Original Article

A randomised, multicentre open-label phase II study to evaluate the efficacy, tolerability and pharmacokinetics of oral vinorelbine plus cisplatin versus intravenous vinorelbine plus cisplatin in Chinese patients with chemotherapy-naive unresectable or metastatic non-small cell lung cancer

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Background: A phase II study to evaluate the efficacy, tolerability and pharmacokinetics of oral or intravenous vinorelbine (VRL) plus cisplatin (CDDP) in Chinese patients with non-small cell lung cancer (NSCLC).

Methods: One hundred and thirty-one patients were randomised to oral VRL 60 mg/m^2 (arm A) or intravenous VRL 25 mg/m^2 (arm B) on days 1 and 8, plus CDDP 80 mg/m^2 on day 1 (both arms). VRL was increased to 80 mg/m^2 (arm A) or 30 mg/m^2 (arm B) in cycles 2–4 in the absence of toxicity. Primary efficacy endpoint was objective response rate (ORR). VRL pharmacokinetics was evaluated for possible drug-drug interactions with CDDP.

Results: ORR was 25.8% in arm A and 23.1% in arm B. Disease control rate was 72.7% in arm A, 72.3% in arm B. Median overall survival was 16.1 months in arm A and 19.0 months in arm B. Median progression-free survival was 4.6 months in arm A and 4.9 months in arm B. Forty-three point nine percent and 86.2% of patients had grade 3/4 neutropenia in arms A and B, respectively; incidence of febrile neutropenia was low (6.1% and 9.2%, respectively). Frequency of grade 3/4 non-haematological adverse events was also low. VRL pharmacokinetics was not affected by co-administration of CDDP.

Conclusions: Oral and intravenous VRL in combination with CDDP is effective and well-tolerated in Chinese patients with advanced NSCLC. VRL pharmacokinetics is unaffected by CDDP co-administration. Oral VRL could be an effective alternative to intravenous VRL as a first-line treatment for NSCLC, as it optimises treatment convenience while maintaining high efficacy.

Keywords: Non-small cell lung cancer (NSCLC); oral vinorelbine (oral VRL); intravenous vinorelbine (intravenous VRL); cisplatin (CDDP); Chinese patients

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Introduction

Lung cancer is a leading cause of cancer-related mortality worldwide, accounting for approximately a fifth of all cancer related deaths (1). According to a 2012 WHO report, it is the most common form of cancer in men worldwide (1.2 million, 16.7% of the total), with the highest estimated age-standardised incidence rates in central and eastern Europe (53.5 per 100,000) and eastern Asia (50.4 per 100,000) (1). Most cases are diagnosed at locally advanced or metastatic stages. In this setting, chemotherapy has been shown to prolong survival when compared with best supportive care (2). Until 1990, the most active available agents were cisplatin (CDDP)/carboplatin, cyclophosphamide/ifosfamide, mitomycin C, vinblastine/vindesine, and etoposide/teniposide. Since then, new highly active third-generation drugs [vinorelbine (VRL), gemcitabine, and taxanes such as paclitaxel or docetaxel] have been introduced.

Platinum-based doublet regimens, particularly CDDP doublets, are now the mainstay of front-line palliative treatment of advanced non-small cell lung cancer (NSCLC) (3). First-line platinum-based doublet regimens for advanced NSCLC are recommended to be given for four to six cycles, with a maximum of six cycles reserved for patients who respond to therapy and have good tolerance (4,5).

Intravenous VRL, a semi-synthetic vinca alkaloid, has been for many years a reference regimen in combination with CDDP, particularly in Europe. Many attempts were made through large phase III trials conducted around the world to challenge this efficacy; none of them demonstrated better efficacy (6-12). Since the mid-1990s, median survival of patients has been around 10 months.

Currently, intravenous VRL is approved worldwide for treatment of advanced NSCLC and advanced breast cancer. A new oral formulation of VRL has been primarily developed as a line extension of the intravenous formulation. Oral VRL was developed as soft gelatin capsules and is characterised by an absolute bioavailability of 40%, with the same inter-individual variability as the intravenous formulation (13). Its absorption is rapid and bioavailability is not influenced by food (14).

Oral and intravenous doses that achieve equivalent plasma exposure were established at 60 mg/m² oral for 25 mg/m² intravenous VRL, and 80 mg/m² oral for 30 mg/m² intravenous VRL. In clinical trials, oral VRL has shown efficacy and safety results similar to those of intravenous VRL, both as a single agent and in combination with a platinum salt (15-17).

The metabolism of VRL primarily involves CYP3A4 liver enzymes, except for 4-O-deacetyl-vinorelbine (DVRL), the only active metabolite likely formed by carboxyl-esterases (18). Metabolites are qualitatively similar between oral and intravenous dosing, and bile is the major route of elimination. Urine is only a minor route of elimination (less than 10%) and mostly concerns the parent compound (19). CDDP has a known renal toxicity and is suspected to interact with other drugs at the hepatic level. Therefore, a potential pharmacokinetic drug-drug interaction between VRL and CDDP might arise in the presence of altered hepatic function.

Since 2014, VRL has been approved for treatment of locally advanced, unresectable NSCLC in China (20). Few studies have evaluated the efficacy and tolerability of VRL alongside its pharmacokinetic profile when administered orally or intravenously in Chinese patients. Thus, the present study was designed to evaluate the efficacy (in terms of tumour response) and tolerability of oral and intravenous VRL alone and when administered concomitantly with standard doses of CDDP in Chinese patients with locally advanced/metastatic NSCLC. Pharmacokinetic analyses of oral and intravenous VRL were also performed to provide estimates of individual VRL pharmacokinetic parameters and to investigate the influence of CDDP co-administration on VRL pharmacokinetic in Chinese patients.

