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# Therapeutic Efficacy and Pharmacokinetics of Vindesine and Vindesine-Cisplatin in Previously Treated Patients with Non-Small Cell Lung Carcinoma*

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***Summary.*** *Twenty-nine patients with non-small cell lung cancer refractory to prior therapy were treated with either vindesine (VDS) alone (3 mg/m² every week) or the combination of VDS plus cisplatin (DDP) (100 mg/m² every 28 days). Serial blood and urine samples were colletected to assess the pharmacokinetics of VDS and DDP. All patients were evaluable for toxicity and 27 were evaluable for response. No objective antitumor responses were observed. Peripheral neuropathy manifested by paresthesias, muscle weakness, and constipation were observed in 20 treated patients, and hematologic toxicity consisting of thrombocytopenia and/or leukopenia occurred in 18 patients. The plasma and urinary pharmacokinetics of VDS and DDP measured in this study indicate that VDS and DDP do not interfere with each other and that the pharmacokinetics in previously treated and untreated patients are similar.*

*The antitumor responses and degree of toxicity observed in this trial compare unfavorably with previously reported VDS and VDS-DDP trials in previously untreated patients with this disease and suggest that prior exposure to chemotherapy might both decrease antitumor activity and enhance toxicity of these chemotherapeutic agents.*

## Introduction

Vindesine (VDS) and *cis*-diamminedichloroplatinum (DDP) have been identified as active single agents for treatment of non-small cell lung carcinoma (NSCLC) [1, 4, 5, 8, 10, 15]. The combination of VDS plus DDP has shown increased activity against NSCLC, producing major objective (complete and partial) responses in 43% of 81 previously untreated patients [6].

We therefore initiated a study of VDS alone against VDS + DDP to test the clinical efficacy of these chemotherapies as salvage therapy for patients with inoperable NSCLC who had relapsed after treatment with other combination chemotherapies or radiotherapy or both. In addition we investigated potential drug-drug interaction between these agents.

## Materials and Methods

*Patient Population.* Patients with histologically documented metastatic NSCLC refractory to previous therapy were eligible for this clinical and pharmacokinetic trial. All patients had progressive and measurable or otherwise evaluable disease. Measurable lesion(s) required the presence of clearly defined tumor margins so that the longest perpendicular diameters could be assessed. Evaluable lesions were visible and accessible but did not allow for precise measurements of both perpendicular diameters. Patients were defined as having limited disease if the tumor was confined by all clinical measurements to one lung including mediastinal or ipsilateral supraclavicular nodes. Disease beyond these confines was classified as extensive.

Eligibility criteria included: no recent radiotherapy (< 4 weeks) or chemotherapy (< 4 weeks; < 8 weeks for nitrosoureas), a white blood cell count > 3,500/μl, a platelet count > 100,000/μl, normal liver function tests, and resolution of all toxicities from previous therapy. Patients with active cardiac disease, a creatinine clearance < 60 cm³/min, a CALGB performance score > 3, or with no measurable or evaluable tumor were excluded from study. Written, informed consent was obtained from all patients prior to study.

Prior to therapy all patients were carefully evaluated and staged for disease including: history and physical examination, performance status determination (CALGB scale) [2], tumor measurements by appropriate technique, blood cell counts, liver function tests, blood urea nitrogen (BUN), serum creatinine, 24-h creatinine clearance, chest, and other appropriate roentgenograms. Radionuclide scanning of liver, bone, and brain were performed when history, physical, or laboratory evaluation indicated possible metastatic involvement of the respective organ. During therapy, physical examinations, blood cell counts, and patient's performance status were reassessed at weekly visits. Tumor measurements, BUN, creatinine clearance, liver function tests, and chest roentgenogram were repeated at 3- to 4-week intervals. Radionuclide scans were repeated as clinically indicated to evaluate signs, symptoms, and any evidence of response.

