory malignancies, no accurate estimate of antitumour efficacy can be made. However, the achievement of objective responses in three out of 31 patients is sufficiently promising to warrant exploration of this schedule in phase II trials [14, 15].

The results of this study indicate that vinflunine is a generally well tolerated agent, with neutropenia, mucositis and constipation as its major DLT; cardiac effects are less well-defined and will need careful follow-up in subsequent trials, even though their relationship to the administration of vinflunine is currently unclear. Furthermore, due to the study design (i.e. determination of MTD after one administration), and the limited experience with long-term treatment, this will also require subsequent clinical data.

Vinflunine pharmacokinetics was linear in the investigated dose range (30–400 mg/m²). Vinflunine given as a 10-min i.v. infusion every 3 weeks is suitable for wider evaluation in phase II trials at a recommended dose of ≤350 mg/m² and is likely to be associated with clinical activity in less heavily pretreated populations [16].

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References