Methods

Study design and patients

This was a prospective, multicentre, open-label, randomised phase II trial conducted between January 2008 and September 2009 at six oncology centres in China. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP), local laws and applicable regulatory requirements. The study protocol and its related documents were approved by local Ethics Committees (IRB/EC) and Competent Authorities. All patients provided written informed consent for participation in the study.

Eligible patients were men or non-pregnant, non-lactating women, with cytologically or histologically confirmed diagnosis of NSCLC, stage IIIB, IV or in operable relapsed disease at any stage; not previously treated with chemotherapy or immunotherapy, aged 18–

75 years (patients above 65 years having no more than 3 co-morbidities affecting cardiac, pulmonary, liver or renal function). Patients had at least one uni-dimensionally measurable lesion according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.0 (21). Other inclusion criteria were: Karnofsky performance status ≥80%; life-expectancy >3 months; adequate bone marrow, hepatic and renal function, as defined by neutrophils $\geq 2.0\times10^9$/L, platelets $\geq 100\times10^9$/L, haemoglobin >11 g/dL or 6.8 mmol/L, total bilirubin ≤1.5× upper limit of normal (ULN), transaminases <2.5× ULN, alkaline phosphatases <5× ULN, creatinine ≤ULN or creatinine clearance ≥60 mL/min. Patients with a local relapse, which was liable to be treated by radiation therapy, or those who had received radiotherapy within 4 weeks prior to study entry were excluded. Other exclusion criteria were: >10% weight loss within the past 3 months; long-term oxygen therapy; pre-existing symptomatic pleural effusion requiring tapping; active central nervous system disorder, brain metastasis or leptomeningeal involvement; symptomatic neuropathy (sensory) > grade 1 according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC V2.0); cardiac failure or myocardial infarction within past 3 months, uncontrolled hypertension or arrhythmia, unstable diabetes, uncontrolled hypercalcaemia, clinically significant active infection requiring intravenous antibiotics within 2 weeks before study entry; superior vena cava syndrome; malabsorption syndrome or disease significantly affecting gastro-intestinal function or major resection of the stomach or proximal small bowel that could affect absorption of oral VRL; known hypersensitivity to drugs having a chemical structure similar to the study drugs; history of other malignancies, except if more than 5 years without recurrence or patients with a history of adequately treated basal cell carcinoma of the skin or carcinoma in-situ of the cervix.

Treatment methods

Patients were randomly assigned in a 1:1 ratio to receive oral VRL plus CDDP (arm A) or intravenous VRL plus CDDP (arm B). Stratified randomisation was done centrally prior to registration according to a minimisation procedure by centre and disease stage at screening (IIIB, IV or relapse).

Study treatment was initiated within 7 days after randomisation. In the first cycle, VRL was administered orally at 60 mg/m^2 on days 1 and 8 in arm A, or intravenously at 25 mg/m^2 on days 1 and 8 in arm B in combination with 80 mg/m^2 CDDP on day 1 (in both arms). VRL dose was increased to 80 mg/m^2 (arm A) or 30 mg/m^2 (arm B) in cycles 2–4 in the absence of grade 3–4 neutropenic infection; febrile neutropenia (FN) according to Pizzo's definition (22); grade 3 neutropenia lasting for more than ≥7 days; or grade 4 neutropenia. One treatment cycle consisted of a 3-week treatment period. Patients were treated for a maximum of 4 cycles, unless there was progressive disease (PD), unacceptable toxicity or the patient refused to continue with the trial.

Oral VRL was supplied as 20, 30, or 40 mg soft gel capsules that had to be taken after a light meal in the presence of a physician or a nurse of the department. The capsules had to be swallowed with a glass of water without chewing or sucking them. Intravenous VRL was administered as a 6–10-minute intravenous infusion under the supervision of a nurse. Oral and intravenous VRL, and commercial CDDP were supplied by Pierre Fabre Médicament to the centres. CDDP was administered intravenously according to the investigational centre's routine practice either immediately after the intake of oral VRL, or 30 to 60 minutes after completion of intravenous VRL infusion. Anti-emetic treatment with a 5-HT$_3$ antagonist such as ondansetron or granisetron was recommended with oral VRL administration. Preventive anti-emetic treatment was prescribed after CDDP infusion. Hydration on the day of CDDP administration was given according to the investigational centre's routine practice.

Prior to any dose administration, absolute neutrophil count (ANC) had to be $\geq 1.5\times10^9$/L and platelets $\geq 75\times10^9$/L. If a patient required a cycle delay, both drugs were delayed for a maximum of 2 weeks. Dose modifications were permitted as follows: day 8 of VRL was skipped if grade ≥2 haematological toxicities occurred within a cycle; dose was reduced for subsequent cycles if toxicity grade was ≥3. VRL dose escalation was not permitted for patients who experienced either grade 3 toxicity ≥7 days or one episode of grade 4 haematological toxicity or FN or neutropenic infection during a previous cycle. In case of neurological toxicity of grade ≥2, the treatment was delayed, and the patient reassessed one week later and CDDP dose was reduced by 50% for subsequent cycles. If neurological toxicity grade >2 persisted for >2 weeks or grade ≥3, the patient was discontinued from the study. In case of renal toxicity, CDDP dose was reduced by 50% if creatinine clearance was between 45–54 mL/min despite adequate hydration; if creatinine clearance remained <45 mL/min for

more than 2 weeks, the patient was discontinued. Treatment was discontinued for patients with grade 3–4 hearing loss.