Pre-treatment patient characteristics are outlined in Table 1. Patients were treated with either VDS alone or VDS + DDP, depending on prior exposure to DDP as part of previous combination chemotherapy. Those patients with prior DDP treatment were allocated to VDS alone, whereas those without DDP exposure received the VDS + DDP combination. Five patients without prior DDP treatment refused the combination because of anticipated nausea and vomiting and were treated with VDS alone. Vinca and platinum pharmacokinetics were assessed in patients receiving VDS and DDP, and the vindesine data were compared with those of patients treated

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**Table 1.** Pre-treatment patient characteristics

| Characteristics | Number of patients | |
|---|---|---|
| | VDS alone | VDS + DDP |
| Patients entered | 15 | 14 |
| Male: female | 11 : 4 | 7 : 7 |
| Age in years, median (range) | 58 (46–72) | 57 (45–69) |
| Histologic subtype | | |
| Adenocarcinoma | 10 | 9 |
| Squamous cell carcinoma | 2 | 5 |
| Large cell undifferentiated carcinoma | 3 | 0 |
| CALGB performance score | | |
| 0–1: 2–3 | 5 : 10 | 2 : 12 |
| Measurable disease | 15 | 12 |
| Otherwise evaluable disease | 0 | 2 |
| Extent of disease | | |
| Limited | 5 | 5 |
| Extensive | 10 | 9 |
| Prior therapy: | | |
| Chemotherapy: | | |
| CTX-Adr-VP16-213 plus DDP | 10 | 0 |
| CTX-Adr-VP16-213 | 0 | 5 |
| Other non-DDP or vinca-based regimens | 5 | 7 |
| Radiotherapy alone | 0 | 2 |

with VDS alone, including those without prior DDP exposure. Platinum pharmacokinetic data were compared with those of patients treated at our institution with a comparable dose of DDP as a single agent.

VDS, supplied by Eli Lilly and Company, Indianapolis, Indiana, (3 mg/m$^2$) was given in both treatment regimens by rapid IV infusion once a week for the first 6 weeks and then on an every-2-weeks schedule. Patients treated with VDS + DDP received DDP at a dose of 100 mg/m$^2$ every 4 weeks. In an attempt to reduce DDP-related nephrotoxicity, all patients were pre-hydrated (the night before DDP therapy) with 2 l 5 g% glucose in 0.45 g% NaCl. One hour before DDP treatment a continuous IV infusion of mannitol at the rate of 6.25 g/h was started, and this was continued for 6 h. DDP was reconstituted in 2 l 0.45 g% NaCl and infused at a constant rate over 6 h. Immediately after the DDP administration, 1 l 0.45 g% NaCl containing 20 mEq KCl was infused at the rate of 150 cm$^3$/h and then total fluid output (urine plus emesis) was replaced IV volume for volume every 2 h until the following morning. Adequate hydration was maintained with further IV fluid if nausea and vomiting persisted for more than 18 h after therapy. Chemotherapy was continued if measurable disease remained stable or improved and and there was also no evidence of unacceptable toxicity.

Subsequent VDS dosage modifications were based on the blood cell count on the 8th day of each treatment according to the following criteria: if the WBC was $\geq$ 3,500/μl and the platelet count was $>$ 100,000/μl then the same dose was repeated; if the WBC was between 2,500 and 3,500/μl and/or the platelet count was between 75,000 and 100,000/μl then the subsequent VDS dose was reduced to 1.5 mg/m$^2$. If by 8 days after the previous VDS dose, the WBC was $<$ 2,500/μl and/or the platelet count was $<$ 75,000/μl, then subsequent therapy was delayed until full hematologic recovery occurred. Each DDP dose initiated a new treatment cycle. If on day 28 of the previous cycle the WBC count was $<$ 3,500/μl and/or the platelet count was $<$ 100,000/μl, then DDP was withheld until full hematologic recovery occurred and given at 100 mg/m$^2$. VDS was withheld on both regimens if severe peripheral neurotoxicity occurred and DDP was withheld if the creatinine clearance fell to less than 50cm$^3$/min.

Separate response criteria were used for measurable and evaluable disease. These have been reported in detail by Eagon at al. [3]. A complete remission (CR) required the total disappearance of all tumor and tumor-related signs and symptoms and applied to both measurable and evaluable disease. A partial remission (PR) applied only to measurable disease and required a $>$ 50% reduction in the sum of the products of perpendicular diameters of all measurable lesions. A regression applied only to evaluable disease and required a definite decrease in size agreed upon by two investigators. Stable measurable disease implied a $<$ 50% reduction or $<$ 25% increase in the indicator lesion(s) with no appearance of new lesions. Stable evaluable disease required no definite increase or a decrease in tumor size agreed upon by two investigators, and no new lesions. Progressive, measurable disease required an increase by at least 25% in the size of any measurable lesions or the appearance of new lesion(s). Progressive, evaluable disease required a definite increase in size of the lesions or the appearance of a new lesion agreed upon by two investigators.