Primary prophylactic use of colony stimulating factor was not allowed during the study. Growth factors could be given in case of FN or neutropenic infection according to the centre's rules. Full supportive care included antibiotics, anti-diarrhoeals, analgesics, and anti-emetics. transfusion of blood products was allowed.

Study procedures

Pre-treatment evaluations included complete medical history, physical examination, audiogram, complete blood cell counts (CBC) and biochemistry tests. During the treatment period, biochemistry tests were performed prior to each treatment cycle; CBC counts were done on days 1 and 8 of each treatment cycle. Tumour assessment was carried out at baseline, then every 2 cycles using the same methods throughout the study to ensure comparability. After the completion of 4 treatment cycles, tumour assessments were performed every 3 months until documented progression. All tumour responses had to be confirmed 4 weeks later. An independent review panel (IRP) was organised in each centre to review all responses and stabilisations. The IRP was kept blinded to the treatment received by the patients. The investigators assessed toxicities during the entire study period by recording adverse events (AE), vital sign measurements and global physical examination.

Study endpoints

The efficacy of two drug combinations (i.e., oral VRL plus CDDP, and intravenous VRL plus CDDP) was determined in terms of tumour response. The primary efficacy endpoint was objective response rate (ORR). Secondary efficacy endpoints included disease control rate (DCR), time to first response, duration of response, time to treatment failure, progression-free survival (PFS) and overall survival (OS).

Statistical methods

The one-sample multiple-testing procedure for phase II clinical trials described by Fleming was used to test the hypothesis that anti-tumour activity would be between a minimum response rate P_0 =0.15, for which further investigation was not required, and a response rate P_A =0.30 implying efficacy at an acceptable level, with type I error $\alpha \leq 0.05$, and type II error $\beta \leq 0.02$ (23). Using this hypothesis, the total required sample of evaluable patients was 120 (60 in each treatment arm). All randomised and treated patients were included in the intent-to-treat (ITT) analysis and were analysed for safety. The evaluable population was defined as all eligible patients who underwent a full evaluation of target and non-target lesions and had received at least 2 cycles of study treatment (including patients with PD documented before the second cycle).

The Kaplan-Meier method was used to estimate the duration of response and survival outcomes. Safety analysis was performed on the population evaluable for safety; defined as all patients who received at least one dose of study medication in the assigned treatment arm. All statistical analyses were performed using SAS software, version 8.2 for Windows (SAS Institute, Cary, NC, USA).

Pharmacokinetic assessments

Blood samples for pharmacokinetic evaluation of VRL and its active metabolite 4-O-deacetylvinorelbine (DVRL) were collected during cycle 1 in both treatment arms: on day 1 when VRL was co-administered with CDDP and on day 8 when VRL was administered alone. Pharmacokinetic analysis was conducted using a limited sampling strategy at the following time points for arm A: 0 h (just before oral intake of VRL), 1 h 30 min, 3, 6, 11 and 24 h after oral intake. For arm B, the blood sampling time-points were: 0 h (just before intravenous infusion of VRL), immediately at the end of infusion, 3, 6, 11 and 24 h after infusion.

VRL and its active metabolite, DVRL, were assayed in whole blood by liquid chromatography-tandem mass spectrometry (LC/MS-MS) method with a lower limit of quantification of 0.25 ng/mL (24). Absolute total clearance (Cl_{tot}) for the intravenous route and apparent total clearance (Cl_{tot}/F) for the oral route were obtained on both days by Bayesian forecasting based on the limited concentrations dataset per individual and using previously developed population pharmacokinetic models (25,26). The drug-drug interaction with CDDP was evaluated separately for each route of administration by comparing individual VRL pharmacokinetic parameters between day 1 (VRL + CDDP) and day 8 (VRL alone). Statistical evaluation was performed by a two-way ANOVA test including "DAY" and "PATIENT" factors (5% nominal risk). For DVRL, no pharmacokinetic parameters could be calculated based on the sparse sampling schedule implemented in the current study. Instead, a descriptive and graphical approach was

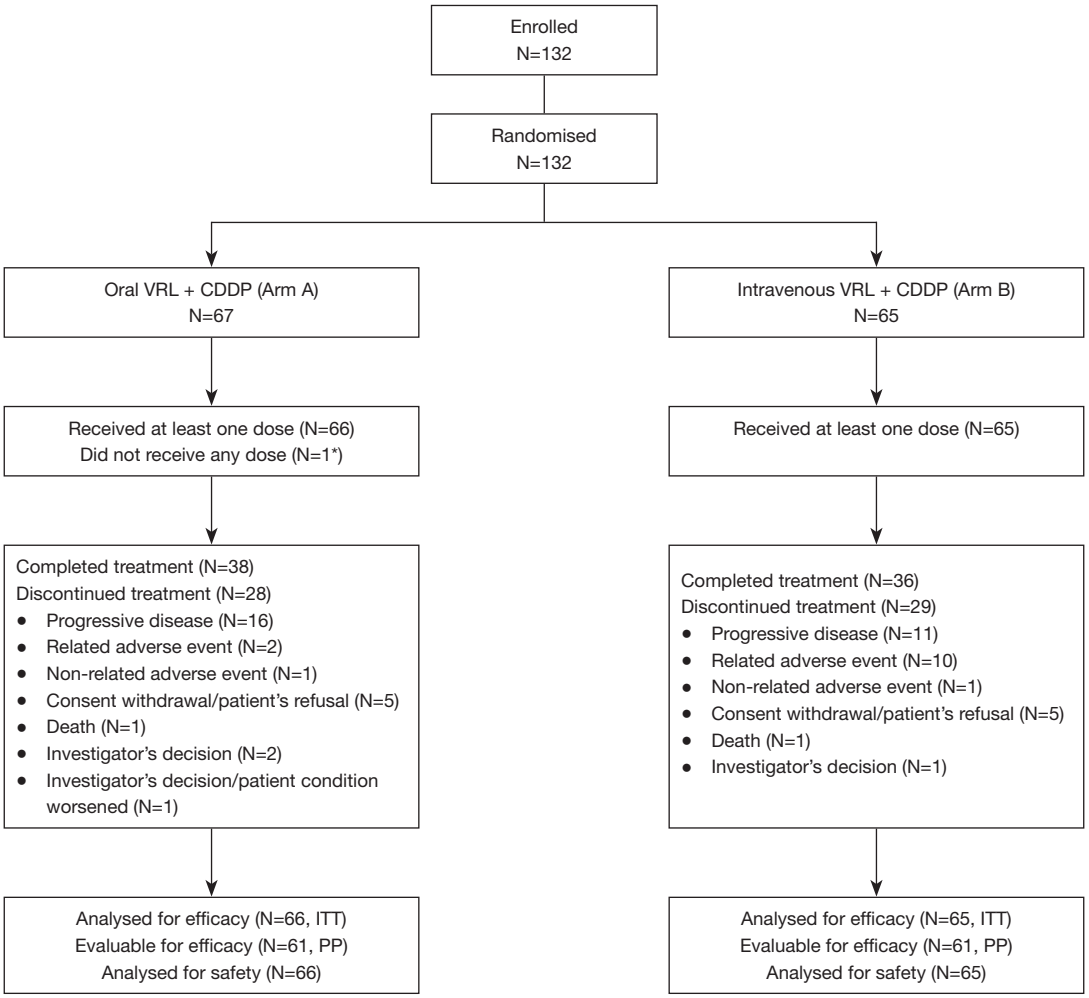

Figure 1 Patient disposition by treatment arm. *, withdrew consent before any study drug administration. CDDP, cisplatin; ITT, intent-to-treat; PP, per protocol; VRL, vinorelbine.

used to compare individual concentration *vs.* time profiles between days.

Results

Patient disposition and baseline demographics

Patient disposition is shown in *Figure 1*. A total of 132 patients were enrolled and randomised (67 in arm A and 65 in arm B). One patient in arm A withdrew consent before undergoing any study treatments; this patient was excluded from analysis. Of 131 randomised and treated patients (ITT population), 74 (56.5%) completed the study treatment as per protocol (i.e., 4 cycles) (38 in arm A and 36 in arm B) and 57 discontinued treatment (28 in arm A and 29 in arm B). The main reason for treatment discontinuation was PD in 42.1% and 30.5% of the patients in arm A and arm B, respectively.

Patient demographics are shown in *Table 1*. The median (range) age of patients in arm A [52.1 (33.3–71.9) years] was lower than that in arm B [57.9 (25.7–70.9) years]. In both arms, more than half of patients were histologically diagnosed with adenocarcinoma of the lung; all patients with histologically confirmed diagnosis of NSCLC were included in the study. The majority of the patients had metastatic disease (74.2% in arm A and 72.3% in arm B), with 2 or more organs involved at study entry (94.0% in arm A and 96.9% in arm B). All patients were deemed fit to receive the platinum-based combination therapy.

Table 1 Patient baseline demographics and disease characteristics (ITT population)

Variables	Arm A (oral VRL + CDDP) (N=66)	Arm B (intravenous VRL + CDDP) (N=65)
Age in years, median (range)	52.1 (33.3–71.9)	57.9 (25.7–70.9)
Age category		
<50 years	25 (37.9)	17 (26.2)
50–65 years	34 (51.5)	40 (61.5)
≥65 years	7 (10.6)	8 (12.3)
Gender (male)	42 (63.6)	44 (67.7)
Karnofsky performance status		
80	21 (31.8)	24 (36.9)
≥90	45 (68.2)	41 (63.1)
Histology at diagnosis		
Adenocarcinoma	35 (53.0)	37 (56.9)
Adenoid cystic carcinoma	1 (1.5)	–
Squamous/ epidermoid	18 (27.3)	22 (33.8)
Large cell	1 (1.5)	–
Unknown	11 (16.7)	6 (9.2)
Stage at diagnosis		
IA/IB	2 (3.0)	2 (3.1)
IIA	1 (1.5)	–
IIIA	1 (1.5)	1 (1.5)
IIIB	18 (27.3)	17 (26.2)
IV	44 (66.7)	45 (69.2)
Extent of disease at study entry		
Loco-regional	17 (25.8)	18 (27.7)
Metastatic	49 (74.2)	47 (72.3)
Number of organs involved		
1	4 (6.1)	2 (3.1)
≥2	62 (94.0)	63 (96.9)
Organs involved, n (%)		
Lung	63 (95.5)	63 (96.9)
Liver	7 (10.6)	9 (13.8)
Soft tissue	2 (3.0)	–
Bone	23 (34.8)	25 (38.5)
Pleural effusion	12 (18.2)	20 (30.8)
Lymph nodes	54 (81.8)	54 (83.1)
Other*	–	8 (12.3)

Data are presented as n (%) unless otherwise specified. *, other: breast, adrenals. CDDP, cisplatin; ITT, intent-to-treat; VRL, vinorelbine.