*Pharmacokinetics.* At specified times after drug administration, blood samples were collected in heparinized tubes and centrifuged at 1,000 *g* for 10 min, after which plasma was removed. An aliquot of plasma was frozen at −20° C until analyzed. Protein-free ultrafiltrates were prepared by centrifuging 3 ml of the remaining plasma in Centriflo CF50A membranes (Amicon Corp., Lexington, MA, USA) at 1,000 *g* for 20 min at 4° C. Urine samples were collected at the time of voiding, measured, and stored at −20° C, either individually or as pooled 6- or 24-h collections.

Plasma, plasma ultrafiltrates, and urine samples were analyzed for platinum (Pt) by flameless atomic absorption spectrometry, employing the same instrumentation and methodology previously reported [9]. Plasma and urine samples were analyzed for VDS by a previously published radioimmunoassay technique [13]. Anti-vinca antiserum (Lot no. 24-245-2-R) was graciously provided by Dr Mary Root of the Eli Lilly Research Laboratories, Indianapolis, Indiana. $^3$H-Vinblastine sulfate (specific activity 10.4 Ci/mmole) was purchased from the Amersham Corporation (Arlington Heights, Ill.) and isotopically unlabelled VDS was used in generating standard curves. It was not possible to measure VDS content in plasma ultrafiltrates since VDS adheres to the Centriflo CF50A membrane.

Plasma half-lives of Pt and VDS were calculated with the linear regression analysis available commercially through the computer programs of Tymshare Corp., Houston, Texas, USA.

## Results

Fourteen patients received DDP+VDS therapy and 15 received VDS alone. All patients were evaluable for toxicity and 27 of the 29 were evaluable for response. Two patients receiving DDP+VDS were evaluable only for toxicity. One of these patients refused further therapy after one dose each of VDS and DDP. The second patient died of sepsis on day 8 of

the first cycle. Since the patient had normal WBC and platelet counts, the death was not considered to be drug-related.

No objective antitumor responses (PR or CR) were observed among the 27 evaluable patients. Calculated from the first day of therapy, the median time to progression was 69 days (range, 28–180) and 77 days (range, 39–231) for VDS- and VDS-DDP-treated patients, respectively. Median survival was 86 days (range 38–455) for patients treated with VDS alone, and 77 days (range 52–330) for patients treted with VDS-DDP. There were no significant differences between VDS- and VDS-DDP-treated groups with respect to median time to progression or median survival.

Toxicity data were available on 92 VDS doses given to 15 patients treated with VDS as a single agent and on 23 DDP courses (77 VDS doses) given to 14 patients treated with the VDS-DDP combination. In patients treated with VDS alone the median number of VDS doses per patient was 7 (range, 2–13), while in the VDS-DDP-treated group the median numbers of VDS and DDP courses were 6 (range, 1–12) and 2 (range, 1–4), respectively. Hematologic and non-hematologic toxicities produced by the two-drug regimens are summarized in Table 2.

Fifty-four percent of VDS- and 79% of VDS-DDP-treated patients developed WBC counts $< 3{,}000/\mu l$. Among these patients, the median lowest leukocyte count produced by VDS alone was 1,250/μl (range, 600–2,300) and that produced by VDS-DDP was 1,450/μl (range, 800–2,300). Thrombocytopenia (platelet count $< 100{,}000/\mu l$) was observed only in patients treated with the VDS+DDP combination. The lowest platelet counts observed in the four thrombocytopenic patients ranged from 15,000 to 78,000/μl. No drug-related death occurred. One patient treated with VDS alone developed *Streptococcus sanguis*, type II, bacteremia during granulocytopenia, but responded to systemic antibiotics. No WBC or platelet transfusions were necessary during this trial.

Peripheral neuropathy was the most prominent non-hematologic toxic effect in this trial. The neurotoxicity was most often manifested by decreased deep tendon reflexes, distal paresthesias, muscle weakness, and constipation. The degree of neurotoxicity generally appeared to be VDS-dose-related and seldom appeared during the first 3 weeks of therapy. Mild to moderate neuropathy was observed in 18 of the 29 treated patients. One patient developed signs of progressive pronounced neuropathy and motor weakness. Due to the severity of the symptoms treatment was stopped in this patient after 3 and 11 doses of DDP and VDS, respectively. Constipation occurring during this trial was mild (1 patient) to moderate (2 patients) and was alleviated by laxatives. According to the study design, VDS dose was reduced by 50% in cases with moderate constipation.

Nephrotoxicity, defined as a 20% fall in creatinine clearance from the pre-treatment level, developed in two patients after one and four courses of DDP, respectively. Renal function tests did not return to normal in these patients and both patients were thereafter continued on VDS alone. All patients receiving DDP developed nausea and vomiting.