Drug delivery

The mean duration of therapy was 10.7 weeks in arm A and 11.3 weeks in arm B, with a median of 4 (range, 1–4) cycles. Median relative dose intensity was equivalent between the two arms for VRL (89.3% and 81.4%, respectively) and for CDDP (92.1% and 91.6%, respectively). Ninety-two (71.9%) patients had a VRL dose escalation at cycle 2: 54 patients (84.4%) from 60 to 80 mg/m² (arm A) and 38 patients (59.4%) from 25 to 30 mg/m² (arm B). Cycle delay (>2 days) occurred in 25% of the patients in arm A and 31.6% of the patients in arm B. Day 8 was cancelled in 2.3% of the cycles in arm A and in 4.2% of the cycles in arm B. The main reason for day 8 cancellation was haematological toxicity, which occurred in 1 out of 5 cases in arm A and in 7 out of 9 cases in arm B. A total of 10 (15.2%) patients had at least one VRL dose reduction in arm A *vs.* 17 patients (24.6%) in arm B. CDDP administration was reduced for only 4 (6.1%) patients in arm A and 1 (1.5%) patient in arm B.

Efficacy

Investigator- and IRP-assessed efficacy results are shown in *Table 2*. The ORR was calculated based on partial responses achieved by patients in arms A and B. IRP-assessed ORR was 25.8% in arm A and 23.1% in arm B, while

Table 2 Efficacy results as assessed by investigators and independent review panel (ITT population)

Variables	Arm A (oral VRL + CDDP) (N=66)	95% CI	Arm B (intravenous VRL + CDDP) (N=65)	95% CI
Independent review panel				
Partial response (ORR)	17 (25.8)	15.8–38.0	15 (23.1)	13.5–35.2
Stable disease	31 (47.0)	–	32 (49.2)	–
Disease control rate[a]	48 (72.7)	60.4–83.0	47 (72.3)	59.8–82.7
Progressive disease	2 (3.0)	–	2 (3.1)	–
Non-evaluable disease	–	–	4 (6.2)	–
Investigator assessment				
Partial response (ORR)	13 (19.7)	10.9–31.3	19 (29.2)	18.6–41.8
Stable disease	35 (53.0)	–	32 (49.2)	–
Disease control rate[a]	48 (72.7)	60.4–83.0	51 (78.5)	66.5–87.6
Progressive disease	14 (21.2)	–	10 (15.4)	–
Non-evaluable disease	4 (6.1)	–	4 (6.2)	–
Other efficacy endpoints				
Time to treatment failure (months), median	3.4	3.1–5.0	3.4	3.0–3.9
PFS (months), median	4.6	3.2–5.1	4.9	3.6–6.2
OS (months), median	16.1	10.0–24.9	19.0	11.9–25.3

Data are presented as n (%) unless otherwise specified. [a], partial response + stable disease. CDDP, cisplatin; CI, confidence interval; ITT, intent-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; VRL, vinorelbine.

investigator-assessed ORR was 19.7% in arm A and 29.2% in arm B. DCR was assessed by both IRP and investigator to be more than 70% in both arms. IRP-assessed time to first response was 1.4 months (95% CI: 1.3–3.0 months) in arm A and 1.5 months (95% CI: 1.3–3.5 months) in arm B, while investigator-assessed time to first response was 1.4 months (95% CI: 1.2–3.0 months) in arm A and 1.4 months (95% CI: 1.2–2.8 months) in arm B. The median PFS was 4.6 months (95% CI: 3.2–5.1 months) in arm A and 4.9 months (95% CI: 3.6–6.2 months) in arm B. With a censor rate of 30% in arm A and 23% in arm B, the median OS was 16.1 months (95% CI: 10.0–24.9 months) in arm A and 19.0 months (95% CI: 11.9–25.3 months) in arm B (*Figure 2*).

Safety and tolerability

Haematological toxicity was common in both treatment arms with grade 3/4 neutropenia occurring in 29 (43.9%) patients in arm A and 56 (86.2%) patients in arm B (*Table 3*). Grade 3/4 haematological toxicity was less commonly reported in patients receiving oral VRL than intravenous VRL. The incidence of FN was low; only 4 (6.1%) patients in arm A and 6 (9.2%) patients in arm B reported FN. Five patients required red blood cell transfusion: one patient in arm A and four patients in arm B.

The most frequent non-haematological AE were nausea, vomiting and anorexia, but the incidence of grade 3/4 events was low (*Table 3*). Diarrhoea was reported in 16 (24.2%) and 12 (18.5%) patients in arm A and arm B, respectively. There were three deaths during the study. One patient (arm A) died due to PD and two patients (one in each arm) died from pneumonia during cycle one; both events were assessed as possibly related to study treatment.

Pharmacokinetics analyses

Pharmacokinetic analyses were performed on blood samples taken from 21 patients who received oral VRL (arm A) and 17 patients who received intravenous VRL (arm B) on days 1 and 8.

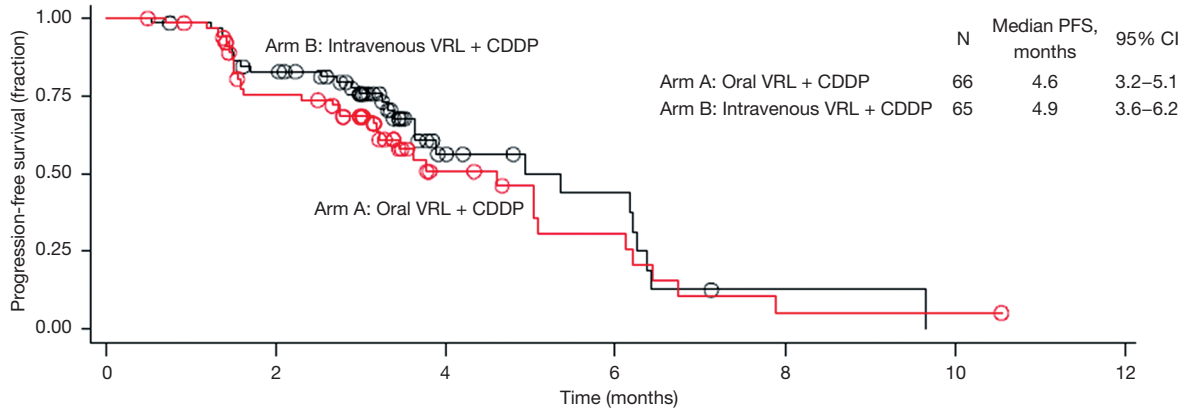

Figure 2 Progression-free survival (PFS) curves for treatment arm A (oral VRL + CDDP) and arm B (intravenous VRL + CDDP). Open circles represent censored data. CI, confidence interval; CDDP, cisplatin; ITT, intent-to-treat; VRL, vinorelbine.

VRL and DVRL plasma concentration profiles

Individual plasma concentration profiles of VRL and its metabolite, DVRL, were compared between day 1 and day 8 (*Figure 3*). For both routes of administration, individual VRL plasma concentration profiles overlapped when day 1 data were superimposed upon day 8 data. There was little to no accumulation of VRL from day 1 to day 8 (*Figures 3A,B*). DVRL accumulated at low concentration levels (below 10 ng/mL) after oral administration (*Figure 3C*) or intravenous infusion (*Figure 3D*).

Clearance of oral and intravenous VRL

The mean apparent clearance of oral VRL was similar between the two treatment modalities: 175±93.6 L/h (VRL + CDDP) *vs.* 138±56.5 L/h (VRL alone). As depicted in *Figure 4A*, no obvious trend (decrease or increase between day 1 and day 8) was observed, indicating the absence of CDDP effect on oral VRL pharmacokinetics. The mean total clearance of intravenous VRL appeared tended to be lower (by ~25%) when combined with CDDP (26.1±10.5 L/h) than when given alone (34.6±8.82 L/h; $P<0.05$). However, this difference was observed in only a few patients. As depicted in *Figure 4B*, an increase in total clearance from day 1 to day 8 was obvious only for patients who exhibited low clearance (below 20 L/h) on day 1 before returning to values between 20–40 L/h on day 8. Consequently, the mean total body clearance on day 1 was lower than on day 8 for this subset of patients.

Discussion

In the present study, we evaluated the efficacy of two drug combinations in Chinese patients with NSCLC in terms of tumour response. The primary efficacy endpoint of this study, ORR, was similar for oral and intravenous routes of VRL in combination with CDDP, thus demonstrating the efficacy of both routes in first-line treatment of advanced NSCLC in Chinese patients. Other secondary efficacy parameters, including DCR, median PFS, and median OS, support this conclusion. These results are also consistent with previous experience with oral and intravenous VRL/CDDP combination regimens in European patients, which were associated with similar response rates (6,11,13,27).

Discrepancies between IRP-assessed and investigator-assessed efficacy results were observed and were expected. Independent reviews are conducted primarily to discern and minimise bias that may be introduced by the investigators (28). As such, blinded independent reviews are recommended for clinical trials studying tumour response or disease progression (28-32).

The two regimens had similar safety profiles, in line with the previously reported randomised studies with this combination (11,15,27). Neutropenia, the most commonly reported haematological toxicity, was rarely complicated with FN, which is particularly encouraging in light of high rates of FN reported in studies with other agents. First-line agents such as paclitaxel and docetaxel have been associated with high incidence of bone marrow suppression and FN (up to 26% of patients), including high incidence rates in the first cycle (33,34). This has been a cause of additional patient care and treatment costs. Concerning non-haematological toxicity, gastro-intestinal side effects were frequent but could be easily managed by anti-emetics and dietary education.

Table 3 Most commonly (>5%) reported adverse events (ITT population)