**Table 2.** Drug toxicity observed among 15 and 14 patients with NSCLC treated with VDS and VDS + DDP, respectively

| Characteristics | Number of patients | |
|---|---|---|
| | VDS alone | VDS + DDP |
| Lowest WBC count/μl | | |
| ≤ 1,000 | 2 | 2 |
| > 1,000–≤ 2,000 | 4 | 7 |
| > 2,000–≤ 3,000 | 2 | 1 |
| Lowest platelet count/μl | | |
| ≤ 20 | 0 | 1 |
| > 20–≤ 50 | 0 | 1 |
| > 50–≤ 100 | 0 | 2 |
| Peripheral neuropathy | | |
| None | 6 | 4 |
| Mild-moderate | 9 | 9 |
| Severe[a] | 0 | 1 |

[a] Interfering with normal physical activities

*Pharmacokinetics*

When administered without DDP, VDS disappeared from plasma with an early $t_{1/2}$ of 2.6 ± 2.4 h and a terminal $t_{1/2}$ of 23.8 ± 10.7 h (Fig. 1, Table 3). Our times of plasma sampling do not allow analysis of the VDS plasma $t_{1/2}$ alpha as reported by others [11, 13]; however, the values of 2.6 and 23.8 h agree well with the values of 1.65 ± 0.74 h and 0.91 ± 0.37 h reported by these authors for the $t_{1/2}\beta$ of VDS and the values of 20.2 ± 8.2 h and 24.2 ± 10.4 h reported by Ostrow et al. and Owellen et al. for the terminal $t_{1/2}$ of VDS. The administration of DDP with VDS did not alter the plasma behavior of VDS (Fig. 1, Table 3). Moreover, there were no alterations of the

**Table 3.** Pharmakokinetic data of vindesine and platinum

| Chemotherapy regimen<br>Pharmacokinetics of | VDS alone<br>VDS | VDS + DDP<br>VDS-given with platinum | VDS + DDP<br>VDS-given 1 week post DDP | VDS + DDP<br>Platinum |
|---|---|---|---|---|
| No. of studied courses | 13 | 5 | 3 | 7 |
| Parameters (mean ± SD) | | | | |
| Peak plasma (ng/ml) | 10.6 ± 7.1 | 15.4 ± 5.8 | 17.8 ± 3.6 | |
| (μg/ml) | | | | 3.0 ± 0.6 |
| $t_{1/2}$ beta (h) | 2.6 ± 2.4 | 2.0 ± 0.8 | 2.7 ± 0.7 | |
| $t_{1/2}$ gamma (h) | 23.8 ± 10.7 | 20.6 ± 13.4 | 16.5 ± 3.0 | 141.4 ± 34.0 |
| Free peak (pt) (μg/ml) | | | | 0.71 ± 0.1 |
| Free pt. $t_{1/2}$ (h) | | | | 0.85 ± 0.3 |
| 24-h urinary excretion (% administered dose) | 1.4 ± 1.3 | 6.1 ± 5.6 | 1.6 ± 1.1 | 13.8 ± 2.2 |

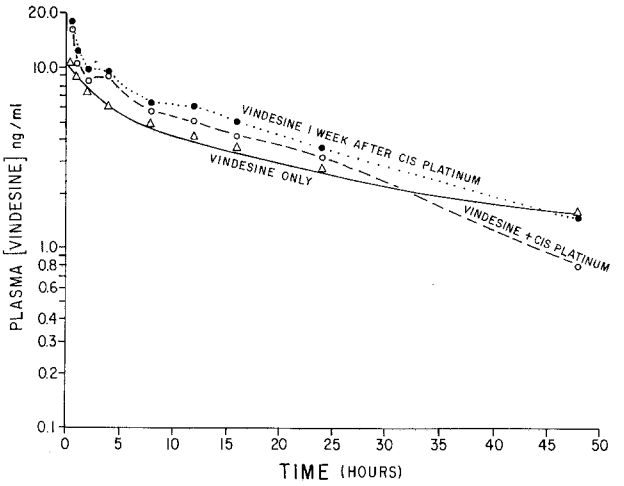


**Fig. 1.** Plasma concentrations of vindesine in patients receiving vindesine without cisplatin (△———△), vindesine with cisplatin (○ – – – ○), or vindesine 1 week after cisplatin (●· · · · ·●). *Points* represent means of 13, five, and three determinations, respectively