Adverse events (NCI-CTCAE version 2.0)	Arm A (oral VRL + CDDP) (N=66)			Arm B (intravenous VRL + CDDP) (N=65)		
	Overall	Grade 3	Grade 4	Overall	Grade 3	Grade 4
Haematological toxicities						
Anaemia	64 (97.0)	6 (9.1)	–	65 (100.0)	13 (20.0)	3 (4.6)
Leukopenia	51 (77.3)	12 (18.2)	8 (12.1)	60 (92.3)	31 (47.7)	9 (13.8)
Neutropenia	55 (83.3)	7 (10.6)	22 (33.3)	60 (92.3)	17 (26.2)	39 (60.0)
Thrombocytopenia	40 (60.6)	–	–	39 (60.0)	3 (4.6)	–
Febrile neutropenia*	4 (6.1)	–	–	6 (9.2)	–	–
Non-haematological toxicities						
Gastrointestinal disorders						
Abdominal pain	7 (10.6)	–	–	4 (6.2)	–	–
Constipation	14 (21.2)	–	–	20 (30.8)	1 (1.5)	1 (1.5)
Diarrhoea	16 (24.2)	11 (16.7)	–	12 (18.5)	–	–
Nausea	53 (80.3)	8 (12.1)	–	55 (84.6)	6 (9.2)	–
Vomiting	44 (66.7)	10 (15.2)	1 (1.5)	43 (66.2)	9 (13.8)	1 (1.5)
General disorders and administration site condition						
Chest pain	16 (24.2)	3 (4.5)	–	16 (24.6)	3 (4.6)	–
Fatigue	30 (45.5)	1 (1.5)	–	29 (44.6)	3 (4.6)	–
Pyrexia	5 (7.6)	1 (1.5)	–	6 (9.2)	–	–
Infections and infestations						
Pneumonia	4 (6.1)	1 (1.5)	–	7 (10.8)	5 (7.7)	–
Metabolism and nutrition disorders						
Anorexia	43 (65.2)	9 (13.6)	–	46 (70.8)	5 (7.7)	1 (1.5)
Musculoskeletal and connective tissue disorders						
Bone pain	7 (10.6)	1 (1.5)	–	7 (10.8)	1 (1.5)	–
Nervous system disorders						
Dizziness	6 (9.1)	–	–	6 (9.2)	–	–
Respiratory, thoracic and mediastinal disorders						
Cough	12 (18.2)	1 (1.5)	–	12 (18.5)	1 (1.5)	–
Dyspnoea	8 (12.1)	1 (1.5)	–	8 (12.3)	1 (1.5)	–
Hiccups	5 (7.6)	–	–	5 (7.7)	–	–
Skin and subcutaneous tissue disorders						
Alopecia	12 (18.2)	–	–	12 (18.5)	–	–

Data are presented as n (%). *, according to Pizzo's definition (22). CDDP, cisplatin; ITT, intent-to-treat; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; VRL, vinorelbine.

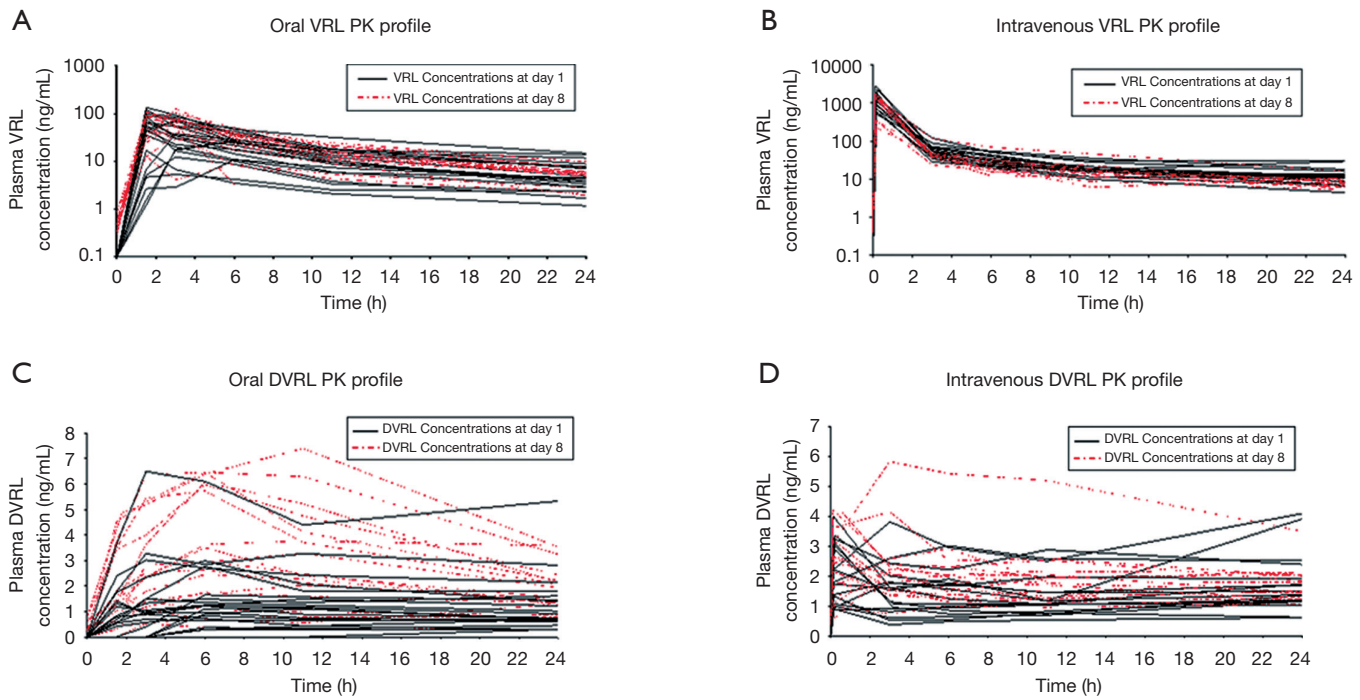

Figure 3 Overlay of day 1 and day 8 profiles for plasma concentration vs. time in individual patients for VRL (A,B) and its metabolite, DVRL (C,D). Oral VRL dose was 60 mg/m^2 and intravenous dose was 25 mg/m^2. CDDP, cisplatin; VRL, vinorelbine; DVRL, 4-O-deacetyl-vinorelbine; PK, pharmacokinetics.