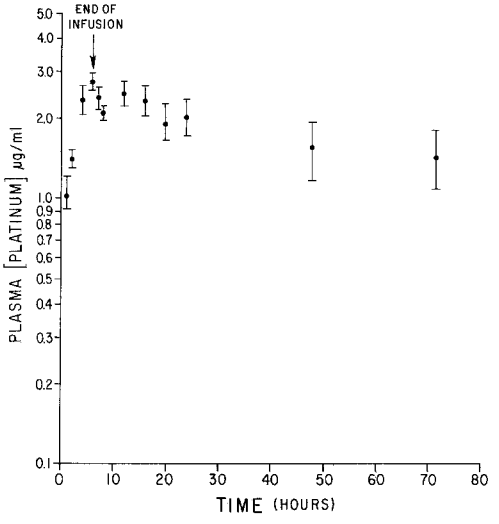


**Fig. 2.** Plasma concentrations of platinum in patients receiving cisplatin with vindesine. *Points* represent the means and *bars*, SEM of values from seven patients

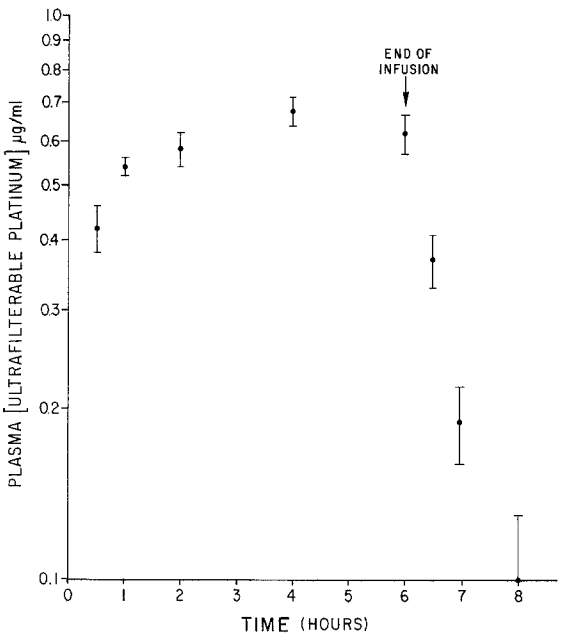


**Fig. 3.** Plasma concentrations of ultrafilterable platinum in patients receiving cisplatin with vindesine. *Points* represent the means and *bars*, SEM of values from seven patients

plasma pharmacokinetics when VDS was given 1 week after combined VDS-DDP therapy (Fig. 1, Table 3). The urinary excretion of VDS was not affected by concomitant or prior DDP therapy (Table 3); however, our measurements of the percentage of a dose excreted in the urine during the first 24 h after VDS injection are substantially lower than the 13.2 ± 5.9% urinary excretion reported by Owellen et al. [13].

VDS exerted no observable effect on the plasma pharmacokinetics of DDP. The peak plasma concentrations of total and unbound Pt (Figs. 2 and 3, Table 3) are comparable to those reported by us [12] and by others [7, 14] for DDP administered as a single agent. Similarly, the plasma $t_{1/2}$ of total and unbound Pt (Figs. 2 and 3, Table 3) are similar to those observed in patients receiving DDP alone [7, 12–14]. In addition, VDS did not appear to alter the urinary excretion of Pt. The percentage of a DDP dose excreted in 24 h by patients in this study is no different from the percentage excreted by patients receiving DDP alone [7, 12, 14].

## Discussion

The data from this study indicate that VDS pharmacokinetics in previously treated and untreated patients are similar and that the pharmacokinetics of both VDS and DDP are not affected by co-administration of the other drug. In addition pretreatment with DDP did not alter subsequent VDS pharmacokinetics.

The lack of antitumor activity of VDS or VDS-DDP for NSCLC in this study is in contrast with results presented in other publications [1–6]. In addition, the rate of significant hematologic toxicity in the present study was greater than that reported in other series, and there was less patient tolerance of the therapy. In contrast to other studies in which patients with NSCLC were initially treated with VDS or VDS-DDP, all but two of our patients had received prior aggressive combination chemotherapy. One might thus infer that the poorer tolerance to treatment and the lack of antitumor activity for either VDS or VDS-DDP observed in this trial may have been influenced by the prior chemotherapy exposure.

On the basis that prior aggressive combination chemotherapy may reduce the response to new chemotherapeutic agents, we believe that further testing of new drugs or new combinations in NSCLC are best performed in patients who have not had prior chemotherapy.

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