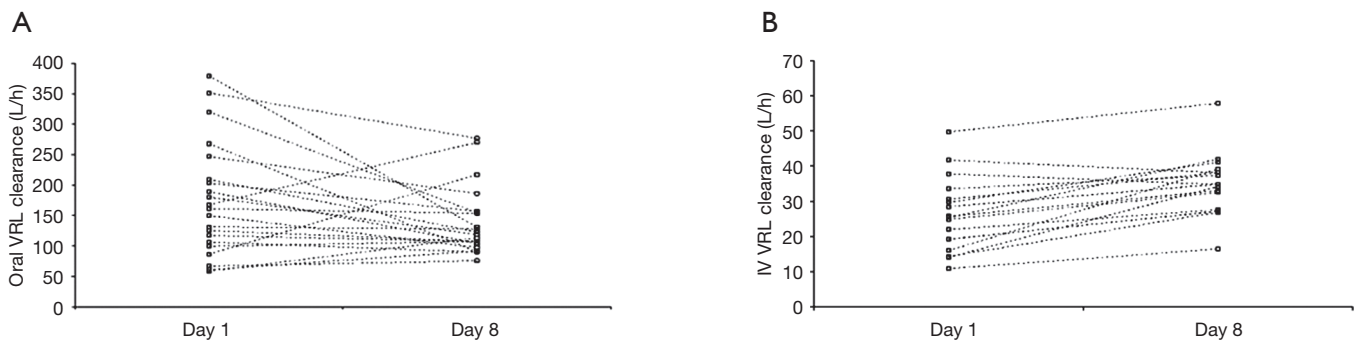

Figure 4 Individual patient profiles for (A) apparent oral VRL clearance (N=21) and (B) absolute intravenous VRL clearance (N=17) for day 1 (VRL + CDDP) and day 8 (VRL alone). CDDP, cisplatin; IV, intravenous; VRL, vinorelbine.

Oral chemotherapy, when effective, may offer better convenience and advantages for patients and physicians over standard intravenous chemotherapy (35). Current research is focused on developing oral formulations active against NSCLC, and several agents are already approved or are in development (36,37). The availability of effective oral chemotherapy may offer more flexibility to patients who are living in remote areas or are far from oncology clinics (38). Oral chemotherapy also reduces anxiety in patients who are afraid of injections (37,39), and may be more appropriate when venous access is problematic. Our results demonstrated better tolerability with oral VRL than with intravenous VRL; less patients receiving oral VRL than intravenous VRL discontinued day 8 treatment due to toxicity. Indeed, studies have shown that most patients prefer oral to intravenous therapy, assuming similar

efficacy (37,40). Patient preference for oral *vs.* intravenous VRL administration was evaluated in a randomised trial in advanced NSCLC. Oral VRL plus platinum salt was preferred by 3 out of 4 patients; moreover, patients reported that their everyday life was less affected due to less time spent at the clinic and the possibility of taking the day 8 dose at home (41).

In addition to assessing efficacy, another objective of this study was to assess the pharmacokinetics parameters of oral and intravenous VRL in Chinese patients and examine potential drug-drug interaction with CDDP. The risk of VRL interaction with CDDP could be considered low, since VRL is only poorly eliminated by the kidney. Thus far, amongst numerous CDDP-VRL combination studies, only two trials have explored potential pharmacokinetic drug-drug interactions of orally or intravenously administered VRL (42,43). Both studies were conducted in European populations and did not demonstrate any CDDP-VRL interaction.

Our study presented valuable insights into the pharmacokinetic profile of oral/intravenous VRL, alongside efficacy and tolerability, in an all-Chinese patient population. We observed no effect of CDDP on the pharmacokinetic behaviour of VRL. With oral administration of VRL, apparent clearance was not affected by CDDP co-administration. With intravenous administration, VRL clearance was affected by CDDP, but only in a small subset of patients. For the majority of patients, there appeared to be no effect of CDDP. Similarly, although few patients exhibited higher DVRL concentrations, there were no observed difference in clinical responses or incidence of AEs compared to the other patients. The present study in Chinese patients thus confirmed the previous observations regarding lack of interaction between VRL (oral or intravenous) and CDDP in European populations (42,43).

Conclusions

In summary, oral VRL in combination with CDDP is effective and well-tolerated in Chinese patients with advanced NSCLC. The efficacy of oral VRL was comparable to that of intravenous VRL, as suggested by ORR, DCR, PFS and OS results. Furthermore, the safety profile of both routes was also similar. Similar pharmacokinetic behaviour was observed for oral and intravenous VRL, independent of CDDP co-administration. Oral VRL is an attractive option for first-line treatment of NSCLC, combining treatment convenience with a high level of efficacy and safety.

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Footnote

Conflicts of Interest: JP Burillon, M Riggi, A Petain, P Ferre are employees of Institut de Recherche Pierre Fabre, France (the sponsor of the study). The other authors have no conflicts of interest to declare.

Ethics Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol and its related documents were approved by local Ethics Committees (IRB/EC) and Competent Authorities, namely, the ethics committees of Sun Yat-sen University Cancer Center, Beijing Cancer Hospital, Fujian Provincial Tumor Hospital, Fudan University Cancer Hospital, and Zhejiang Cancer Hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Disclaimer: The data that support the findings of this study are available from Pierre Fabre Médicament but restrictions apply to the availability of these data and so are not publicly available. Data are however available upon reasonable request and with the permission of Pierre Fabre Médicament. The corresponding author had full access to all data and was responsible for the decision to submit for publication.

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